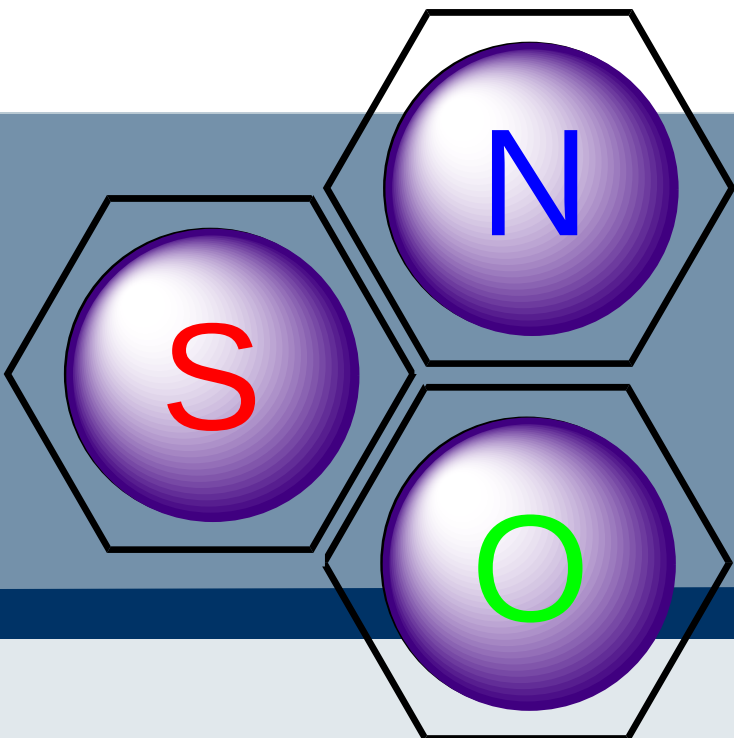
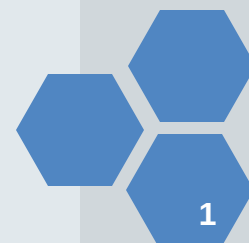
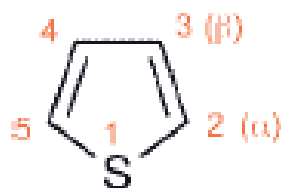


Chapter 9



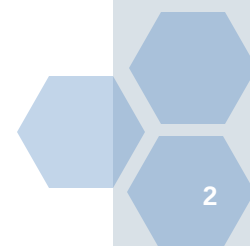
Thiophenes





thiophene

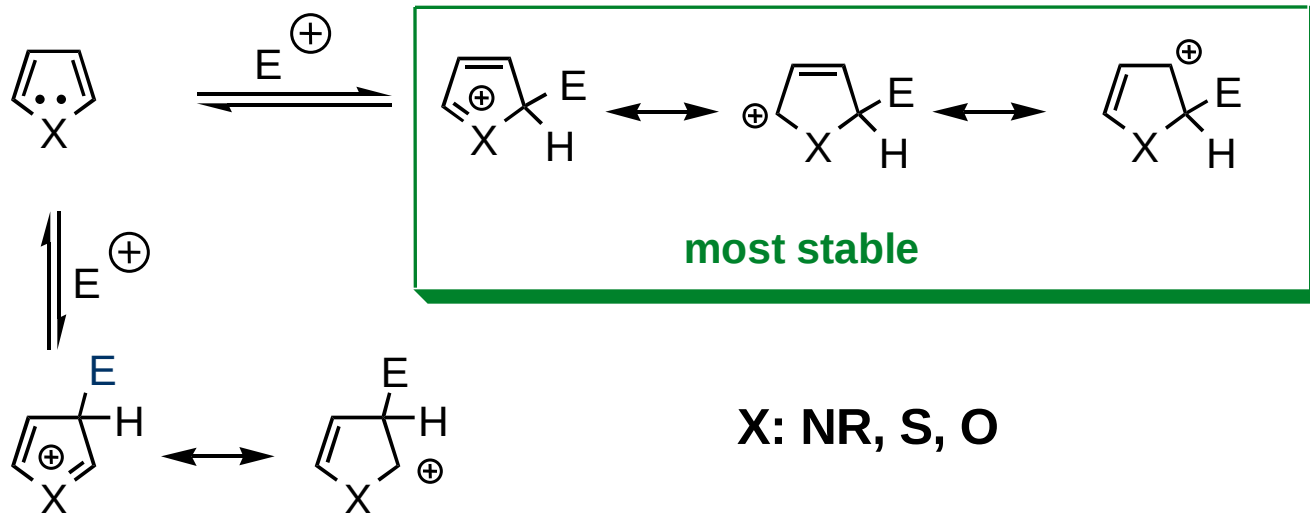
The simple thiophenes are stable liquids that closely resemble the corresponding benzene compounds in boiling points and even in smell. They occur in coal-tar distillates – the discovery of thiophene in coal-tar benzene provides one of the classic anecdotes of organic chemistry.





THIOPHENES

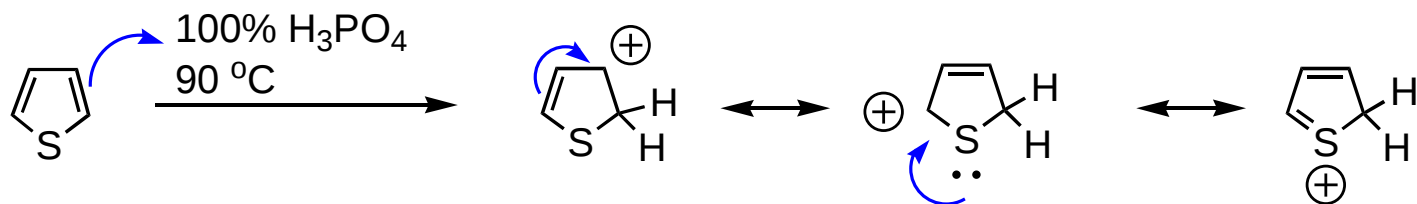
Reactions with electrophiles at C **Preferably at C-2 / C-5 (α -positions)**





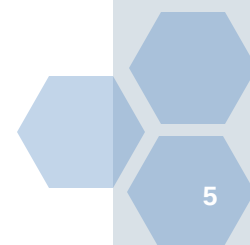
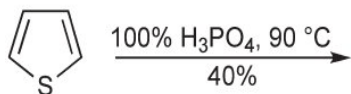
-Protonation

- Much more stable under acidic conditions than pyrroles and furans
- Protonation at C-2 /C-5





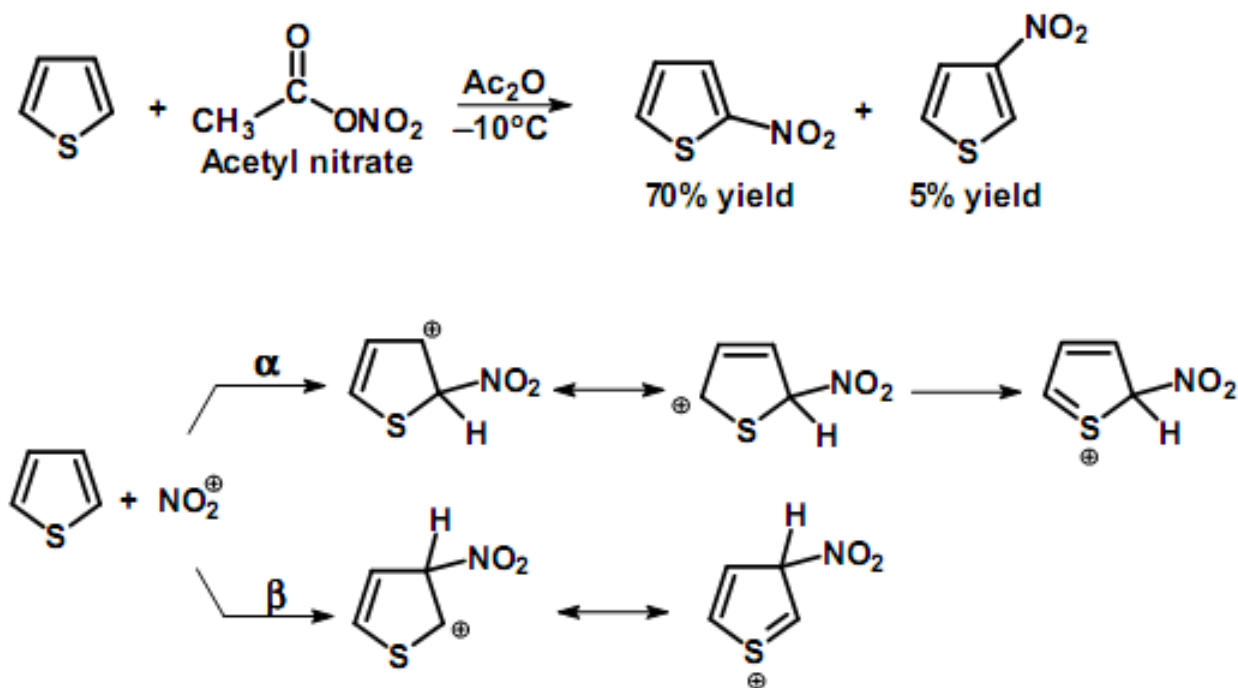
The action of hot phosphoric acid on thiophene leads to a trimer; its structure suggests that, in contrast with pyrrole, the electrophile involved in the first C–C bonding step is the α -protonated cation.



Nitration

- Not complete selectivity
- Not HNO_3 (explosions)

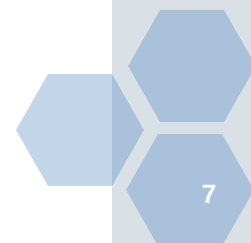
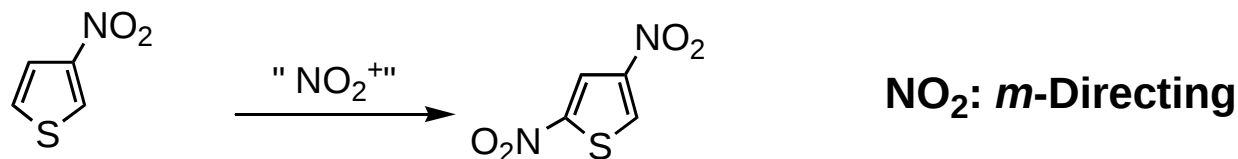
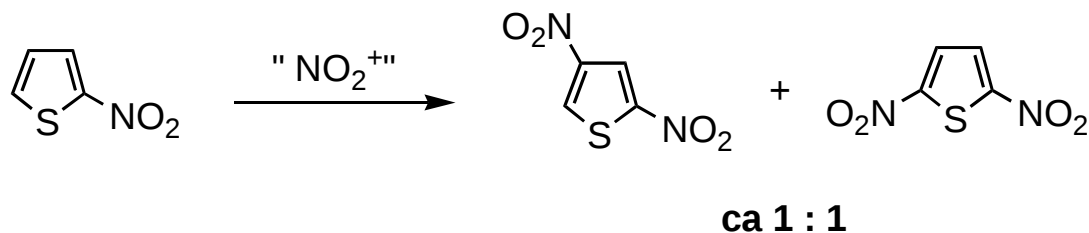
Nitration of thiophene needs to be conducted in the absence of nitrous acid, which can lead to an explosive reaction; the use of acetyl nitrate or nitronium tetrafluoroborate is satisfactory





Reactions with electrophiles at C

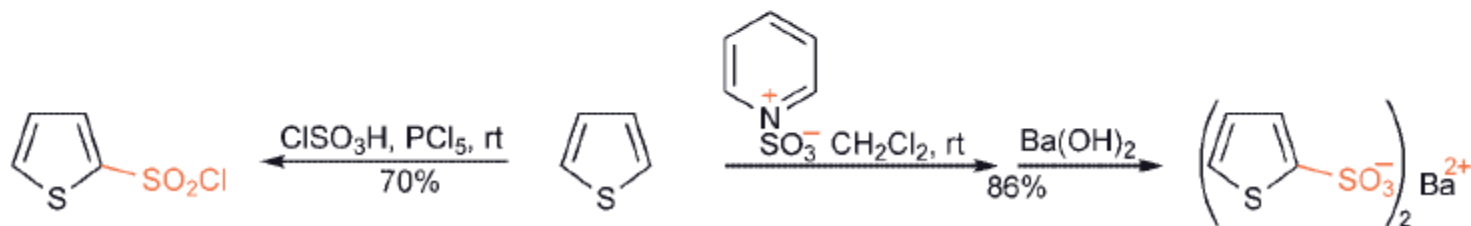
Further nitration of either 2- or 3-nitrothiophenes also leads to mixtures: equal amounts of 2,4- and 2,5- dinitrothiophenes from the 2- isomer, and mainly 2,4- dinitrothiophene from 3-nitrothiophene.





