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Ortho-Substitution of the Benzene Ring in 3-Arylsydnones Mediated by Butyllithium

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ABSTRACT: *C(4), C′(2)-Double substitution was achieved in good yields by reacting 3-arylsydnones with BuLi and then with a suitable electrophile in THF at −50°C.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:549–552, 1998

INTRODUCTION

The nature and biological activities of sydnones have drawn considerable attention [1]. During the derivatization of 3-arylsydnones, substitution takes place only at the C(4) position of the sydnone rings [2]. However, a stronger electrophilic reagent, such as the nitronium ion, can effect substitution at the C(3) position of the aryl ring [C′(3)] if the C(4) position is blocked [3]. This *meta*-substitution can be explained in terms of the mesoionic nature of the sydnone ring, the N(3) with its formal positive charge having an electron-withdrawing nature, which retards the substitution reaction on the N(3)-aryl ring and directs the incoming group to the C′(3) (i.e., the meta) position if the electrophile is sufficiently reactive. However, these reactions do not proceed under conditions suitable for benzene because of the different nature of these compounds. Thus, several sydnone derivatives have been prepared by use of a metal-bromine exchange process between a Grignard reagent (or an alkyllithium) and the 3-aryl-4-bromosydnones, followed by the addition of an electrophile [2a, 4]. Recently, a double lithiation of 3-(2-bromophenyl)sydnone was used to prepare fused-ring sydnones [5]. The present work extends the reaction of lithiated sydnones with trisubstituted silyl halides (R_3SiX) and the disubstituted phosphoryl halides (R_2PX). With double equivalents of butyllithium and the electrophile, a second substitution reaction at C(2) of the phenyl ring [C′(2)] is obtained. This process is useful for synthetic applications.

RESULTS AND DISCUSSION

Organolithium and Grignard reagents are common intermediates in organic syntheses. Organolithiums can be prepared by an exchange reaction between an alkyl halide and an alkyllithium (such as *n*-butyllithium or methyllithium) or by reacting an alkyl halide with metallic lithium. A C(4)-bromine of the sydnone ring can be exchanged with *n*-BuLi at low temperature. We used this process to prepare some C(4)-substituted and both C(4)- and C′(2)-disubstituted derivatives by varying the mole ratio of butyllithium and the electrophile. The sydnone ring tends to undergo a ring-opening reaction under strongly basic conditions. Thus, the reactions were performed at a low temperature to avoid decomposition of the sydnone ring. Similar yields were obtained by use of either a 4-bromosydnone or an unbrominated sydnone (yields 83% vs. 80%). Surprisingly, a hydrogen of the phenyl ring can be exchanged with lithium even if it exhibits low acidity ($pKa = 20$ for C(4)-H[6] and = 43 for Ph–H[7]). The activation of C(phenyl)-H might be due to the electron-withdrawing nature of N(3) and the ability of N(2) to coordinate with the

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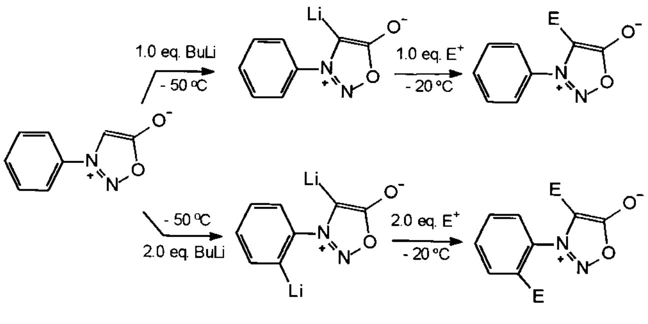
lithium on C′(2). Therefore, unbrominated sydnones could be used. The yields were generally good for a wide range of electrophiles, including R_2PCl and R_3SiCl.

The C(4)-substituted derivatives were generally obtained when limited amounts of butyllithium and the electrophile were used. Reaction of compound **1** with two equivalents of *n*-BuLi and PPh_2Cl gave exclusively the disubstituted product **4**, that is, a C(4), C′(2)-bis(diphenylphosphino)-derivative. Ordinarily, the electron-withdrawing nature of N(3) of a sydnone will direct an electrophile to the C′(3) position of a 3-aryl-4-substituted sydnone. In our system, the second substitution occurs at the C′(2) position (Scheme 1). The N(2) atom of the sydnone ring has been reported to bear a fractional negative charge [3b, 8], based on various theoretical calculations. N(2) can apparently promote lithiation at the C′(2) position by formation of a five-membered ring intermediate (**a**) [9]. This intermediate enables substitution at the C′(2) position (Scheme 2).

