

Pyridines from Azabicyclo[3.2.0]-hept-2-en-4-ones through a Proposed Azacyclopentadienone

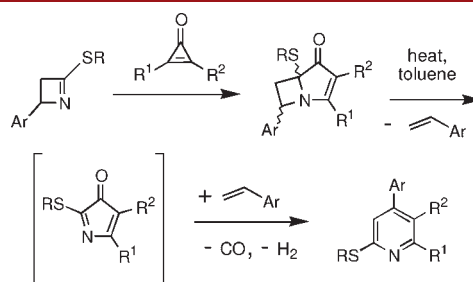
Karl Hemming,* Musharraf N. Khan, Vishnu V. R. Kondakal, Arnaud Pitard, M. Ilyas Qamar, and Craig R. Rice

Institute for Materials, Medicines and Molecular Sciences, Division of Chemistry, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, West Yorkshire, HD1 3DH, United Kingdom

k.hemming@hud.ac.uk

Received October 29, 2011

ABSTRACT



62 to 79%; 7 examples; regioselective;

azacyclopentadienone intermediate trapped.

Pyridines have been formed by heating azabicyclo[3.2.0]hept-2-en-4-ones in toluene. The generation of a 3-azacyclopentadienone intermediate via a [2 + 2]-cycloreversion is proposed as the key step. A Diels–Alder reaction of a styrene, extrusion of carbon monoxide, and loss of hydrogen then gives the pyridine. The process parallels the well-known synthesis of benzenes from cyclopentadienones. The azabicyclo[3.2.0]hept-2-en-4-ones were synthesized from the reaction between readily available cyclopropenones and 1-azetines, in which the cyclopropenones behave as all-carbon 1,3-dipolar equivalents.

The pyridine ring occupies a position of great importance to the synthetic chemist due to its relevance in the pharmaceutical industry, in the agrochemical industry, in

natural product chemistry, and in materials science.^{1–3} It is thus the case that the synthesis of the pyridine ring by the use of new cycloaddition¹ and other² methodologies continues to be of current value, and such recent contributions ensure that this most studied³ of areas remains a rich source for significant discoveries. Among the more recent¹ and established³ cycloaddition methodologies, the use of azacyclopentadienone in pyridine synthesis remains an

(1) (a) Wang, Y.-F.; Tof, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411. (b) D'Souza, B. R.; Lane, T. K.; Louie, J. *Org. Lett.* **2011**, *13*, 2936. (c) Coffinier, D.; El Kaim, L.; Grimaud, E.; Orru, R. V. A. *Tetrahedron Lett.* **2011**, *52*, 3023. (d) Kral, K.; Hapke, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2434. (e) Chughtai, M.; Eagan, J. M.; Padwa, A. *Synlett* **2011**, 215. (f) Garcia, P.; Evanno, Y.; George, P.; Sevriv, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030. (g) Coffinier, D.; El Kaim, L.; Grimaud, L.; Hadrot, S. *Tetrahedron Lett.* **2010**, *51*, 6186. (h) Chuang, T.-H.; Chen, Y.-C.; Pola, S. *J. Org. Chem.* **2010**, *75*, 6625. (i) Miclo, Y.; Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Malacria, M.; Gandon, V.; Aubert, C. *Synlett* **2010**, 2314. (j) Sakai, T.; Danheiser, R. L. *J. Am. Chem. Soc.* **2010**, *132*, 13203. (k) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474. (l) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (m) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (n) Barluenga, J.; Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764.

(2) (a) Dagorn, F.; Yan, L.-K.; Gravel, E.; Leblanc, K.; Maciuk, A.; Poupon, E. *Tetrahedron Lett.* **2011**, *52*, 3523. (b) Wu, P.; Cia, X. M.; Wang, Q. F.; Yan, C. G. *Synth. Commun.* **2011**, *41*, 841. (c) Liu, J.; Wang, C.; Wu, L.; Liang, F.; Huang, G. *Synthesis* **2010**, 4228. (d) Shen, L.; Cao, S.; Wu, J.; Hui, L.; Zhang, J.; Wu, M.; Qian, X. *Tetrahedron Lett.* **2010**, *51*, 4866. (e) Chen, Z.; Zhu, J.; Xie, H.; Li, S.; Wu, Y.; Gong, Y. *Org. Lett.* **2010**, *12*, 4376. (f) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570. (g) Rizk, T.; Bilodeau, E. J.-F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8325. (h) Hu, J.; Zhang, Q.; Yuan, H.; Liu, Q. *J. Org. Chem.* **2008**, *73*, 2442. (i) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629. (j) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602.

