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Torquoselective 6π-Electron Electrocyclic Ring Closure of 1-Azatrienes Containing Acyclic Chirality at the *C*-Terminus

Nadiya Sydorenko, Richard P. Hsung,* and Eymi L. Vera

Division of Pharmaceutical Sciencies and Department of Chemistry, Rennebohm Hall, 777 Highland Avenue, University of Wisconsin, Madison, Wisconsin 53705-2222

rhsung@wisc.edu

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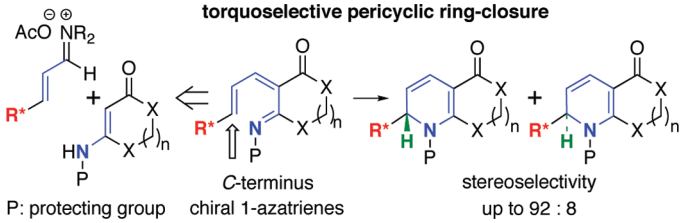
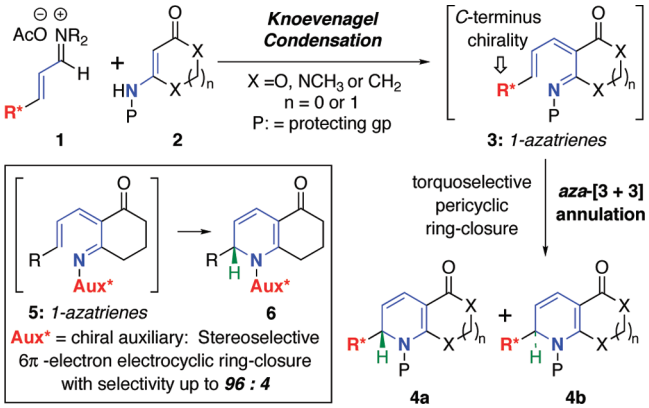
ABSTRACT



Torquoselective pericyclic ring closures of 1-azatrienes that contain acyclic chirality at the *C*-terminus are described herein.

Pericyclic processes represent an important venue in organic synthesis.We have been developing an aza-[3 + 3] annulation reaction[1−5] involving a Knoevenagel-type condensation of the *in situ* generated iminium ions **1** with vinylogous amides **2** followed by a 6π-electron electrocyclic ring closure of 1-azatrienes **3**[6,7] en route to 1,2-dihydropyridines **4** (Scheme 1). While this annulation has become an attractive strategy[1,2] for constructing various nitrogen heterocycles, it provides a unique opportunity to develop approaches toward a stereo-

Scheme 1



(1) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (c) Coverdale, H. A.; Hsung, R. P. *ChemTracts* **2003**, *16*, 238.

(2) For a review on vinylogous amide chemistry, see: Kucklander, U. Enaminones as Synthons. In *The Chemistry of Functional Groups: The Chemistry of Enamines Part I*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994; p 523.

(3) For recent studies in this area, see: (a) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, ASAP. (b) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (c) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (d) Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. *Tetrahedron* **2004**, *60*, 5433. (e) Ji, S.-J.; Jiang, Z.-Q.; Lu, J.; Loh, T.-P. *Synlett* **2004**, 831. (f) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827. (g) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286. For interesting related studies, see: (h) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2003**, *5*, 1689 and references therein. (i) Hong, B. C.; Wu, M. F.; Tseng, H. C.; Liao, J. H. *Org. Lett.* **2006**, *8*, ASAP.

(4) For our work on intermolecular aza-[3 + 3], see: (a) Sydorenko, N.; Hsung R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732. (b) McLaughlin, M. J.; Hsung, R. P.; Cole, K. C.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. (c) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.