Reaction of compound **1** with 1.5 equivalents of *n*-BuLi and subsequently with one equivalent of PPh_2Cl gave only the monosubstituted product **3**. Compound **3** was formed regioselectively with an excess of BuLi and a limited amount of PPh_2Cl. This might be due to the steric hindrance of a bulky phosphino group in its approach to C′(2) and formation of a relatively stable five-membered ring intermediate **a** for the competitive substitution.

The presence of two oxygens on a phosphorus atom, such as in 1,2-ethylene (**18**) and 1,2-phenylene (**19**) phosphorochloridite, should enhance the electrophilicity of the phosphorus atom (Scheme 2). We expected that these compounds would behave as good electrophiles for this reaction system. However, with the former, a hydrogen of the ethylene moiety undergoes lithium exchange with the 3-phenylsydnonyllithium to yield the unbrominated sydnone (**1**). The reaction of lithiated sydnone **1** with compound **19** gave some unidentified material. Reactions of chlorodi(tert-butyl)phosphine with a mixture of 3-arylsydnone and *n*-butyllithium (mole ratio 2:1:2) yielded only the monosubstituted products at C(4) regardless of the nature of the substituents already present. This might be due to the higher steric hindrance of the *t*-butyl group that retards the possible competitive reaction.

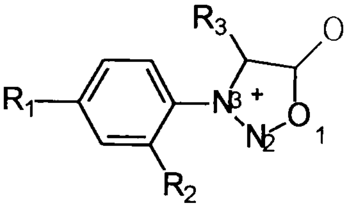


E^+: R_2P^+; R_3Si^+

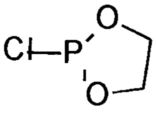
SCHEME 1

CONCLUSION

Normal electrophilic substitutions of the aryl group of arylsydnones yield the *meta*-substituted products. In our substitution reactions via an organolithium intermediate, N(2) of the sydnone ring is able to stabilize the carbon(aryl)-lithium that favors binding at the C′(2) position to form a five-membered ring intermediate. In a second electrophilic substitution of



SCHEME 2 R_1, R_2, R_3: H, H, H (1); H, H, Br (2); H, PPh_2, PPH_2 (3); H, H, PBu^t_2 (4); H, H, $SiMe_3$ (5), H, $SiMe_3$, $SiMe_3$ (6); H, $SiPh_3$, $SiPh_3$ (7); MeO, H, H, (8); MeO, H, PPh_2 (9); MeO, PPh_2, PPh_2 (10); MeO, H. PBu^t_2 (11); MeO, $SiMe_3$, $SiMe_3$ (12); MeO, $SiPh_3$, $SiPh_3$ (13); NO_2 H, H (14); NO_2, H, PPh_2 (15); NO_2, PPH_2, PPH_2 (16); NO_2, PBu^t_2, PBu^t_2 (17).



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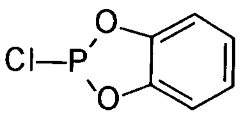

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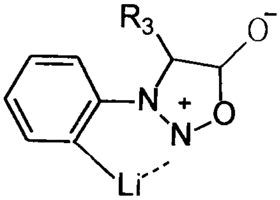

a

this complex, the double-substitution process results in an *ortho*-substituted product. This character allows us to prepare C′(2)-substituted sydnones that are often difficult to prepare by the general procedure, that is, nitrosation of an N-substituted amino acid followed by dehydration to give ring closure.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC-250 instrument with deuteriochloroform as the solvent and tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL DX-300 double-focusing mass spectrometer. Samples were introduced via a direct-insertion probe. The ionization energy was 70 eV. Microanalyses were performed on a Heraeus CHN-O-Rapid analyzer. 3-Arylsydnones and 3-phenyl-4-bromosydnone were prepared as described in the literature [10]. Tetrahydrofuran (THF) was distilled from sodium-ketyl before use. The reaction was performed under a nitrogen atmosphere.

