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SILICA GEL-ASSISTED REDUCTION OF NITROSTYRENES TO 2-ARYL-1-NITROALKANES WITH SODIUM BOROHYDRIDE

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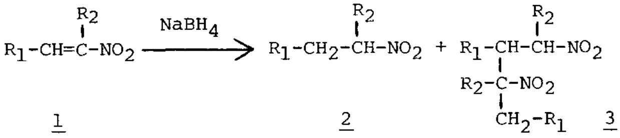
Summary: Reduction of a variety of nitrostyrenes with sodium borohydride in the presence of silica gel in a mixture of chloroform and 2-propanol furnished the corresponding nitroalkanes free of dimers in near quantitative yields.

Nitroalkanes are useful synthetic intermediates and their utility has greatly increased in recent years due to improvements in methodologies for the conversion of the nitro functionality to other functional groups, most notably, carbonyl,[1] nitrile oxide,[2] and amino[3] groups. Among the nitroalkanes, 2-aryl-1-nitroethanes are of special interest since they provide access to a variety of phenylethylamines of biochemical and pharmacological interest.[4] In addition, double deprotonation of 2-aryl-1-nitroethanes leads to intermediates which are synthetically equivalent to enamines and enolates of normal reactivity ("double umpolung").[5]

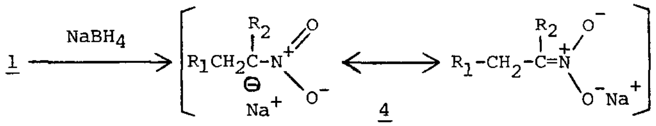
A widely used method[6],[7] for the synthesis of nitroalkanes involves $NaBH_4$ reduction of conjugated nitroalkenes which in turn are synthesized by nitromethylenation[8] of aliphatic or aromatic aldehydes. Reduction of nitroalkenes (1, R_1 = alkyl) derived from aliphatic aldehydes[7] or ketones[9] by $NaBH_4$ usually proceed smoothly to give the corresponding nitroalkanes (2) in good yields. In some cases, however, small amounts of dimeric products are also formed, although their formation can be completely suppressed using acidic conditions.[7] In contrast, the reduction of nitrostyrenes (1, R_1 = aryl) with $NaBH_4$ usually produces the corresponding nitroalkane 2 together with the dimeric product 3 (R_1 = aryl), often in comparable yields.[6], [7] The problem of dimer formation is most severe in the case of vinyl unsubstituted nitrostyrenes (1, R_2 = 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.[7] We now report a simple and high yielding method for reduction of nitrostyrenes to nitroalkanes without the formation of dimers.



$$R_1\text{-CH=}\overset{R_2}{\overset{|}{C}}\text{-NO}_2 \xrightarrow{NaBH_4} R_1\text{-CH}_2\text{-}\overset{R_2}{\overset{|}{CH}}\text{-NO}_2 + R_1\text{-CH}(\text{-}\overset{R_2}{C}(\text{-NO}_2)\text{-CH}_2\text{-}R_1)\text{-}\overset{R_2}{\overset{|}{CH}}\text{-NO}_2$$

1 2 3

The dimeric product 3 is believed to be formed by the Michael addition of the resonance stabilized α-carbanion 4 to 1. Formation of dimeric products even under acidic conditions may be due to a number of factors including considerable stability of the carbanion 4, high



reactivity of the nitrostyrenes toward nucleophiles and the extreme sensitivity of $NaBH_4$ towards acids making effective maintenance of low pH conducive to the formation of monomeric products difficult. These considerations point toward the inadequacy of homogeneous reaction conditions, whether acid catalyzed or not, since these conditions allow the presence of both the Michael acceptor 1 and the Michael donor 4 in the same phase.