unexploited avenue, an absence that is all the more curious given the well-known⁴ process by which the corresponding all-carbon diene, cyclopentadienone, is used to access the benzene ring. The absence of azacyclopentadienone based pyridine syntheses is undoubtedly related to the difficulties encountered in accessing this elusive system either in stable form or from readily available suitable precursors. The 2-azacyclopentadienone ring **1** (see Figure 1) is rare, but its formation and use are known.⁵ Of particular relevance to our work, species **1** has been generated from a polymeric 5-sulfonate of 2-oxopyrrolidine and shown to act as a diene toward a polymer supported alkyne, allowing access to one example of a pyridine ring.⁶ Work by the same group⁷ gave access to a single example of the even more elusive 3-azacyclopentadienone **2**, generated in similar fashion as an unstable intermediate from a polymeric 1-acyl 3-oxopyrrolidine. A stable 3-thione analogue of azacyclopentadienone **2** has also been reported.⁸ In view of this scarcity and lack of applicability, there is a requirement for new methods which allow the generation of 3-azacyclopentadienones. We wish to report one such method in this paper and show that such systems can be used to generate pyridines.

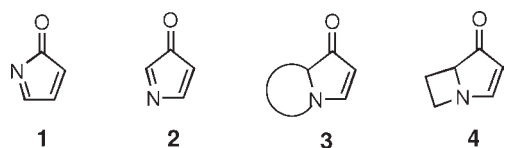
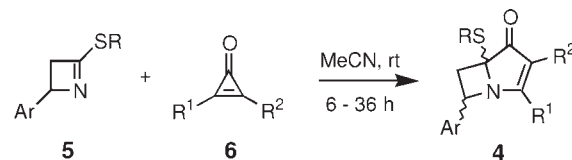


Figure 1. Azacyclopentadienones and bicyclic pyrrolinones.

Our work started with the synthesis of a range of azabicyclo systems **3** which incorporate the 3-oxopyrrolidine moiety. We investigated the azabicyclo[3.2.0]hept-2-en-4-one system **4** on the basis that this system might readily yield the desired azacyclopentadienone. Our first example of this system, compound **4a** (Table 1), was

synthesized as an unstable, but isolable, mixture of diastereoisomers from the reaction of 2-methylthio-4-(4-tolyl)-1-azetine **5a** with diphenylcyclopropenone **6a**, a reaction in which the cyclopropenone acts as an all-carbon 1,3-dipolar equivalent. The chemistry and applications of cyclopropenones⁹ and their acetals/ketals¹⁰ have gained momentum in recent years, and there are also other reports of imines reacting with cyclopropenones.¹¹ The topic of 3-carbon 1,3-dipole equivalents is an area of importance in its own right due to the potential for such processes to provide access to 5-membered rings in [3 + 2]-cycloaddition reactions.¹²

Table 1. Reaction of Cyclopropenones with 1-Azetines



entry	product	Ar	R	R ¹	R ²	yield (%)	[diast. ratio]
1	4a	4-Tol	Me	Ph	Ph	63	[3:2]
2	4b	Ph	Et	Ph	Ph	63	[5:3]
3	4c	Ph	Me	H	Ph	52	[6:5]
4	4d	Ph	Me	Ph	Ph	62	[5:4]
5	4e	4-Tol	Et	Ph	Ph	66	[3:2]
6	4f	2-Naphth	Me	Ph	Ph	51	[3:2]
7	4g	Ph	Et	n-Bu	n-Bu	58	[3:2]

(3) For reviews, see: (a) Keller, P. A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 7, pp 217–308. (b) Hill, M. D. *Chem.—Eur. J.* **2010**, *16*, 12052.

(4) (a) Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, *65*, 261. (b) Hafner, K.; Goliasch, K. *Angew. Chem.* **1961**, *73*, 538. (c) Gaviña, F.; Costero, A. M.; Gil, P.; Luis, S. V. *J. Am. Chem. Soc.* **1984**, *106*, 2077. (d) Nantz, M. H.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 5298. (e) Yamaguchi, K.; Utsumi, K.; Yoshitake, Y.; Harano, K. *Tetrahedron Lett.* **2006**, *47*, 4235. (f) Haramata, M.; Gomes, M. G. *Eur. J. Org. Chem.* **2006**, 2273. (g) Pearson, A. J.; Zhou, Y. *J. Org. Chem.* **2009**, *74*, 4242.