Typical Procedure for the Substitution of 3-Arylsydnones

Under a nitrogen atmosphere, to a solution of 3-phenylsydnone (**1**, 0.91 g, 4.9 mmol) in THF (15 mL) with use of a magnetic stirrer at −50°C, a solution of *n*-BuLi (1.6 M, 3.1 mL, 5.0 mmol) was added dropwise. After the mixture had been stirred at that temperature for 0.5 hour, $(C_6H_5)_2PCl$ (0.82 mL, 5.0 mmol) was added. After an additional 4 hours at −20°C, the mixture was allowed to warm to RT and then treated with ice water (30 mL). 4-Diphenylphosphino-3-phenylsydnone (**3**) (1.61 g [80% yield]) was obtained as light yellow flat crystals upon filtration and crystallization from CH_2Cl_2. The physical properties and spectroscopic data of the new products obtained by this general process are summarized as follows.

Products from 3-Phenylsydnone **1** *in Reaction with Chlorodiphenylphosphine.* 3-(2-Diphenylphosphinophenyl)-4-diphenylphosphinosydnone **3**: yield 74%; mp 204–205°C; ^{1}H NMR δ 7.21–7.63 (m, $C_6\underline{H}_5P$ and $C_6\underline{H}_5$); IR 1750 (ν_{CO}) cm^{-1}; MS *m/z* (%) 472 ([M-NO-CO])$^+$, 21); 185 (100); anal. calcd for $C_{32}H_{24}N_2O_2P_2$: C, 72.45; H, 4.56; N, 5.28. Found: C, 72.59; H, 4.71; N, 5.33.

Chloro-di-(tert-butyl)phosphine. 4-(Di-(tert-butyl)phosphino-3-phenylsydnone **4**: yield 67%; mp 143–144°C; ^{1}H NMR 1.25 (s, 18H, C $[CH_3]_3$), 7.43–7.63 (m, 5H, C_6H_5); IR 1742 (ν_{CO}) cm^{-1}; MS *m/z* (%) 306 (M$^+$, 16), 250 (14); 57 (100); anal. calcd for $C_{16}H_{23}N_2O_2P$: C, 62.73; H, 7.57; N, 9.17. Found: C, 62.70; H, 7.54; N, 9.16.

Chlorotrimethylsilane. 4-Trimethylsilyl-3-phenylsydnone **5**: yield 85%; mp 105–106°C; ^{1}H NMR δ 0.09 (s, 9H, CH_3), 7.47 (dd, 2H, *J* = 1.3, 7.5 Hz), 7.68–7.57 (m, 3H); IR 1740 (ν_{CO}) cm^{-1}; MS *m/z* (%) 234 (M$^+$, 9), 176 (42); 73 (100); anal. calcd for $C_{11}H_{14}N_2O_2Si$: C, 56.38; H, 6.02; N, 11.95. Found: C, 56.40; H, 6.09; N, 11.78.

3-(2-Trimethylsilylphenyl)-4-trimethylsilylsydnone **6**: yield 75%; mp 61–62°C; ^{1}H NMR δ 0.05 (s, 9H, syd-Si$[C\underline{H}_3]_3$), 0.16 (s, 9H, Ar-Si$[C\underline{H}_3]_3$), 7.29 (d, 1H, *J* = 7.5 Hz), 7.50–7.73 (m, 3H); IR 1741 (ν_{CO}) cm^{-1}; MS *m/z* (%) 306 (M$^+$, 4), 291 (9), 248 (60), 73 (100); anal. calcd for $C_{14}H_{22}N_2O_2Si_2$: C, 54.86; H, 7.23; N, 9.14. Found: C, 54.96; H, 7.18; N, 9.10.

Chlorotriphenylsilane. 3-(2-Triphenylsilylphenyl)-4-triphenylsilylsydnone **7**: yield 68%; mp 256–258°C; ^{1}H NMR δ 7.25–7.69 (m, 34H, Ar-H); IR 1741 (ν_{CO}) cm^{-1}; MS *m/z* (%) 620 (M$^+$-NO-CO, 33), 260 (Si$[C_6H_5]^+$, 100); anal. calcd for $C_{44}H_{34}N_2O_2Si_2$: C, 77.84; H, 5.05; N, 4.13. Found: C, 77.80; H, 5.03; N, 4.10.

