Illinois Academy of Science Transactions, Vol. 47, 1955

SUBSTITUTION IN THE 2,5-POSITIONS OF THIOPHENE[1]

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Six possible resonating structures may be written for thiophene (fig. 1). Nucleophyllic substitution in forms 4 to 6 would add the entering substituent at the sulfur atom which would lead either to rearrangement or rupture of the ring. Form 2 would give predominantly the 3-substituted derivative. Since monosubstitution was found to give predominantly the 2-isomer in all our work, we have concluded that form 3 is the most important resonating charged form.

Formation of a disubstituted derivative from the 2-monosubstituted thiophene would theoretically yield a mixture of 2,3- and 2,5-derivatives if the monosubstituent were ortho-para-directing on the benzene ring, while a meta-directing group on the 2-position of thiophene would yield a 2,4-derivative. Our experience has shown that regardless of whether the monosubstituent in the 2-position is ortho-para- or meta-directing, a second substituent enters the 5-position preferentially. This again would show form 3 of the resonance forms of thiophene to be predominant since there are two isomeric resonating forms of form 3. Although a 2,3-disubstituted derivative is possible with the monosubstituent as a typical electron withdrawing group because of the alternate polarization of the various positions around the ring, still the 2,5-derivative seems to be formed because of the greater directive influence of the sulfur atom (fig. 2). The same is true with a monosubstituent that tends to activate the 4-position.

2-NITROTHIOPHENE-5-CARBOXYLIC ACID

Attempts to prepare this compound were made by five different methods (fig. 3).

1.—Acetyl thiophene was readily obtained (68% yields), but subsequent nitration gave less than 5% yield of 2-acetyl-5-nitrothiophene. During nitration two side reactions occurred: (1) the acetyl group was removed with the formation of a mixture of 2-nitrothiophene and 2,5-dinitrothiophene; and (2) the thiophene ring was destroyed. Removal of the acetyl group cannot be explained merely by the effect of the nitric acid, since later it was found that other monosubstituted derivatives could be nitrated. Destruction of the thiophene ring can be explained by the presence of the resonating charged forms 4 to 6. Oxidation of the acetyl group prior to nitration was also unsuccessful and gave comparable results.

2 and 3.—Bromination followed by nitration gave 50% yields of 2-bromo-5-nitro thiophene. Repeated attempts to prepare the Grignard reagent were unsuccessful. Apparently the presence of the nitro

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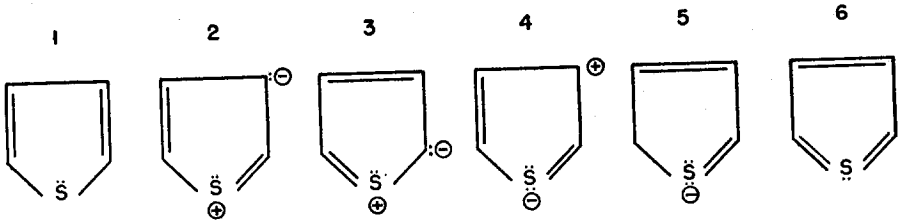


FIG. 1.

group causes the bromine atom to be less active; the starting material was recovered unchanged. Likewise attempts to form the 2-nitro-5-nitrile from the corresponding nitro-bromo derivative resulted in recovery of the starting material.

4 and 5.—The 2-iodo-5-nitrothiophene was obtained in 50% yields. Attempts to prepare the more active sodio derivative with subsequent carbonation resulted in the apparent disruption of the molecule. The presence of the nitro group may cause attachment of the sodium atom to the sulfur atom with resulting ring scission. In the hope that the iodine atom would be more labile than the corresponding bromine atom, we attempted to prepare the nitro-nitrile from the nitro-iodo derivative, but again the starting product was recovered.

All the above reactions are reported in the literature for aromatic derivatives and/or simple thiophene derivatives. The inability to form nitrothiophene-carboxylic acid in over 5% yields by any of the above methods can be attributed to one of three causes: (1) rupture of the thiophene ring possibly because the entering group attaches onto the sulfur atom; (2) removal of other groups from the ring particularly during nitration; and (3) inhibition by the nitro group of the normal reaction of other groups attached to the ring.

THIOPHENE-2,5-DICARBOXYLIC ACID

Five different methods were used in attempting to prepare this compound (fig. 4).

1.—Because 2-acetyl thiophene is easily prepared and oxidized to the corresponding acid, we attempted to prepare the 2,5-diacetyl thiophene. An acetyl group in the 2-position seemed to cause the remaining positions on the thiophene ring to become less active, since less than a 5% yield of a diacetyl derivative could be obtained.

