

SHORT COMMUNICATION

Stereoselective synthesis of homoallyl nitroalkane derivatives via base-promoted regioselective decarboxylation in Baylis-Hillman derivatives[§]Maloy Nayak^[a] and Sanjay Batra*^[a]**Keywords:** Homoallyl nitroalkane / regioselective / Baylis-Hillman / decarboxylation / bis-allylnitroalkane

The regioselective decarboxylation during the saponification of the nitroalkanoates synthesized from the Baylis-Hillman acetates of acrylates to stereoselectively afford homoallyl nitroalkane is described. In contrast the similar nitroalkanoates derived from the

Baylis-Hillman acetates of acrylonitrile gave bis allyl nitroalkanes.

[a] Medicinal and Process Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001, India
Fax+91-522-2623405, 2623938
E-mail: batra_san@yahoo.co.uk, s_batra@cdri.res.in
§ CDRI Communication no. 7756

Introduction

Nitroalkanes are vital synthetic building blocks in organic chemistry. The facile transformation of the nitro-group to amine, imines, hydroxylamine, and carboxylic acids 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 generation of a variety of nitrile oxides as substrates for 1,3-dipolar cycloaddition reactions.^[3]

On the other hand, synthetic applications of the Baylis-Hillman derivatives are paramount as reflected from the recent literature. The most attractive feature of 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 using the Baylis-Hillman derivatives. During the course of one such work we discovered that the dialkanoate produced by S_N2'-reaction between ethyl nitroacetate and the Baylis-Hillman acetate upon treatment with base undergo decarboxylative protonation to afford homoallyl nitroalkane containing a primary nitro group. Although synthesis of allyl nitroalkane bearing primary nitro group has been achieved in Baylis-Hillman chemistry,^[5] synthesis of

group on the α-carbon has precedence^[6] and may be considered analogous to the decarboxylation experienced with α-keto acids or malonic acids under basic conditions. In context of the Baylis-Hillman chemistry, however, we have observed that a strong base is unable to effect the decarboxylation in α-keto acid or malonic acid.^[7] Kim and co-workers very recently demonstrated that decarboxylative protonation can be achieved in the Baylis-Hillman derivatives via Pd-salts for either obtaining 1,5-dicarbonyl compounds or conducting aralkylation.^[8] During the course of this study identical reaction of nitroalkanoates afforded from the Baylis-Hillman adducts of acrylonitrile unexpectedly produced bisallylnitroalkanes. These new observations prompt us to report the findings of our study herein.

Results and Discussion

At first, dialkanoates which served as the starting materials were prepared following the literature procedure.^[9] The acetyl derivatives (**1a-h,2-4**) of the Baylis-Hillman adducts were treated with ethyl nitroacetate in the presence of K₂CO₃ in DMF to afford the required compound (**5a-h,6-8**) (Scheme 1). Initially, treatment of **5a** with NaOH in aqueous methanol led to consumption of the

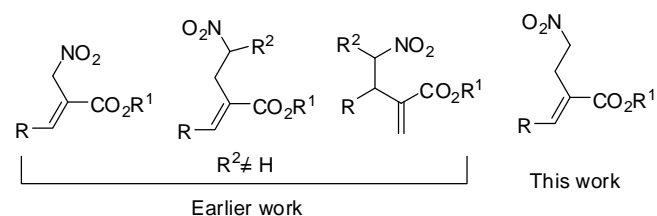
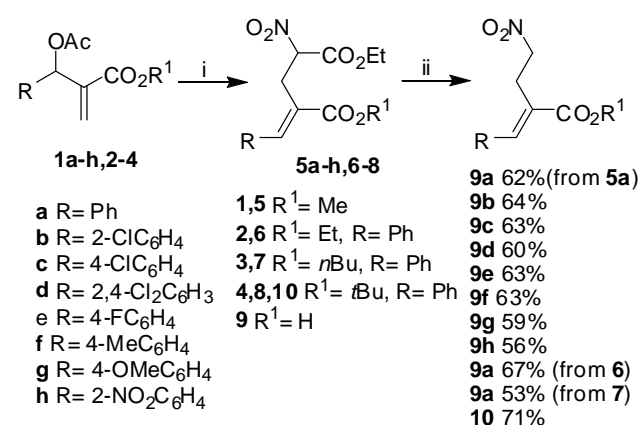


