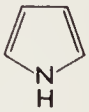
4

FURAN, PYRROLE, AND THIOPHENE

THE UNSATURATED MONOHETERO ATOMIC five-membered ring systems, namely, furan [**1**], pyrrole [**2**], and thiophene [**3**], although embodying a cis-dienoid component in their structures, do not in general display

[1]

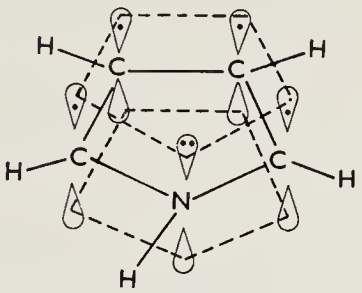


[2]

[3]

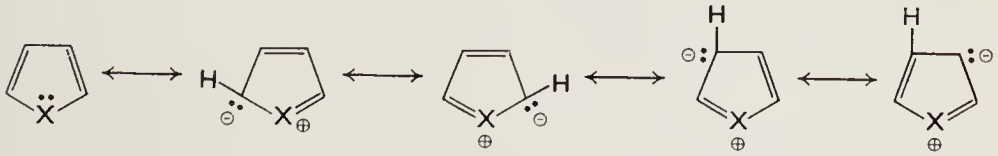
reactivities characteristic of analogous molecules such as cyclopentadiene. Rather, the reactions of these heterocycles (see below) suggest that they are endowed with considerable aromatic character, although there exists a wide variation in their chemical properties.[1]

From the molecular orbital point of view, these molecules are described as consisting of planar pentagons with sp^2-hybridized carbon atoms. Each of the four carbon atoms has 1 electron remaining in a p_z orbital, while the hetero atom has two such p-electrons. These p orbitals overlap to give rise to π-clouds above and below the ring (as exemplified for pyrrole in [4]); since the π-clouds contain 6 electrons, a stable closed shell of electrons ("aromatic sextet") exists and renders stability to the ring.



[4]

In the alternative valence-bond description, these molecules are considered as resonance hybrids of a number of contributing structures. This approach describes pictorially the result of the delocalization of the hetero atomic lone pair of electrons, namely, the acquisition



[5] [6] [7] [8] [9]

by the ring carbons of a degree of negative character. Structure [5] is the major contributor because no separation of charge is involved; of the remaining resonance structures, [6] and [7] would be expected to outweigh [8] and [9] in importance because of the smaller charge separation involved and because the chromophore is conjugated (as opposed to the cross-conjugation in the latter two formulas). Of considerable importance is the fact that, whereas two uncharged resonance structures may be written for benzene, for furan, pyrrole, and thiophene only one valence-bond structure with no charge separation is possible. This limitation is reflected in the experimental

and calculated heats of combustion which demonstrate that the stabilization energies of the heterocycles are approximately half that of benzene, Table 4–1. Also, because the electronegativities of the

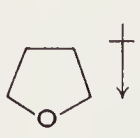
TABLE 4–1 ▪

Heats of Combustion and Stabilization Energies of the Five-Membered Heterocycles[2]

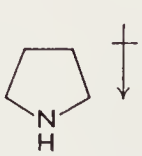
Compound	ΔH, kcal/mole Exptl.	Calcd.	S.E.
Benzene	789	827	37.9
Furan	507	523	16
Pyrrole	578	594	16
Thiophene	612	623	11

hetero atoms are in the order oxygen > nitrogen > sulfur, resonance structures **[6]**–**[9]** are less important in the case of furan relative to pyrrole and thiophene (oxygen is most resistant to releasing its pair of electrons) and, in consequence, furan is the least "aromatic" of the three heterocycles.

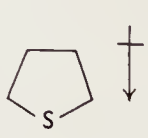
Additional evidence in support of the delocalized structures is available from bond length measurements (the bonds of the heterocycles are intermediate in length between the usual single and double bonds), microwave and ultraviolet spectra, and dipole moments. In the latter studies, comparison of the dipole moments of the heterocycles with those of appropriate reference compounds with known dipole vectors (arrow tip points to negative end of dipole) indicates electron pair delocalization into the ring and thus, significant contributions of the polar resonance structures.



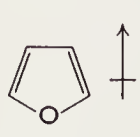
1.7D



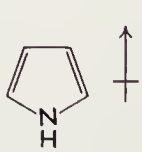
1.57D



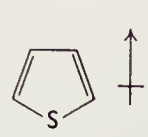
0.52D



0.7D

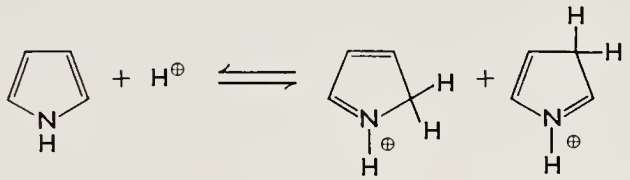


1.80D



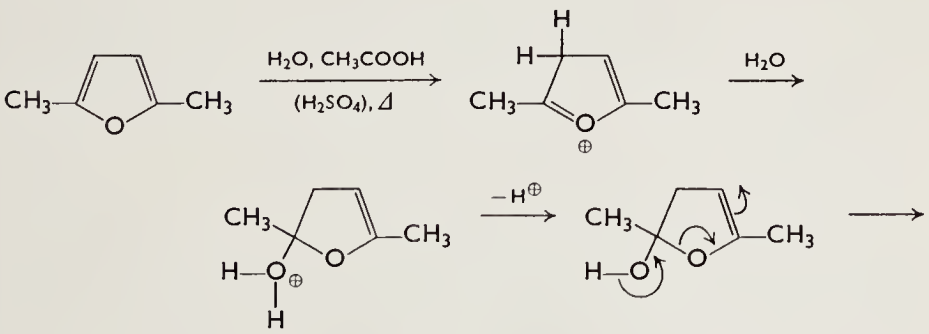
1.87D

The aromaticity of these heterocycles is therefore dependent upon the two electrons which the hetero atom contributes to the π-system. In the case of pyrrole, this requirement deprives the nitrogen atom of the pair of electrons commonly associated with organic amines, and therefore pyrrole can form a salt only at the expense of its aromatic character. Pyrrole, therefore, is a very weak base ($pK_a = 0.4$) which in fact is protonated preferably at a ring carbon in strong acid,[3] and which is polymerized under such conditions presumably by attack of a nonprotonated pyrrole molecule upon its conjugated acid.[4]



(major) (*Ref. 5*)

Furans react violently with strong acids, but careful hydrolysis in dilute mineral acids can produce 1,4-dicarbonyl compounds in good yield. The presence of electron-withdrawing substituents on the

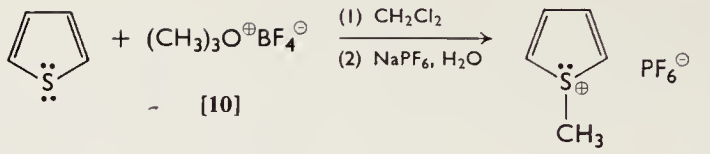


$CH_3COCH_2CH_2COCH_3$ (*Ref. 6*)

(86–90%)

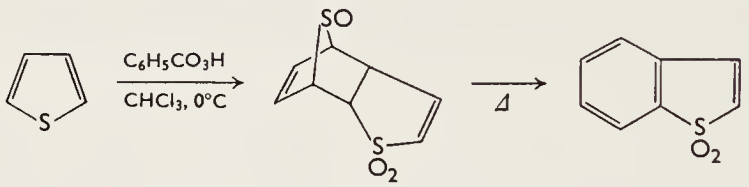
furan nucleus lowers the basicity of the heterocycle and renders it more stable to mineral acid.

Thiophene, although virtually devoid of basic properties, does react with Meerwein's reagent [**10**] to yield a stable S-methylthiophenium salt.[7] Apparently, therefore, the "extra" lone electron pair



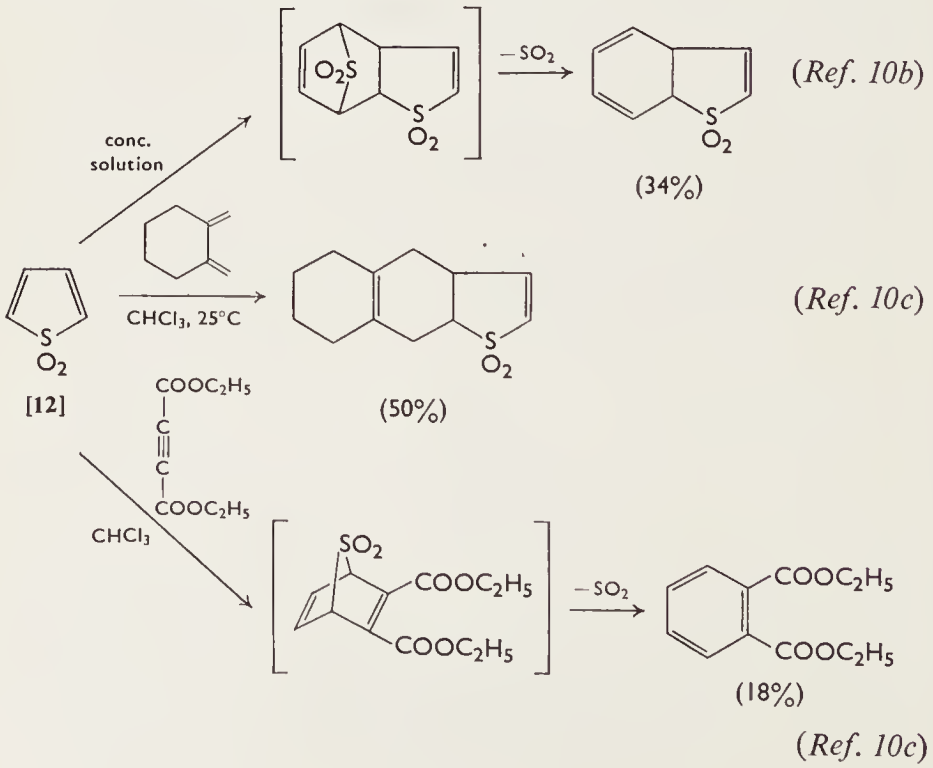
[10] (*Ref. 7*)

on sulfur can become coordinated in certain cases without destruction of the ring. Attempts to oxidize thiophene leads to **[11]** which presumably results via a Diels-Alder reaction of the intermediate



[11] (*Refs. 8, 9*)

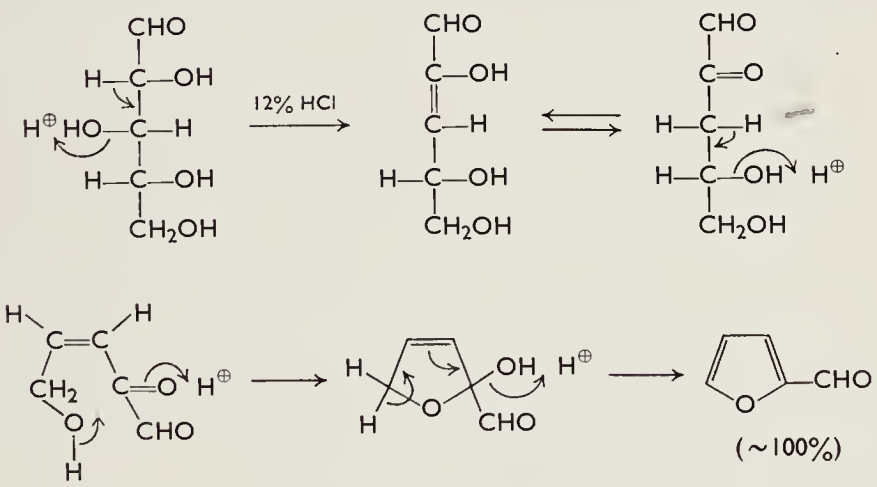
thiophene sulfoxide to thiophene sulfone. Thiophene-1,1-dioxide **[12]** has been synthesized in six steps from butadiene sulfone[10a] and was found to be stable only in dilute solution. It is extremely reactive and may function as a diene or dienophile in the Diels-Alder reaction. Several examples are given below. The reactions of **[12]** are thus



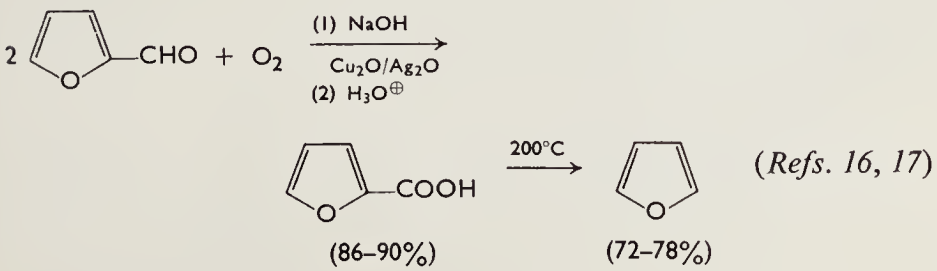
characteristic of an unsaturated compound, not of an aromatic species. Thiophene-1-oxide has also been obtained in solution, but is even less stable than **[12]**, and dimerizes spontaneously by a similar diene-type reaction.[11]

SYNTHETIC APPROACHES

Furan **[1]** is available cheaply from its 2-aldehyde derivative, furfural, which in turn is obtained readily by acid hydrolysis of the polysaccharides in oat hulls or other naturally occurring substances which contain pentose fragments such as corncobs[12] and straw. Passage of the aldehyde in the vapor phase over catalysts such as nickel (280°C)[13] or lime (350°C)[14] gives furan in high yields. Al-

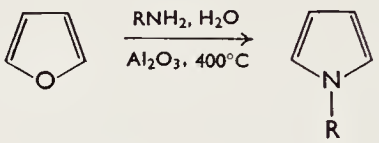


ternatively, furfural can be converted to furoic acid by the Cannizzaro reaction,[15] or preferably by air oxidation in the presence of alkaline cuprous and silver salts[16]; the acid can then be thermally decarboxylated to furan.[17]

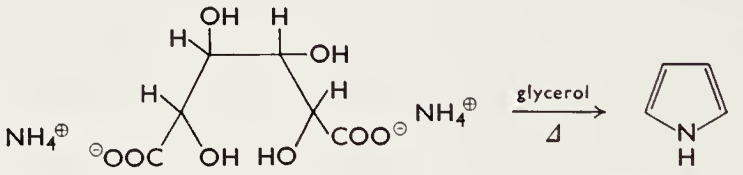


(*Refs. 16, 17*)

Pyrrole [2] is prepared commercially by the fractional distillation of coal tar and bone oil or by the passage of furan, ammonia, and steam over an alumina catalyst at 400°C. In the latter process, a primary amine may be substituted for the ammonia in which case a



1-substituted pyrrole is obtained. An improved method for preparing pyrroles from furans involves the intermediate 2,5-dialkoxytetrahydrofurans (see p. 135). Pyrrole may also be obtained conveniently in the laboratory by heating ammonium mucate[18]; at the

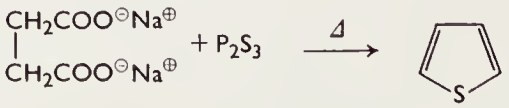


(37–40%)

(*Ref. 18*)

elevated temperature, the ammonium salt dissociates into the free acid, which undergoes dehydration, decarboxylation, and finally cyclization with the ammonia.