2, 3, 4, and 5.—We attempted to prepare the dicarboxylic acid from 2,5-dibromothiophene by (2) prior formation of the dinitrile, (3) direct carbonation of the disodio derivative, (4) Grignard reaction and (5) reaction with ethyl chloroformate. Attempts to form the dinitrile resulted in recovery of the starting product. Attempts at direct carbonation resulted in decomposition of the molecule. This plus prior work seemed to indicate that the metallation reaction is somewhat specific and not generally applicable. Attempts to form the Grignard reagent resulted in an unexpected removal of one bromine atom with the subsequent formation of only thiophene-2-carboxylic acid. A comparable reaction

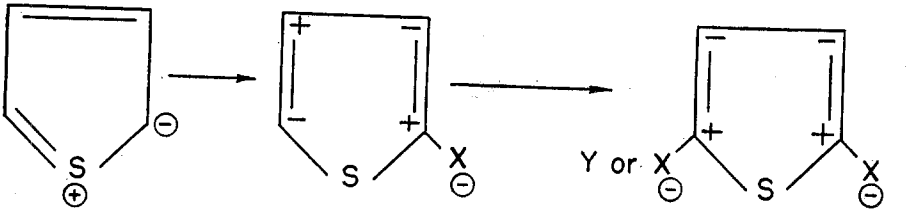


FIG. 2.

resulted when ethyl chloroformate was used.

In all our experimental attempts to prepare a disubstituted derivative of thiophene by direct substitution, it was noticed that only when the monosubstituent is a strong electron-attracting group could a second substituent be introduced. Thus the diacetyl-, acetyl-nitro-, and nitrocarboxylic acid could not be obtained easily. According to the literature this is also true with the dialkyl-derivatives. However, the dinitro, dibromo, nitro-bromine, and the corresponding chloro and iodo compounds could be obtained with relative ease. Furthermore, replacement of a negative group when a second negative group was also attached to the ring did not occur with what could be considered normal ease. Whether this is a general rule or a coincidence can be determined only by further work.

ACKNOWLEDGMENTS

We wish to offer our sincere appreciation to the Research Corporation, founded by the late Frederick Cottrell, for granting financial aid to make this research project possible.

