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Selective transannular ring transformations in azirino-fused eight-membered *O*,*N*- or *S*,*N*-heterocycles†

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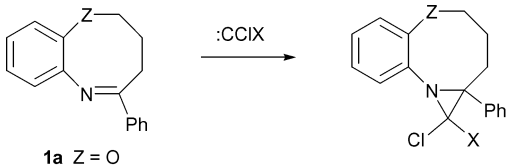
The first examples of transannular ring transformations in azirino-fused eight-membered *O*,*N*- or *S*,*N*-heterocycles involving selective aziridine ring opening and medium-sized ring contraction are described, which provide an access to functionalized 1,4-benzox(thi)azines or 1,3-benzox(thi)azoles.

Transannular cyclizations are actively used not only by organic synthetic chemists,[1] but also by Nature to build polycyclic systems from medium-sized precursors.[2] The cyclizations are mainly used in the preparation of carbocyclic systems[1] and, more rarely, of oxygen-containing[3] or nitrogen-containing[4] heterocyclic systems. Transannular reactions involving sulfur are poorly studied.[5] A wide range of transannular cyclizations were realized in polycyclic systems containing an oxirane ring fused with medium-sized rings.[1b,3a,4c,d,6] Mechanistically they start with an electrophilic epoxide ring opening and the generation of a carbocation which is susceptible to cyclization. To the best of our knowledge only one related cyclization involving azirino-fused medium-sized rings has so far been realised.[7] In this letter we wish to report the unusual transannular reactions involving O and S atoms of 1,1-dihalogeno-1a,2,3,4-tetrahydro-1*H*-azirino[2,1-*e*][1,6]benzoxazocines **2a**,**c** and the corresponding benzothiazocines **2b**,**d** containing an aziridine fused with eight-membered *N*,*O*- or *N*,*S*-rings.

Compounds **2** were prepared by the cycloaddition of dichloro- or fluorochlorocarbenes to the C=N bond[8] of 1,6-benzoxazocine **1a** or 1,6-benzothiazocine **1b** (Scheme 1).



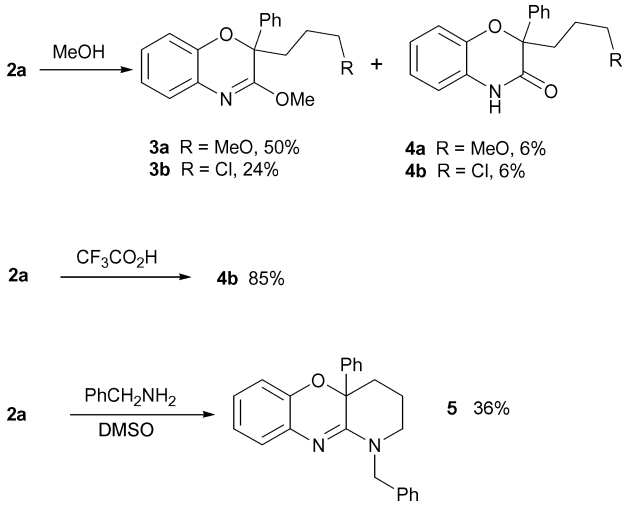
1a Z = O
1b Z = S

2a Z = O, X = Cl, 88%
2b Z = S, X = Cl, 48%
2c Z = O, X = F, 66%
2d Z = S, X = F, 32%

Scheme 1

Whilst 1,1-dichloro-1,3,4,8b-tetrahydroazireno[2,1-*a*]isoquinolines can give the cleavage products of any of the three aziridine bonds,[9a,b] the most typical transformation of 1,3-diaryl-2,2-dihalogenoaziridines by heating or treating with nucleophiles is ring opening with cleavage of the N–C(3) aziridine bond.[9] One might therefore expect that, on heating compounds **2a**–**d**, nine-membered heterocycles are formed by a cleavage of the C(1a)-N(10) bond. Instead, 1,4-benzoxazine derivatives **3a**,**b** and **4a**,**b** were isolated after heating azirinobenzoxazocine **2a** in methanol. Reaction of azirinobenzoxazocine **2a** in trifluoroacetic acid followed by chromatographic purification on silica yielded benzoxazine **4b** in high yield. In the reaction of azirinobenzoxazocine **2a** a transannular ring contraction reaction occurred along with the opening of the three-membered ring.

