

Formation of 2-Aryl-3,4,5-trichlorothiophenes from Iodoarenes and Trichloro-2-thienylcopper or Copper(I) Trichloro-2-thenoate

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3,4,5-Trichloro-2-thienylcopper, prepared from trichloro-2-thienyllithium and copper(I) bromide, was reacted with 4-iodoanisole in pyridine, to give the corresponding 2(4-methoxyphenyl)trichlorothiophene selectively.

Copper(I) 3,4,5-trichloro-2-thenoate was prepared, and its decarboxylative coupling with 4-iodoanisole was investigated.

The reactions were followed, and compared, by means of gas chromatographic analysis. In the early stages of the decarboxylative coupling, the transient accumulation of trichloro-2-thienylcopper was indicated by the presence of 2,3,4-trichlorothiophene after hydrolysis of the aliquots.

During the last few years, the interest in arylcopper compounds has increased rapidly, and their properties have been investigated by several authors.¹⁻⁹ Arylcopper compounds have been suggested as intermediates in some copper-promoted reactions. The Ullmann biaryl synthesis¹⁰ is one example, and the decarboxylative coupling of carboxylic acids in the presence of copper(I) oxide¹¹⁻¹⁴ is another. These reactions usually have been performed at temperatures around 200°, where most arylcopper compounds are unstable and not expected to accumulate.

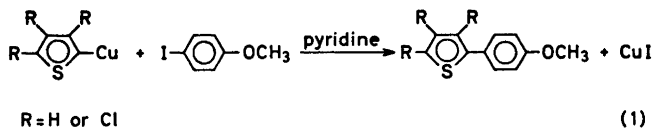
We have previously reported investigations of the decarboxylative coupling between 2-thenoic or 2-furoic acids and iodoarenes in the presence of copper(I) oxide,¹² and also the unsymmetrical coupling between 2-thienylcopper and iodoarenes.⁹ By analogy with the effect of fluorine on the stability of arylcopper compounds,³ chlorine substituents in the thiophene ring could be expected to stabilize a thienylcopper compound. Also, the trichloro-2-thienyl group forms σ -bonds to transition metals as iron, nickel, and manganese. These σ -bonded derivatives show enhanced thermal and oxidative stabilities in comparison to the corresponding 2-thienyl derivatives.¹⁵ Electron-attracting substituents could also be expected to increase the rate of decarboxylation of an aromatic acid.

We have, therefore, investigated the decarboxylation of copper(I) trichloro-2-thenoate and the coupling with 4-iodoanisole, and compared the reaction with the unsymmetrical coupling between trichloro-2-thienylcopper and 4-iodoanisole. 4-Iodoanisole was chosen because of its slow reaction with arylcopper compounds.⁹

Some organocopper compounds have been found to form Meisenheimer complexes with 1,3,5-trinitrobenzene.¹⁶ We also wanted to explore this possibility with trichloro-2-thienylcopper.

RESULTS

Trichloro-2-thienyl-lithium was added to a suspension of copper(I) bromide in ether at -30° . The copper(I) bromide slowly dissolved during the addition. The homogeneous solution was used without isolating the trichloro-2-thienylcopper formed.



Pyridine was added to the solution, the ether was evaporated, and the temperature was slowly raised to 115° . The 4-iodoanisole was added. Small samples were withdrawn from the reaction mixture, hydrolysed and analyzed by gas chromatography. The course of the reaction is shown in Fig. 1. The coupling product 2-(4-methoxyphenyl)-trichlorothiophene (reaction 1, R = Cl) was formed in good yield (about 65 %, based on the butyllithium). The reaction was essentially complete within 40 min. Traces of hexachloro-2,2'-bithienyl were observed by gas chromatography, but since its amount did not change during the reaction, it probably was formed during the preparation of trichloro-2-thienylcopper.

Treatment of trichloro-2-thienyl-lithium with carbon dioxide afforded 3,4,5-trichloro-2-thenoic acid. This product was allowed to react with an equimolar amount of copper(I) oxide in boiling toluene, to produce copper(I) trichloro-2-thenoate in 90 % yield.