17.1.1.3 Sulfonation

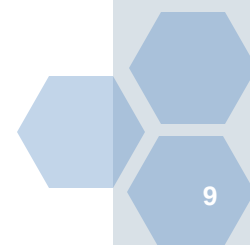
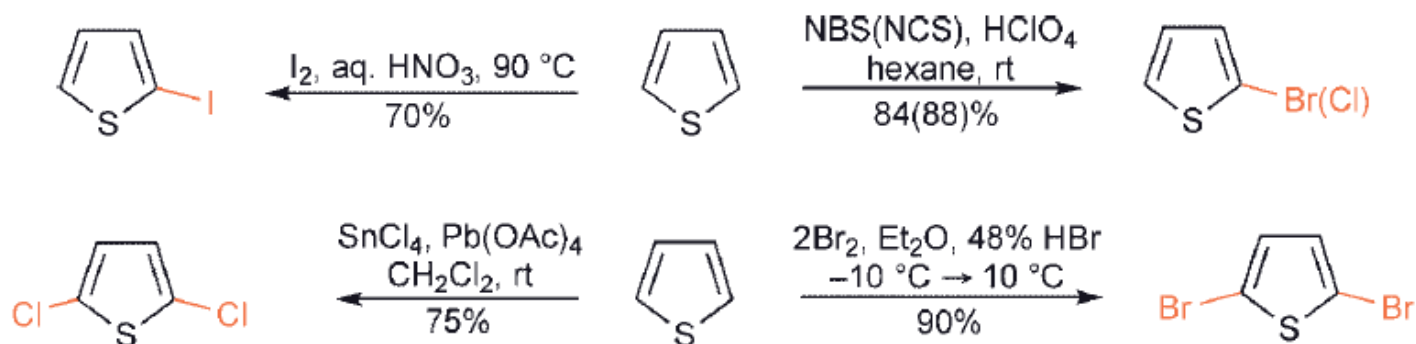
As discussed in the introduction, the production of thiophene-2-sulfonic acid by sulfuric acid sulfonation of the heterocycle has been long known;¹⁵ use of the pyridine–sulfur-trioxide complex is probably the best method.¹⁶ 2-Chlorosulfonation¹⁷ and 2-thiocyanation¹⁸ are similarly efficient.





Halogenation

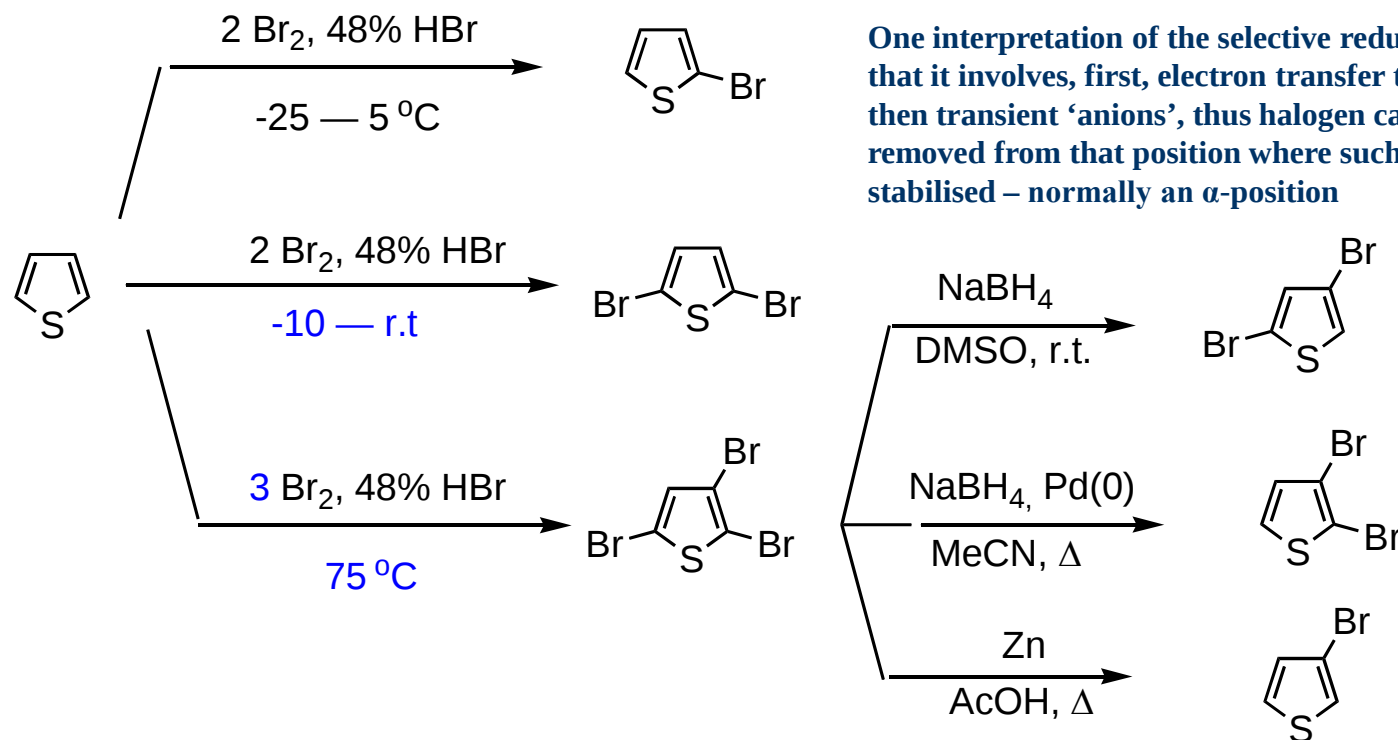
Halogenation of thiophene occurs very readily at room temperature and is rapid even at $-30\text{ }^{\circ}\text{C}$ in the dark; tetrasubstitution occurs easily. The rate of halogenation of thiophene at $25\text{ }^{\circ}\text{C}$ is about 10^8 times that of benzene. 2-Bromo-, 2-chloro- and 2-iodothiophenes and 2,5- dibromo - and 2,5- dichlorothiophenes can be produced cleanly under various controlled conditions.



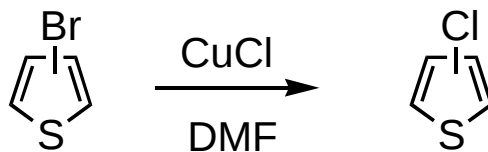


Reactions with electrophiles at C

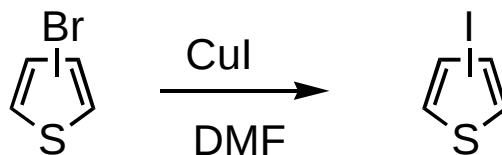
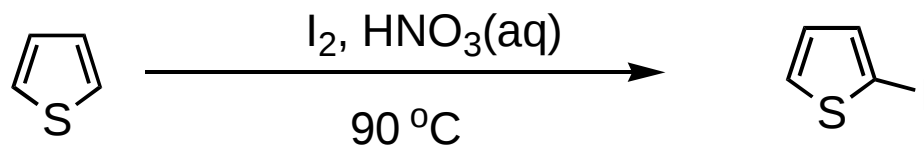
Bromination



Multibromination occurs readily at room temperature and even at -30°C • Careful control of reaction conditions is required to ensure mono-bromination



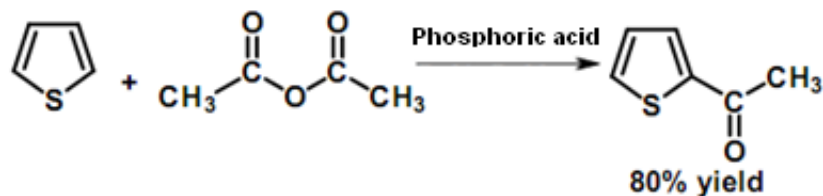
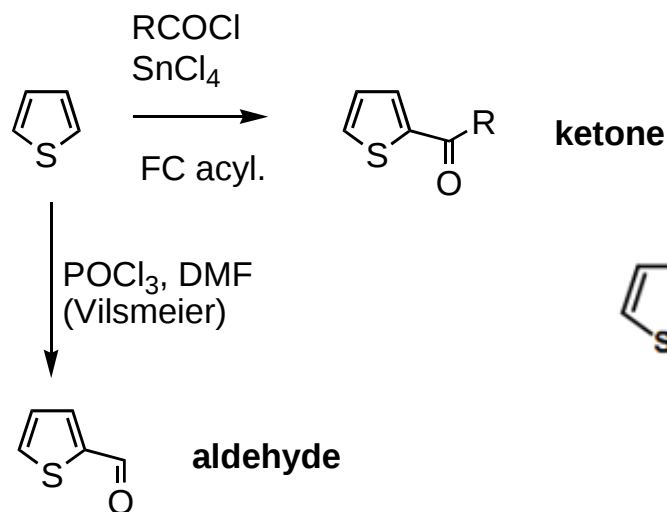
Iodination





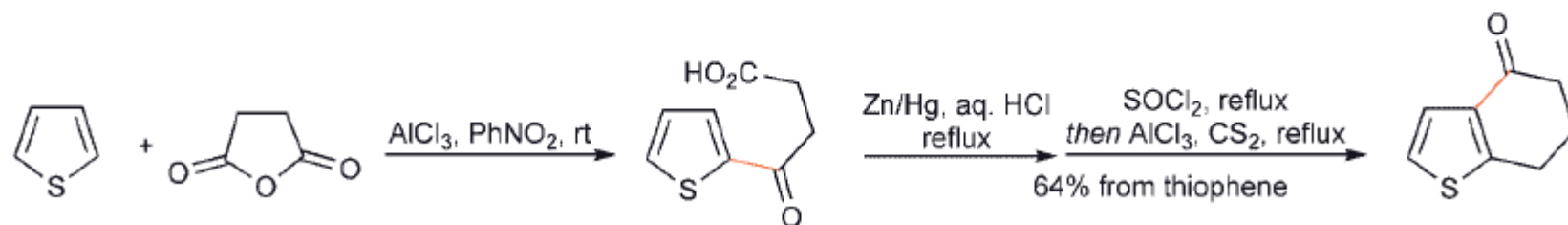
The Friedel – Crafts acylation of thiophenes is a much - used reaction and generally gives good yields under controlled conditions, despite the fact that **aluminium chloride reacts with thiophene to generate tars**; this problem can be avoided by using **tin tetrachloride** and adding the catalyst to a mixture of the thiophene and the acylating agent. Acylation with anhydrides, catalysed by phosphoric acid is an efficient method.

(strong Lewis acid, AlCl_3 leads to polym.)





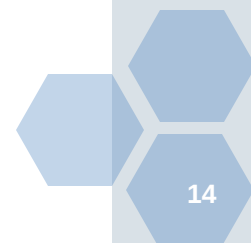
In acylations, almost exclusive α -substitution is observed, but where both α -positions are substituted, β -substitution occurs easily. This is nicely illustrated by the two ketones produced in the classic sequence shown below.^{38,39}





17.1.1.6 Alkylation

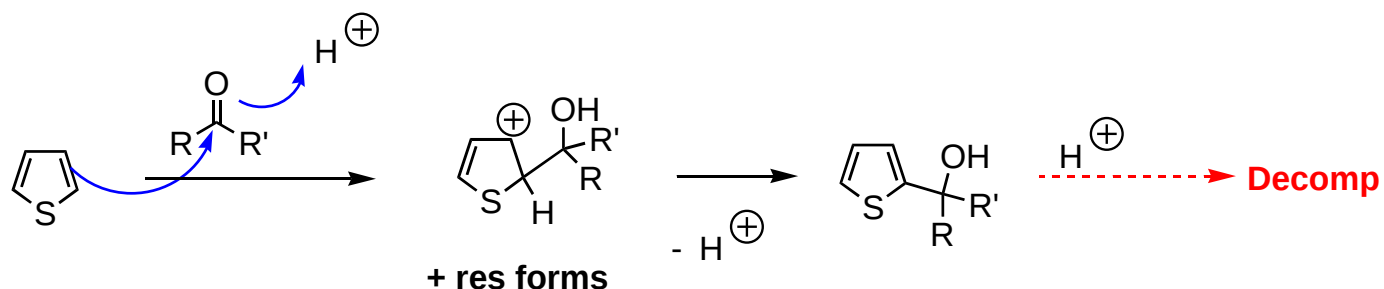
Alkylation occurs readily, but is rarely of preparative use, an exception being the efficient 2,5-bis-*t*-butylation of thiophene.⁴⁰





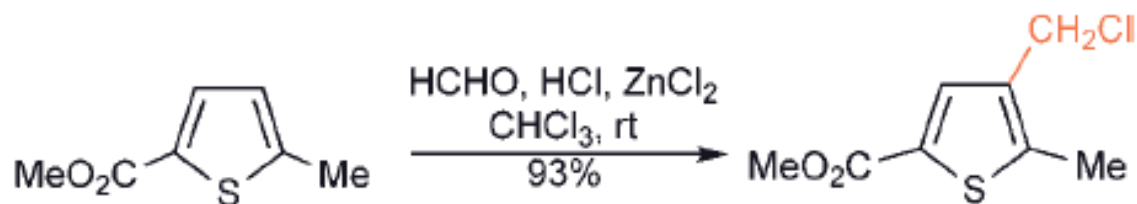
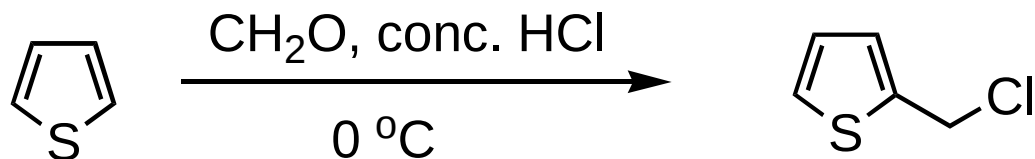
Condensation with carbonyl compounds

Acid-catalysed reaction of thiophene with aldehydes and ketones is not a viable route to hydroxyalkyl - thiophenes, for these are unstable under the reaction conditions.



