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Facile Synthesis of 2-Nitroalkanols by Tetramethylguanidine (TMG)-Catalyzed Addition of Primary Nitroalkanes to Aldehydes and Alicyclic Ketones

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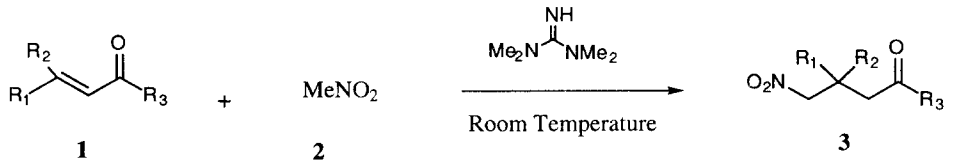
Abstract: Tetramethylguanidine-catalyzed addition of primary nitroalkanes to aldehydes and alicyclic ketones constitutes a practical means to perform the nitro-aldol reaction (Henry reaction). The very mild conditions employed, together with the short reaction times, make the procedure tolerant of a range of functionalities and highly versatile for the synthesis of a variety of 2-nitroalkanols. © 1997 Elsevier Science Ltd.

Nitroalkanes are versatile building blocks and intermediates in organic synthesis, primarily due to the ease of carbon-carbon bond forming reactions of derived species such as nitronate anions, silyl nitronates, and nitrile oxides.[1-4] Among nitroalkanes, 2-nitroalkanols are particularly versatile intermediates for the synthesis of nitroalkenes, 2-aminoalcohols and α-nitroketones; [1-3] moreover, they are of importance because of their biological activity as fungicides.[5]

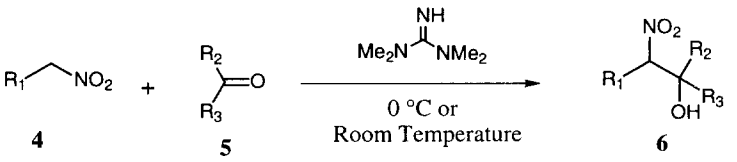
Classical preparation of 2-nitroalkanols involves base-catalyzed addition of a nitroalkane to a carbonyl compound (Henry reaction), the most widely used condensing agents being alkali and alkaline alkoxides in alcoholic solution.[2,6-9] Improved procedures have been recently introduced by Rosini et al.,[9,10] who effected the addition of nitroalkanes to aliphatic aldehydes on an alumina surface, and by Wollenberg et al.[11] through a fluoride ion-catalyzed reaction of nitromethane to aliphatic aldehydes. However, these methods, although efficient, are not of general applicability, being generally limited to aliphatic aldehydes. Therefore, the development of new methodologies for the preparation of 2-nitroalkanols is very attractive owing to their synthetic value.

In this letter we report our preliminary results concerning the tetramethylguanidine(TMG)-catalyzed addition of nitroalkanes to aldehydes and ketones as a practical means to perform the nitro-aldol addition reaction. Our own previous observation of the ability of TMG to catalyze the Michael addition of nitromethane to α,β-unsaturated carboxylic acid esters as well as α,β-unsaturated ketones[12,13] (Scheme 1) suggested to us to extend its utility to bring about the nitroaldol addition reaction (Scheme 2).



Scheme 1

Hence, when an aldehyde (1 mmol) was solubilized at 0 °C in nitromethane (10 ml) in the presence of a catalytic amount of TMG (two drops), the addition reaction took place smoothly giving rise to the 2-nitroalcohols in good yield (Table).[14] The reaction can be applied both to aromatic and aliphatic aldehydes simply through a slight modification of the reaction conditions (see times and temperatures in Table). Attempts to perform the reaction in organic solvents (i.e. dichloromethane, acetonitrile or toluene) in the presence of one equivalent of nitromethane, resulted in somewhat lower yields, the formation of the 1,3-dinitro derivative being concomitant. Moreover, when nitroethane was used, the nitro-aldol addition occurred in good yields but without diastereoselectivity .



