Copper-Mediated Vicarious Substitution of 1,3-Dinitrobenzene with Iodophenols or Iodomethyl Phenyl Sulfoxide/Sulfone

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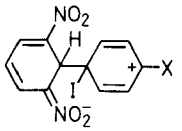
1,3-Dinitrobenzene reacts with 4-iodophenol or 2-iodophenol in the presence of copper(I) *tert*-butoxide and pyridine to give 2′,6′-dinitrobiphenyl-4-ol and 1-nitrodibenzofuran, respectively, in good yield. Similarly, iodomethyl phenyl sulfone or sulfoxide and 1,3-dinitrobenzene are selectively converted into 2,6-dinitrobenzyl phenyl sulfone and sulfoxide, respectively. We believe that the reactions proceed via Meisenheimer intermediates formed from 1,3-dinitrobenzene and the iodophenol, from which a proton and copper(I) iodide are eliminated. The result is a copper-mediated, selective vicarious nucleophilic substitution of hydrogen at C-2 of 1,3-dinitrobenzene.

In this paper, we describe the efficient and regioselective cross-coupling of iodophenols and of iodomethyl phenol sulfone/sulfoxide with 1,3-dinitrobenzene in the presence of copper(I) *tert*-butoxide, a coupling that also has mechanistic implications.

Nitroarenes, in particular 1,3-dinitrobenzene and 1,3,5-trinitrobenzene, are known to couple with iodoarenes in the presence of copper(I) to give unsymmetric nitrobiaryls.[1-3] The mechanism of such copper(I)-promoted couplings has not been well understood.[4] We are presently considering a mechanism involving copper-promoted nucleophilic attack by the iodoarene on the nitroarene to give a zwitterionic "Meisenheimer–Wheland" intermediate (**1**), which eliminates a proton and iodide anion, the latter as copper(I) iodide, to give the observed coupling products.

Our hypothesis is based on an analogy to Mąkosza's vicarious nucleophilic substitution,[5] by which, for example, nitrobenzene, chloromethyl phenyl sulfone, and strong base react to give 2- and 4-nitrobenzyl phenyl sulfones. The formation of *C*-Meisenheimer compounds from 1,3,5-trinitrobenzene and phenols (or amines)[6] and of similar σ-complexes between dinitrobenzofurazan oxide and electron-rich (hetero)arenes or phenols and amines are known.[7,8] In contrast, the formation of hydroxynitrobiphenyls from anions of hindered phenols and halonitrobenzenes proceeds by direct nucleophilic substitution.[9] If our hypothesis were valid the anions of 2- and 4-iodophenols should be expected to couple readily with 1,3-dinitrobenzene or 1,3,5-trinitrobenzene, via intermediate Meisenheimer-iodocyclohexadienone complexes (e.g., **2**). To test the hypothesis, we submitted 4-iodophenol to the reactions with 1,3-dinitrobenzene and with 1,3,5-trinitrobenzene in the presence of copper(I) *tert*-butoxide[10] and potassium *tert*-butoxide in pyridine. The reaction of 4-iodophenol and 1,3-dinitrobenzene with equimolecular amounts of copper(I) *tert*-butoxide and potassium *tert*-butoxide gave 2′,6′-dinitrobiphenyl-4-ol (**3**, 75%). The corresponding reaction with 1,3,5-trinitrobenzene gave the disubstitution product, 2′,4′,6′-trinitro-*m*-terphenyl-4,4″-diol (**4**, 53%), but surprisingly no mono- or trisubstitution products.



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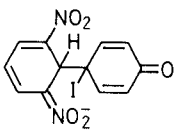

