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Sydnone Ring as an *ortho*-Director of Lithiation, 3: One-Pot Regiospecific *o*-Acylation and Subsequent Sydnone 4-Substitution

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Abstract: Readily available 3-phenylsydnone (**1**) reacts with *n*-butyllithium/N,N,N′,N′-tetramethylethylenediamine (TMEDA) to form the dilithio species **2**, which can be acylated regiospecifically at the *ortho*-aryl position using N-methoxy-N-methylamides (Weinreb's amides) followed by reaction with a second, more reactive electrophile at the sydnone C-4 position. Asymmetrically substituted arylsydnones **7** are obtained in 57–86% yield.

Keywords: Acylation, lithiation, mesoionic compounds, sydnones

Some years ago, we reported the *first* utilization of the sydnone ring as a director of *ortho*-lithiation using *n*-butyl lithium (Scheme 1).[1,2] Therein, 3-phenylsydnone (**1**) reacted with 2.2 equivalents of *n*-BuLi in the presence of N,N,N′,N′-tetramethylethylenediamine (TMEDA), and subsequent treatment with a variety of electrophiles gave the corresponding disubstituted sydnones **3** in 85–93% yield, presumably via the dilithio intermediate **2**. Having established that dilithiation was possible, we were interested to see whether the site of electrophilic substitution could be controlled. The pK_a of the sydnone ring proton had been estimated to be approximately 18–20,[3] and accordingly, it appeared likely that, in **2**, the anion at the *ortho*-position would be considerably more reactive than that on the sydnone ring. Selectivity for the *ortho*-position was of considerable interest because much of our previous work had utilized

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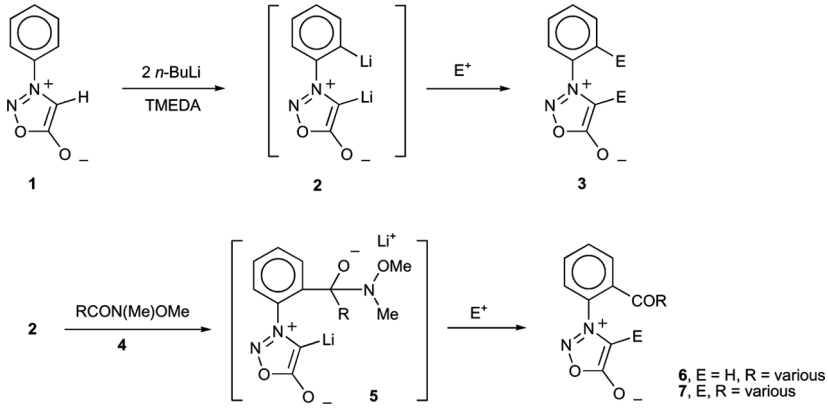

Scheme 1. Asymmetric substitution of 3-phenylsydnone.

ortho-substituted arylsydnones as precursors to differently substituted sydnones,[4] fused ring sydnones,[5] or to various heterocycles.[6] Indeed, complete selectivity for the *ortho*-aryl position was realized using methyl iodide as electrophile [3-(2-tolyl)sydnone resulted]; however, extension to the preparation of other *ortho*-alkyl sydnones was problematic because ethyl iodide did not react under these conditions, presumably because of competitive elimination. The most consistent results were obtained using a weak electrophile such as an N-methoxy-N-methylamide (Weinreb's amide) **4**,[7] and the corresponding *o*-acyl arylsydnones **6** were obtained in 40–90% yield (Scheme 1). The success of this approach relied not only on the greater nucleophilicity of the *ortho*-anion (in **2**) but also on the key characteristic of such reactions, namely that after initial attack of the *ortho*-anion upon the amide, in the resultant intermediate (cf. **5**), effective complexation of the lithio intermediate prevented further reaction with excess organolithium reagent or the anion on the sydnone ring because the carbonyl group was not "revealed" until after workup. We were interested in the possibility that after selective reaction of the dianion **2** with a Weinreb's amide, it might be possible to react the resultant sydnone carbanion **5** with a more reactive electrophile, yielding **7** on workup. This possibility was particularly intriguing because in 1993 we had shown that *o*-acyl-4-bromosydnones **7** (E = Br) react with HBr to form novel 1-bromocarbonyl indazoles.[6b] However, the utility of this transformation was hampered by the relative inaccessibility of the starting bromo species **7** (E = Br). We now report that the latter (and related species **7**, E = I, $SiMe_3$, SPh, CHO) can be prepared in good yield (57–86%) in a one-pot process starting from readily available 3-phenylsydnone (**1**).