We thought if the reduction of 1 is carried out in a nonpolar aprotic solvent with $NaBH_4$ in the presence of an insoluble protic phase, for example, silica gel,[10] there is a good possibility[10] that the highly polar and negatively charged intermediate 4 will be formed on the silica gel surface and consequently will accept a proton to give 2 before it has a chance to undergo Michael addition to 1. In practice, however, small amounts of a protic solvent were also required. The most effective combination of aprotic and protic solvents turned out to be a mixture of chloroform[11] and 2-propanol.[12] As shown in Table 1, the amount of silica gel required to suppress the formation of dimeric product completely varied but was in the range of 1-3 g/mmol of nitrostyrene. The experimental details are illustrated with the reduction of 2,3-dimethoxyphenyl β-nitrostyrene to 2-(2,3-dimethoxyphenyl)-1-nitroethane (entry 5, Table 1). To an efficiently stirred mixture of the nitrostyrene (209 mg, 1 mmol), silica gel (2 g, column chromatography grade, Baker), 2-propanol (3 ml), chloroform (16 ml) was added $NaBH_4$ (156 mg, 4.1 mmol) in ~ 40 mg portions over a period of 15 min at 25°C. The mixture was stirred for additional 15 min, by which time the yellow color due to the nitrostyrene has completely disappeared. Excess $NaBH_4$ was decomposed with dil HCl and the mixture was filtered. The filter was washed with CH_2Cl_2 and the combined filtrates were washed with brine, dried (Na_2SO_4) and then evaporated in vacuo to dryness to give 199 mg (94%) of 2-(2,3-dimethoxyphenyl)-1-nitroethane as a colorless oil. The product was homogeneous by TLC (silica gel, CH_2Cl_2, R_f 0.81). When only 1 g of silica gel was used in the above reduction, a trace of dimeric product (R_f 0.65, silica gel, CH_2Cl_2) was also formed although not detectable by ^1H NMR. In contrast, the reduction of the above nitrostyrene in acetonitrile[7] at pH 3-6 has been reported to give 56% of the monomer together with 30% of the dimer.

The method reported herein is rapid, operationally simple and most importantly affords pure products directly in near quantitative yields under mild conditions.

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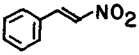
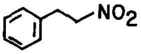
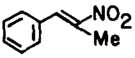
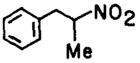
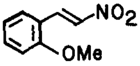
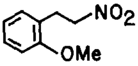
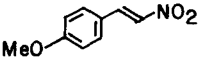
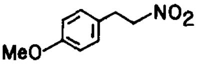
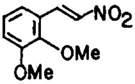
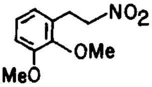
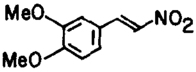
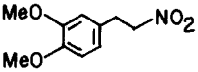
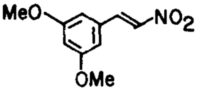
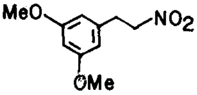
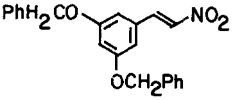
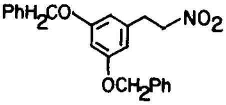
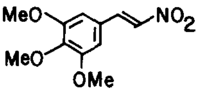
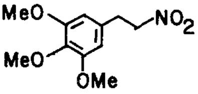
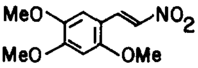
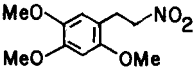
Table I. Silica Gel-Assisted Reduction of Nitrostyrenes to Nitroalkanes[a]

Entry	Nitrostyrene[b]	Silica Gel in g/mmol Nitrostyrene	Time in min	Nitroalkane[c,d]	% Yield[e]
1		1.5	25		93
2		1	45		93
3		1	50		92
4		3	25		94
5		2	30		94
6		3	30		92
7		2	15		90
8		1	35		98
9		2	35		94
10		2.5	40		94

[a] All reductions were conducted at 25°C with ~4 mmol of $NaBH_4$/mmol of the nitrostyrene in a mixture of $CHCl_3$ (8 ml/g of silica gel) and 2-propanol (1.5 ml/g of silica gel.) [b] See Note 13. [c] For ^{1}H-NMR data see Note 14. Satisfactory mass spectral data for all compounds and analytical data for the new compounds were also obtained. [d] For synthesis by previously described methods see: Ref. 7 for Entry 1, 2 and 5; Ref. 5 for Entry 4 and 6; Ref. 15 for β-deuterated Entry 10. [e] Yields refer to pure (by NMR), isolated products.

