Nucleophilic aromatic substitution of 2-sulfonyl-substituted 1-methoxynaphthalenes with Grignard reagents

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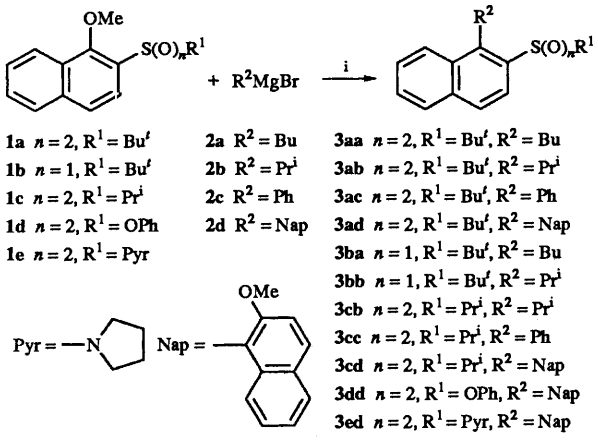
2-Alkylsulfonyl, -phenoxysulfonyl or -sulfamoyl substituted 1-methoxynaphthalenes **1** undergo nucleophilic displacement of the 1-methoxy group when treated with Grignard reagents; the chiral sulfamoyl-substituted naphthalene **1f** on treatment with the 2-methoxy-1-naphthyl Grignard reagent **2d** induced axial chirality to give the 1,1′-binaphthyl **3fd** in 80% diastereoisomeric excess (de).

Previous papers from this laboratory [1,2] have disclosed that the oxazoline functionality required for the Meyers reaction [3] can frequently be replaced by an ester group to carry out chelation-assisted nucleophilic aromatic substitution (S_NAr). In our continuing efforts in this area, we recently reported the use of a diphenylphosphinoyl group as the activator for the S_NAr reaction of 2-(diphenylphosphinoyl)-1-methoxynaphthalene with various nucleophiles.[4] As a rational extension of this work to other activating substituents, we have initiated a study of oxygenated sulfur-based functionalities taking into account their effective electron-withdrawing ability *via* induction as well as resonance; this enables such compounds to undergo a diversity of transformations.[5] Recently, Julia and his co-workers have reported that the *tert*-butylsulfonyl group is displaced from *tert*-butyl aryl sulfones on treatment of the latter with Grignard reagents in the presence of a nickel catalyst;[6] further, Sargent's group reported the synthesis of 1,1′-binaphthyls by the displacement of the 1-arylsulfinyl group from 2-oxazolinyl-1-(arylsulfinyl)naphthalenes.[7] These reports have prompted us to disclose our own preliminary observations on the S_NAr reactions of 2-sulfonyl- or 2-sulfinyl-1-methoxynaphthalenes (Scheme 1).

Initially, we examined the reaction of 2-*tert*-butylsulfonyl-1-methoxynaphthalene **1a** with Grignard reagents **2a–c** (2.0 equiv.) in diethyl ether–benzene at room temperature. In the absence of a nickel catalyst, the *tert*-butylsulfonyl moiety was unaffected, while the S_NAr products **3aa–ac** were obtained in good yields after purification by column chromatography (Table 1, entries 1–3).† In contrast, a sulfinyl substituent seemed to activate the *ortho*-alkoxy substituent insufficiently for displacement to take place as exemplified by the reactions of 2-*tert*-butylsulfinyl-1-methoxynaphthalene **1b** with Grignard reagents **2a, b** (entries 5 and 6). Reaction of the sulfone **1a** with the 2-methoxy-1-naphthyl Grignard reagent **2d** needed to be carried out in refluxing diethyl ether–benzene to give the binaphthyl compound **3ad** in a moderate yield (entry 4). As CPK-molecular models suggest, this may be attributable to the steric hindrance between the *tert*-butylsulfonyl group and the bulky Grignard reagent. In fact, reduction of the steric bulk of the 2-substituent from *tert*-butyl- **1a** to isopropyl-sulfonyl **1c** substantially improved the substitution with the sterically less-demanding Grignard reagents **2b, c** (entries 7 and 8). It is noteworthy that methoxy displacement proceeded faster than proton abstraction from the isopropyl moiety by these Grignard reagents (see below). However, the yield of the substitution product **3cd** was not improved for the naphthyl Grignard reagent **2d** (entry 9). Termination of the reaction with [$^2H_4$]acetic acid showed substantial incorporation of deuterium into the isopropyl moiety, an indication that from the substrate sulfone **1c** there was concurrent formation of the α-sulfonyl carbanion, an entity highly resistant to S_NAr attack.