Table 1. Reactions of 3-phenylsydnone (**1**) with BuLi/TMEDA and Weinreb's amides followed by a second electrophile to afford **7a–i**

Entry	**7**	R (in **4** and **7**)	E^+	E (in **7**)	Yield (%)
1	a	C_6H_5	TMSCl	TMS	71
2	b	4-BrC_6H_4	TMSCl	TMS	61
3	c	4-$MeOC_6H_4$	MSCl	TMS	63
4	d	CH_3	TMSCl	TMS	59
5	e	$ClCH_2$	TMSCl	TMS	57
6	f	C_6H_5	Br_2	Br	84
7	g	C_6H_5	I_2	I	74
8	h	C_6H_5	PhSSPh	SPh	82
9	i	C_6H_5	DMF	CHO	86

Thus, treatment of **1** with 2.2 equivalents of *n*-butyllithium in tetrahydrofuran (THF) and TMEDA at −78°C, followed by a Weinreb's amide and a second electrophile [Br_2, I_2, Me_3SiCl, PhSSPh, or dimethylformamide (DMF)], provides an attractive avenue to otherwise difficultly accessible 4-substituted *o*-acylarylsydnones **7**. The initial part of the study was conducted using different Weinreb's amides followed by the same second electrophile, namely, chlorotrimethylsilane, and the resultant products, **7a**–**e**, were obtained in 57–71% yield (Table 1, entries 1–5). With the generality of the process established using differently functionalized Weinreb's amides, we elected to maintain the same Weinreb's amide **4** (R=Ph) and vary the second electrophile (Br_2, I_2, PhSSPh, or DMF). The resultant products, **7f–i**, were obtained in 74–86% yield (Table 1, entries 6–9). The identities of the products were confirmed by satisfactory combustion analyses, the presence of the sydnone C=O stretching vibration at ∼1750 cm^{-1} in their infrared (IR) spectra, and the expected chemical shifts and splitting patterns in their proton and carbon NMR spectra.

Overall, we have developed a useful, one-pot preparation of 4-substituted *ortho*-acyl or aroyl phenylsydnones **7** from readily available 3-phenylsydnone (**1**), and we intend to explore further the scope and limitations of the present discovery.

EXPERIMENTAL

General Procedure for the Preparation of 4-Substituted 3-(2-(Acyl or Aroyl)phenyl)sydnones 7

To a stirred solution of 3-phenylsydnone (**1**) (0.25 g, 1.54 mmol) in dry THF (150 mL) at −78°C under an atmosphere of dry nitrogen gas,

TMEDA (0.29 mL, 1.93 mmol) and then *n*-butyllithium (2.19 mL, 3.39 mmol, 1.55 M in hexane) were added dropwise. After 0.5 h, the appropriate N-methoxy-N-methylamide **4** (1.77–1.85 mmol) was added to the golden-yellow solution, and after an additional 1–2 h, the second electrophile (1.85 mmol for entries 1 and 2 or 1.93 mmol for entries 3–9) was added. After warming to 0°C over 2 h, the mixture was quenched with aqueous hydrochloric acid (100 mL, 10% v/v) and then extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford the corresponding *o*-acylated 4-substituted sydnone **7** as a dark oil. The latter was triturated with hexane/ether (1:1, v:v) (for **7a**, only), and the residual oil was purified by column chromatography (silica gel, dichloromethane as eluant) followed by recrystallization from dichloromethane/hexane (for **7a–e, h**) or dichloromethane/benzene/hexane (for **7f, g, i**) to afford colorless crystals.

3-(2-Benzoylphenyl)-4-trimethylsilylsydnone (7a)

Using N-methoxy-N-methylbenzamide (**4**, R=Ph) (0.293 g, 1.77 mmol) and chlorotrimethylsilane (0.201 g, 1.85 mmol) in the general procedure gave the title compound (0.372 g), mp 150–152°C. Found: C, 64.06; H, 5.45; N, 8.38. Calc. for $C_{18}H_{18}N_2O_3Si$: C, 63.88; H, 5.36; N, 8.28. ν_{max} (KBr): 3067, 2965, 1729, 1663, 1400, 1277, 932, 847, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 9H), 7.42–7.73 (m, 9H); ^{13}C NMR ($CDCl_3$): −1.92 [Si($\underline{C}H_3)_3$], 107.73 (sydnone C-4), 126.90, 128.53, 129.99, 130.22, 131.32, 131.55, 133.98 (aromatic CH), 134.45, 135.84, 135.95 (aromatic quaternary C), 173.07 (sydnone C=O), 192.41 (ketone C=O) ppm.