The commercial synthesis of thiophene [3] involves the cyclization of butane, butadiene, or butenes with sulfur; the constituents are preheated to 600°C and passed rapidly (contact time about 1 second) through a reaction tube, the exit gases from which are cooled rapidly. The unreacted materials are recycled, and the redistilled thiophene is of 99% purity.[19] On a laboratory scale, thiophene is prepared by heating an intimate mixture of sodium succinate and phosphorus trisulfide.[20] This method finds utility in the fact that the position of



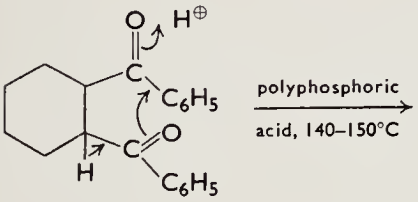
(25–30%)

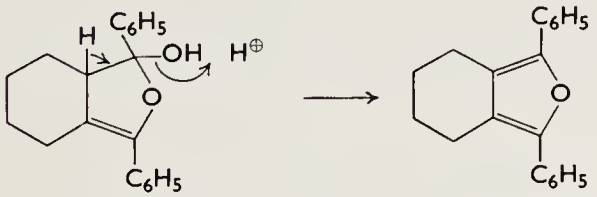
(*Ref. 20a*)

substituents on the heterocycle can be controlled by proper selection of the substituted succinic acid.[20b, 21]

The Paal-Knorr Synthesis[22]

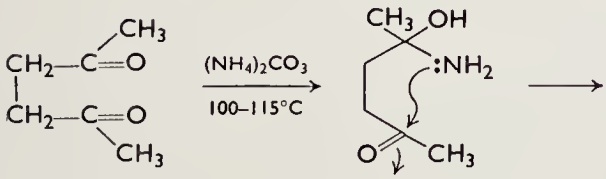
The general procedure whereby an enolizable 1,4-dicarbonyl compound is heated either with a dehydrating agent (H_2SO_4, P_2O_5, $ZnCl_2$, etc.), ammonia or a primary amine, or an inorganic sulfide is known as the Paal-Knorr synthesis. Because of the ready availability of a wide variety of such dicarbonyl compounds, the reaction is of very wide applicability. The mechanistic aspect of this group of reactions has been little studied, but probable reaction pathways are suggested below. The driving force in all of these processes

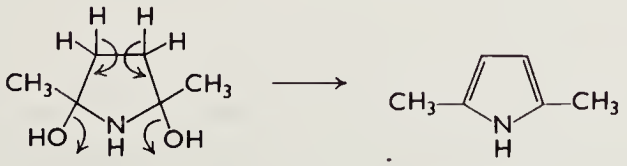




(*Ref. 23*)

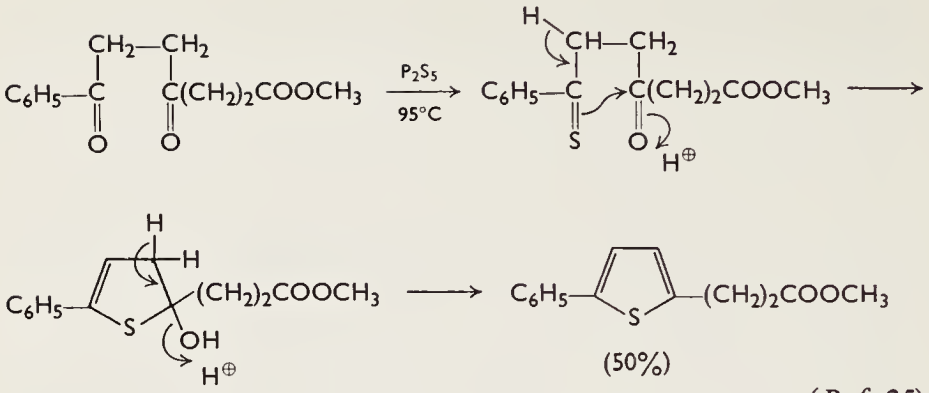
(62%)





(*Ref. 24*)

(81–86%)

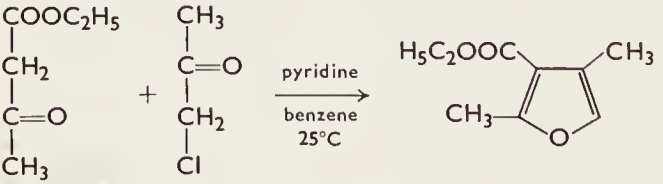


(*Ref. 25*)

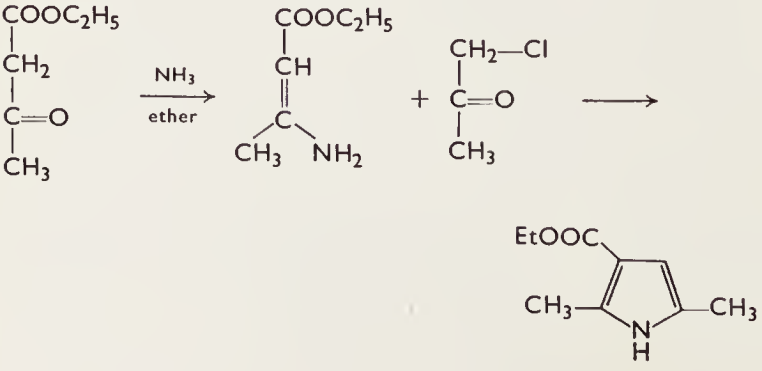
results from the stabilization gained in formation of the aromatic heterocycle.

The Feist-Benary Furan Synthesis[26] and the Hantzsch Pyrrole Synthesis[27]

The reaction of an α-haloketone or aldehyde with a β-keto ester (or β-diketone) in the presence of a base such as sodium hydroxide or pyridine leads to the formation of furans. When a nitrogen base such as ammonia or a primary amine is employed, reaction with the keto ester generally precedes condensation with the halocarbonyl component, and a pyrrole results predominantly. The first reaction very likely proceeds by means of initial O-alkylation followed by



(*Ref. 28*)

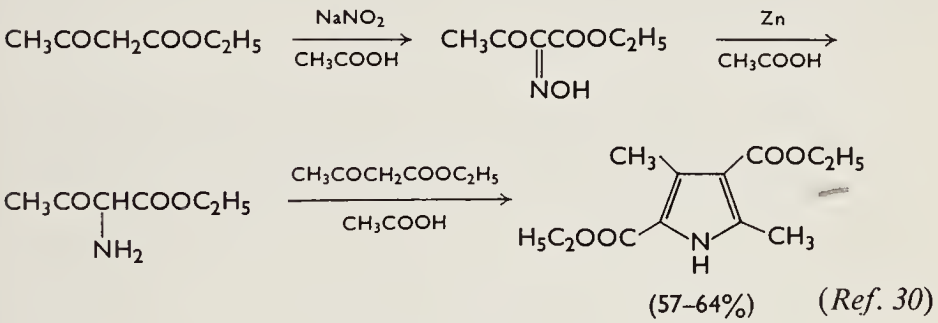


(*Ref. 27*)

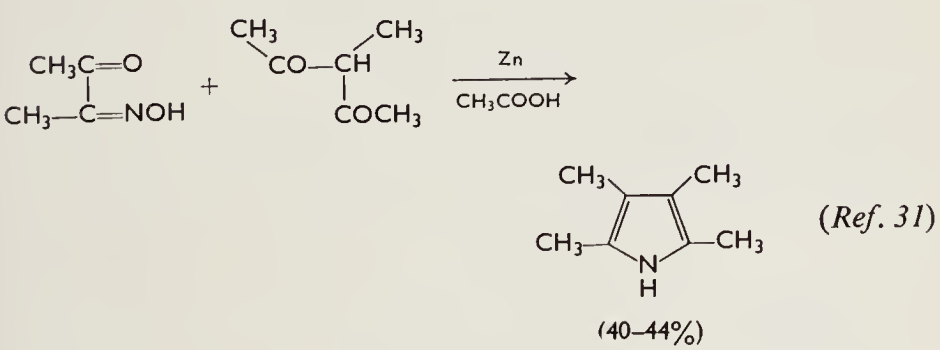
C_3—C_4 ring closure. Pyrroles result when formation of intermediate enamines is possible in which case the usual enamine C-alkylation pathway is operative and is followed by N—C_2 cyclization.

The Knorr Pyrrole Synthesis[29]

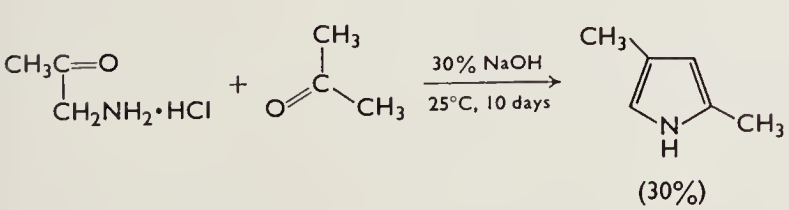
The condensation of an α-aminoketone or α-amino-β-keto ester with a ketone or keto ester in the presence of such reagents as acetic acid (frequently) or alkali (less frequently) gives rise to pyrroles in good yields. The Knorr reaction represents the most general and widely applicable pyrrole synthesis. The α-aminoketones are usually



(57–64%) (*Ref. 30*)



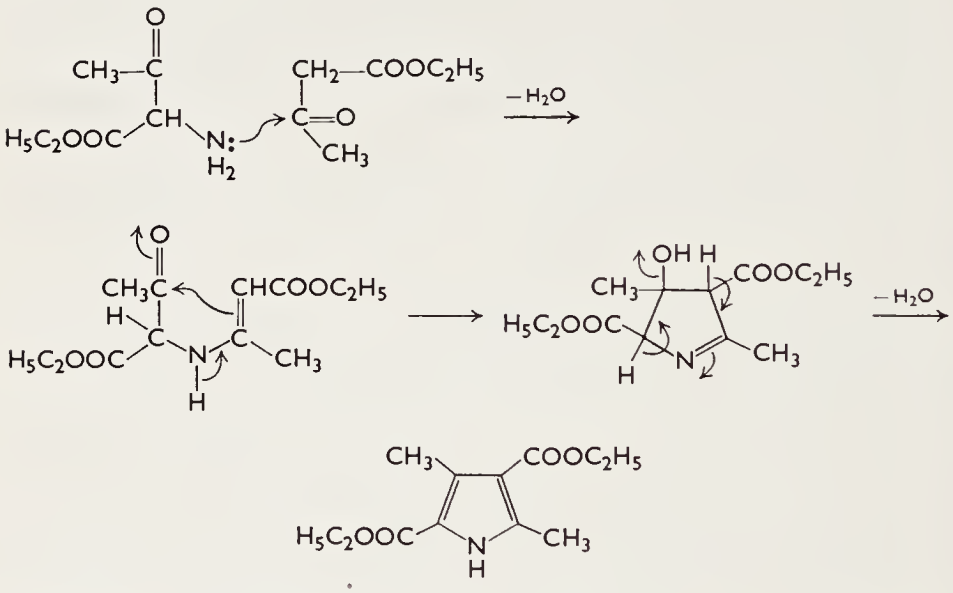
(40–44%) (*Ref. 31*)



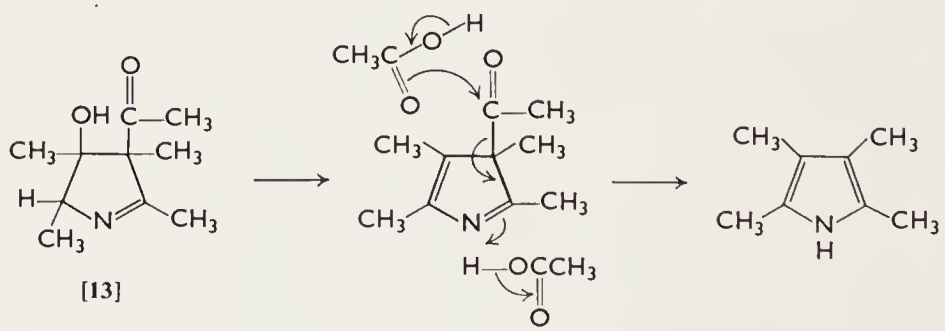
(30%) (*Ref. 32*)

prepared by nitrosation of β-keto esters or β-diketones to give the related oxime which is reduced subsequently with zinc in acetic acid. Generally, the ring closure is effected most conveniently by preparing

and condensing the α-aminoketone in the same operation[33]; the reductive conditions do not affect the coreactant. Numerous variations of this reaction have been used; the primary limitation resides in the propensity of the α-aminoketone to dimerize,[34] if the ketone or keto ester is not sufficiently reactive to condense at an appreciable rate. The mechanistic details of the Knorr synthesis have not been investigated, but the following sequence appears likely:



In the second example selected above, intermediate **[13]** is formed and deacylation leads to the pyrrole, probably as shown below:

