NITROALKANE SYNTHESIS. A CONVENIENT METHOD FOR ALDEHYDE REDUCTIVE NITROMETHYLATION

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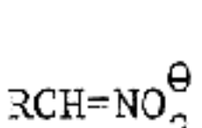
Our interest in the intramolecular cycloaddition of nitrile oxides with olefins as a tool for natural product synthesis prompts this report of a simple one-pot synthesis of nitroalkanes from aldehydes. Nitroalkanes are useful precursors to these dipolar intermediates.[1] Further, the considerable progress in synthetic methodologies for the conversion of a nitro functional group to other functionality under mild conditions, particularly the carbonyl[2] and amino[3] groups suggests that formation of nitroalkanes will become increasingly more important. Methods which proceed under conditions generally suitable to complex natural product synthesis will be especially useful.[4]

Nitroalkanes are readily deprotonated to their nitronates 1;[1,2] however, these reagents are rather poor nucleophiles and normally they undergo predominant O-alkylation with electrophiles.[5,6a] The situation has recently been improved by the introduction of the more nucleophilic, α,α-doubly deprotonated nitroalkanes (2). With their enhanced reactivity, these intermediates afford substantially improved ratios of C- to O-alkylation. The scope of this method, however, is limited since α,α-disubstituted nitroalkanes and also nitroalkanes with additional acidifying groups at the β-nitro position, form α,3-doubly deprotonated species such as 3 and 4.[6] A further important limitation of this method is the reported low yields when nitromethane is employed for generation of the nucleophile.[6a,6d]



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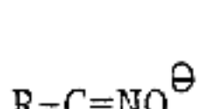

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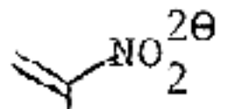

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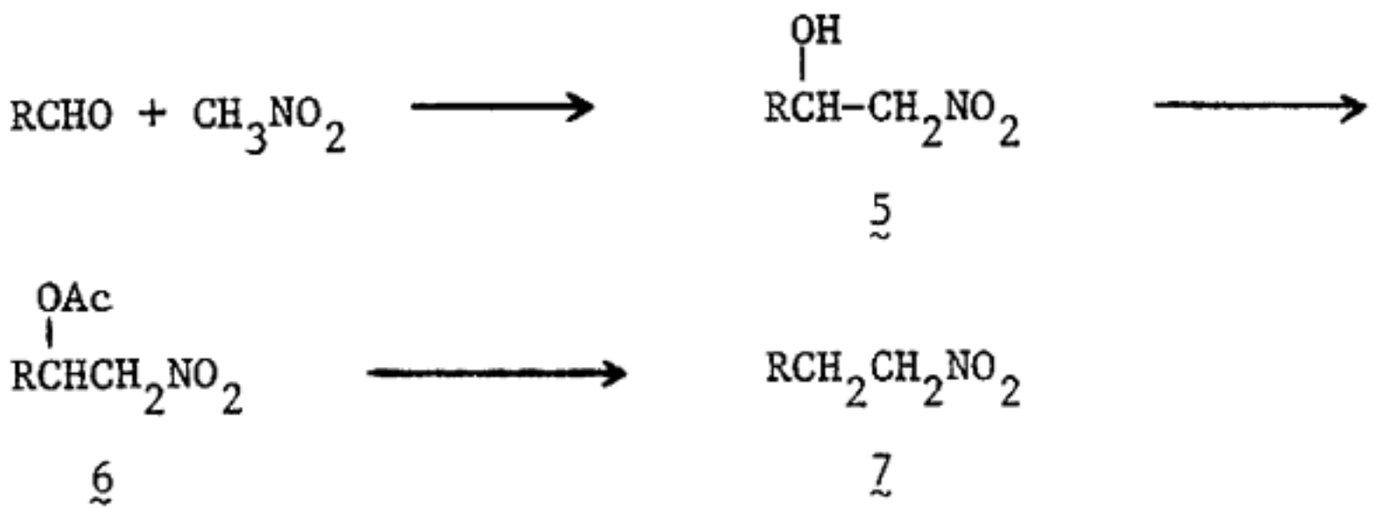
Base catalyzed condensation of an aldehyde and a nitroalkane[7] followed by acylation and reductive elimination is another viable method for nitroalkane preparation.[8] Although a one-pot procedure involving successive additions of reagents has been reported,[9] the method is not well suited to natural product synthesis. Consequently, intermediates are usually isolated,[4] which accounts at least in part, for the poor overall yields.[8]

The reported one-pot procedure[9] proceeds by mixing without solvent: nitromethane, the

aldehyde, and a catalytic quantity of either triethylamine or powdered potassium hydroxide. Acidification with concentrated sulfuric acid followed by addition of acetic anhydride forms the β-acetoxynitroalkane (6, Scheme I). Finally, reduction with sodium borohydride in dimethylsulfoxide affords the nitroalkane (7).

Scheme I.



