ORGANIC
LETTERS

2006
Vol. 8, No. 18
3975−3977

Synthesis of Novel Heterocyclic Structures via Reaction of Isocyanides with *S-trans*-Enones

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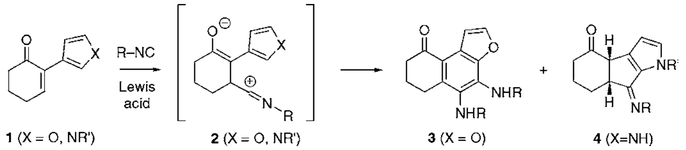
Received June 13, 2006

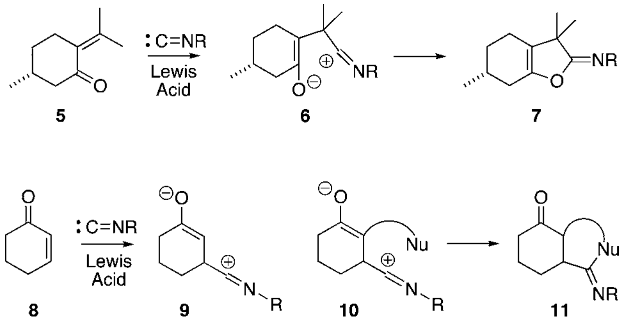
ABSTRACT



The reaction of enone 1, bearing an internal nucleophilic moiety, i.e., furan or pyrrole (X = O, NR′), with isocyanides is presented. The formation of products resulting from the reaction of the zwitterionic intermediate 2 with a second equivalent of isocyanide prior to cyclization to give 3, as well as the direct formation of 4 from 2, is described.

The cycloaddition of isocyanides with heterodienes affords a diverse array of five-membered ring products.[1−3] Saegusa[2] and subsequently Chatani[3] have shown that addition of isocyanides to *S-cis*-enones leads to the formation of iminolactone products, i.e., **7**, via intramolecular collapse of the zwitterionic intermediate **6** that is obtained on Lewis acid-catalyzed addition of an isocyanide to the enone (Scheme 1). The analogous reaction of an *S-trans*-enone, i.e., cyclohexenone **8**, would generate a zwitterionic intermediate **9** that could not undergo analogous intramolecular collapse. However, incorporation of a nucleophilic substituent into **9** would result in intermediate **10**, which could undergo cyclization via addition of the pendant nucleophile (Nu) to the nitrilium intermediate to give, after protonation, **11**. We report herein that such a strategy leads to a novel approach to the synthesis of a diverse array of polycyclic ring systems.

Scheme 1. Reaction of Isocyanides with *S-cis*- and *S-trans*-Enones



We first examined the proposed reaction sequence using furan as the nucleophilic substituent, as shown with **1**

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(1) For examples of the cycloaddition of isocyanides with heterodienes to give five-membered rings, see: (a) Deyrup, J. A.; Killion, K. K. *Heterocycl. Chem.* **1972**, 1045−1048. (b) Marchand, E.; Morel, G.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, *133*, 903−912. (c) Morel, G.; Marchand, E.; Foucaud, A. *J. Org. Chem.* **1990**, *55*, 1721−1727. (d) Morel, G.; Marchand, E.; Foucaud, A. *J. Org. Chem.* **1985**, *50*, 771−778. (e) Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L. *J. Org. Chem.* **1989**, *54*, 1185−1191. (f) Morel, G.; Marchand, E.; Sinbandhit, S.; Carlier, R. *Eur. J. Org. Chem.* **2001**, 655−662. (g) Nair, V.; Mathew, B.; Vinod, A. U.; Mathen, J. S.; Ros, S.; Monon, R. S.; Varma, R. L.; Srinivas, R. *Synthesis* **2003**, 662−664. (h) Rigby, R. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587−5591. (i) Rigby, R. H.; Qabar, M.; Ahmed, G.; Hughes, R. C. *Tetrahedron* **1993**, *49*, 10219−10228. (j) Foucaud, A.; Razorilalana-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639−3644. (k) Quai, M.; Frattini, S.; Vendrame, U.; Mondoni, M.; Dossena, S.; Cereda, E. *Tetrahedron Lett.* **2004**, *45*, 1413−1416. (l) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975−8976.

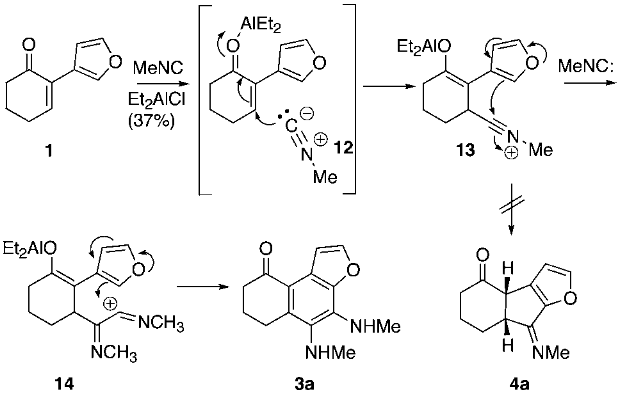
(2) Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741−743.

