Copper-Catalyzed Reaction of Aryl Iodides with Active Methylene Compounds

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Reaction of aryl halides with carbon nucleophiles such as anions of active methylene compounds promoted by copper species, forming a carbon–carbon bond, is a useful tool for preparation of substituted aromatic compounds.[1] The reaction usually requires a stoichiometric amount of copper(I) salt, unless the halides are activated by an *o*-carboxylate group.[1] On the other hand, we have recently reported that reaction of aryl and vinyl iodides with terminal alkynes efficiently proceeds by using a catalyst system of CuI–PPh_3 in the presence of potassium carbonate as base to give unsymmetrical acetylenes.[2] This observation prompted us to make investigation into the reaction of aryl halides with other carbon nucleophiles. As a result, we found that the above-mentioned reaction with active methylene compounds could catalytically proceed to give the corresponding coupled products in good yield when the reaction was carried out in DMSO (eq 1).[3]

$$\underset{\mathbf{1}}{ArX} + \underset{\mathbf{2}}{CH_2R^1R^2} \qquad (1)$$

1a: Ar=C_6H_5, X=I
b: Ar=4-MeC_6H_4, X=I
c: Ar=4-ClC_6H_4, X=I
d: Ar=1-naphthyl, X=I
e: Ar=2-naphthyl, X=I
f: Ar=C_6H_5, X=Br

2a: R^1=CN, R^2=COOEt
b: R^1=R^2=CN
c: R^1=R^2=COMe

$$\xrightarrow[K_2CO_3/DMSO]{\text{Cat. CuI}} \underset{\mathbf{3}}{ArCHR^1R^2}$$

3a: Ar=C_6H_5, R^1=CN, R^2=COOEt
b: Ar=4-MeC_6H_4, R^1=CN, R^2=COOEt
c: Ar=4-ClC_6H_4, R^1=CN, R^2=COOEt
d: Ar=1-naphthyl, R^1=CN, R^2=COOEt
e: Ar=2-naphthyl, R^1=CN, R^2=COOEt
f: Ar=C_6H_5, R^1=R^2=CN
g: Ar=2-naphthyl, R^1=R^2=CN
h: Ar=C_6H_5, R^1=R^2=COMe

Table I summarizes the results for the reaction of iodobenzene (**1a**) with ethyl cyanoacetate (**2a**) under various conditions. The reaction using CuI (10 mol % based on the halide used) in the presence of K_2CO_3 in DMSO at 120 °C for 20 h gave ethyl cyanophenylacetate in a yield of 85% (78% after isolation). It also proceeded smoothly in the presence of 5 mol % of CuI. Addition of PPh_3 (PPh_3/CuI = 2.0) considerably decreased the product yield. This is in contrast with the coupling reaction with terminal alkynes, where addition of PPh_3 was essential for the reaction to proceed catalytically.[2] The use of tri-*n*-butylamine in place of K_2CO_3 as base inhibited the reaction completely. These results suggest that the present reaction is very susceptible to the compounds having coordinating property, while **2a** may act as the donor ligand.[4] On the other hand, various copper salts could be used for the reaction except CuO. ESR spectrum of the reaction solution using $CuCl_2$ showed only a very weak peak for copper(II) species, suggesting that the catalytically active species may be monovalent, as has been proposed for the stoichiometric reactions.[1a] Anion of **2a** might act as the reductant of Cu(II) to Cu(I).

Table I. Reaction of Iodobenzene (1a) with Ethyl Cyanoacetate (2a)[a]

catalyst	conv of 1a[b] (%)	yield of 3a[b] (%)	catalyst	conv of 1a[b] (%)	yield of 3a[b] (%)
CuI	93	85(78)[c]	CuCl	95	88
CuI[d]	72	67	Cu_2O	87	78
CuI[e]	90	89	$CuCl_2$	87	77
CuI[f]	20	0	$Cu(OAc)_2$	94	89
CuI[g]	72	62	CuO	14	3
CuBr	94	89			

[a] The reaction was carried out in DMSO (5 mL) at 120 °C under N_2. [1a]:[2a]:[cat.]:[K_2CO_3] = 2:4:0.2:8 (in mmol). [b] Determined by GLC. [c] Isolated yield [d] Reaction in DMF. [e] [CuI] = 0.1. [f] N-(*n*-Bu)$_3$ in place of K_2CO_3 was used. [N-(*n*-Bu)$_3$] = 8.0. [g] PPh_3 was added. [PPh_3] = 0.4.