3-(2-(4-Bromobenzoyl)phenyl)-4-trimethylsilylsydnone (7b)

Using N-methoxy-N-methyl-4-bromobenzamide (**4**, R=4-BrC_6H_4) (0.431 g, 1.77 mmol) and chlorotrimethylsilane (0.201 g, 1.85 mmol) in the general procedure gave the title compound (0.390 g), mp 133–134°C. Found: C, 51.94; H, 4.03; N, 6.71. Calc. for $C_{18}H_{17}BrN_2O_3Si$: C, 51.81; H, 4.11; N, 6.71. ν_{max} (KBr): 3065, 2959, 1730, 1663, 1582, 1385, 1274, 929, 846, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 9H), 7.57–7.74 (m, 8H); ^{13}C NMR ($CDCl_3$): −1.72 [Si($\underline{C}H_3)_3$], 107.88 (sydnone C-4), 125.21, 127.05, 131.42, 131.65, 131.95, 135.48 (aromatic CH), 129.66, 132.58, 134.28, 134.38 (aromatic quaternary C), 172.97 (sydnone C=O), 191.34 (ketone C=O) ppm.

3-(2-(4-Methoxybenzoyl)phenyl)-4-trimethylsilylsydnone (7c)

Using N-methoxy-N-methyl-4-methoxybenzamide (**4**, R=4-$MeOC_6H_4$) (0.361 g, 1.85 mmol) and chlorotrimethylsilane (0.209 g, 1.93 mmol) in the general procedure gave the title compound (0.358 g), mp 128–130°C. Found: C, 61.84; H, 5.36; N, 8.21. Calc. for $C_{19}H_{20}N_2O_4Si$: C, 61.94; H, 5.47; N, 7.60. ν_{max} (KBr): 3071, 2968, 1733, 1655, 1599, 1396, 1264, 931, 848 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.14 (s, 9H), 3.87 (s, 3H), 6.91 (d, 2H), 7.65–7.75 (m, 6H); ^{13}C NMR ($CDCl_3$): −1.98 [Si($\underline{C}H_3$)$_3$], 55.54 (O$\underline{C}H_3$), 107.72 (sydnone C-4), 113.86, 126.82, 129.89, 130.58, 131.50, 132.50 (aromatic CH), 128.75, 130.26, 136.45, 164.34 (aromatic quaternary C), 173.10 (sydnone C=O), 190.75 (ketone C=O) ppm.

3-(2-Acetylphenyl)-4-trimethylsilylsydnone (7d)

Using N-methoxy-N-methylacetamide (**4**, R=Me) (0.191 g, 1.85 mmol) and chlorotrimethylsilane (0.209 g, 1.93 mmol) in the general procedure gave the title compound (0.251 g), mp 93–94°C. Found: C, 56.63; H, 5.84; N, 10.02. Calc. for $C_{13}H_{16}N_2O_3Si$: C, 56.50; H, 5.84; N, 10.14. ν_{max} (KBr): 3065, 2965, 1769, 1685, 1487, 1382, 1256, 1128, 1008, 841 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ −0.14 (s, 9H), 1.82 (s, 3H), 7.60–7.74 (m, 4H); ^{13}C NMR ($CDCl_3$): 0.67 [Si($\underline{C}H_3$)$_3$], 26.04 (CO$\underline{C}H_3$), 111.01 (sydnone C-4), 114.31, 125.10, 130.04, 132.29 (aromatic C$\underline{H}$), 132.97, 145.84 (aromatic quaternary C), 163.41 (sydnone C=O), 196.70 (ketone C=O) ppm.

3-(2-Chloroacetylphenyl)-4-trimethylsilylsydnone (7e)

Using 2-chloro-N-methoxy-N-methyl-acetamide (**4**, R=$ClCH_2$) (0.255 g, 1.85 mmol) and chlorotrimethylsilane (0.209 g, 1.93 mmol) in the general procedure gave the title compound (0.271 g), mp 121–122°C. Found: C, 50.19; H, 4.90; N, 9.07. Calc. for $C_{13}H_{15}ClN_2O_3Si$: C, 50.24; H, 4.86; N, 9.01. ν_{max} (KBr): 3066, 2974, 2936, 1733, 1710, 1600, 1498, 1408, 1347, 1223, 845, 768 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 9H), 4.59 (s, 2H), 7.59–7.99 (m, 4H); ^{13}C NMR ($CDCl_3$): −2.37 [Si($\underline{C}H_3$)$_3$], 46.50 (CH_2), 107.44 (sydnone C-4), 128.31, 130.11, 132.76, 133.54 (aromatic CH), 132.35, 134.22 (aromatic quaternary C), 176.75 (sydnone C=O), 191.70 (ketone C=O) ppm.

