PREPARATION AND TRAPPING OF 3-LITHIUM-O-LITHIOPHENOXIDE

Harold G. Selnick,* Michelle L. Bourgeois, John W. Butcher, and Ellen M. Radzilowski

Merck Research Laboratories, West Point, Pennsylvania 19486

Abstract: 3-Bromophenol and 3-Bromothiophenol are converted into the title compounds by proton abstraction followed by halogen-metal exchange with tert-butyllithium. The resulting dianions are then trapped on carbon with various electrophiles.

While exploring the synthesis of compounds with anti-viral activity, it was desirable to make use of a synthon such as 2. In principle this material should be easily derived from 3bromophenol (or 3 - bromothiophenol) by deprotonation and then halogen-metal exchange. The preparation of ortho and para lithium-O-lithiophenoxide and lithium-S-lithiothiophenoxide has been previously reported.¹ The pioneering work of Gilman demonstrated that these dianionic species can indeed be generated by metal - halogen exchange with n-butyllithium. The dianions are then conveniently trapped by carbon dioxide at carbon. Talley has since explored the reactivity of the ortholithium-O-lithiophenoxide with aldehydes and ketones² and Posner³ has reported the preparation of ortholithium-O-lithiophenoxide by directed ortho deprotonation. Recently, a number of publications presenting the directed ortho lithiation of thiophenols to give ortholithium-S-lithiothiophenoxide have appeared.⁴



Curiously, the preparation and reactions of the corresponding meta isomers (eg Eqn. 1) have not been described. Protected forms of 3-bromophenol (methyl⁵ or silyl⁶ ether) have been used for the halogen-metal exchange. The resulting anions were trapped with an electrophile, and the protecting groups were subsequently removed. The ability to generate unprotected 2 or its equivalent would obviate the need for protecting group manipulations. This paper describes the convenient preparation and trapping of these species.

When 3-bromophenol was treated under the standard conditions for halogen-metal exchange (>2 eq. n-BuLi, ether or THF, 0° or room temperature, 1-2 hours), 1,2 starting material was the primary material isolated after aqueous workup. However, when tert-butyllithium was used, both 3-bromophenol and 3-bromothiophenol underwent a rapid and clean conversion to the

Entry	Substrate	Electrophile	Product	MP(°C)	Yield
1	HO Br	Mo-O. N. Mo	HOUT	70-72	60 %
2	11	Me ^{-O} N Me	HOUT	114-116 IR. ¹¹ 113-115	68 %
3	••	Me ⁻⁰ -N Me	HOUTUN	97-100	50 %
4		Mo C ₇ H ₁₅	HO HO C ₇ H ₁₅	oli	59 %
5	•	Dimethyl acetamide	HO	92-94 lit. ¹¹ 95-97	35 %
6		H Me	HO H Me	72-73	62 %
7	11	1) SO ₂ (g) 2) NH ₂ OSO ₃ H	HOSO2NH2	163-164 lit. ¹³ 164	61 %
8	HO	о ме ^{, С} 7н ₁₅	HO Me C ₇ H ₁₅	107-109	90 %
9	HS Br	Me-0-N Me	AcS	75-76	71 %
10	HS Br	Me ⁻⁰ N Me	Acs	60-61	76 %

Table	1

corresponding diamons at -76° C. The reactions can be carried out in either or THF and formation of the dianion is essentially complete within 15 minutes at this temperature.⁷ Addition of an appropriate electrophile and warming results in trapping on carbon. Initially there was concern that halogen-metal exchange might compete with deprotonation of the acidic phenolic hydrogen as the first event. This was not the case as treatment of the 3-bromophenol with one equivalent of tert-butyllithium in ether at -78°C and then aqueous workup gave only recovered starting materiai (HPLC, NMR).

In the present study the dianions generated at -78° C were trapped with 2-nonanone, dimethylacetamide, isovaleraldehyde, and several N,O-dimethylhydroxamides. ⁸ The results are shown in the table.^{9,10} The yields reported are for isolated and purified materials and are based on the amount of starting electrophile. Higher yields of product are obtained if the dianionic intermediate is used in excess as some protonation of the dillithic species prior to reaction appears to be unavoidable in our hands. The major byproduct in the case of the Weinreb type amides is the result of fragmentation of the N,O-dimethylhydroxamide to give the N-methyl amide due to excess tert-buty-lithium.¹² In the case of the para-lithio examples (entries 8 and 10), the use of tertbuty)lithium greatly accelerates the rate of formation of the dilanion and is therefore an improvement over the published procedures.¹ For the thiophenol examples (entries 9 and 10) the workup included treatment with acetyl chloride. The products were then characterized as their thioacetates.

Acknowledgements: The authors wish to thank Drs. Gerald Ponticello and David Claremon for helpful discussions during the course of this work and Jean Kaysen for preparation of the massuscript.