Products from 3-(4-Anisyl)sydnone **8** *in Reaction with Chlorodiphenylphosphine.* 3-(4-Anisyl)-4-(diphenylphosphino)sydnone **9**: yield 91%; mp 136–138°C; ^{1}H NMR δ 3.90 (s, 3H, OCH_3), 7.07 (d, 2H, *J* = 9.0 Hz), 7.35–7.50 (m, 12H, C_6H_5P); IR 1760 (ν_{CO}) cm^{-1}; MS *m/z* (%) 376 (M$^+$, 14), 318 (52), 185 (100); anal. calcd for $C_{21}H_{17}N_2O_3P$: C, 67.02; H, 4.55; N, 7.44. Found: C, 67.00; H, 4.63; N, 7.44.

3-(2-Diphenylphosphino-4-methoxyphenyl)-4-diphenylphosphinosydnone **10**: yield 85%; mp 127–128°C; ^{1}H NMR δ 3.72 (s, 3H, OCH_3), 6.72 (dd, 1H, *J* = 3.5, 2.8 Hz), 7.01 (dd, 1H, *J* = 8.7, 2.8 Hz), 7.18–7.48 (m, 21H); IR 1749 (ν_{CO}) cm^{-1}; MS *m/z* (%) 515 ([*M*-CH_3-NO]$^+$, 8), anal. calcd for $C_{33}H_{26}N_2O_3P_2$: C, 70.71; H, 4.68; N, 5.00 Found: C, 70.58; H, 4.79; N, 5.12.

Chloro-di-(tert-butyl)phosphine. 3-(4-Ansiyl)-4-(di-[tert-butyl])phosphinosydnone **11**: yield 66%; mp 105–106°C; ^{1}H NMR δ 1.27 (s, 9H, CH_3); 1.37 (s, 9H, CH_3), 3.69 (s, 3H, OCH_3), 7.02 (d, 2H, *J* = 8.8 Hz), 7.36 (d, 2H, *J* = 8.8 Hz); IR 1739 (ν_{CO}) cm^{-1}; MS *m/z* (%) 336 (M$^+$, 48), 280 (36), 57 (100); anal. calcd for $C_{17}H_{25}N_2O_3P$: C, 60.70; H, 7.49; N, 8.33. Found: C, 60.91; H, 7.15; N, 8.49.

Chlorotrimethylsilane. 3-(2-Trimethylsilyl-4-methoxyphenyl)-4-trimethylsilyl)sydnone **12**: yield 65%; mp 85–86°C; ^{1}H NMR δ 0.07 (s, 9H, Si-C$[CH_3]_3$), 0.15 (s, 9H, Ar-SiC[CH$_3$]$_3$), 3.89 (s, 3H, OCH$_3$), 6.98 (dd, 1H, *J* = 8.5, 2.8 Hz), 7.21 (d, 1H, *J* = 2.8 Hz), 7.38 (d, 1H, *J* = 8.5 Hz); IR 1739 (ν_{CO}) cm^{-1}; MS *m/z (%)* 336 (M $^+$, 6), 278 (100), 73 (37); anal. calcd for $C_{15}H_{24}N_2O_3Si_2$: C, 53.53; H, 7.19; N, 8.32. Found: C, 53.29; H, 7.12; N, 8.29.

Chlorotriphenylsilane. 3-(2-Triphenylsilyl-4-methoxyphenyl)-4-triphenylsilyl)sydnone **13**: yield 67%; mp 210–211°C; ^{1}H NMR δ 3.62 (s, 3H, OCH$_3$), 7.25–7.43 (m, 31H, Ar–H), 7.62 (dd, 2H, *J* = Hz); IR 1737 (ν_{CO}) cm^{-1}; MS *m/z (%)* 650 (M$^+$-NO-CO, 42), 260 (Ph$_3$Si$^+$, 100); anal. calcd for $C_{45}H_{36}N_2O_3Si_2$: C, 76.24; H, 5.12; N, 3.95. Found: C, 76.22; H, 5.03; N, 4.08.

Products from 3-(4-Nitrophenyl)sydnone **14** *in Reaction with Chlorodiphenylphosphine.* 4-Diphenylphosphino-3-(4-nitrophenyl)sydnone **15**: yield 32%; mp 174–175°C; ^{1}H NMR δ 7.38–7.52 (m, 10H, Ar–H), 7.76 (d, 2H, *J* = 7.0 Hz), 8.48 (d, 2H, *J* = 7.0 Hz); IR 1755 (ν_{CO}) cm^{-1}; MS *m/z (%)* 391 (M$^+$, 17), 333 (18), 185 (100); anal. calcd for $C_{20}H_{14}N_3O_4P$: C, 61.39; H, 3.61; N, 10.74. Found: C, 61.38; H, 3.55; N, 10.59.

