Tetrahedron Letters 51 (2010) 1341–1343

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of novel pyrazoles via [2+3]-dipolar cycloaddition using alkyne surrogates

Sureshbabu Dadiboyena [a], Edward J. Valente [b], Ashton T. Hamme II [a,*]

[a] Department of Chemistry and Biochemistry, College of Science, Engineering and Technology, Jackson State University, Jackson, MS 39217, USA
[b] Department of Chemistry, University of Portland, 5000 N. Willamette Blvd., Portland, OR 97203, USA

ARTICLE INFO

Article history:
Received 22 December 2009
Revised 6 January 2010
Accepted 7 January 2010
Available online 13 January 2010

Keywords:
Cycloaddition
Regioselectivity
Heterocycles
Alkyne surrogate
Dehydrohalogenation

ABSTRACT

The syntheses of an important class of hitherto unreported novel pyrazoles are described. The regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles was achieved by the Huisgen cyclization of nitrile imines with a trisubstituted bromoalkene. The substituted bromoalkene functions as an alkyne synthon which was used to construct 5,5-disubstituted bromopyrazoline intermediates that undergo aromatization to the analogous pyrazoles through the loss of HBr. The cycloaddition regioselectivity was confirmed through single X-ray crystal data of one of the pyrazoles.

1. Introduction

Heterocycles are popularly known for displaying a wide range of biological properties,[1] and the recent success of pyrazole-based COX-II inhibitors and their application in medicinal chemistry have amplified the importance of pyrazoles.[2] Several pharmaceutical drugs including celecoxib[2] and rimonabant[3] utilize the pyrazole as their core molecular entity,[4,5] and a regioselective synthetic method for the synthesis of these and other substituted pyrazoles is still in demand.[3,5–7] (Fig. 1) One of the most frequently used protocols for pyrazole synthesis is 1,3-dipolar cycloaddition, and the usual dipolarophiles for this purpose are alkynes[8] and alkyne equivalents.[6,9] The use of alkyne synthons[9,10] can serve to alleviate many of the alkyne preparatory and cycloaddition regioselectivity issues. These alkyne proxies are usually alkenes that have a functional group that can be eliminated in situ during cycloaddition.[9,10] Recently, we reported the application of geminally disubstituted alkenes, with a bromine atom as one of the substituents, as effective alkyne replacements toward the regioselective synthesis of disubstituted isoxazoles.[11] In order to build upon this premise, we investigated the application of this protocol toward the regioselective construction of tetrasubstituted pyrazoles. Herein we

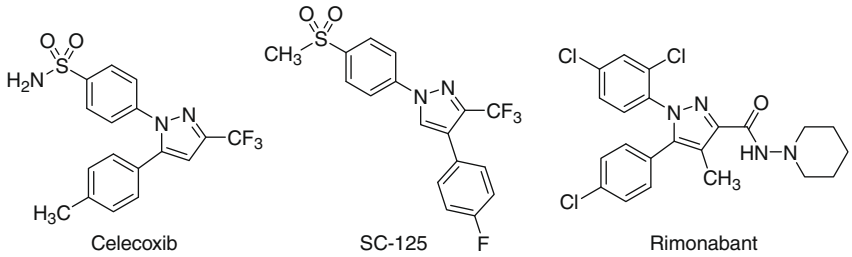
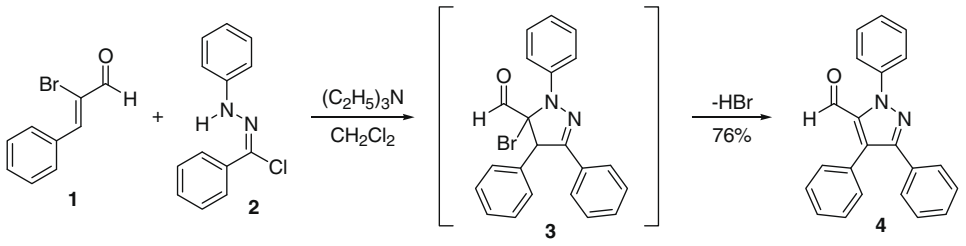


Figure 1. Examples of pharmaceutically relevant pyrazoles.