Next, we examined the effect of a decrease in the steric bulk of the 2-substituted activator. Although it was expected that a 2-alkoxysulfonyl group would have decreased electron-withdrawing ability,[8] 1-methoxy-2-(phenoxysulfonyl)naphthalene **1d** reacted readily with the naphthyl Grignard reagent **2d** at room temperature to give the binaphthyl **3dd** in a good yield



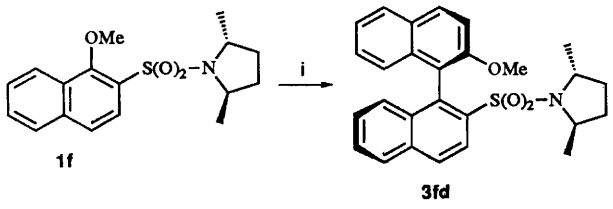
Scheme 1 *Reagents:* i, Et_2O–PhH

Table 1 The S_NAr reactions of 2-sulfonyl- or 2-sulfinyl-substituted 1-methoxynaphthalenes **1** with Grignard reagents **2**

Entry	Substrate	Nucleophile (equiv.)	[Time (*t*/h)]	Product	Yield (%)
1	**1a**	**2a** (2.0)	[3][a]	**3aa**	72
2	**1a**	**2b** (2.0)	[6.5][a]	**3ab**	71
3	**1a**	**2c** (2.0)	[2][a]	**3ac**	71
4	**1a**	**2d** (2.0)	[2][b]	**3ad**	52
5	**1b**	**2a** (2.0)	[76][b]	**3ba**	16
6	**1b**	**2b** (2.0)	[19][b]	**3bb**	0
7	**1c**	**2b** (2.0)	[1][a]	**3cb**	91
8	**1c**	**2c** (2.0)	[1][a]	**3cc**	89
9	**1c**	**2d** (2.0)	[2][b]	**3cd**	33
10	**1d**	**2d** (2.0)	[6][a]	**3dd**	76
11	**1e**	**2d** (3.0)	[36][a]→[6][b]	**3ed**	42

[a] Room temp. [b] Reflux.

† All new compounds were substantiated by spectral data and elemental analyses. Yields are for the isolated pure products.



1f 3fd

Scheme 2 *Reagents and conditions:* i, **2d**, Et_2O–PhH, room temp. 36 h, then reflux 6 h (48% yield, 80% de)

(entry 10); this showed that decreased steric hindrance compensated for the reduced electronic effect. It was found that even a 2-dialkylaminosulfonyl-substituted compound **1e** underwent S_NAr attack, although sluggishly (entry 11). We were pleased, however, to find that a chiral sulfamoyl auxiliary could bring about highly effective asymmetric induction with two naphthalene components; thus, on treatment with the Grignard reagent **2d**, 2-[(2*R*,5*R*)-dimethylpyrrolidinylsulfonyl]-1-methoxynaphthalene **1f** gave the 1,1′-binaphthyl **3fd** of 80% diastereoisomeric purity (de) (Scheme 2). The absolute stereochemistry of the induced axis‡ was assigned to be a*R* by correlation to enantiomerically pure 2-amino-2′-methoxy-1,1′-binaphthyl.[9] Further studies on chiral discrimination mechanisms are in progress.

