CHEMISTRY LETTERS, pp. 399-402, 1981.

UNUSUAL FRIEDEL-CRAFTS REACTION OF 2,5-DICHLORO-3-CHLOROMETHYLTHIOPHENE WITH BENZENE AND SOME ALKYLBENZENES

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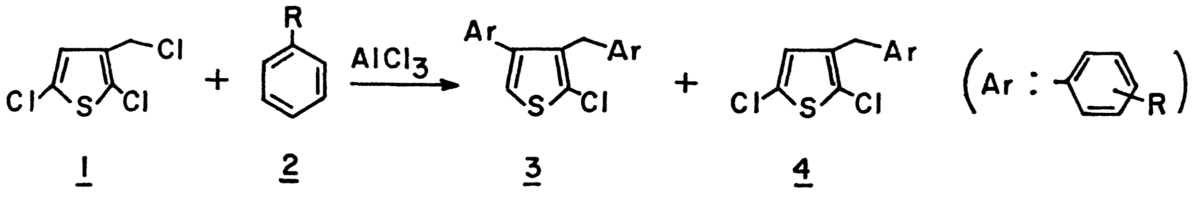
The reaction of 2,5-dichloro-3-chloromethylthiophene with benzene and some alkylbenzenes in the presence of aluminum chloride yielded the unusual 4-aryl-3-arylmethyl-2-chlorothiophenes as the major products.

The usefulness of 2,5-dichlorothiophene as a starting substance has been demonstrated in the syntheses of certain 3-substituted and 3,4-disubstituted thiophenes, which can not be prepared by direct substitution of thiophene.[1)] Thus, appropriate group is introduced to the ß-position of 2,5-dichlorothiophene, and then the chlorine atoms blocking the α-positions are removed from the resulting ß-substituted 2,5-dichlorothiophenes.

We have found an unusual Friedel-Crafts reaction of 2,5-dichloro-3-chloromethylthiophene (1) with benzene and some alkylbenzenes in the presence of aluminum chloride, in which the chlorine atom blocking the 5-position is removed with the introduction of an aryl group into the neighboring 4-position.

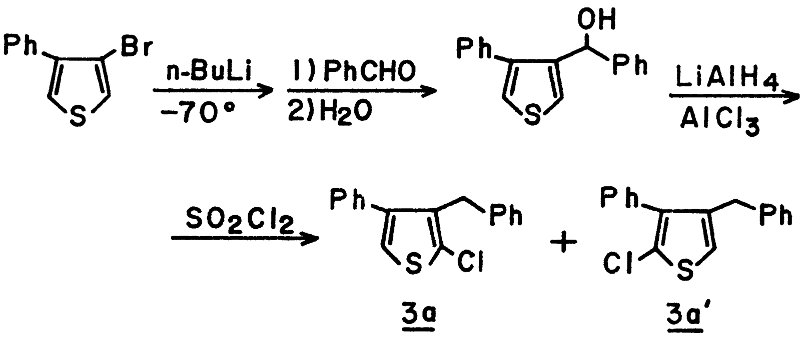


a : R = H ; b: R = CH_3 ; c : R = C_2H_5

Scheme I

Aluminum chloride (0.01 mol) was added to the cooled solution (ca. -5°C) of 1 (0.01 mol) in benzene (2a; 0.11 mol). The reaction mixture was stirred for 10 min and then at room temperature for 90 min. Column chromatography (silica gel/hexane) of the product afforded 3-benzyl-2-chloro-4-phenylthiophene (3a; bp 140-143°C/10^{-4}mmHg) in 77% yield along with the expected 3-benzyl-2,5-dichlorothiophene (4a; bp 80-84°C/10^{-4}mmHg) in 9% yield. With half equivalent mole of aluminum chloride, 3a and 4a were formed in almost equal yields (Table 1).

The structure of 3a was assigned on the basis of its elemental analysis[2)] and spectral data [MS (70 eV) m/e 284 (M^+); UV λmax (MeOH) 231sh (4.20), 252sh (3.94); NMR (CCl_4) δ 6.8-7.4 (m, 11H), 3.90 (s, 2H)]. The mass and NMR spectra indicate the presence of two phenyl groups. The UV spectrum suggests that 3a has a 3-phenylthiophene skeleton rather than 2-phenylthiophene one;[3)] this was confirmed by the formation of 3-benzyl-4-phenylthiophene [5; bp 126-129°C/10^{-4}mmHg; MS m/e 250 (M^+); UV λmax (MeOH) 229sh (4.15), 247 (4.05); NMR (CCl_4) δ 6.9-7.4 (m, 11H), 6.76 (dt, J_{25}=3.4 Hz and J_{CH_2-2}=0.9 Hz, 1H),[4)] 3.86 (br s, 2H)], the dechlorinated product, in an attempted desulfurization of 3a with Raney Nickel. The structure of 3a was finally determined by comparing its NMR spectrum with those of the monochlorinated products (3a and 3a') of 5 which were obtained according to Scheme 2.[5)]



Scheme 2

Similarly, the reaction of 1 with toluene (2b) and ethylbenzene (2c) afforded corresponding 4-aryl-3-arylmethyl-2-chlorothiophenes (3b and 3c) as major products in good yields. The results are summarized in Table 1.

