

Synthesis of β -Phenylethylamines from Styrene Derivatives

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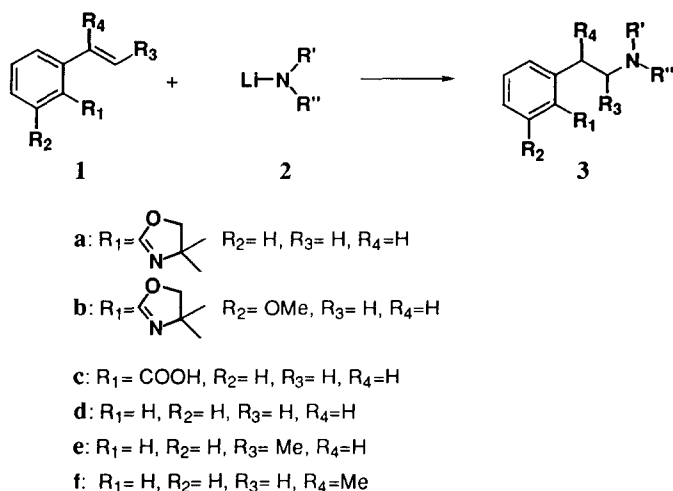
Abstract: β -Phenylethylamines are prepared from the styrene derivatives: 4,4-dimethyl-2-(2-vinylphenyl)-2-oxazoline, 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline, 2-vinylbenzoic acid, styrene, β -methylstyrene, and α -methylstyrene. © 1998 Elsevier Science Ltd. All rights reserved.

β -Phenylethylamines are of interest not only because of the different and interesting pharmacological properties of the simplest members of this family (adrenergic, sympathomimetic, anorexic, etc.),¹ but also for their presence in a large number of skeletons of more complicated structures: phenanthrene alkaloids, aporphines, berberines, benzylisoquinolines, etc. There are several methods for their preparation;² here we investigate a new strategy towards the preparation of β -phenylethylamines based on the addition of lithium amides to styrenes. Our previous studies on the chemistry of styrene derivatives^{3,4} in which we studied the 1,6-conjugate addition to *o*-vinylphenyloxazolines of alkyl and phenyllithium compounds, and its application to the synthesis of 3-*n*-alkylphthalides, showed us that, at least, when styrene bore 2-oxazoline substituent those nucleophilic additions to the exocyclic double bond were possible without any subsequent polymerization. Traditionally treatment of styrene with lithium and sodium amides has been limited to the synthesis of polystyrenes by anionic polymerization, and to our knowledge there are no reports on the isolation of the β -phenylethylamines derived from the first carbanion formed in the chain polymerization.⁵ Later reports⁶ have shown that alkylbenzenes could be isolated from the addition of alkyllithium to exocyclic double bond even in the absence of an oxazoline ring.

In this paper we communicate the addition of lithium salts of primary and secondary amines, obtained from the parent amine and *n*-butyllithium, to several styrene derivatives (scheme 1). Additions to 4,4-dimethyl-2-(2-vinylphenyl)-2-oxazoline⁷ (**1a**) and 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (**1b**) were carried

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out at 0°C affording good yields of β -phenylethylamines.⁸ With both compounds, we tried several amides observing that lithium amides from primary amines generally afforded poorer yields than the ones from secondary amines (table 1, entries 1-16). In case of **1b** most of lithium amides added in higher yields than for **1a**, probably due to the presence of the methoxy group in the benzene ring, we had observed this effect previously in the carbolithiation reaction.³



Scheme 1

Reactivity of 2-vinylbenzoic acid⁹ (**1c**) was similar to that of 2-vinylphenyloxazoline **1a**; even, styrene (**1d**) suffers the addition of the lithium amides without anionic polymerization, in a similar way to the addition of organolithium reagents recently reported.⁶ In this case we can observe that the yields are lower (table 1, entries 22-26), this result can be explained by the lower stability of the benzylic anion formed after addition due to the lack of the oxazoline group. We studied the influence of the solvent in the reaction of styrene with morpholine observing that the best yield was obtained in THF (table 1, entry 23), meanwhile yields decreased in ethyl ether (31%) and no reaction was observed in hexane.

