

2-Arylthiophenes and 2-Arylfurans by Decarboxylative Couplings of 2-Thenoic and 2-Furoic Acids with Iodoarenes

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Decarboxylative coupling of 2-thenoic or 2-furoic acids with iodobenzene or 4-methoxy-, 4-methyl-, or 4-nitro-iodobenzene using copper(I) oxide and boiling quinoline gives the corresponding 2-phenylthiophenes or -furans in 10–20 % yield. 2,5-Diphenylthiophenes or -furans and symmetrical biphenyls are the major by-products.

2-Nitrobenzoic acids are easily decarboxylated. When such acids are heated in quinoline solution with copper(I) oxide and iodobenzene derivatives, carbon dioxide and water are given off and 2-nitrobiphenyls are formed in fair yields.¹ This decarboxylative coupling seems to be closely related to the classical Ullmann biaryl synthesis and calls to mind the particular reactivity of *o*-halogenonitrobenzenes in this reaction.²

2-Thenoic and 2-furoic acids are also known to be easily decarboxylated.^{3,4} 2-Halogenothiophenes are very reactive in Ullmann reactions² and it has been shown that 2-thienylcopper gives 2-phenylthiophenes on reaction with iodobenzenes in quinoline.⁵ The 2-halogenofurans are very reactive and rather unstable but have so far apparently not been used in Ullmann biaryl syntheses.

We have investigated the reactions of 2-thenoic and 2-furoic acids with copper(I) oxide and some representative iodoarenes, namely iodobenzene, *p*-iodoanisole, *p*-iodotoluene, and *p*-iodonitrobenzene in quinoline solution at *ca.* 240°. The results are summarised in Table 1.

Both acids reacted rapidly and gave off more than 90 % of the theoretical amount of carbon dioxide within 15 min (Fig. 1). The other products were isolated by chromatography. 2-Phenylthiophenes and 2-phenylfurans were isolated in yields of 10–20 %. The small amounts of the 2,5-diphenylthiophenes and -furans that were also isolated were probably formed from the monophenyl compounds by further reaction with copper(I) oxide and the iodoarene as described earlier for 2,5-diphenylthiophene.⁵ The yields of coupling products were thus low and apparently the greater proportion of the acids was converted to thiophene and furan, respectively. Generally 20 to 45 % of the iodo compound was recovered unchanged. Somewhat surprisingly

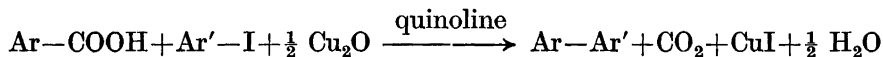
Table 1. Products (%) isolated from decarboxylative coupling of 2-thenoic and 2-furoic acids (Ar-COOH) with 4-substituted iodobenzenes (Ar'-I, 4-substituent R). Yields of the 2,5-diphenylthiophenes(furans) (Ar-Ar'₂) are based on the acids.

R	Ar=2-thienyl				Ar=2-furyl			
	Ar-Ar'	Ar-Ar' ₂	Ar'-I	Ar'-Ar'	Ar-Ar'	Ar-Ar' ₂	Ar'-I	Ar'-Ar'
H	13	7	> 2		14.5	0.5	12.5	
CH ₃ O	18	2	29		19	1	23	
CH ₃	11	2	46	3.5	14	2	35	5.5
NO ₂	9	3	22		12	0.5?	25	2

symmetrical biphenyls were isolated in most cases, though no bithienyl or bifuryl have been detected (UV).

The reactions of iodobenzene with 2-thenoic and 2-furoic acids required purified quinoline and then gave results comparable with those for the other iodoarenes.

2-Thenoic and 2-furoic acids thus follow the same pattern as that found with the 2-nitrobenzoic acids and can be used for decarboxylative couplings:



Due to the low yields the preparative value of these couplings in the thiophene and furan series seems to be limited at present. However, the couplings of 2-furoic acid seem to open up further possibilities for copper-promoted coupling reactions of furans. The results further demonstrate that the α -position in thiophene is very versatile as far as copper-promoted reactions are concerned. 2-Arylthiophenes can be formed by classical Ullmann coupling² and also by reactions in quinoline between 2-thienylcopper and iodoarenes, by decarboxylative coupling and by reaction between a thiophene and an iodoarene in the presence of copper(I) oxide.⁵ It seems very likely that all these reactions proceed *via* a common intermediate, 2-thienylcopper. The results thus give further support to the hypothesis that copper-catalysed decarboxylation and the Ullmann reaction proceed *via* a common intermediate, an arylcopper.

