2,3-Heteroaromatic ring-fused cyclohexanones *via* heteroaromatic homo-Nazarov cyclization of donor–acceptor substituted cyclopropanes†

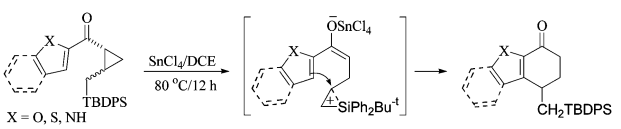
Veejendra K. Yadav* and Naganaboina Vijaya Kumar

Received (in Cambridge, UK) 31st March 2008, Accepted 7th May 2008
First published as an Advance Article on the web 18th June 2008
DOI: 10.1039/b805348k

Heteroaryl 2-silylmethyl-substituted cyclopropyl ketones rearrange under Lewis acid conditions *via* heteroaromatic homo-Nazarov cyclization to form 2,3-heteroaromatic ring fused 4-*t*-butyldiphenylsilylmethyl-substituted cyclohexanones.

Fused heteroaromatic rings serve as key building blocks in many biologically important natural products.[1–4] The acid-catalyzed ring closure of heteroaryl vinyl ketones to cyclopentanones fused with heteroaromatic rings is known as heteroaromatic Nazarov cyclization.[5,6] An electron-withdrawing group present at the position 2 or 3 of the heterocyclic ring does not allow its Friedel–Crafts alkylation by the initially formed cation due to deactivation of the ring.[7] To facilitate this transformation, one is required to mask the carbonyl group. Nazarov cyclization provides the requisite masking of the carbonyl group in the form of an enolate. Analogous to the heteroaromatic Nazarov cyclization, an acid-induced transformation of a cyclopropyl heteroaryl ketone into a cyclohexanone fused with a heteroaromatic ring may be called heteroaromatic homo-Nazarov cyclization.[8] We have lately been studying the construction of various carbocycles and heterocycles using silylmethyl-substituted cyclopropanes bearing a vicinal electron-withdrawing substituent as inherent 1,3- and 1,4-dipoles.[9] This presented an opportunity to consider the reactions of heteroaryl 2-*t*-butyldiphenylsilylmethyl-substituted cyclopropyl ketones *via* the homo-Nazarov protocol to form 2,3-heteroaromatic ring-fused 4-*t*-butyldiphenylsilylmethyl-substituted cyclohexanones (Scheme 1). Herein, we present our results and demonstrate from a variety of examples that the reaction is general.

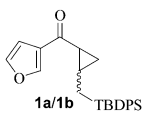
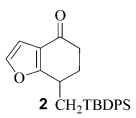
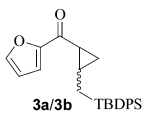
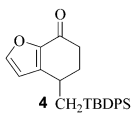
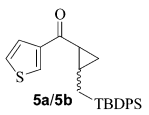
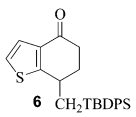
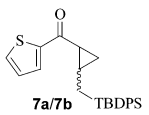
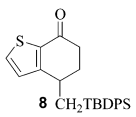
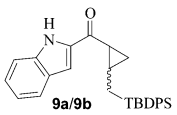
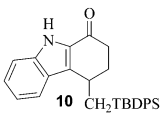
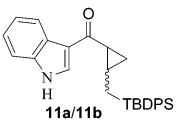
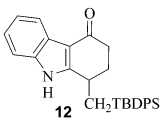
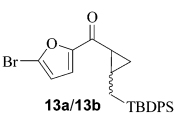
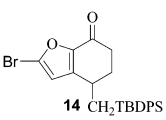
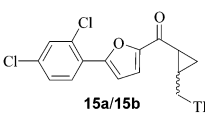
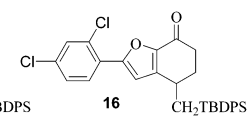
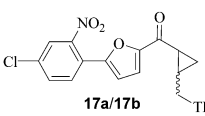
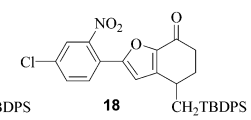
We commenced our study using the relatively more reactive substrates **1a**/**1b** that underwent heteroaromatic homo-Nazarov cyclization on admixture with $SnCl_4$ in dichloromethane at 0 → 30 °C for 48 h to furnish the furan-fused cyclohexanone **2** in 40% yield. Other Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$ and $Cu(OTf)_2$, and solvents such as cyclohexane, acetonitrile, toluene and nitromethane were less effective than $SnCl_4$ and



Scheme 1 Homo-Nazarov cyclization.

