

Copper-promoted Arylation of Pentafluorobenzene

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Pentafluorobiphenyls are formed in 40–70 % yields from pentafluorobenzene and iodobenzene, 2-nitro-, 4-nitro-, 2,6-dimethoxy- or 4-methoxy-iodobenzene, and copper(I) oxide in refluxing pyridine. At 80° 2-iodonitrobenzene gives pentafluoroiodobenzene in addition to the biaryl.

Copper-promoted arylations of electron-rich aromatic systems like 2-arylthiophenes and 2-arylfurans, leading to 2,5-diarylthiophenes and -furans, have been reported.^{1,2} Benzthiazole gives 2-arylbenzthiazoles with iodobenzenes and copper(I) oxide.³ Aromatic compounds with strongly electron-attracting substituents are likewise susceptible to copper-promoted reactions. 1,3,5-Trinitrobenzene and 1,3-dinitrobenzene form nitrobiaryls with iodoarenes and copper(I) oxide in quinoline.^{4–8} The copper-promoted arylation of electron-deficient aromatic systems has now been extended to pentafluorobenzene.

Pentafluorobiphenyls are obtained in 40–70 % yields from pentafluorobenzene, an iodobenzene and copper(I) oxide or silver oxide in refluxing pyridine (reaction 1).



The experimental results of the coupling reactions are summarised in Table 1. Substituents in the iodobenzene significantly affect reaction rates. The reactivity of various substituted iodobenzenes towards pentafluorobenzene and copper(I) oxide in pyridine decreases in the following approximate order: 2-nitro > 4-nitro > none \approx 2,6-dimethoxy > 4-methoxy. Similar orders have been observed for the reactions between iodobenzenes and phenylcopper,⁹ 2-thienylcopper,¹⁰ and phenylethynylcopper.¹¹ However, the corresponding order for iodoarenes towards 1,3-dinitrobenzene in the presence of copper(I) oxide in quinoline is: 2,6-dimethoxy > 4-methoxy > none > 4-nitro. In the latter case 2-iodonitrobenzene gave nitrobenzene and no biphenyl at all.⁵

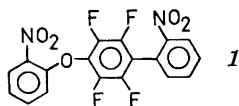
Table 1. Yields of biphenyls from equimolar amounts of pentafluorobenzene, copper(I) oxide, and halogenoarenes in refluxing pyridine.

Halogenoarene	Product	Yield %	Reaction time h
2-Iodonitrobenzene	2,3,4,5,6-Pentafluoro-2'-nitrobiphenyl	69	4
2-Bromonitrobenzene	2,3,4,5,6-Pentafluoro-2'-nitrobiphenyl	10	24
4-Iodonitrobenzene	2,3,4,5,6-Pentafluoro-4'-nitrobiphenyl	37	50
Iodobenzene	2,3,4,5,6-Pentafluoro-biphenyl	57	67
2,6-Dimethoxybenzene	2,3,4,5,6-Pentafluoro-2',6'-dimethoxybiphenyl	52	72
4-Methoxyiodobenzene	2,3,4,5,6-Pentafluoro-4'-methoxybiphenyl	41	168

A nitro substituent in the iodobenzene, especially in the *ortho* position, increases the rate in reaction 1. Similar *ortho* effects are well known from the Ullmann reaction¹² and from copper-catalysed halogen exchange in haloarenes.¹³

Pentafluoriodobenzene (32 %) is formed slowly, together with the unsymmetrical coupling product (24 %), when 2-iodonitrobenzene, pentafluorobenzene, and copper(I) oxide are reacted at 80°. To see whether pentafluoriodobenzene was an intermediate in the unsymmetrical coupling between pentafluorobenzene and 2-iodonitrobenzene in refluxing pyridine, we followed the reaction by gas chromatography – mass spectrometry. Small samples were withdrawn at intervals, hydrolysed and analysed. As no pentafluoriodobenzene was detected, it seems that this compound is formed in a reaction proceeding simultaneously with the coupling reaction at 80°. When pentafluorobenzene was treated with iodine in refluxing pyridine, pentafluoriodobenzene was formed even in the absence of copper(I) oxide, but in a lower yield (25 %).