4a: R_1 = H;
4b: R_1 = Me

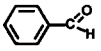
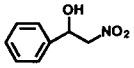
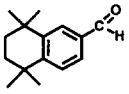
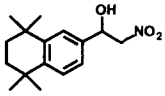
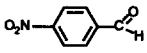
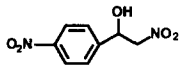
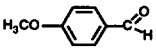
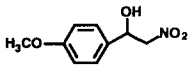
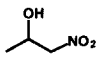
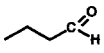
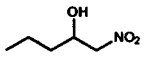
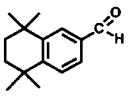
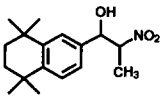
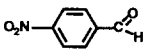
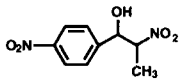
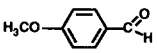
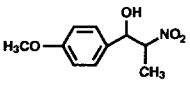
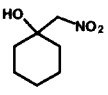
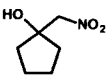
Scheme 2

On the other hand, the condensation of aliphatic as well as alicyclic ketones with primary nitroalkanes usually takes place in the presence of alkaline alkoxides in alcoholic solution. The use of aliphatic amines as catalysts has also been tried, resulting in the prevalent formation of 1,3-dinitro-paraffins or the nitroalkene derivatives.[15] Furthermore, Lambert and Lowe[15] claimed the preparation of 2-nitroalkanols using triethylamine as the catalyst, without reporting any experimental detail. We observed that TMG catalyzes the Henry addition of nitromethane to cycloalkanones at room temperature producing good yield of the desired 2-nitroalkanols after the required time (see Table). Acetophenone failed to give condensation products, at least under these conditions, whereas the reaction of aliphatic ketones such as acetone, 2-butanone or 2-hexanone, resulted in somewhat lower yield possibly due to the preferential self-condensation reaction.

In summary, as shown in Table, the present methodology is particularly suitable using aldehydes and alicyclic ketones as substrates allowing an easy isolation of the desired adducts in excellent to good yields. Aromatic aldehydes gave the corresponding nitroalcohol derivatives as the only detectable products in good yields.

In conclusion, this method offers significant advantages over existing methods, especially in terms of milder reaction conditions, shorter reaction times, and that anhydrous solvents or reagents and inert atmosphere conditions are not required. Interestingly, the TMG-catalyzed addition of nitromethane to

Table: Synthesis of 2-Nitroalkanols by TMG-Catalyzed Henry Reaction[a]

Entry	Carbonyl Compd.	Nitroalkane	Reaction time and Temp.	Product	Yield %
1		**4a**	30 min 0 °C		94
2		**4a**	30 min r.t.		98
3		**4a**	15 min 0 °C		97
4		**4a**	60 min 0 °C		73
5		**4a**	60 min r.t.		69
6		**4a**	60 min r.t.		67
7		**4b**	30 min r.t.		89[b]
8		**4b**	15 min 0 °C		88[b]
9		**4b**	60 min 0 °C		74[b]
10		**4a**	48 h r.t.		71
11		**4a**	8 h r.t.		56

a) For experimental procedure see ref 14. b) No diastereoselectivity was observed

cyclohexanone afforded the corresponding nitroalcohol in 71% yield, thus comparing very favourably with the methodology described in "Organic Syntheses".[16]

Finally, considering the ease of operation and the simplicity of workup of the developed methodology one may expect its widespread application for industrial purposes such as generating combinatorial 2-nitroalkanols libraries.

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14. Typical experimental procedure: a solution of 0.01 mol of the carbonyl compound in 10 ml of the primary nitroalkane was cooled at 0 °C and then two drops of tetramethylguanidine were added. The reaction was allowed to stand at 0 °C (or at room temperature in the case of ketones) for the time indicated in the Table, then it was diluted with Brine, acidified with 5% HCl solution and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ and after removing the solvent the pure 2-nitroalkanol was obtained by distillation or by flash chromatography.
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