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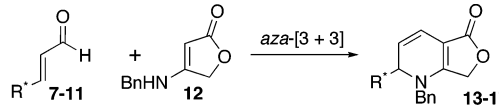
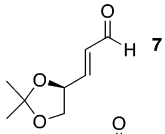
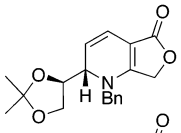
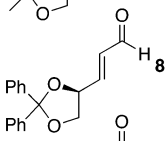
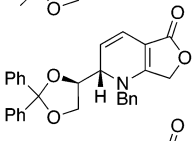
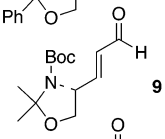
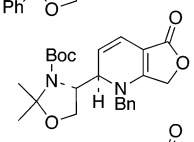
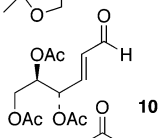
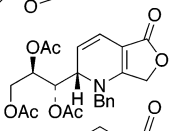
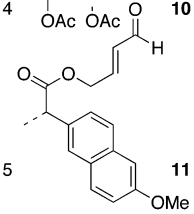
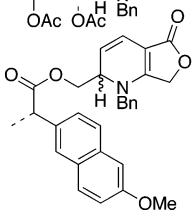
selective pericyclic ring closure of 1-azatrienes, leading to chiral 1,2-dihydropyrindes. Such efforts have been largely overlooked with the elegant exception of Tanaka and Katsumura's electrocyclic ring closure using chiral amines[8] and our own report of a torquoselective ring closure of 1-azatrienes **5** employing a chiral auxiliary on the nitrogen atom en route to 1-azadecalins **6**.[9] A more general and practical approach remains elusive.[10] We report here a torquoselective[11] pericyclic ring-closure of 1-azatrienes containing acyclic chirality at the *C*-terminus.

To establish an initial level of torquoselectivity, we prepared chiral α,β-unsaturated aldehydes **7**−**11**[12−15] and employed them as precursors for generating 1-azatrienes bearing chirality at the *C*-terminus through the aza-[3 + 3] annulation reaction with *N*-benzyltetronamide **12** under standard reaction conditions.[4,9] The feasibility and stereoselectivity for their respective annulation reactions are summarized in Table 1.[16]

Table 1. Aza-[3 + 3] Annulations with *N*-Benzyltetronamide



entry	chiral enal[a,b]	cycloadduct	T [°C]	yield[c] [%]	ratio[d]
1	 7	 13	150	66	76 : 24
2	 8	 14[e]	150	63	62 : 38
3	 9	 15	160	32	83 : 17
4	 10	 16[f]	150	64	75 : 25
5	 11	 17	150	73	61 : 39

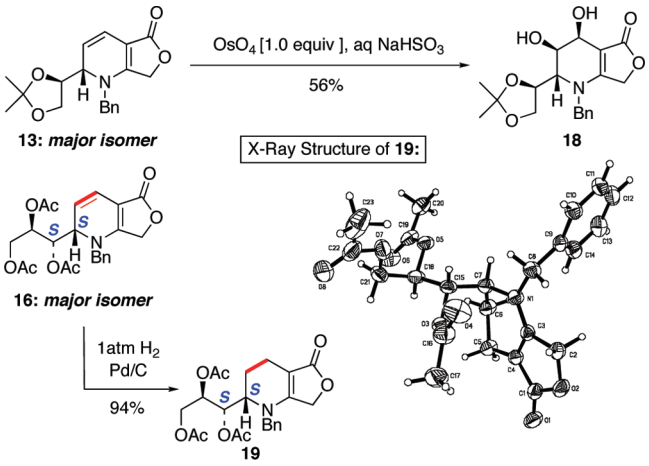
[a] The iminium salt was generated using 1 equiv of piperidine and 1 equiv of Ac_2O at 85 °C for 1 h. [b] All reactions were carried out in EtOAc/toluene (2:3) in a sealed tube for 24−72 h. [c] Isolated yields only. [d] Ratios determined by ^1H NMR. [e] Two diastereomers are inseparable. [f] Stereochemistry is confirmed through the X-ray analysis of the corresponding derivative (see Scheme 2).

It was found that most of the diastereoselectivities are modest with the best dr being 83:17 while employing chiral enal **9** (entry 3). However, the yield for the annulation product **15** was poor, and this is likely due to the steric encumbrance of the *N*-Boc group. It is consistent with our earlier finding that bulky β-substituents of enals can hinder ring closures of 1-azatrienes and diminish the annulation yield.[4b,9a]

On the other hand, the annulation yields are good when employing enal **7** and **10**,[17] and their stereoselectivities are comparable with the respective dihydropyridines **13** and **16** possessing ratios of 76:24 and 75:25 (entries 1 and 4). The reaction with the more bulky diphenyl acetonide enal **8** (entry 2) showed a notable decrease in selectivity for **14** (62:38) relative to **13**. Dihydropyridine **17** obtained from the reaction with enal **11** was also formed with low diastereoselectivity. In this case, the chirality in enal **11** is likely too remote from the newly formed stereogenic center of **17** to be significant for asymmetric induction, although it is still surprising to still see any stereoinduction.

