3840 © *1993 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn.*, ***66****, 3840—3842(1993)* [Vol. 66, No. 12

Facile Alkoxyl Exchange of 2-Methoxybenzoates via Nucleophilic Aromatic Substitution with Sodium Alkoxides in Dimethylformamide

Tetsutaro HATTORI, Seiichi SATOH, and Sotaro MIYANO*
Department of Biochemistry and Engineering, Faculty of Engineering, Tohoku University,
Aramaki-Aoba, Aoba-ku, Sendai 980

(Received July 12, 1993)

Synopsis. Methyl 2-methoxybenzoate undergoes facile nuclear-methoxyl displacement by treatment with sodium butoxide or isopropoxide in dimethylformamide.

We have reported facile construction of biaryl skeletons in excellent yields via the reaction of 1-methoxy-2-naphthoates or 2-methoxybenzoates with aryl Grignard reagents.[1,2] The reaction corresponds to a nucleophilic aromatic substitution (S_NAr) of the methoxyl group by aryl nucleophiles with an ester substituent as the activating group. Oxygen-leaving groups are not readily replaced in aromatic nuclei,[3] and carbonyl groups do not have a strong activating effect.[4] Thus, although good leaving groups such as fluoro and nitro may be replaced in carbonyl-substituted aryls to undergo the S_NAr reaction in polar aprotic solvents,[5] displacement of alkoxyl moieties from such aryls has rarely been found.[6,7] Hence, we examined whether nucleophiles other than aryl Grignard reagents can enter into the S_NAr reaction of alkoxy-substituted aromatic carboxylic esters. Here we report facile displacement of the methoxyl group from 2-methoxybenzoates with sodium alkoxides, a process, to the best of our knowledge, that has not been reported before.

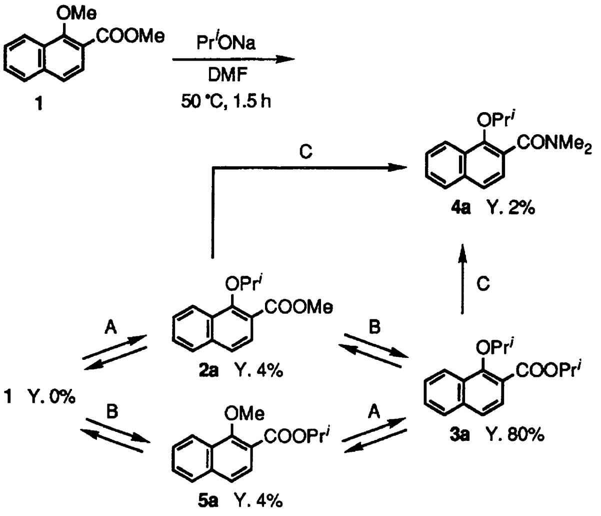
The naphthalene nucleus is more labile to the S_NAr reaction than the benzene ring. Treatment of methyl 1-methoxy-2-naphthoate **1** with excess (10 molar amounts) sodium isopropoxide in dimethylformamide (DMF) at 50 °C for 1.5 h afforded the S_NAr products **2a**—**4a** in a total yield of 86% (Scheme 1), but methyl 2-methoxybenzoate **6** was almost unchanged after similar treatment. Severe reaction conditions (90 °C for 3 h) forced the displacement of the methoxyl group from **6** with sodium butoxide (Run 1) and isopropoxide (Run 2) as summarized in Table 1 (Chart 1). Alkaline decomposition of DMF to give sodium dimethylamide explains the concomitant formation of *N*,*N*-dimethylbenzamides **4**. *N*,*N*-Dimethyl-2-methoxybenzamide **10** remained unchanged after similar treatment with sodium isopropoxide, showing that the formation of **4** follows nuclear-methoxyl displacement. S_NAr products were also obtained in a moderate yield by reaction with sodium benzyloxide (Run 4), but not with *t*-butoxide or phenoxide (Runs 3 and 5).

3-Methoxybenzoate **7** did not react (Run 6), but 4-methoxybenzoate **8** gave the S_NAr products in an appreciable yield (Run 7), so the activating effect of the ester substituent affects the *ortho* position, far less effectively the *para* position, and does not affect the *meta* position. Conjugate addition of the nucleophile followed by elimination of the methoxide seemed to accomplish the net S_NAr process.[1] Although the electronic effect of the ester substituent seems critical considering the fact that 8-methoxy-2-naphthoate **9** did not undergo the substitution reaction (Run 8), coordination of the methoxyl leaving group and the ester carbonyl group on the metal center may assist the addition-elimination process (Chart 2).