References and Notes:

- The generation of the para lithio species requires temperatures of 25° and above for 0.5 to 2 hours for 50 75 percent conversion. a) Gilman, H.; Arntzen, C. E.; Webb, F. J. J. Org. Chem. 1945, 10, 374. b) Gilman, H. Organic Reactions 1951, 6, 339.
- a) Talley, J. J.; Evans, I. A. J. Org. Chem. 1984, 49, 5267. b) For a similar case involving dihydridic phenols see: Saa, J. M.; Morey, S.; Frontera, A.; Costa, A. Tetrahedron Lett. 1991, 32 (49), 7313.
- 3. Posner, G. H.; Canella, K. A. J. Am. Chem. Soc. 1985, 107, 2571.
- a) Block, E.; Ofori-Okai, G.; Zubieta, J. J. Am. Chem. Soc. 1989, 111, 2327. b) Figuly, G. D.; Loop, C. K.; Martin, J. C. J. Am. Chem. Soc. 1989, 111, 654. c) Smith, K.; Lindsay, C. M.; Pritchard, G. J. J. Am. Chem. Soc. 1989, 111, 665.
- 5. Bird, T. G. C.; Bruneau, P.; Crawley, G. C.; Edwards, M. P.; Foster, S. J.; Girodeau, J-M.; Kingston, J. F.; McMillan, R. M. *J. Med. Chem.* **1991**, *34*, 2176.

- 6. Misra, R. N.; Brown, B. R.; Han, W-C.; Harris, D. N.; Hedberg, A.; Webb, M. L.; Hall, S. E. J. Med. Chem. 1991, 34, 2882.
- 7. The deprotonation step was presumably complete within seconds. The halogen-metal exchange step was assumed to be complete in 5 10 minutes. If ether is used as solvent the dianion tends to precipitate at low temperatures.
- 8. Weinreb, S. M.; Nahm, S. Tetrahedron Lett., 1981, 22, 3815.
- 9. All products were characterized by the appropriate spectral and analytical means and, when available, by comparison to authentic materials.
- Typical experimental procedures are provided for entries 3 and 9: For entry 3: A solution of 3-bromophenol (346 mg, 2 mmole) in THF (30 mL) was cooled to -78° C under an inert atmosphere. A solution of freshly opened tert-butyllithium (4 mL of a 1.7 M solution, 6.8 mmole) was then added via syringe. The pale yellow solution was stirred at -78°C for 5 minutes. A solution of N-methyl-N-methoxy-2-picolinamide (332 mg, 2 mmole)in THF (5 mL) was then added and the reaction warmed to room temperature. The mixture was poured into saturated sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 * 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica gel using 2% methanol/chloroform as eluent to give 198 mg (50 %). MP: 97-100°C (Ether/Hexane); IR 3330.3, 1666.3, 1582.1, 1448.6, 1315.5 cm^{-1; 1}NMR (CDCl3) δ 8.68 (app d, J = 4 Hz, 1H), 8.05 (app d, J = 7.5 Hz, 1 H), 7.95 (dt, J = 2, 7.5 Hz, 1 H), 7.58 - 7.48 (m, 2 H), 7.41-7.39 (m, 1 H), 7.28 (t, J = 7.8 Hz, 1 H), 7.02 - 6.94 (m, 1 H) 6.3 (br s, 1 H); Analysis calcd. for C12H9NO2: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.40; H, 4.63; N, 7.02.

For entry 9: To a solution of m-bromothiophenol (1.5 gm, 7.93 mmole) in anhydrous THF (40ml) under argon and at -78°c was added 1.7M tert-butyllithium/pentane (9.33 ml. ,15.86 mmole). The light yellow solution was stirred at -78°C for 5 min. afterwhich a solution of cyclohexyl-N,O-dimethylhydroxyamide (0.453 gm., 2.64 mmole) in THF (10ml) was slowly added. The reaction was stirred an additional 10 min. followed by addition of acetyl chloride (1.13 ml., 15.86 mmole). The reaction was allowed to warm to room temperature, poured into water (50ml) and product extracted with ethyl acetate (2 \pm 50 ml). The ethyl acetate was dried over sodium sulfate, filtered, concentrated, and chromatographed on silica (5% ethyl acetate/hexane) to give 0.49 gm. (71%). MP: 75-76 °C(Hexane); IR 2930.8, 2853.6, 1708.3, 1681.0 (cm⁻¹);¹H NMR (CDCl3) δ 7.92-8.0 (m, 2H) ,7.59(d t, J=7.6 and 1.5 Hz, 1H), 7.52(t, J=6.6 Hz, 1H), 3.23 (t t, J=11.1 and3.2 Hz, 1H), 2.46 (s,3H), 1.2-2.0(m, 10H). Anal. Calcd. for C15H1802S: C, 68.67; H, 6.92. Found C, 68.20; H, 6.88. FAB HRMS Calcd. for C15H1802S: 263.1106. Found: 263.1119

- 11. Authentic material purchased from Aldrich chemical company.
- 12. Graham, S. L.; Scholz, T. H. Tetrahedron Lett., 1990, 31, 6269.
- 13. Parke, D. V.; Williams, R. T. J. Chem. Soc., 1950, 1757.

(Received in USA 22 July 1992; accepted 19 January 1993)