Tetrahedron Letters 53 (2012) 3322–3324

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of novel multifunctional amino alcohols from nitroparaffins and α,β-unsaturated aldehydes

Asghar A. Peera [a,*], Ian A. Tomlinson [b]

[a] The Dow Chemical Company, 1500 E. Lake Cook Road, Buffalo Grove, IL, USA
[b] The Dow Chemical Company, 1691 N. Swede Road, Midland, MI, USA

ARTICLE INFO

Article history:
Received 29 March 2012
Revised 12 April 2012
Accepted 17 April 2012
Available online 24 April 2012

Keywords:
Michael addition
Henry reaction
Amino alcohol
Hydrogenation
Nitroalkane

ABSTRACT

A series of novel multifunctional amino alcohols were prepared by tandem Michael–Henry reaction by reacting nitroalkanes such as 2-nitropropane with readily available α,β-unsaturated aldehydes. The dinitro compounds were further reduced by catalytic hydrogenation to obtain respective diamines. This synthetic route provides a very convenient method of preparing multifunctional amino alcohols.

The conjugate addition of carbanions to electron poor alkenes is one of the most fundamental carbon–carbon bond forming reaction in organic synthesis. This process is referred to as Michael addition.[1] Conjugate addition using highly stabilized carbanions are of great interest since a growing number of reactions can be carried out in environmentally benign solvents such as water and using only catalytic amount of basic promoter.[2] Nitroalkanes are important source of stabilized carbanions since the high electron withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α-position.[3–5] Nitroalkanes when treated with a wide variety of both organic and inorganic bases can easily generate nitronate anions which act as carbon nucleophiles and can further be reacted with common electrophiles such as haloalkanes,[6] aldehydes (Henry reaction),[4,7] Michael acceptors leading to carbon–carbon bond formation.[1] The nitro groups can further be reduced to their respective amines by catalytic hydrogenation.

There are several reports in the open literature that talk about Michael reactions of nitroalkanes. However, most of them are limited to α,β-unsaturated ketones, esters or amides. Achieving a clean Michael reaction of α,β-unsaturated aldehydes is thought to be difficult because of the competitive Henry reaction occuring readily due to the highly reactive aldehyde. Specialized organocatalysts are needed to obtain the reactivity only at the alkene position and leaving the aldehyde unreacted.[8] In this report we take advantage of the both reactive sites to introduce tandem Michael–Henry reaction to prepare dinitro alcohols (Scheme 1).

The R_1 and R_2 groups comes from the nitroparaffin while the R group is dependent on the α,β-unsaturated aldehyde. This route allows the efficient synthesis of highly functionalized molecules in fewer steps and also permits the addition of a variety of moieties ranging from long chain hydrocarbons, cyclic alkanes and aromatic systems. The manipulation of the R_1 and R_2 group in the nitroalkane and the R group on the α,β-unsaturated aldehydes creates the ability to build a library of useful materials. The other advantage this route provides is to obtain materials with only primary amines which have markedly different reactivities and are anticipated to be very useful in combinatorial synthesis. These materials are also anticipated to be better and more efficient neutralizers and can be used in smaller quantities making them more cost efficient when used in coatings or metal working formulations.

In this study, 2-nitropropane (2-NP) was choosen as the nitroalkane while crotonaldehyde and cinnamaldehyde were selected as the α,β-unsaturated aldehydes due to their cost and availability. These two materials also allow an initial evaluation of the

R = H, Me, Ph; R_1 = H, Me, Alkyl; R_2 = H.Me, Alkyl

Scheme 1. Generalized tandem Michael–Henry reaction scheme.

* Corresponding author. Tel.: +1 847 808 3792; fax: +1 847 808 3708.
E-mail address: APeera@dow.com (A.A. Peera).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.078

structure–property relationship in a particular application due to the difference in the moiety at the R position. The first reaction performed was reacting excess 2-NP with crotonaldehyde in the presence of catalytic amount of base. Reaction depicted in Scheme 2, gave 2,5,6-trimethyl-2,6-dinitroheptan-3-ol (**1**) as a white solid in high yield.[9]

Several bases were evaluated including 1,1,3,3-tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and triethylamine. When DBU was used as a base, the reaction proceeded more rapidly and the product was obtained in higher purity. The reaction was also conducted with varying the molar ratio of crotonaldehyde to 2-NP. The amount of 2-NP used in excess was from 2.1 to 6 equiv. At 6 equiv the reaction rapidly went to completion, however, almost 4 equiv of 2-NP are wasted because recovery of the nitroalkanes is typically avoided due to the potential hazards. Optimization of the reaction conditions with 2-NP used at 2.8 M equiv with respect to crotonaldehyde gave the desired product in acceptable reaction time and yield.

