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The Effects of the Reaction Conditions on the Metalation of Phenyl *p*-Toluenesulfonate (Phenyl Tosylate)

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Directed *ortho* metalation of phenyl *p*-toluenesulfonate (phenyl tosylate) was carried out and the reaction was found to be controlled by the conditions (base, solvent, temperature, with or without ligand) to some extent.

Key words phenyl tosylate; *ortho* metalation; lithiation

The directed *ortho* metalation (DoM) and related lateral metalation methodologies have been widely developed and extended for a variety of applications in natural products syntheses.[1-3]

The DoM process of phenols using methoxymethyl, dialkylaminocarbonyl, bis(dialkylamino)phosphoryl as protecting and activating groups has been well studied.[1,4] In general, the products are subsequently treated under hydrolytic conditions to obtain the unmasked phenols (Fig. 1, route A). However, it is necessary to remove completely the metalated group including the oxygen atom if an unsubstituted location on the aromatic ring is desired (Fig. 1, route B). For example, aryl *O*-carbamates (–OC(O)NR$_2$) are known to be reduced to unsubstituted derivatives by Ni-catalyzed Grignard reaction,[5] but this reaction is rather severe for practical use. Aryl *p*-toluenesulfonates (aryl tosylates) are known to be reduced to give deoxygenated phenyl compounds in excellent yields by aqueous sodium borohydride–nickel chloride systems.[6]

Furthermore, *ortho* metalation and the subsequent electrophilic substitution of alkyl arenesulfonates furnishes a variety of *ortho*-substituted alkyl arenesulfonates.[7] Consequently, we wished to develop a new group for metalation (sulfonyloxy group), which could be easily removed after DoM reactions. Here we report studies on *ortho* metalation of phenyl *p*-toluenesulfonate (phenyl tosylate) under various reaction conditions.

Initially *ortho* metalation of phenyl ethane-, methane-, and *p*-toluenesulfonate using *n*-BuLi or *sec*-BuLi as a base in tetrahydrofuran (THF) at −78 °C was examined. Under these conditions, metalation of methane- and ethanesulfonates of phenol gave substantial amounts of phenol and unidentified products, presumably formed by direct attack of *n*- and *sec*-BuLi on the sulfonate sulfonyl group, and gave none of the desired *o*-tolyl sulfonate derivatives. When phenyl tosylate (**1**) was lithiated with 2.2 eq of

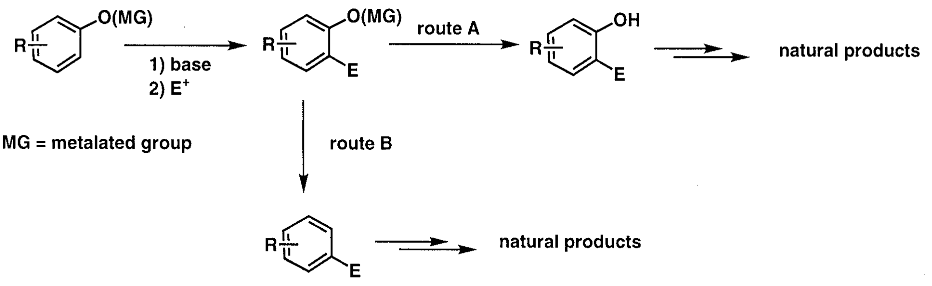

Fig. 1

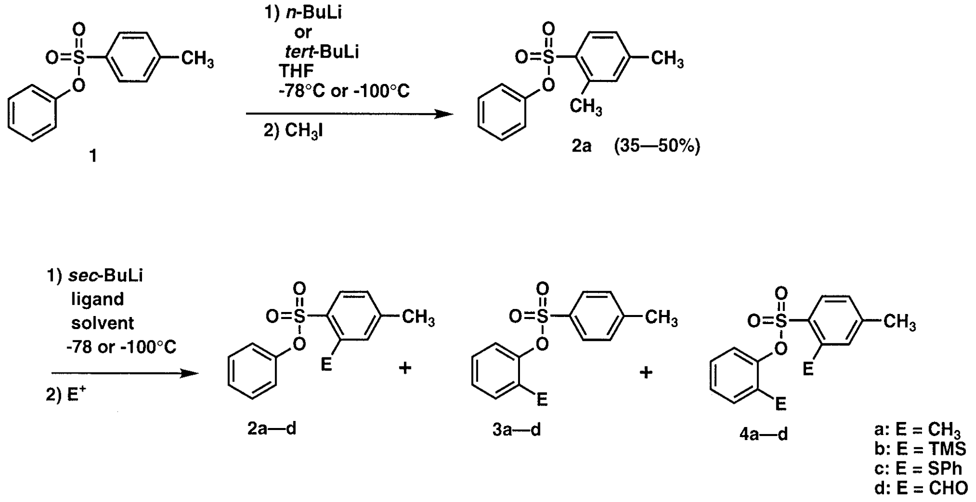

Fig. 2

Table 1. Results of Metalation of Phenyl Tosylate under Various Reaction Conditions