To unambiguously determine the stereochemical assignment, dihydropyridine **13a** was successfully dihydroxylated to give diol **18** as a single diastereomer (Scheme 2).

Scheme 2



Unfortunately, all attempts to grow a single crystal from **18** or its acetonide derivatives failed. Fortuitously, monohydrogenation of the major isomer of **16** provided **19** that allowed

(5) For intramolecular aza-[3 + 3], see: (a) Swidorski, J. J.; Wang, J.; Hsung R. P. *Org. Lett.* **2006**, *8*, 777. (b) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. W. *J. Org. Chem.* **2005**, *70*, 4248. (c) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Organic Biomol. Chem.* **2005**, *3*, 2140. (d) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. (e) Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516.

(6) For leading references on electrocyclic ring-closures involving 1-azatrienes, see: (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem* **1995**, *60*, 1763. (b) de Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 4051. For an earlier account, see: (c) Oppolzer, V. W. *Angew. Chem.* **1972**, *22*, 1108.

(7) For some recent studies of the ring-closure of azatrienes, see: (a) Meketa, M. L.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1443. (b) Alajarín, M.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, A.; Bautista, D. *Org. Lett.* **2005**, *7*, 5281.

(8) For recent elegant accounts on stereoselective ring-closure of 1-azatrienes, see: (a) Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660. (b) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099. (c) Tanaka, K.; Kobayashi, T.; Mori, H.; Katsumura S. *J. Org. Chem.* **2004**, *69*, 5906.

(9) a) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. W. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (d) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145.

us to obtain X-ray quality crystals. The X-ray structure of **19** reveals the assignment for the major isomer of **16** to be *S* for the new stereocenter. The absolute stereochemistry of cycloadducts **13**−**15**, **17**, and **23**−**29** were assigned by comparison to **16**.

Other examples of such a stereoselective approach to pericyclic ring closure of 1-azatrienes are shown in Table 2.[18] It was found that the best stereoselectivity was obtained

Table 2. Variations in the Amides

entry	enal[a,b,c]	amide	cycloadduct	T [°C]	yield[d] [%]	ratio[e]
1	**7**[a]	**20**	**23**	110	58	75 : 25
2	**10**[a]	**20**	**24**	130	49	77 : 23
3	**11**[a]	**20**	**25**[f]	130	65	54 : 46
4	**10**[b]	**21**	**26**	170	61	69 : 31
5	**11**[b]	**21**	**27**[f]	180	84	59 : 41
6	**10**[b]	**22**	**28**	150	76	83 : 17
7	**11**[b]	**22**	**29**[f]	150	75	66 : 34

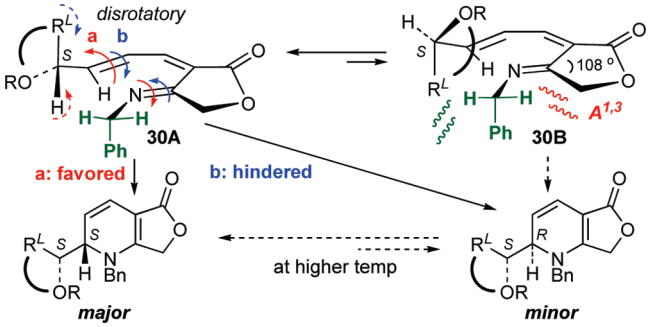
[a] The iminium salt was generated using 1 equiv of piperidine and 1 equiv of Ac_2O at 85 °C for 1 h. [b] The iminium salt was generated using 1 equiv of piperidine trifluoroacetate salt at 85 °C for 1 h. [c] All reactions were carried out in EtOAc/toluene (2:3) in a sealed tube for 24−72 h. [d] Isolated yields only. [e] Ratios determined by ^{1}H NMR. [f] The two diastereomers are inseparable.

from the reactions of the iminium salt derived from enal **10**, which gave dihydropyridines **24**, **26**, and **28** with ratios of 77:23, 69:31, and 83:17, respectively (entries 2, 4, and 6). Similarly, annulations of amides **20**−**22** with the iminium salt derived from enal **11** proceeded in a rather stereorandom manner (entries 3, 5, and 7).