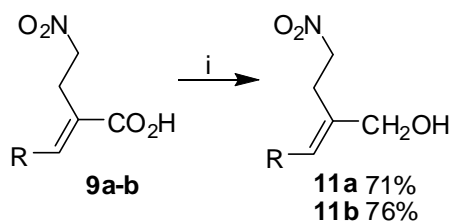
Figure 1. Nitroalkanes from the Baylis-Hillman chemistry

homoallyl nitroalkane bearing primary nitro group from Baylis-Hillman adduct remains unreported (Fig. 1). An insight into the literature reveal that decarboxylation due to the presence of nitro

Scheme 1. Reagents and conditions- (i) Ethyl nitroacetate, K₂CO₃, DMF, rt, 45 min. (ii) LiOH, THF-H₂O (1:1), rt, 8 h,

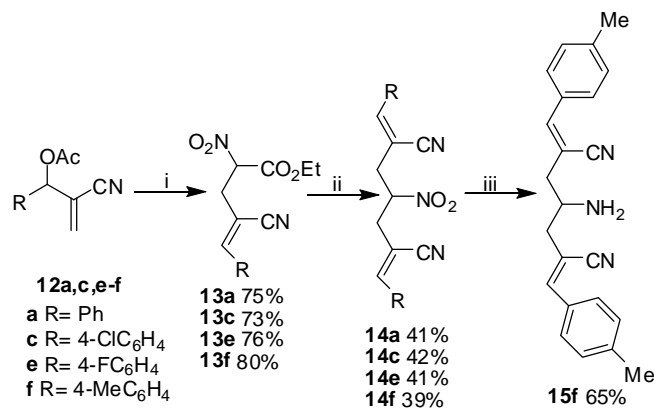
starting material within 8 h. Isolation and purification of the crude material furnished a product which was spectroscopically analyzed to be **9a** as *E*-isomer, exclusively. Notably the mass spectrum of **9a** when recorded in the electron spray mode (positive or negative) did not display the molecular ion peak but the high

resolution electron ionization mass spectrum 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 *E*-isomer only, indicating the general nature of the reaction. Substituting the methoxycarbonyl group in **5a** with ethoxycarbonyl or *n*-butoxycarbonyl did not alter the course of 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 the 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 NaBH₄-mediated reduction in the presence of isobutylchloroformate and NMM under aqueous condition to yield **11a–b**, respectively (Scheme 2). This result not only established the presence of the acid functionality in **9** but also provided a facile route to δ -aminoalcohol which may become useful intermediate for further investigations.



Scheme 2. Reagents and conditions. (i) Isobutylchloroformate, NMM, NaBH₄, THF-H₂O, 0°C, 5 min.

In the light of these results it became imperative to evaluate nitroalkanoates synthesized from the S_N2'-reaction between the ethyl nitroacetate and the acetyl derivative of Baylis-Hillman adduct afforded from acrylonitrile for similar reaction. Accordingly compounds **13a,c,e-f** were synthesized via treatment of acetates **12a,c,e-f** with ethyl nitroacetate in the presence of K₂CO₃ in DMF at room temperature. Initial reaction of **13a** with LiOH did not produce the desired product and was, therefore, replaced with NaOH. Fortunately, treating **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 bis allyl nitroalkane **14c,e,f**. The plausible mechanism for the formation of **14** is delineated in Fig. 2. It is assumed that in the presence of NaOH, a retro-Michael process in **13** involving the conjugate addition of OH anion may have occurred followed by elimination of nitroester anion leading to intermediate I. Attack of anion of **13** on this intermediate may have produced intermediate II which upon decarboxylation would finally afford the product **14**. In the 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 (K₂CO₃, Et₃N, NaH). Based on 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 be proceeding in a concerted fashion. In order to investigate whether **14** may serve as precursor to new allyl amine, one of the representative analog **14f** was reduced in the presence of Fe-AcOH to afford **15f**, successfully.



Scheme 3. Reagents and conditions- (i) Ethyl nitroacetate, K₂CO₃, DMF, rt, 1 h. (ii) NaOH, THF-H₂O (1:1), rt, 9–11 h. (iii) Fe-AcOH, reflux, 3 h