* Corresponding author. Tel.: +1 601 979 3713; fax: +1 601 979 3674.
E-mail address: ashton.t.hamme@jsums.edu (A.T. Hamme).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.01.017

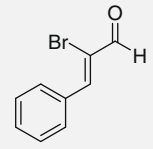
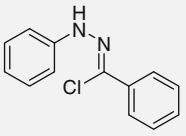
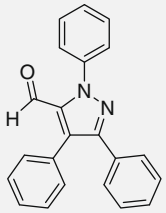
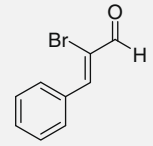
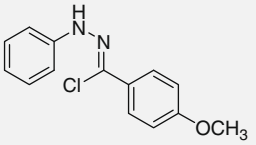
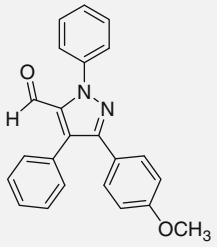
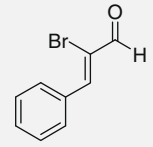
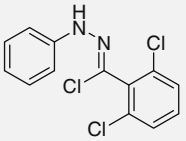
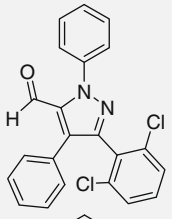
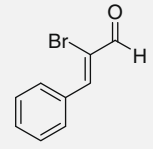
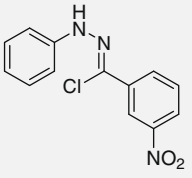
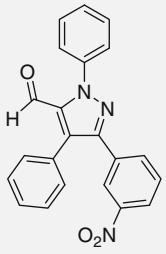
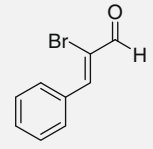
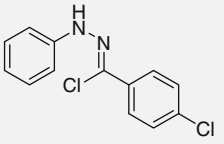
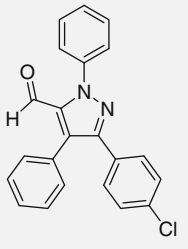


Scheme 1. Pyrazole synthesis from α-bromocinnamaldehyde through the 5-bromo pyrazoline intermediate **3**.

report the synthesis of 1,3,4,5-tetrasubstituted pyrazoles through the regioselective 1,3-dipolar cycloaddition of a nitrile imine with a trisubstituted bromoalkene which serves as an alkyne surrogate.

While investigating the synthesis of pyrazoles and pyrazolines, we discovered that when α-bromocinnamaldehyde (**1**) was used as the alkene, pyrazole (**4**)[12,13] was the only product isolated. (Scheme 1) The most probable driving force for the formation of **4** is the creation of a stable aromatic system through the loss of HBr. Since the reaction conditions are basic, it is quite possible for the bromo alkene, **1**, to decompose to the corresponding alkyne before reacting with the nitrile imine. In order to rule out this reaction pathway, compound **1** was exposed to triethylamine for 24 h at

Table 1
1,3,4,5-Tetrasubstituted pyrazoles isolated from the 1,3-dipolar cycloaddition reaction

Entry	Alkene	α-Chloro hydrazone	Product	Yield (%)
1				76
2				70
3				86
4				73
5				84

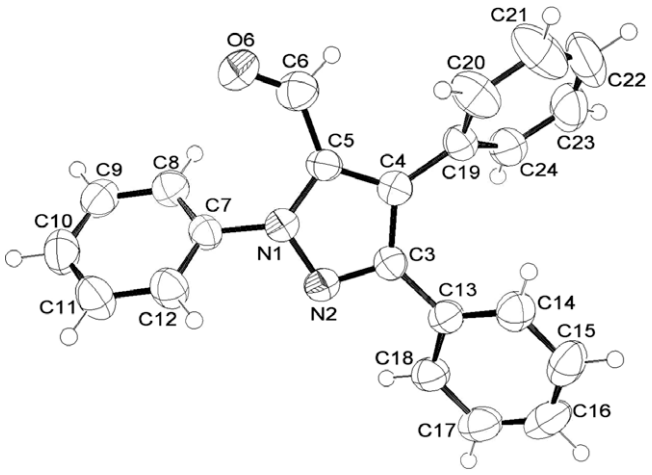


Figure 2. Thermal ellipsoid plot of **4** drawn at the 50% probability level.[13]

room temperature, and no decomposition to the corresponding alkyne was observed. The study of the 1,3-dipolar cycloaddition reaction of compound **1** with other nitrile imines was undertaken in order to determine the general efficacy of α-bromocinnamaldehyde as an alkyne equivalent. All these cycloadditions occurred with complete regiochemical integrity in reasonable to good isolated yields. The results of the cycloaddition of **1** with five different nitrile imines with various functionalities are shown in Table 1.