3-(2-Diphenylphosphino-4-nitrophenyl)-4-diphenylphosphinosydnone **16**: yield 40%; 152–153°C; ^{1}H NMR δ 7.41–7.52 (m, 20H, Ar–H), 7.76–7.84 (m, 3H, Ar–H); IR 1723 (ν_{CO}) cm^{-1}; MS *m/z (%)* 575 (M$^+$, 1), 376 (100); anal. calcd for $C_{32}H_{23}N_3O_4P_2$: C, 66.79; H, 4.03; N, 7.30. Found: C, 66.75; H, 4.09; N, 7.24.

Chloro-di-(tert-butyl)phosphine. 4-(Di-(tert-butyl)phosphino)-3-(4-nitrophenyl)sydnone **17**: yield 76%; mp 157–159°C; ^{1}H NMR δ 1.37 (s, 9H, 3 × CH$_3$), 1.44 (s, 9H, 3 × CH$_3$), 7.94 (d, 2H, *J* = 9.5 Hz), 8.52 (d, 2H, *J* = 9.5 Hz); IR 1756 (ν_{CO}) cm^{-1}; MS *m/z (%)* 351 (M$^+$ $-C_4H_8$, 5), 57 (100); anal. calcd for $C_{16}H_{22}N_3O_4P$: C, 54.70; H, 6.31; N, 11.96. Found: C, 54.65; H, 6.33; N, 11.91.

REFERENCES

[1] C. G. Newton, C. A. Ramsden, *Tetrahedron, 38,* 1982, 2965.

[2] (a) T. Fuchigami, C. S. Chen, T. Nonaka, *Bull. Chem. Soc. Jpn., 59,* 1986, 483 and 487; (b) M. Y. Yeh, H. J. Tien, L. Y. Huang, M. H. Chen, *J. Chin. Chem. Soc., 30,* 1983, 29; (c) H. J. Tien, M. Ohta, *Synthesis,* 1974, 152; (d) M. Y. Yeh, H. J. Tien, T. Nonaka, *J. Org. Chem., 48,* 1983, 1382; (e) H. J. Tien, G. M. Fang, S. T. Lin, L. L. Tien, *J. Chin. Chem. Soc., 39,* 1992, 107.

[3] (a) P. M. Weintraub, R. E. Bambury, *Tetrahedron Lett.,* 1969, 579; (b) H. J. Tien, S. T. Lin, J. T. Sheu, *Can. J. Chem., 72,* 1994, 1610.

[4] (a) H. Dichopp, *Chem. Ber., 111,* 1980, 1830; (b) V. N. Kalinin, S. F. Min, *J. Organomet. Chem., 352,* 1988, C34.

[5] K. Turnbull, D. M. Krein, *Synthesis,* 1996, 1183.

[6] C. V. Greco, B. P. O'Reilly, *J. Heterocycl. Chem., 7,* 1970, 1433.

[7] A. Streitwieser Jr., P. J. Scanon, H. M. Niemeyer, *J. Am. Chem. Soc.,*, 94, 1972, 7936.

[8] (a) O. J. Martensson, *J. Mol. Struct., 9,* 1971, 321; (b) G. H. Schmid, *J. Mol. Struct., 5,* 1970, 236; (c) M. H. Palmer, A. J. Gaskell, M. S. Baber, *J. Mol. Struct., 12,* 1972, 197; (d) J. O. Morley, *J. Chem. Soc. Perkin Trans. 2,* 1995, 253.

[9] (a) P. Beak, A. I. Meyers, *Acc. Chem. Res., 19,* 1986, 356; (b) P. Beak, V. Snieckus, *Acc. Chem. Res., 15,* 1982, 306; (c) N. S. Narasimhan, R. S. Mali, *Top. Curr. Chem., 138,* 1987, 63; (d) M. Reuman, A. I. Meyers, *Tetrahedron, 41,* 1985, 837.

[10] R. A. Eade, J. C. Earl, *J. Chem. Soc.,* 1946, 591; (b) R. A. Eade, J. C. Earl, *J. Chem. Soc.,* 1948, 2307; (c) W. Baker, W. D. Ollis, V. D. Poole, *J. Chem. Soc.,* 1949, 307.