A similar transformation also occurred when the azirinobenzoxazocine **2a** was heated with benzylamine in DMSO solution. In this case a domino reaction terminates after the formation of an additional piperidine ring, giving the pyrido[3,2-*b*][1,4]benzoxazine derivative **5** (Scheme 2).



Scheme 2

The structure of **5** was determined from its ^{1}H and ^{13}C NMR spectra and further elucidated by X-ray diffraction (Fig. 1).‡

Unexpectedly it was found that, in contrast to protic acid catalysis, the reaction of azirinobenzoxazocine **2a** with Lewis acid gives rise to the formation of a five-membered 1,3-oxazole ring rather than a six-membered 1,4-oxazine ring. Thus, 1,3-benzoxazole **6** was isolated as a product of the reaction of **2a** with $ZnCl_2$ (Scheme 3).

A similar transformation occurred when azirinobenzothiazocine **2b** was reacted with $ZnCl_2$. Benzothiazole **7** was isolated as the sole product of this reaction. In contrast to azirinobenzoxazocine **2a**, heating azirinobenzothiazocine **2b** in methanol did not, however, result in the formation of a new six-membered ring. Instead, compound **8**, a derivative of benzothiazole, was obtained in 55% yield. In trifluoroacetic acid, however, a new six-membered ring (benzthiazine **9**) was formed from both azirinobenzothiazocine **2b** as well as from azirinobenzoxazocine **2a**.

† Electronic supplementary information (ESI) available: Spectroscopic data, analytical data and experimental procedures. See DOI: 10.1039/b512409c

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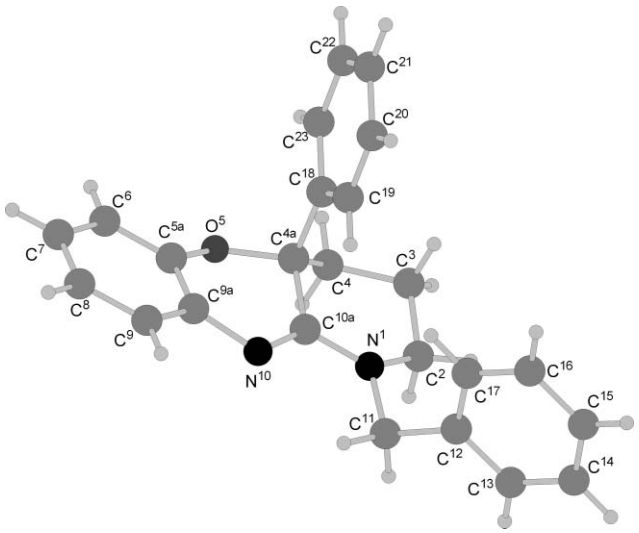
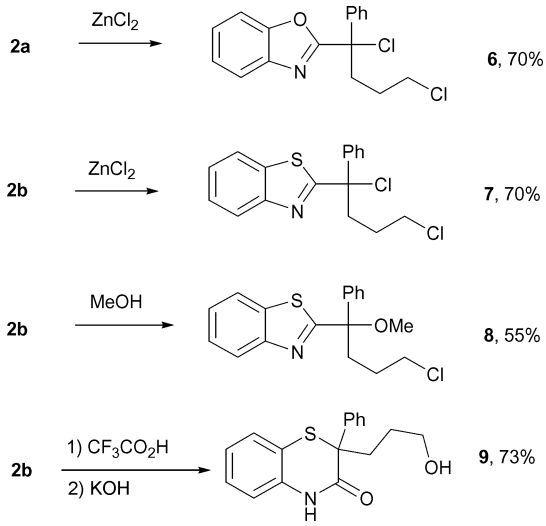
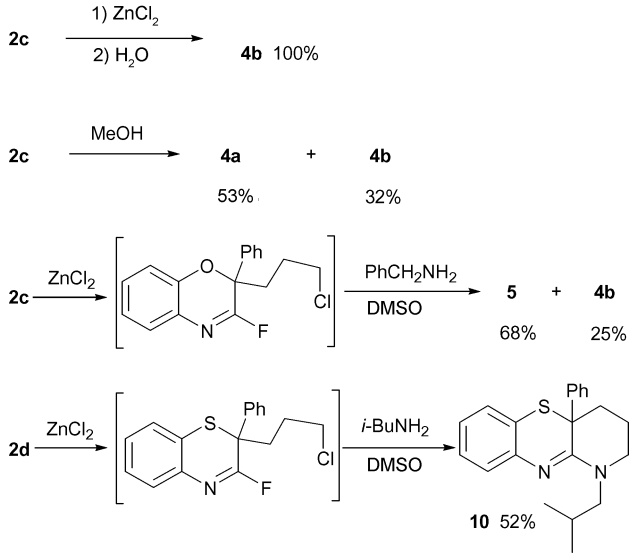