Copper(I) trichloro-2-thenoate was decarboxylated in boiling pyridine. More than 90 % of the total yield of carbon dioxide was evolved within 15 min. Hydrolysed samples from the reaction mixture after approx. 10 min reaction time contained substantial amounts of trichlorothiophene (reaction 2) and traces of hexachloro-2,2'-bithienyl. In those withdrawn later, the trichlorothiophene concentration decreased.

Copper(I) trichloro-2-thenoate was also decarboxylated in the presence of 4-iodoanisole in boiling pyridine (reaction 3). Small samples were withdrawn from the reaction mixture, hydrolysed and analysed by GLC (Fig. 2). The yields are based on the copper(I) trichloro-2-thenoate. The curve for the formation of hexachloro-2,2'-bithienyl has been omitted because of the uncertainty in the determination of its concentration (see Experimental). Its

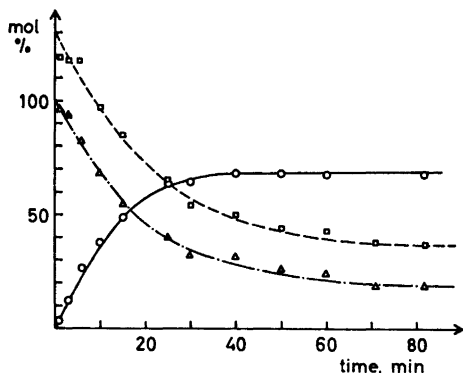


Fig. 1. Reaction between 3,4,5-trichloro-2-thienylcopper and 4-iodoanisole in pyridine at 115°. O, 2-(4-methoxyphenyl)-trichlorothiophene; □, 2,3,4-trichlorothiophene; Δ, 4-iodoanisole.

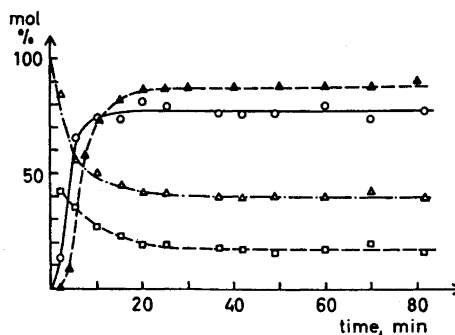
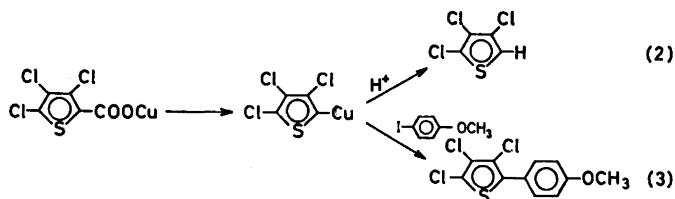


Fig. 2. Decarboxylation of copper(I) trichloro-2-thenoate in the presence of 4-iodoanisole in pyridine at 115°. ▲, carbon dioxide; O, 2-(4-methoxyphenyl)-trichlorothiophene; Δ, 4-iodoanisole; □, 2,3,4-trichlorothiophene.



formation was essentially complete within 10 min. The coupling product was formed in good yield (ca. 75 %) within 20 min, together with some trichlorothiophene and hexachloro-2,2'-bithienyl (10–15 %).

Trichloro-2-thienylcopper and trinitrobenzene were reacted in pyridine at -20° under nitrogen. The solution turned intensely red. After hydrolysis, hexachloro-2,2'-bithienyl (yield ca. 75 %, based on trichloro-2-thienylcopper) and trinitrobenzene (ca. 35 % of the added amount) were isolated. No Meisenheimer complex or its oxidation product, trinitrophenyl-2-trichlorothiophene, could be isolated. A Meisenheimer complex is formed on reaction between 2,6-dimethoxyphenylcopper and trinitrobenzene.¹⁶ The formation of hexachlorobithienyl and the decrease in the trinitrobenzene concentration indicates that trinitrobenzene acts as an oxidising agent towards the reactive copper compound. Nitrobenzene has been used to oxidise some arylcopper derivatives to biaryls.⁴

DISCUSSION

Trichloro-2-thienylcopper is formed in the reaction between trichloro-2-thienyllithium and copper(I) bromide, but so far, it has not been isolated. Very recently, similar results have been obtained by Gilman *et al.*¹⁷ No hexa-

chlorobithienyl is formed when trichloro-2-thienylcopper is heated to 115° in pyridine.

