Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 43–46
Tetrahedron Letters

Conjugate base catalysed one-pot synthesis of pyrazoles from β-formyl enamides

Anil Saikia, Madan G. Barthakur, Moyurima Borthakur, Chandan J. Saikia, Utpal Bora and Romesh C. Boruah*

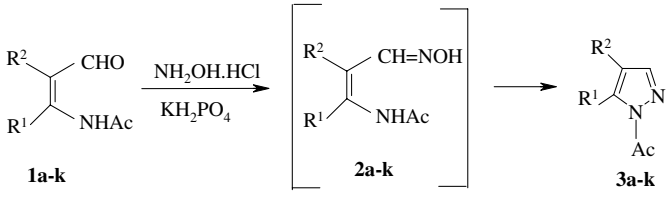
Medicinal Chemistry Division, Regional Research Laboratory, Jorhat 785006, India

Received 25 August 2005; revised 14 October 2005; accepted 25 October 2005
Available online 14 November 2005

Abstract—A novel one-pot synthesis of pyrazoles has been accomplished by the reaction of β-formyl enamides with hydroxylamine hydrochloride catalysed by potassium dihydrogenphosphate in acid medium.

The synthesis of pyrazoles has received considerable attention because of their applications in pharmaceutical and agrochemical industries being due to their antipyretic, anti-inflammatory, herbicidal, insecticidal and fungicidal properties.[1] More recently, extensive studies have focused on aryl pyrazoles for exhibiting cyclooxygenase-2 (COX-2) and non-nucleoside HIV-1 reverse transcriptase inhibitory properties.[2,3] Among several methods available for the preparation of pyrazoles, the condensation of hydrazine with 1,3-dicarbonyl compounds[4] and the nitrene insertion reaction[5] are widely employed strategies. However, the generality of these reactions is vitiated by the severe reaction conditions or multi-step sequences usually required to access the starting materials.[6] As a result, efforts have been and are still being made to find and develop more general and versatile synthetic methodologies for pyrazoles.[7] The biological activities of heterosteroids[8,9] make them important targets for synthetic chemists. Research efforts in our laboratory towards the synthesis of newer heterosteroids afforded β-formyl enamides as organic synthons.[10] In continuation of our interest in the use of β-formyl enamides in organic synthesis, we report herein a novel, simple and high yielding one-pot synthesis of pyrazoles from the reaction of β-formyl enamides with hydroxylamine hydrochloride catalysed by potassium dihydrogenphosphate in acid medium.

In a typical reaction, 3β-acetoxy-17-acetamido-16-formyl-androst-5,16-diene **1a**[11] and hydroxylamine hydrochloride were mixed with potassium dihydrogenphosphate in ethanol and the mixture stirred at room temperature for 1 h. Work-up of the reaction did not yield the expected aldoxime **2a**, rather it afforded a cyclised pyrazolo-androsteroid **3a** in 94% yield (Scheme 1). The product was characterised by spectral and analytical analysis.[12] The ^{1}H NMR spectrum of **3a** exhibited a characteristic singlet proton signal at



1a-k **2a-k** **3a-k**

Scheme 1.

Keywords: β-Formyl enamide; Conjugate base; Hydroxylamine hydrochloride; Pyrazole.
* Corresponding author. Tel.: +91 376 2370327; fax: +91 376 2370011; e-mail: rc_boruah@yahoo.co.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.10.145

$\delta = 8.38$ for the aromatic pyrazole proton. The ESI mass spectra showed a molecular ion peak at m/z 419 (M^++Na). Examination of Table 1 shows that the reaction occurred in good yields in all cases examined, varying from 79–94% and affording pyrazoles as sole products. It is noteworthy that steroidal, alicyclic, aliphatic and aromatic β-formyl enamides **1b**–**i** all gave rise to the corresponding pyrazoles **3b**–**i** in high yields (Table 1).

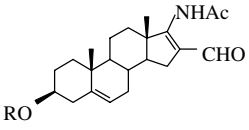
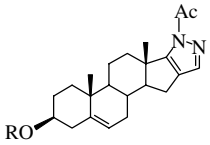
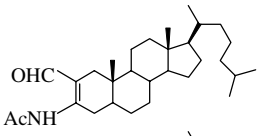
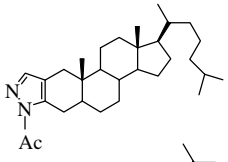
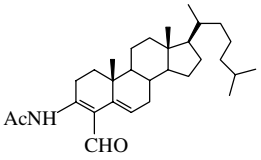
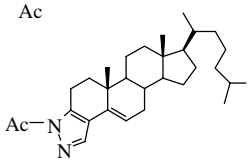
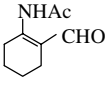
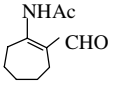
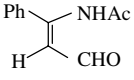
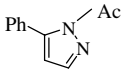
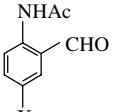
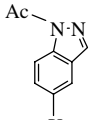
The reaction of β-formyl enamide **1a** with hydroxylamine hydrochloride was similarly catalysed by dipotassium hydrogenphosphate or sodium acetate to afford **3a** in excellent yield. However, replacement of KH_2PO_4 with pyridine or sodium methoxide led to the corresponding aldoxime **2a**, exclusively, without formation of **3a**. The use of pyrrolidine or morpholine gave **3a** as a minor product. On the other hand, the reaction of **1a** with hydroxylamine hydrochloride without base led to a mixture of products **2a** and **3a**. However, when the oximation of β-formyl enamide **1a** was carried with a 50% aqueous solution of hydroxylamine or a mixture of equimolar equivalents of $NH_2OH{\cdot}HCl$–Et_3N, it afforded the corresponding aldoxime **2a** without formation of pyrazole **3a**.[13]

