Silyl Nitronates: Improved Nitro-aldol Reactions and Reductive Routes to 2-Aminoalcohols

By ERNEST W. COLVIN and DIETER SEEBACH

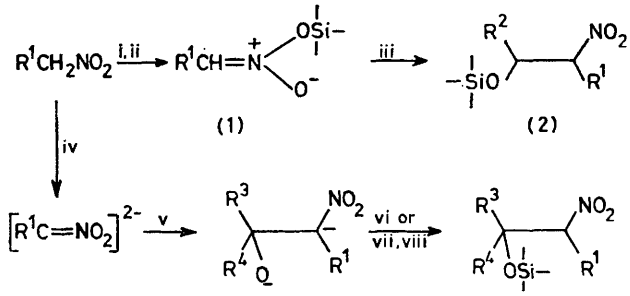
(*Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, ETH-Zentrum, Universitätstrasse* 16, *CH*-8092 *Zürich, Switzerland*)

Summary The preparation of silyl nitronates from both primary and secondary nitroalkanes, their fluoride-ion catalysed reaction with carbonyl compounds, and the ready lithium aluminium hydride reduction of the so-formed protected nitro-alcohols to 2-aminoalcohols are described.

2-AMINOALCOHOLS are of major biological and synthetic importance, particularly, in the latter case, for use in the Tiffenau–Demjanov[1] and related deaminative rearrangements. Hitherto, the main route to such compounds has been hydride reduction of free or protected[2] cyanohydrins, permitting only a one-carbon atom homologation of the carbonyl substrate.

2-Nitroalcohols have found little use in the preparation of 2-aminoalcohols, owing to the frequently low isolated yields[3] in the nitro-aldol condensation, except in those cases involving nitromethane itself, and the lack of a generally applicable method of reduction of 2-nitroalcohols. Methods which have been used include catalytic hydrogenation over Raney nickel[4] and electrolytic reduction,[5] neither of which has any broad utility.

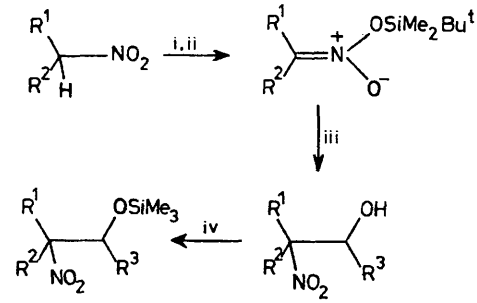
We report a combination of methods which overcomes the above problems, is well suited to use of the higher nitroalkanes, and which, we hope, will lead to a much greater use of 2-nitroalcohols as synthetic intermediates. Primary nitroalkanes, such as 1-nitrohexane, readily form silyl nitronates[6a] (**1**) by sequential treatment at −78 °C in tetrahydrofuran (THF) with lithium di-isopropylamide and either trimethylsilyl or t-butyldimethylsilyl chloride; evaporation of the solvent *in vacuo*, suspension of the residue in pentane, filtration through Celite, and distillation gives the silyl nitronates (**1**) in isolated yields that are higher (*ca.* 75%) than in either of the two published routes[6b] to such species.



SCHEME 1. Reagents: i, $LiNPr^i_2$—THF; ii, Me_3SiCl or Bu^tMe_2SiCl; iii, $Bu^n_4N^+F^-$–R^2CHO, R^2 = alkyl or aryl; iv, $2Bu^nLi$–hexamethylphosphoramide–THF; v, R^3COR^4, R^3 = alkyl, aryl, or H, R^4 = alkyl or aryl; vi, Bu^tMe_2SiCl; vii, AcOH; viii, Me_3SiCl–$(Me_3Si)_2NH$ or Bu^tMe_3SiCl–imidazole.

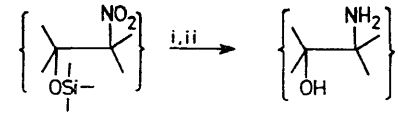
Such silyl nitronates react readily, at −78 °C in THF in the presence of a catalytic amount of tetra-n-butylammonium fluoride,[7] with a wide range of aliphatic and aromatic aldehydes to give the derived 2-nitroalcohol *O*-silyl ethers† (**2**) in excellent yields: *e.g.*, n-heptanal (71%), 2,2-dimethylpropanal (57%), benzaldehyde (78%), *p*-methoxybenzaldehyde (70%), and *p*-nitrobenzaldehyde (91%). Ketones (cyclohexanone, benzophenone) are unreactive under such conditions, but react efficiently with nitroalkane dianions;[8] the resulting intermediates can be silylated *in situ* with t-butyldimethylsilyl chloride, or the isolated nitro-aldols can be subsequently silylated[9] with trimethylsilyl chloride–hexamethyldisilazane (Scheme 1) or t-butyldimethylsilyl chloride–imidazole.

Secondary nitroalkanes, such as 2-nitropropane, also form silyl nitronates, though in lower (30—40%) yields; such nitronates are less stable than those derived from primary nitroalkanes, and are prepared as the t-butyldimethylsilyl derivatives. They react similarly with aliphatic and aromatic aldehydes under fluoride ion catalysis, although here the adducts are isolated as the free nitroalcohols; subsequent silylation gives the protected nitroaldols in overall yields of 30—40% (Scheme 2).



SCHEME 2. Reagents: i, $LiNPr^i_2$–THF; ii, Bu^tMe_2SiCl; iii, $Bu^n_4N^+F^-$–R^3CHO, R^3 = alkyl or aryl; iv, Me_3SiCl–$(Me_3Si)_2NH$.

Regardless of the particular silyl protection or of the substitution pattern (Schemes 1 and 2), it has been found that such silyl-protected 2-nitroalcohols undergo smooth nitro-group reduction to 2-aminoalcohols† on addition to $LiAlH_4$ in refluxing ether (Scheme 3); apparently the silyl



SCHEME 3. Reagents: i, $LiAlH_4$–Et_2O; ii, sat. aq. Na_2SO_4.

group is not lost prior to nitro-group reduction, which affords 2-aminoalcohols in distilled yields of 50—85%: attempted reduction with $LiAlH_4$ of the unprotected 2-nitroalcohols results in bond scission followed by reduction of the original components of the substrate; for example, the benzaldehyde–1-nitrohexane adduct gives only benzyl alcohol and 1-aminohexane.[10]

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† Obtained as mixtures of diastereoisomers, where applicable.

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[6] (a) Further aspects of the chemistry of silyl nitronates will be published separately; (b) K. Torssell and O. Zeuthen, *Acta Chem. Scand.*, 1978, **B32**, 118; M. V. Kashutina, S. L. Ioffe, and V. A. Tartakovskii, *Doklady Acad. Nauk. S.S.S.R.*, 1974, **218**, 109.
[7] 5 mol % of Fluka product was heated for 4 h at 90 °C and 0·1 mmHg; see also R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimuzu, *J. Amer. Chem. Soc.*, 1977, **99**, 1265. No reaction occurred in the absence of the catalyst, nor did the catalyst itself induce any reaction between the aldehyde and a nitroalkane; see also G. Hesse and V. Jäger, *Annalen*, 1970, **740**, 79; S. Colonna, H. Hiemstra, and H. Wynberg, *J.C.S. Chem. Comm.*, 1978, 238.
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