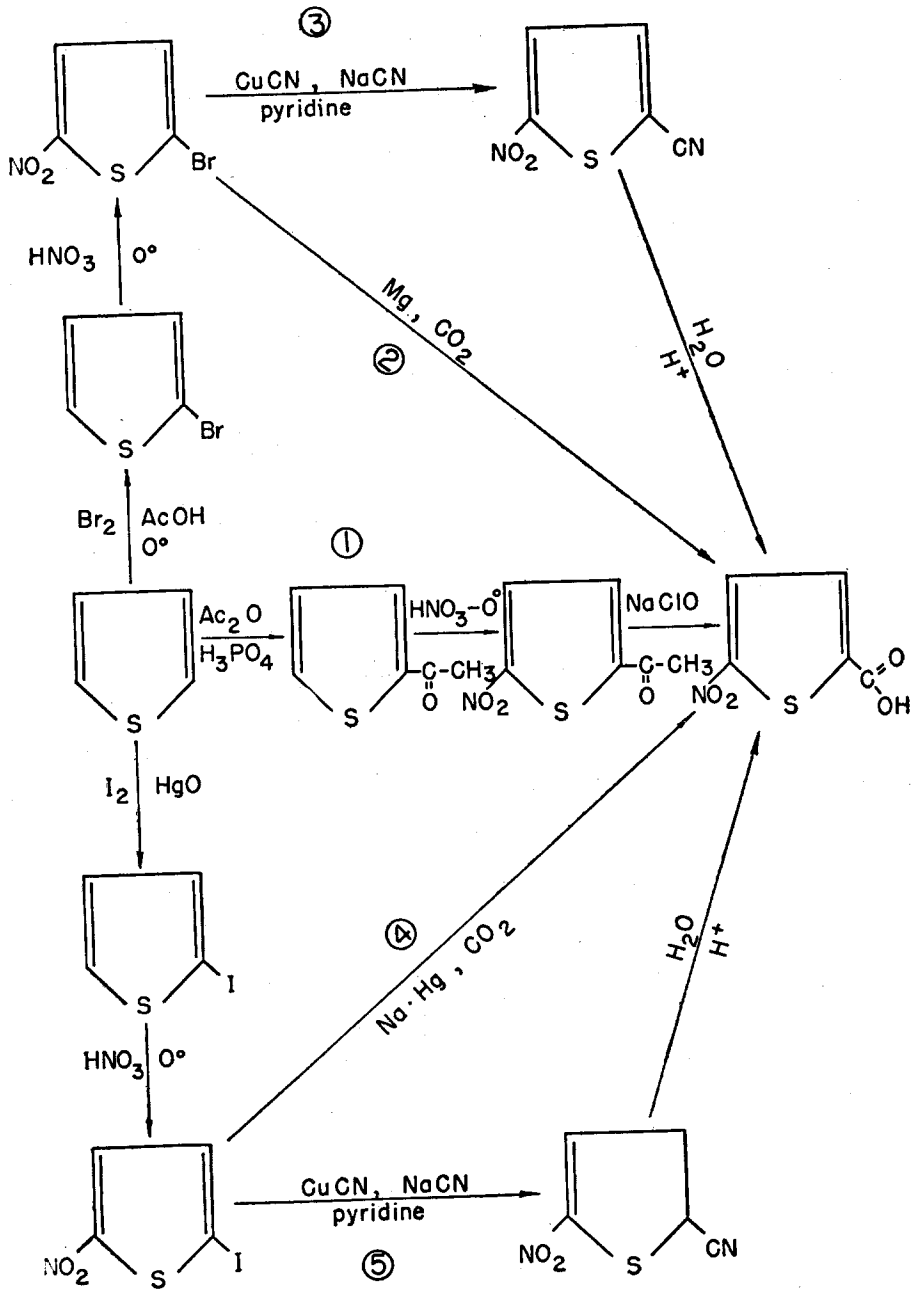
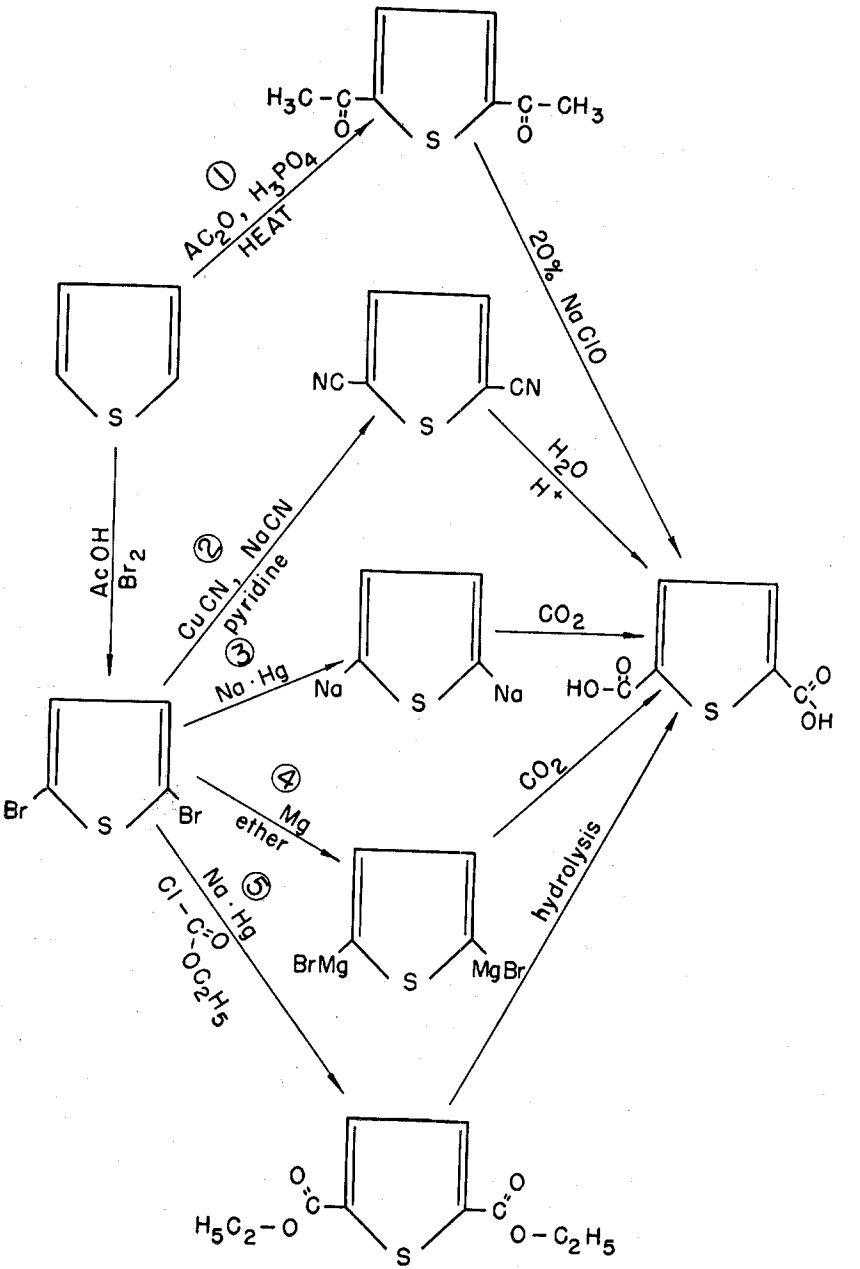

③
CuCN , NaCN
pyridine
NO2
S
Br
CN
HNO3
0°
Mg , CO2
②
H2O
H+
Br2
AcOH
0°
①
Ac2O
H3PO4
HNO3–0°
NaClO
C-CH3
O
NO2
OH
I2
HgO
I
④
Na·Hg , CO2
HNO3
0°
⑤

FIG. 3.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O
C-CH3
O
S
① Ac2O, H3PO4
HEAT
20% NaClO
NC
CN
S
H2O
H+
AcOH
Br2
② CuCN, NaCN
pyridine
③ Na·Hg
Na
S
Na
CO2
HO-C
O
C
O
OH
Br
S
Br
④ Mg
ether
CO2
hydrolysis
⑤ Na·Hg
Cl-C=O
OC2H5
BrMg
S
MgBr
H5C2-O
O
C
C
O
O-C2H5
S

FIG. 4.