A KH_2PO_4-mediated treatment of aldoxime **2a** was conducted successively in acidic, neutral and basic conditions. It was observed that in acidic medium (pH 6), the cyclised product **3a** was obtained in excellent yield (92%), whereas, reaction attempted at pH 7 or pH 8 failed to afford **3a**.

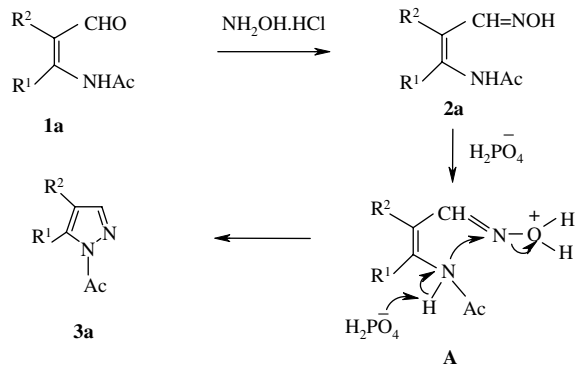
A possible mechanism for pyrazole formation is shown in Scheme 2. Under acidic conditions, aldoxime **2a** undergoes protonation to form intermediate **A**, abstraction of the amide NH proton being facilitated by the conjugate base $H_2PO_4^-$. Intramolecular attack of the nucleophilic nitrogen onto the electron-deficient imine nitrogen followed by loss of water led to cyclised product **3a**. The failure of aldoxime **2a** to react with potassium dihydrogenphosphate under neutral conditions supports the requirement for acid mediation.

In conclusion, we have developed an efficient synthesis of pyrazoles from β-formyl enamides employing a con-

Table 1. Reaction of β-formyl enamides with hydroxylamine hydrochloride[a]

Entry	β-Formyl enamide		Time (h)	Product		Yield[b]
1		**1a**, R = Ac	2		**3a**	94
2		**1b**, R = Bz	2		**3b**	86
3		**1c**	2		**3c**	85
4		**1d**	2		**3d**	84
5		**1e**	2		**3e**	87
6		**1f**	3		**3f**	81
7		**1g**	2		**3g**	93
8		**1h**, X = H	2		**3h**	79
9		**1i**, X = Cl	2		**3i**	82

[a] Reactions were carried using potassium dihydrogenphosphate as catalyst.
[b] Isolated yields.



Scheme 2.

jugate base catalysed intramolecular cyclisation reaction in acidic medium. We have demonstrated that the incorporation of an acetamido group adjacent to an aldoxime moiety facilitated the cyclisation to afford the pyrazole in a one-pot reaction. The methodology reported herein represents a new preparation of pyrazoles and is expected to be a general route for one-pot combinatorial synthesis of a wide range of annelated pyrazoles.

Acknowledgements

We are grateful to the Department of Science and Technology, New Delhi for financial support and the Director, R. R. L. Jorhat for his keen interest in this work.