Department of Chemistry, Indian Institute of Technology, Kanpur, 208016, India. E-mail: vijendra@iitk.ac.in
† Electronic supplementary information (ESI) available: Experimental details and spectroscopic data of all new compounds. See DOI: 10.1039/b805348k

Table 1 Cyclization of (2-*t*-butyldiphenylsilylmethyl)cyclopropyl heteroaryl ketones with $SnCl_4$ in dichloroethane[a]

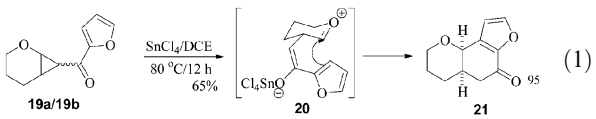
Entry	Substrate	Product	Yield (%)[b]
1	 **1a/1b**	 **2**	85
2	 **3a/3b**	 **4**	80
3	 **5a/5b**	 **6**	80
4	 **7a/7b**	 **8**	80
5	 **9a/9b**	 **10**	85
6	 **11a/11b**	 **12**	80
7	 **13a/13b**	 **14**	80
8	 **15a/15b**	 **16**	85
9	 **17a/17b**	 **18**	70[c]

[a] All the reactions were carried out using 4 equivalents of distilled $SnCl_4$ at 80 °C in dichloroethane for 12 h. [b] Isolated yields. [c] 3-Butenyl-5-(4-chloro-2-nitrophenyl)-2-furyl ketone was also isolated in 15% yield.

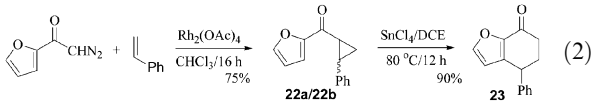
dichloromethane. 1,2-Dichloroethane (DCE) offered similar results to dichloromethane under the above reaction conditions. However, a reaction in DCE at 80 °C for 12 h furnished the desired product in 85% yield (Table 1, entry 1). The *cis*-**1a** and *trans*-**1b** generated the same product in identical yields when reacted separately. Further, there was no epimerization of one isomer into the other and both the isomers required the same time for completion. Thus, isomeric mixtures of the reacting substrates were used for other reactions.

Encouraged by the above result, we ventured to study other donor–acceptor substituted cyclopropanes[10] to assess the generality of the protocol. Both 3- as well as 2-substituted furan and thiophene substrates (entries 1–4 and 7–9) reacted very well to generate the desired products. The success with the 2-substituted furan and thiophene substrates is indeed noteworthy in view of the general observation that an electrophilic substitution at position 3 is less facile than an electrophilic substitution at position 2 in heteroaromatic compounds except the indoles.[11] The higher temperature probably allows the 2-substituted furan and thiophene reactants (entries 2 and 3, respectively) to achieve the requisite transition states with near as much facility as the corresponding 3-substituted reactants. Indeed, *cis*-**3a** and *trans*-**3b** were found to be inert to $SnCl_4$ in dichloromethane at 0 → 30 °C for 48 h.