Entry	Solvent	Base/ligand	E^+	E	Temp. (°C)	Compounds (Yield %)		
1	THF	*n*-BuLi/–	CH_3I	CH_3–	-78	**2a** (39)	**3a** (0)	**4a** (0)
2	THF	*n*-BuLi/–	CH_3I	CH_3–	-100	**2a** (50)	**3a** (0)	**4a** (0)
3	THF	*sec*-BuLi/–	CH_3I	CH_3–	-78	**2a** (0)	**3a** (13)	**4a** (29)
4	THF	*sec*-BuLi/–	CH_3I	CH_3–	-100	**2a** (0)	**3a** (30)	**4a** (29)
5	THF	*sec*-BuLi/TMEDA	CH_3I	CH_3–	-78	**2a** (0)	**3a** (5)	**4a** (32)
6	THF	*sec*-BuLi/TMEDA	CH_3I	CH_3–	-100	**2a** (0)	**3a** (30)	**4a** (15)
7	THF	*tert*-BuLi/–	CH_3I	CH_3–	-78	**2a** (35)	**3a** (0)	**4a** (0)
8	Toluene	*n*-BuLi/–	CH_3I	CH_3–	-78	**2a** (0)	**3a** (0)	**4a** (0)
9	Toluene	*sec*-BuLi/–	CH_3I	CH_3–	-78	**2a** (0)	**3a** (0)	**4a** (0)
10	Toluene	*sec*-BuLi/TMEDA	CH_3I	CH_3–	-78	**2a** (0)	**3a** (19)	**4a** (13)
11	Toluene	*sec*-BuLi/TMEDA	CH_3I	CH_3–	-100	**2a** (0)	**3a** (38)	**4a** (trace)
12	Toluene	*sec*-BuLi/TMEDA	TMSCl	TMS	-100	**2b** (0)	**3b** (50)	**4b** (8)
13	Toluene	*sec*-BuLi/TMEDA	$(PhS)_2$	PhS	-100	**2c** (0)	**3c** (15)	**4c** (20)
14	Toluene	*sec*-BuLi/TMEDA	DMF	OHC–	-100	**2d** (0)	**3d** (23)	**4d** (trace)

sec-BuLi at -78 °C for 1 h and quenched with CH_3I at -78 °C, 13% of the desired *o*-tolyl tosylate (**3a**) and 29% of the undesired compound (**4a**), which were lithiated at *ortho* positions of both the phenyl and the *p*-toluene ring, were obtained (21% of the starting material was recovered), while 39% of phenyl 2,4-dimethylbenzenesulfonate (**2a**) was obtained when lithiation was done with 2.2 eq of *n*-BuLi (15.5% of the starting material was recovered) (Table 1, entries 1, 3).[8] We modified the reaction conditions (base, ligand, solvent, temperature) for the selective metalation of phenyl tosylate in an attempt to obtain a high yield of *ortho* lithiated product (**3a**). As can be seen in the Table 1, improved *ortho* metalation at the desired position to give *o*-tolyl tosylate (**3a**) was achieved by the use of *sec*-BuLi with or without *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at -100 °C in THF, though substantial amounts of undesired **4a** were still formed (entries 4, 6). The use of toluene as a solvent without TMEDA resulted in no metalation and recovery of the starting material (entries 8, 9).

The best result was obtained when *sec*-BuLi and TMEDA were used in toluene at -100 °C (entry 11). *ortho* Metalation at *p*-toluene ring to give **2a** was also observed in THF when *tert*-BuLi (at -78 °C) was used as a base (entry 7). Quenching of the reaction with electrophiles other than CH_3I showed that this condition is suitable for the effective *ortho* metalation of phenyl tosylate (entries 12—14).

We are attempting to extend this observation to other aromatic tosylates and to apply the reaction to the synthesis of natural products.

Experimental

All materials not explicitly mentioned were purchased from Wakenyaku Co., Nacalai Tesque Co., and Aldrich Chemical Co. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX-200 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm) relative to TMS. Mass spectra (MS) were obtained on JMS-HX/HX-110A instruments. Melting points were measured on a Yanagimoto micro melting point apparatus without correction. THF was distilled from sodium/benzophenone under an argon atmosphere. Toluene was distilled from sodium under an argon atmosphere. TMEDA was distilled from CaH_2 under nitrogen and stored under argon.