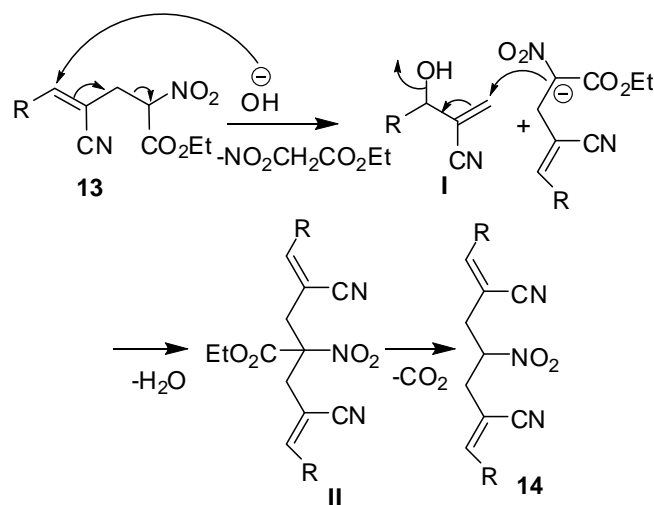


Figure 2. Plausible pathway for the formation of product **14**

Conclusions

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

Supporting Information Copies of ¹H- and ¹³C-NMR spectra for most of the compounds have been provided.

Acknowledgments

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

- [1] a) A. G. M. Barrett, G. G. Grabowski, *Chem. Rev.* **1986**, *86*, 751–762. b) *Nitro Compounds: Recent Advances in Synthesis and Chemistry* (Eds. H. Feuer, A. T. Nielsen) Wiley VCH: Weinheim, **1990**. c) *The Chemistry of Amino, Nitroso, Nitro and Related Groups* (Ed S. Patai) Wiley: Chichester, UK, **1996**. d) N. Ono in *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, New York, **2001**. e) O.

- M. Berner, L. Tedeschi, D. Enders *Eur. J. Org. Chem.* **2002**, 1877-1894. f) G. Rosini, R. Ballini, *Synthesis* **1988**, 833-847.
- [2] R. Ballini, A. Palmieri, P. Righi *Tetrahedron* **2007**, *63*, 12099-12121.
- [3] a) I. N. N. Namboothiri, N. Rastogi, *Top. Heterocyclic Chem.* **2008**, 1-44 and references cited therein. b) I. N. N. Namboothiri, A. Hassner, *Top. Curr. Chem.*, **2001**, 216, 1-49 and references cited therein. c) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235-3285. d) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561-3651. e) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765-2810. f) C. Najera, J. M. Sansano, *Angew. Chem. Int. Ed.* **2005**, *44*, 6272-6276. g) Kanemasa, S. *Synlett* **2002**, 1371-1387.
- [4] a) V. Singh, S. Batra *Tetrahedron* **2008**, *64*, 4511-4574 and references cited therein. b) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1-48 and references cited therein.
- [5] a) R. Bauchet, E. Le Rouille, A. Foucad, *Bull. Soc. Chim. Fr.* **1991**, *128*, 267-271. b) A. Chamakh, M. M'hirsi, J. Villieras, J. Lebreton, H. Amri, *Synthesis* **2000**, 295-299. c) D. Basavaiah, J. S. Rao, *Tetrahedron Lett.* **2004**, *45*, 1621-1625. d) M. J. Lee, K. Y. Lee, D. Y. Park, J. N. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 1281-1285. e) H. S. Lee, S. J. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2006**, *27*, 1063-1066. f) D. Y. Park, S. J. Kim, T. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2006**, *47*, 6315-6319.
- [6] a) A. Dahnz, G. Helmchen, *Synlett* **2006**, 697-700. b) V. G. Nenajdenko, S. V. Druzhinin, E. S. Balenkova, *Tetrahedron Lett.* **2005**, *46*, 8853-8855.
- [7] a) For base mediated hydrolysis of α -ketoester in the Baylis-Hillman derivative V. Singh, S. Madapa, S. Batra *Synth. Comm.* **2008**, *38*, 2113-2124. b) The base promoted hydrolysis of the Baylis-Hillman derivative obtained via S_N2' -reaction of diethylmalonate and the Baylis-Hillman acetate of acrylate produces a triacid. M. Nayak and S. Batra, **2009** unpublished results.
- [8] a) S. Gowrisankar, K. H. Kim, S. H. Kim, J. N. Kim *Tetrahedron Lett.* **2008**, *49*, 6241-6244. b) J. M. Kim, S. H. Kim, H. S. Lee, J. N. Kim *Tetrahedron Lett.* **2009**, *50*, 1734-1737.
- [9] V. Singh, S. Batra *Eur. J. Org. Chem.* **2007**, 2970-2976.

Received: ((will be filled in by the editorial staff))
 Published online: ((will be filled in by the editorial staff))