The 2- and 3-substituted indoles **9a**/**9b** and **11a**/**11b** generated the desired products **10** and **11** in 85% and 80% yields, respectively (entries 5 and 6). Interestingly, protection of the nitrogen was not necessary. Heteroaryls like 5-bromo-2-furyl cyclopropyl ketones **13a**/**13b** (entry 7) and 5-(2,4-dichlorophenyl)-2-furyl cyclopropyl ketones **15a**/**15b** (entry 8) reacted smoothly to generate **14** and **16** in 80 and 85% yields, respectively. The reaction of the somewhat electron-deficient 5-(4-chloro-2-nitrophenyl)-2-furyl cyclopropyl ketones **17a**/**17b** also proceeded reasonably well to generate **18** in 70% yield along with the simple silicon-eliminated product, 3-butenyl 5-(4-chloro-2-nitrophenyl)-2-furyl ketone, in 15% yield (entry 9). The successful reaction of **17a**/**17b** demonstrates a remarkable ring-closing efficiency of the present homo-Nazarov protocol.



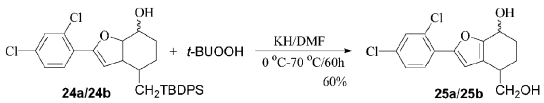
(1)



(2)

We next examined the reactions of substrates bearing other electron-donating substituents, oxygen and phenyl in particular. The substrates **19a**/**19b** were smoothly transformed into the tricyclic product **21** in 65% yield. The *cis* ring junction in **21** was ascertained from the *J* value (3.2 Hz) and also from NOE measurements. Under the Lewis acid condition, **19a**/**19b** is expected to generate the oxonium-enolate **20** which ring closes, under stereoelectronic control, from the axial site to result in the observed *cis* ring junction (eqn (1)). Likewise, a 1 : 2 isomeric mixture of the cyclopropyl ketones **22a** and **22b**, bearing a phenyl group as the donor substituent, was prepared from $Rh_2(OAc)_4$-catalyzed addition of the carbene generated from 2-furyldiazoketone[12] to styrene and transformed conveniently into 2,3-furano-4-phenylcyclohexanone **23** in 90% yield (eqn (2)).

Murphy and Wattanasin have previously studied the cyclization of aryl 2-alkyl/aryl-substituted cyclopropyl ketones to 2,3-aryl-fused 4-alkyl/aryl-substituted cyclohexanones.[13] The difficulty in further easy chemical manipulation of the 4-alkyl/aryl group limits its synthetic usage. Since the silicon acts as a masked hydroxyl group,[14] the present protocol extends the synthetic scope of the homo-Nazarov cyclization considerably. As a representative example, a 1 : 1.5 diastereomeric mixture of the alcohols **24a** and **24b**, obtained from the reduction of **16** with $LiAlH_4$, was transformed into a 1 : 1.5 diastereomeric mixture of the corresponding diols **25a** and **25b** in 60% yield (eqn (3)). Oxidative cleavage of the σ_{C-Si} bond in the ketone itself was unclean under these reaction conditions.



(3)

In summary, we have developed the first synthesis of 4-silylmethyl/hydroxymethyl-substituted 2,3-heteroaromatic ring-fused cyclohexanones in high yields *via* a heteroaromatic homo-Nazarov cyclization.[15] The development of an asymmetric version using chiral Lewis acids will expand the scope of the present protocol even further.

V.K.Y. thanks the Department Science & Technology (DST) and the Council of Scientific & Industrial Research (CSIR), Govt. of India, for funding. N.V.K. thanks CSIR and IIT Kanpur for Research Fellowship.

Notes and references

1 For 1,2,3,9-tetrahydrocarbazol-4-one, see: (*a*) S. Elz and W. L. Heil, *Bioorg. Med. Chem. Lett*., 1995, **5**, 667; (*b*) X. Li and R. Vince, *Bioorg. Med. Chem. Lett*., 2006, **14**, 2942; (*c*) G. Romeo, L. Materia, V. Pittala, M. Modica, L. Salerno, M. Siracusa, F. Russo and K. P. Minneman, *Bioorg. Med. Chem. Lett*., 2006, **14**, 5211.