While these ratios are modest, it provides an opportunity to examine this ring closure more closely from a mechanistic perspective. It is not obvious that one should expect any diastereomeric induction during the ring-closure step of the aza-[3 + 3] annulation given the high degree of conformational freedom of the chirality at the *C*-terminus of these 1-azatrienes. Toward this end, we proposed a model based on a potential rotational preference to rationalize observed torquoselectivity.

As shown in Scheme 3, there are two predominant conformations, **30A** and **30B**, with both minimizing allyl strains

Scheme 3



by placing the largest R^L group at the allylic position in the plane of the *C*-terminus vinyl strand. While both can undergo ring-closure, simple molecular modeling reveals that 1-azatriene **30A** could have an advantage over **30B** given the remote steric interaction (in green) between the *N*-Bn group and the *C*-terminus allylic substituent. With 1-azatriene **30A** as the preferred conformation, a disrotatory ring closure in the direction **a** (in red) should be favored to give the observed major isomer because the direction **b** (in blue) would bring the R^L group (dotted arrow in blue) into closer contact with the *N*-Bn group.

With this model in mind, we should note that 6π-electron electrocyclic ring-closure can be reversible,[19,20] especially at high temperatures, leading to ratios reflecting thermodynamic stabilities of the two diastereomeric isomers. We did

(10) For a review on rotational preferences leading to diastereomeric induction during a 6π-electron electrocyclic ring closure, see: Okamura, W. H.; de Lera, A. R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Paquette, L. A., Vol. Ed.; Pergamon Press: New York, 1991; Vol. 5, pp 699−750.

(11) For some examples of torquoselective processes, see: (a) Harmata, M.; Lee, D. R.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1881. (b) Harmata, M.; Schreiner, P. R.; Lee, D. R.; Kirchhoefer, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 10954. (c) Murakami, M.; Hasegawa, M.; Igawa, H. *J. Org. Chem.* **2004**, *69*, 587. (d) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 189. (e) Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441. (f) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1970.

(12) (a) Earle, M. J.; Abdur-Rashid, A.; Priestley, N. *J. Org. Chem.* **1996**, *61*, 5697. (b) Brown, J. M.; Leppard, S. J.; Oakes, J.; Thornthwaite, D. *Chirality* **2000**, *12*, 496.

(13) (a) Campbell, A. D.; Raynham, T. M., Taylor, R. J. K *Synthesis* **1998**, *12*, 1707. (b) Zhang, X.; Ni, W.; van der Donk, W. A. *J. Org. Chem.* **2005**, *70*, 6685.

(14) Gonzales, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267.

(15) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018.

(16) See the Supporting Information.

(17) For a study employing enal **10** in oxa-[3 + 3] annulations with 4-hydroxy-2-pyrones, see: Sagar, R.; Singh, P.; Kumar, R.; Maulik, P. R.; Shaw, A. K. *Carbohydr. Res.* **2005**, *340*, 1287.

(18) Despite our efforts, we were not able to render the reaction of **7** to proceed feasibly with either aminopyrone **21** or amide **22**.

(19) For a review on rotational preferences leading to diastereomeric induction during a 6π-electron electrocyclic ring closure, see: Okamura, W. H.; de Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Paquette, L. A., Vol. Ed.; Pergamon Press: New York, 1991; Vol. 5, pp 699−750.

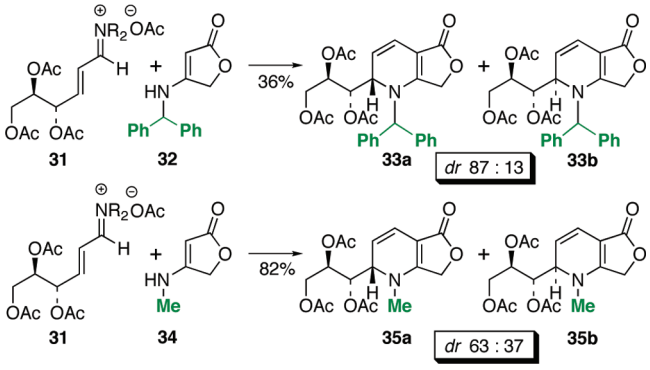
(20) For a recent computational study, see: Cabaleiro-Lago, E. M.; Rodríguez-Otero, J.; Santiago M. Varela-Varela, S. M.; Penã-Gallego, A.; Hermida-Ramon, J. M. *J. Org. Chem.* **2005**, *70*, 3921.

