Copper-Promoted Reaction of Aryl Iodides with Activated Methine Compounds

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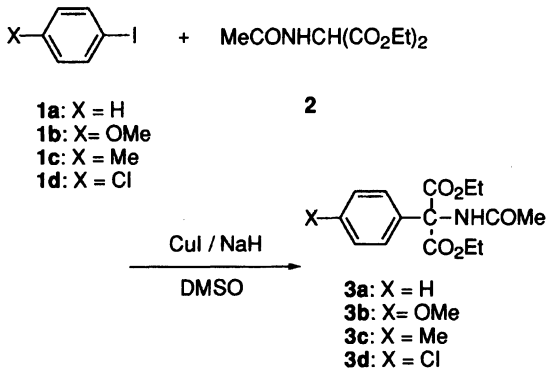
The reaction of aryl iodides with an activated methine compound, diethyl acetamidomalonate, can efficiently proceed in the presence of CuI and NaH in DMSO to give diethyl acetamido(aryl)malonates, which may be useful precursors for α-arylglycines, in good yields. Although the reaction with another methine substrate, ethyl 2-cyanopropionate, also affords the expected coupling products, no substitution products are obtained in the case of diethyl methylmalonate, arenes together with an oxidative coupling compound of the ester being formed.

The 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 preparing substituted aromatic compounds.[1—5] We have recently reported that the reaction of aryl iodides with some active methylene compounds can efficiently proceed in the presence of copper(I) iodide in DMSO using K_2CO_3 as base, and have also demonstrated that methylation of the coupling products, which are obtained using ethyl cyanoacetate, with methyl iodide, followed by hydrolysis can afford 2-arylpropionic acids which are known to be antiinflammatory agents.[6]

α-Arylglycines are of importance as the structural components of a number of β-lactam antibiotics. Thus, new, effective synthetic methods for producing them are of considerable interest.[7] We have considered that the copper-promoted substitution reaction mentioned above could be employed for their synthesis. Consequently, the reaction of aryl iodides with diethyl acetamidomalonate was examined in the present work. While the reaction of active halides such as benzyl chlorides and bromides with acetamidomalonate esters is well known,[8] that of aryl halides, to our knowledge, has not so far been reported. Moreover, reactions using ethyl 2-cyanopropionate and diethyl methylmalonate as well as diethyl acetamidomalonate were also carried out in order to investigate the reactivities of these tertiary substrates in copper(I)-mediated substitution. These results are described herein.

Results and Discussion

Reaction of Iodobenzene (1a) with Diethyl Acetamidomalonate (2). When the reaction of **1a** (1 mmol) with **2** (2 mmol) using NaH (2 mmol) was carried out in the presence of CuI (0.5 mmol) in DMSO at 80 °C for 24 h under nitrogen, diethyl acetamido(phenyl)malonate (**3a**) was produced in 21% yield based on the amount of **1a** used, the conversion of **1a** being 42% (Scheme 1 (X = H) and Entry 1 in Table 1).



Scheme 1.

Table 1. Reaction of Aryl Iodides (**1a—d**) with Diethyl Acetamidomalonate (**2**)[a]

Entry	Iodide	[1] : [2] : [NaH] : [CuI][b]	Conv. of **1**/%[c]	Yield of **3** (%)[c]
1	**1a**	1 : 2 : 2 : 0.5	42	**3a** (21)
2	**1a**	1 : 2 : 1 : 0.5	39	**3a** (29)
3	**1a**	1 : 3 : 2 : 0.5	71	**3a** (52)
4	**1a**	1 : 3 : 1 : 0.5	79	**3a** (60)
5	**1a**	1 : 4 : 4 : 0.5	63	**3a** (34)
6	**1a**	1 : 4 : 2 : 0.5	78	**3a** (69)
7	**1a**	1 : 4 : 2 : 0.2	70	**3a** (58)
8	**1a**	1 : 4 : 2 : 2	82	**3a** (71)
9	**1a**	1 : 4 : 2 : 4	100	**3a** (98)
10[d]	**1a**	1 : 4 : 2 : 0.5	83	**3a** (50)
11	**1b**	1 : 4 : 2 : 0.5	98	**3b** (96)
12	**1c**	1 : 4 : 2 : 0.5	81	**3c** (73)
13	**1d**	1 : 4 : 2 : 0.5	29	**3d** (21)

a) The reaction was carried out in DMSO at 80 °C under nitrogen for 24 h. b) In mmol. c) Determined by GLC analysis. d) Reaction at 100 °C.