Dehalogenation of the iodoarene is a side reaction (1,3-dimethoxybenzene 3 %, nitrobenzene 2 % from 2-iodonitrobenzene, 13 % from 4-iodonitrobenzene). The reactions with 2-iodo- and 2-bromonitrobenzene also give 2-nitrophenol (15 and 35 %, respectively). When the reaction time is prolonged in these cases, fluorine substitution occurs. Thus, a small amount of 4-(2-nitrophenoxy)-2,3,5,6-tetrafluoro-2'-nitrobiphenyl (*I*) is formed, probably *via* copper assisted attack of a 2-nitrophenolate anion on pentafluoro-2-nitrobiphenyl. The position of fluorine substitution was determined by fluorine magnetic resonance. The copper-assisted nucleophilic displacement of fluorine has been studied recently.¹⁴



Silver oxide was found to be about as efficient as copper(I) oxide in promoting the reaction between pentafluorobenzene and 4-methoxyiodobenzene. Without copper- or silver oxide, no coupling reactions were observed. Nor did we find coupling products from reactions between pentachlorobenzene and 2-iodonitrobenzene or 4-methoxyiodobenzene in the presence of copper(I) oxide in pyridine or quinoline. Pentafluorobenzene reacts with 2-iodonitrobenzene more than twenty times faster in pyridine than in quinoline at 116°.

Pentafluorophenylcopper is a plausible intermediate in the coupling reactions. Both pentafluorophenylcopper and -silver react with iodoarenes¹⁵⁻¹⁷ in dimethylformamide and tetrahydrofuran. If the formation of pentafluorophenylcopper were rate-determining, the couplings with different iodoarenes should all proceed at the same rate. The different reaction rates for the various halogenoarenes thus suggest that the iodoarene is also involved in the rate-determining step. The order of reactivity observed for iodobenzenes with pentafluorobenzene and copper(I) oxide in pyridine agrees with those found for iodobenzenes and organocopper compounds.⁹⁻¹¹

An alternative reaction path might be the formation of an arylcopper-compound and copper(I) iodide from the iodoarene and copper(I) oxide. The arylcopper so formed would then react with pentafluorobenzene. However, we have not detected any reaction between 2,6-dimethoxyphenylcopper and pentafluorobenzene, even in refluxing pyridine. 2,6-Dimethoxyphenylcopper forms a σ -complex, with 1,3,5-trinitrobenzene which can be oxidised to the corresponding biaryl.⁷

Preliminary experiments show that thiophene may react similarly to pentafluorobenzene. Thiophene, copper(I) oxide, and 2-iodonitrobenzene give in refluxing pyridine 2(2-nitrophenyl)thiophene and 2-iodothiophene (about 10 % of each; GLC-MS evidence).

EXPERIMENTAL

Melting points were determined on a micro hot stage. NMR-spectra were recorded on a Varian A 60 A spectrometer and mass spectra on an LKB 9000 instrument. Pentafluorobenzene (Fluka) was used without purification. Pyridine (A.R.) was dried over sodium hydroxide and distilled from phosphorus pentoxide. 2,6-Dimethoxyphenylcopper was prepared according to Ref. 7. Previously known compounds were identified by spectral methods.

General procedure for the coupling reactions. Pentafluorobenzene (0.01 mol), halogenoarene (0.01 mol), copper(I) oxide (0.01 mol), and pyridine (about 50 ml) were mixed in a reaction vessel and refluxed (116°) under a nitrogen atmosphere. Ether (about 600 ml) was added to the cooled reaction mixture and the copper iodide pyridine complex was filtered off together with unreacted copper(I) oxide. The filtrate was extracted with 2 M hydrochloric acid to remove remaining pyridine, washed with water and dried (MgSO₄). The solution was then concentrated in vacuum and the components were separated by column chromatography or by vacuum distillation.

Coupling with 2-iodonitrobenzene. The reaction was terminated after 4 h, by which time no iodonitrobenzene remained. The products were separated by vacuum distillation. Nitrobenzene (0.02 g, 2 %) and 2-nitrophenol (0.21 g, 15 %) distilled together and were separated by extraction with 2 M sodium hydroxide. The yield of 2,3,4,5,6-pentafluoro-2'-nitrobiphenyl, pale yellow crystals, b. p. 100° 0.5 mmHg, m. p. 81–83° (lit.¹⁸ 84–84.5°), was 2.00 g, 69 %. (Found: C 49.7; H 1.5; F 33.0; N 5.0. Calc. for C₁₂H₄F₅NO₂: C 49.9; H 1.4; F 32.9; N 4.8). IR, NMR, and mass spectra were in accordance with the suggested structure.

In another experiment the temperature was kept at 80° for 120 h. The reaction mixture was worked up in the usual way. Pentafluoroiodobenzene (0.94 g, 32 %) was distilled at about 50 mmHg. The distillation was continued in vacuum and gave a mixture of 2-iodonitrobenzene (0.90 g, 36 %) and pentafluoro-2-nitrobiphenyl (0.70 g, 24 %). The amount of each substance was determined by GLC.