In conclusion, ester substituents activate *o*-alkoxyl group for the alkoxyl exchange reaction.

Experimental

Measurements and materials were similar to those described elsewhere unless otherwise noted.[1] Merck Lobar column (2.5 cm i.d.×31 cm) packed with LiChroprep Si 60 was used for routine preparative LC. Melting points are uncorrected. Compounds **1**[1] and **10**[8] were prepared as described in the literature. Compound **7** [bp 72 °C/0.5 mmHg$^{\#}$ (lit,[9] 121—124 °C/10 mmHg)] was prepared from the corresponding benzoyl chloride and methanol in benzene–pyridine in the presence of 4-dimethylaminopyridine.[1] Compound **9** was prepared as follows. 1,8-Naphthalenecarbolactone[10] (3.50 g, 20.6 mmol) was treated with 3.0 molar amounts of sodium methoxide in DMF (70 ml) at room temperature for

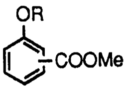
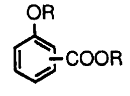
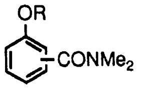


A: Nucleophilic aromatic substitution
B: Trans esterification
C: Amidation

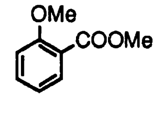
Scheme 1.

#1 mmHg=133.322 Pa.

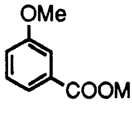
Table 1. Displacement of Nuclear Methoxyl Group with Sodium Alkoxides in DMF[a)]

Run	Substrate	RONa	Method[b)]						
				2	/%	**3**	/%	**4**	/%
1	**6**	Bu^{n}ONa	A	**2b**	3	**3b**	67	**4b**	14
2	**6**	Pr^{i}ONa	A	**2c**	1	**3c**	61	**4c**	10
3	**6**	Bu^{t}ONa	B	**2d**	0	**3d**	0	**4d**	0
4	**6**	PhCH$_2$ONa	C	**2e**	7	**3e**	17	**4e**	15
5	**6**	PhONa	B	**2f**	0	**3f**	0	**4f**	0
6	**7**	Pr^{i}ONa	A	**2g**	0	**3g**	0	**4g**	0
7	**8**	Pr^{i}ONa	A	**2h**	0	**3h**	16	**4h**	6
8	**9**	Pr^{i}ONa	A	**2i**	0	**3i**	0	**4i**	0

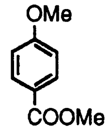
a) Reaction conditions: Substrate 12.0 mmol; alkoxide/substrate=10.0 (mol/mol); DMF (50 ml); 90 °C (3 h). b) See Experimental.



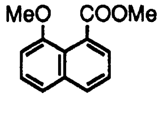
6



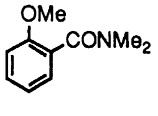
7



8

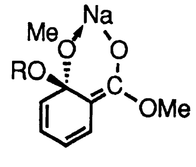


9

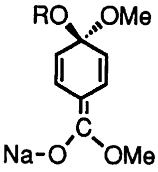


10

Chart 1.



11a



11b

Chart 2.

1 h. To the mixture was added 10.83 g of methyl iodide and the resulting mixture was heated at 60 °C for 40 min. After the usual workup, column chromatography on a silica-gel column with elution by dichloromethane gave 4.21 g of **9** as colorless crystals (95%); mp 58.3—59.1 °C (lit,[11)] 51—52 °C).

Alkoxyl Exchange Reactions. Sodium alkoxides were prepared by three methods, suitable to the properties of the parent alcohols. In method A, sodium butoxide and isopropoxide were prepared from sodium in a large excess of alcohol, which was then distilled off. In method B, sodium *t*-butoxide and phenoxide were prepared from alcohols and sodium hydride in DMF. In method C, sodium benzyloxide was prepared from sodium hydride in a slight excess of alcohol. Typical examples are described below.

