A Facile Synthesis of Pyrazolines from Baylis–Hillman Adducts

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(Received October 1, 2007; CL-071081; E-mail: yadavpub@iict.res.in)

Baylis–Hillman adducts undergo smooth 1,3-dipolar cycloaddition reaction with ethyl diazoacetate in the presence of 2-iodoxybenzoic acid to produce pyrazolines in high yields under mild reaction conditions.

Baylis–Hillman adducts are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo nucleophilic substitution reactions contributes largely to their synthetic value.[1–4] The versatility of the functionality present in Baylis–Hillman adducts makes them the valuable synthetic intermediates for the synthesis of a variety of heterocycles such as quinolines, pyrimidones, isoxazolines, pyrazolones, pyrrolidines, indolizines, azetidinone, diazacyclophanes, and chromanones as well as biologically active natural products including α-alkylidene-β-lactams, α-methylene-γ-butyrolactones, mikanecic acids, frontalin, trimethoprim, sarkomycin, ilmofosine nuciferol, and many others.[5] However, there have been no reports for the synthesis of pyrazolines from Baylis–Hillman adducts via a 1,3-dipolar cycloaddition reaction.

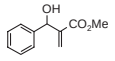
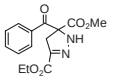
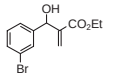
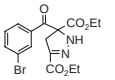
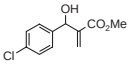
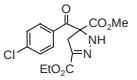
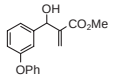
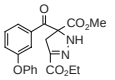
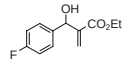
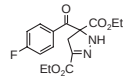
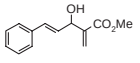
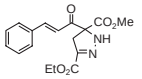
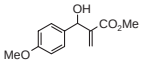
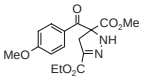
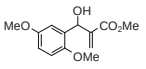
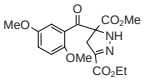
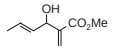
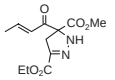
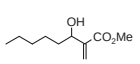
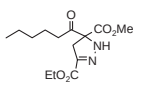
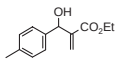
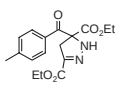
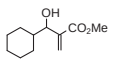
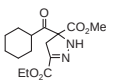
Pyrazolines are important class of heterocycles which exhibit potent biological activities, e.g. antibacterial,[6] antifungal,[7] antidiabetic,[8] anti-inflammatory,[9] antidepressant agents,[10] and active against many Mycobacterias.[11] Herein, we report a rapid synthesis of pyrazolines with high yields under mild reaction conditions from Baylis–Hillman adducts via one-pot oxidative 1,3-dipolar cycloaddition reaction promoted by IBX. Initially, we examined the oxidative cycloaddition reaction of methyl 2-[hydroxy(phenyl)methyl]acrylate (**1A**) with ethyl diazoacetate in the presence of 1.2 equiv of IBX in DMF. The reaction proceeded smoothly at room temperature and the pyrazoline **3A** was obtained in 85% yield (Scheme 1).

This result encouraged us to examine other substituted Baylis–Hillman adducts (Table 1). Interestingly, this method worked well with substrates derived from both aliphatic and aromatic aldehydes. In all cases, the reactions were clean and afforded the pyrazolines in good yields. The reaction conditions were compatible with various functionalities such as halides, aryl methyl ethers, esters, and alkenes (Table 1). All products were characterized by ^{1}H NMR, IR, and mass spectrometry. Among the various hypervalent iodine reagents examined, including iodosobenzene (PhIO), iodosobenzene diacetate [PhI(OAc)$_2$], and Dess–Martin periodinane (DMP), 2-iodoxybenzoic acid was found to be best in terms of conversion. Other

1A **2** **3A**

Scheme 1.

Table 1. Synthesis of pyrazolines from Baylis–Hillman adducts

Entry	B.H.adducts	Pyrazolines[a]	Reaction time/h	Yield/%[b]
1			2	85
2			2	90
3			2	82
4			3	80
5			2	85
6			4	80
7			3	83
8			3	82
9			4	82
10			6	85
11			3	87
12			5	85

[a]All products were characterized IR, ^{1}H NMR and mass spectrometry analysis. [b]Isolated yields.

oxidizing agents such as Oxone®, CAN, MnO_2, and $KBrO_3$ failed to produce the desired product as no oxidation of Baylis–Hillman adducts occured. To investigate whether iodosobenzoic acid, the by-product of oxidation with IBX plays any crucial role in cycloaddition, a separate reaction was carried out with isolated oxidized Baylis–Hillman adduct and ethyl diazoacetate. The reaction was found to proceed smoothly inferring no role of the by-product from oxidation reaction in our protocol. However, the yields were better in a one-pot reaction rather than two-step sequence done conventionally.[12] In the absence of IBX, no cycloaddition took place even after heating at 80 °C for longer reaction times (2–6 h). As a solvent,

DMF yielded the best result compared to other solvents such as CH_3CN, THF, DMSO, and EtOAc. The scope of IBX promoted one-pot oxidative cycloaddition reaction was investigated with various Baylis–Hillman adducts and the results are presented in the Table 1.