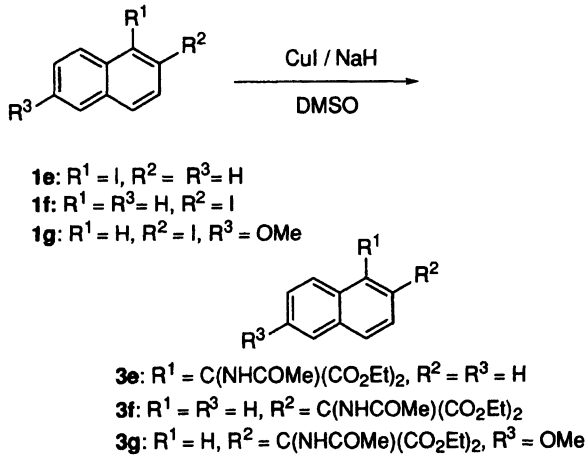
Although an increase in the amount of each of **2** and NaH to 4 mmol increased the conversion of **1a** to some extent, the yield of **3** was still low (Entry 5). It was of interest that reducing

the amount of NaH relative to **2** considerably increased both the conversion of **1a** and the yield of **3a** (Entries 4 and 6 vs. Entries 3 and 5). Thus, **3a** was obtained in a yield of 69% by using **2**, NaH, and CuI in a ratio of 4 : 2 : 0.5 (in mmol) (Entry 6). While the reaction proceeded in the presence of a catalytic amount of CuI (Entry 7), an excess amount of the promoter was needed to obtain the complete disappearance of **1a** (Entries 7, 8, and 9); with 4 mmol of CuI, **3a** was obtained in an almost quantitative yield. At a higher temperature of 100 °C, the product yield was considerably low, because of the decomposition of a part of **3a**, once formed (Entry 10).

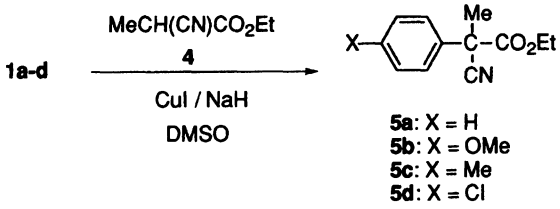
The results for the reactions of 4-substituted iodobenzenes **1b**, **1c**, and **1d** (1 mmol) with **2** (4 mmol) using NaH (2 mmol) and CuI (0.5 mmol) are also recorded in Table 1 (Entries 11, 12, and 13). It was of interest that the reactivity order of **1a—d**, judged from the conversions, followed the sequence **1b**>**1c**>**1a**>**1d**, indicating that electron-donating substituents enhance the reaction. This is in marked contrast to the fact that copper-promoted nucleophilic substitution reactions of aryl halides are usually accelerated by electron-withdrawing substituents.[1)]

Table 2 summarizes the results for the reactions of **1a—d**, 1- and 2-iodonaphthalenes (**1e**) and (**1f**), and 2-iodo-6-methoxynaphthalene (**1g**) with **2** in a larger scale ([**1**] : [**2**] : [NaH] : [CuI] = 3 : 12 : 6 : 12, in mmol) (Schemes 1 and 2). Irrespective of the substrates, the corresponding coupled products **3a—g** could be isolated in good yields. The hydrolysis of acetamidomalonates to amino acids has been well documented,[8)] and, therefore, the present reaction may be useful as a route to α-arylglycines. From Table 2, the unusual substituent electronic effect may also be confirmed; the reaction of **1b** (X = OMe) was completed within a considerably shorter period compared with that of **1d** (X = Cl). Subsequently, the reactions of **1a—d** with two other activated methine compounds were examined for a comparison.

Reaction with Ethyl 2-Cyanopropionate (4). When the reaction of **1a** (1 mmol) with **4** (4 mmol) using NaH (2 mmol) and CuI (0.5 mmol) was performed in DMSO at 80 °C for 24 h under nitrogen, ethyl 2-cyano-2-phenylpropionate (**5a**) was produced in 23% yield (Scheme 3 and Entry 1 in Table 3). Although an increase in the amount of CuI to 1.3 mmol improved the product yield up to 55% (Entry 3), any further addition of the promoter detrimentally reduced both the conversion of **1a** and the yield of **5a** (Entries 4 and 5).[9)] The use of 4 mmol of NaH in the presence of 1.3 mmol of CuI reduced the product yield, as did the reaction with **2** (Entry 6). A substituent electronic effect on the reaction was observed to a small, but meaningful, extent; the reactivity order of **1a—d**, judged from the conversions, followed the sequence **1d**>**1a**>**1c**>**1b** (Entries 3, 7—9, and 10—13). Although this order is reverse to that observed in the reaction with **2**, it is consistent with that in various copper-promoted



Scheme 2.