References and notes

1. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 291–298; (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd.: Oxford, 1996; Vol. 3, pp 1–75.
2. (a) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365; (b) Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. *J. Med. Chem.* **2002**, *45*, 1511–1517; (c) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039–3042; (d) Price, M. L. P.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2000**, *122*, 9455–9466.
3. Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. *J. Med. Chem.* **2000**, *43*, 1034–1040.
4. Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347–429.
5. Moody, C. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 21–28.
6. (a) Almirante, N.; Cerri, A.; Fedrizzi, G.; Marazzi, G.; Santagostino, M. *Tetrahedron Lett.* **1998**, *39*, 3287–3290; (b) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *Synlett* **2004**, 2299–2302.
7. (a) Majid, T.; Hopkins, C. R.; Pedgrift, B.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 2137–2139; (b) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Lakshmi, P. N.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8587–8590; (c) Kim, M.; Wiemer, D. F. *Tetrahedron Lett.* **2004**, *45*, 4977–4980; (d) Hanamoto, T.; Hakoshima, Y.; Egashira, M. *Tetrahedron Lett.* **2004**, *45*, 7573–7576; (e) Singh, S. K.; Reddy, M. S.; Shivaramakrishna, S.; Kavitha, D.; Vasudev, R.; Babu, J. M.; Sivalakshmidevi, A.; Rao, Y. K. *Tetrahedron Lett.* **2004**, *45*, 7679–7682; (f) Ahmed, S.; Longchar, M.; Boruah, R. C. *Ind. J. Chem.* **1999**, *38B*, 125–127.
8. (a) Hong, C. I. In *Antitumor Steroids*; Blickenstaff, R. T., Ed.; Academic Press: New York, 1992; pp 1–142; (b) Potter, G. A.; Barrie, S. E.; Jarman, M.; Rowland, M. G. *J. Med. Chem.* **1995**, *38*, 2463–2471; (c) Jarman, M.; Barrie, S. E.; Llera, J. M. *J. Med. Chem.* **1998**, *41*, 5375–5381; (d) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006–2007.
9. (a) Njar, V. C. O.; Klus, G. T.; Brodie, A. M. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2777–2782; (b) Li, J.; Li, Y.; Son, C.; Brodie, A. M. H. *J. Med. Chem.* **1996**, *39*, 4335–4339; (c) Ling, Y.; Li, J.; Liu, Y.; Kato, K.; Klus, G. T.; Brodie, A. *J. Med. Chem.* **1997**, *40*, 3297–3304.
10. (a) Boruah, R. C.; Ahmed, S.; Sharma, U.; Sandhu, J. S. *J. Org. Chem.* **2000**, *65*, 922–925; (b) Sharma, U.; Ahmed, S.; Boruah, R. C. *Tetrahedron Lett.* **2000**, *41*, 3493–3495; (c) Ahmed, S.; Boruah, R. C. *Tetrahedron Lett.* **1996**, *37*, 8231–8232; (d) Chetia, A.; Longchar, M.; Lekhok, K. C.; Boruah, R. C. *Synlett* **2004**, 1309–1311.
11. Steroidal D-ring and cyclic β-formyl enamides were prepared by Vilsmeier reaction of the corresponding conjugated oximes following a reported procedure: Boruah, R. C.; Ahmed, S.; Sharma, U.; Sandhu, J. S. *Ind. J. Chem.* **1999**, *38B*, 274–282; Steroidal A-ring and acyclic β-formyl enamides were prepared by Vilsmeier reactions of the corresponding enamides in turn accessible from 3-ketocholestanone and acetophenone, respectively, following a reported procedure: Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237–1241.
12. Illustrative experimental procedure. Pyrazolo-androsteroid **3a**: To a solution of 3β-acetoxy-17-acetamido-16-formyl-androst-5,16-diene (**1a**, 0.327 g, 0.82 mmol) in ethanol (40 ml) was added hydroxylamine hydrochloride (0.112 g, 1.62 mmol) and potassium dihydrogenphosphate (0.220 g, 1.62 mmol) and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was poured into ice-cold water (50 ml), neutralised with aqueous $NaHCO_3$ solution, extracted with dichloromethane (2×25 ml), the extract washed with water and dried over anhydrous sodium sulfate. Removal of the solvent and column chromatography of the residue over silica gel using ethyl acetate/hexane (8/2) as eluant afforded pyrazolo-androsteroid **3a**, yield 0.305 g (94%), mp 206–207 °C; IR ($CHCl_3$) ν 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, s), 5.42 (1H, br s), 4.61 (1H, m), 2.71 (3H, s), 2.04 (3H, s), 1.10 (3H, s), 1.00 (3H, s), 2.92–1.02 (17H, m); ^{13}C NMR ($CDCl_3$) δ 170.96, 170.40, 158.15, 141.91, 140.58, 133.65, 121.96, 74.05, 56.27, 50.56, 45.73, 38.44, 37.20, 33.17, 31.50, 31.11, 30.07, 28.56, 28.04, 21.81, 20.74, 20.32, 19.70, 17.26; Mass spectra: m/z 419 (M^++Na), 397 (M^++1); Anal Calcd for $C_{24}H_{32}N_2O_3$: C, 72.70; H, 8.13; N, 7.06%. Found: C, 72.60; H, 8.28; N, 6.96%.
13. 3β-Acetoxy-17-acetamido-androst-5,16-dieno-16-aldoxime **2a**, mp 167–169 °C; IR ($CHCl_3$) ν 3405, 2940, 1730,

1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, s), 7.48 (1H, br s), 5.35 (1H, br s), 4.60 (1H, m), 2.15 (3H, s), 2.06 (3H, s), 1.12 (3H, s), 1.04 (3H, s), 2.75–0.95 (17H, m); ^{13}C NMR ($CDCl_3$) δ 172.45, 171.90, 153.53, 144.82, 141.35, 136.55, 120.43, 75.10, 57.20, 50.88, 44.32, 39.74, 38.52, 34.08, 31.90, 31.37, 31.22, 28.97, 27.67, 21.76, 20.21, 20.13, 19.55, 17.86; Mass spectra: m/z 413 (M^+-1), 395 [(M^+-1)−18], 353, 335, 293; Anal. Calcd for $C_{24}H_{34}N_2O_4$: C, 69.54; H, 8.27; N, 6.76%. Found: C, 69.85; H, 8.12; N, 6.96%.