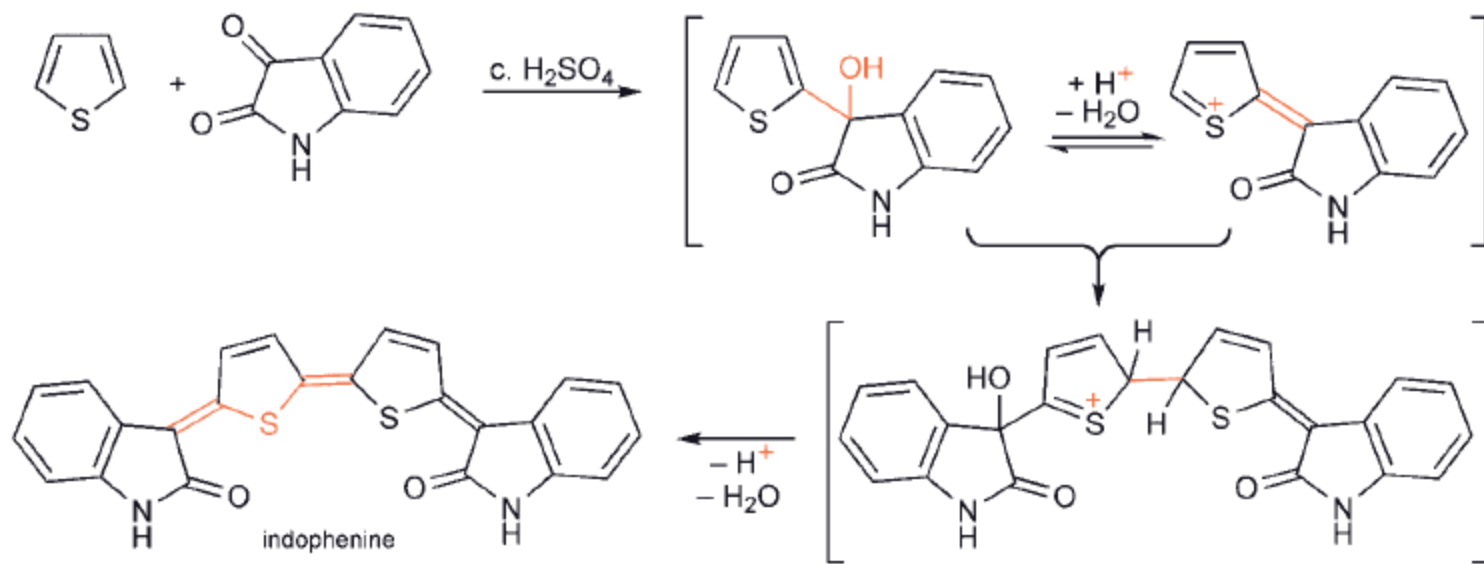


Condensation with carbonyl comps, cont.





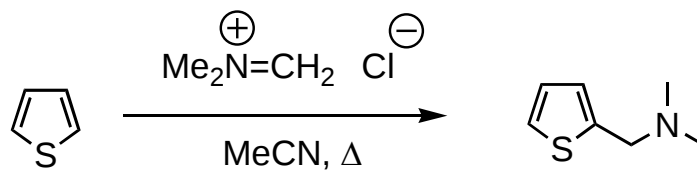
A reaction of special historical interest, mentioned in the introduction to this chapter, is the condensation of thiophene with isatin in concentrated sulfuric acid, to give the deep blue indophenine⁴⁵ as a mixture of geometrical isomers.⁴⁶



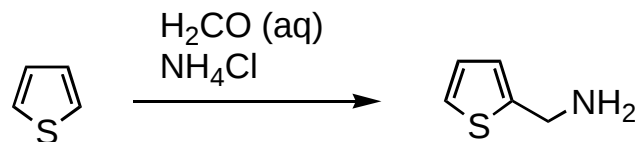


Condensation with imines / iminium ions

Thiophene (and furan): Preformed reagent generally required



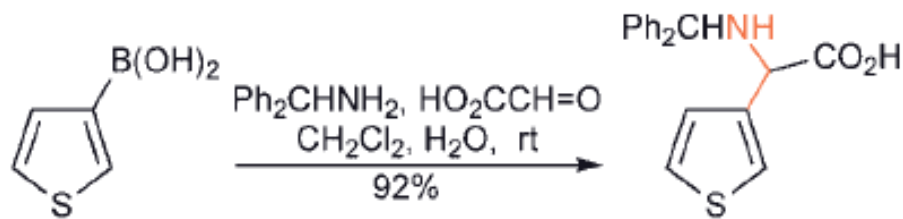
But:





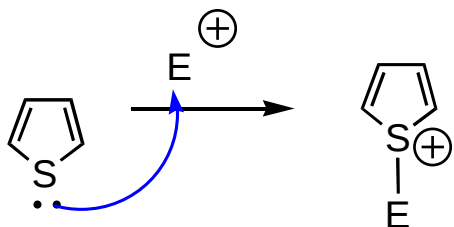
The Petasis reaction

Another device for bringing thiophenes into reaction with Mannich intermediates is to utilise thiophene boronic acids – the Petasis reaction; primary aromatic amines can also be used as the amine component.

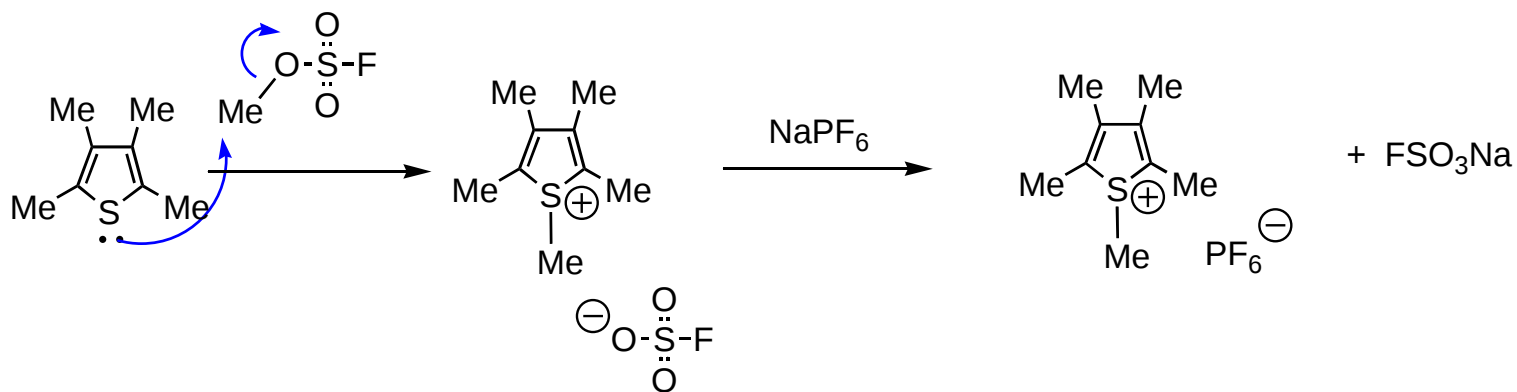




Reactions with electrophiles at Sulfur



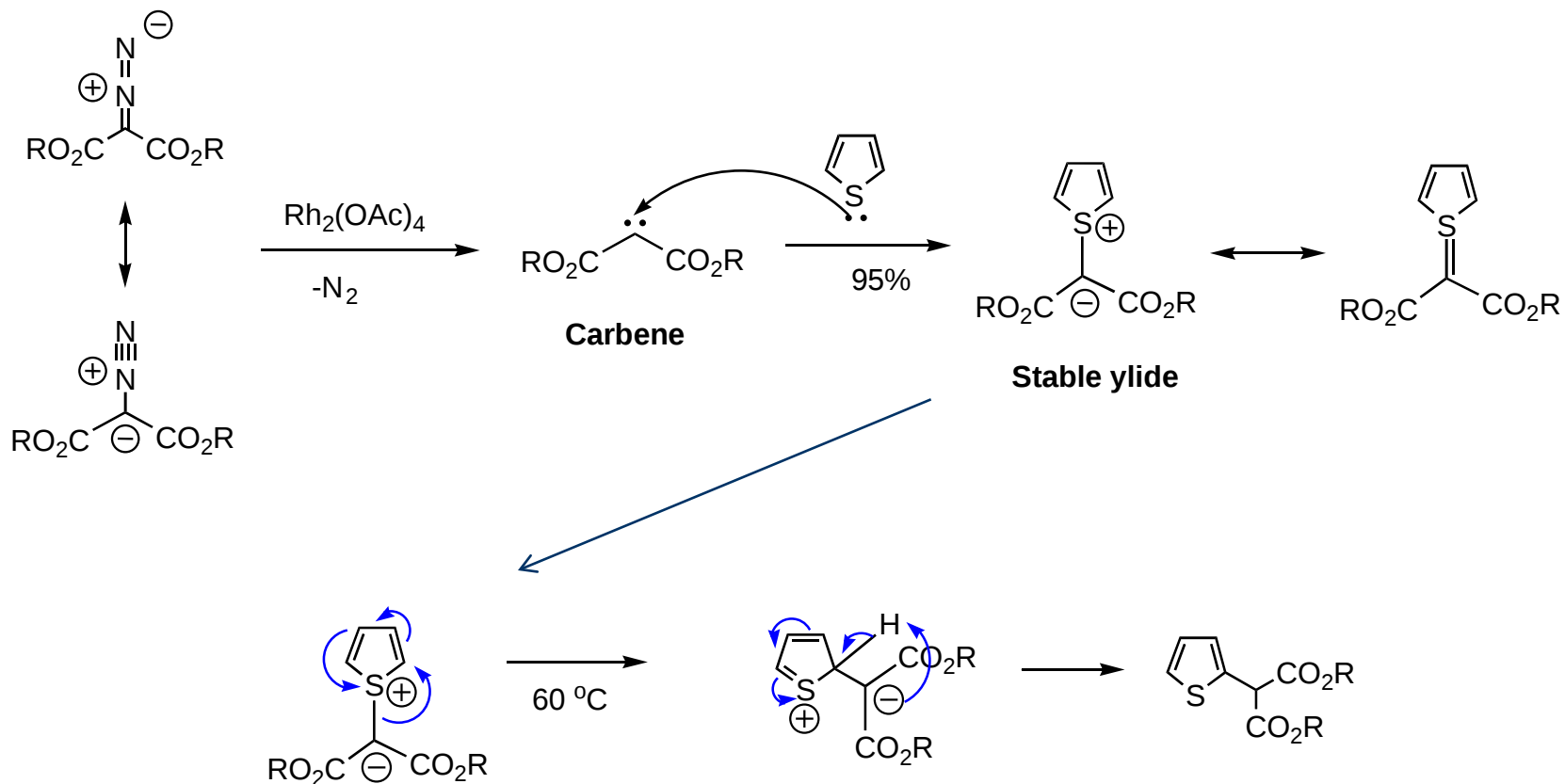
- Possible for thiophene; S in 3rd row
- Not possible for furan / pyrrole; O and N in 2nd row
- Probably sp^3 S. tetrahedral
- Works best for electron rich thiophenes





