Journal of Labelled Compounds and Radiopharmaceuticals - Vol. XX, No. 8

SILICA GEL-ASSISTED REDUCTION OF NITROSTYRENES TO 2-ARYL-2-[^{2}H]-1-NITROETHANES WITH SODIUM BORODEUTERIDE

Achintya K. Sinhababu and Ronald T. Borchardt*

Department of Medicinal Chemistry
University of Kansas
Lawrence, Kansas 66045

SUMMARY

Reduction of nitrostyrenes with sodium borodeuteride in the presence of silica gel (70-270 mesh) in a mixture of chloroform and 2-propanol gave the corresponding deuterated nitroethanes in near quantitative yields, free of dimeric products with 72-81% deuterium incorporation. The method was applied to the synthesis of 2-phenyl-, 2-[4-methoxyphenyl]-, 2-[3,4-dimethoxyphenyl]-, 2-[3,4,5-trimethoxyphenyl]-, and 2-[2,4,5-trimethoxyphenyl]-2-[^{2}H]-1-nitroethanes.

Key Words: Silica gel-assisted, deuterium labelling, 2-aryl-2-[^{2}H]-1-nitroethanes, phenylethylamines, sodium borodeuteride.

INTRODUCTION

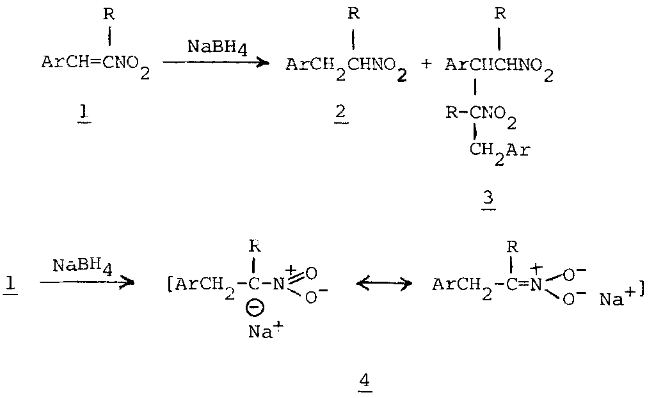
A variety of side chain deuterium and tritium labelled phenylethylamine derivatives, including catecholamines and the neurotoxin 6-hydroxydopamine are of biochemical and pharmacological interest (1-10). One of the major methods for their synthesis involves initial reduction of appropriate nitrostyrenes with $NaBD_4$ or $NaBT_4$ to the 2-[^{2}H]- or 2-[^{3}H]-2-aryl-1-nitroethanes (3,10). These nitroethane derivatives are then further reduced to give the corresponding labelled phenylethylamines (3,10).

One major problem associated with the reduction of nitrostyrene 1 with $NaBH_4$ (and hence, $NaBD_4$ and $NaBT_4$) is that in addition to the desired monomeric nitroethane derivative 2, dimeric product 3 is also formed, often in yields comparable to the yields of the monomeric product (11). The dimeric product 3 is believed to be formed by the Michael addition of the resonance stabilized

*To whom correspondence should be sent.

0362-4803/83/081027-07$01.00
© 1983 by John Wiley & Sons, Ltd.

Received January 19, 1983
Revised April 13, 1983



α-carbanion 4 to 1. The problem of dimer formation is most severe in the case of vinyl unsubstituted nitrostyrenes (1, R=H). Even when the pH of the reaction mixture is maintained between the limits 3-6, dimeric products are still formed, often in significant amounts (11).