In conclusion, we have described a novel and efficient protocol for the one-pot oxidative cycloadditon of Baylis–Hillman adducts with ethyl diazoacetate using IBX as the efficient oxidant to produce various substituted pyrazolines in high yields.[13] The method offers several advantages such as mild reaction conditions, cleaner reaction profiles, operational simplicity, and use of inexpensive and readily available reagents, which makes it a useful and attractive strategy for the preparation of various substituted pyrazolines.

DCB and AKB thank CSIR, New Delhi for the award of fellowships.

References and Notes

1 a) K. Y. Lee, J. N. Kim, J. M. Kim, *Tetrahedron Lett.* **2003**, *44*, 6737. b) K. Y. Lee, J. M. Kim, J. N. Kim, *Tetrahedron* **2003**, *59*, 385. c) Y. J. Im, K. Y. Lee, T. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2002**, *43*, 4675.

2 a) J. N. Kim, J. M. Kim, K. Y. Lee, *Synlett* **2003**, 821. b) J. N. Kim, H. S. Kim, J. H. Gong, Y. M. Chung, *Tetrahedron Lett.* **2001**, *42*, 8341.

3 a) S. E. Drewes, N. D. Emslie, *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079. b) H. M. R. Hoffmann, J. Rabe, *Helv. Chim. Acta* **1984**, *67*, 413. c) H. M. R. Hoffmann, J. Rabe, *J. Org. Chem.* **1985**, *50*, 3849.

4 a) H. M. R. Hoffmann, J. Rabe, *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. b) R. Buchholz, H. M. R. Hoffmann, *Helv. Chim. Acta* **1991**, *74*, 1213. c) F. Ameer, S. E. Drewes, R. Hoole, P. T. Kaye, A. T. Pitchford, *J. Chem. Soc., Perkin Trans. 1* **1985**, 2713.

5 D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811.

6 D. Nauduri, G. D. Reddy, *Chem. Pharm. Bull. (Tokyo)* **1998**, *46*, 1254.

7 S. S. Korgaokar, P. H. Patil, M. T. Shah, H. M. Parekh, *Indian Pharm. Sci.* **1996**, *58*, 222.

8 J. H. Ahn, H. M. Kim, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhee, S. D. Yang, H. G. Cheon, S. S. Kim, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4461.

9 R. H. Udupi, A. R. Kushnoor, A. R. Bhat, *Indian J. Heterocycl. Chem.* **1998**, *8*, 63.

10 A. A. Bilgin, E. Paska, R. Sunal, *Arzneim.-Forsch.* **1993**, *43*, 1041.

11 a) M. A. Ali, M. S. Yar, M. Kumar, G. S. Pandian, *Nat. Prod. Res.* **2007**, *21*, 575. b) S. G. Kucukguzel, S. Rollas, *Farmaco* **1975**, *64*, 1075. c) Ş. G. Küçükgüzel, S. Rollas, H. Erdeniz, M. Kiraz, A. C. Ekinci, A. Vidin, *Eur. J. Med. Chem.* **2000**, *35*, 761. d) A. A. Santilli, D. H. Kim, F. J. Gregory, *J. Pharm. Sci.* **1975**, *64*, 1057. e) M. Shaharyar, A. A. Siddiqui, M. A. Ali, D. Sriram, P. Yogeeswari, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3947. f) M. Shaharyar, A. A. Siddiqui, M. A. Ali, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4571. g) M. A. Ali, M. Shaharyar, A. A. Siddiqui, *Eur. J. Med. Chem.* **2007**, *42*, 268.

12 In two-step sequence, isolated yields of the oxidized Baylis–Hillman adducts were found to be low. This may be attributed towards the high reactivity of the oxidized product of Baylis–Hillman adducts.

13 General experimental procedure: A mixture of Baylis–Hillman adduct (1.0 mmol), IBX (1.2 mmol), and ethyl diazoacetate (1.2 mmol) in DMF (7 mL) was stirred at room temperature until complete reaction took place. The mixture was then diluted with water (15 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with water (2×10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude reaction mixture was purified by column chromatography using hexane:ethyl acetate (9:1) as eluent to afford pure pyrazolines.

Published on the web (Advance View) May 10, 2008; doi:10.1246/cl.2008.624