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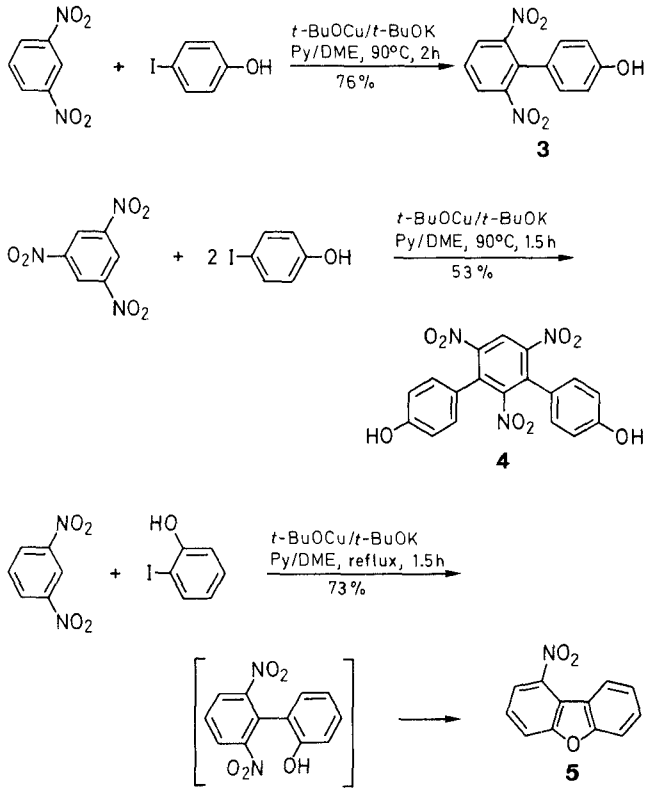
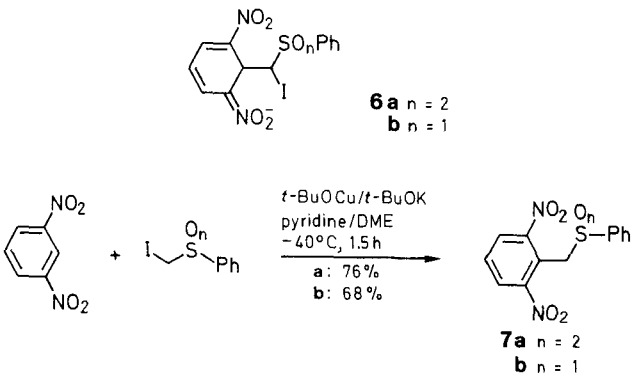
In the coupling of 2-iodophenol with 1,3-dinitrobenzene, the primary product, 2′,6′-dinitrobiphenyl-2-ol, cyclized immediately to afford 1-nitrodibenzofuran (**5**, 73%) in a



one-pot synthesis. This is to be expected since 2',6'-dinitrobiphenyl-2-ol is known to cyclize readily.[3] On the other hand, a preliminary experiment with 2-iodoaniline gave 2-amino-2',6'-dinitrobiphenyl (24%, mp 176–178°C).

Nitrobenzene itself gave no coupling. In the absence of copper there was no reaction between 1,3-dinitrobenzene and iodophenols. Thus, copper is required for the reaction and copper also directs the substitution to the 2-position of 1,3-dinitrobenzene. The directive effect of the copper differs from that of potassium in the ordinary vicarious nucleophilic substitutions with α-chlorosulfones, which couple mainly in the 4-position of 1,3-dinitrobenzene.[11]

Thus, the hypothesis has a predictive value. For further exploration of the reaction we tested the corresponding reactions with iodomethyl phenyl sulfone and with iodomethyl phenyl sulfoxide, in which cases we expected Meisenheimer intermediates of type **6**. The reactions proceeded well at −40°C and gave exclusively 2,6-dinitrobenzyl phenyl sulfone (**7a**) and sulfoxide (**7b**), respectively. Corresponding reactions with iodosulfones without copper are known to give low yields and isomers.[11] There was no coupling of the chloro analogues in the presence of copper *tert*-butoxide.