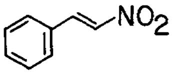
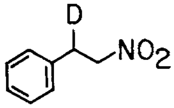
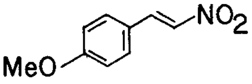
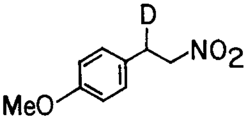
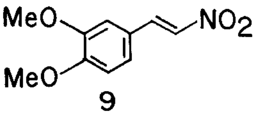
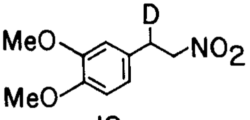
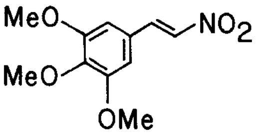
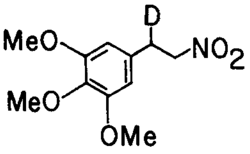
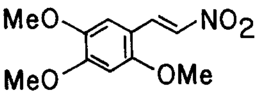
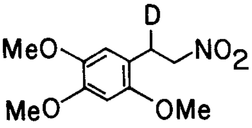
We have recently shown (12) that the formation of dimeric products can be suppressed virtually completely and the monomeric products can be isolated in 90-98% yields by conducting the reduction in the presence of silica gel in a relatively nonpolar solvent system (6:1 $CHCl_3$/2-propanol). The ability of silica gel to suppress dimer formation apparently derives from its ability to bind polar materials. This binding process is enhanced in the presence of a nonpolar solvent system (13). It was postulated (12) that in the silica gel-assisted reduction of 1 with $NaBH_4$ in a relatively nonpolar solvent system, the resonance stabilized α-carbanion 4 is formed on the silica gel surface and consequently 4 accepts a proton from the silica gel surface before it has a chance to undergo Michael addition to 1. In this paper we report the results of silica gel-assisted reduction of nitrostyrenes with $NaBD_4$.

RESULTS AND DISCUSSION

To determine the optimum reaction conditions for the reductions using $NaBD_4$, the reductions were first conducted with $NaBH_4$. As we reported earlier (12), the reductions with $NaBH_4$ were effected at 25°C in a mixture of $CHCl_3$ and 2-propanol in the presence of varying amounts of silica gel. The amount of silica gel needed to suppress dimer formation varied but was in the range of 1-3 g/mmol of the nitrostyrene reduced. We found that essentially an identical

Table I

Reduction of Nitrostyrenes with $NaBD_4$ in the Presence of Silica Gel[a] in 6:1 $CHCl_3$-2-Propanol

Nitrostyrene	Deuterium Labelled Product	Reaction time (min) (g silica gel per mmol nitrostyrene)	% Deuterium incorporation[b] (% isolated yield)
 5	 6	25 (1.5)	81 (95)
 7	 8	35 (3)	73 (94)
 9	 10	40 (3)	72 (92)
 11	 12	35 (2)	81 (96)
 13	 14	40 (2.5)	77 (97)

[a] Silica gel 60, 70-270 mesh (Brinkmann). [b] As determined by mass spectral analysis.

Table II

^{1}H NMR Spectral Data[a]: Chemical Shifts (δ)[b], Couplings[c] and Coupling Constants (J)

Hydrogen / Compound	$-CH^{\beta}D-CH_2^{\alpha}-NO_2$ or, $-CH^{\beta}=CH^{\alpha}-NO_2$			Other Hydrogens δ
	$\delta\alpha$ coupling	$\delta\beta$ coupling	$J_{\alpha,\beta}$ in Hz	
5	8.01 d	7.53 d	13.5	7.48 (s, 5H, Ph)
6	4.58 d	3.26 t	7.8	7.27 (s, 5H, Ph)
7	7.97 d	7.46 d	13.5	3.87 (s, 3H, OMe), 6.93 (d, J=9Hz, 2H, Ar), 7.49 (d, J=9Hz, 2H, Ar).
8	4.55 d	3.22 t	7.4	3.77 (s, 3H, OMe), 6.83 (d, J=9Hz, 2H, Ar), 7.13 (d, J=9Hz, 2H, Ar).
9	7.97 d	7.48 d	13.5	3.93 (s, 6H, OMe), 6.82-7.25 (m, 3H, Ar).
10	4.62 d	3.23 t	7.5	3.85 (s, 6H, OMe), 6.66-6.92 (m, 3H, Ar).
11	7.95 d	7.49 d	13.5	3.92 (s, 9H, OMe), 6.77 (s, 2H, Ar).
12	4.63 d	3.26 t	7.5	3.86 (s, 9H, OMe), 6.44 (s, 2H, Ar).
13	8.13 d	7.71 d	13.5	3.87 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.53 (s, 1H, Ar), 6.89 (s, 1H, Ar).
14	4.56 d	3.22 5	7.5	3.83 (s, 6H, OMe), 3.87 (s, 3H, OMe), 6.55 (s, 1H, Ar), 6.72 (s, 1H, Ar).