Scheme 3.

Table 2. Preparation of Diethyl Acetamido(aryl)malonates (**3a—g**)[a)]

Iodide	Time/h	Yield of **3** (%)[b)]
1a	22	**3a** (95)
1b	6	**3b** (90)
1c	21	**3c** (89)
1d	24	**3d** (95)
1e	5	**3e** (84)
1f	4	**3f** (89)
1g	2	**3g** (88)

a) The reaction was carried out in DMSO at 80 °C under nitrogen. [**1**] : [**2**] : [NaH] : [CuI] = 3 : 12 : 6 : 12 (in mmol). b) Isolated yield.

Table 3. Reaction of **1a—d** with Ethyl 2-Cyanopropionate (**4**)[a)]

Entry	Iodide	CuI / mmol	Time / h	Conv. of **1**/%[b)]	Yield of **5** (%)[b)]
1	**1a**	0.5	24	43	**5a** (23)
2	**1a**	1.0	24	68	**5a** (53)
3	**1a**	1.3	24	69	**5a** (55)
4	**1a**	2.0	24	65	**5a** (48)
5	**1a**	4.0	24	55	**5a** (41)
6[c)]	**1a**	1.3	24	71	**5a** (35)
7	**1b**	1.3	24	58	**5b** (51)
8	**1c**	1.3	24	67	**5c** (51)
9	**1d**	1.3	24	75	**5d** (59)
10	**1a**	1.3	4	33	**5a** (25)
11	**1b**	1.3	4	21	**5b** (23)
12	**1c**	1.3	4	30	**5c** (32)
13	**1d**	1.3	4	40	**5d** (32)
14[d)]	**1d**	1.3	4	37	**5d** (25)

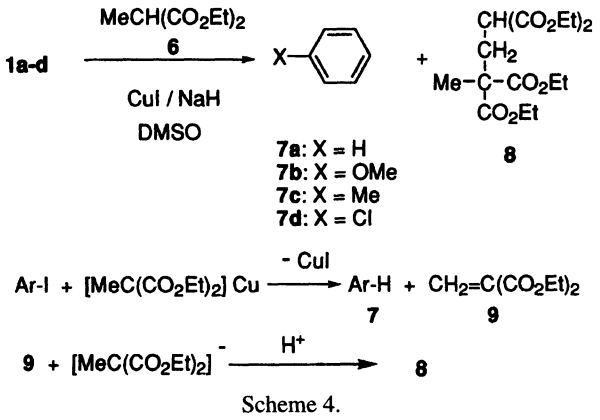
a) The reaction was carried out in DMSO at 80 °C under nitrogen. [**1**] : [**4**] : [NaH] = 1 : 4 : 2 (in mmol). b) Determined by GLC analysis. c) [**1**] : [**4**] : [NaH] = 1 : 4 : 4 (in mmol). d) In the presence of *m*-dinitrobenzene (0.6 mmol).

nucleophilic substitution reactions.[1)]

The reactions of **1b** and **1d** with ethyl acetamido(cyano)-acetate were also carried out for a comparison. Although the iodides were consumed to some extent, the product mixtures were intractable.

Reaction with Diethyl Methylmalonate (6). The reaction of **1a—d** (3 mmol) with **6** (12 mmol) was conducted using NaH (6 mmol) and CuI (4 mmol), as for those with **2** and **4** (Scheme 4 and Table 4). It was somewhat surprising that (a) benzenes **7a—d** together with an oxidative coupling compound **8** of the methine substrate were formed as the characterizable products, no substitution products being detected, and (b) the reactivity order of **1a—d** was found to be **1d>1b>1a>1c**, suggesting that both the electron-withdrawing and donating substituents may enhance the reaction. These observations are apparently different from those using **2** and **4**.