(5) (a) Murai, M.; Kawai, S.; Miki, K.; Ohe, K. *J. Organomet. Chem.* **2007**, *692*, 579. (b) Murai, M.; Miki, K.; Ohe, K. *J. Org. Chem.* **2008**, *73*, 9174. (c) Ohno, M.; Sekido, M.; Matsuura, T.; Noda, M. *Heterocycl. Commun.* **2007**, *13*, 273. (d) Yokotsuji, D. L. S.; Dailey, W. P.; Kende, A. S.; Birzan, L.; Liu, K. *J. Phys. Chem.* **1995**, *99*, 15870.

(6) Gaviña, F.; Costero, A. M.; Andreu, M. R.; Carda, M.; Luis, S. V. *J. Am. Chem. Soc.* **1988**, *110*, 4017.

(7) Gaviña, F.; Costero, A. M.; Andreu, M. R.; Ayet, M. D. *J. Org. Chem.* **1991**, *56*, 5417.

(8) Koutentis, P. A.; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2765.

(9) (a) Manova, R.; van Beek, T. A.; Zuilhof, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5428. (b) Orski, S. V.; Poloukhine, A. A.; Arumugam, S.; Mao, L. D.; Popik, V. V.; Locklin, J. *J. Am. Chem. Soc.* **2010**, *132*, 11024. (c) Poloukhine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G. J.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769.

(10) (a) Qiao, Y.; Chu, T. S. *J. Org. Chem.* **2011**, *76*, 3086. (b) Patel, P. R.; Boger, D. L. *Org. Lett.* **2010**, *12*, 3540. (c) Patel, P. R.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8527.

(11) (a) Heimgartner, H.; Stierli, F.; Prewo, R.; Bieri, J. H. *Helv. Chim. Acta* **1983**, *66*, 1366. (b) Eicher, T.; Rohde, R. *Synthesis* **1985**, 619. (c) Hemming, K.; Redhouse, A. D.; Smalley, R. K.; Thompson, J. R.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1992**, *33*, 2231. (d) Gomaa, M. A.-M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 341. (e) Aly, A. A.; Hasan, A. A.; Ameen, M. A.; Brown, A. B. *Tetrahedron Lett.* **2008**, *49*, 4060. (f) O'Gorman, P. A.; Chen, T.; Cross, H. E.; Naem, S.; Pitard, A.; Qamar, M. I.; Hemming, K. *Tetrahedron Lett.* **2008**, *49*, 6316.

(12) (a) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695. (b) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317. (c) Grover, H. K.; Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 220. (d) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 4354. (e) Scott, M. E.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 8154. (f) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848. (g) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (h) Trost, B. M.; Bringley, D. A.; Silverman, S. M. *J. Am. Chem. Soc.* **2011**, *133*, 7664. (i) See also ref 1a.

We next found that the treatment of **4a** in boiling toluene for <24 h resulted in the complete consumption of the starting material and the formation of the pyridine **7a** (Scheme 1) in good yield. A mechanism for this process is proposed in Scheme 1. An overall [2 + 2]-cycloreversion reaction gives the desired 3-azacyclopentadienone **9a** plus styrene **8a**. This initial process may be stepwise, polar or free-radical, and we are unable at the moment to discern between these possibilities. Recombination of species **9a** and **8a** in a regioselective [4 + 2]-cycloaddition would then give the cycloadduct **10a**. Extrusion of carbon monoxide and aromatization then give the pyridine **7a**. The regiochemistry of the process was established by 2-D NMR studies and by X-ray crystallographic studies on the final pyridine.¹³ Based upon this result, we synthesized other azabicyclo[3.2.0]hept-2-en-4-ones **4** to act as pyridine precursors. As shown in Table 1, a series of 1-azetines **5** reacted smoothly with the cyclopropanones **6** to give the azabicyclo[3.2.0]hept-2-en-4-ones **4b–g**. Again, these were found to be unstable but isolable mixtures of diastereoisomers, which were used within 24 h. Phenylcyclopropanone gave only the 3-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one regioisomer **4c**, presumably due to the 1-azetine attacking the least hindered cyclopropanone carbon. We have found that other monosubstituted cyclopropanones react in the same manner with 5-, 6-, and 7-membered cyclic imines.^{11f} Diphenylcyclopropanone was commercially available, phenylcyclopropanone was synthesized by the cyclization of 1-bromo-3-chloro-3-phenyl acetone acetal,¹⁴ and dibutylcyclopropanone was synthesized from the reaction of dichlorocarbene with decyne and subsequent hydrolysis.¹⁵ It is noteworthy that a large range of other di- and monosubstituted cyclopropanones is available by these and other¹⁶ routes. The 1-azetines were readily available by alkylation of the corresponding thio- β -lactam, which was in turn available from the treatment of the β -lactam with Lawesson's reagent.¹⁷