2 For 5,6-dihydro-4*H*-benzofuran-7-one, see H. Nagano and T. Takahashi, *Bull. Chem. Soc. Jpn*., 1978, **51**, 3335.

3 For 6,7-dihydro-5*H*-benzofuran-4-ones, see: (*a*) K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji and M. Naito, *Tetrahedron Lett*., 1971, **31**, 2961; (*b*) for the synthesis of evodone, see: P. A. Jacobi, D. G. Walker and I. M. A. Odeh, *J. Org. Chem*., 1981, **46**, 2065; (*c*) R.-R. Juo and W. Herz, *J. Org. Chem*., 1985, **50**, 700; (*d*) for the total synthesis of curzerenone and epicurzerenone, see: M. Miyashita, T. Kumazawa and A. Yoshikoshi, *J. Org. Chem*., 1984, **49**, 3728; (*e*) A. Gopalan and P. Magnus, *J. Org. Chem*., 1984, **49**, 2317; (*f*) A. Gopalan and P. Magnus, *J. Am. Chem. Soc*., 1980, **102**, 1756; (*g*) for the synthesis of furanoeremophilane-3,6-dione and ligularone, see: M. Tada, Y. Sugdmoto and T. Takahashi, *Chem. Lett*., 1979, 1441.

4 For the synthesis of uleine alkaloids possessing 2,3,4,9-tetrahydrocarbazol-1-one skeleton, see: (*a*) M. Amat, M. Pérez, N. Llor, M. Martinelli, E. Molins and J. Bosch, *Chem. Commun*., 2004, 1602; (*b*) M. H. Schmitt and S. Blechert, *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 1474.

5 (*a*) For reviews on Nazarov cyclization, see: K. L. Habermas, S. E. Denmark and T. K. Jones, *Org. React*., 1994, **45**, 1; (*b*) H. Pellisier, *Tetrahedron*, 2005, **61**, 6479; (*c*) A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577; (*d*) M. A. Tius, *Eur. J. Org. Chem*., 2005, 2193; (*e*) for recent examples of Nazarov cyclization, see: T. D. White and F. G. West, *Tetrahedron Lett*., 2005, **46**, 5629; (*f*) S. Giese, R. D. Mazzola, Jr, C. M. Amann, A. M. Arif and F. G. West, *Angew. Chem., Int. Ed*., 2005, **44**, 6546; (*g*) F. Dhoro and M. A. Tius, *J. Am. Chem. Soc*., 2005, **127**, 12472; (*h*) M. Janka, W. He,

I. E. Haedicke, F. R. Fronczek, A. J. Frontier and R. Eisenberg, *J. Am. Chem. Soc.*, 2006, **128**, 5312; (*i*) T. N. Grant and F. G. West, *J. Am. Chem. Soc.*, 2006, **128**, 9348; (*j*) T. N. Grant and F. G. West, *Org. Lett.*, 2007, **9**, 3789.

6 For aromatic Nazarov cyclization, see: (*a*) G. Liang, Y. Xu, I. B. Seiple and D. Trauner, *J. Am. Chem. Soc.*, 2006, **128**, 11022; (*b*) for heteroaromatic Nazarov cyclization, see: J. A. Malona, M. J. Colbourne and A. J. Frontier, *Org. Lett.*, 2006, **8**, 5661; (*c*) S. Song, D. W. Knight and M. A. Whatton, *Org. Lett.*, 2006, **8** 163.

7 (*a*) P. P. Yadav, P. Gupta, A. K. Chaturvedi, P. K. Shukla and R. Maurya, *Bioorg. Med. Chem. Lett.*, 2005, **13**, 1497; (*b*) A. Zuse, P. Schmidt, S. Baasner, K. J. Bohm, K. Muller, M. Gerlach, E. G. Gunther, E. Unger and H. Prinz, *J. Med. Chem.*, 2006, **49** 7816.

8 We would like to name the present ring-closing protocol homo-Nazarov cyclization for its full mechanistic similarily with the conventional Nazarov cyclization. For a previous usage of this terminology, see: O. Tsuge, S. Kanemasa, T. Otsuka and T. Suzuki, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2897.