Table 1. Reaction of 2,5-Dichloro-3-chloromethylthiophene (1) with Benzene and Some Alkylbenzenes a)

Ar-H	Mole ratio 1/2/AlCl$_3$	Reaction products Yield (%) b)		UV spectral data of 3 λ_{max}^{MeOH} nm (log ε)
2a	1:11:0.5	3a (41)	4a (47)	231sh (4.20), 252sh (3.94)
	1:11:1	3a (77)	4a (9)	
2b	1:11:1	3b (68) c)d)	4b (10) c)	223 (4.30), 236sh (4.20), 253sh (3.94)
2c	1:11:1	3c (72) c)	4c (--) e)	223 (4.35), 236sh (4.26), 252sh (4.01)

a) Reaction conditions: 1, 0.01 mole; 10 min under cooling (ca. -5 °C) and additional 90 min at room temperature. b) Isolated yield based on 1 used. c) Data on a mixture of the isomers due to the difference in the position of the alkyl groups on the benzene rings. d) From the isomeric mixture, 2-chloro-3-(p-methylbenzyl)-4-(p-tolyl)thiophene was isolated as colorless crystals, mp 85-86 °C. MS (70 eV) m/e 312 (M$^+$); UV λmax (MeOH) 225 (4.34), 236sh (4.26), 253sh (3.96); NMR (acetone-d) δ 7.22 (s, 1H), 7.13 (s, 4H), 7.06, 6.97 (AA'BB'm, 2H), 6.80, 6.88 (AA'BB'm, 2H), 3.94 (s, 2H), 2.27 (s, 3H), 2.19 (s, 3H). e) Not determined.

It was found that 4a also gave 3a when treated with aluminum chloride in benzene under similar conditions; this suggests the intermediacy of the normal products, 4, for the formation of the unusual products, 3. However, the entire reaction pathway is not clear at present.

The results obtained here are of interest not only from the theoretical points of view concerning the reactivity of thiophene, but also from the preparative one. Namely, the results suggest a simple route for the syntheses of some 4-substituted-3-arylthiophenes which are accessible only by multi-step synthesis, and, in addition, demonstrate that chlorine atom should be utilized with care as blocking group for α-positions of thiophene ring under certain acidic conditions.

The authors wish to thank Professor H. Obara for valuable suggestions, and to Dr. J. Onodera for mass spectral measurements.

References and Notes

1) For example: S. Gronowitz, Arkiv Kemi, 8, 441 (1956); D. W. H. MacDowell, T. B. Patrick, B. K. Frame, and D. L. Ellison, J. Org. Chem., 32, 1226 (1967).

2) Satisfactory analyses were obtained for all new products.

3) 2-Phenylthiophene, λmax (MeOH) 220sh (3.82), 282 (4.17); 3-phenylthiophene, λmax (MeOH) 226 (4.07), 258 (4.13).

4) a) The coupling constants between two protons in disubstituted thiophenes are: J_{25}=3.20-3.65 Hz, J_{35}=1.25-1.70 Hz, J_{34}=3.45-4.35 Hz, J_{45}=4.90-5.80 Hz. S. Gronowitz, "Advances in Heterocyclic Chemistry," Vol. 1, ed. by A. R. Katritzky, Academic Press, New York (1963), p. 7. b) For the side-chain couplings in thenyl derivatives, see, for example: T. Sone and K. Takahashi, Org. Magn. Resonance, 3, 527 (1971).

5) Chlorination of 5 with sulfuryl chloride gave an unisolable mixture of the 2-chloro (3a) and the 5-chloro derivatives (3a') as shown by its elemental analysis and NMR spectrum [(CCl_4) δ 6.8-7.4 (m) and 6.54 (t, J=1.0 Hz) (aromatic ring, 11H), 3.90 (s) and 3.66 (s) (CH_2, 2H)]. The 1:2:1 triplet at 6.54 ppm is assigned to the ring proton at the 2-position and the broad singlet at 3.66 ppm to the methylene protons of 3a' on the basis of the multiplicity of the ring proton signal due to the coupling with the adjacent ß-methylene protons;[4b)] decoupling measurement confirmed the assignment. The singlet at 3.90 ppm is accordingly ascribable to the methylene protons of 3a. The corresponsing absorption is observed in the spectrum of the product formed in the unusual Friedel-Crafts reaction.

(Received December 16, 1980)