Reaction of 6 with Sodium Isopropoxide (Method A): To 36.0 g of dry isopropyl alcohol was added sodium (2.80 g, 122 mmol), and the mixture was refluxed for 2 h under nitrogen. After the excess alcohol was distilled off, the residue was heated at 110 °C under reduced pressure for 1 h to give sodium isopropoxide, which contained 10.12 g of residual isopropyl alcohol (168 mmol). Then the residue was dissolved in DMF (50 ml). To the solution was added **6** (2.00 g, 12.0 mmol), and the mixture was heated at 90 °C for 3 h. After being cooled to room temperature, the mixture was poured into 300 ml of 2 M[##] HCl and extracted several times with diethyl ether. The combined ether extracts were washed with brine and dried over MgSO$_4$. After volatile compounds were evaporated off, the residue was purified by preparative LC with elution by dichloromethane to give 250 mg of **4c** (10%) and a mixture of esters, which was further purified with hexane–dichloromethane (1/1) as the eluent to give 23.0 mg of **2c** (1%) and 1.64 g of **3c** (61%).

2c: IR (liq. film) 1727 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.37 (6H, d, J=6.2 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 3.88 (3H, s, CH$_3$), 4.58 (1H, sept, J=6.2 Hz, CH), and 6.80—7.83 (4H, m, Ar-H).

3c: IR (liq. film) 1725 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.36 (12H, d, J=6.2 Hz, $\mathrm{CH(C\underline{H}_3)_2\times 2}$), 4.59 (1H, sept, J=6.2 Hz, OCH), 5.25 (1H, sept, J=6.2 Hz, COOCH), and 6.79—7.77 (4H, m, Ar-H). Found: C, 70.51; H, 8.11%. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%.

4c: IR (liq. film) 1631 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.30 (6H, d, J=5.9 Hz, $\mathrm{CH(C\underline{H}_3)_2}$), 2.85 (3H, s, CH$_3$), 3.10 (3H, s, CH$_3$), 4.54 (1H, sept, J=5.9 Hz, CH), and 6.79—7.45 (4H, m, Ar-H). Found: C, 69.33; H, 8.24; N, 6.56%. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%.

Reaction of 6 with Sodium *t*-Butoxide (Method B): To a suspension of NaH (2.90 g, 121 mmol) in dry DMF (50 ml) was added slowly *t*-butyl alcohol (10.7 g, 144 mmol), and the mixture was stirred at room temperature for 15 min and then heated at 90 °C for 1 h. To the mixture was added **6** (2.00 g, 12.0 mmol) and the mixture was stirred at 90 °C for 3 h. It was cooled to room temperature and worked up as above. Preparative LC gave no nuclear-methoxyl displacement products.

Reaction of 6 with Sodium Benzyloxide (Method

[##] 1 M=1 mol dm^{-3}.

C): To 2.90 g of NaH (121 mmol) was added slowly dry benzyl alcohol (31.0 g, 287 mmol). The mixture solidified, so it was melted by being warmed to 90 °C and was stirred for 30 min. To this mixture was added DMF (50 ml) and **6** (2.00 g, 12.0 mmol), and the mixture was stirred at 90 °C for 3 h. It was cooled to room temperature and worked up as above. Preparative LC with elution by dichloromethane–ethyl acetate (9/1) gave 460 mg of **4e** (15%) and a mixture of esters, which was further purified with hexane–ethyl acetate (9/1) as the eluent to give 205 mg of **2e** (7%) and 652 mg of **3e** (17%).

2e: IR (liq. film) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.89 (3H, s, CH_3), 5.17 (2H, s, CH_2), and 6.84—7.91 (9H, m, Ar-H). Found: C, 74.11; H, 5.79%. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82%.

3e: IR (liq. film) 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.16 (2H, s, OCH_2), 5.34 (2H, s, $COOCH_2$), and 6.83—7.93 (14H, m, Ar-H). Found: C, 79.45; H, 5.77%. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70%.

4e: IR (liq. film) 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.84 (3H, s, CH_3), 3.10 (3H, s, CH_3), 5.11 (2H, s, CH_2), and 6.88—7.42 (9H, m, Ar-H). Found: C, 75.54; H, 6.84; N, 5.33%. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%.

Similar reactions gave the following products. See Table 1 and Scheme 1 for reaction conditions and yields.