Each of the azabicyclo[3.2.0]hept-2-en-4-ones **4b–g** gave the desired pyridine **7b–g** in good to reasonable yields when heated in boiling toluene (Table 2). It is of note that the presence of the C2-thioalkyl substituent in the pyridines **7a–g** offers the potential of Pd-catalyzed functionalization of the type reported by Liebeskind.¹⁸ The handling of the unstable azabicyclo[3.2.0]hept-2-en-4-ones **4** may be improved by telescoping the cyclopropanone addition and heating steps, and we are currently exploring the potential of this process.

To obtain evidence for this mechanism, we have been able to show that the proposed intermediate 3-azacyclopentadienone **9b** can be trapped by heating **4b** in the

(13) Crystallographic data have been deposited at the Cambridge Crystallographic data Centre as a CIF deposit with file number 847593. Copies of these data can be obtained free of charge on application to CCDC, email deposit@ccdc.cam.ac.uk. The CIF is also included in the supplementary data; see Supporting Information.

(14) Ando, R.; Sakaki, T.; Jikihara, T. *J. Org. Chem.* **2001**, *66*, 3617.

(15) Netland, K. A.; Gundersen, L.-L.; Rise, F. *Synth. Commun.* **2000**, *30*, 1767.

(16) Isaka, S.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045.

(17) See Supporting Information.

(18) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, *5*, 4349.

Scheme 1. Proposed Mechanism for the Formation of Pyridine **7a**

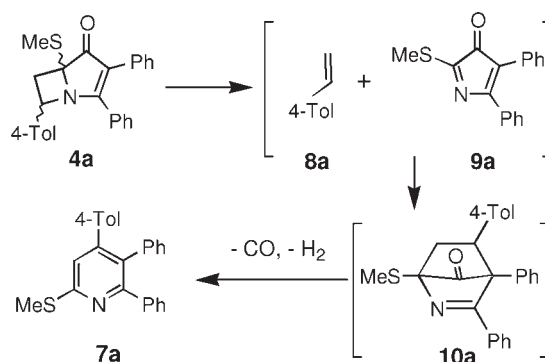
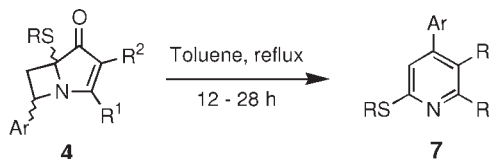
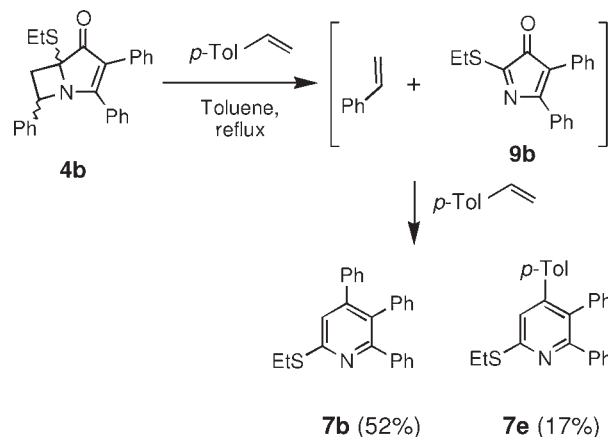


Table 2. Conversion of Azabicyclo[3.2.0]hept-2-en-4-ones **4** into Pyridines **7**