Fig. 1 X-Ray crystal structure of compound **5**.



Scheme 3

When studying the influence of the nature of the halogen atom on transannular transformations of the azirino[2,1-*e*][1,6]benzoxazocines **2** essential distinctions in reactivity of dichloroderivatives **2a**,**b** and chlorofluoroderivatives **2c**,**d** were found (Scheme 4).



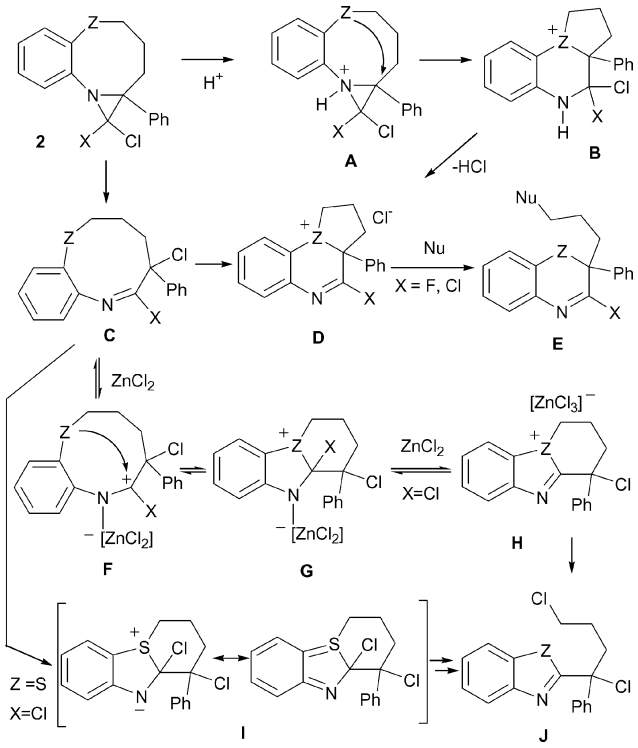
Scheme 4

Unlike dihloro-substituted azirinobenzoxazocine **2a**, chlorofluoro-substituted azirinobenzoxazocine **2c** reacts with zinc chloride to give not the corresponding 1,3-benzoxazole derivative, but the 1,4-benzoxazine derivative **4b**. After heating azirinobenzoxazocine **2c** in methanol under the same conditions as azirinobenzoxazocine **2a** only the corresponding 1,4-benzoxazine derivatives **4a**,**b** were isolated.

Treatment of the chlorofluoro-substituted azirinobenzoxazocine **2c** initially with anhydrous zinc chloride in methylene chloride and then with a primary amine in DMSO gave the pyrido[3,2-*b*][1,4]benzoxazine **5**. Similarly, pyrido[3,2-*b*][1,4]benzothiazine **10** was obtained from azirinobenzothiazocine **2d**.

These results indicate that the transannular reactions leading to formation of a five-membered ring are not characteristic of chlorofluoro-substituted azirinobenzox(thi)azocines **2**, even upon treatment with Lewis acid.

A possible mechanism, accounting for the observed dependence of transunnular reactions on the nature of the halogen and chalcogene atoms, as well as the reaction conditions, is presented in the Scheme 5.