NOTES AND REFERENCES

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10. Silica gel appeared to be a possible protic phase in view of our recent observations (Sinhababu, A. K. and Borchardt, R. T., manuscript in preparation) that when Fe/HOAc induced reductive cyclization of dinitrostyrenes to indoles is conducted in the presence of silica gel, intermolecular reactions involving polar (amine) intermediates and starting dinitrostyrenes are virtually eliminated and the indoles are produced in high state of purity in near quantitative yields.
11. Chloroform was found to be superior to dichloromethane, ether or benzene. Possible reasons for this may be as follows: Chloroform has relatively low dielectric constant which minimizes dissolution of the charged intermediate 4 in the organic phase; its high density facilitates even distribution of silica gel in the reaction mixture, and a variety of nitrostyrenes are very readily soluble in chloroform.
12. Methanol and ethanol, both with higher dielectric constant and much higher dissolving power for sodium borohydride were less satisfactory in suppressing dimer formation.
13. Synthesis of nitrostyrenes. Entry 1: Worral, D. E. *Org. Synth. Coll. Vol. I* (1932), 413; Lloyd, H., Kielar, E. A., Hight, R., Uyeo, S., Falles, H. and Wildman, W. *J. Org. Chem*. (1960) 27, 373; Entry 8: Lee, F. G. H., Dickson, D. E., Suzuki, J., Zirnis, A. and Manian, A. A. *J. Heterocycl. Chem*. (1973) 10, 649.
14. ^{1}H-NMR Data: Chemical shifts (δ) of nitroalkanes in $CDCl_3$; carbon adjacent fo NO_2 is designated α: Entry 1: 3.23 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 4.53 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 7.06-7.50 (m, 5H, Ph).
    Entry 2: δ 1.5 (d, J=7 Hz, 3H, Me), 3.11 (quartet of d, 2H, Hβ), 4.75 (sextet, J=7 Hz, 1H, Hα), 7.05-7.73 (m, 5H, Ph).
    Entry 3: δ 3.28 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.82 (s, 3H, OMe), 4.57 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.83-7.41 (m, 4H, Ar).
    Entry 4: δ 3.21 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.75 (s, 3H, OMe), 4.53 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.82 (d, J=9 Hz, 2H, Ar), 7.10 (d, J=9 Hz, 2H, Ar).
    Entry 5: δ 3.27 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.61 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.65-7.23 (m, 3H, Ar).
    Entry 6: δ 3.23 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.85 (s, 6H, OMe), 4.62 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.63-6.93 (m, 3H, Ar).
    Entry 7: δ 3.22 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.77 (s, 6H, OMe), 4.58 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.35 (s, 3H, Ar).
    Entry 8: δ 3.16 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 4.50 (t, $J_{\alpha,\beta}$=7.5 Hz, Hα), 4.98 (s, 4H, OCH_2), 6.40-6.56 (m, 3H, Ar), 7.36 (s, 10H, Ph).
    Entry 9: δ 3.26 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.83 (s, 9H, OMe), 4.63 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.42 (s, 2H, Ar).
    Entry 10: δ 3.22 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hβ), 3.82 (s, 6H, OMe), 3.87 (s, 3H, OMe), 4.55 (t, $J_{\alpha,\beta}$=7.5 Hz, 2H, Hα), 6.56 (s, 1H, Ar), 6.73 (s, 1H, Ar).
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