2a: IR (liq. film) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.35 (6H, d, J=6.2 Hz, $CH(C\underline{H}_3)_2$), 3.96 (3H, s, CH_3), 4.46 (1H, sept, J=6.2 Hz, CH), and 7.43—8.40 (6H, m, Ar-H). Found: C, 73.94; H, 6.61%. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%.

3a: IR and ^1H NMR spectra were identical with those of the authentic sample.[12)]

4a: IR (liq. film) 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30 (6H, d, J=6.2 Hz, $CH(C\underline{H}_3)_2$), 2.89 (3H, s, CH_3), 3.16 (3H, s, CH_3), 4.46 (1H, sept, J=6.2 Hz, CH), and 7.31—8.35 (6H, m, Ar-H).

2b: IR (liq. film) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 0.81—2.03 (7H, m, $CH_2C_3\underline{H}_7$), 3.88 (3H, s, CH_3), 4.04 (2H, t, J=6.0 Hz, CH_2), and 6.80—7.86 (4H, m, Ar-H).

3b: IR (liq. film) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 0.80—1.92 (14H, m, $CH_2C_3\underline{H}_7 \times 2$), 4.03 (2H, t, J=6.3 Hz, OCH_2), 4.30 (2H, t, J=6.3 Hz, $COOCH_2$), and 6.79—7.84 (4H, m, Ar-H). Found: C, 71.71; H, 8.78%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

4b: IR (liq. film) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 0.78—1.95 (7H, m, $CH_2C_3\underline{H}_7$), 2.84 (3H, s, CH_3), 3.10 (3H, s, CH_3), 3.98 (2H, t, J=6.3 Hz, CH_2), and 6.79—7.46 (4H, m, Ar-H). Found: C, 70.54; H, 8.68; N, 6.26%. Calcd for $C_{13}H_{19}O_2N$: C, 70.56; H, 8.65; N, 6.33%.

3h: IR (liq. film) 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (12H, d, J=6.2 Hz, $CH(C\underline{H}_3)_2 \times 2$), 4.62 (1H, sept, J=6.2 Hz, OCH), 5.22 (1H, sept, J=6.2 Hz, COOCH), 6.75—6.99 (2H, m, Ar-H), and 7.84—8.08 (2H, m, Ar-H). Found: C, 70.44; H, 8.19%. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%.

4h: IR (liq. film) 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.34 (6H, d, J=6.2 Hz, $CH(C\underline{H}_3)_2$), 3.05 (6H, s, $CH_3 \times 2$), 4.58 (1H, sept, J=6.2 Hz, CH), 6.75—6.97 (2H, m, Ar-H), and 7.26—7.50 (2H, m, Ar-H). Found: C, 69.35; H, 8.29; N, 6.60%. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%.

This work was supported by a Grant-in-Aid for Encouragement of Young Scientists No. 05750761 from the Ministry of Education, Science and Culture.

References

1) T. Hattori, H. Hotta, T. Suzuki, and S. Miyano, *Bull. Chem. Soc. Jpn.*, **66**, 613 (1993).

2) T. Hattori, T. Suzuki, and S. Miyano, *J. Chem. Soc., Chem. Commun.*, **1991**, 1375.

3) Review: S. Miyano and H. Hashimoto, *Senryo to Yakuhin*, **33**, 130 (1988).

4) For a general overview, see: J. March, "Advanced Organic Chemistry," 4th ed, Wiley, New York (1992).

5) P. G. Sammes, D. Thetford, and M. Voyle, *J. Chem. Soc., Chem. Commun.*, **1987**, 1373; G. W. Yeager and D. N. Schissel, *Synthesis*, **1991**, 63, and references cited therein.

6) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Chem. Express*, **5**, 569 (1990).

7) F. J. Williams and P. E. Donahue, *J. Org. Chem.*, **42**, 3414 (1977).

8) L. M. Jackman, T. E. Kavanagh, and R. C. Haddon, *Org. Magn. Reson.*, **1**, 109 (1969).

9) F. W. Semmler, *Ber.*, **41**, 1768 (1908).

10) A. J. Birch, M. Salahud-Din, and D. C. C. Smith, *J. Chem. Soc. C*, **1966**, 523.

11) E. Bretscher, H. G. Rule, and J. Spence, *J. Chem. Soc.*, **1928**, 1493.

12) S. Oi, K. Matsunaga, T. Hattori, and S. Miyano, *Synthesis*, **1993**, 895.