Table II. Reaction of Aryl Halides 1 with Active Methylene Compounds 2[a]

1	2	time (h)	product(s), % yield	1	2	time (h)	product(s), % yield
1b	**2a**	20	**3b**, 75	**1f**	**2a**	40	**3a**, 16[c]
1c	**2a**	18	**3c**, 81	**1a**	**2b**	16	**3f**, 55
1d	**2a**	9	**3d**, 47; **4**, 27	**1e**	**2b**	20	**3g**, 73
1e	**2a**	4	**3e**, 70	**1a**	**2c**	4	**3h**, 65[c]; **5**,[d] 11[c]

[a] The reaction was carried out in DMSO (5 mL) at 120 °C under N_2. [1]:[2]:[CuI]:[K_2CO_3] = 2:4:0.2:8. [b] Isolated yield based on 1 charged. [c] GLC yield. [d] Benzyl methyl ketone.

The results of the reaction of a number of aryl iodides **1a–f** with active methylene compounds **2a–c** using CuI are recorded in Table II. The reactions of 4-substituted iodobenzenes **1b,c** and 2-iodonaphthalene (**1e**) with **2a** gave the expected products in good yields (70–81%). In the case of 1-iodonaphthalene (**1d**), a mixture of ethyl cyano(1-naphthyl)acetate (**3d**) (47%) and 1-naphthylacetonitrile (**4**) (27%) was obtained. Malononitrile (**2b**) and acetylacetone (**2c**) could be used in place of **2a**.

The present reaction may be extended to the synthesis of α-arylpropionic acids known as antiinflammatory agents: Addition of iodomethane to the reaction mixture of 2-iodo-6-methoxynaphthalene (**1g**) with ethyl cyanoacetate (**2a**) gave ethyl α-cyano-α-(6-methoxy-2-naphthyl)-propionate (**6**) in 78% which may be hydrolyzed to *naproxen* according to the published procedure (eq 2).[5]

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(2) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.

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(4) ^1H NMR spectrum of **2a** after treatment of it with K_2CO_3 in DMSO-d_6 at 120 °C for 60 min indicated that **2a** was completely transformed to the corresponding anion under the reaction conditions.

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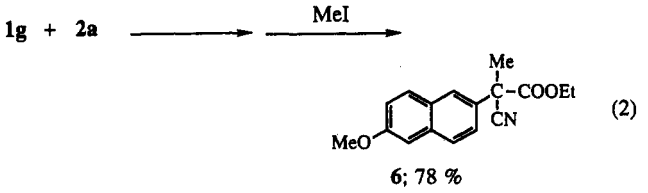
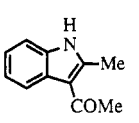


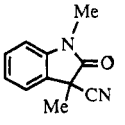
(2)

6; 78 %

It is also worth noting that the reaction of 2-iodoaniline (**1h**) with **2c** could proceed in the presence of 5 mol % of CuI to afford 3-acetyl-2-methylindole (**7**) in 76% yield.[6] Reaction of **1a** with **2a** followed by treatment with iodomethane gave compound **8** (63 %).



7



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Experimental Section

^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for $CDCl_3$ solutions. MS data were obtained by EI. 1- and 2-iodonaphthalenes (**1d,e**)[7] and 2-iodo-6-methoxynaphthalene (**1g**)[7,8] were prepared according to the published procedures. Other halides and active methylene compounds were commercially available. Solvents were purified by standard methods before use. The following experimental details may be regarded as typical in methodology and scale. The purity of each product isolated was judged to be >95% by GC.

Reaction of Iodobenzene (1a) with Ethyl Cyanoacetate (2a). A mixture of **1a** (408 mg, 2.0 mmol), **2a** (452 mg, 4.0 mmol), potassium carbonate (1.1 g, 8 mmol), and CuI (38 mg, 0.2 mmol) in DMSO (5 mL) was stirred at 120 °C for 20 h under nitrogen. The resulting mixture was poured into dilute hydrochloride acid, extracted with ether, and dried over sodium sulfate. Ethyl cyanophenylacetate (**3a**) (294 mg, 78%) was isolated by column chromatography on silica gel using hexane–methylene chloride (5:1, v/v) as eluent:[3b] oil; ^1H NMR δ 1.28 (t, 3 H, J = 7.3 Hz), 4.25 (q, 2 H, J = 7.3 Hz), 4.71 (s, 1 H), 7.40–7.48 (m, 5 H); MS m/z 189 (M^+).

Ethyl cyano(4-methylphenyl)acetate (3b):[3b] oil; ^1H NMR δ 1.28 (t, 3 H, J = 7.3 Hz), 2.36 (s, 3 H), 4.24 (q, 2 H, J = 7.3 Hz), 4.67 (s, 1 H), 7.21–7.35 (m, 4 H); MS m/z 203 (M^+).