When the reaction time in refluxing pyridine was prolonged to 14 h, the yield of pentafluoro-2-nitrobiphenyl decreased to 23 %. On vacuum distillation a higher boiling fraction was collected, from which 4-(2-nitrophenoxy)-2,3,5,6-tetrafluoro-2'-nitrobiphenyl (*I*) 0.11 g, 5 % (based on 2-iodonitrobenzene) was isolated by fractional sublimation, m.p. 198–199°. (Found: C 53.1; H 2.0; F 18.8; N 6.7. Calc. for C₁₈H₈F₄N₂O₅: C 53.0; H 2.0; F 18.6; N 6.7). Mass spectrum (20 eV): *m/e* 408 (48 %; molecular ion), 286 (95 %) and 122 (100 %). IR: 1530, 1350, 1230, 990 cm⁻¹. The fluorine magnetic resonance spectrum (94 MHz) showed an AA'BB' pattern. One half of the spectrum showed an additional coupling (1.0 Hz) to a proton in the adjacent ring. The spectrum was recorded by Dr Torbjörn Drakenberg, Lund.

Coupling with 2-bromonitrobenzene. After 24 h no bromonitrobenzene remained. The products were separated by distillation and extraction as described for 2-iodonitrobenzene. 2,3,4,5,6-pentafluoro-2'-nitrobiphenyl (0.285 g, 10 %), 2-nitrophenol (0.486 g, 35 %) and nitrobenzene (0.174 g, 14 %) were isolated.

Coupling with 4-iodonitrobenzene. After 50 h no iodonitrobenzene remained. The products were separated by vacuum distillation and fractional sublimation. The yield of 2,3,4,5,6-pentafluoro-4'-nitrobiphenyl was 1.07 g, 37 %, m.p. 90–92° (lit.¹⁸ 92°). (Found: C 50.0; H 1.4; N 5.0. Calc. for C₁₂H₄F₅NO₂: C 49.9; H 1.4; N 4.8). Nitrobenzene (0.162 g, 13 %) was also isolated.

Coupling with iodobenzene. After 67 h no appreciable change occurred in the ratio of biphenyl to iodobenzene. GLC-MS indicated iodobenzene and pentafluorobiphenyl. Separation (vacuum distillation) gave 2,3,4,5,6-pentafluorobiphenyl, 1.39 g, 57 %, m.p. 110–111° (lit.¹⁹ 111–112).

Coupling with 2,6-dimethoxyiodobenzene. The reaction was terminated after 72 h, by which time no pentafluorobenzene remained. Separation (silica gel, light petroleum b.p. 40°, toluene) yielded 2,3,4,5,6-pentafluoro-2',6'-dimethoxybiphenyl, m.p. 84° 1.56 g, 52 %. (Found: C 55.3; H 3.1; F 31.4. Calc. for C₁₄H₆F₅O₂: C 55.3; H 3.0; F 31.2). IR, NMR, and MS were in accordance with the proposed structure. 1,3-Dimethoxybenzene (0.04 g, 3 %) was also obtained and 2,6-dimethoxyiodobenzene (0.71 g, 27 %) was recovered.

Coupling with 4-methoxyiodobenzene. The reaction was terminated after 168 h, when no appreciable increase was noted in the ratio coupling product to iodoarene. A light petroleum (b.p. 40°) solution of the crude reaction mixture was filtered through a short silica gel column and then distilled in vacuum. Separation is also readily achieved by fractional sublimation. The yield of 2,3,4,5,6-pentafluoro-4'-methoxybiphenyl m.p. 123–124°, was 1.15 g, 41 %. IR, NMR, and MS were in accordance with the proposed structure. (Found: C 56.9; H 2.7; F 34.4. Calc. for C₁₃H₇F₅O: C 57.0; H 2.6; F 34.6). 4-Methoxyiodobenzene (40 %) was recovered.

In another experiment, silver oxide replaced copper(I) oxide. Naphthalene was used as internal standard. The yield of pentafluoro-4-methoxybiphenyl (about 55 %) was determined by GLC after 170 h. Metallic silver deposited on the walls of the reaction vessel in addition to the silver iodide pyridine complex.

Pentafluoroiodobenzene. Pentafluorobenzene (2 mmol) and iodine (2 mmol) were refluxed in pyridine for 100 h. Naphthalene was used as internal standard. The yield of pentafluoroiodobenzene (25 %) was determined by GLC and was the same whether copper(I) oxide was present or not.

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