General Lithiation Procedure for Phenyl *p*-Toluenesulfonate (Phenyl Tosylate) without TMEDA Phenyl tosylate (**1**) (248 mg, 1.0 mmol) in a solvent was slowly added *via* a cannula to a stirred solution of BuLi (2.2 eq of *n*- or *sec*- or *tert*-, listed in Table 1) in freshly distilled solvent (20 ml) at -78 or -100 °C under an argon atmosphere. After 1 h, 0.3 ml of iodomethane was added to the solution. The reaction mixture was stirred for 1 h at -78 or -100 °C, then aqueous saturated NH_4Cl was added. The reaction mixture was allowed to warm to room temperature and separated. The aqueous phase was extracted three times with ethyl acetate (50 ml × 3). The combined extract was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification and separation by flash chromatography (hexane : ethyl acetate = 9 : 1) provided the desired compound as shown in Table 1.

General Lithiation Procedure for Phenyl Tosylate with TMEDA Under an argon atmosphere, 2.2 eq of *sec*-BuLi was added to a stirred solution of TMEDA (2.2 eq) in distilled solvent at -78 or -100 °C and stirring was continued for 15 min at -78 or -100 °C. A solution of **1** (248 mg) in an anhydrous solvent cooled to -78 °C was added dropwise *via* a cannula and the resulting solution was stirred for 1 h at -78 or -100 °C. An electrophile (4 eq, solution in dry solvent) was added and the resulting mixture was further stirred for 1 h at -78 or -100 °C, quenched with saturated NH_4Cl solution and separated. The aqueous phase was extracted three times with ethyl acetate, and the combined organic extract was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide a crude product. Purification and separation by flash chromatography gave the desired compound as listed in Table 1.

Phenyl 2,4-Dimethylbenzenesulfonate (**2**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.39 (s, 3H), 2.72 (s, 3H), 6.96—7.30 (m, 7H), 7.68 (d, 1H, $J=8.24$ Hz). mp 61—63 °C. *Anal.* Calcd for $C_{14}H_{14}O_3S$: H, 5.38; C, 64.11. Found: H, 5.42; C, 64.08.

o-Tolyl *p*-Toluenesulfonate (*o*-Tolyl Tosylate) (**3a**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 2.45 (s, 3H), 6.97—7.16 (m, 4H), 7.31 (d, 2H, $J=8.25$ Hz), 7.74 (d, 2H, $J=8.25$ Hz). mp 50—51 °C. *Anal.* Calcd for $C_{14}H_{14}O_3S$: H, 5.38; C, 64.11. Found: H, 5.31; C, 64.00.

o-Tolyl 2,4-Dimethylbenzenesulfonate (**4a**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.22 (s, 3H), 2.39 (s, 3H), 2.70 (s, 3H), 6.72—7.20 (m, 6H), 7.73 (d, 1H, $J=8.25$ Hz). MS (FAB^+) *m*/*z*: 277 (MH^+).

o-Trimethylsilylphenyl Tosylate (**3b**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.27 (s, 9H), 2.46 (s, 3H), 7.07—7.47 (m, 6H), 7.85 (d, 2H, $J=8.24$ Hz). MS (FAB^+) *m*/*z*: 321 (MH^+).

o-Trimethylsilylphenyl 4-Methyl-2-trimethylsilylbenzenesulfonate (**4b**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.29 (s, 9H), 0.41 (s, 9H), 2.47 (s, 3H), 6.78—7.50 (m, 5H), 7.63 (d, 1H, $J=1.32$ Hz), 7.93 (d, 1H, $J=8.25$ Hz). MS (FAB^+) *m*/*z*: 393 (MH^+).

o-Phenylthiophenyl Tosylate (**3c**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 6.93—7.58 (m, 9H), 7.31 (d, 2H, $J=8.57$ Hz), 7.70 (d, 2H, $J=8.57$ Hz). MS (FAB^+) *m*/*z*: 356 (M^+).

o-Phenylthiophenyl 4-Methyl-2-phenylthiobenzenesulfonate (**4c**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 6.78—7.54 (m, 16H), 7.81 (d, 1H, $J=7.92$ Hz). MS (FAB^+) *m*/*z*: 464 (M^+).

o-Formylphenyl Tosylate (**3d**): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.46 (s, 3H), 7.21—7.87 (m, 4H), 7.34 (d, 2H, $J=8.25$ Hz), 7.71 (d, 2H, $J=8.25$ Hz), 9.99 (s, 1H). MS (FAB^+) *m*/*z*: 277 (MH^+).

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8) Yields of 5.3% of **3a** and 17.5% of **4a** were obtained and 58% of the starting material was recovered when lithiation was conducted with 1.1 eq of *sec*-BuLi at −78 °C. Similarly, when 1.1 eq of *n*-BuLi was used, 26% of **2a** was obtained with 26% recovery of the starting material.