Experimental

2-[(2*R*,5*R*)-Dimethylpyrrolidinylsulfonyl]-2′-methoxy-1,1′-binaphthyl 3fd

To a solution of the sulfonamide **1f** (252 mg, 0.789 mmol) in dry benzene (5.0 cm^3) was added the Grignard reagent **2d** which had been prepared from 1-bromo-2-methoxynaphthalene (560 mg, 2.36 mmol) and magnesium turnings (100 mg) in dry diethyl ether (5.0 cm^3), dissolution being achieved by the addition of benzene (5.0 cm^3). The mixture was stirred at room temperature for 36 h and then refluxed for 6 h. After work-up, chromatography on a silica gel column with hexane–ethyl acetate (6:1) as the eluent afforded the binaphthyl **3fd** (168 mg, 48%) as crystals, δ_H(250 MHz; $CDCl_3$) 0.87, 0.91 [6 H, d, *J* 6.4, Me (a*R*); d, *J* 6.4, Me (a*S*)], 0.84–2.02 (4 H, m, CH_2), 3.00–3.11, 3.49–3.59 [2 H, m, NCH (a*S*); m, NCH (a*R*)], 3.76, 3.83 [3 H, s, OMe (a*R*); s, OMe (a*S*)] and 6.85–8.32 (12 H, m, ArH).

^{1}H NMR analysis of the sample differentiated well the 2′-methoxy signal of the (a*S*)- and (a*R*)-diastereoisomers. Thus, the axial chirality of the coupling product was determined to be a*R* (80% de) by comparison of its ^{1}H NMR spectrum with that of an authentic sample which had been prepared as follows: Sandmeyer type chlorosulfonylation of (a*S*)-2-amino-2′-methoxy-1,1′-binaphthyl[9] afforded (a*S*)-2-chlorosulfonyl-2′-methoxy-1,1′-binaphthyl, which was treated with (2*R*,5*R*)-dimethylpyrrolidine in benzene–pyridine to give an authentic sample of (a*S*)-**3fd** as crystals, mp 217–218 °C (Found: C, 72.9; H, 6.3; N, 3.0. $C_{27}H_{27}NO_3S$ requires C, 72.8; H, 6.1; N, 3.1%); $[\alpha]_D^{20}$ +92.3 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1323 (SO); δ_H(250 MHz; $CDCl_3$) 0.91 (6 H, d, *J* 6.4, Me), 0.84–1.33 (4 H, m, CH_2), 3.00–3.11 (2 H, m, NCH), 3.83 (3 H, s, OMe) and 6.85–8.32 (12 H, m, ArH).

‡ The descriptors a*R* and a*S* refer to axial chirality.

References

1 T. Hattori, H. Hotta, T. Suzuki and S. Miyano, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 613.
2 T. Hattori, T. Tanaka, Y. Okaishi and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, 1995, 235.
3 M. Reuman and A. I. Meyers, *Tetrahedron*, 1985, **41**, 837; T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297.
4 T. Hattori, J. Sakamoto, N. Hayashizaka and S. Miyano, *Synthesis*, 1994, 199.
5 For recent reviews, see: S. Patai, Z. Rappoport and C. J. M. Stirling, ed. *The Chemistry of Sulfones and Sulfoxides*, J. Wiley & Sons, Chichester, 1988; N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, 1993; A. J. Walker, *Tetrahedron: Asymmetry*, 1992, **3**, 961.
6 J. Clayden, J. J. A. Cooney and M. Julia, *J. Chem. Soc., Perkin Trans. 1*, 1995, 7.
7 R. W. Baker, G. R. Pocock and M. V. Sargent, *J. Chem. Soc., Chem. Commun.*, 1993, 1489.
8 J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968, pp. 61–136.
9 T. Hattori, M. Shijo, J. Sakamoto, S. Kumagai, A. Nakajima and S. Miyano, *J. Chem. Res.*, 1995 (*M*), 124.

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