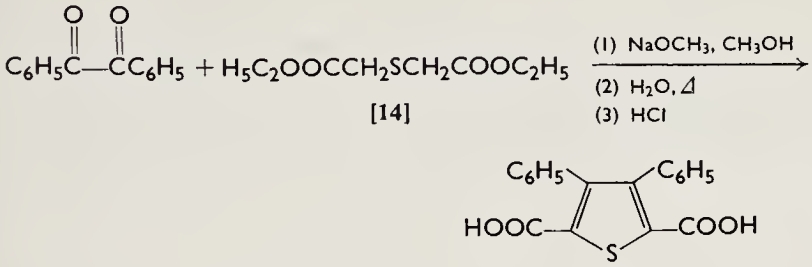


[13]

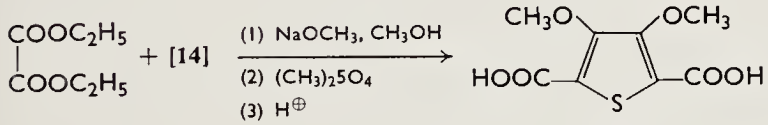
The Hinsberg Thiophene Synthesis[35]

The reaction of α-diketones, α-haloesters, and oxalic esters with diethyl thiodiacetate **[14]** under Claisen-type conditions (usually

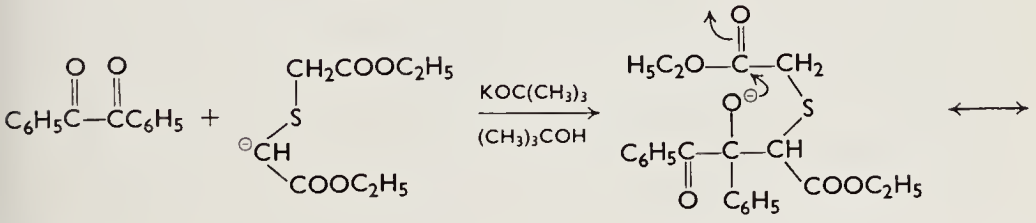
sodium alkoxide in alcohol) produces thiophene derivatives in good yields and has proved to be quite general.[20b] Usually, the reaction is worked up by diluting the alcoholic alkaline mixture with water, refluxing the solution briefly, and isolating the free dicarboxylic acid

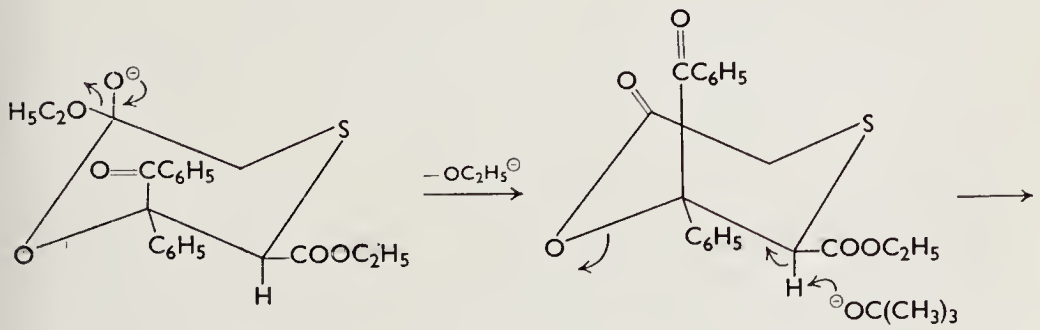


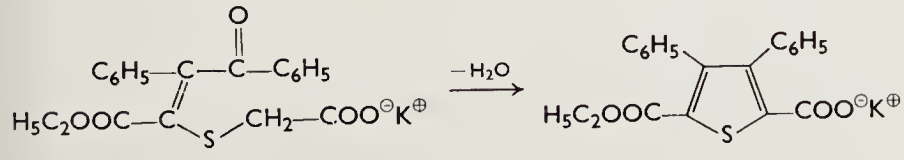
(74%) (*Ref. 36*)



(59%) (*Ref. 37*)







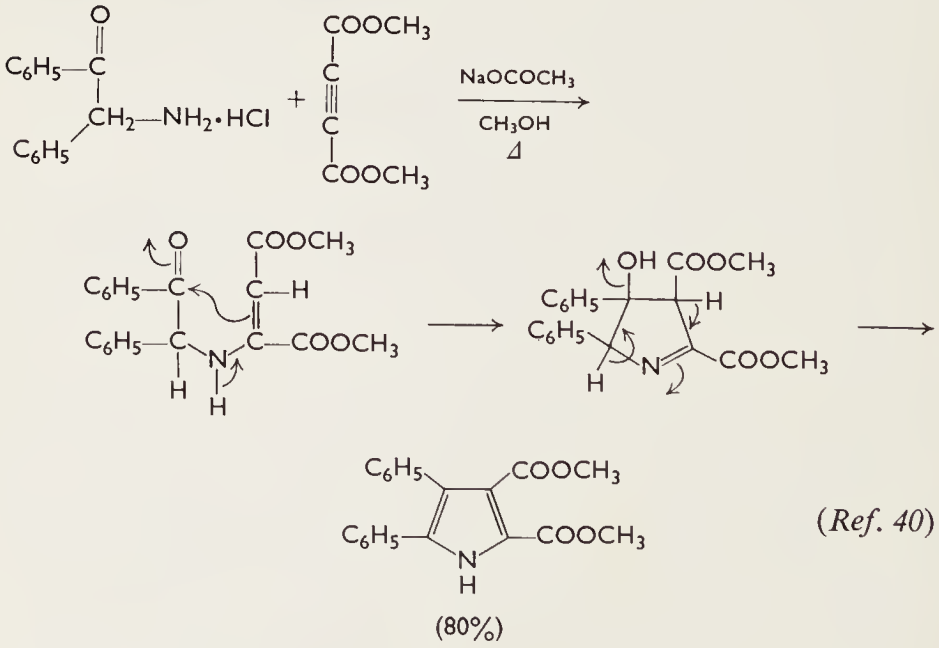
(93%) (*Ref. 39*)

thus formed. This method is of special interest because the thiophene dicarboxylic acids are readily decarboxylated (by pyrolysis) to produce the 3,4-disubstituted thiophenes. Furthermore, by varying the ester component from the sulfur to the oxygen, selenium, and nitrogen analogs, the appropriate corresponding heterocycles can be prepared.[38]

Although the implication that diesters are the primary products in the Hinsberg reaction is rampant in the literature,[20b] it is now known that half-acid half-esters actually result, and that they result from a process which is mechanistically analogous to the Stobbe condensation.[39]

Use of Acetylenedicarboxylic Esters

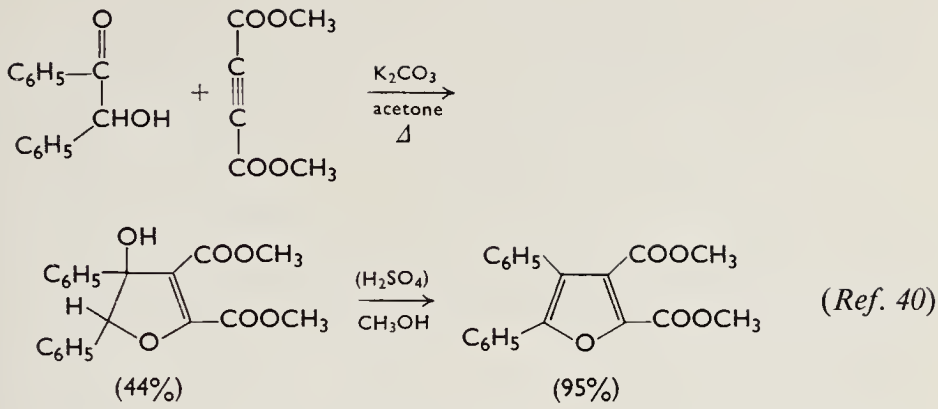
The reaction of acetylenedicarboxylic esters with a variety of nucleophiles yields furan, pyrrole, and thiophene derivatives. The mechanistic course of the additions obviously involves Michael addition followed by cyclization as outlined below.



(80%)

(*Ref. 40*)

Certain of the intermediate hydroxydihydro heterocycles have been isolated and independently "aromatized."[40] This latter step is reminiscent of the mechanism of the Knorr pyrrole synthesis (see p. 111).

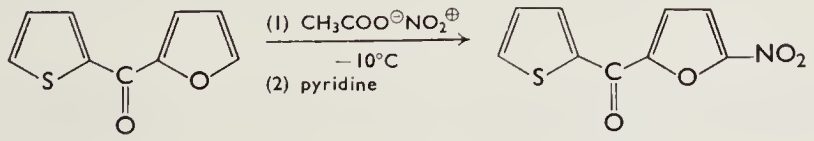


(*Ref. 40*)

REACTIONS

Electrophilic Substitution

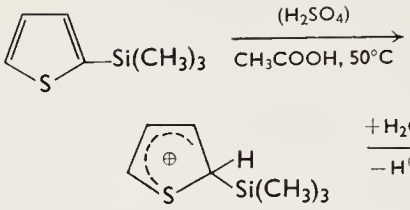
Furan, pyrrole, and thiophene are very reactive toward the usual electrophilic reagents; in fact, their reactivity is in many ways reminiscent of the most reactive benzene derivatives, namely phenols and anilines. This enhanced susceptibility to electrophilic attack is due to the unsymmetrical charge distribution in these heterocycles, whereby the ring carbon atoms are endowed with greater negative charge than in benzene (see p. 103). Of the three systems, furan is slightly more reactive than pyrrole, while thiophene is the least reactive; the following competitive reaction illustrates this point to some degree:



(51%) (*Ref. 41*)

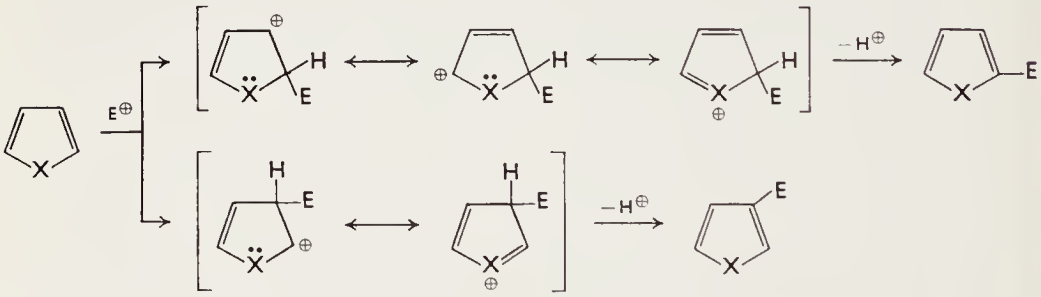
In this regard, the higher reactivity of the 2- and 3-positions of thiophene relative to a single position in benzene is known with some accuracy; the ratio of the rate of protodesilylation (exemplified for the 2-isomer below) for the 2- and 3-substituted thiophene derivatives (k_2/k_3) is 43.5. When compared to benzene, the partial rate factors become 5000 and 115 for the 2- and 3-positions, respectively.[42]

Thiophene is much more stable than furan or pyrrole to acids; this single fact allows greater latitude when selecting conditions for electro-



philic substitution of thiophene, whereas with the other two heterocycles strongly acidic conditions, which would lead to polymerization, must be avoided.

Electrophilic substitution of the title compounds occurs preferentially at the 2-position because the transition state for attack at this site is of lower energy (due to greater resonance stabilization) than that at the 3-position. Since the rate of substitution at either position



is dependent upon the energy difference between ground state of reactants and the particular transition state, that process which passes through the more stable transition state will occur more rapidly (see Figure 4–1).

The sulfonation of thiophene proceeds readily in 95% sulfuric acid at room temperature to give thiophene-2-sulfonic acid in 69–76% yield.[43] Such strongly acidic conditions cannot be utilized for furan and pyrrole, but with 1-proto-1-pyridinium sulfonate [**15**] the respective 2-sulfonic acids can be obtained in 90% yields.[44] It should be noted that benzene and its homologs are not sulfonated by this reagent which is, however, sufficiently reactive to effect substitution of anisole and thiophene (86%).[45]

The direct halogenation of furan is extremely vigorous and useful products rarely are isolated because the liberated hydrogen halide causes polymerization.[46] Under very mild conditions, however, bromine adds to furan to afford the unstable intermediate [**16**] which

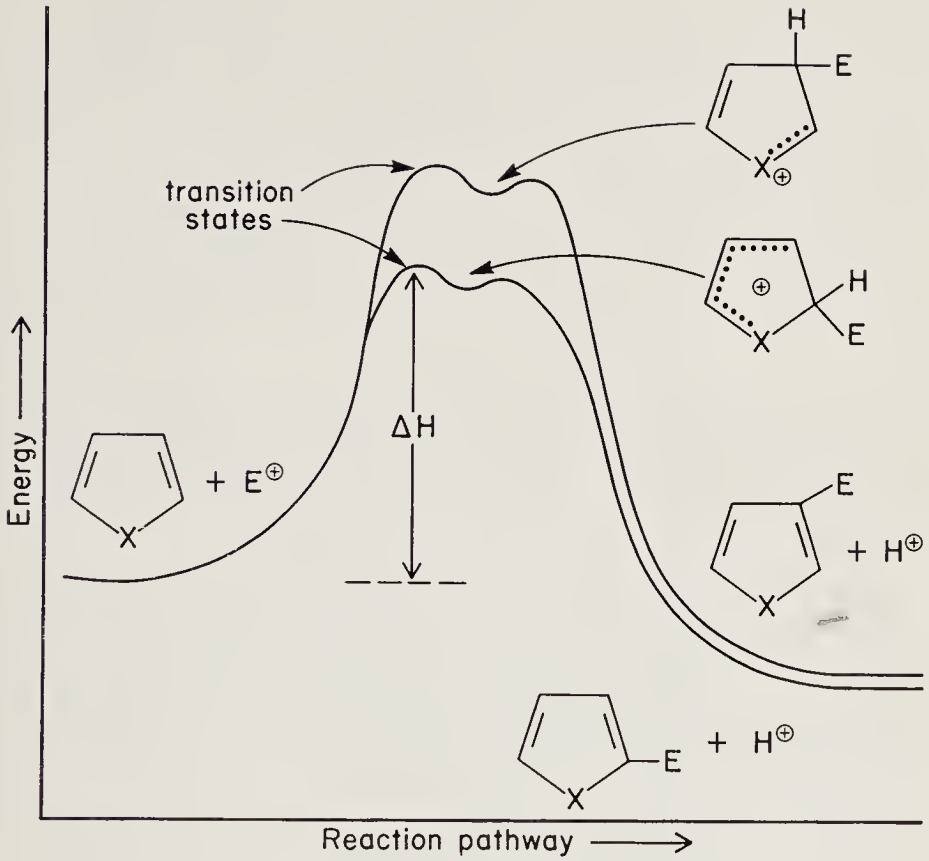
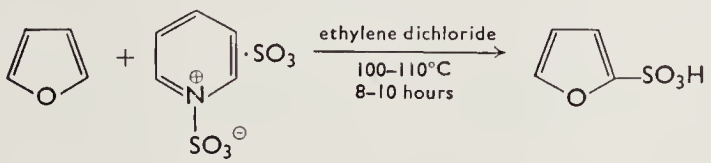