Condensation of nitromethane with an aldehyde without solvent can be inconvenient or even impossible for small scale reactions common in complex natural product synthesis. In our hands, the reported procedure was also quite capricious. Our numerous difficulties and failures in this regard prompted this investigation for alternate methods.[10] We desired a method which proceeds rapidly in organic solution using only a small amount of catalyst.

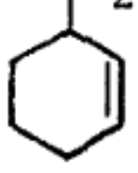
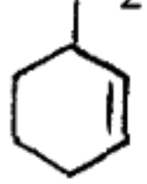
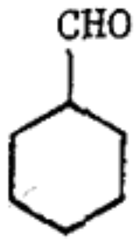
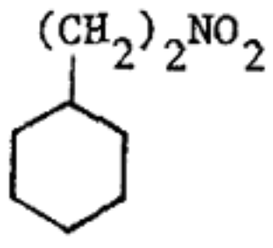
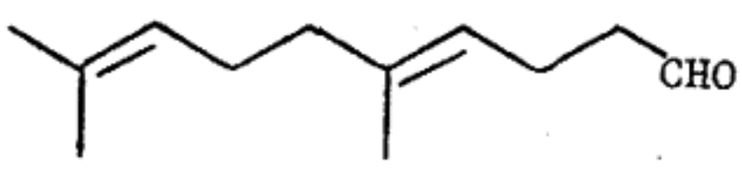
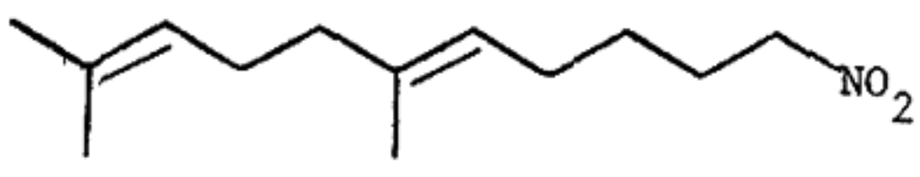
The ability of fluoride ion to form very strong hydrogen bonds[11] as HF_2^-, together with our expectation that the nitromethane condensation would proceed rapidly in protic solvent,[7] led us to explore the use of potassium fluoride in isopropanol. In practice, we found that condensation of nitromethane with an aldehyde proceeds rapidly (ca. 6 h) using potassium fluoride (0.05 equiv) in isopropanol (0.5 M), forming β-hydroxynitroalkanes 5 in high yield.[12] This condensation can be further accelerated by adding a catalytic quantity (0.05 equiv) of 18-crown-6.[13]

Following the condensation, the solvent is evaporated leaving nitro alcohol 5, usually as the only detectable product. Acetylation of 5 proceeds rapidly with acetic anhydride using 4-dimethylaminopyridine as a catalyst (25°C, 30 min).[14] Finally, reduction of acetates 6 occurs uniformly with sodium borohydride in ethanol forming the nitroalkanes 7 (Table I). The experimental details are illustrated for the conversion of 2-cyclohexenylacetaldehyde[17] (8) to 3-(2-cyclohexenyl)-1-nitropropane (9): To a solution of 248 mg (2.00 mmol) of aldehyde 8 in 2 mL of isopropanol was added 5.8 mg (0.1 mmol) of potassium fluoride and 0.24 mL (4.0 mmol) of nitromethane. After 6 h at 23°C, tlc showed one spot for the nitroalcohol at R_f 0.20 (silica gel, $CHCl_3$). The solvent was removed at aspirator pressure and replaced with 4 mL of dry ether. A mixture of acetic anhydride (255 mg, 2.50 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) was added. After 8 h at 23°C formation of the β-nitro acetate was complete (R_f 0.59; silica gel, $CHCl_3$). Finally, evaporation of the ether and addition of 4 mL of 1M ethanolic sodium borohydride with stirring for 1 h completed the sequence. The mixture was acidified with dilute hydrochloric acid, extracted with ether, and the crude product was purified by column chromatography on silica gel to give 264 mg (78%) of the desired nitroalkene 9.[15]

Formation of the acetates 6 using 4-dimethylaminopyridine is superior to concentrated sulfuric acid as catalyst,[9] especially owing to the pH sensitivity[8,16] for nitroalkene reductions, and therefore, the attendant difficulties in adding small quantities of anhydrous acid.

The method reported herein provides a convenient and high-yielding method for the reductive nitromethylation of aldehydes. The reported mild conditions should be compatible with a variety of synthetic needs, particularly those related to natural product synthesis.

Table I. Nitroalkanes Prepared by Aldehyde Nitromethylation.

Aldehyde	Adduct	(Yield %)[a]
$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_7NO_2$	(86)[b]
$CH_3(CH_2)_6CHO$	$CH_3(CH_2)_8NO_2$	(81)[b]
 **8**	 **9**	(78)[b,c]
		(64)
		(90)[c]

[a]The yields were based products isolated by column chromatography. The products exhibited satisfactory nmr and ir data. [b]This product exhibited correct microanalytical data. [c]The starting aldehyde was prepared as previously described (ref 17).

References and Notes

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12. No condensation could be detected after 24 h using THF as solvent.
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