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

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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.
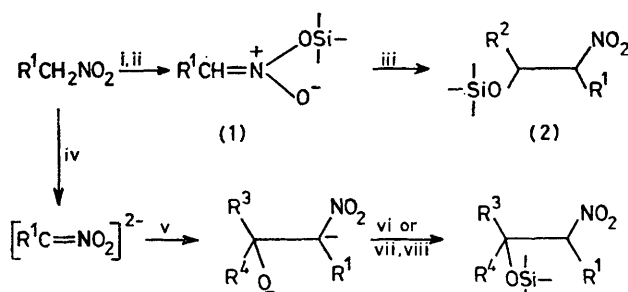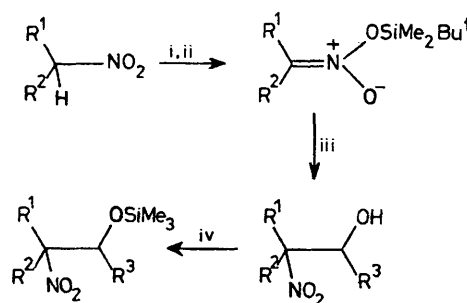

SCHEME 1. Reagents: i, LiNPr₂—THF; ii, Me₃SiCl or BuᵗMe₂-SiCl; iii, Buⁿ₄N⁺F⁻–R²CHO, R² = alkyl or aryl; iv, 2BuⁿLi–hexamethylphosphoramide–THF; v, R³COR⁴, R³ = alkyl, aryl, or H, R⁴ = alkyl or aryl; vi, BuᵗMe₂SiCl; vii, AcOH; viii, Me₃SiCl–(Me₃Si)₂NH or BuᵗMe₂SiCl–imidazole.

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

† Obtained as mixtures of diastereoisomers, where applicable.

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, LiNPrⁱ₂–THF; ii, BuᵗMe₂SiCl; iii, Buⁿ₄N⁺F⁻–R³CHO, R³ = alkyl or aryl; iv, Me₃SiCl–(Me₃Si)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 LiAlH₄ in refluxing ether (Scheme 3); apparently the silyl
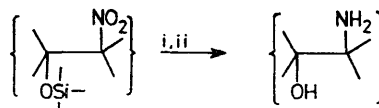
SCHEME 3. Reagents: i, LiAlH₄–Et₂O; ii, sat. aq. Na₂SO₄.

group is not lost prior to nitro-group reduction, which affords 2-aminoalcohols in distilled yields of 50—85%: attempted reduction with LiAlH₄ 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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[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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[9] A. E. Pierce, 'Silylation of Organic Compounds,' Pierce Chemical Company, Rockford, Illinois, 1968, and references therein.

[10] See also A. Dornow and M. Gellrich, *Annalen*, 1955, **594**, 177, and references therein.