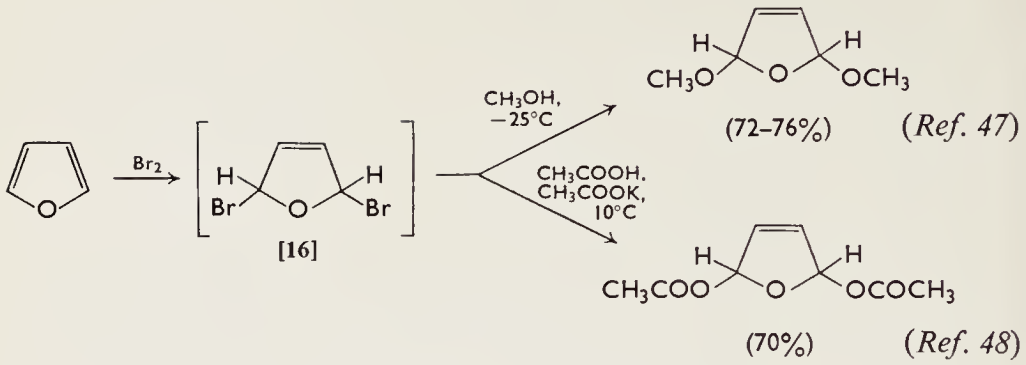
FIGURE 4-1. Energy diagram for the electrophilic substitution of the five-membered unsaturated heterocycles at the 2- and 3-positions.

is solvolyzed rapidly by the medium employed. Furan is brominated by dioxane dibromide at 0°C to give 2-bromofuran in good yield[49]; the mechanism by which this reaction occurs is not known with



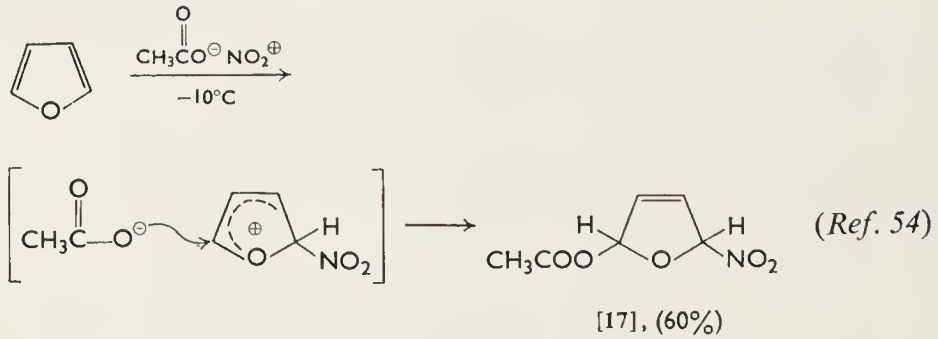
[15] (90%) (*Ref. 44*)

certainty. By comparison, pyrrole also reacts very readily with halogenating agents, and perhalogenated pyrroles are invariably obtained. Thiophene reacts so vigorously with chlorine and bromine



that pure monosubstituted thiophenes are difficult to prepare; contamination with polyhalogenated derivatives generally prevails. The iodination of thiophene proceeds very slowly, but 2-iodothiophene results in good yields from iodination in the presence of mercuric oxide in benzene (75%)[50] or aqueous nitric acid (70%).[51]

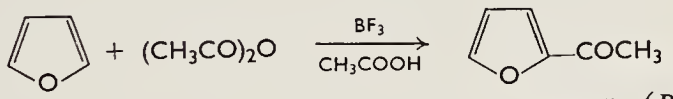
Attempts to nitrate [**1**], [**2**], or [**3**] under conditions normally employed for benzene and its derivatives invariably result in destruction of the heterocycle and tar formation. Instead, successful nitration is achieved with acetyl nitrate (i.e., the mixed anhydride generated from fuming nitric acid and acetic anhydride) at low temperatures. Under these conditions at 5°C, pyrrole affords mainly 2-nitropyrrole (83%), but some (5–7%) of the 3-isomer also is isolated.[52] Similarly at 10°C, thiophene gives rise to 2-nitrothiophene (70%) and 3-nitrothiophene (5%).[53] Furan, on the other hand, reacts initially with this reagent to give the addition compound [**17**][54]; treatment of [**17**] with pyridine removes the elements of



acetic acid and generates 2-nitrofuran.[55] Again in this instance a clear distinction in reactivity is apparent; whereas electrophilic substitution of pyrrole and thiophene are direct and parallel in type

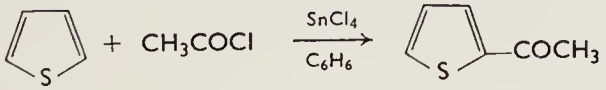
what is observed in benzenoid systems, several such reactions with furan proceed through the formation of 2,5-dihydrofuran derivatives.

Attempts to alkylate furan by the Friedel-Crafts method have proved uniformly unsuccessful because catalysts required for the reaction also catalyze polymerization. Because furans bearing electron-withdrawing groups are more stable to electrophilic attack, acylation of [1] can be achieved readily with a mild Lewis acid since the products are relatively stable to such acids. Best results are obtained when interaction of the unreacted furan with the catalyst



(75–92%) (*Ref. 56*)

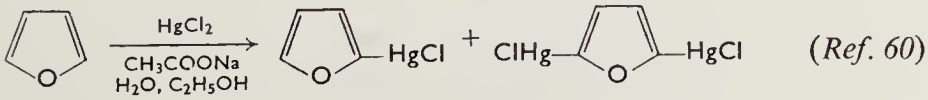
is kept at a minimum. 2-Acetylpyrrole may be obtained merely by heating pyrrole with acetic anhydride in the absence of catalyst.[57] Because of the high stability of thiophene to acidic conditions, Friedel-Crafts acylation of [3] can be achieved with a wide variety of catalysts with excellent results. In the Friedel-Crafts alkylation of



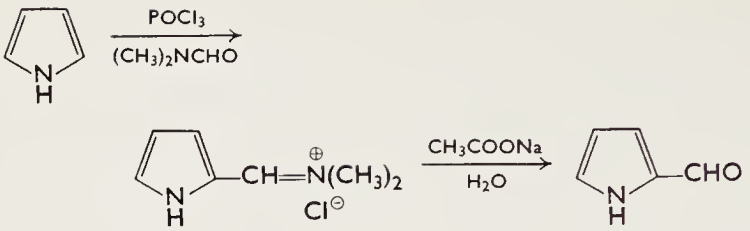
(79–83%) (*Ref. 58*)

thiophene, both the 2- and 3-positions are attacked in ratios varying from 1:1 to 3:1 depending upon the reagent and catalyst employed.[59] This poor selectivity is due to the highly reactive nature of the electrophilic alkyl cations which attack the heterocycle in rather indiscriminate fashion.

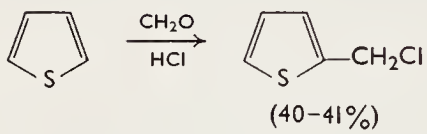
Examples of various other electrophilic substitutions are illustrated in the following equations.



(33.5%) (*Ref. 60*)

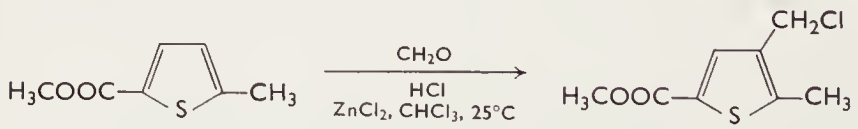


(*Ref. 61*)



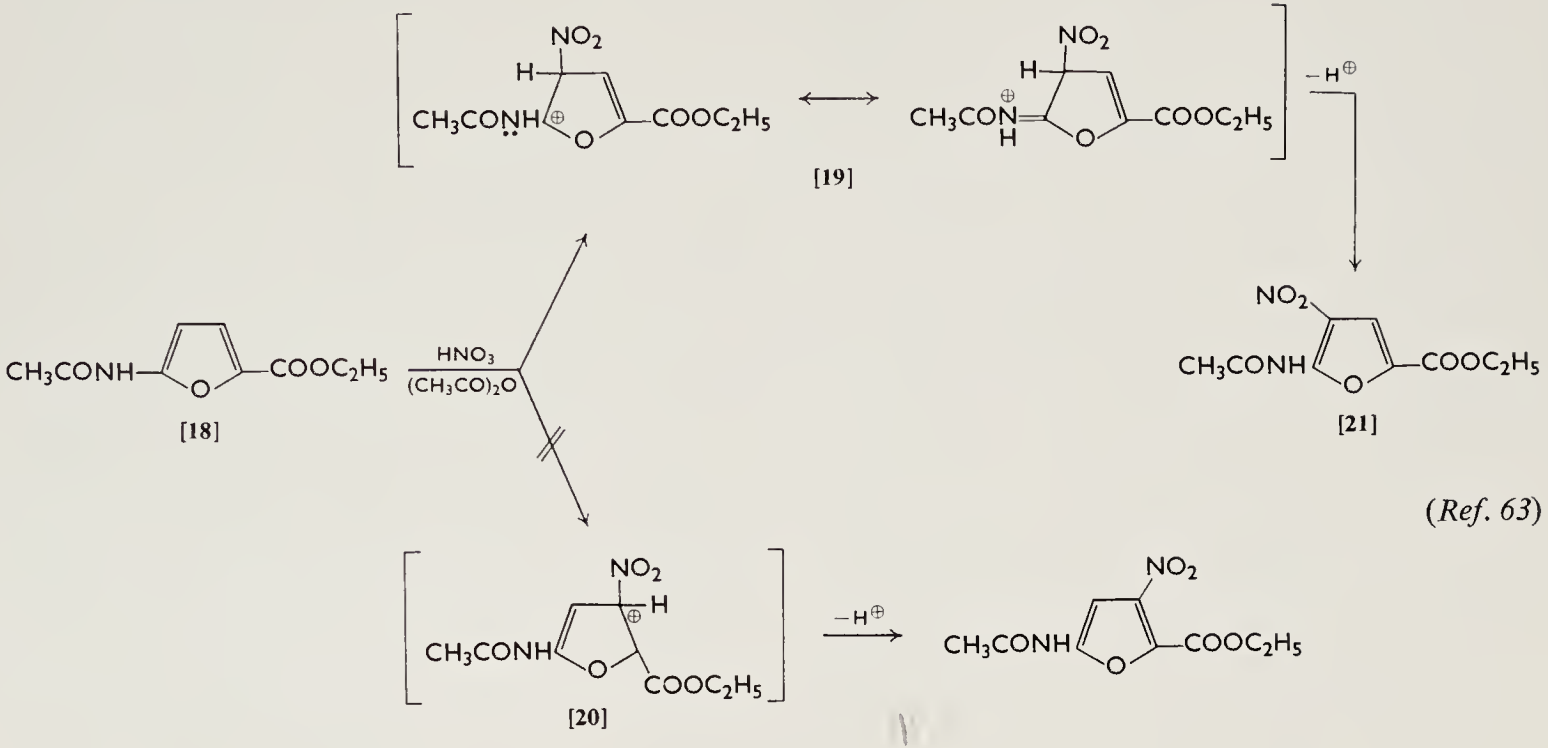
(*Ref. 62*)

When the 2- and 5-positions of the above heterocycles already carry substituents, the electrophile will attack at one or the other, or both, of the available β-positions (carbon atoms 3 and 4). The particular entry position of the electrophile generally is controlled by electronic considerations, that is, that reaction pathway will be favored which will proceed through the transition state of lowest energy. For example, nitration of [**18**] gives rise exclusively to [**21**] by virtue of the fact that intermediate [**19**] is endowed with more resonance stabilization than [**20**], in which the positive charge is located in an energetically unfavorable close proximity to the ester carbonyl group.