3-(2-Benzoylphenyl)-4-bromosydnone (7f)

Using N-methoxy-N-methylbenzamide (**4**, R=Ph) (0.306 g, 1.85 mmol) and bromine (0.308 g, 1.93 mmol) in the general procedure gave the title

compound (0.445 g), mp 164–166°C. Found: C, 51.96; H, 2.64; N, 8.11. Calc. for $C_{15}H_9BrN_2O_3$: C, 52.20; H, 2.63; N, 8.12; ν_{max} (KBr): 3066, 1730, 1661, 1595, 1421, 1275, 1207, 1026, 930, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.54–7.69 (m, 5H), 7.93–8.04 (m, 4H); ^{13}C NMR ($CDCl_3$): 88.08 (sydnone C-4), 127.43, 128.70, 129.37, 131.09, 132.93, 134.04, 135.32 (aromatic CH), 131.32, 134.26, 164.65 (aromatic quaternary C), 165.06 (sydnone C=O), 191.75 (ketone C=O) ppm.

3-(2-Benzoylphenyl)-4-Iodosydnone (7g)

Using N-methoxy-N-methylbenzamide (**4**, R=Ph) (0.306 g, 1.85 mmol) and iodine (0.489 g, 1.93 mmol) in the general procedure gave the title compound (0.449 g), mp 186–188°C. Found: C, 45.83; H, 2.38; N, 7.29. Calc. for $C_{15}H_9IN_2O_3$: C, 45.94; H, 2.31; N, 7.14. ν_{max} (KBr): 3065, 1708, 1663, 1597, 1445, 1273, 1200, 1022, 930, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49–7.91 (m, 9H); ^{13}C NMR ($CDCl_3$): 58.29 (sydnone C-4), 127.11, 128.08, 129.10, 130.61, 132.01, 132.15, 132.75, 133.36, 134.28, 135.17 (aromatic C), 168.14 (sydnone C=O), 191.80 (ketone C=O) ppm.

3-(2-Benzoylphenyl)-4-phenylthiosydnone (7h)

Using N-methoxy-N-methylbenzamide (**4**, R=Ph) (0.306 g, 1.85 mmol) and diphenyl disulfide (0.421 g, 1.93 mmol) in the general procedure gave the title compound (0.473 g), mp 142–144°C. Found: C, 67.46; H, 3.71; N, 7.50. Calc. for $C_{21}H_{14}N_2O_3S$: C, 67.37; H, 3.77; N, 7.48. ν_{max} (KBr): 3072, 1749, 1657, 1596, 1446, 1386, 1279, 1239, 1036, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.22 (s, 5H), 7.38–7.44 (m, 4H), 7.66–7.76 (m, 5H); ^{13}C NMR ($CDCl_3$): 101.56 (sydnone C-4), 126.99, 127.59, 128.55, 128.79, 129.48, 129.70, 131.05, 131.88, 132.16, 133.88 (aromatic CH), 132.27, 133.17, 135.40, 135.76 (aromatic quaternary C), 167.78 (sydnone C = O), 192.40 (ketone C=O) ppm.

3-(2-Benzoylphenyl)-4-formylsydnone (7i)

Using N-methoxy-N-methylbenzamide (**4**, R=Ph) (0.306 g, 1.85 mmol) and N,N-dimethylformamide (0.141 g, 1.93 mmol) in the general procedure gave the title compound (0.368 g), mp 137–138°C. Found: C, 65.03; H, 3.39; N, 9.43. Calc. for $C_{16}H_{10}N_2O_3$: C, 65.31; H, 3.43; N, 9.52. ν_{max} (KBr): 3103, 3041, 1796, 1660, 1595, 1447, 1381, 1278, 932, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.48–7.81 (m, 9H), 9.41 (s, 1H);

^{13}C NMR ($CDCl_3$): 105.97 (sydnone C-4), 124.63, 126.95, 128.64, 129.89, 130.22, 131.44, 132.42, 133.91, 134.61, 135.78 (aromatic C), 166.16 (sydnone C=O), 174.82 (aldehyde C=O), 192.54 (ketone C=O) ppm.

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