Trichloro-2-thienylcopper reacts with iodoarenes, to give 2-aryltrichlorothiophenes in good yield. When the coupling reaction is complete, some 2,3,4-trichlorothiophene still remains in the hydrolysed samples from the reaction (Fig. 1). This indicates that the trichloro-2-thienylcopper reacts with pyridine with the abstraction of a proton.

Trichloro-2-thienylcopper is also formed on the decarboxylation of copper(I) trichloro-2-thenoate, as shown by the presence of trichlorothiophene in the hydrolysed samples, and by the formation of 2(4-methoxyphenyl)trichlorothiophene in the presence of 4-iodoanisole (reactions 2 and 3).

The copper(I) salt of trichloro-2-thenoic acid was used in order to avoid the formation of water on decarboxylation, which takes place on the decarboxylation of carboxylic acids in the presence of copper(I) oxide. The copper(I) salt has been suggested as the precursor of the arylcopper compound in the latter reaction.^{13,14,18}

After completion of the decarboxylation, some trichlorothiophene remains (Fig. 2), due to reaction of the intermediate trichlorothiencylcopper with the solvent.

The formation of hexachloro-2,2'-bithienyl (13 %) on decarboxylation of the copper(I) trichloro-2-thenoate in the presence of 4-iodoanisole could be the result of dimerisation of trichloro-2-thienylcopper. However, hexachloro-2,2'-bithienyl was isolated in low yield only (2 %) from the reaction between trichloro-2-thienylcopper and 4-iodoanisole. Decarboxylation of other arenecarboxylic acids with strongly electron attracting substituents, *e.g.* 2-nitrobenzoic acid¹⁴ and pentafluorobenzoic acid,¹⁸ give the symmetrical biaryls. The corresponding products (2,2'-bithienyl and 2,2'-bifuryl) are, however, not produced from 2-thenoic or 2-furoic acids, respectively.¹³

The formation of 2(4-methoxyphenyl)trichlorothiophene is faster in the decarboxylative coupling than in the reaction between trichloro-2-thienylcopper and 4-iodoanisole. This difference is surprising and should be investigated more closely.

The influence of the three chlorine substituents on the rate of decarboxylation seems to be substantial. 2-Thenoic acid decarboxylates rapidly at 240° in quinoline,¹² while copper(I) trichloro-2-thenoate decarboxylates rapidly at 115° in pyridine (Fig. 2).

The influence of the three electron attracting chlorine substituents on the rate of the unsymmetrical coupling (reaction 2) is not pronounced. In pyridine at 115°, 50 % of the total yield of coupling product was formed within 35 min when R = H (0.4 M solution),⁹ and within 10 min when R = Cl (0.2 M solution).

EXPERIMENTAL

Melting points were determined on a micro hot stage. Infrared spectra were recorded on a Perkin Elmer No. 421 spectrometer, ultraviolet spectra with a Beckman DK 2 instrument, mass spectra with an LKB type 9000, gas chromatograph-mass spectrometer analyzer unit, and gas chromatograms on an Aerograph 204-1B instrument, with 5 % SE 30 on Chromosorb W, connected to a Varian Aerograph model 480 electronic integrator.

All preparations and handling of organometallic compounds were performed under dry oxygen-free nitrogen. Dry reagents and solvents were used, the ether was freshly distilled from lithium aluminium hydride, the pyridine (A.R.) was distilled from phosphorus pentoxide.