---

[a] All spectra were recorded in $CDCl_3$. [b] In parts per million downfield from tetramethylsilane internal standard. [c] Abbreviations for couplings: s, singlet; d, doublet; t, triplet and m, multiplet.

procedure is suitable for the reductions using $NaBD_4$ and the deuterated nitroethanes are produced in near quantitative yields (Table I). The progress of the reactions were conveniently monitored by TLC (silica gel, CH_2Cl_2 or CH_2Cl_2-hexane) and also by observing the disappearance of the yellow color due to the starting material. The site of deuterium labelling in the reduced product was determined by ^1H NMR (Table II) and as expected was the position β to the nitro group. The amount of deuterium incorporation was determined by mass spectral analysis and was in the range of 72-81% for the five nitrostyrenes reduced (Table I). The amounts of deuterium incorporation realized by the present method are slightly less than those reported in the literature (3,10), using $NaBD_4$ in EtOH. For example, reduction of 13 with $NaBD_4$ in EtOH has been shown (10) to proceed in 37% yield with 85% deuterium incorporation. The variation in the amount of deuterium incorporated from one substrate to another, albeit small, cannot be explained readily. No correlations could be found between the percent deuterium incorporation and the amount of silica gel used or the length of the reaction time required in the presence of a fixed amount of $NaBD_4$ and a fixed ratio of $CHCl_3$ and 2-propanol (Table I).

Since the method reported herein for the reduction of nitrostyrenes with $NaBD_4$ is operationally simple and furnishes pure products directly with high deuterium incorporation, it should be of particular value in the synthesis of tritium labelled arylnitroethanes using $NaBT_4$ as the reducing agent.

EXPERIMENTAL

General Methods: ^1H NMR spectra were recorded on a Varian T-60 spectrometer. Electron impact mass spectra were recorded on a Varian MAT CH-5 mass spectrometer with RDS Data System for computer analysis of spectra. The $NaBD_4$ (98 atom % deuterium) was purchased from Sigma Chemical Co. The silica gel used for the silica gel-assisted reactions as well as column chromatography was silica gel 60, 70-270 mesh (Brinkmann).

Synthesis of Nitrostyrenes (14). Nitrostyrenes 5 and 7 were prepared by the procedure of Worral (15). Synthesis of nitrostryenes 9, 11 and 13 in 75-80% yields were carried out using Gairaud and Lappin's method (16) with modification in the isolation procedure and is illustrated with the synthesis of 3,4-dimethoxyβ-nitrostyrene (9). A mixture of 3,4-dimethoxybenzaldehyde (3.32 g, 20 mmol), anhydrous CH_3NO_2 (3.06 g, 50 mmol) and anhydrous NH_4OAc (4.62 g, 60 mmol, dried before use at 0.01 mm of Hg until free flowing) in 20 mL of glacial HOAc was refluxed protected from moisture. TLC (silica gel, CH_2Cl_2) indicated completion of reaction after 1.5 h of reflux. The mixture was cooled to 25°C, poured into 200 mL of water and the precipitated solid was collected by filtration. The crude solid was dissolved in CH_2Cl_2 and the resulting solution was washed with $NaHCO_3$ solution, dried (Na_2SO_4) and then passed directly through a column of silica gel 60 (10 g) in CH_2Cl_2. Further elution with CH_2Cl_2 and evaporation of solvent gave essentially pure 9. Recrystallization from EtOH gave yellow needles (3.3 g, 79%): mp 141-142°C, lit. (16) mp 141-142°C.