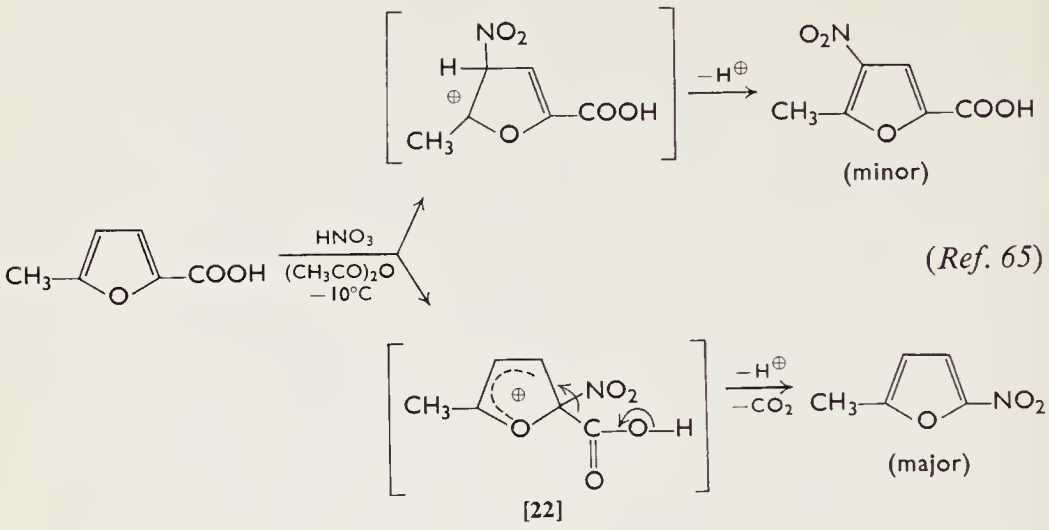


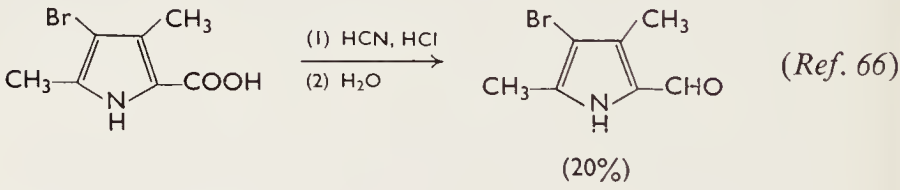
(*Ref. 64*)

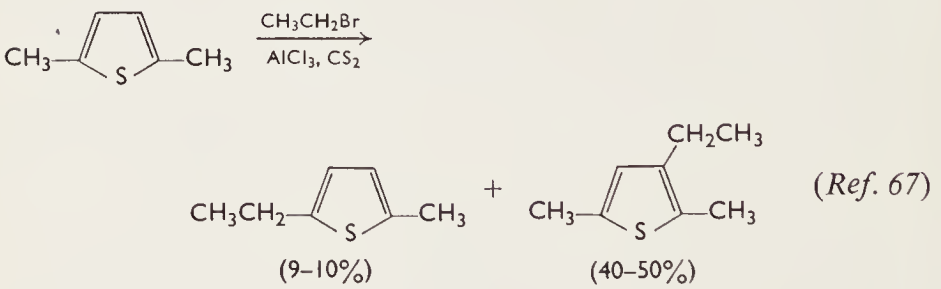
A rather common phenomenon observed in electrophilic substitution of certain 2,5-disubstituted derivatives of furan, pyrrole, and thiophene is the displacement of an atom or group already attached to the nucleus by the entering electrophile. Such substitution with elimination of substituents is more prevalent than in the benzene series because of the much higher relative reactivity of the α-positions in the heterocyclic systems due to stabilization of intermediates such as [**22**] by the hetero atom. This stabilization lowers the energy of the



(*Ref. 63*)

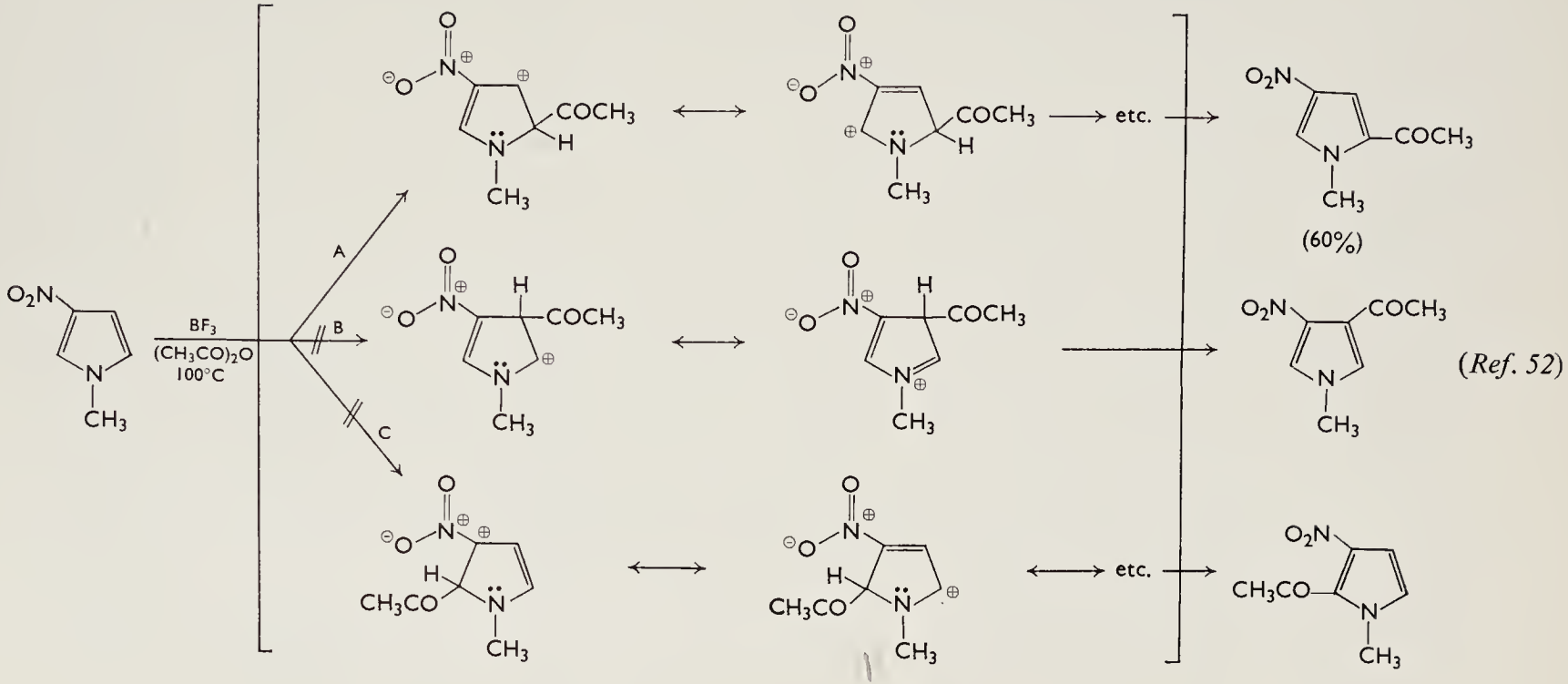






transition state leading to attack at the substituted α-position with the resulting effect that the rate of this process becomes competitive with the rate of substitution at a β-position.

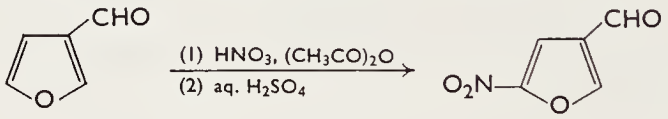
An analysis of the orientation or directive effects of substituents in relation to the introduction of a second substituent into the heterocyclic nucleus is somewhat more complex than in benzene derivatives. In the latter series, the position attacked by an electrophile is determined largely by the electronic characteristics of the group already present. With furan, pyrrole, and thiophene, although the substituent plays a decisive role in the substitution process, the ring



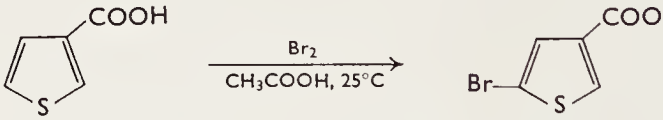
(*Ref. 52*)

hetero atom also exerts a profound directing influence in the manner outlined in earlier examples. The complicating factor is that the oxygen, nitrogen, and sulfur atoms differ substantially in the magnitude of their α-directing effect. These points are illustrated below

(a) ELECTRON-WITHDRAWING 3-SUBSTITUENT. As might be expected from the combined "meta-directing" influence of an electron-withdrawing substituent and the α-directing influence of the hetero atom, the entering group will enter the α-position most remote to the 3-substituent. Of the three possibilities in the acetylation of 1-methyl-3-nitropyrrole, path A is favored heavily over the alternative routes because of the extensive relative stabilization in the cationic intermediate; path C is especially unfavorable because of the proximity of positive charges in one of the resonance contributors. This mechanistic rationale is applicable to all three heterocyclic systems.



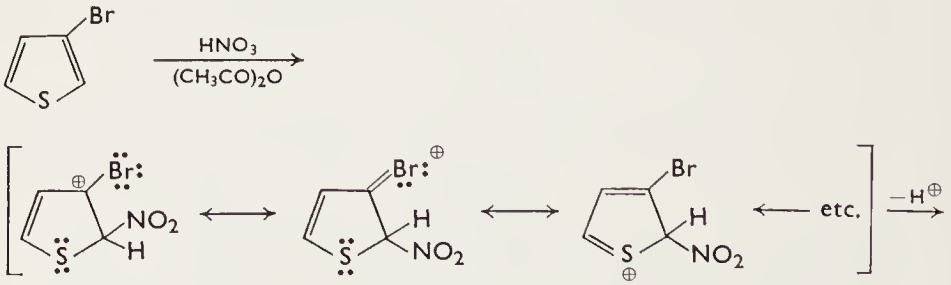
(*Ref. 68*)



(69%)

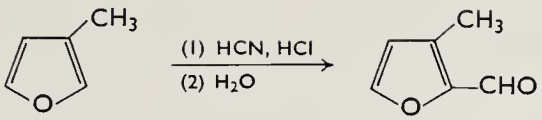
(*Ref. 69*)

(b) ELECTRON-DONATING 3-SUBSTITUENT. Such substituents direct the incoming electrophile to the adjacent 2-position because of the



(55–60%)

(*Ref. 70*)

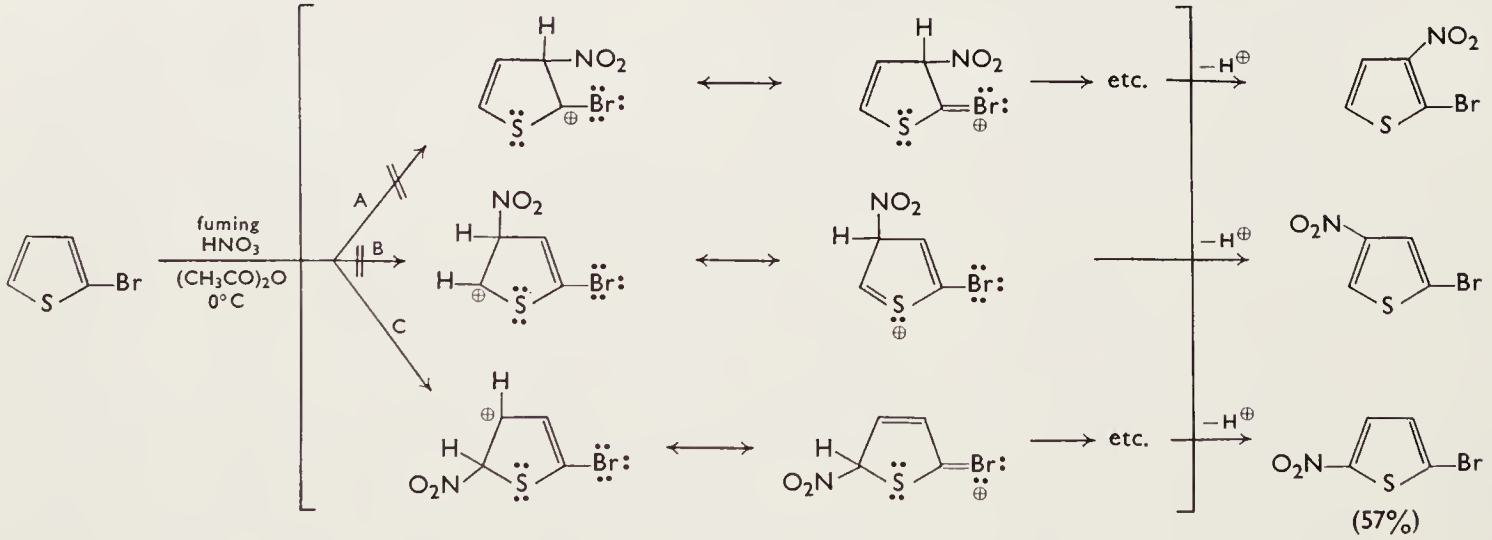


(57%) (*Ref. 71*)

lower energy of the intermediates along that particular reaction pathway. However, in certain derivatives, especially the 3-alkyl heterocycles, the difference in reactivity of the 2- and 5-positions is small; product distribution often is altered by such secondary effects as the relative steric bulk of the alkyl group and/or the entering electrophile. For example, whereas 3-methylthiophene gives upon acylation (92% yield) a mixture consisting of about 80% of the 2,3-isomer and 20% of the 3,5-isomer,[72] acylation of 3-isopropylthiophene affords an isomer ratio of 31:48, respectively,[73] and 3-*tert*-butylthiophene gives rise exclusively to 4-*tert*-butyl-2-acetylthiophene.[74]

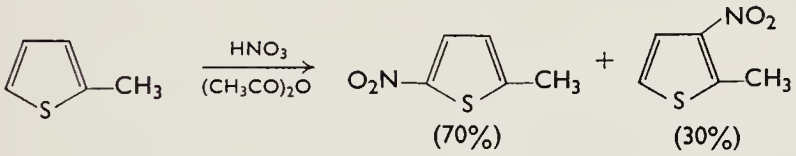
(c) ELECTRON-WITHDRAWING 2-SUBSTITUENT. An electronegative substituent in the 2-position will tend to favor electrophilic substitution in the 4-position; however, this effect is in direct competition with the α-directing effect of the hetero atom which dictates attack at the 5-position. Actually, the ratio of products obtained is a result of the relative capabilities of the two opposing factors to control the substitution reaction and of the selectivity of the electrophilic reagent. Thus, it has been found that nitration of 2-nitrofuran yields only the 2,5-dinitro compound,[75] that 2-nitrothiophene leads to a mixture of 85% of 2,4-dinitro- and 15% of 2,5-dinitro-isomers,[76] and that 2-nitropyrrole gives the dinitro derivatives in a ratio of about 4:1, respectively.[77] Similarly, nitration of 2-acetylfuran furnishes only 2-acetyl-5-nitrofuran,[78] but upon nitration of the corresponding 2-acetylthiophene and 2-acetylpyrrole the 2,4- and 2,5-dinitro derivatives are isolated in ratios of roughly 1:1[79] and 2:1,[77, 80] respectively. The above examples show the overwhelming α-directing effect of the hetero oxygen atom of furan, which influence is much less domineering in the case of the sulfur and nitrogen atoms of thiophene and pyrrole. Several exceptions to this pattern of reactivity are known, but will not be discussed here.