9 For the synthesis of carbocycles, see: (*a*) V. K. Yadav and V. Sriramurthy, *Angew. Chem., Int. Ed.*, 2004, **43**, 2669; (*b*) V. K. Yadav and V. Sriramurthy, *Org. Lett.*, 2004, **6**, 4495; (*c*) V. K. Yadav, N. Vijaya Kumar and M. Parvez, *Chem. Commun.*, 2007, 2281; (*d*) for the synthesis of heterocycles, see: V. K. Yadav and R. Balamurugan, *Org. Lett.*, 2001, **3**, 2717; (*e*) V. K. Yadav and R. Balamurugan, *Chem. Commun.*, 2002, 514; (*f*) V. K. Yadav and R. Balamurugan, *Org. Lett.*, 2003, **5**, 4281; (*g*) V. K. Yadav and N. Vijaya Kumar, *J. Am. Chem. Soc.*, 2004, **126**, 8652.

10 (*a*) J. R. Y. Salaun, *Small Ring Compounds in Organic Syntheis III, Topics in Current Chemistry*, ed. A. de Meijere, Springer-Verlag, Berlin, Heidelberg, Germany, 1991, vol. 144, p. 1; (*b*) H. Hudlicky and J. W. Reed, *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon Press, Oxford, 1991, vol. 5, p. 899; (*c*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151.

11 (*a*) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, Ltd., NY, 1976, ch. 3; (*b*) J. A. Malona, M. J. Colbourne and A. J. Frontier, *Org. Lett.*, 2006, **8**, 5661.

12 (*a*) N. R. Rosenquist and O. L. Chapman, *J. Org. Chem.*, 1976, **41**, 3326; (*b*) R. L. Danheiser, R. F. Miller, R. G. Brisbois and S. G. Park, *J. Org. Chem.*, 1990, **55**, 1959.

13 (*a*) W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1982, 271; (*b*) W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1029.

14 (*a*) H.-J. Knölker, G. Baum, O. Schmitt and G. Wanzl, *Chem. Commun.*, 1999, 1737; (*b*) Z.-H. Peng and K. A. Woerpel, *Org. Lett.*, 2002, **4**, 2945; (*c*) D. Liu and S. A. Kozmin, *Org. Lett.*, 2002, **4**, 3005; (*d*) V. K. Yadav and V. Sriramurthy, *J. Am. Chem. Soc.*, 2005, **127**, 16366; (*e*) V. K. Yadav, N. Vijaya Kumar and M. Parvez, *Chem. Commun.*, 2007, 2281.

15 (*a*) *Typical procedure for the $SnCl_4$-induced heteroaromatic homo-Nazarov reaction of* **1a** *and* **1b** *in dichloroethane*. A solution of **1a** and **1b** (194 mg, 0.5 mmol), in dichloroethane (80 mL) was taken in a round bottom flask and mixed with a solution of $SnCl_4$ (237 μL, 2.0 mmol) in dichloroethane (10 mL) using a syringe. The reaction was heated to 80 °C and stirred for 12 h before quenching with saturated aqueous $NaHCO_3$ (20 mL). The content was stirred vigorously for 10 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic solution was washed with brine, dried, filtered, and concentrated. The crude material was purified by radial chromatography to obtain the product **3** (159 mg, 82%) as a light yellow liquid; (*b*) *Transformation of the TBDPS function into a hydroxyl function by oxidative cleavage of the σ_{C-Si} bond in* **24a**/**24b**. *t*-BuOOH (70%, 95 μL, 0.99 mmol) was added dropwise to an ice-cold suspension of KH (50 mg, 1.23 mmol, 30% dispersion in mineral oil, washed with 3 × 2 mL of hexanes) in DMF (2 mL). After 10 min, a solution of **24a**/**24b** (a mixture of *cis*- and *trans*-isomers, 66 mg, 0.123 mmol) in DMF (3 mL) was added. The mixture was stirred at 70 °C for 60 h and quenched by adding solid $Na_2S_2O_3$ (300 mg). The reaction mixture was stirred for 30 min and partitioned between water (5 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and dried. The crude material was purified by column chromatography over silica gel to obtain the pure products **25a**/**25b** (a mixture of *cis*- and *trans*-isomers), 22 mg, 60%, colorless liquid.