The facile formation of this intermediate in the thiophene series parallels other α -metallations of thiophene⁶ and it seems probable that the 2-thienyl-

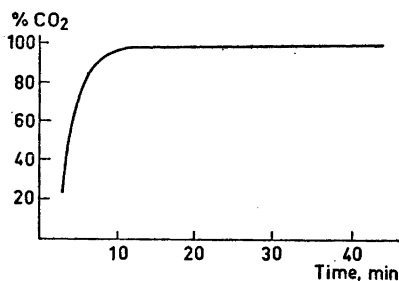


Fig. 1. Carbon dioxide evolution in the reaction between 2-thenoic acid and *p*-iodonitrobenzene.

copper is stabilised by coordination of the copper atom to the sulphur atom. This is analogous to the presumed stabilisation of 2-nitrophenyl- and 2,6-dinitrophenylcopper intermediates.^{7,8} No formation of 2,2'-bithienyl or 2,2'-bifuryl has been observed in the present investigation. Apparently the unsymmetrical couplings are favoured just as in the decarboxylative coupling of *o*-nitrobenzoic acids and in the copper(I) oxide-promoted coupling of *m*-dinitrobenzenes.^{2,7-9}

So far information concerning the copper-promoted reactions of furans is scarce but the analogies with the thiophene reactions are striking. It should be noted that the 2-phenylfurans apparently also react further with copper(I) oxide and iodobenzenes to give 2,5-diphenylfurans.

EXPERIMENTAL

Melting points were determined on a micro hot stage. Infrared spectra were recorded on Perkin Elmer No. 421 or 237 spectrometers, ultraviolet spectra with a Beckman DK 2 instrument, NMR spectra on a Varian A 60 A spectrometer and gas chromatograms on an Aerograph 204-1B with 5 or 10 % SE 30 on Chromosorb W.

Generally a good quality of synthetic quinoline ("Min. 99 %, puriss") was used in the experiments. It contained, however, small amounts of a neutral contaminant (possibly a methylnaphthalene), m.p. *ca.* 29–34°, and of a basic impurity which could give rise to triarylaminines by reaction with iodoarenes. In experiments with iodobenzene purified quinoline was used (see 2-thenoic acid and iodobenzene).

The structures of all known compounds were checked by NMR spectroscopy.

General procedure

A reaction flask (100 ml) was fitted with a gas inlet tube reaching the bottom and a reflux condenser (occasionally also a mechanical stirrer). The condenser was connected to an absorption train with a U-tube containing activated charcoal and anhydrous magnesium perchlorate that was connected *via* a three-way valve to tubes for carbon dioxide absorption (Ascarite and magnesium perchlorate). The reaction flask was charged with quinoline (25 ml), 2-thenoic acid or 2-furoic acid (0.01 mole), iodoarene (0.01 mole), and copper(I) oxide (0.006 mole). Nitrogen was passed through the apparatus and the flask was placed in a metal bath kept between 235 and 240°. The Ascarite tubes were weighed at short intervals. Within 15 min more than 90 % of the theoretical quantity of carbon dioxide had been evolved. The reaction was interrupted after 50–60 min and the mixture, when cool, was diluted with *ca.* 200 ml ether. A yellow crystalline complex of copper iodide and quinoline precipitated and was filtered off. The filtrate was extracted with dilute hydrochloric acid to remove remaining quinoline and after washing with water and drying, the solvent was removed at reduced pressure and the crude reaction product was investigated with thin-layer chromatography (silica gel, molybdato-phosphoric acid spray) and gas chromatography. The products were isolated by chromatography on silica gel.

2-Thenoic acid and p-iodoanisole. Reaction time 54 min. CO₂ yield > 88 % (losses). Chromatography of the crude reaction product (2.52 g) gave: (a) *p*-iodoanisole (0.67 g), m.p. 42–48°; (b) 0.43 g crude product, m.p. 100–107°, recrystallised from methanol to give 2-(4-methoxyphenyl)thiophene (0.34 g), m.p. 104–107°. Further recrystallisation raised the m.p. to 106–107°, lit.¹⁰ m.p. 107–108°; (c) *ca.* 0.3 g crude product, m.p. 198–218°, recrystallised from benzene to give 2,5-bis(4-methoxyphenyl)thiophene (0.06 g), m.p. 221–222°, lit.¹¹ m.p. 215–216°; (d) 0.07 g of a product, m.p. 174–217°. The infrared spectrum showed a band at 1710 cm⁻¹; the product was not further investigated.