Reactions with electrophiles at Sulfur

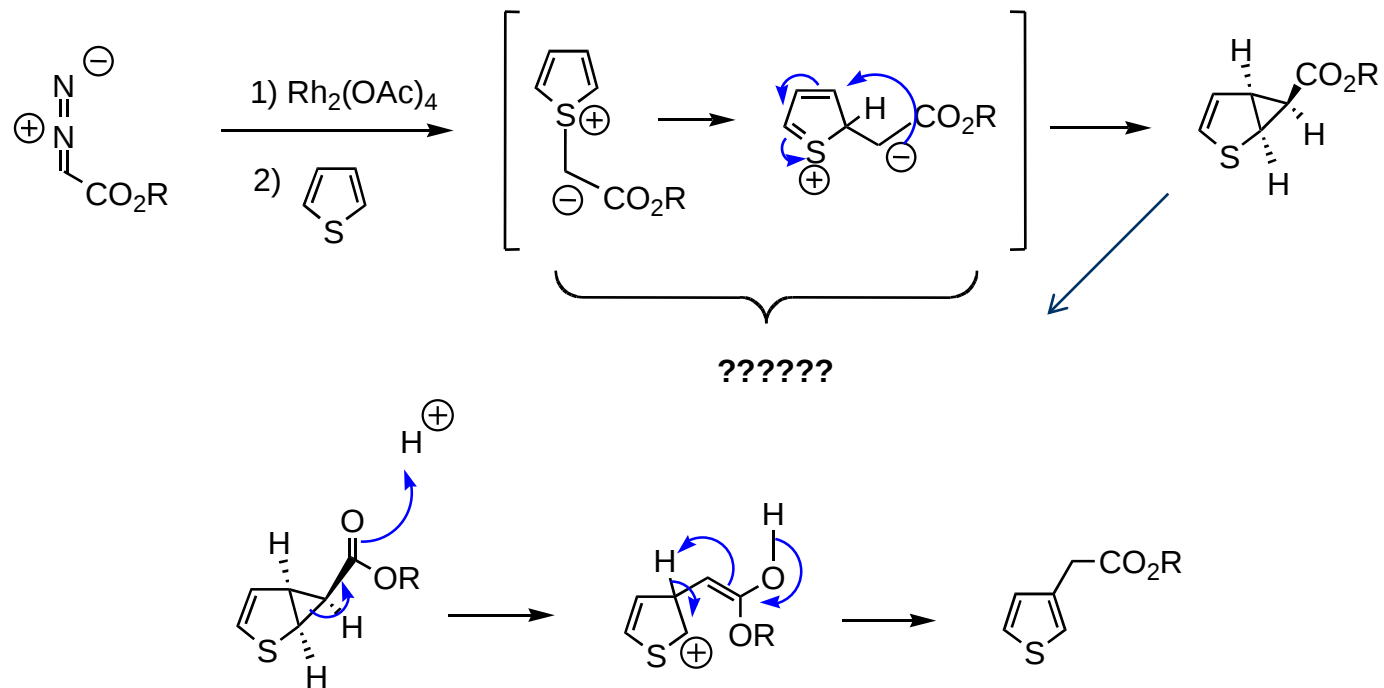
React. with carbenes





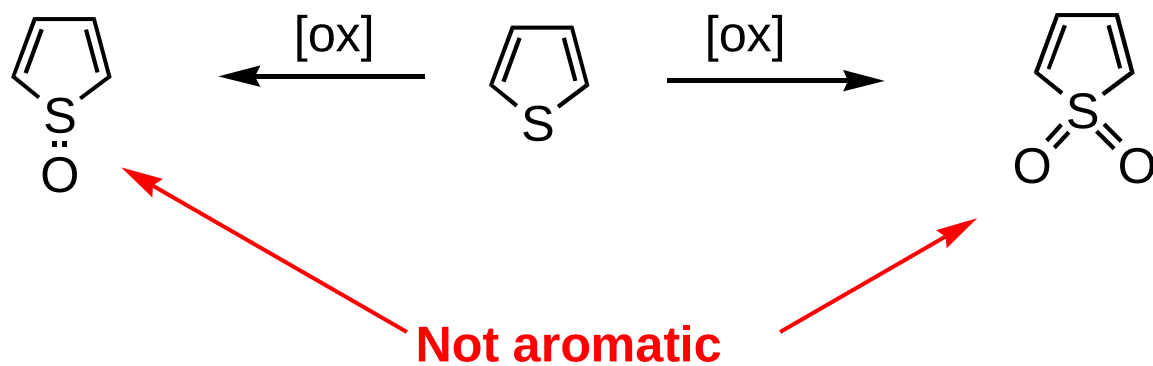
Reactions with electrophiles at Sulfur

React. with carbenes





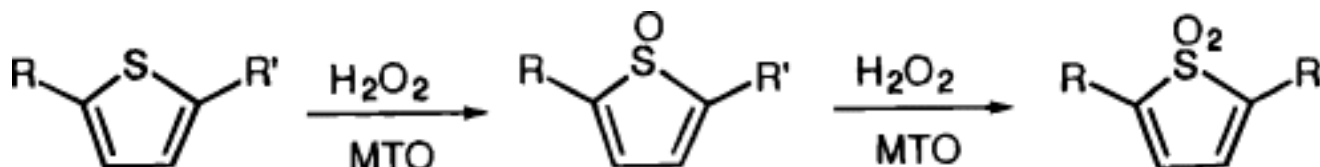
Oxidation





Oxidation

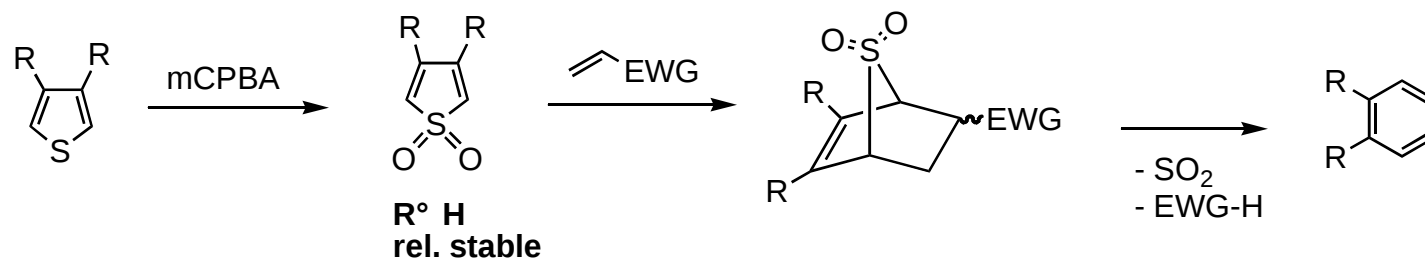
The oxidation of thiophene derivatives by hydrogen peroxide is catalyzed by methyltrioxorhenium(VII) (CH_3ReO_3). This compound reacts with hydrogen peroxide to form 1:1 and 1:2 rhenium peroxides, each of which transfers an oxygen atom to the sulfur atom of thiophene and its derivatives. Complete oxidation to the sulfone occurs readily by way of its sulfoxide intermediate.



Inorg. Chem., 1996, 35 (25), pp 7211–7216



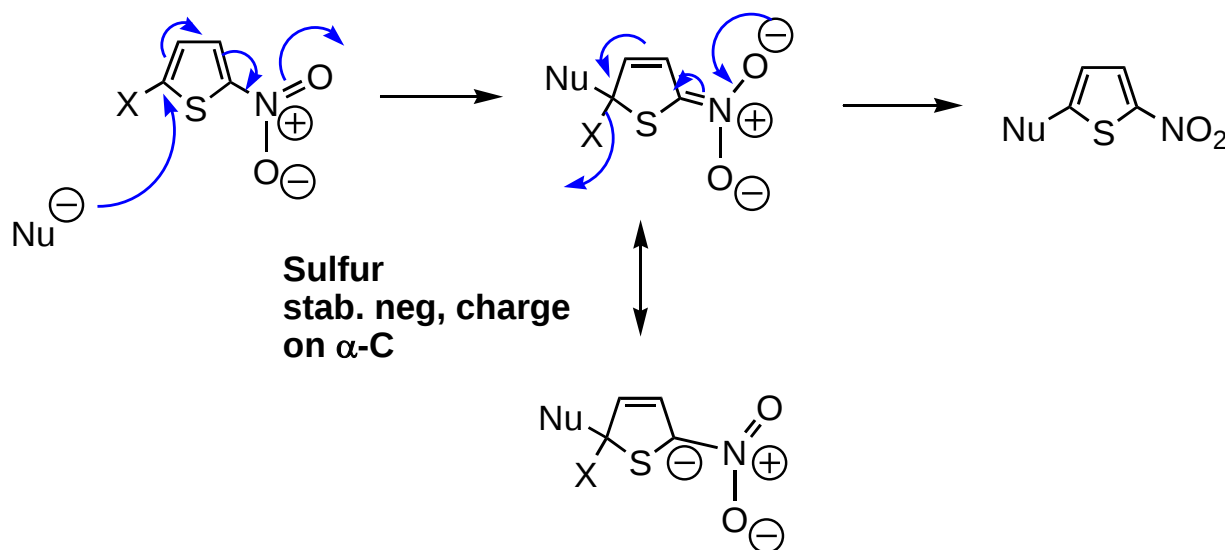
Oxidation





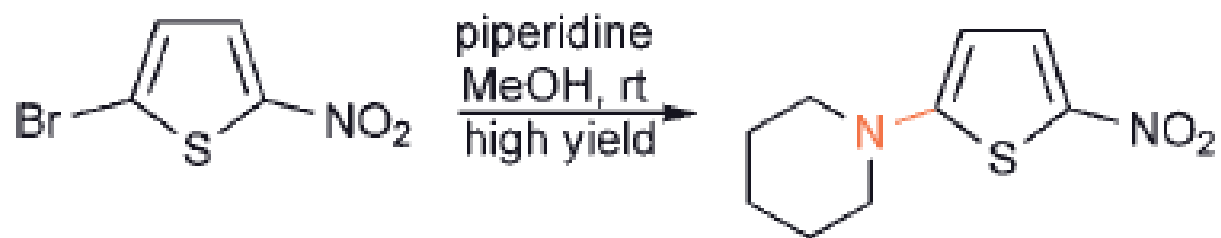
Reactions with nucleophiles

Nitro substituents activate the displacement of leaving groups like halide, as in benzene chemistry, and extensive use of this has been made in thiophene work. Such nucleophilic displacements proceed at least 10^2 times faster than for benzenoid counterparts, and this may be accounted for by participation of the sulfur in the delocalisation of charge in the Meisenheimer intermediate.





Reactions with nucleophiles

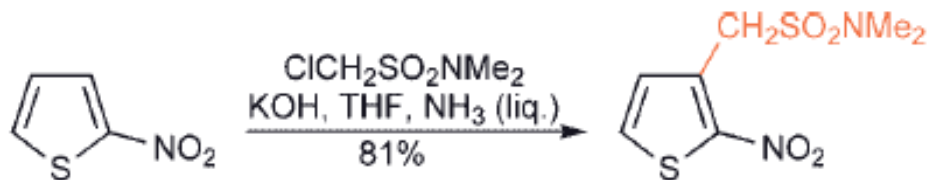
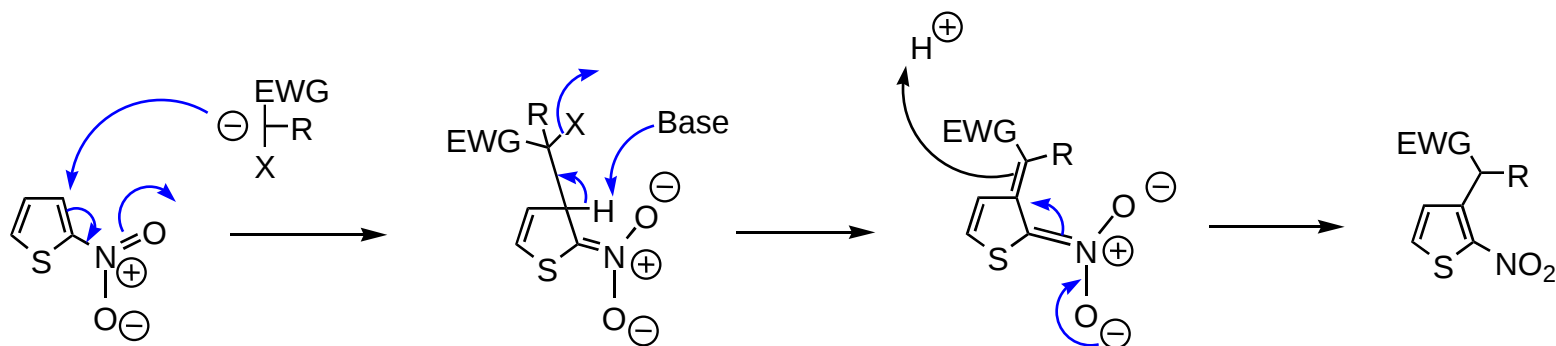