The reaction conditions were also studied to obtain insight into the relative reaction kinetics of the Michael addition and the Henry reaction. The Michael addition of the nitroalkane to the olefin of crotonaldehyde occurs efficiently when the nitroalkanes/base solution was maintained between 0 and 10 °C, the reaction required room temperature or higher to obtain an efficient nitroaldol reaction between the aldehyde and the nitroalkane. This difference in relative reaction conditions is maintained at ambient temperatures and it was determined that dropwise addition of the crotonaldehyde to the nitroalkane at room temperature was suitable to get both the Michael and Henry reaction to go sequentially. This reaction of 2-NP with crotonaldehyde is highly exothermic and careful monitoring of the reaction is necessary to prevent a potential runaway reaction in scale-up. Lower temperatures are only useful if the intention is to add only 1 equiv of nitroalkane at the alkene position and avoid getting the nitroaldol reaction. For these studies it was desirable to drive the reactions to completion at both active sites of the molecule.

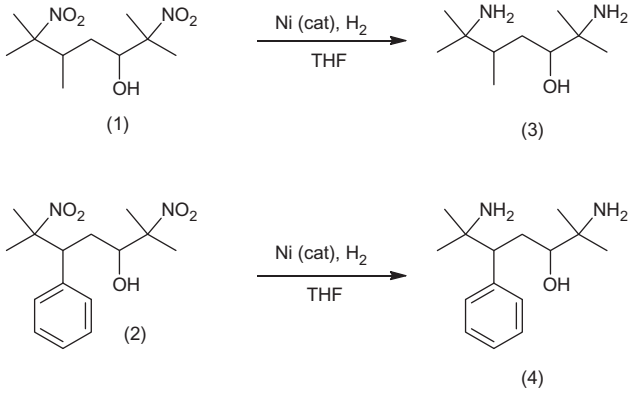
The subsequent reaction used cinnamaldehyde as the α,β-unsaturated aldehyde target. This allows the introduction of a phenyl moiety into the product which could be of significant interest in some applications especially when low volatile organic compounds (VOC) and thermal stability is desired. The reaction conditions were similar to those used for efficient conversion of crotonaldehyde. Once again the best results to get 2,6-dimethyl-2,6-dinitro-5-phenylheptan-3-ol (**2**)[10] was with dropwise addition of the cinnamaldehyde at room temperature in the presence of DBU (Scheme 3).

Compounds (**1**) and (**2**) obtained from the tandem Michael–Henry reaction were further hydrogenated under high pressure in the presence of Raney Nickel as catalyst to give the corresponding amino compounds (Scheme 4).

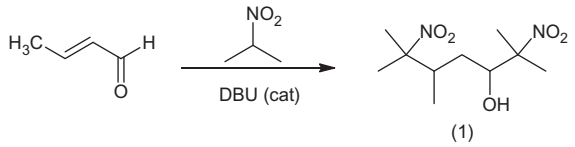
The reaction was run using THF as the solvent due to the dinitro material having higher solubility (>50%) compared to methanol where the solubility was less than 30%. The reduction reactions were straightforward and went to completion in 2 h or less.

In the case of compound (**1**), the reaction was carried out at 55 °C under 600 psi of hydrogen pressure and using 10–20% by weight of nickel catalyst. The reaction progressed well, giving the desired compound, 2,6-diamino-2,5,6-trimethylheptan-3-ol (**3**) as the major product with 2,2,3-trimethylpyrrolidine (m/z = 113, [M+H] = 114) as a minor impurity as determined by GC/MS. It is believed that the 2,2,3-trimethylpyrrolidine is formed as a result of reversal of the Henry reaction in compound (**1**) in the autoclave. The presence of an amine and carbonyl in the same molecule results in imine formation followed by reduction to the 2,2,3-trimethylpyrrolidine. The boiling point of the impurity is sufficiently different than the desired product and can be readily removed by prolonged evaporation on a rotary evaporator at 55–60 °C. Compound (**2**) was also reduced by catalytic hydrogenation under the same conditions as adopted for the compound (**1**). In this case also, the major product was the desired compound, 2,6-diamino-2,6-dimethyl-5-phenylheptan-3-ol (**4**) (Scheme 3). However, some reversal of Henry reaction was also observed, resulting in 2,2-dimethyl-3-phenylpyrrolidine (m/z = 175, [M+H] = 176) as an impurity as established by GC/MS. This material also could be separated easily but only by Kugelrohr distillation.