Reaction Scheme. The most plausible common key intermediates, which attack aryl iodide **1**, may be copper salts of **2**, **4**, and **6** generated in situ.[1)] The salts possibly exist as certain clusters. They are, however, described as CuNu (Nu^- = anion of **2**, **4**, or **6**) for simplicity (Scheme 5). There may exist three possible paths of the reaction of **1** with CuNu at the initial stage:[1)] (a) attack of the nucleophile attached to copper on the *ipso*-position of **1**, (b) single-electron transfer

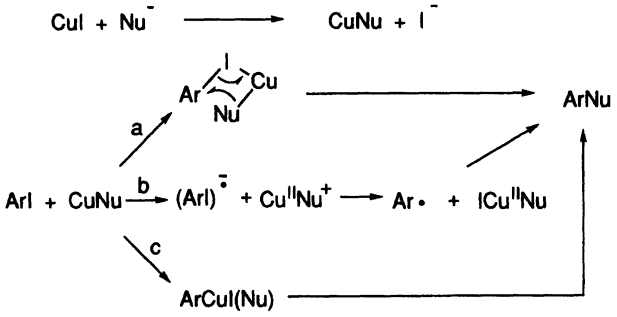


Scheme 4.

Table 4. Reaction of **1a—d** with Diethyl Methylmalonate (**6**)[a)]

Iodide	Time	Conv.	Products	
	h	of **1**/%[b)]	**7** (%)[b)]	**8**/%[b)]
1a	4	12	**7a** (—[c)])	4
1b	4	18	**7b** (11)	11
1c	4	4	**7c** (—[c)])	3
1d	4	35	**7d** (26)	23
1d[d)]	4	36	**7d** (27)	17
1a	24	26	**7a** (—[c)])	12
1b	24	35	**7b** (25)	26
1c	24	17	**7c** (—[c)])	10
1d	24	57	**7d** (43)	52

a) The reaction was carried out in DMSO at 80 °C under nitrogen. [**1**]:[**6**]:[NaH]:[CuI] = 3:12:6:4 (in mmol). b) Determined by GLC analysis. c) Not determined. d) In the presence of *m*-dinitrobenzene (0.9 mmol).



Scheme 5.

of CuNu to aryl iodide, and (c) oxidative addition of **1** to CuNu. Each path would lead to ArNu.

In the reaction with **2**, paths b and c do not seem to participate, since the observed substituent electronic effect, which enhances the reaction by electron-donating substituents, is not consistent with them. Thus, the reaction might proceed by path a, where it is rather S_N1-like. The fact that the use of a smaller amount of NaH relative to **2** gave favorable results seems to be in harmony with this mechanism; a relatively lower concentration of anion of **2** may afford less anionic cluster species. Although isolation and characterization of copper–**2** complex were undertaken, success has not yet been realized.

It was confirmed that the conversion of **1d** in the reaction with **4** was not affected by the addition of *m*-dinitrobenzene (Table 3), suggesting that path b is less possible.[10—13)] Although path c for the reaction with **4** to give **5** can not be ruled out, it appears to also be less probable, since the observed substituent electronic effect is considerably small to rationalize it.[14)] Therefore, it may be reasonable to consider that the reaction mainly takes place by path a, and that the transition state is rather S_N2-like. The different substituent effects between the reactions with **2** and **4** may be due to their nucleophilicities; the unusual effect in the case of **2** may be attributed to the three electron-withdrawing groups in **2**, which make it less nucleophilic.

The results concerning the reaction with **6** appear to be less common. It was confirmed that the addition of *m*-dinitrobenzene did not retard the reaction of **1d** with **6** (Table 4). One of the possible paths leading to **7** and **8** may involve the formation of labile diethyl methylenemalonate (**9**) together with **7** and the successive reaction of **9** with another anion of **6** (Scheme 4). However, the mode of the initial reaction is not definitive at the present stage.

In conclusion, it has been observed that the copper(I)-promoted reaction of aryl iodides with activated methine compounds is markedly affected by the identity of the latter substrates. Fortunately, diethyl acetamidomalonate can efficiently react with aryl iodides, providing a useful route to α-arylglycines.

Experimental

^{1}H NMR spectra were obtained with a JEOL JNM-GSX-400 spectrometer for $CDCl_3$ solutions. GLC-MS data were obtained with a Shimadzu QP-2000A spectrometer. GLC analysis was car-

ried out using a Shimadzu GC 8A gas chromatograph equipped with a Silicone OV-17 glass column (ϕ2.6 mm×1.5 m). Aryl iodides **1e—g** were prepared by the methods reported previously.[15] Other starting materials were commercially available. The experimental details given below may be regarded as typical in methodology and scale.