Preparation of trichloro-2-thienylcopper. Butyl-lithium (15 ml, Fluka 20–25 % in hexane) in diethyl ether (ca. 50 ml) was added to tetrachlorothiophene (40 mmol) in ether (ca. 50 ml) at -30° over a period of 33 min. After additional stirring for 2.5 h, the yellow trichloro-2-thienyllithium solution was transferred to a funnel. Dry copper(I) bromide¹⁹ (25 mmol) was suspended in ether (ca. 50 ml) in a reaction flask, and the flask was placed in a cooling bath, kept at -30° . The trichloro-2-thienyllithium was added over a period of 40 min with magnetic stirring. During the addition, the colour of the suspension changed from pale yellow to bright yellow to brown, and the copper(I) bromide slowly dissolved. The brownish solution was stirred for 1 h and then kept in the refrigerator overnight.

The concentration of the butyl-lithium was ca. 2.0–2.2 M, and an excess tetrachlorothiophene was used, to displace the equilibrium as far as possible towards the trichloro-2-thienyllithium. Assuming an 80–85 % conversion to trichloro-2-thienyllithium, an equimolar amount of copper(I) bromide was used.¹⁵ The trichloro-2-thienylcopper was not isolated from the ether solution.

Trichloro-2-thienylcopper and 4-iodoanisole. An ether solution of trichloro-2-thienylcopper (80 ml, 0.20–0.25 M) and pyridine (80 ml) were mixed in a reaction flask and slowly heated in an oil bath under a stream of nitrogen. When the ether had evaporated and the solution had reached 115° , 4-iodoanisole (16 mmol) and 2-methoxynaphthalene (0.20 g) were added. The reaction mixture was kept at 115° . Small samples were withdrawn from the reaction mixture at short intervals, hydrolysed with 2 M hydrochloric acid, extracted with toluene, and analysed by gas chromatography. The reaction was interrupted after 130 min by cooling. The mixture was diluted with ca. 300 ml ether, extracted with 2 M hydrochloric acid, and then washed with water. After drying over sodium sulphate, the ether was evaporated. Chromatography on silica gel of the crude reaction product (5.8 g) gave: hexachloro-2,2'-bithienyl, recrystallized from toluene (0.06 g; 1.6 %), m.p. 190° , lit.²⁰ m.p. $189.5-190^\circ$; 2(4-methoxyphenyl)trichlorothiophene, contaminated by 4-iodoanisole (3.65 g); recrystallization in ethanol gave pure 2(4-methoxyphenyl)trichlorothiophene (3.04 g; 65 % based on 4-iodoanisole), m.p. $110-111^\circ$, (Found: C 45.1; H 2.5; S 10.8; Cl 36.1. Calc. for $C_{11}H_7Cl_3OS$: C 45.1; H 2.4; S 10.9; Cl 36.2); 2-methoxynaphthalene, recrystallized from methanol (0.16 g).

Trichloro-2-thienylcopper and trinitrobenzene. An ether solution of trichloro-2-thienylcopper (40 ml, ca. 0.20 M) was mixed with trinitrobenzene (8 mmol) in pyridine (100 ml) at -20° under nitrogen. The solution immediately turned intensely red. This colour slowly changed to brownish-red, at the same time as some precipitate was formed, while the solution was slowly allowed to attain room temperature. The mixture was stirred for 1 h at room temperature, water was added, and the precipitate filtered off. Recrystallization from toluene gave hexachloro-2,2'-bithienyl (1.1 g; ca. 75 %, based on trichloro-2-thienylcopper). Excess hydrochloric acid was added to the water-pyridine solution, which then was extracted with ether (200 ml). The ether solution was washed with water and concentrated. The solid residue was recrystallized from ethanol, to give trinitrobenzene (0.64 g; 35 %). No 2(trinitrophenyl)trichlorothiophene was observed.

3,4,5-Trichloro-2-thenoic acid. 3,4,5-Trichloro-2-thienyllithium was prepared from tetrachlorothiophene and carbonated with CO_2 , m.p. after sublimation $230-231^\circ$, lit.²¹ m.p. $223-224^\circ$.

Copper(I) 3,4,5-trichloro-2-thenoate. 3,4,5-Trichloro-2-thenoic acid (10.4 mmol) was reacted with Cu_2O (5.1 mmol) in refluxing toluene under N_2 for 21 h. The red colour of Cu_2O disappeared, and a slightly yellow suspension remained. The solid was filtered off and washed with hot toluene. The yield of dry copper(I) salt was 2.70 g (90 %). The IR spectrum showed the characteristic change in carboxyl frequency and that no acid was left. (Found: S 10.7; Cl 35.7. Calc. for $C_5Cl_3O_2SCu$: S 10.9; Cl 36.2.)