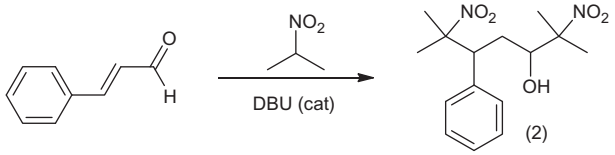
The reaction sequence has been extended with other nitro compounds. For example, nitrocyclohexane has been used with crotonaldehyde to prepare 1,3-bis(1-nitrocyclohexyl)butan-1-ol (**5**). This dinitro compound was further reduced under the same hydrogenation conditions describe earlier to form the desired



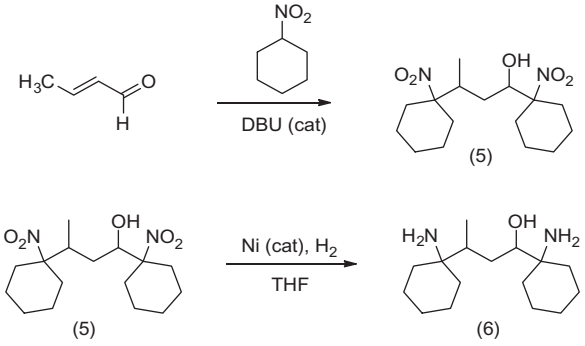
Scheme 4. Reduction reaction of compounds (**1**) and (**2**) to get the desired diamino materials.



Scheme 2. Reaction of crotonaldehyde with 2-NP.



Scheme 3. Reaction of cinnamaldehyde with 2-NP.



Scheme 5. Reaction scheme to prepare 1,3-bis(1-nitrocyclohexyl)butan-1-ol (**5**) and 1,3-bis(1-aminocyclohexyl)butan-1-ol (**6**).

amino alcohol that is 1,3-bis(1-aminocyclohexyl)butan-1-ol (**6**) (m/z = 268.3, [M+H] = 269.3) (Scheme 5)

In summary, we have developed an efficient two steps route to preparing multifunctional amino alcohols. The first step allows us to obtain dinitro compounds by tandem Michael–Henry reaction followed by catalytic hydrogenation as the second step of the sequence. These novel multifunctional materials can be used in a variety of applications such as neutralizer in coatings and personal care, curing agents and crosslinkers for epoxy and polyurethane applications, gas scavengers and corrosion inhibitors.[11]

Acknowledgment

The authors would like to thank Dr. Li Wang for providing analytical support in characterizing all the new materials reported in the manuscript

Supplementary data

Supplementary data (detailed experimental procedures, full characterization, copies of ^{1}H, ^{13}C and ^{13}C DEPT-135 NMR and GC–MS of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.078.

References and notes

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.
2. Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.
3. Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
4. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
5. Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Wiley: Chichester, 1996.
6. Seebach, D.; Lehr, F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 505.
7. Luzzio, F. *Tetrahedron* **2001**, *57*, 915.
8. (a) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307; (b) Manzano, R.; Andrés, J.; Álvarez, R.; Muruzábal, M.; de Lera, A.; Pedrosa, R. *Chem. Eur. J.* **2011**, *17*, 5931.
9. Smith, C. W. U.S. Patent 1949, US 2475996 19490712.
10. Black, D.; Boscacci, A. *Aust. J. Chem.* **1976**, *29*, 2511.
11. Peera, A.; Tomlinson, I. U.S. Patent **2011** US 20110152574; Peera, A.; Tomlinson, I. U.S. Patent **2011** US 20110152401; Peera, A.; Tomlinson, I. U.S. Patent **2011** US 20110147649; Peera, A.; Tomlinson, I. U.S. Patent **2011** US 20110152407.