Reaction of Iodobenzene (1a) with Diethyl Acetamidomalonate (2). In a 100 cm^3 two-necked flask was placed NaH dispersed in mineral oil (144 mg, 6 mmol), which was then washed with pentane under nitrogen, after which **2** (2.60 g, 12 mmol) and DMSO (10 cm^3) were added; the mixture was stirred at room temperature until it became homogeneous. Then, **1a** (612 mg, 3 mmol), CuI (2.29g, 12 mmol), and DMSO (8 cm^3) were added and the resulting mixture was stirred at 80 °C for 22 h. It was poured into aqueous potassium hydroxide and extracted with dichloromethane. Product **3a** (835 mg, 95%) was isolated by column chromatography on silica gel using hexane–ethyl acetate (3 : 1, v/v) as eluent.

Diethyl Acetamido(phenyl)malonate (3a): Mp 66—68 °C (lit,[16] 75 °C); MS *m/z* 293 (M^+); ^{1}H NMR δ = 1.27 (6H, t, J = 7.3 Hz), 2.15 (3H, s), 4.23—4.49 (4H, m), 7.15 (1H, s), 7.30—7.38 (3H, m), 7.52—7.62 (2H, m).

Diethyl Acetamido(4-methoxyphenyl)malonate (3b): Mp 67—69 °C; MS *m/z* 323 (M^+); ^{1}H NMR δ = 1.27 (6H, t, J = 7.3 Hz), 2.14 (3H, s), 3.79 (3H, s), 4.24—4.32 (4H, m), 6.86—6.89 (2H, m), 7.13 (1H, s), 7.50—7.53 (2H, m). Found: C, 59.80; H, 6.81; N, 4.13%. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33%.

Diethyl Acetamido(4-methylphenyl)malonate (3c): Mp 86—88 °C ; MS *m/z* 307 (M^+); ^{1}H NMR δ = 1.27 (6H, t, J = 7.3 Hz), 2.14 (3H, s), 2.33 (3H, s), 4.22—4.34 (4H, m), 7.12 (1H, s), 7.15—7.17 (2H, m), 7.45—7.48 (2H, m). Found: C, 62.57; H, 6.92; N, 4.51%. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56%.

Diethyl Acetamido(4-chlorophenyl)malonate (3d): Mp 92—94 °C; MS *m/z* 327, 329 (M^+); ^{1}H NMR δ = 1.27 (6H, t, J = 7.3 Hz), 2.15 (3H, s), 4.24—4.33 (4H, m), 7.16 (1H, s), 7.30—7.36 (2H, m), 7.53—7.56 (2H, m). Found: C, 55.17; H, 5.78; N, 4.14; Cl, 10.47%. Calcd for $C_{15}H_{18}ClNO_5$: C, 54.97; H, 5.54; N, 4.27; Cl, 10.82%.

Diethyl Acetamido(1-naphthyl)malonate (3e): Mp 151—153 °C; MS *m/z* 343 (M^+); ^{1}H NMR δ = 1.20 (6H, t, J = 7.3 Hz), 2.04 (3H, s), 4.23—4.38 (4H, m), 6.62 (1H, s), 7.26—7.62 (4H, m), 7.79—7.85 (3H, m). Found: C, 66.44; H, 6.22; N, 3.98%. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08%.

Diethyl Acetamido(2-naphthyl)malonate (3f): Mp 114—116 °C; MS *m/z* 343 (M^+); ^{1}H NMR δ = 1.29 (6H, t, J = 7.3 Hz), 2.19 (3H, s), 4.24—4.37 (4H, m), 7.25 (1H, d, J = 4.9 Hz), 7.44—7.50 (2H, m), 7.58—7.84 (4H, m), 8.00 (1H, d, J = 1.5Hz). Found: C, 66.52; H, 6.20; N, 4.08%. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08%.

Diethyl Acetamido-(6-methoxy-2-naphthyl)malonate (3g): Mp 130—132 °C; MS *m/z* 373 (M^+); ^{1}H NMR δ = 1.29 (6H, t, J = 7.3 Hz), 2.19 (3H, s), 3.91 (3H, s), 4.27—4.35 (4H, m), 7.10—7.36 (3H, m), 7.71—7.73 (3H, m), 7.92 (1H, s). Found: C, 64.45; H, 6.27; N, 3.73%. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75%.

