DOI: 10.1002/ejoc.200900337

Stereoselective Synthesis of Homoallyl Nitroalkane Derivatives through Base-Promoted Regioselective Decarboxylation of Baylis–Hillman Derivatives[‡]

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Keywords: Nitroalkanes / Regioselectivity / Baylis–Hillman / Decarboxylation / Allylic compounds

The regioselective decarboxylation of nitroalkanoates synthesized from Baylis–Hillman acetates of acrylates proceeds stereoselectively to afford homoallyl nitroalkanes. In contrast, nitroalkanoates derived from Baylis–Hillman acetates of acrylonitrile gave bisallyl nitroalkanes.

Introduction

Nitroalkanes are vital synthetic building blocks in organic synthesis. The facile transformation of the nitro group into an amine, imine, hydroxylamine, or carboxylic acid group make the synthesis of a variety of nitroalkanes a subject of constant study.[1] Nitroalkanes even allow efficient synthesis of fine chemicals in short sequences.[2] Primary nitroalkanes are reliable substrates for the generation of a variety of nitrile oxides as substrates for 1,3-dipolar cycloaddition reactions.[3]

The synthetic applications of Baylis–Hillman derivatives are paramount, as reflected from the recent literature. The most attractive feature of the product furnished by this C–C bond-forming reaction is the presence of three functional groups, which can be suitably modified for obtaining a plethora of heterocyclic scaffolds.[4] Our laboratory has disclosed a number of general approaches for the synthesis of different aza-heterocyclic systems by using Baylis–Hillman derivatives. During the course of one such work, we discovered that the dialkanoates produced by the S_N2' reaction between ethyl nitroacetate and the Baylis–Hillman acetates upon treatment with base undergo decarboxylative protonation to afford homoallyl nitroalkanes containing a primary nitro group. Although the synthesis of allyl nitroalkanes bearing a primary nitro group has been achieved in Baylis–Hillman chemistry,[5] the synthesis of homoallyl nitroalkanes bearing a primary nitro group from Baylis–Hillman adducts remains unreported (Figure 1). Decarboxylation due to the presence of a nitro group on the α-carbon has literature precedence[6] and may be considered analogous to the decarboxylation experienced with α-keto acids or malonic acids under basic conditions. In the context of Baylis–Hillman chemistry, however, we have observed that a strong base is unable to effect the decarboxylation of α-keto acids or malonic acids.[7] Kim and co-workers very recently demonstrated that decarboxylative protonation can be achieved in Baylis–Hillman derivatives with the use of palladium salts for either obtaining 1,5-dicarbonyl compounds or conducting aralkylation.[8] During the course of this study, the identical reaction of nitroalkanoates afforded from Baylis–Hillman adducts of acrylonitrile unexpectedly produced bisallyl nitroalkanes. These new observations prompt us to report the findings of our study herein.

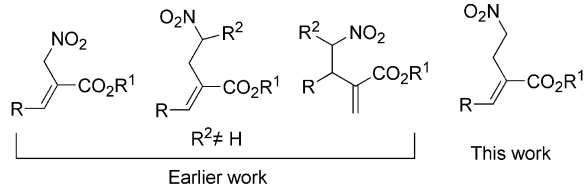

Figure 1. Nitroalkanes from Baylis–Hillman chemistry.

Results and Discussion

At first, dialkanoates that served as the starting materials were prepared following the literature procedure.[9] Acetyl derivatives **1a**–**h** and **2**–**4** of the Baylis–Hillman adducts were treated with ethyl nitroacetate in the presence of K_2CO_3 in DMF to afford required compounds **5a**–**h** and **6**–**8** (Scheme 1). Initially, treatment of **5a** with NaOH in aqueous methanol led to consumption of the starting material within 8 h. Isolation and purification of the crude material furnished a product that was spectroscopically analyzed

[‡] CDRI Communication no. 7756

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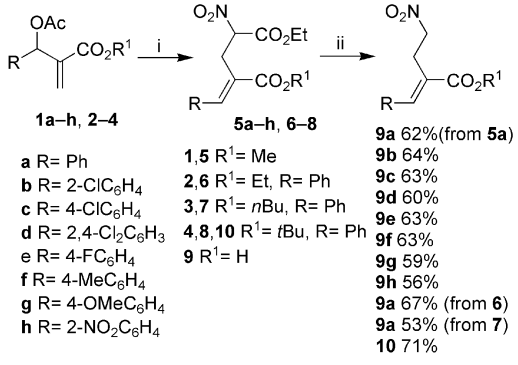
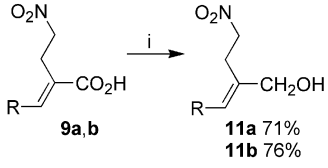
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900337.

to be the *E*-isomer of **9a**, exclusively. Notably, the mass spectrum (ESI+) of **9a** did not display the molecular ion peak, but the high-resolution mass spectrum (ESI) showed the required mass. During optimization, different bases were investigated and it was observed that the best yield was achieved when LiOH was used for the reaction. Treating other derivatives **5b**–**h** with LiOH under aqueous conditions smoothly produced the corresponding nitroalkane derivatives **9b**–**h** as the *E*-isomer only, indicating the general nature of the reaction. Substituting the methoxycarbonyl group in **5a** with an ethoxycarbonyl or *n*-butoxycarbonyl group did not alter the course of the reaction. Respective compounds **6** and **7**, in turn prepared from **2** and **3**, upon similar treatment yielded **9a** in 67 and 53% yield. Reaction of compound **4** bearing the *tert*-butoxycarbonyl group under identical conditions, expectedly, furnished product **10**. With the aim to provide chemical evidence for the presence of the acid moiety in compound **9**, in a representative study **9a**,**b** were subjected to $NaBH_4$-mediated reduction in the presence of isobutylchloroformate and *N*-methylmorpholine (NMM) under aqueous conditions to yield **11a**,**b** (Scheme 2). This result not only established the presence of the acid functionality in **9** but also provided a facile route to δ-amino alcohols, which may become useful intermediates for further investigations.