Finally, in order to check the scope of this reaction we did some experiments with β -methylstyrene (**1e**) and α -methylstyrene (**1f**) but higher temperatures (room temperature) with longer reaction times (1 day) were needed and the yields are poorer. The lowest yield corresponding to the α -methylstyrene according with the presence of the α -methyl group unstabilizing the benzylic anion.

We highlight the good yield obtained in the addition of the amides derived from benzylamines (table 1, entries 5, 6, 13, 14, 20, 21, and 25). These can be considered as equivalents of H₂N⁻ or RNH⁻, so since the benzyl group can be removed smoothly, this becomes an easy way to obtain primary or secondary β -phenylethylamines.

In conclusion, this study yields a simple and successful method for the synthesis of β -phenylethylamines from styryl compounds.

Table 1. Reactions of Styrene Derivatives with Lithium Amides

Entry	Styrene derivative	R'	+	R''	Temp.	Product	Yield (%)
1	1a	CH ₃ CH ₂		CH ₃ CH ₂	0°C	3a	77
2		CH ₂ CH ₂ CH ₂ CH ₂ CH ₂			0°C	3a	90
3		CH ₂ CH ₂ -O-CH ₂ CH ₂			0°C	3a	81
4		CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂			0°C	3a	91
5		PhCH ₂		CH ₃	0°C	3a	98
6		PhCH ₂		H	0°C	3a	75
7		n-Bu		H	0°C	3a	53
8		3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂		H	0°C	3a	44
9	1b	CH ₃ CH ₂		CH ₃ CH ₂	0°C	3b	94
10		CH ₂ CH ₂ CH ₂ CH ₂ CH ₂			0°C	3b	98
11		CH ₂ CH ₂ -O-CH ₂ CH ₂			0°C	3b	94
12		CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂			0°C	3b	99
13		PhCH ₂		CH ₃	0°C	3b	92
14		PhCH ₂		H	0°C	3b	99
15		(CH ₃) ₃ C		H	0°C	3b	21
16		3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂		H	0°C	3b	47
17	1c	CH ₃ CH ₂		CH ₃ CH ₂	0°C	3c	61
18		CH ₂ CH ₂ -O-CH ₂ CH ₂			0°C	3c	85
19		CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂			0°C	3c	91
20		PhCH ₂		CH ₃	0°C	3c	65
21		PhCH ₂		H	0°C	3c	40 ^b
22	1d	CH ₃ CH ₂		CH ₃ CH ₂	0°C	3d	69
23		CH ₂ CH ₂ -O-CH ₂ CH ₂			0°C	3d	73
24		CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂			0°C	3d	77
25		PhCH ₂		CH ₃	0°C	3d	71
26		PhCH ₂		H	0°C	3d	41
27	1e	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂			r. t.	3e	58
28		CH ₂ CH ₂ -O-CH ₂ CH ₂			r. t.	3e	52
29		CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂			r. t.	3e	51
30		PhCH ₂		CH ₃	r. t.	3e	33
31	1f	CH ₂ CH ₂ CH ₂ CH ₂			r. t.	3f	38
32		CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂			r. t.	3f	32
33		PhCH ₂		CH ₃	r. t.	3f	20

^a All compounds were fully characterized by NMR and MS.

^b The product was isolated as N-benzyl-3,4-dihydroisoquinolone by treatment with DCC because the addition product, an aminoacid, was of difficult purification.

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8. General Procedure: The styrene derivative (0.5-3 mmol) in dry THF was added to a solution of lithium amide, prepared by addition of n-BuLi (250 mol%, 1.6M in hexanes) to a solution of the amine (250 mol%), in dry THF at 0°C. The mixture was stirred at 0°C overnight for styrenes **1a**, **1b**, **1c**, and **1d**, and at room temperature for 1 day for styrenes **1e** and **1f**. The reaction mixture was quenched with MeOH, evaporated and purified either by column chromatography on silica gel eluted with ethyl acetate-hexane-diethylamine in the case of phenethylamines **3a**, **3b**, **3d**, **3e** and **3f**, or by ion exchange chromatography (Dowex 50x 8-50, H⁺ form, eluted with 1M aqueous pyridine) in the case of phenethylamines **3c**.
9. 2-Vinylbenzoic acid was prepared from 2-carboxybenzaldehyde by Wittig reaction (Ph₃PCH₃Br/*t*-BuOK).