2-Thenoic acid and p-iodotoluene. Reaction time 51 min. CO₂ yield 99 %. Chromatography of the crude reaction product (1.75 g) gave: (a) *p*-iodotoluene (1.01 g), m.p.

31–34°; (b) 0.28 g crude product, m.p. 61–65°, recrystallised from ethanol to give 2(4-methylphenyl)thiophene (0.19 g), m.p. 63–66°, lit.¹² m.p. 63–64°; (c) 0.04 g crude product, m.p. 100–113°, NMR spectrum, UV spectrum (and m.p.) show that the compound is 4,4'-dimethylbiphenyl, lit.¹³ m.p. 121°; (d) 0.10 g product, m.p. 140–165°, recrystallised from ethanol to give 2,5-bis(4-methylphenyl)thiophene (0.04 g), m.p. 173–177°, lit.¹² m.p. 171°.

2-Thenoic acid and p-iodonitrobenzene. Reaction time 53 min. CO₂ yield 100%. Chromatography of the crude reaction product (1.86 g) gave: (a) *p*-iodonitrobenzene (0.54 g), m.p. 168–173°; (b) 0.26 g product, m.p. 132–138°, recrystallised from ethanol to give 2(4-nitrophenyl)thiophene (0.18 g), m.p. 130–132° (after sublimation), lit.¹⁰ m.p. 137–138°; the UV spectrum agrees with that reported¹⁰ (on standing this compound or its solutions became green); (c) 0.21 g of a mixture which seemed to contain two products, m.p. ca. 140° and ca. 160°, which were not further investigated; and (d) 0.5 g of a mixture (m.p. ca. 255°) which on recrystallisation from ethyl acetate gave 2,5-bis(4-nitrophenyl)thiophene (0.08 g), m.p. 249–254°, lit.¹¹ m.p. 253–254°; UV spectrum in agreement with that reported.¹¹

2-Furoic acid and p-iodoanisole. Reaction time 65 min. CO₂ yield 100%. The crude reaction product (1.81 g) contained a crystalline material which was filtered off, (0.04 g) washed with methanol and recrystallised from methanol to give 2,5-bis(4-methoxyphenyl)furan (0.03 g), m.p. 190–193°, lit.¹⁴ m.p. 195–196°. Chromatography of the remaining reaction products gave: (a) *p*-iodoanisole (0.55 g), m.p. 47–49°; (b) 0.70 g of a product, m.p. 48–58°, recrystallised from methanol to give 2(4-methoxyphenyl)furan (0.34 g), m.p. 58–63° (from methanol-water, m.p. 55–58°). (Found: C 75.9; H 5.8. Calc. for C₁₁H₁₀O₂: C 75.8; H 5.8). The ultraviolet spectrum showed a maximum at 283 nm (ϵ 49 000) and shoulders at 280 and 295 nm. The NMR spectrum shows three methoxy protons (δ =3.7), two furan protons (δ =6.3), one furan proton (δ =7.3), and four benzene protons (AB pattern). The 2(4-methoxyphenyl)furan became discoloured on standing.

2-Furoic acid and p-iodotoluene (0.02 mole scale!). Reaction time 54 min. Yield of CO₂ > 85% (losses). Chromatography of the crude reaction product (3.59 g) gave: (a) 1.54 g *p*-iodotoluene, m.p. 30–33°; (b) 2(4-methylphenyl)furan (0.75 g) as an oil, which solidified in the refrigerator, distillation gave 0.44 g, b.p. 57° at 0.1 mm, m.p. ca. 0–2°; (c) 0.06 g of crude 4,4'-dimethylbiphenyl, m.p. 118–121°, lit.¹³ m.p. 121°. (d) 2,5-bis(4-methylphenyl)furan (0.19 g), m.p. 167–168°, lit.¹⁵ m.p. 165–166°.