These examples show a general and regioselective copper-mediated vicarious substitution of 2-H in 1,3-dinitrobenzene with anionic iodo compounds and copper(I); a similar mechanism might be operative in the copper-promoted couplings of nitroarenes with iodoarenes.[1,2]

Details of the mechanism remain to be explored. In analogy with vicarious substitution, we assume the rapid formation of a Meisenheimer compound (**1**), followed by a slower proton elimination and formation of copper(I) iodide. The elimination of copper(I) iodide can be compared with the favored formation of copper iodide and *Z*-silyl enol ethers in the conjugate addition of iodotrimethylsilane-activated monoorganocopper compounds to α,β-unsaturated carbonyl compounds.[12] Copper may also play a role in the initial attack on the nitro compound even though we do not yet know the nature of the copper(I) iodophenoxides or the copper derivatives formed from the iodomethyl sulfone or iodomethyl sulfoxide. The nucleophilic reactivity of copper(I) 4-iodophenoxide in the 4-position[8] may be related to the unusual structure of a lithium phenylthiocuprate which is due to the location of a negative charge in the *para* position.[14] The orientation leading to the 2-substituted derivatives of 1,3-dinitrobenzene could be related to favored chelation of copper in the Meisenheimer compound or to favored elimination from this complex. We conclude that our present reaction belongs to a more general type of copper-mediated nucleophilic aromatic substitutions with marked regioselectivity.

The hypothesis of copper-mediated vicarious nucleophilic aromatic substitution should be considered as an alternative to other possible mechanisms such as oxidative addition/reductive elimination. It may also be considered for the cross-coupling of arylcopper compounds with iodoarenes,[14] in the mechanism of the classical Ullmann synthesis of biaryls,[15,16] and for other copper-promoted reactions, such as decarboxylative coupling.[17] Similar mechanisms can be taken into consideration in cross-couplings using other transition metals.

Melting points were determined under a microscope using a Mettler FP 52 apparatus. Microanalyses were carried out at Analytische Laboratorien, D-5270 Gummersbach, Germany. Mass spectra were measured on a Finnigan 1020 Automated GC/MS with capillary column. IR spectra were recorded on a Perkin-Elmer Model 1600 FT-IR instrument. ^{1}H-NMR spectra were recorded on a Varian XL-400 instrument. We used Merck Kieselgel (230–400 mesh ASTM) for flash chromatographic separation of the products and Merck Kieselgel 60 F for analytical TLC.

Copper(I) chloride was prepared from $CuCl_2$.[10] Commercially available *t*-BuOK was sublimed. 2-Iodophenol (mp 41–43°C; Lit.[18] mp 43°C) was prepared via diazotization of 2-iodoaniline. 4-Iodophenol (mp 91–92°C; Lit.[19] mp 94°C) was prepared via diazotization of 4-aminophenol. Both iodophenols have remarkably foul odors. Iodomethyl phenyl sulfone was prepared from CH_2I_2 and sodium benzenesulfinate.[20] Iodomethyl phenyl sulfoxide was obtained from chloromethyl phenyl sulfoxide and KI in DMSO.[21]

1,2-Dimethoxyethane (DME) was distilled from Na/benzophenone under N_2. Pyridine was distilled from CaH_2 under N_2. Copper(I) *tert*-butoxide is very sensitive to O_2 and was prepared *in situ*.[2] All reactions were carried out under argon in rigorously dried equipment.

2′,6′-Dinitrobiphenyl-4-ol (3):
Copper(I) chloride (500 mg, 5 mmol) is added to *t*-BuOK (651 mg, 5 mmol) in DME (5 mL) and the mixture is stirred for 3 h at r.t. Pyridine (12 mL) and 1,3-dinitrobenzene (698 mg, 4.15 mmol) are then added giving a reddish suspension. A solution of 4-iodophenol (990 mg, 4.5 mmol) and *t*-BuOK (505 mg, 4.5 mmol) in DME (5 mL) is added. The mixture is stirred at 85–90 °C for 2–3 h, then quenched with 1.2 M aq. HCl at r.t., and extracted with CH_2Cl_2 (2 × 50 mL). The extract is washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Product **3** is isolated by column chromatography using CH_2Cl_2 as eluent to give pale yellow crystals; yield: 819 mg (76%); mp 188–189 °C (CH_2Cl_2/cyclohexane).

$C_{12}H_8N_2O_5$	calc.	C 55.39	H 3.10	N 10.77	O 30.74
(260.2)	found	55.53	2.99	10.84	30.54;

MS (70 eV): m/z = 260 (M^+, 64%), 243 (5), 213 (13), 197 (14), 169 (8), 139 (92), 115 (28), 102 (38), 69 (100).