(d) ELECTRON-DONATING 2-SUBSTITUENT. When analyzing the energetics of electrophilic attack at the various positions of [**1**], [**2**], or [**3**] substituted with an electropositive substituent at the 2-position in the manner outlined for the nitration of 2-bromothiophene, it



(*Ref. 81*)

becomes apparent that the substituent can stabilize the intermediates formed in routes A and C. However, if the 2-substituent is weakly directing as in the case of halogen and alkyl groups, the α-directing capability of the hetero atom is the prevailing effect and substitution at the 5-position is favored heavily. When the activating influence of a 2-substituent is more pronounced, such as, for example, with $—OCH_3$, $—SCH_3$, and $—NHCOCH_3$ groups, substitution at the 3-position is often more prevalent. The nature of the electrophilic reagent also plays a role in the isomer distribution, but this effect has not yet been studied systematically.[82]



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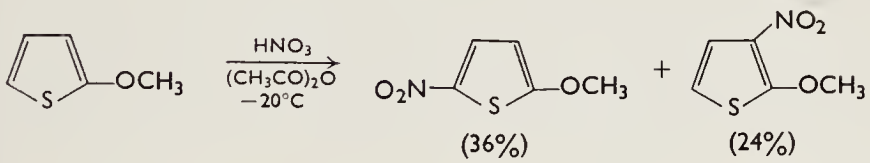

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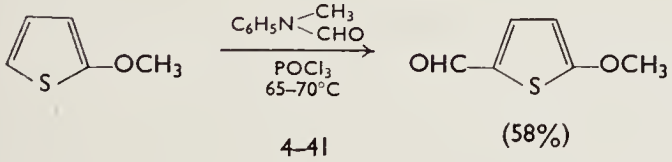


(*Ref. 85*)

Nucleophilic and Radical Substitutions

Nucleophilic and radical substitution reactions of the five-membered unsaturated monohetero atomic ring systems has been investigated much less than electrophilic substitution, especially in the case of pyrroles, and are not as well understood.[86]

Although the halogen-substituted furans and thiophenes are relatively inert to nucleophilic substitution (for example, neither 2-bromo- nor 2-iodofuran react with sodium methoxide at 100°C),[87] their reactivity is somewhat greater than that of the corresponding aryl halides. With reference to Table 4–2, it is evident from an examination of the values of the rate-controlling free energy of

TABLE 4–2 ▪

Activation Parameters for Nucleophilic Displacement in Piperidine at 200°C[88]

Compound	ΔE^*, kcal	ΔF^*, kcal	ΔS^*, e.u.
2-Chlorofuran	22	41.2	−42
Chlorobenzene	27	43.3	−42
2-Bromofuran	22	39.1	−39
Bromobenzene	24	41.4	−42
2-Iodofuran	31	38.7	−19
2-Iodo-5-methylfuran	26	39.5	−29
Iodobenzene	23.6	40.7	−38.2

activation that the furans have a slightly more reactive carbon-halogen bond than the benzene analogs. Of some interest is the fact that a 5-methyl group in this series causes a 2.2-fold decrease in rate.

As in the benzene series, the introduction of powerful electron-withdrawing groups, such as the nitro substituent, greatly facilitates nucleophilic substitution. In such examples, the activated halogen-substituted five-membered ring heterocycles are far more reactive than their benzenoid counterparts (see Table 4–3). Because the

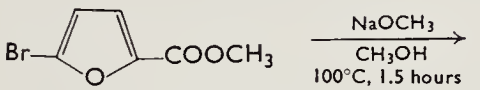
TABLE 4–3 ▪

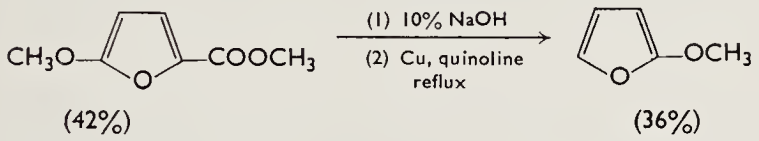
Relative Pseudo First Order Rates of Displacement with Piperidine at 25°C[89]

Compound	Rate
m-Bromonitrobenzene	1
p-Bromonitrobenzene	185
o-Bromonitrobenzene	1620
5-Bromo-2-nitrothiophene	2.84×10^4
2-Bromo-3-nitrothiophene	6.32×10^5
5-Bromo-3-nitrothiophene	Very fast
4-Bromo-2-nitrothiophene	1360
3-Bromo-3-nitrothiophene	2.5×10^6
4-Bromo-3-nitrothiophene	Very fast[90]

rates of such displacement processes are sufficiently rapid, such reactions find considerable synthetic utility. The most useful activating group is the carboxy or carboalkoxy function because of the ease with which it can be removed, as shown in the following

examples. Halothiophenes and furans which are not activated by an electron-withdrawing substituent, often can be made to undergo substitution under forcing conditions as, for example, in **[23]**.





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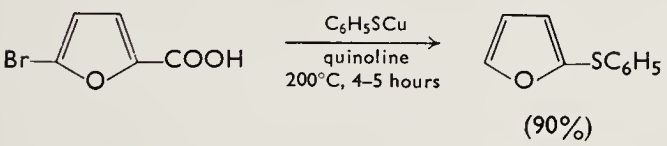

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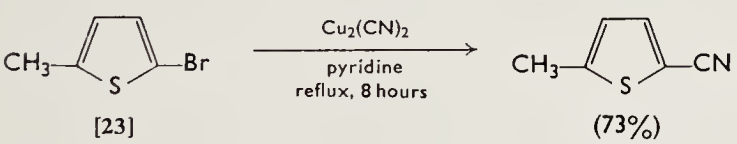
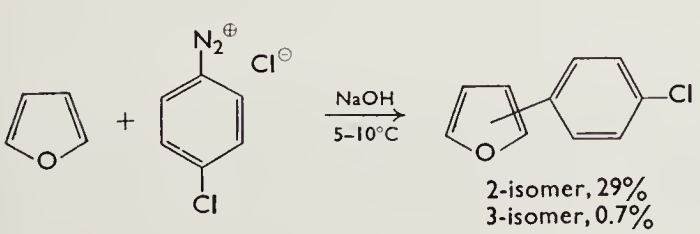


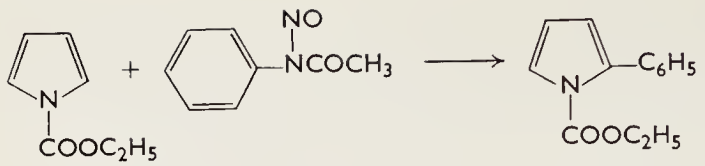
(*Ref. 92*)

The greater reactivity of the heteroaromatics can be attributed to the inductive effect of the hetero atom which increases slightly the electron deficiency at the halogen-bearing carbon (relative to benzene); however, this effect must be small because it is opposed by resonance effects and the possible repulsion of the approaching nucleophile by the *p*-electrons of the oxygen or sulfur atom.

Relatively little attention has been directed to radical substitution of the five-membered heterocycles. However, it has been established that homolytic attack at the 2-position predominates or is exclusive, as illustrated in the following examples. When thiophene is treated



(*Ref. 93*)



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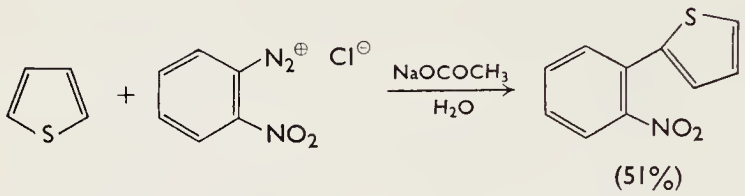
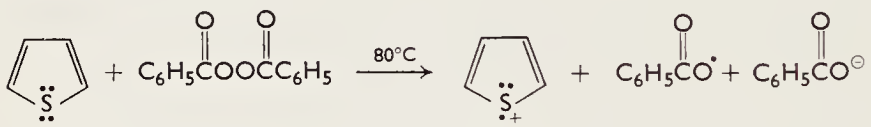


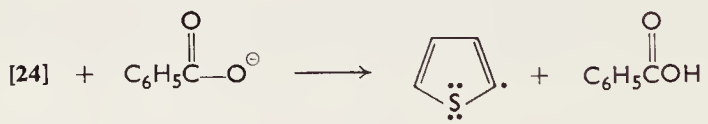
(*Ref. 95*)

(51%)

with radical sources which can readily yield stable anions (e.g., benzoate or iodide, see Table 4–4), results suggest that in these instances a 1-electron transfer process is favored; that is, an initially formed



[24]



[25]

radical cation (e.g., [**24**]) eventually is converted to a thienyl radical (e.g., [**25**]), and ultimately to products. In cases where stable

TABLE 4–4 ▪

Biaryl Fractions from Homolytic Phenylations of Thiophene[96]

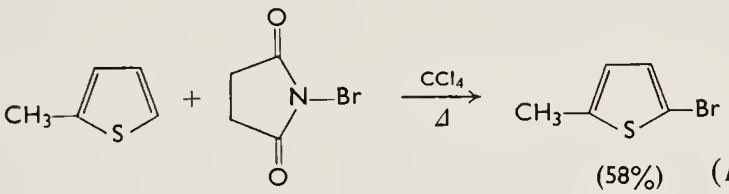
Product, mole %	Radical source[a]			
	A	B	C	D
2-Phenylthiophene[b]	22.8	86.7	63.0	63.1
3-Phenylthiophene	—	13.3	37.0	5.5
2,2′-Bithienyl	15.8	—	—	24.5
2,3′-Bithienyl	18.3	—	—	6.8

[a] Source: A, dibenzoyl peroxide; B, phenylazotriphenylmethane in air; C, phenylazotriphenylmethane in nitrogen; D, iodobenzene.

[b] Yield of 2-phenylthiophene (based on radical source): A, 3.75%; B, 0.91%; C, 0.58%; D, 3.25%.

nucleophiles cannot form (generally the situation in the examples studied to date), direct substitution of the heterocycle apparently occurs. Under such circumstances bithienyls would not be expected, and indeed are not observed (see Table 4–4 for example).

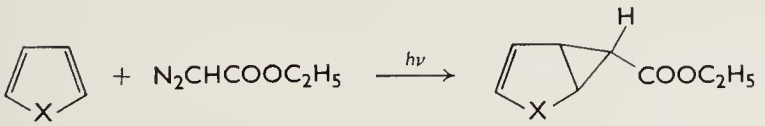
Thiophene can be converted conveniently to 2-bromothiophene through the agency of N-bromosuccinimide by a process which is believed to be radical in nature.[97] Bromination of 2-methylthiophene with the same reagent under conditions which, in the case of



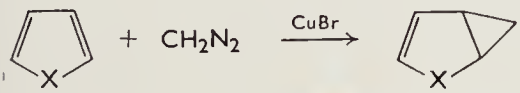
(58%) (*Ref. 98*)

toluene, would lead to halogenation of the methyl substituent gives 5-bromo-2-methylthiophene and only very small amounts of 2-bromomethylthiophene. Such behavior reflects the greater reactivity of the thiophene ring relative to a similarly substituted benzene ring toward homolytic substitution.

Furan and thiophene undergo normal addition reactions with carbenes. The photolytic decomposition of diazoacetic ester or the cuprous bromide-catalyzed reactions of diazomethane with these

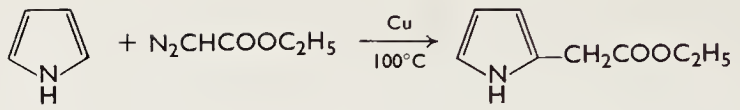


X=O, 33%
S, 23% (*Ref. 99*)

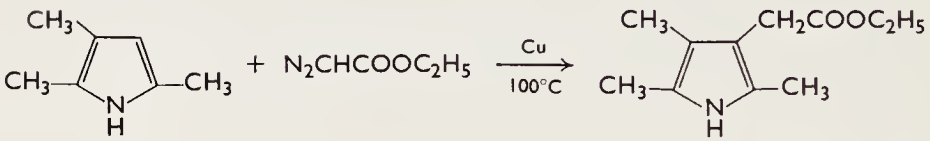


X=O, 50%
S, 22% (*Ref. 100*)

heterocycles gives the anticipated cyclopropane derivatives. Pyrroles, on the other hand, when subjected to the copper-catalyzed decomposition of diazoacetic ester give the normal product of electrophilic substitution. Examples of α- and β-attack are known.

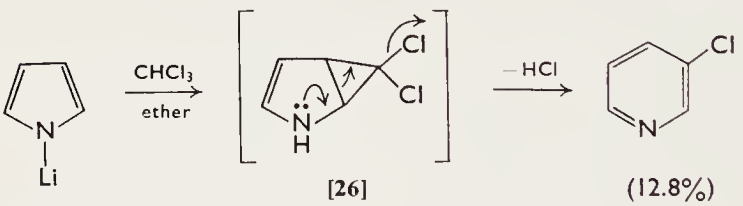


(50%) (*Ref. 101*)

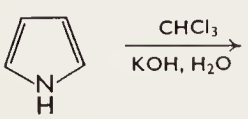


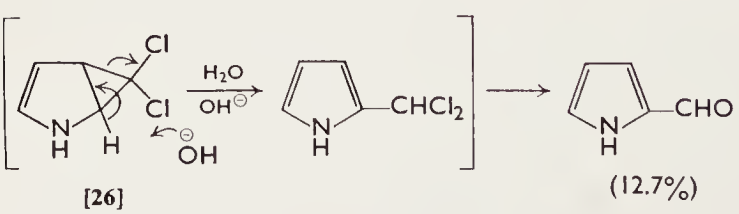
(*Ref. 101*)

Submission of pyrrole to the Reimer-Tiemann reaction (strong base and $CHCl_3$),[102] conditions which are known to favor dichlorocarbene formation, yields 3-chloropyridine or pyrrole-2-aldehyde depending upon the particular reagents employed. The bicyclic intermediate [**26**] has been postulated in these transformations.