Reactions with nucleophiles

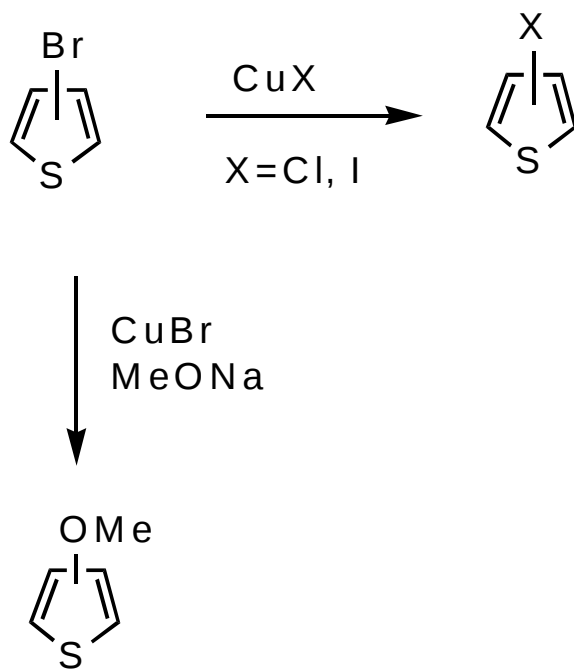
Nitrogroups also permit the operation of VNS processes, as illustrated below:

Vicarious Nu subst (VNS)





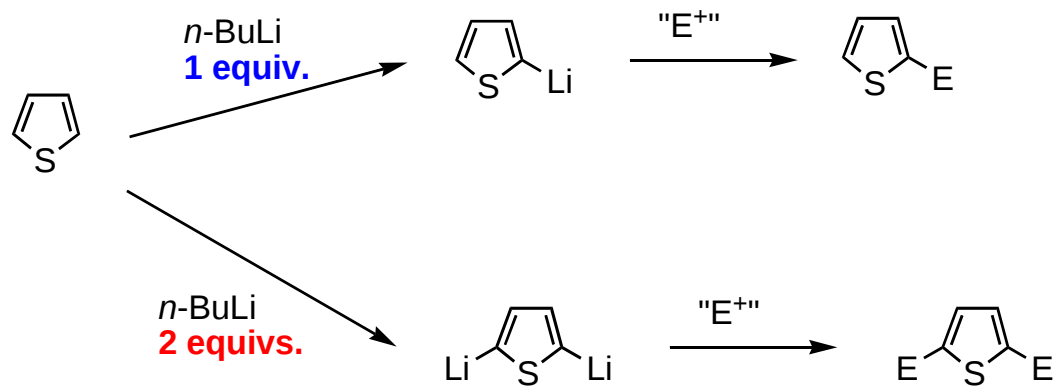
Copper and copper(I) salts have been used extensively in thiophene chemistry to catalyse displacement of bromine and iodine, but not chlorine, in simpler halo – thiophenes.



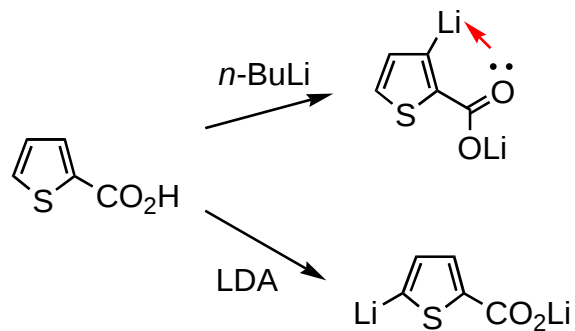


C-metallation and further reactions

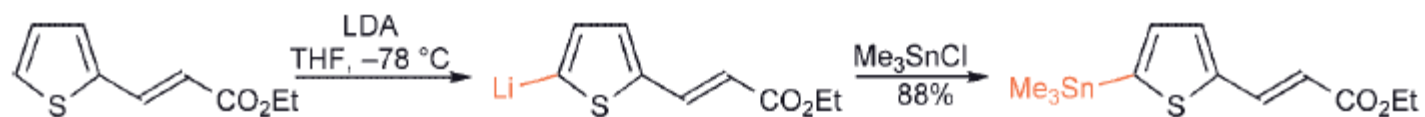
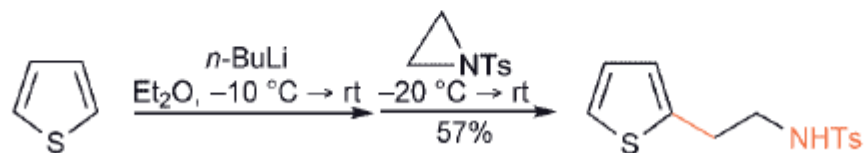
In the 2 / 5 pos.



3-Litiation with ODG

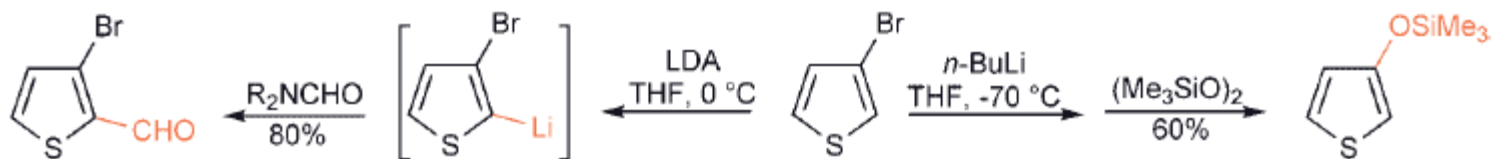
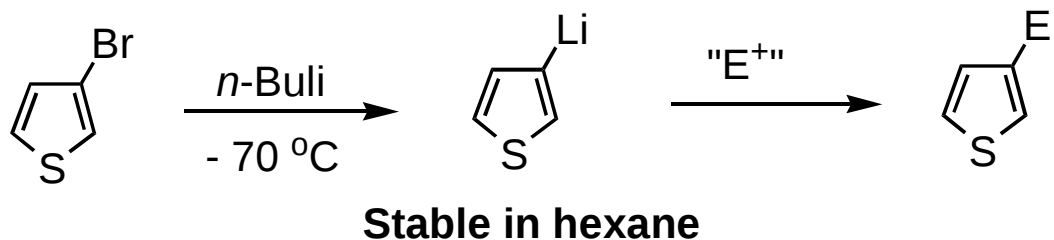


C-metallation and further reactions

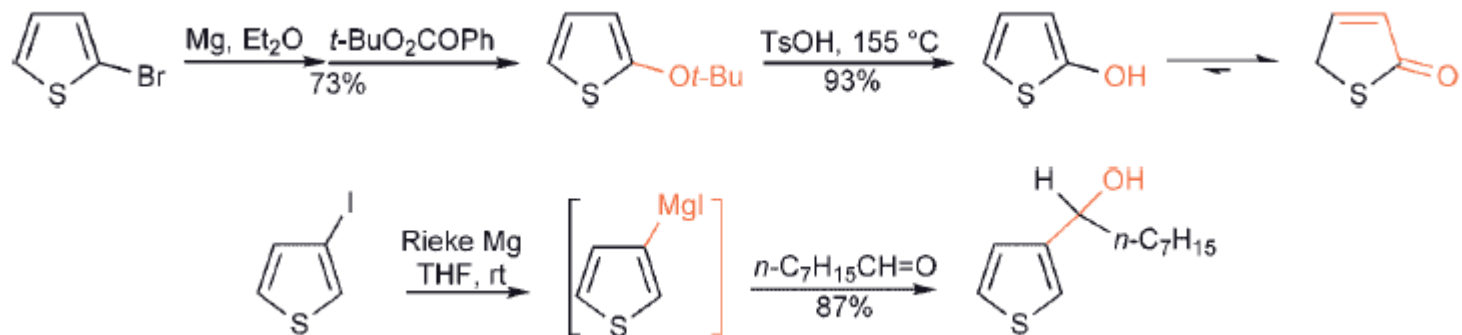


Metal – Halogen Exchange

Bromine and iodine at either α - or β - positions undergo exchange with alkyllithiums giving lithiated thiophenes.



Metal – Halogen Exchange



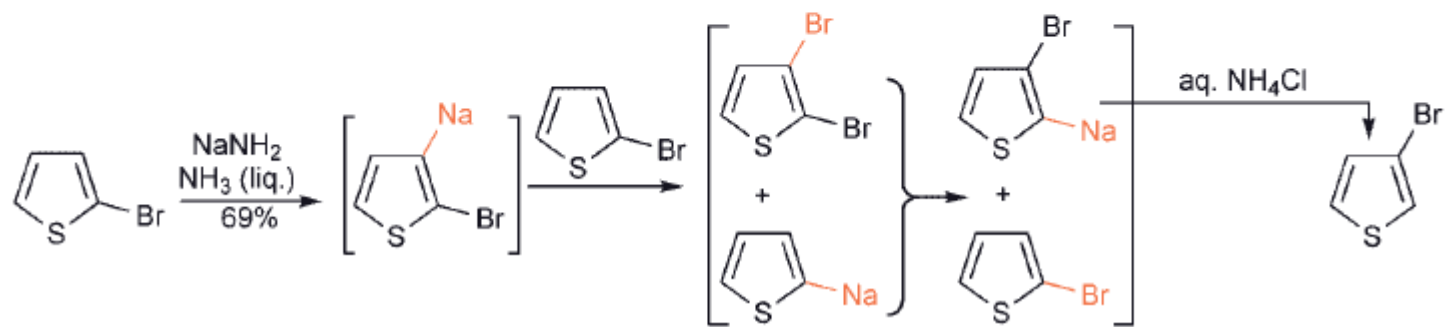
Rieke metals are highly reactive metal powders prepared by the methods developed by Reuben D. Rieke. Rieke metals are highly reactive because they have high surface area and lack surface oxides which retard reaction.

Rieke metals are usually prepared by a reduction of a THF suspension of an anhydrous metal chloride with an alkali metal. Typical alkali metals used in this method are potassium, sodium, and lithium. For example, the preparation of Rieke magnesium employs potassium as the reductant:

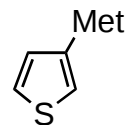
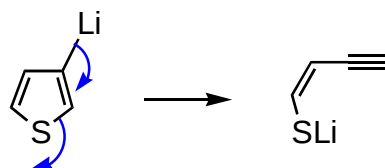




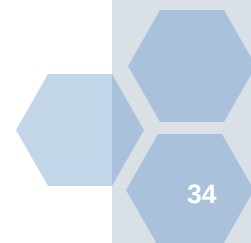
There are two complications that can arise in the formation and the use of lithiated thiophenes: the occurrence of a 'Base Catalysed Halogen Dance',¹⁰³ and the isomerisation or ring opening of 3-lithiated thiophenes. As an example of the first of these, and one in which the phenomenon is put to good use, consider the transformation of 2-bromothiophene into 3-bromothiophene by reaction with sodamide in ammonia.¹⁰⁴ The final result is governed, in a set of equilibrations, by the stability of the final anion: the system settles to an anion in which the charge is both adjacent to halogen *and* at an α -position.