Ethyl 2-Cyano-2-phenylpropionate (5a): Oil; MS *m/z* 159 (M−44); ^{1}H NMR δ = 1.25 (3H, t, J = 7.3 Hz), 1.96 (3H, s), 4.18—4.30 (2H, m), 7.35—7.44 (3H, m), 7.52—7.54 (2H, m). Found: C, 70.61; H, 6.49; N, 6.88%. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89%.

Ethyl 2-Cyano-2-(4-methoxyphenyl)propionate (5b):[17] Oil; MS *m/z* 233 (M^+); ^{1}H NMR δ = 1.25 (3H, t, J = 7.3 Hz), 1.93 (3H, s), 3.82 (3H, s), 4.20—4.25 (2H, m), 6.90—6.93 (2H, m), 7.42—7.45 (2H, m).

Ethyl 2-Cyano-2-(4-methylphenyl)propionate (5c):[17] Oil; MS *m/z* 217 (M^+); ^{1}H NMR δ = 1.25 (3H, t, J = 7.3 Hz), 1.93 (3H, s), 2.36 (3H, s), 4.18—4.27 (2H, m), 7.09—7.21 (2H, m), 7.39—7.41 (2H, m).

Ethyl 2-Cyano-2-(4-chlorophenyl)propionate (5d): Oil; MS *m/z* 237, 239 (M^+); ^{1}H NMR δ = 1.26 (3H, t, J = 7.3 Hz), 1.94 (3H, s), 4.23—4.26 (2H, m), 7.37—7.40 (2H, m), 7.46—7.49 (2H, m). Found: C, 60.81; H, 5.12; N, 5.95; Cl, 14.97%. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89; Cl, 14.92%.

Tetraethyl 1,1,3,3-Butanetetracarboxylate (8):[18] Oil; MS *m/z* 301 (M−OEt); ^{1}H NMR δ = 1.22—1.28 (12H, m), 1.41 (3H, s), 2.55 (2H, d, J = 6.0 Hz), 3.52 (1H, t, J = 6.0 Hz), 4.12—4.22 (8H, m).

References

1) J. Lindley, *Tetrahedron*, **40**, 1433 (1984), and references cited therein.

2) J. Setsune, K. Matsukawa, H. Wakemoto, and T. Kitao, *Chem. Lett.*, **1981**, 367.

3) H. Suzuki, T. Kobayashi, Y. Yoshida, and A. Osuka, *Chem. Lett.*, **1983**, 193.

4) H. Suzuki, T. Kobayashi, and A. Osuka, *Chem. Lett.*, **1983**, 589.

5) H. Suzuki, Q. Yi, J. Inoue, K. Kusume, and T. Ogawa, *Chem. Lett.*, **1987**, 887.

6) K. Okuro, M. Furuune, M. Miura, and M. Nomura, *J. Org. Chem.*, **58**, 7606 (1993).

7) M. J. O'Donnell and W. D. Bennett, *Tetrahedron*, **44**, 5389 (1988).

8) J. H. Jones, in "Comprehensive Organic Chemistry," ed by I. O. Sutherland, Pergamon Press, Oxford (1979), Vol. 2, p. 815.

9) Hydrolysis of **5** may afford 2-arylpropionic acids. However, two-step route to **5** including treatment of **1** with ethyl cyanoacetate followed by methylation seems to be synthetically favorable.[6]

10) R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, **87**, 4520 (1965).

11) J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978).

12) X. M. Zhang, D. L. Yang, and Y. C. Liu, *J. Org. Chem.*, **58**, 224 (1993).

13) *p*-Dinitrobenzene was found to directly react with **4** in the presence of NaH without CuI to give ethyl 2-cyano-2-(4-nitrophenyl)propionate, whereas the *m*-isomer did not. Such a nucleophilic substitution of *p*-dinitrobenzene was previously reported: N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, **41**, 1560 (1976).

14) J. K. Kochi, "Organometallic Mechanisms and Catalysis," Academic Press, New York (1978).

15) F. B. Dains and F. Eberly, *Org. Synth.*, Coll. Vol. II, 355 (1943).

16) T. Sheradsky and Z. Nir, *Tetrahedron Lett.*, **2**, 77 (1969).

17) R. P. Kozyrod, J. Morgan, and J. T. Pinhey, *Aust. J. Chem.*, **44**, 369 (1991).

18) A. Citterio, R. Santi, T. Fiorani, and S. Strologo, *J. Org. Chem.*, **54**, 2703 (1989).