Decarboxylation of copper(I) trichloro-2-thenoate. A three-necked 100 ml flask, equipped with a magnetic stirrer, a gas inlet tube and a condenser, was charged with copper(I) trichloro-2-thenoate (4 mmol) in pyridine (25 ml). The condenser was connected to an absorption train with two U-tubes, containing activated charcoal and anhydrous magnesium perchlorate, respectively, and a three-way valve to U-tubes for carbon dioxide

absorption (Ascarite and magnesium perchlorate). The reaction was performed under a stream of nitrogen at 115°. The Ascarite tubes were weighed at short intervals, and small samples were withdrawn from the reaction mixture and treated as above. Within 15 min, more than 90 % of the total yield of carbon dioxide had been evolved. The total yield was 96 % of the theoretical quantity. The gas chromatograms showed the presence of trichlorothiophene and hexachloro-2,2'-bithienyl. The retention times were compared with those of authentic samples. The trichlorothiophene concentration decreased during the reaction. The colour of the reaction mixture changed from light brownish green to dark brown. The reaction was interrupted after 80 min by cooling. The reaction mixture was worked up. The crude reaction product was sublimed to give a few mg of hexachloro-2,2'-bithienyl, m.p. 189–192°.

Decarboxylation of copper(I) trichloro-2-thenoate in the presence of 4-iodoanisole. A three-necked flask (100 ml), equipped as in the preceding experiment, was charged with copper(I) trichloro-2-thenoate (3.7 mmol) and 4-iodoanisole (3.7 mmol) in pyridine (25 ml) with 2-methoxynaphthalene (0.05 g) as internal standard. The reaction was performed under a stream of nitrogen at 115°. The Ascarite tubes were weighed at short intervals, small samples were withdrawn from the reaction mixture, and treated as above. The total yield of carbon dioxide was 89 %. More than 90 % of this was evolved within 15 min. The error in the GLC determination of the relatively small peak area of the hexachloro-2,2'-bithienyl is probably large, as its peak comes very close to and is partly overlapped by the big peak produced by 2(4-methoxyphenyl)trichlorothiophene.

The delay of 2 min for the evolution of carbon dioxide (Fig. 2) was probably due to the transport time for the carbon dioxide from the reaction flask to the absorption train.

Gas chromatographic mass spectral analysis of the sample withdrawn after 2 min reaction confirms the presence of trichlorothiophene, 4-iodoanisole, 2-methoxynaphthalene, 2(4-methoxyphenyl)trichlorothiophene and hexachloro-2,2'-bithienyl.

The mass spectrum of trichlorothiophene showed the parent ion at m/e 186 (rel. int. 100) and main fragments at m/e 151 (30), 141 (4), 116 (10), and 107 (35), corresponding to losses of Cl, CHS, 2 Cl, and CClS, respectively.

The mass spectrum of 2(4-methoxyphenyl)trichlorothiophene showed the parent ion at m/e 292 (rel. int. 100) and main fragments at m/e 277 (53) and 249 (25), corresponding to losses of CH₃ and C₂H₅O, respectively.

The mass spectrum of hexachloro-2,2'-bithienyl showed the parent ion at m/e 370 (rel. int. 100) and main fragments at m/e 335 (82), 300 (48), and 291 (21), corresponding to losses of Cl, 2 Cl, and CClS, respectively. The observed isotopic pattern for each fragment in all three spectra was in accord with that calculated.

The reaction was interrupted after 155 min, and the mixture worked up as usual. The crude reaction product was chromatographed on silica gel. 2(4-Methoxyphenyl)trichlorothiophene, m.p. 109°, and hexachloro-2,2'-bithienyl (0.09 g, 13 %), m.p. 183–185°, were isolated. Recrystallization from toluene gave 0.05 g hexachlorobithienyl (7 %, calculated on the copper(I) trichloro-2-thenoate), m.p. 186–189°.

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