In Et_2O over -25°C :



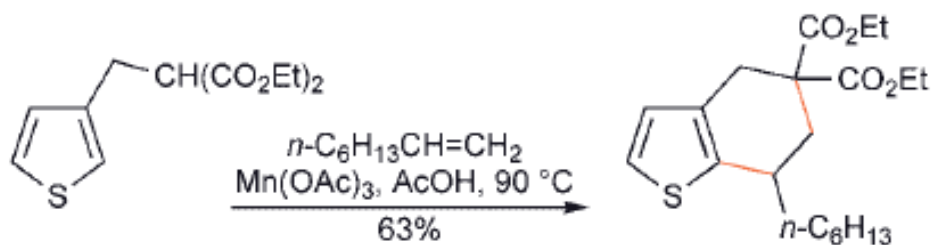
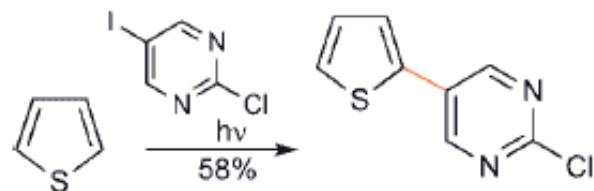
Met: ZnX , MgX
Stable at RT





Reaction with radicals, Seldom synthetically useful

Radicals generated in various ways have been utilised in elaborating thiophenes and in ring - closing reactions; examples are shown below:

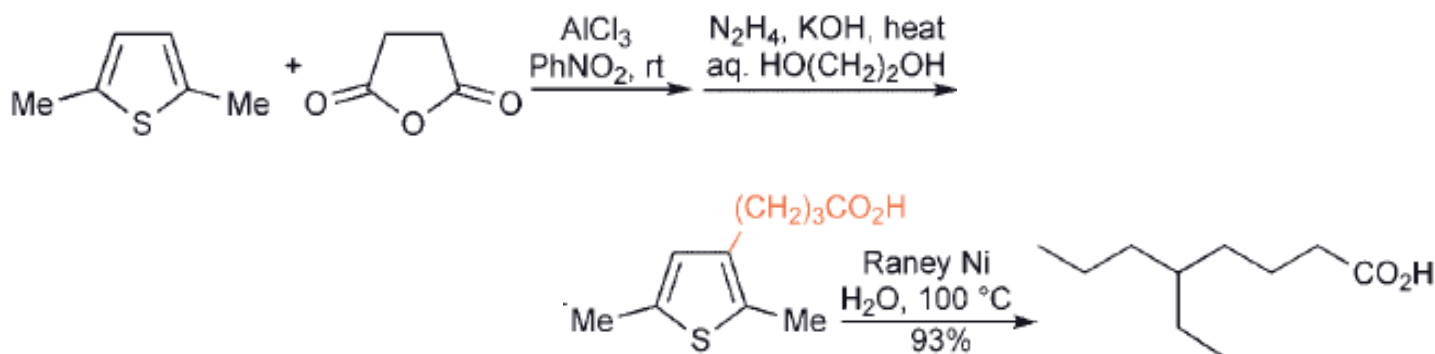




Catalytic reductions of the thiophene ring, or of substituents attached to it, are complicated by two factors:

- 1- poisoning of the catalyst and
- 2- the possibility of competing hydrogenolysis – reductive removal of sulfur, particularly with Raney nickel

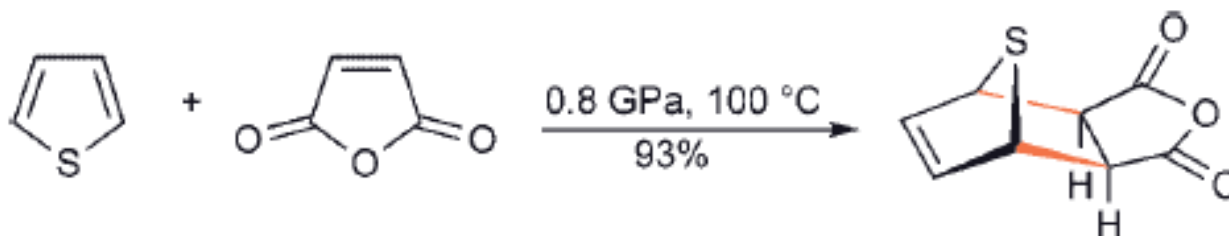
Indeed the use of thiophenes as templates on which to elaborate a structure, followed finally by desulfurisation, is an important synthetic strategy.





Cycloadditions

Unactivated thiophenes show little tendency to react as 4 π components in a Diels – Alder sense; however, maleic anhydride will react with thiophene to produce an adduct in high yield, under extreme conditions.





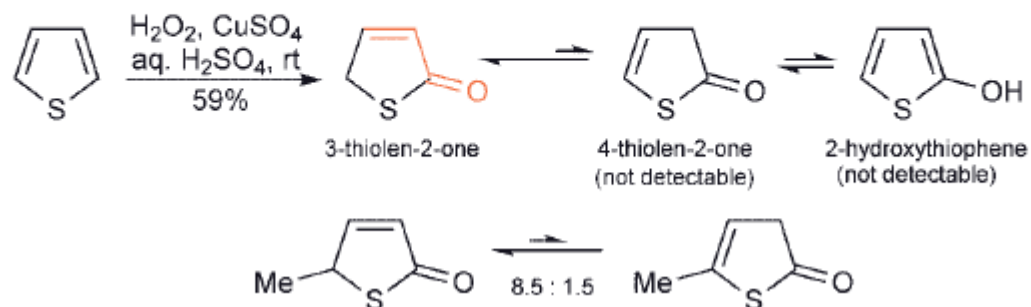
Electrophilic alkynes will react with thiophenes under vigorous conditions, though the initial adduct extrudes sulfur, and substituted benzenes are obtained as products. Thus, both α - and β - methoxy - substituted thiophenes react with dimethyl acetylenedicarboxylate in xylene to give modest yields of phthalates resulting from sulfur extrusion from initial adducts; in acetic acid as solvent, only substitution products are obtained.





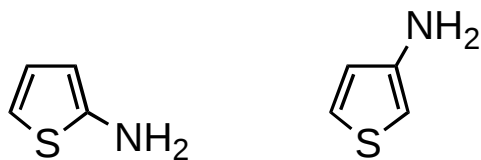
Oxythiophenes

These compounds are much more difficult to handle and much less accessible than phenols. Neither 2-hydroxythiophene nor its 4-thiolen-2-one tautomer are detectable, the compound existing as the conjugated enone isomer, 3-thiolen-2-one,¹³³ which can be obtained directly by oxidation of thiophene.¹³⁴





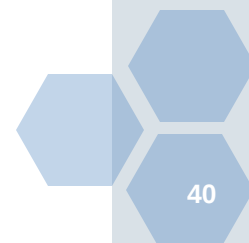
Aminothiophenes



Only amino
Generally **unstable**

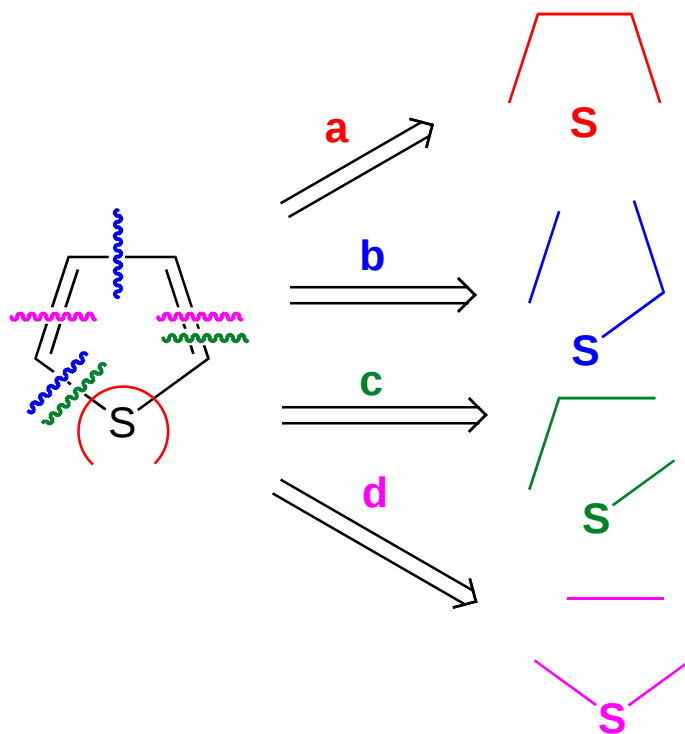
c.f. Aminopyrroles

-Amino (not iminoform) - **unstable**





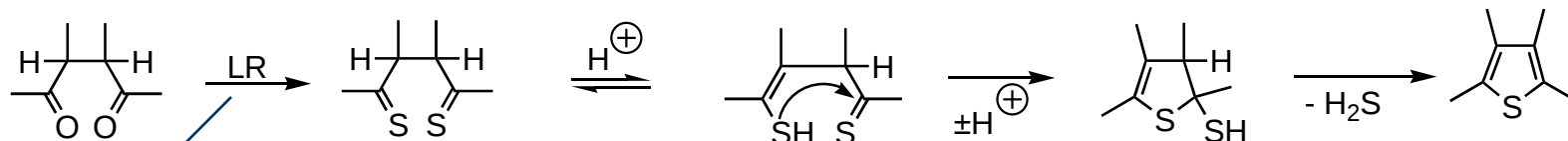
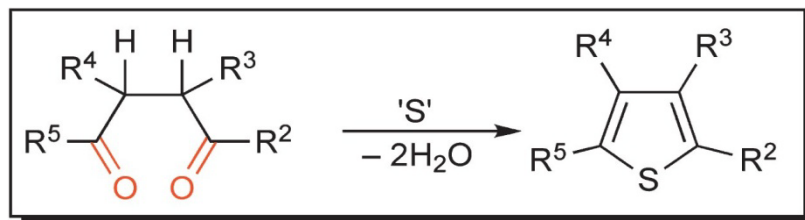
Synthesis of Thiophenes



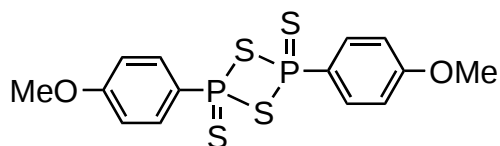


Carbonyl condensations

Strategy a:



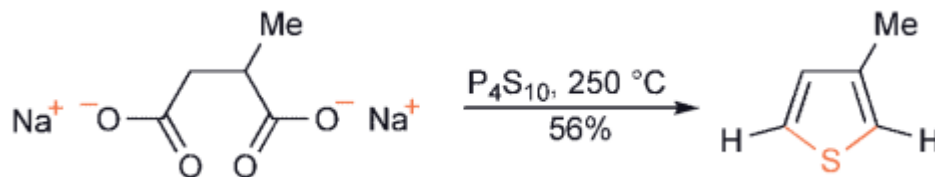
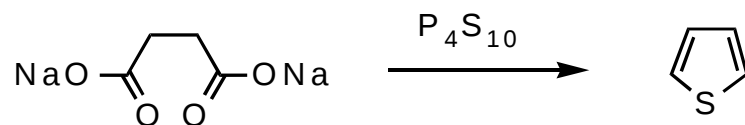
LR: Lawesons reagent





Strategy a, cont.: Reactions with electrophiles at Sulfur

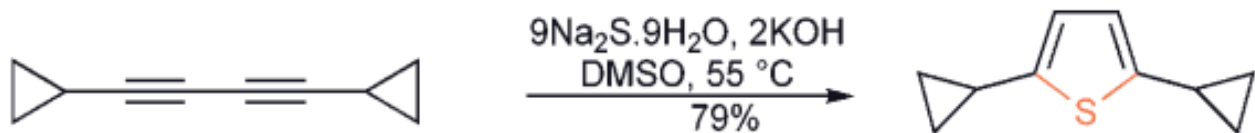
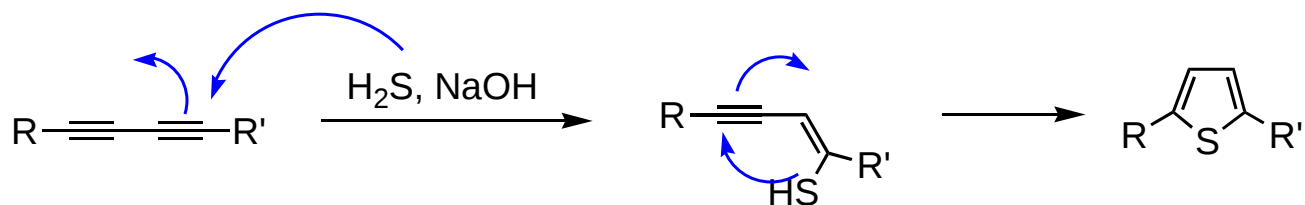
When the process is applied to 1,4 - dicarboxylic acids, a reduction must occur at some stage, for thiophenes, and **not 2- or 5-oxygenated thiophenes result.**





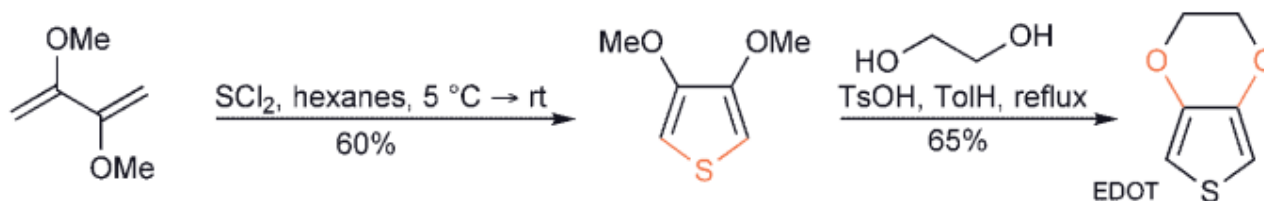
Use of conjugated diynes

Much use has been made of conjugated diynes, which are also at the oxidation level of 1,4 – dicarbonyl compounds, which react smoothly with hydrosulfide or sulfide, under mild conditions, to give 3,4-unsubstituted thiophenes.