(*Ref. 103*)

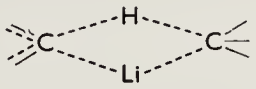




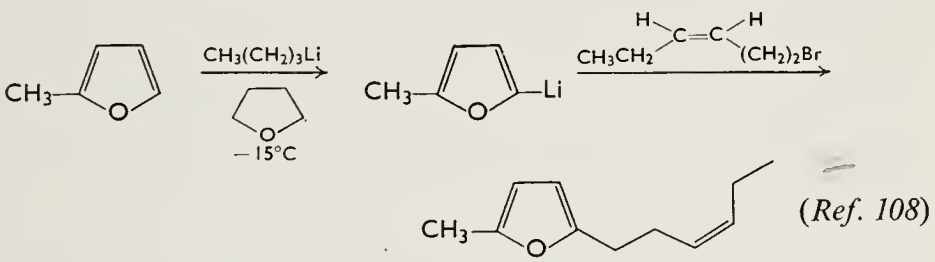
(*Ref. 104*)

Metalations and halogen-metal interconversion reactions of [**1**] [**2**], and [**3**] may be considered as nucleophilic substitution on hydrogen and halogen, respectively, and therefore will be discussed here. Furan[105] and thiophene[106] are metalated in high yield when treated with *n*-butyllithium; 2-furyllithium and 2-thienyllithium result. The

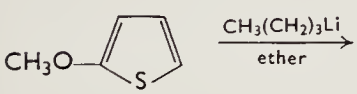
metalation reaction is believed to proceed via a four-centered process in which almost complete carbon-hydrogen bond cleavage occurs in the transition state. This mechanism is in accord with the large

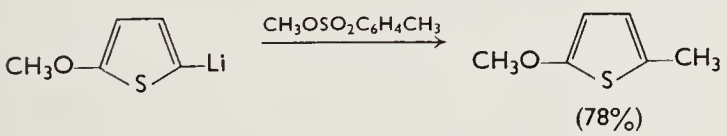


isotope effects observed with thiophenes labeled in the 2-position, that is, $k_H/k_D = 6.6$ and $k_H/k_T = 16$.[107] The high selectivity for α-attack is evidenced by the fact that 2-substituted furans and thiophenes are metalated exclusively in the 5-position. When both



(*Ref. 108*)



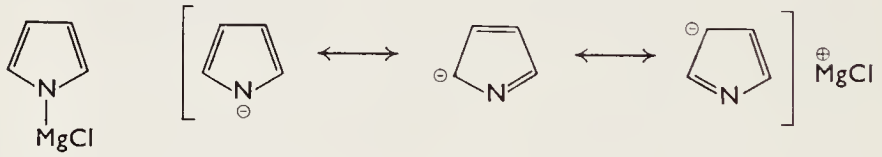


(*Ref. 109*)

α-positions carry substituents, this specificity obviously cannot be operative; in fact, metalation of 2,5-disubstituted derivatives may or may not occur, the reactivity apparently being dependent upon the nature of these substituents. Thus, although 2-methoxy-5-methylthiophene is metalated in the 3-position, 2,5-dimethylthiophene does not react.[84] For purposes of comparison, it should be noted that benzene is metalated extremely slowly and to a very small extent by *n*-butyllithium in ether.[110] Metalation studies of 3-substituted thiophenes have shown that substituents also exert a directive effect in this process. For example, whereas 3-methylthiophene is metalated predominantly in the 5-position,[109, 111] the 3-methoxy,[112] 3-methylthio-,[113] and 3-bromo-derivatives[111a] are metalated in the

2-position. These data can be interpreted on the basis of the inductive effect of the particular substituent on the acidity of the 2- or 5-hydrogen; as a result of the electron-releasing effect of the 3-methyl group, the 2-hydrogen is relatively less acidic than the 5-hydrogen while the reversal of this situation occurs with the electronegative substituents.

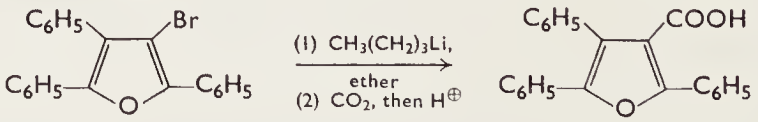
Pyrrole reacts readily with a wide variety of Grignard reagents to give the pyrrole Grignard reagent,[114] the structure of which has been the subject of much controversy. Recent physical evidence suggests that pyrrylmagnesium chloride consists predominantly of an N—MgX **[27]** or ionic species **[28]**.[115] Alkylation of pyrrylmagnesium bromide with a series of alkyl halides results in the



[27] [28]

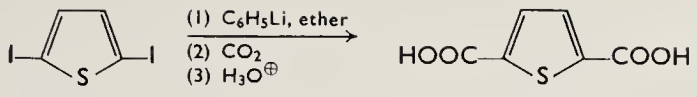
formation of isomeric 2- and 3-alkylpyrroles (generally with the former predominating to the extent of 1.5–3.0 to 1) and polyalkylpyrroles.[116] Only 2-acylpyrroles result from the acylation of the same reagent with acyl halides or esters.[116] Thus, magnesium (and also lithium) salts of pyrrole give mainly products of C-alkylation. In contrast, the sodium and potassium salts of pyrrole form predominantly N-alkylated products.[117] Because the percentage of N-alkylation decreases with the coordinating ability of the metal ion and increases with the solvating power of the medium, dissociation of the pyrryl-metal ion pair is believed to favor N-alkylation.[117]

Bromo- and iodo-substituted furans and thiophenes undergo halogen-metal interconversion with *n*-butyl- or phenyllithium and



(65%) (*Ref. 119*)

give rise to the corresponding heterocyclic lithium derivatives in high yield.[118] Such conversions are especially important from a synthetic viewpoint in the case of the 3-halo-derivatives because they yield

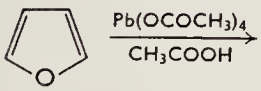


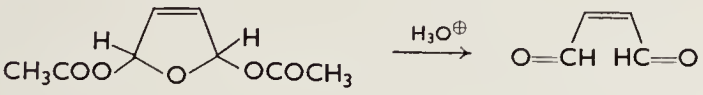
(53%) (*Ref. 120*)

Grignard reagents only with difficulty or not at all. Because an acidic (NH) hydrogen remains in N-unsubstituted 3-halogeno pyrroles, and therefore prototropic shifts can be expected, such 3-lithium derivatives are generally only stable at $-70°C$ for several hours.[121]

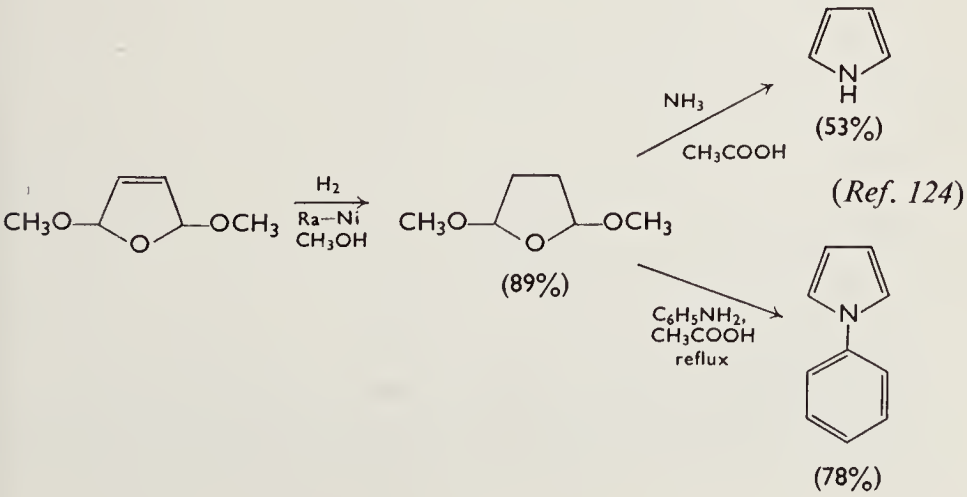
Ring Cleavage and Addition Reactions[122]

Furan, pyrrole, and thiophene vary considerably in the ease with which they undergo ring cleavage reactions. The opening of the furan ring, for example, can be effected with a wide variety of reagents. The conversion of furans to 1,4-dicarbonyl compounds with dilute mineral acids has been discussed earlier (see p. 105). 2,5-Dialkoxy- and 2,5-diacyloxydihydrofurans, which result in high yield from 1,4-additions to furan (see p. 118), have proven to be very useful synthetic intermediates.[123]



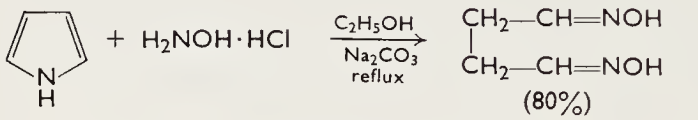


(*Ref. 123*)

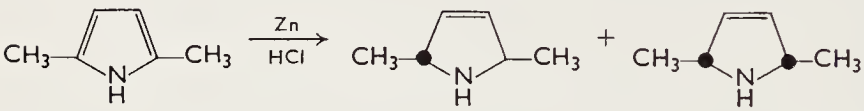


(*Ref. 124*)

In contrast, the pyrrole ring is not cleaved readily by acids (see p. 105) or bases, but when pyrrole is refluxed with an alcoholic solution of hydroxylamine hydrochloride, succindialdoxime is obtained. Δ^3-Pyrrolines are formed in the reduction of pyrroles with zinc and acid.

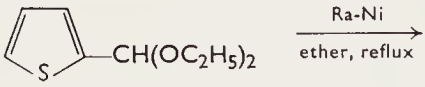


(Ref. 125)

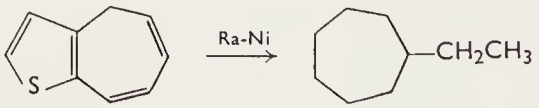


(3.5:1) *(Ref. 126)*

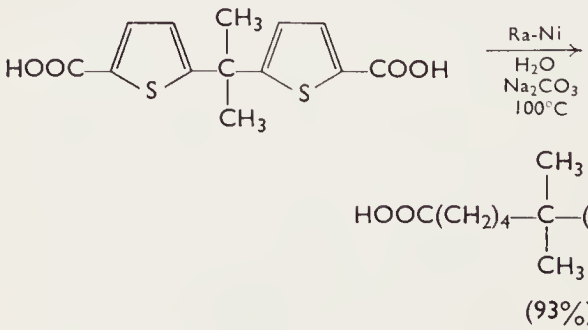
Being the most "aromatic" of the three systems (see p. 104), thiophene is the most resistant to ring-opening reactions. A uniquely important cleavage of thiophenes, however, is embodied in the Raney nickel desulfurization procedure,[127] which has received wide application as a synthetic pathway to a variety of compounds. Several examples are given below.



(Ref. 128)



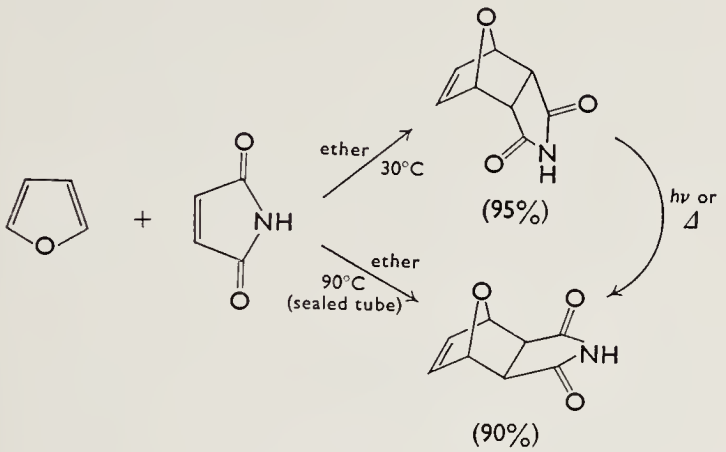
(Ref. 129)



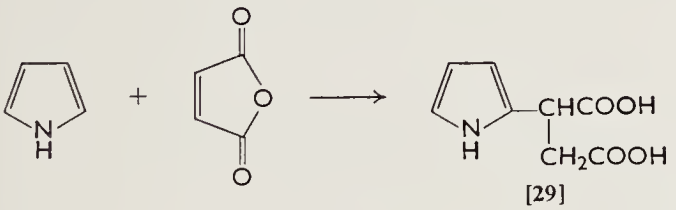
(Ref. 130)

The same wide variety in reactivity of [**1**], [**2**], and [**3**] is observed in addition reactions. Whereas furan and its derivatives behave as typical dienes in the Diels-Alder reaction, pyrroles undergo such

condensations with considerable difficulty, it at all. For example pyrrole reacts with maleic anhydride to give only a product of substitution [**29**],[132] and acetylenedicarboxylic acid adds to 1-benzylpyrrole to afford [**30**] in 8.5% yield, together with α-substituted

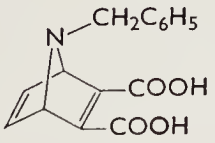


(*Ref. 131*)



(*Ref. 132*)

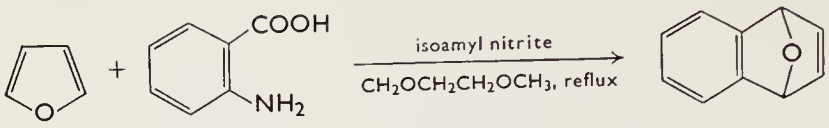
[**29**]



[**30**]

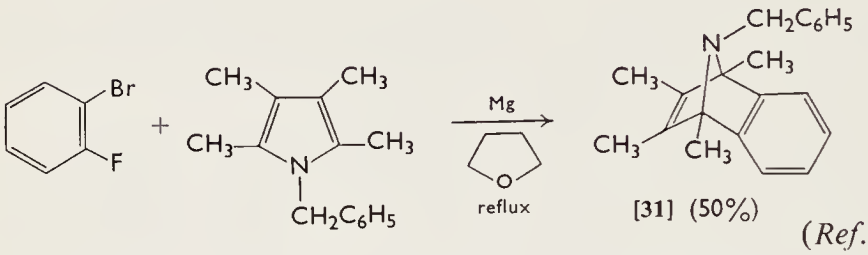
products.[133] Thiophene does not enter into reaction with dienophiles.[134, 135]

The addition of benzyne to furans has been found to proceed readily and in good yield.[136] Substituted pyrroles have been found generally to give N-substituted 1- and 2-naphthylamines, and not the expected 1,4-imines.[137] Apparently, the Diels-Alder reaction occurs to form the imines, but the latter immediately rearrange to the naphthylamines. This theory is substantiated by the isolation of the stable imines [**31**] and [**32**].