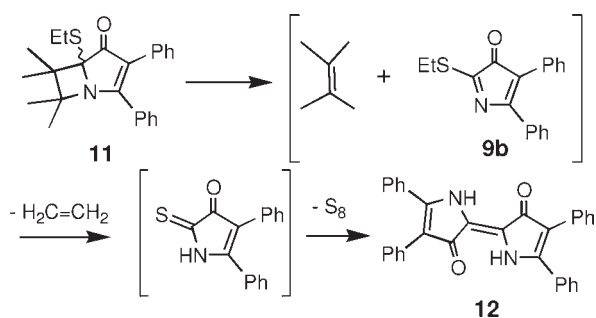


entry	product	Ar	R	R ¹	R ²	yield (%)
1	7a	4-Tol	Me	Ph	Ph	79
2	7b	Ph	Et	Ph	Ph	75
3	7c	Ph	Me	H	Ph	62
4	7d	Ph	Me	Ph	Ph	71
5	7e	4-Tol	Et	Ph	Ph	72
6	7f	2-Naphth	Me	Ph	Ph	69
7	7g	Ph	Et	n-Bu	n-Bu	73

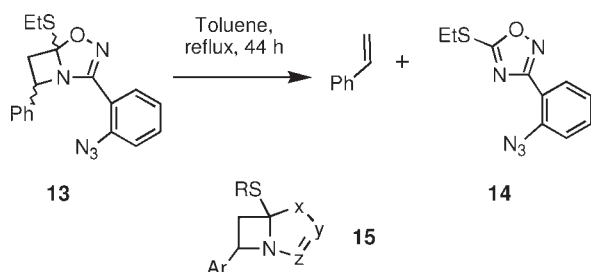
Scheme 2. Evidence for the Proposed Mechanism



Scheme 3. Formation of Bipyrrolinone **12** from Azabicyclo[3.2.0]hept-2-en-4-one **11**



Scheme 4. Formation of 1,2,4-Oxadiazole **14** from Oxadiazabicyclo[3.2.0]heptene **13**



presence of a second styrene to give an easily separated mixture of two pyridines, **7b** and **7e** (Scheme 2). It is also of note that we have previously shown^{11c} that the tetramethyl adduct **11** (Scheme 3) forms the pyrrolylidene-pyrrolone **12** upon heating in dichlorobenzene, a

(19) For the synthesis of this compound, see: Hemming, K.; Loukou, C.; Elkatip, S.; Smalley, R. K. *Synlett* **2004**, 101.

(20) We had anticipated that the azide group may trap the styrene, but saw no evidence of such a process.

process that is consistent with the formation of intermediate **9b**, which then undergoes loss of ethene followed by dimerization with loss of sulfur. Furthermore (Scheme 4), when 2-ethylthio-4-phenyl-1-azetine was reacted with the nitrile oxide derived from 2-azidobenzohydroximoyl chloride,¹⁹ the resultant cycloadduct **13** also underwent a process consistent with the proposed [2 + 2]-cycloreversion to give the expectedly stable 1,2,4-oxadiazole **14** as the product,²⁰ indicating that such cycloreversions may be a general facet of the chemistry of fused bicyclic azetidines of general type **15**, an aspect that we are now exploring more fully. We are currently exploring other reactions that can trap and utilize the proposed intermediate 3-azacyclopentadienones **9**, as enophiles, ynophiles, or dienophiles.

In conclusion, a new protocol for the synthesis of pyridines has been developed using the reaction of cyclopropenones with 1-azetidines, where the cyclopropenone functions as an all-carbon 1,3-dipole. When heated in toluene, the resulting azabicyclo[3.2.0]hept-2-en-4-ones behave in a manner that is consistent with the generation of an intermediate 3-azacyclopentadienone generated through a [2 + 2]-cycloreversion. This intermediate undergoes a Diels–Alder reaction with the styrene product of the cycloreversion, followed by extrusion of carbon monoxide and aromatization to generate pyridines. This process parallels the synthesis of benzenes from cyclopentadienones.

Acknowledgment. This work was supported by University of Huddersfield Studentships (to M.N.K., V.R.V.K., A.P., and M.I.Q.). We thank Dr Neil McLay, University of Huddersfield, for NMR and mass spectroscopy support, and the EPSRC national mass spectroscopy service, University of Wales, Swansea for HRMS.

Supporting Information Available. Experimental procedures and characterization data for **4a–g**, **5**, **6**, **7a–g**, **13**, and **14**; copies of ¹H and ¹³C spectra of these compounds; X-ray data for **7a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.