Finally in this category, the efficient synthesis of 3,4-dimethoxythiophene from 2,3-dimethoxy-1,3-butadiene on reaction with sulfur dichloride is notable; it was easily transformed into 'EDOT' (31.6.6.1).¹⁵¹ Here the sulfur source is electrophilic in character.

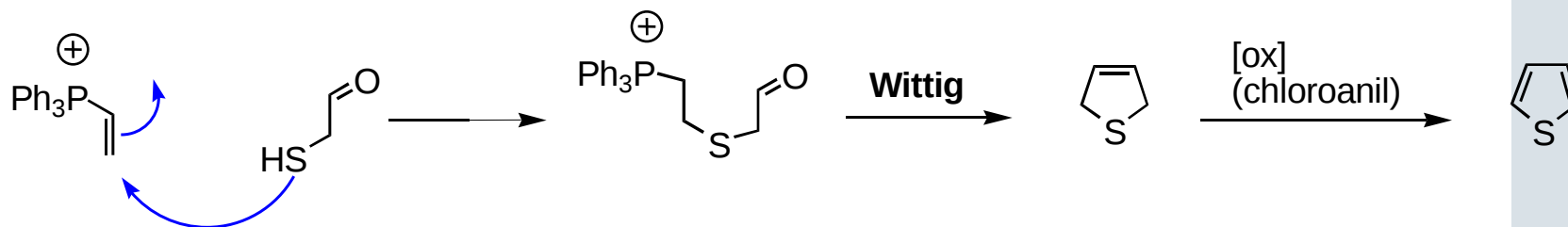


3,4-ethylenedioxythiophene



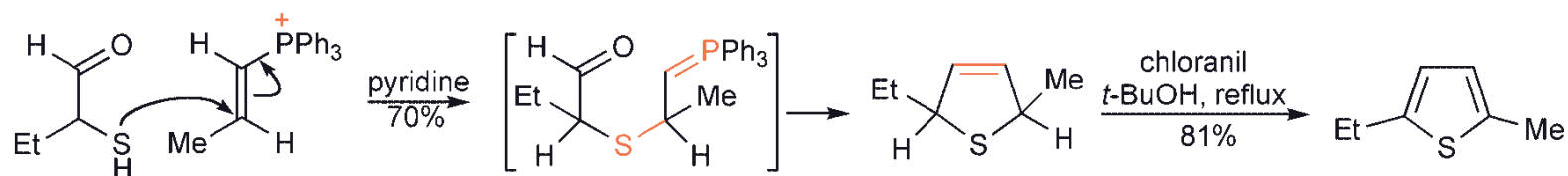
From α -Thio - Carbonyl Compounds

Strategy b:

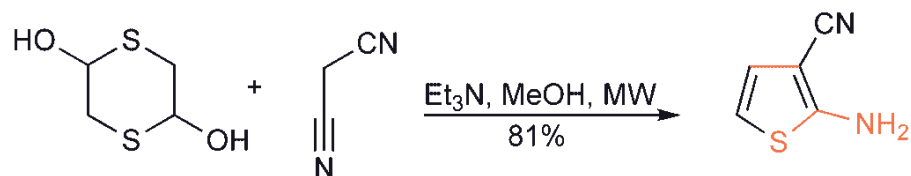




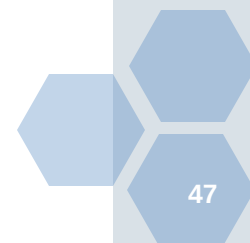
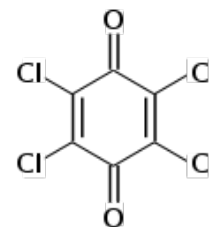
2-Keto-thiols add to alkenyl-phosphonium ions, affording ylides, which then ring close by Wittig reaction and give 2,5-dihydrothiophenes, which can be dehydrogenated.¹⁵⁷ Thiophene-2-esters can be comparably produced, without the need for dehydrogenation, by reaction of the 2-keto-thiol with methyl 3-methoxyacrylate.¹⁵⁸



Microwave irradiation in the presence of triethylamine was used for the synthesis of 4,5-unsubstituted 2-amino-thiophenes using thioacetaldehyde dimer.¹⁵⁹



Chloranil:

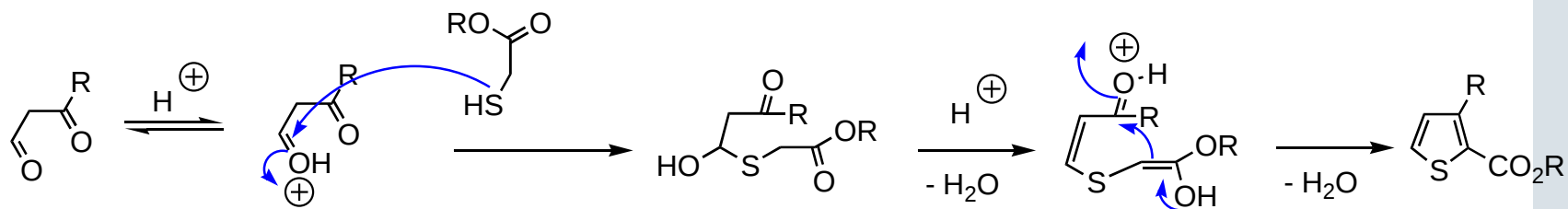
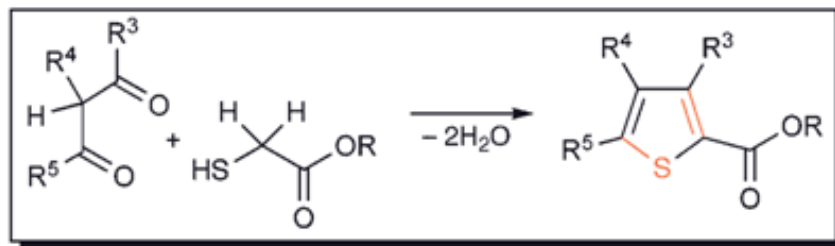




From Thioglycolates and 1,3 - Dicarbonyl Compounds

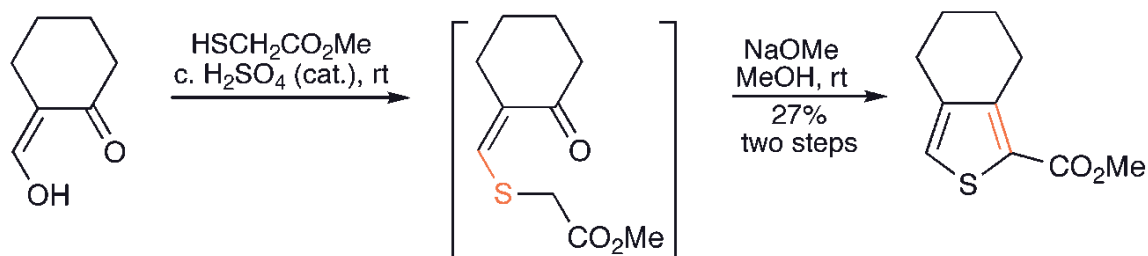
Strategy c:

Thioglycolates react with 1,3-dicarbonyl compounds (or equivalents) to give thiophene-2-carboxylic acid esters.





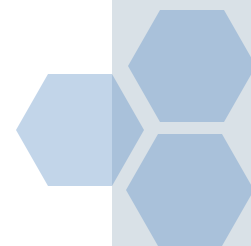
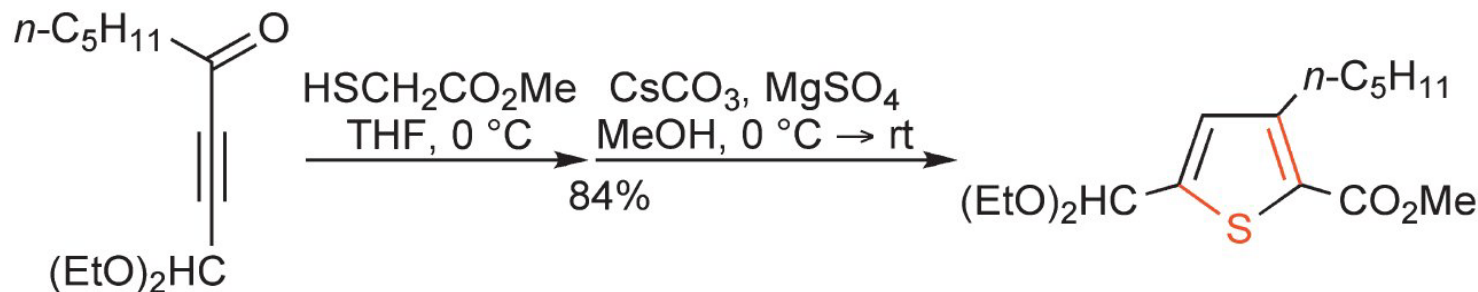
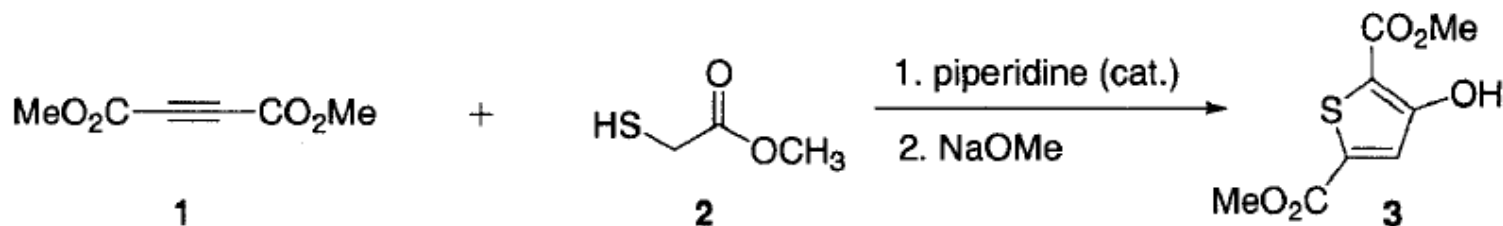
In most of the examples of this approach, thioglycolates, as donors of an S–C unit, have been reacted with 1,3-keto-aldehydes, to give intermediates that can be ring closed to give thiophenes, as exemplified below.¹⁵⁴