Ethyl cyano(4-chlorophenyl)acetate (3c):[3b] oil; ^1H NMR δ 1.29 (t, 3 H, J = 7.3 Hz), 4.25 (q, 2 H, J = 7.3 Hz), 4.69 (s, 1 H), 7.41 (s, 4 H); MS m/z 223 (M^+).

Ethyl cyano(1-naphthyl)acetate (3d):[3b] oil; ^1H NMR δ 1.25 (t, 3 H, J = 7.3 Hz), 4.25 (q, 2 H, J = 7.3 Hz), 5.37 (s, 1 H), 7.50–7.64 (m, 3 H), 7.72 (d, 1 H, J = 2.9 Hz), 7.92 (d, 2 H, J = 8.3 Hz), 8.01 (d, 1 H, J = 8.3 Hz); MS m/z 239 (M^+).

Ethyl cyano(2-naphthyl)acetate (3e):[3b] oil; ^1H NMR δ 1.28 (t, 3 H, J = 7.3 Hz), 4.26 (q, 2 H, J = 7.3 Hz), 4.88 (s, 1 H), 7.52–7.56 (m, 3 H), 7.77–7.91 (m, 3 H), 7.96 (s, 1 H); MS m/z 239 (M^+).

Phenylmalononitrile (3f): mp 66–68 °C (from hexane–methylene chloride) (lit.[9] mp 67–68 °C); ^1H NMR δ 5.07 (s, 1 H), 7.49–7.52 (m, 5 H); MS m/z 142 (M^+).

2-Naphthylmalononitrile (3g): mp 124–125 °C (from hexane–methylene chloride) (lit.[10] mp 123–124 °C); ^1H NMR δ 5.23 (s, 1 H), 7.51–7.54 (m, 1 H), 7.59–7.62 (m, 2 H), 7.88–7.91 (m, 2 H), 7.97–8.01 (m, 2 H); MS m/z 192 (M^+).

3-Phenylpentane-2,4-dione (3h):[11] oil; ^1H NMR δ 1.89 (s, 6 H), 7.16–7.18 (m, 2 H), 7.33–7.40 (m, 3 H), 16.66 (s, 1 H); MS m/z 176 (M^+).

1-Naphthylacetonitrile (4):[12] oil; ^1H NMR δ 4.14 (s, 2 H), 7.46–7.61 (m, 3 H); MS m/z 167 (M^+).

Preparation of 6. Reaction of 2-iodo-6-methoxynaphthalene (**1g**) (284 mg, 1 mmol) with **2a** (226 mg, 2 mmol) was carried out for 20 h under the typical reaction conditions described above. Then, the resulting mixture was treated with iodomethane (284 mg, 2 mmol) at rt for 4 h after which it was poured into dilute hydrochloric acid, extracted with ether, and dried over sodium sulfate. Product **6** (219 mg, 78%) was isolated by column chromatography on silica gel using hexane–methylene chloride (4:1, v/v) as eluant:[5] oil; ^1H NMR δ 1.25 (t, 3 H, J = 7.3 Hz), 2.03 (s, 3 H), 3.93 (s, 3 H), 4.24 (q, 2 H, J = 7.3 Hz), 7.13–7.21 (m, 2 H), 7.52–7.55 (m, 1 H), 7.76–7.78 (m, 2 H), 7.93–7.94 (m, 1 H); MS m/z 283 (M^+).

3-Acetyl-2-methylindole (7): mp 197–199 °C (from hexane–benzene) (lit.[6] 195 °C); ^1H NMR δ 1.45 (t, 3 H, J = 7.3 Hz), 2.73 (s, 3 H), 4.40 (q, 2 H, J = 7.3 Hz), 7.16–7.25 (m, 2 H), 7.28–7.30 (m, 1 H), 8.10–8.20 (m, 1 H), 8.48 (br, s, 1H); MS m/z 173 (M^+).

3-Cyano-1,3-dimethylindol-2-one (8): mp 75–76 °C (from hexane–benzene); ^1H NMR δ 1.82 (s, 3 H), 3.26 (s, 3 H), 6.90 (d, 1 H, J = 7.8 Hz), 7.16 (d, 1 H, J = 7.8 Hz), 7.39–7.44 (m, 2 H); ^{13}C NMR δ 23.36, 26.97, 42.09, 109.14, 117.62, 123.74, 123.84, 126.82, 130.31, 142.54, 170.96; MS m/z 186 (M^+). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.94; H, 5.42; N, 15.05. Found: C, 71.09; H, 5.44; N, 15.08.

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