Reduction of β-Nitrostyrene with Sodium Bis-(2-methoxyethoxy)-aluminium Dihydride. A Convenient Route to Substituted Phenylisopropylamines

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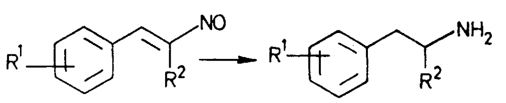
Summary β-Arylethylamines may be generated conveniently and in good yields by reduction of the corresponding styryl precursors with 'Redal' [sodium bis-(2-methoxyethoxy)aluminium dihydride].

β-ARYLETHYLAMINES (**2**) can be generated in good yield by a variety of synthetic procedures.[1] The most applicable method involves a Knoevenagel condensation of appropriately substituted benzaldehydes with nitroalkane;[2] $LiAlH_4$[2] or Raney nickel[3] reduction (elevated temperature, pressure) of the intermediate β-nitrostyryl derivative (**1**) then affords the phenethylamine. Since we observed incomplete reduction of phenolic β-nitrostyrenes using $LiAlH_4$ in ethereal solvents, we investigated the reactivities of the recently developed hydride reductants. We describe a general preparative method for the generation of a pharmacologically interesting series using sodium bis-(2-methoxyethoxy)-aluminium dihydride (Redal) as the reductant. Aliphatic nitro-compounds are reduced to amines using this reducing agent;[4,5] by contrast, aryl nitro-compounds afford azo-, azoxy-, or hydrazo-compounds[4,5] depending on conditions and manner of addition of the reductant.

In our laboratory, β-nitrostyryl derivatives are smoothly reduced to β-phenethylamines in yields comparable to or greater than that afforded by other methods (Table 1).†

Table 1. Conversion of β-nitrostyrenes into β-phenethylamines†



(1) (2)

R^1	R^2	Yield (%)	M.p. (t/°C)
3,4-Methylenedioxy	Me	85	180—181[a]
3,5-Dimethyl-4-methoxy	Me	87	255—257[a]
3,5-Dimethyl-4-hydroxy	Me	75	100—102[b]

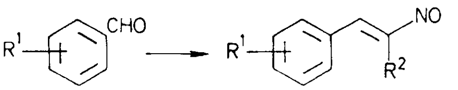
[a] As hydrochloride salt.
[b] As free amine.

A solution of the β-nitrostyrene (1 mmol) in dry benzene is added at room temperature to $Na(MeOCH_2CH_2)_2AlH_2$ (8—10 mmol) in benzene and the mixture is heated under reflux for 2—17 h, cooled, hydrolysed with water, and filtered. Evaporation of benzene and 2-methoxyethanol followed by vacuum distillation affords the free amine in the case of non-phenolic compounds, while phenolic compounds are isolated by recrystallization or column chromatography.

Preparation of two of the β-nitrostyrenes by generalized methods[1] gave large amounts of dimeric byproducts, and instead we used a procedure, initially recorded by Ho *et al.*,[6] which should find general application particularly where substitution on the benzaldehyde renders it electronically less reactive or sterically hindered to attack by nitroalkane anion, and the nitrostyryl derivative that does form begins to dimerize.

Preliminary results are in Table 2; the reflux times are critical.

Table 2. Knoevenagel condensations on substituted benzaldehydes and nitroethane



(1)

R^1	Yield	Reflux (min)
3,5-Dimethyl-4-hydroxy	81	10
3,5-Dimethyl-4-methoxy	88	5
2,6-Dimethoxy-4-methyl	85	6

Typically, a solution of the substituted benzaldehyde (1 mmol) and NH_4OAc (1·25 mmol) in nitroethane was refluxed for the specified time. The mixture was cooled immediately in liquid N_2 or acetone–solid CO_2, diluted with CH_2Cl_2, and filtered while cold. Solvent was removed *in vacuo*, and the remaining β-nitrostyrene was recrystallized by known procedures.[6]

Financial support from the President's Research Fund Simon Fraser University, and from the National Research Council, and the award of a Simon Fraser University scholarship (to J.R.B.) is acknowledged.

(*Received* 12*th December* 1973; *Com.* 1682.)

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† Satisfactory i.r., n.m.r., and mass spectra, and elemental analyses were obtained for these derivatives.

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