

Directed Metallation of Model Adrenaline Compounds

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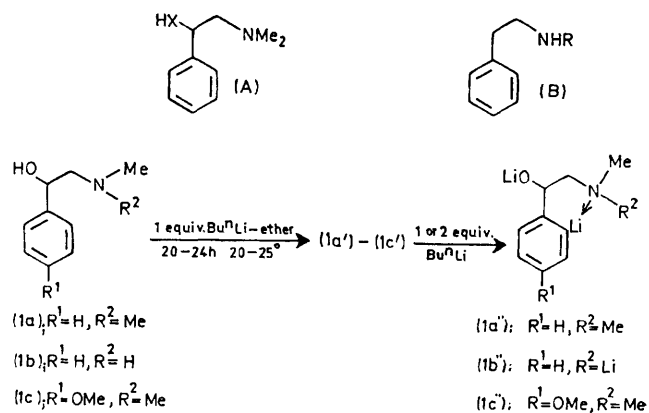
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Summary Metallation of three α -hydroxy- β -phenethylamines gave a series of 1,2-disubstituted benzenes upon condensation with a variety of electrophiles; these hydroxyethylamine substituents are among the most complex substituents to provide directed metallation.

β -PHENETHYLAMINES have important physiological properties, and the preparation of their ortho-substituted derivatives using the directed metallation reaction¹ has been sought to examine ortho moderation of the amine function.

In contrast to *NN*-dimethylaminoethylferrocene,^{2,3} *NN*-dimethyl- β -phenethylamine gave a directed metallation product in very low yield,^{3,4} the main product being polystyrene which presumably arose *via* base-induced elimination of dimethylamine. Two attempts to avoid this elimination were made; (i) dimetallation of a phenethylamine system (A) containing an acidic α -substituent, where ionization of the proton attached at X would significantly decrease the acidity of the benzyl proton and (ii) dimetallation of the monoalkyl phenethylamine system (B) where initial metallation of the secondary amine group would decrease acidity of the benzyl protons, and reduce the leaving group capability of the amine as amide ion.

Directed metallation of the α -hydroxyphenethylamine systems [(1a)—(1c)], which constitute examples of structure



SCHEME 1

(A) has been achieved (Scheme 1). (1b) also possessed a secondary amine function and thus combines features of

both A and B. Initial metallation of the hydroxyl proton in systems [(1a)—(1c)] gave the alkoxide species [(1a')—(1c')], 2 equiv. of BuⁿLi produced significant metallation to give (1a'') and (1c''), and 3 equiv. were required to form (1b''). Condensation of the 2-lithio intermediates with electrophiles give the corresponding ortho-substituted benzenes in moderate to good yields (Table). In most cases no products from reaction at the nucleophilic centres at oxygen or nitrogen were isolated.

TABLE

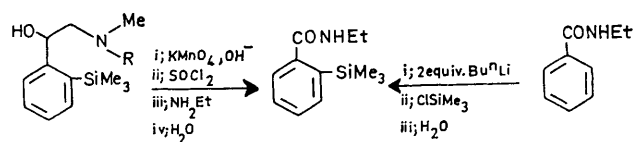
Products from treatment of lithio-intermediates with various electrophiles.

Lithio-intermediate	Electrophile	Ortho-substituent introduced	Yield (%) ^a
(1a'')	ClSiMe ₃	SiMe ₃	61
(1a'')	Ph ₂ CO	CPh ₂ OH	48
(1a'')	MeI	Me	47
(1a'')	(CH ₂ O) _x	CH ₂ OH	33
(1b'')	ClSiMe ₃	SiMe ₃	21
(1c'')	Ph ₂ CO	CPh ₂ OH	48

^a Analytical data for these compounds were all satisfactory.

For most of the products the ortho disposition of the substituents could be deduced from the absorption in the fingerprint region of their i.r. spectra. In addition, for the benzophenone adducts, an upfield shift of 10.5 and 16 Hz of the -NMe₂ resonance relative to that in the starting material, (1a) and (1c) respectively, showed the ortho

orientation of the diphenylcarbinol group in these products.⁵ However, for the products of the reaction of (1a) and (1b) with trimethylchlorosilane, strong absorptions due to the trimethylsilyl group obscured part of the fingerprint region, and chemical proof of structure was necessary. 2-Tri-



R=H or Me

SCHEME 2

methylsilyl-*N*-ethylbenzamide was prepared by two distinct metallation routes. Hauser and Puterbaugh had demonstrated that metallation of *N*-methylbenzamide occurred only at the ortho position,⁶ and this behaviour also applies to the *N*-ethyl analogue.⁷ The second route to 2-trimethylsilyl-*N*-ethyl benzamide involved oxidation to -CO₂H of the hydroxyaminoethyl side-chain of the trimethylsilyl adducts of (1a) and (1b), and conversion *via* the acid chloride to the ethylamide. Since the products obtained by the two routes (Scheme 2) were identical, the ortho disposition of substituents in these molecules was verified.

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¹ For reviews on directed metallation, *cf.* E. Kaiser and D. W. Slocum in 'Organic Reactive Intermediates,' ed. S. McManus, Academic Press, New York, 1973, pp. 337—415; D. W. Slocum and D. I. Sugarman in 'Directed Metallation,' Advances in Chemistry Series, number 130, ed. A. Langer, American Chemical Society, Washington, 1974, pp. 227—247.

² D. W. Slocum, T. R. Engelmann, and C. A. Jennings, *Austral. J. Chem.*, 1968, **21**, 2319.

³ D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, 1971, **36**, 377.

⁴ N. S. Narasimhan and A. C. Ranade, *Tetrahedron Letters*, 1968, 603.

⁵ D. W. Slocum and C. A. Jennings, *J.C.S. Chem. Comm.*, 1972, 54.

⁶ W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 853.

⁷ D. W. Slocum, unpublished observation.