The 2(4-methylphenyl)furan became red on standing. (Found: C 83.0; H 6.4. Calc. for C₁₁H₁₀O: C 83.5; H 6.4). The NMR spectrum shows three methyl protons (δ =2.03), four benzene protons (AB pattern), and three furan protons (δ =6.05, 6.20, 7.05). The UV spectrum shows two maxima, 217 nm (ϵ =10 700) and 269 nm (ϵ =10 200).

2-Furoic acid and p-iodonitrobenzene. Reaction time 52 min. Yield of CO₂ 90%. Chromatography of the crude reaction product (1.88 g) gave: (a) 0.62 g crude *p*-iodonitrobenzene, m.p. 168–170°; (b) 0.34 g, m.p. 126–130°, recrystallised from cyclohexane gave 2(4-nitrophenyl)furan (0.23 g), m.p. 132–134° (sublimation gave m.p. 134–135°, lit.¹⁰ m.p. 134–135°); (c) 0.09 g, m.p. 133–140°, recrystallised from ethanol, m.p. 140–143°, not further investigated; (d) 0.12 g, m.p. 115–150°, recrystallised from ethanol, m.p. 165–180°; not further investigated; (e) 0.10 g crude product, m.p. ca. 200°; recrystallisation from benzene gave 4,4'-dinitrobiphenyl (0.03 g), m.p. 243° (after transitions at ca. 190° and 220°); (f) 0.11 g, m.p. 235–248°, fractional crystallisation from cyclohexane and ethyl acetate gave small amounts of 4,4'-dinitrobiphenyl and an orange-coloured compound, m.p. 275–277°, after sublimation, which could be 2,5-bis(4-nitrophenyl)furan (396 nm, ϵ 29 000).

2-Thenoic acid and iodobenzene. This reaction in ordinary quinoline gave little, if any, 2-phenylthiophene or 2,5-diphenylthiophene. Reagent grade quinoline (Merck z. Chrom.) was therefore purified by extracting a solution in hydrochloric acid several times with ether. The solution was made alkaline, the quinoline recovered was dried, distilled through a 50 cm Vigreux column at ca. 15 mm, and the middle fraction redistilled from phosphorus pentoxide.

Reaction time 60 min. CO₂ yield 99%. Ca. 0.20 g thiophene (possibly contaminated by benzene) was collected in a cooling trap. The crude reaction product (1.28 g) solidified partly and was crystallised from methanol and from ethanol to give pure 2,5-diphenylthiophene (0.15 g), m.p. 153–155°, lit.¹¹ m.p. 150–151°, UV spectrum also in accord with literature values.¹¹ The material in the mother liquors was distilled to give 0.04 g

iodobenzene and 0.33 g crude product, m.p. 29–33°. Recrystallisation from methanol gave 2-phenylthiophene (0.21 g), m.p. 31–35°, lit.¹⁰ m.p. 37°, identified also by the UV spectrum.¹⁰ Gas chromatograms indicated that the amount of unreacted iodobenzene was somewhat larger than the amount actually isolated. No sure evidence was obtained for the presence of biphenyl.

2-Furoic acid and iodobenzene. This reaction was run in quinoline, purified as described above. Reaction time 60 min. CO₂ yield 99 %. Distillation of the crude product (1.03 g) gave 0.75 g of a mixture (b.p. 100–110°/23 mm) of iodobenzene and 2-phenylfuran.

Chromatography (SiO₂, pentane) of the distillate gave (a) iodobenzene (0.26 g) and (b) 2-phenylfuran (0.21 g) which solidified in the refrigerator, m.p. ca. –3°, b.p. 95°/11 mm, $n_D^{26.8}=1.5939$, lit.¹⁸ $n_D^{20}=1.5920$, b.p.¹⁶ 92–95°/10 mm, UV spectrum in agreement with reported values.¹⁰ The NMR spectrum shows two furan protons ($\delta=6.3$ and 6.5). The third furan proton is hidden in the phenyl multiplet ($\delta=ca. 7.3$).

GLC of the distilled reaction product shows the presence of considerably more 2-phenylfuran than was isolated after chromatography on SiO₂ (0.21 g). The 2-phenylfuran became red on standing overnight.

The material in the distillation residue was treated with active charcoal and recrystallised from methanol to give 2,5-diphenylfuran (ca. 10 mg), m.p. 78–82°, after sublimation 79–85°, lit.¹⁷ m.p. 88°; the UV spectrum agrees with that reported.¹⁸

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