(3) (a) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812−7813. (b) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761−766.

10.1021/ol061451c CCC: $33.50

(Scheme 2).[4] Exposure of **1** (1 equiv) and methyl isocyanide **12** (0.9 equiv) to 1.1 equiv of diethylaluminum chloride in THF at 23 °C for 18 h led to none of the expected cyclopentafuran **4a**, but instead to the formation of **3a**, which results from the reaction of intermediate **13** with a second equivalent of isocyanide to give **14** prior to cyclization. Similar double-addition products have been observed by Rigby[5] and Chatani[3] in attempted [4+1] cycloadditions of heterodienes with isocyanides.

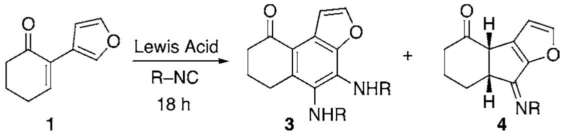
Scheme 2. Double-Addition Products in the Reaction of **1** with Methyl Isocyanide



The effect of the alkyl substituent of the isocyanide in the partitioning of intermediate **13** between cyclization to give **4** and reaction with an additional equivalent of isocyanide to give **3** (via **14**) was next examined. We reasoned that increasing the steric effect of the alkyl group R could disfavor the addition of a second equivalent of isocyanide that would lead to the intermediate corresponding to **14** and therefore promote the formation of the monoaddition product **4**. In the event, however, changing the R group on the isocyanide from methyl to *tert*-butyl increased the yield of the double-addition product **3b** (R = *t*-Bu) from 37 to 58%, and none of the monoaddition product **4b** (R = *t*-Bu) was observed (see Table 1, entry 2). The increased reactivity of *tert*-butyl isocyanide could be attributed to the inductive electron-donating effect of the *tert*-butyl group relative to methyl.

In contrast, the use of electron-rich aromatic isocyanides, i.e., *p*-methoxyphenyl **16** (Table 1, entry 3), does not increase the efficiency of the formation of **3c** (R = 4-MeOPh; 43% yield). However, the effect of the more sterically demanding 2,6-dimethylphenyl isocyanide **17** on the course of the cyclization is significant. Reaction of **1** and **17** gave the double-addition product **3d** (R = 2,6-dimethylphenyl) in 47% yield, accompanied by the formation of the monoaddition product **4d** (R = 2,6-dimethylphenyl), albeit in 14% yield (Table 1, entry 4). Replacement of diethylaluminum chloride with stoichiometric or catalytic gallium chloride afforded **3d** in 77−79% yield, and none of the monoaddition product **4d** was observed (Table 1, entries 6 and 7).

Table 1. Effect of Isocyanide Substitution and the Nature of the Lewis Acid on the Cyclization Reaction

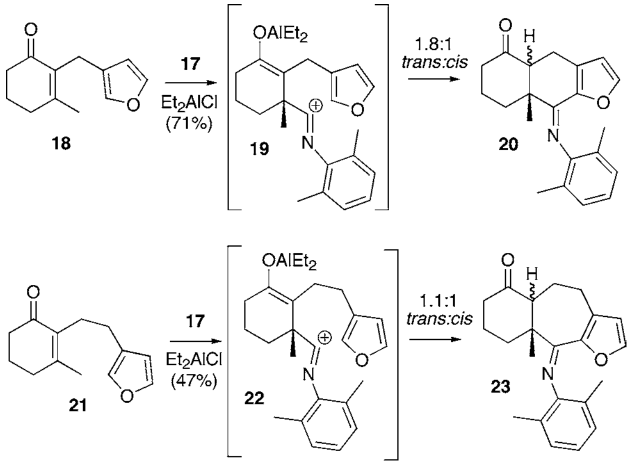


entry	R	Lewis acid (equiv)	solvent	temp, °C	products	
					3 (%)	**4** (%)
1	Me, **12**	Et_2AlCl (1.1)	THF	25	**3a** (37)	^{a}
2	*t*-Bu, **15**	Et_2AlCl (1.2)	THF	25	**3b** (58)	^{a}
3	4-MeOPh, **16**	Et_2AlCl (1.2)	THF	25	**3c** (43)	^{a}
4	2,6-Me_2Ph, **17**	Et_2AlCl (1.2)	THF	25	**3d** (47)	**4d** (14)
5	2,6-Me_2Ph, **17**	Et_2AlCl (1.2)	PhMe	25	**3d** (52)	**4d** (16)
6	2,6-Me_2Ph, **17**	$GaCl_3$ (1.0)	PhMe	25	**3d** (79)	^{a}
7	2,6-Me_2Ph, **17**	$GaCl_3$ (0.1)	PhMe	60	**3d** (77)	^{a}

^{a} Not observed.