The existence of pyrazole (**4**) as a crystalline solid enabled us to perform X-ray studies to reveal compound's regio-structural features. Compound **4** was unambiguously confirmed by X-ray structural analysis as a 1,3,4,5-tetrasubstituted pyrazole where the benzene rings are located at the 3 and 4 positions of the pyrazole. (Fig. 2) This X-ray analysis provided evidence that the Huisgen cyclization occurred through intermediate **3** as shown in Scheme 1. The structures of the remaining pyrazoles were elucidated based upon their NMR spectroscopic data.

2. Conclusion

In summary, we report a facile and regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles through the 1,3-dipolar cycloaddition of nitrile imines with α-bromocinnamaldehyde (**1**) as an alkyne surrogate.[14] The construction of the stable aromatic pyrazole system could be the driving force behind the dehydrobromination process. Along with the NMR data, X-ray crystallographic analysis also confirmed the regiochemistry of the distinctive pyrazole compounds. Future investigations of 1,3-dipolar cycloaddition reactions with various alkyne surrogates toward the synthesis of pyrazoles and other heterocyclic compounds are in progress.

Acknowledgments

We thank the National Institutes of Health MBRS-SCORE and RCMI programs (3S06 GM 008047-34S1 and G12RR13459 (NMR and Analytical CORE facilities)) and the National Science Foundation NSF-RISE program (HRD-0734645). E.J.V. gratefully acknowledges the support of the National Science Foundation grant MRI 0618148 and the W. M. Keck Foundation for crystallographic resources.

References and notes

1. Shen, D.; Shu, M.; Chapman, K. T. *Org. Lett.* **2000**, *2*, 2789.
2. 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.
3. Deng, X.; Mani, N. S. *Org. Lett.* **2008**, *10*, 1307.
4. (a) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 6787; (b) Elguero, J.. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, p 1.
5. Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505.
6. Donohue, A. C.; Pallich, S.; McCarthy, T. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2817.
7. (a) Chiericato, M.; Croce, P. D.; Carganico, G.; Maiorana, S. *J. Heterocycl. Chem.* **1979**, *16*, 383; (b) Abunada, N. M.; Hassaneen, H. M.; Kandile, N. G.; Miqdad, O. A. *Molecules* **2008**, *13*, 1501.
8. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565; (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633; (c) Browne, D. L.; Vivat, J. F.; Plant, A.; Gomez-Bengoa, E.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2009**, *131*, 7762.
9. (a) Oh, L. *Tetrahedron Lett.* **2006**, *47*, 7943; (b) de Lucchi, O.; Modena, G. *Tetrahedron* **1984**, *40*, 2585; (c) Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schurmann, M.; Preut, H.; Jacob, T.; Arndt, H.-D. *J. Am. Chem. Soc.* **2008**, *130*, 13219; (d) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381; (e) Chandrasekhar, S.; Rajaiah, G.; Srihari, P. *Tetrahedron Lett.* **2001**, *42*, 6599.
10. (a) Easton, C. J.; Hughes, C. M.; Tiekink, E. R. T.; Lubin, C. E.; Savage, G. P.; Simpson, G. W. *Tetrahedron Lett.* **1994**, *35*, 3589; (b) Easton, C. J.; Heath, G. A.; Hughes, C. M. M.; Lee, C. K. Y.; Savage, G. P.; Simpson, G. W.; Tiekink, E. R. T.; Vuckovic, G. J.; Webster, R. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1168; (c) Jimenez, R.; Perez, L.; Tamariz, J.; Salgado, H. *Heterocycles* **1993**, *35*, 591.
11. (a) Dadiboyena, S.; Xu, J.; Hamme, A. T., II *Tetrahedron Lett.* **2007**, *48*, 1295; (b) Xu, J.; Hamme, A. T., II *Synlett* **2008**, 919; (c) Hamme, A. T., II; Xu, J.; Wang, J.; Cook, T.; Ellis, E. *Heterocycles* **2005**, *65*, 2885.
12. Dawood, K. M.; Fuchigami, T. *J. Org. Chem.* **2005**, *70*, 7537.
13. Structural information for pyrazole **(4)** has been deposited with the CCDC as 744851, available free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).
14. *General experimental procedure for the 1,3-dipolar cycloaddition*: A solution of α-bromocinnamaldehyde (**1**) (3 mmol) and the hydrazonyl chloride (3 mmol) in 10 mL of either dry chloroform or dichloromethane was treated with triethylamine (0.46 mL, 3.3 mmol). The reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete (7–10 h), the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel by using a hexanes–ethyl acetate ratio as an eluant system. This procedure provided pure pyrazole products for entries **1**–**5** in 70–86% yield.