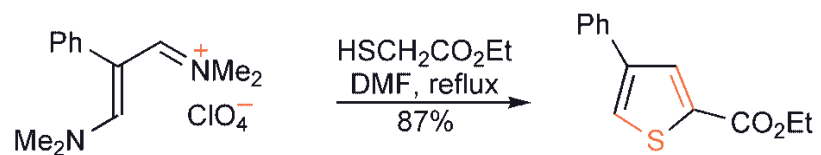
Fiesselmann Thiophene Synthesis

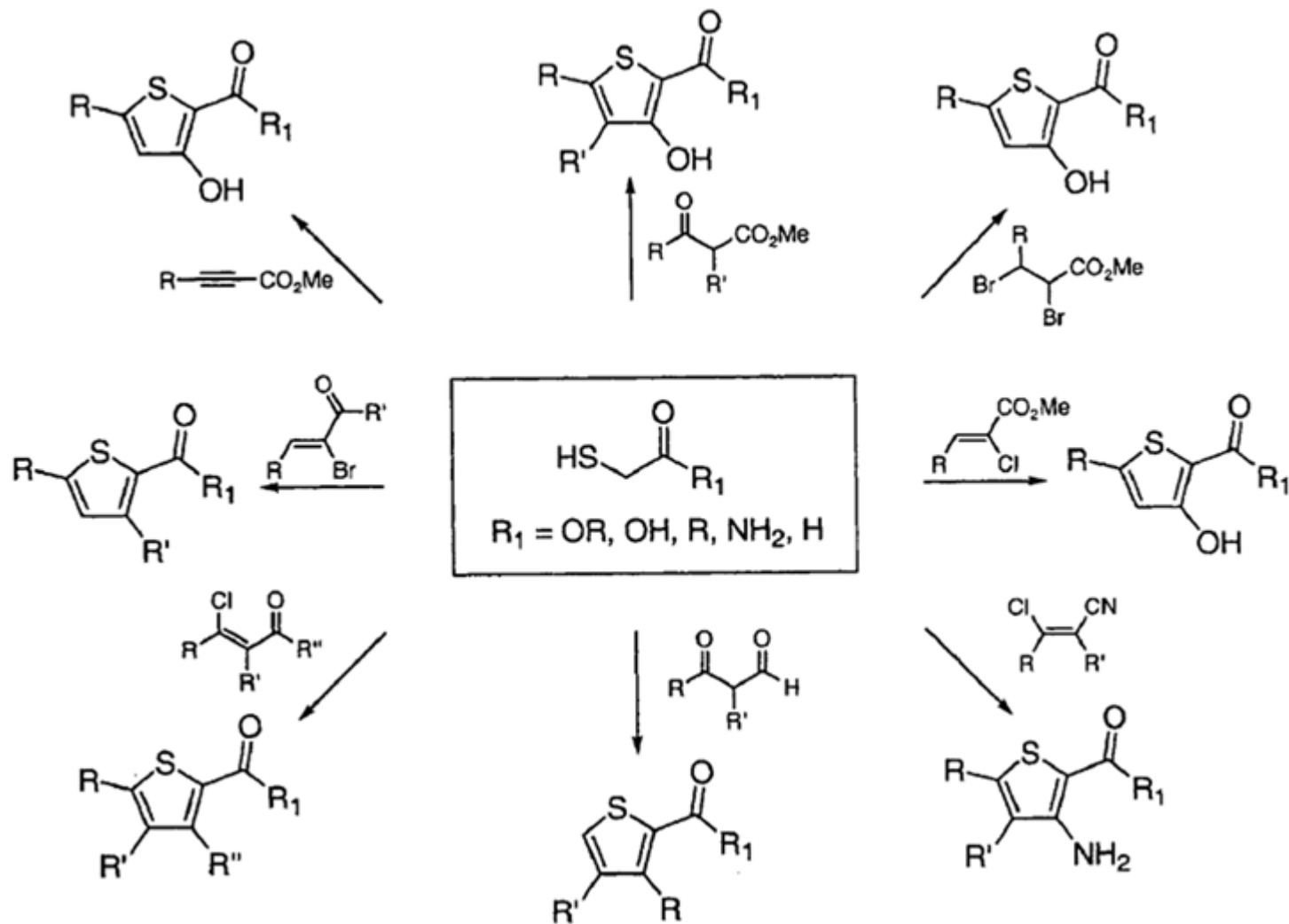
The Fiesselmann thiophene synthesis involves the condensation reaction of thioglycolic acid derivatives with acetylenic esters, which upon treatment with base results in the formation of **3-hydroxy-2-thiophenecarboxylic acid derivatives**.





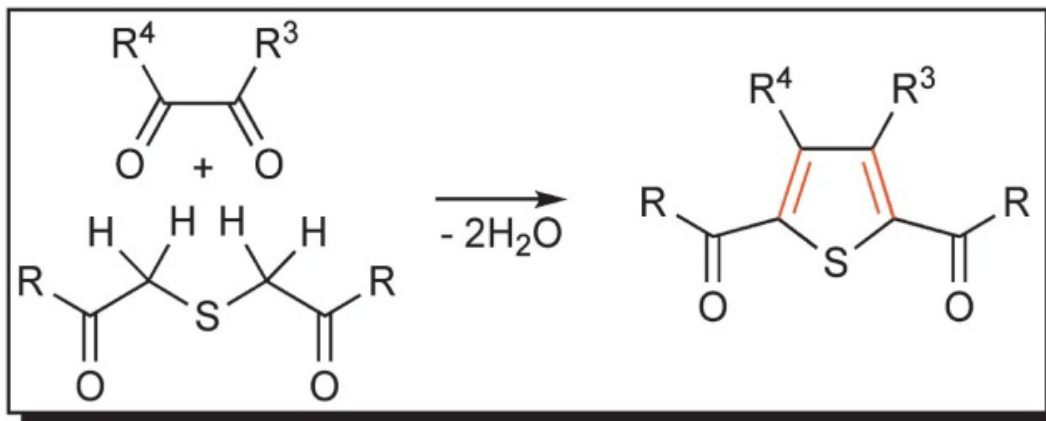
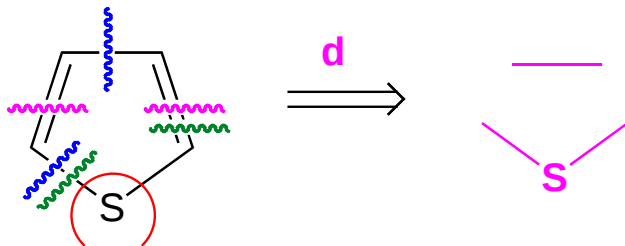
Vinamidinium salts used as 2-substituted malondialdehyde synthons, produce 3,5-unsubstituted thiophenes.¹⁵⁶



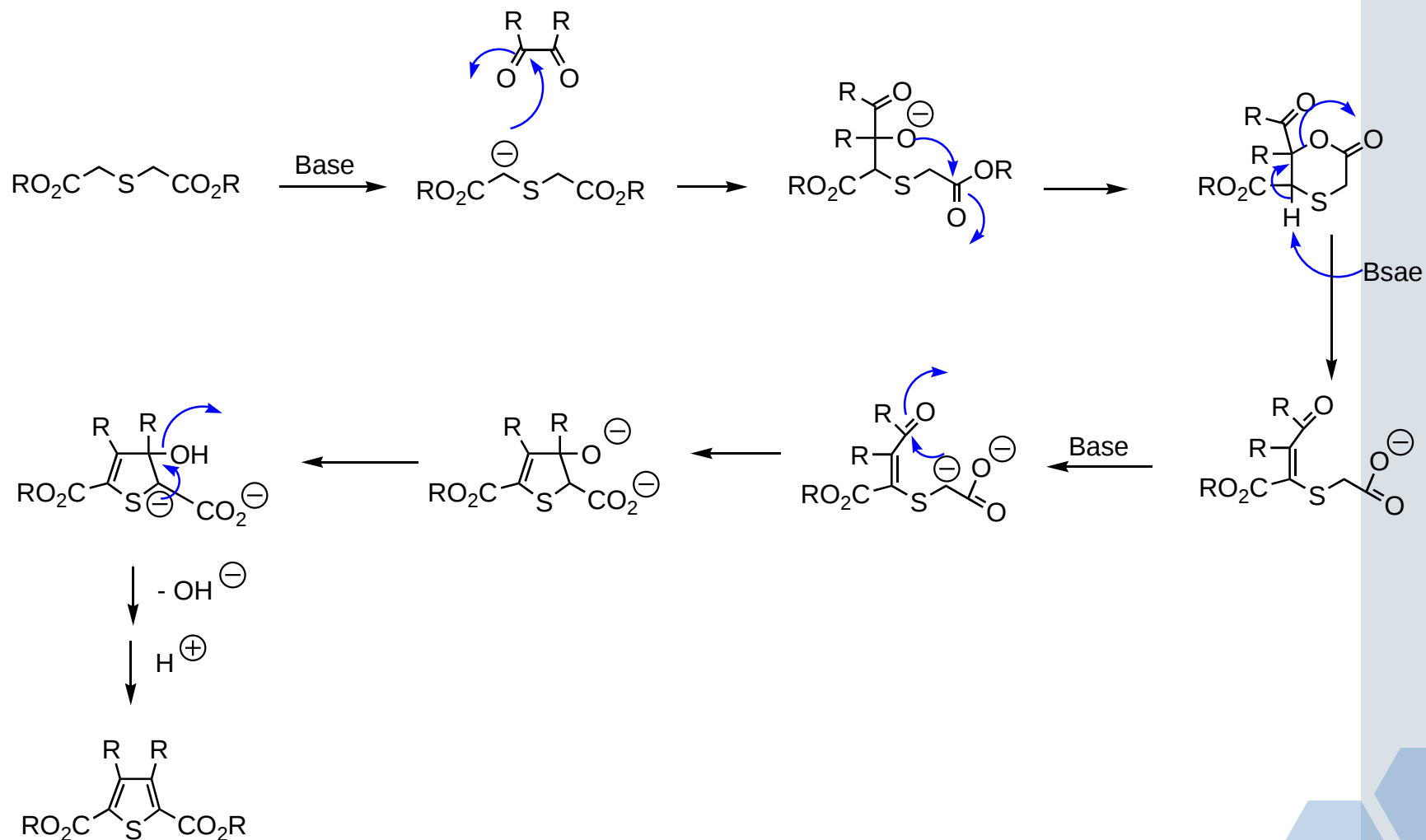


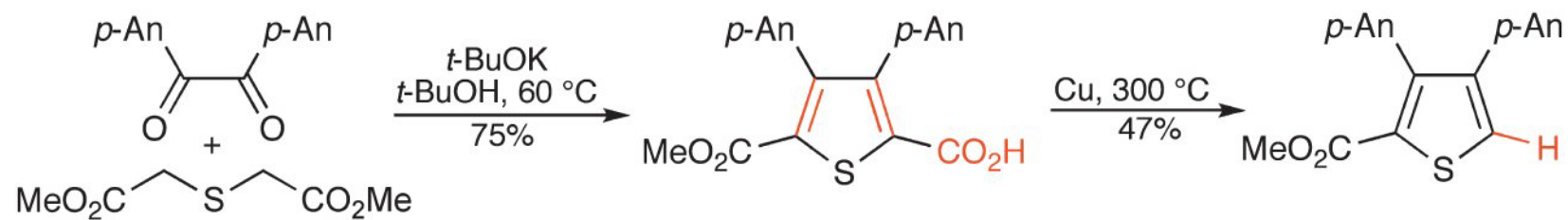


Strategy d



Mechanism:

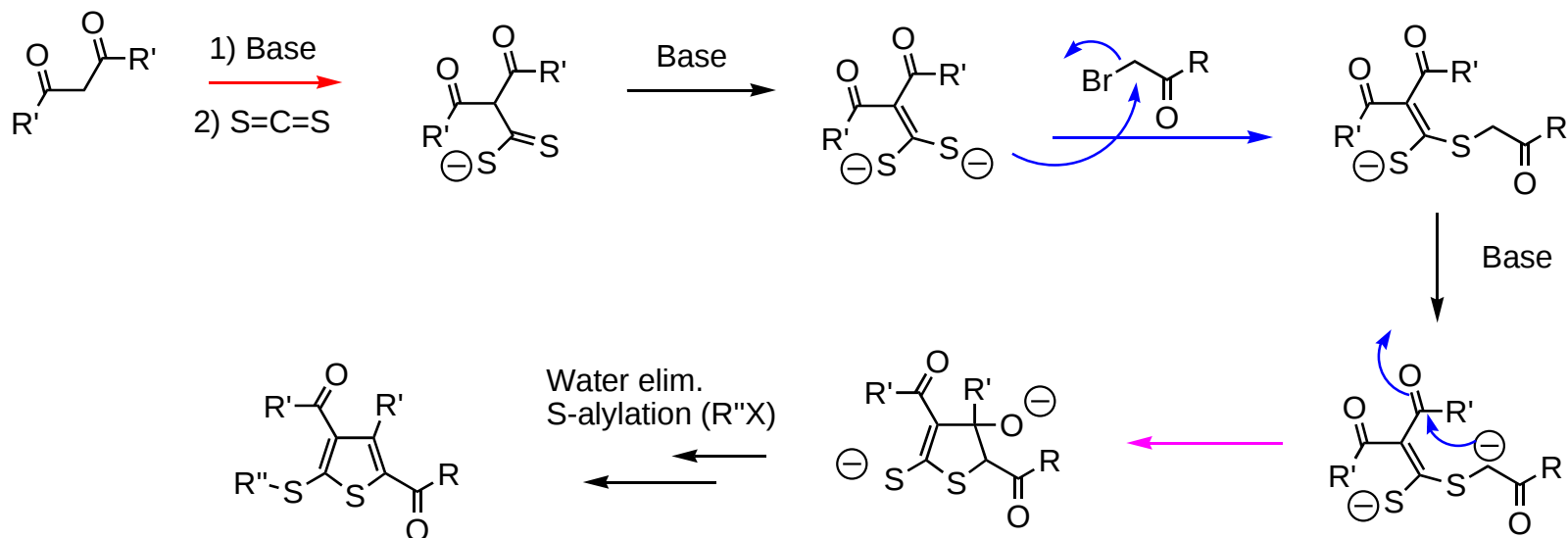
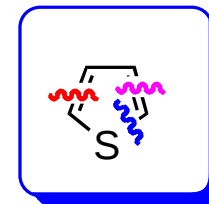






Miscellaneous carbonyl reactions

Using Carbon Disulfide:





Miscellaneous carbonyl reactions

From Thio – Diketones:

