Tetrahedron Letters,Vol.24,No.36,pp 3795-3798,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

ORTHO-AMINATION OF LITHIATED TERTIARY BENZAMIDES. SHORT ROUTE TO POLYSUBSTITUTED ANTHRANILAMIDES

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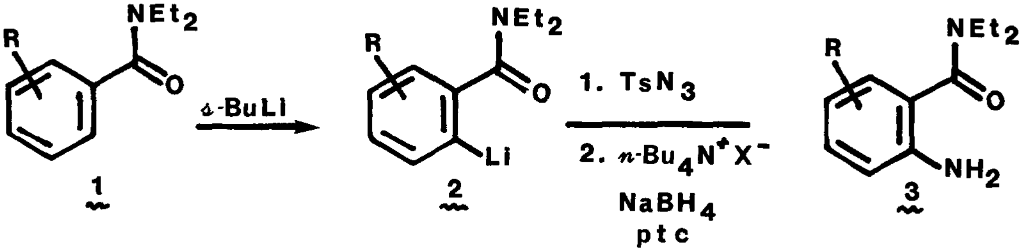
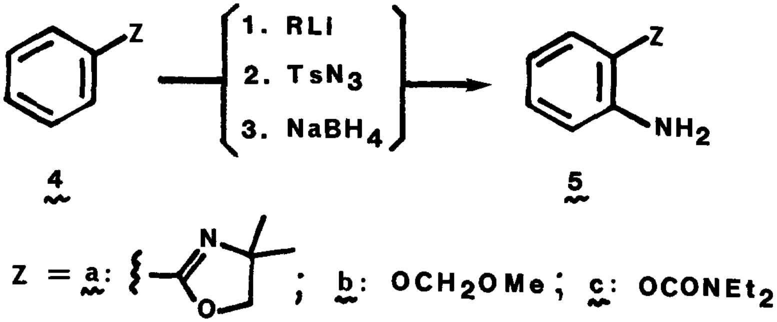
Summary Directed lithiation of benzamides (1), phenyloxazoline (4a), methoxymethoxybenzene (4b), and O-phenyl carbamate (4c) followed by sequential treatment with TsN_3 and $NaBH_4$ constitutes a general route to synthetically useful amino aromatics 3 and 5.

We wish to report a convenient procedure for the introduction of the $^+NH_2$ synthon into ortho lithiated tertiary benzamides[1] which provides a general entry into diversely substituted anthranilamides (Scheme). We also demonstrate the utility of this procedure for ortho amination of other aromatic substrates derived by the directed metalation method (4a-c). Although a number of useful $^+NH_2$ synthetic equivalent reagents have been recently developed,[2] few have been applied in context of a directed ortho metalation tactic.[2b,3,4] Our method extends the scope of benzamide directed metalation chemistry[1] and allows preparation of polysubstituted anthranilic acid derivatives which are poorly accessible by classical electrophilic substitution.[5,6]



Scheme

Lithiation of N,N-diethyl benzamide (1a) under standard conditions[1] (1 equiv s-BuLi/TMEDA/THF/-78°C/1 h) followed by sequential treatment with tosyl azide (1 equiv) according to the excellent procedure of Spagnolo et al[7] gave the lithio tosyl triazoline. Although this intermediate could be isolated, overall yield efficiency was best achieved by direct reduction with $NaBH_4$ under phase transfer conditions[8] to give the anthranilamide 3a. Similarly, a number of substituted N,N-diethylbenzamides 1 were converted into the corresponding anthranilamides 3 in modest to good yields (Table). Methoxybenzamides 1b-1d,1g, and 1i give generally good yields of products, the most favorable cases being the otherwise poorly accessible compounds in which $^{+}NH_2$ has been introduced in between the OMe and amide function (1a, 1g, 1i). *p*-Methyl substituents show no interference as evidenced from examples 1e and 1i. Transmetalation of the *o*-lithiated species into the corresponding Grignard reagent using $MgBr_2 \cdot 2Et_2O$, a useful tactic for introduction of aliphatic aldehydes and allyl units,[9] leads to insignificant improvement in yield of anthranilamide (1b). The low yield of 1f may be the result of complications due to benzyne formation[10] although lowering the temperature did not produce higher yields.



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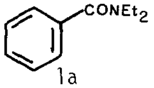
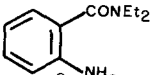
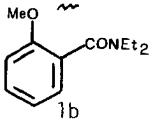
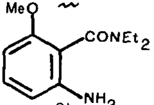
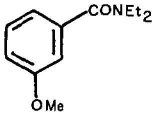
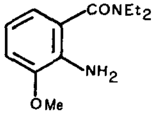
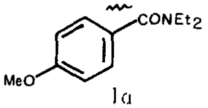
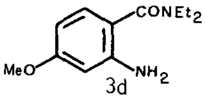
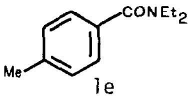
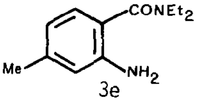
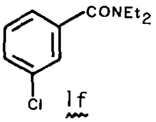
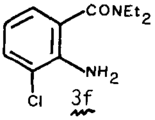
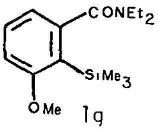
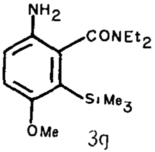
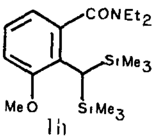
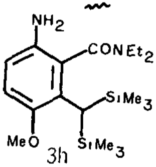
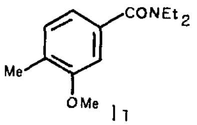
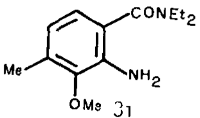
The directed metalation mediated ortho-amination procedure was extended to phenyl oxazoline 4a,[11] methoxymethoxy 4b,[12] and carbamate 4c[13] systems to give the 1,2-disubstituted aromatics 5a, 5b, and 5c respectively in good yields.[14] The procedure followed for 4a and 4c was identical to that used for the diethylbenzamides 1 whereas the methoxymethoxy case 4b required metalation with *t*-BuLi at 0°C in Et_2O solution.[12]

Compounds 1g and 1h incorporate respectively silicon protection of reactive aromatic C-H and C-Me sites.[15] Desilylation of 1g (TBAF/THF-H_2O/RT/1 h)[15] and 1h (1.TFA/reflux/36 h, 2. aqNa_2CO_3/MeOH/reflux/24 h) provided N,N-diethyl-5-methoxyanthranilamide (80%, bp 100°C/0.7 mm) and N,N-diethyl-5-methoxy-6-methylanthranilamide (78%, bp 115°C/0.1 mm) respectively.

The aromatic directed metalation strategy is thus usefully adopted for the ortho introduction of the $^{+}NH_2$ synthon in carbon (1, 4a)- and oxygen (4b, 4c)-based systems. The anionic control of regiospecificity allows synthesis of polysubstituted anthranilamides which cannot be derived via electrophilic substitution (e.g. via NO_2^{+}). Silicon protection (1g) provides for isomer flexibility (3c vs desilylated 3g). Finally, benzamides[1] and

TABLE Ortho Amination of Tertiary Benzamides

Benzamide	Anthranilamide[a]	Yield, %[b]	Mp(bp)[c] °C (solvent)
 1a	 3a	40	70/0.1 mm
 1b	 3b	66 71[d]	72-73 (Et_2O-hexane)
 1c	 3c	55	85/0.15 mm
 1d	 3d	34	100/0.1 mm
 1e	 3e	82	70/0.2 mm
 1f	 3f	31 36[e]	90/0.15 mm
 1g	 3g	69	96-98 dec (EtOAc-hexane)
 1h	 3h	47	120.5-121 ($EtOH$-H_2O)
 1i	 3i	69	90/0.05 mm

[a] Products show analytical and spectral (IR, NMR, MS) data consistent with their assigned structures. [b] All yields are of purified (chromatographed or distilled) materials. [c] Bps represent air bath temperatures of the Kugelrohr distillations. [d] Obtained via Li → MgBr transmetalation (see ref. 9). [e] Obtained by lithiation at -100°C.

aryl oxazolines[4,11] are potential hydrolytic precursors for anthranilic acids which are useful synthetic intermediates.[16] Extension of this method to other ortho metalation directors may be envisaged.[17]

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17. The financial support of NSERC of Canada through Grants-in-aid of research and a Graduate Scholarship (to J.N.R.) is gratefully acknowledged.

(Received in USA 9 June 1983)