We next examined a strategy for the selective formation of the monoaddition product corresponding to **4** via introduction of methylene spacers between the enone and the nucleophilic furan, i.e., **18** and **21** (Scheme 3). We reasoned that the zwitterionic intermediate **19** resulting from the addition of isocyanide **17** to enone **18** would undergo facile six-membered ring formation to generate **20**, in analogy to the facile six-membered ring formation observed with **14** to give **3** with no further incorporation of isocyanide (Scheme 2).

Scheme 3. Monoaddition Products via Reaction of Homologated Substrates **18** and **21** with Isocyanide **17**



In the event, reaction of **18**, which was readily prepared from Hagemann's ester,[6] with 2,6-dimethylphenyl isocyanide **17** led to the selective formation of **20** in 71% yield, as a 1.8:1 mixture of trans/cis stereoisomers. As expected, the yield of the seven-membered ring formation is somewhat attenuated. Cyclization of enone **21**,[7] similarly prepared from

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(4) Enone **8** was prepared via Suzuki coupling of 2-bromocyclohexenone with 3-furyl-boronic acid.

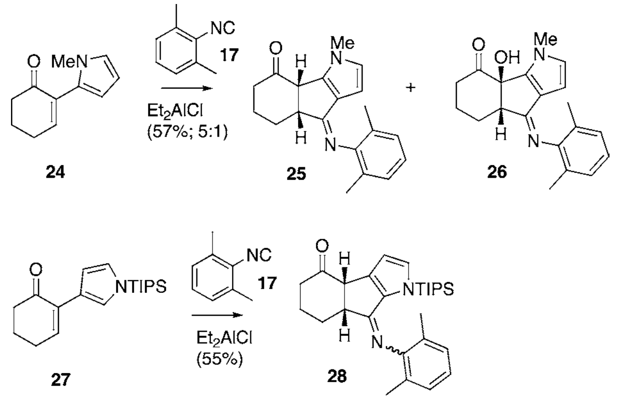
(5) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766−1767.

(6) The preparation of **17** was followed from: Chakraborty, A.; Kar, G. K.; Ray, J. K. *Tetrahedron* **1997**, *53*, 2989−2996.

Hagemann's ester, afforded imine **23** in 47% yield as a 1.1:1 mixture of trans/cis diastereomers.

We have also examined the replacement of the furan moiety in **1** (Scheme 2) with pyrrole (Scheme 4). The requisite substrates **24**[8a] and **27**[8b] were prepared by palladium-catalyzed cross-coupling reactions. Although reaction of 2-pyrrole **24** with 2,6-dimethylphenyl isocyanide gave **25**, accompanied by minor amounts of the oxidation product **26**[9] (57% combined yield), the analogous reaction of 3-pyrrole **27** led to the exclusive formation of **28** in 55% yield. The exclusive formation of monoaddition products corresponding to **4** (Scheme 2) in the reactions of both **24** and **27** is consistent with the increased nucleophilicity of pyrrole relative to furan, promoting five-membered ring formation at the expense of the reaction of the zwitterionic intermediate with a second equivalent of isocyanide.

Scheme 4. Monoaddition Products via Reaction of Pyrroloenones with Isocyanide **17**



These results establish that the reaction of substituted enones with isocyanides can lead to the selective formation of products that formally result from either [4+1] or [4+1+1] cycloaddition products. The application of this methodology to the synthesis of diverse polycyclic systems is currently underway in our laboratories, and our results will be reported in due course.

Acknowledgment. We would like to thank the NIH, GlaxoSmithKline, Merck, and Amgen for their generous support of this work.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Mal, S. K.; Kar, G. K.; Ray, J. K. *Tetrahedron* **2004**, *60*, 2805−2811.

(8) (a) Compound **24** was prepared from the Stille reaction of 2-bromo-2-cyclohexenone and *N*-methyl-2-tributylstannanepyrrole using $PdCl_2(PPh_3)_2$ as the catalyst. (b) Compound **27** was prepared from the Negishi coupling of 2-iodo-2-cyclohexenone and the pyrrolylzinc species of 1-(triisopropylsilyl)-3-iodopyrrole with $Pd(PPh_3)_4$ as the catalyst.

(9) The spontaneous oxidation of the C−H bond flanked between a carbonyl and an indole or a pyrrole has been observed by others: (a) De la Figuera, N.; García-López, M. T.; Herranz, R.; González-Muñiz, R. *Heterocycles* **1998**, *48*, 2061−2070. (b) Kurihara, T.; Nasu, K.; Inoue, M.; Ishida, T. *Chem. Pharm. Bull.* **1982**, *30*, 383−385. (c) Kurihara, T.; Nasu, K.; Haginaga, S.; Mihara, K. *Chem. Pharm. Bull.* **1984**, *32*, 4410−4418. (d) Stojanovic, M. N.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 9343−9446. (e) De la Figuera, N.; García-López, M. T.; Herranz, R.; González-Muñiz, R. *Heterocycles* **1998**, *48*, 2061−2070.