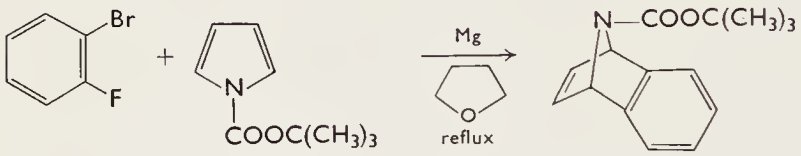
(51%)

(*Ref. 136b*)



[31] (50%)

(*Ref. 138*)

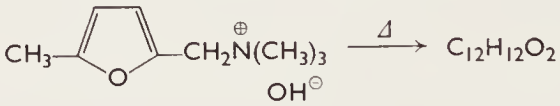


[32] (35–41%)

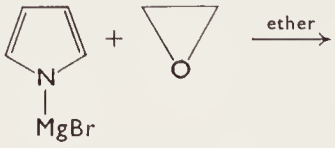
(*Ref. 139*)

Exercises

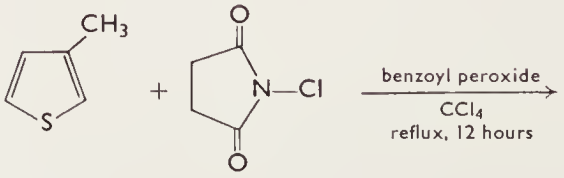
1. Predict the major product of the following reactions:

(a) 

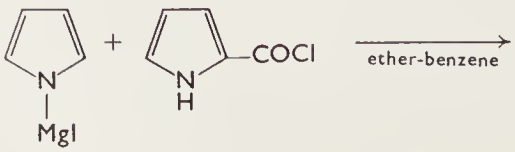
(*Ref. 140*)

(b) 

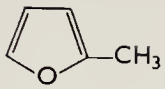
(*Ref. 141*)

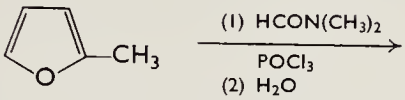
(c) 

(*Ref. 142*)

(d) 

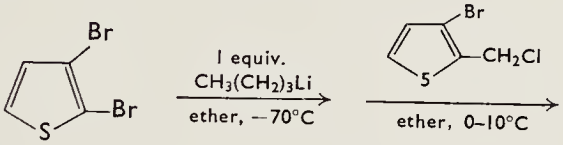
(*Ref. 143*)

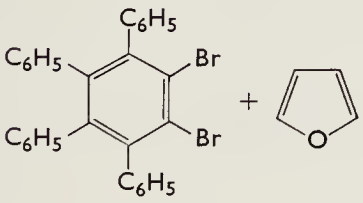
(e)  (*Ref. 144*)

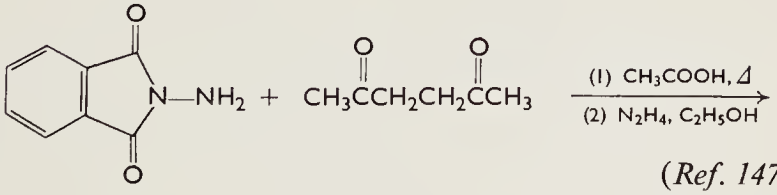
(f)  (*Ref. 144*)

(g) $CH_3OOCCH_2NHC_2H_5 + CH_3OOC{-}C{\equiv}C{-}COOCH_3$

$$\xrightarrow[\text{(2) K, toluene}]{\text{(1) ether}} \xrightarrow[\text{(3) neutralization}]{} C_{10}H_{13}NO_5$$ (*Ref. 145*)

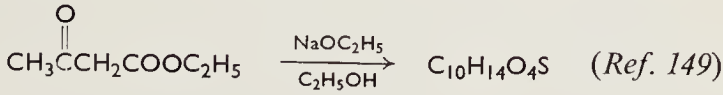
(h)  (*Ref. 146*)

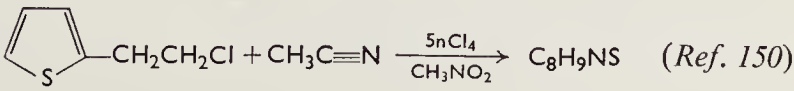
(j)  (*Ref. 148*)

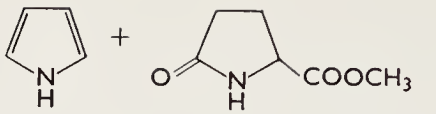
(i) 

(*Ref. 147*)

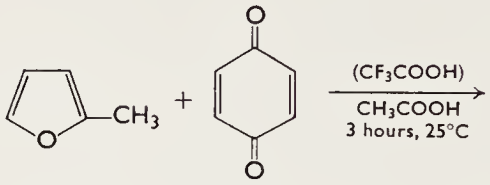
(k) 

 (*Ref. 149*)

(l)  (*Ref. 150*)

(m) 

(*Ref. 151*)

(n) 

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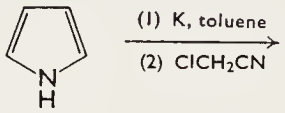
(o) 

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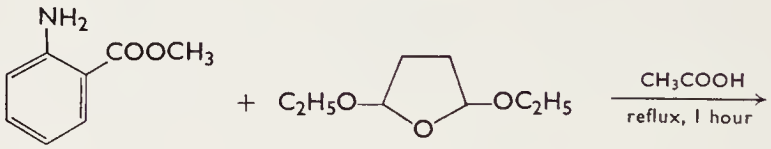
(p) 

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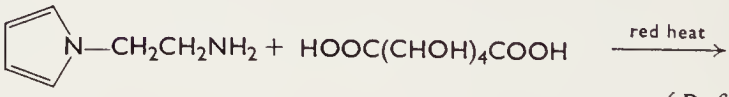
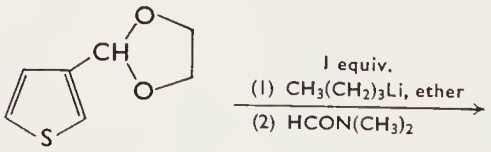
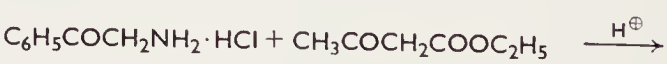
(q) 

(*Ref. 153*)

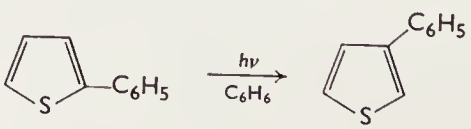
(r) 

(*Ref. 155*)

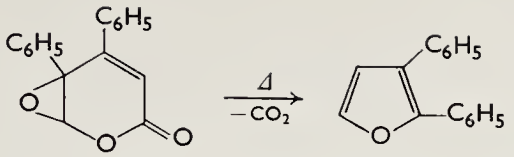
(s) 

(*Ref. 156*)

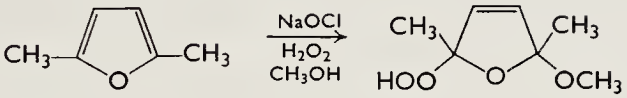
2. Suggest a reasonable mechanism for each of the following transformations:

(a) 

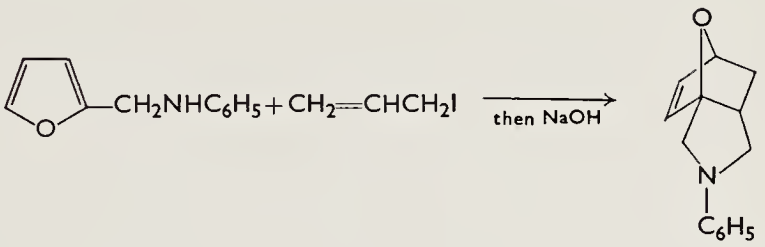
(*Ref. 157*)

(b) 

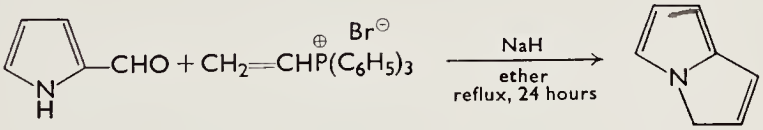
(*Ref. 158*)

(c) 

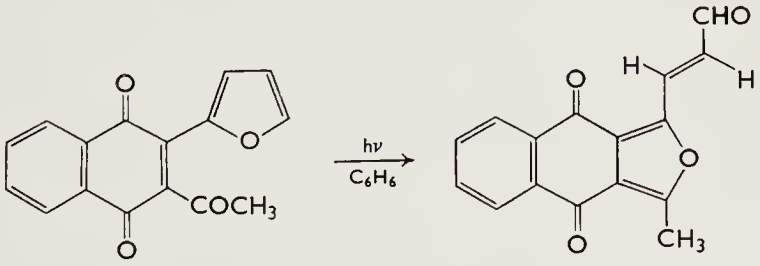
(*Ref. 159*)

(d) 

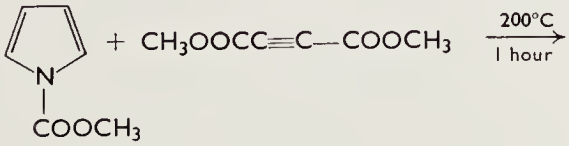
(*Ref. 160*)

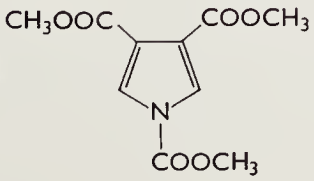
(e) 

(*Ref. 161*)

(f) 

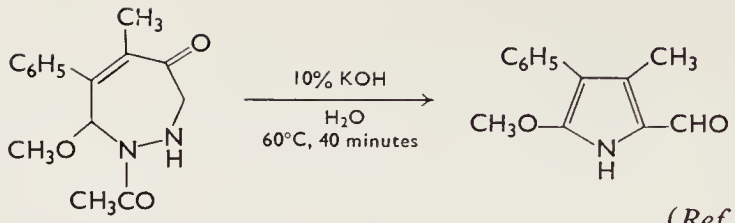
(*Ref. 162*)

(g) 



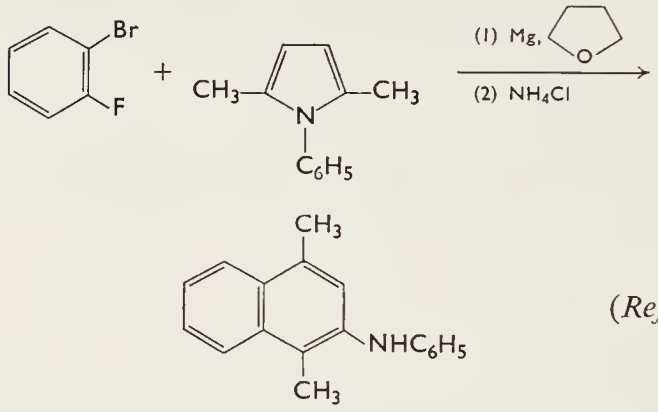
(*Ref. 163*)

(h)



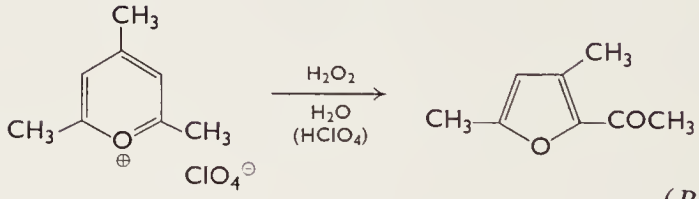
(*Ref. 164*)

(i)



(*Ref. 137a*)

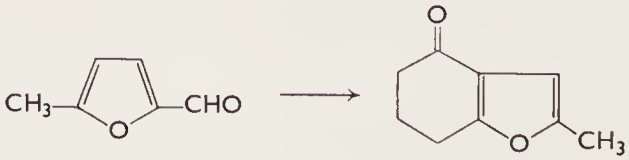
(j)



(*Ref. 165*)

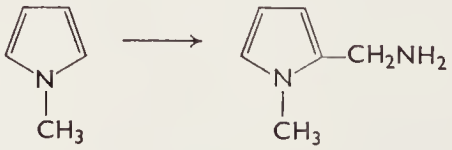
3. Devise synthetic pathways by which each of the denoted starting materials may be converted to the indicated products:

(a)



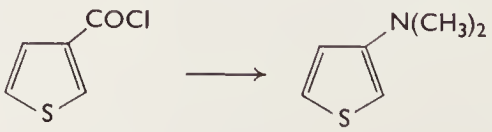
(*Ref. 144*)

(b)

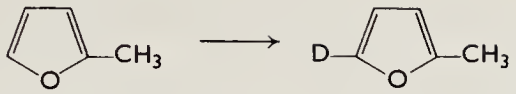


(*Ref. 153*)

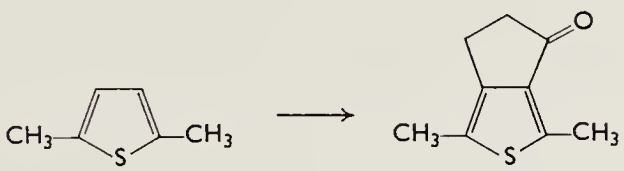
(c)



(*Ref. 166*)

(d)  (*Ref. 167*)

(e)  (*Ref. 167*)

(f)  (*Ref. 168*)

References and Notes

(1) For this reason, the extrapolation of an observation made, for example, with a furan derivative to a prediction of the behaviour of a related pyrrole or thiophene derivative *under the same conditions* may be erroneous.

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