carry out relevant equilibration experiments employing **13** or **16** with a starting ratio of 1:1 and found that the respective ratios reported in Table 1 (entries 1 and 4) could be reached ultimately but at temperatures higher than (~250 °C) the reaction temperature.[21] This suggests that equilibration under the reaction conditions can play a role in the selectivity but it is likely not the only factor. Thus, the aforementioned rotational preference in the proposed model remains a possible rationale.

By examining our model more closely, it reveals two interesting factors. First, the size of the nitrogen substituent should influence the rotational preference with the larger substituent providing higher dr. Second, a greater $A^{1,3}$-strain interaction (see **30B**: in red) may also enhance the selectivity because it can push the nitrogen substituent closer toward the *C*-terminus allylic fragment, thereby further favoring both the conformation **30A** and a disrotatory ring-closure in the direction **a**. Based on these two assertions, we pursued the following studies to further support our proposed model.

As shown in Scheme 4, tetronamides **32** and **34**[22] were prepared and reacted with the chiral iminium salt **31**

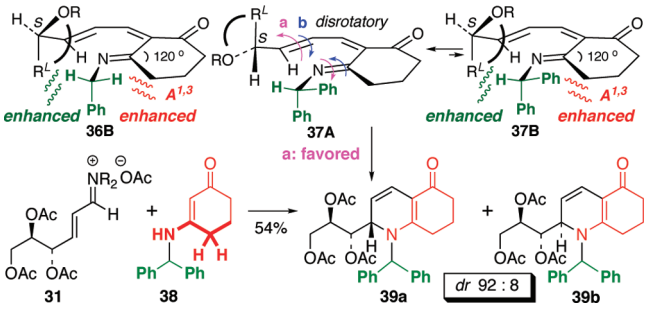
Scheme 4



(generated from **10**). As predicted above, with a much bulkier *N*-diphenylmethyl group (in green), tetronamide **32** provided the cycloadducts **33a** and **33b** with an improved ratio of 87:13 from that of **16**, although the yield was lower. At the same time, with a smaller *N*-methyl group (in green), tetronamide **34** gave the corresponding annulation products **35a** and **35b** at much higher yield (82%) but with a noticeable loss of stereoselectivity (63:37). These two experiments are in agreement with the first suggested assertion.

The second assertion is already consistent with the fact that amide **22** provided a higher dr in **28** (entry 6 of Table 2) than *N*-benzyltetronamide **12** that gave **16** (entry 4 of Table 1). The larger internal angle of the six-membered ring shown in 1-azatriene **36B** (see Scheme 5) should lead to an

Scheme 5



enhanced allylic strain (in red) relative to **30B** (in Scheme 3) and an enhanced interaction between the *N*-Bn group and allylic fragment (in green). As suggested above, these enhancements collectively can further favor a disrotatory ring closure in the direction **a** through the conformation **36A** (not shown but respective to **36B**), thereby giving **28** in higher dr than **16**.

With this analysis, to put it altogether, an *N*-diphenylmethyl group as shown in **37** should provide an even higher torquoselectivity via ring-closure in the direction **a** through the conformation **37A** (Scheme 5). This prediction was confirmed with the reaction of amide **38**, which provided dihydropyridine **39** with the highest torquoselectivity (92:8).

We have described here a torquoselective ring closure of 1-azatrienes containing acyclic chirality at the *C*-terminus, which represents an unexplored venue for stereochemical control of this pericyclic process.

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Supporting Information Available: Experimental details, NMR spectral characterization data for all new compounds, as well as X-ray structrural data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060932T

(21) Theoretical calculations using SPARTAN-'02 at B3LYP/6-31G* level were neither conclusive nor consistent as to which diastereomeric isomer is more stable energetically.

(22) (a) Greenhill, J. V.; Tomassini, T. *Tetrahedron Lett.* **1974**, *31*, 2683. (b) Shandala, M. Y.; Ayoub, M. T.; Mohammad, M. J. *J. Heterocycl. Chem.* **1984**, *21*, 1753.