General Procedure for the Silica Gel-Assisted Reduction of Nitrostyrenes with $NaBD_4$: To a stirred mixture of the nitrostyrene (1 mmol), silica gel 60 (see Table I for amounts), 2-propanol (1.5 mL/g of silica gel) and $CHCl_3$ (6 mL/mL of 2-propanol) at 25°C was added $NaBD_4$ (168 mg, 4 mmol) in 3-4 portions over a period of 15-20 min. The progress of the reaction was monitored by TLC (silica gel, CH_2Cl_2 or CH_2Cl_2-hexane) and/or by the visual observation of the disappearance of the yellow color due to the starting nitrostyrene. After the reaction was complete (see Table I for reaction times; these times include time needed to add $NaBD_4$), excess $NaBD_4$ was decomposed by adding 1 N HCl with cooling. The mixture was filtered immediately and the filter was washed with CH_2Cl_2. The combined filtrates were washed with brine, dried (Na_2SO_4) and then evaporated in vacuo to dryness to give the deuterated arylnitroethane. See Table I for isolated yields and percent deuterium incorporation and Table II for ^1H NMR data.

Acknowledgements: The support of this work through a grant from the National Institute of Neurological and Communicative Disorders and Stroke (NS-15692) and a postdoctoral fellowship to AKS from the American Heart Association - Kansas Affiliate is gratefully acknowledged.

REFERENCES

1. Perel, J. M., Dawson, D. K., Dayton, P. G. and Goldberg, L. I. - J. Med. Chem. 15:714 (1972).
2. Taylor, K. B. - J. Biol. Chem. 219:451 (1974).

3. Rotman, A., Daly, J. W. and Creveling, C. R. - J. Labelled Compounds 11: 445 (1975).
4. Battersby, A. R., Sheldrake, P. W., Staunton, J. and Williams, D. C. - J. Chem. Soc. Perkin I, 1056 (1976).
5. McGraw, N. P., Callery, P. S. and Castagnoli, Jr., N. - J. Med. Chem. 20: 185 (1977).
6. Battersby, A. R., Staunton, J., Summers, M. C. and Southgate, R. - J. Chem. Soc. Perkin I, 45 (1979).
7. Jacob III, P., Kline, T. and Castagnoli, Jr., N. - J. Med. Chem. 22:662 (1979).
8. Klinman, J. P., Humphries, H. and Voet, J. G. - J. Biol. Chem. 255:11648 (1980).
9. May, S. W., Phillips, R. S., Mueller, P. W. and Herman, H. H. - J. Biol. Chem. 256:2258 (1981).
10. Borchardt, R. T. and Simmons, J. E. - J. Labelled Compounds Radiopharm. 19:433 (1982).
11. Meyers, A. I. and Sircar, J. C. - J. Org. Chem. 32:4134 (1967).
12. Sinhababu, A. K. and Borchardt, R. T. - Tetrahedron Lett. 24:227 (1983).
13. The idea of using silica gel to suppress dimer formation in the reduction of a nitrostyrene with $NaBH_4$ or $NaBD_4$ arose from our observation that a variety of 2,β-dinitrostyrenes can be reductively cyclized using Fe/HOAc in the presence of silica gel and a nonpolar solvent system to give the corresponding indoles in near quantitative yields: Sinhababu, A. K. and Borchardt, R. T. - J. Org. Chem. Submitted.
14. For reviews see: (a) Jones, G. - Org. Reactions, 15,254 (1967). (b) Mathieu, J. and Weill-Raynal, J. "Formation of C-C Bonds," Vol. 1, Thieme, Stuttgart, 1973, pp. 244-248.
15. Worral, D. E. - Org. Synth. Coll. 1:413 (1932).
16. Gairaud, C. B. and Lappin, G. R. - J. Org. Chem. 18:1 (1953).