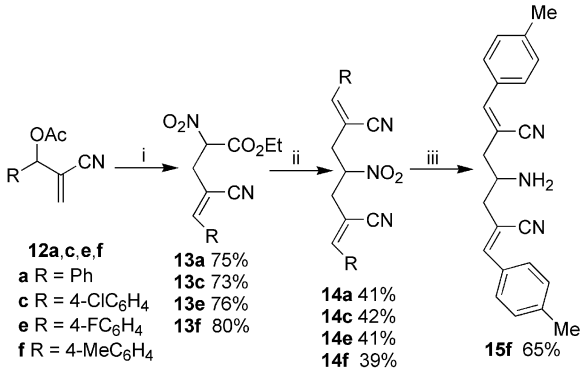


Scheme 1. Reagents and conditions: (i) ethyl nitroacetate, K_2CO_3, DMF, room temp., 45 min; (ii) LiOH, THF/H_2O (1:1), room temp., 8 h.



Scheme 2. Reagents and conditions. (i) isobutylchloroformate, NMM, $NaBH_4$, THF/H_2O, 0 °C, 5 min.

In light of these results it became imperative to evaluate nitroalkanoates synthesized from the S_N2' reaction of ethyl nitroacetate with the acetyl derivatives of Baylis–Hillman adducts resulting from acrylonitrile for the similar reaction. Accordingly, compounds **13a**,**c**,**e**,**f** were synthesized by treatment of acetates **12a**,**c**,**e**,**f** with ethyl nitroacetate in the presence of K_2CO_3 in DMF at room temperature. Initial reaction of **13a** with LiOH did not produce the desired product and was, therefore, replaced with NaOH. Fortunately, treatment of **13a** with NaOH under aqueous condition resulted in the formation of a product, the structure of which was delineated as **14a** on the basis of spectral analysis (Scheme 3). Reaction of analogous substrates **13c**,**e**,**f** in the presence of NaOH produced the corresponding bisallyl nitroalkanes **14c**,**e**,**f**. The plausible mechanism for the formation of **14** is delineated in Figure 2. It is assumed that in the presence of NaOH, a retro-Michael process in **13** involving the conjugate addition of an OH anion may have occurred followed by elimination of a nitroester anion leading to intermediate **I**. Attack of the anion of **13** on this intermediate may have produced intermediate **II**, which upon decarboxylation would finally afford product **14**. In an attempt to gain support for this mechanism the precursor of **12**, i.e., the Baylis–Hillman adduct (represented by intermediate **I**) was independently treated with **13** in the presence of different bases (K_2CO_3, Et_3N, NaH). On the basis of the proposed mechanism it was envisaged that this reaction would produce **14**. Unfortunately under all attempted conditions this reaction was unavailing. This implied that in the presence of NaOH the retro-Michael process followed by the attack of the anion of **13** would proceed in a concerted fashion. In order to investigate whether **14** may serve as a precursor to new allylamine, representative analog **14f** was reduced in the presence of Fe-AcOH to afford **15f** successfully.



Scheme 3. Reagents and conditions: (i) ethyl nitroacetate, K_2CO_3, DMF, room temp., 1 h; (ii) NaOH, THF/H_2O (1:1), room temp., 9–11 h; (iii) Fe-AcOH, reflux, 3 h.

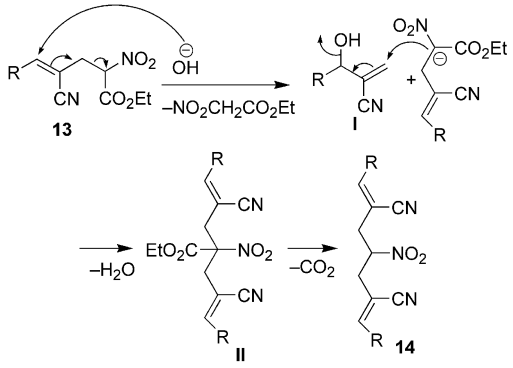


Figure 2. Plausible pathway for the formation of product **14**.

Conclusions

In summary, we have disclosed a facile method for the stereoselective generation of homoallyl nitro derivatives through the base-promoted regioselective decarboxylation of the nitroalkanoates of Baylis–Hillman adducts of acrylates under mild conditions. These derivatives are envisioned to be valuable intermediates for new cyclic frameworks. In contrast, similar nitroalkanoates from Baylis–Hillman adducts of acrylonitrile under identical reaction conditions provide facile access to new bisallyl nitroalkane systems.

Supporting Information (see footnote on the first page of this article): Experimental details, full characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for the prepared compounds.

Acknowledgments

M. N. gratefully acknowledges financial support in the form of a fellowship from the Council of Scientific and Industrial Research, New Delhi. This work was accomplished under a project funded by the Department of Science and Technology, N. Delhi (SR/SI/OC-16/2006).

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Received: March 28, 2009
Published Online: June 3, 2009