IR (KBr): ν = 3450, 1525, 1350 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS) δ = 4.93 (s, 1H, OH), 7.88 (d, 2H, J = 8 Hz, H-2, H-6), 7.15 (d, 2H, J = 8 Hz, H-3, H-5), 7.63 (t, 1H, J = 8 Hz, H-4′), 7.95 (d, 2H, J = 8 Hz, H-3′, H-5′).

2′,4′,6′-Trinitro-*m*-terphenyl-4,4″-diol (4):
Copper(I) chloride (1100 mg, 11 mmol) is added to *t*-BuOK (1234 mg, 11 mmol) in DME (11 mL). The mixture is stirred at room temperature for 1.5 h, then pyridine (25 mL) and 1,3,5-trinitrobenzene (1066 mg, 5 mmol) are added. A solution of 4-iodophenol (2420 mg, 11 mmol) and *t*-BuOK (1234 mg, 11 mmol) in DME (11 mL) is added to the reddish suspension. The mixture is stirred at 90 °C for 1.5 h and then quenched and worked up as described for compound **3**. Column chromatography (4% MeOH in CH_2Cl_2) gives greenish crystals of compound **4**; yield: 1.038 g (53%); mp 253–255 °C (CH_2Cl_2/cyclohexane).

($C_{18}H_{11}N_3O_8$)	calc.	C 54.42	H 2.79	N 10.58	
(397.3)	found	54.16	2.89	10.40	

MS (70 eV): m/z = 397 (M^+, 40%), 235 (13), 189 (25), 93 (38), 69 (100), 65 (49).

IR (KBr): ν = 3420.6, 1610, 1540, 1346 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 5.10 (s, 2H, OH), 6.90 (d, 4H, J = 8.0 Hz, H-2, H-6, H-2″, H-6″), 7.17 (d, 4H, J = 8.0 Hz, H-3, H-5, H-3″, H-5″), 8.48 (s, 1H, H-5′).

1-Nitrobenzofuran (5):
Copper(I) chloride (275 mg, 2.75 mmol) is added to *t*-BuOK (309 mg, 2.75 mmol) in DME (3 mL). The mixture is stirred at r.t. for 1 h, then pyridine (7 mL) and 1,3-dinitrobenzene (420 mg, 2.50 mmol) are added giving a reddish suspension. A solution of 2-iodophenol (650 mg, 2.75 mmol) and *t*-BuOK (309 mg, 2.75 mmol) in DME (3 mL) is added. The mixture is refluxed for 1.5 h, quenched with 1 M aq. HCl at r.t., and worked up as described for compound **3**. Column chromatography (35% CH_2Cl_2 in cyclohexane) gives compound **5** as pale yellow crystals; yield: 394 mg (73%); mp 121 °C (Lit.[3] mp 119–121 °C).

The mass and IR spectra agree with those reported.[4]

^{1}H-NMR ($CDCl_3$): δ = 8.68 (dm, 1H, J = 8.0 Hz, H-8), 8.23 (dd, 1H, J = 8.0, 0.8 Hz, H-2), 7.91 (dd, 1H, J = 8.0, 0.8 Hz), 7.62 (m, 3H, H-3, H-5, H-6), 7.46 (ddd, 1H, J = 8.0, 6.4, 2.0 Hz, H-7).

The ^{13}C-NMR spectrum and a COSY experiment also verified the structure.

2,6-Dinitrobenzyl Phenyl Sulfone (7a):
Copper(I) chloride (210 mg, 2.1 mmol) is added to a suspension of *t*-BuOK (494 mg, 4.4 mmol) in DME (20 mL) at 0 °C. The mixture is stirred at room temperature for 30 min, then pyridine (0.7 mL) and 1,3-dinitrobenzene (504 mg, 3.0 mmol) are added. The reddish mixture is cooled to −40 °C and a solution of iodomethyl phenyl sulfone (592 mg, 2.1 mmol) in DME (10 mL) is added slowly through a fine cannula over 10 min. The mixture is kept at −40 °C for 1.5 h, then allowed to warm to −20 °C, quenched with 1.2 M aq. HCl (20 mL), and worked up as described for compound **3**. Column chromatography (33% cyclohexane in CH_2Cl_2) gives **7a** as colorless crystals; yield: 514 mg (76%); mp 220 °C (CH_2Cl_2/cyclohexane). (Lit.[11] mp 218–219 °C).

^{1}H-NMR ($CDCl_3$): δ = 5.43 (s, 2H, CH_2SO_2), 7.55 (t, 2H, J = 7.9, 1.1, H-3′, H-5′), 7.72 (m, 4H, H-4, H-2′, H-4′, H-6′), 8.16 (d, 2H, J = 8.6 Hz, H-3, H-5).

^{13}C-NMR ($CDCl_3$/TMS): 51.7, 117.1, 128.6, 129.2, 129.6, 130.5, 131.8, 137.6, 151.2.

2,6-Dinitrobenzyl Phenyl Sulfoxide (7b):
Prepared from iodomethyl phenyl sulfoxide, worked up, and chromatographed as described for **7a** to give **7b** as colorless crystals; yield: 435 mg (68%); mp 133.5 °C (2-propanol).

$C_{13}H_{10}N_2O_5S$	calc.	C 50.98	H 3.29	N 9.15
(306.3)	found	50.74	3.41	9.04

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.86 (d, 1H, J = 13.6 Hz, CH_2SO), 5.12 (d, 1H, J = 13.6 Hz, CH_2SO), 7.34 (d, 2H, J = 8.0 Hz, H-3′, H-5′), 7.44 (t, 2H, J = 7.2 Hz, H-2′, H-6′), 7.52 (m, 1H, H-4′), 7.64 (t, 1H, J = 8.0 Hz, H-4), 8.11 (d, 2H, J = 8.4 Hz, H-3, H-5).

^{13}C-NMR ($CDCl_3$/TMS): δ = 53.0, 120.2, 124.5, 129.3, 130.0, 130.2, 132.6, 142.3, 152.0.

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(1) Björklund, C.; Nilsson, M. *Acta Chem. Scand.* **1968**, *22*, 2338; 2581.
(2) Cornforth, Sir John; Sierakowski, A.F.; Wallace, T.W. *J. Chem. Soc., Chem. Comm.* **1979**, 294; *J. Chem. Soc., Perkin Trans. 1* **1982**, 2299.
(3) Sierakowski, A.F. *Aust. J. Chem.* **1983**, *36*, 1281.
(4) Björklund, C.; Nilsson, M.; Wennerström, O. *Acta Chem. Scand.* **1970**, *24*, 3599.
(5) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.
(6) Terrier, F. *Chem. Rev.* **1981**, *82*, 77.
(7) Hallé, J.-C.; Simmonine, M.-P.; Pouet, M.-J.; Terrier, F. *Tetrahedron Lett.* **1983**, *24*, 2255.
(8) Buncel, E.; Renfrow, R.A.; Strauss, M.J. *J. Org. Chem.* **1987**, *52*, 488.
(9) Stahly, G.P. *J. Org. Chem.* **1985**, *50*, 3091.
(10) Whitesides, G.M.; Sadowski, J.S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829.
(11) Mąkosza, M.; Glinka, T.; Kinowski, A.J. *Tetrahedron* **1984**, *40*, 1863.
(12) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1989**, *45*, 535.
(13) Corazza, F.; Floriani, C.; Zehnder, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1270.
(14) Malmberg, H.; Nilsson, M. *Tetrahedron* **1986**, *42*, 3981.
(15) Fanta, P. *Synthesis* **1974**, 9, and earlier reviews by Fanta.
(16) Ebert, G.W.; Rieke, R.D. *J. Org. Chem.* **1988**, *53*, 4482.
(17) Nilsson, M. *Acta Chem. Scand.* **1966**, *20*, 423.
(18) Whitmore, F.C.; Hanson, E.R. *Org. Synth. Coll. Vol. I* **1932** 319.
(19) Dains, F.B.; Eberly, F. *Org. Synth. Coll. Vol. II* **1943**, 355.
(20) Jończyk, A.; Pytlewski, T. *Synthesis* **1978**, 883.
(21) Hojo, M.; Masuda, R.; Saeki, T.; Uyeda, S. *Synthesis* **1976** 697.