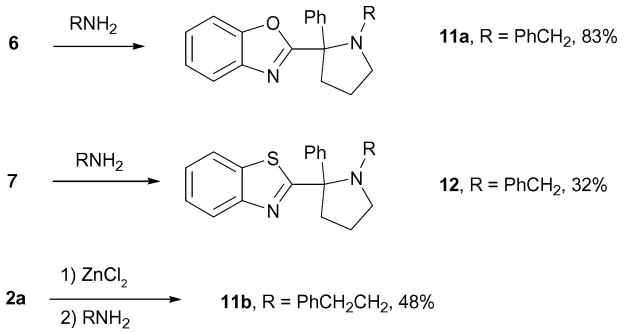
Scheme 5

In strong protic acid (CF_3CO_2H) ring opening of the protonated aziridine in **A** occurs by transannular nucleophilic attack of the endocyclic O or S atom, leading to **B**. Further transformations of this intermediate **B**, including elimination of HCl and attack by an external nucleophile, will lead to intermediate **E**, which is a precursor of all benzox(thi)azine derivatives obtained in CF_3CO_2H.

In the absence of a highly acidic medium the usual thermal transformation of dihalogenoaziridine to nine-membered imidoyl halogenide **C** occurs.[9,10] Further transformation of the imidoyl halogenide **C** depends on the nature of the chalcogene (O/S) and on the presence of Lewis acid in the reaction mixture. The Lewis acid catalyses the transformation of intermediate **C** to the onium salt **H**, firstly, making the imidoylic carbon atom more electrophilic and secondly, facilitating elimination of a chloride ion.[11] The onium salt **H** is a precursor of the benzox(thi)azole derivative **J**. When Z = S the transformation of **C** to **J** can also be realized in the absence of $ZnCl_2$, possibly because

of an additional stabilization due to hypervalent bonding in intermediate **I**, which is formed by the addition of the S atom to the C=N bond.[12] When X = F the transformation of **G** to **H** cannot, however, be realized since fluoride is a very bad leaving group and the equilibrium is shifted in the direction of intermediate **D**. The six-membered ring compounds are the only products in this case.

It should be noted that the dichlorides **6**,**7** can serve as suitable building blocks for the preparation of 2-pyrrol-2-yl derivatives of 1,3-benzoxazole and 1,3-benzothiazole. Thus, compounds **11**,**12** can be easily prepared from the dichlorides **6**,**7** and primary amines. These compounds can also be prepared directly from compounds **2** in a one-pot mode without isolation of intermediate dichlorides (Scheme 6).



Scheme 6

In conclusion, we report the first examples of transannular ring transformations in azirino-fused eight-membered *O*,*N*- or *S*,*N*-heterocycles involving selective aziridine ring opening and medium-sized ring contraction, which provide an access to functionalized 1,4-benzox(thi)azines or 1,3-benzox(thi)azoles. Halogenated 1a,2,3,4-tetrahydro-1*H*-azirino[2,1-*e*][1,6]benzoxazocines and benzothiazocines can be considered as attractive precursors for the preparation of unknown 2,3,4,4a-tetrahydro-1*H*-pyrido[3,2-*b*][1,4]benzox(thi)azine derivatives by a domino or one-pot reaction with primary amines.

Acknowledgements

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Notes and references

‡ Crystal data for **5**: $C_{24}H_{22}N_2O$, $M = 354.44$, triclinic, $a = 9.4130(19)$, $b = 10.281(2)$, $c = 11.618(2)$ Å, $\alpha = 101.32(3)$, $\beta = 109.63(3)$, $\gamma = 112.28(3)°$, $U = 909.85(30)$ Å^3, $T = 133(2)$ K, space group $P-1$ (no. 2), $Z = 2$, λ(Mo Kα) = 0.71073 Å, 9324 reflections measured, 3128 unique ($R_{int} = 0.062$) which were used in all calculations. The final $wR(F_2)$ was 0.1196 (all data). CCDC reference number 283218. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512409c

1 (*a*) A. C. Cope, M. M. Martin and M. A. McKervey, *Q. Rev. Chem. Soc.*, 1966, **20**, 119–152; (*b*) D. C. Harrowven and G. Pattenden, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming, and G. Pattenden, Pergamon Press, Oxford, 1991, vol. 3, p. 379–411.
2 (*a*) D. E. Cane, *Chem. Rev.*, 1990, **90**, 1089–1103; (*b*) G. Appendino, G. C. Tron, T. Jarevång and O. Sterner, *Org. Lett.*, 2001, **3**, 1609–1612.
3 For recent examples, see: (*a*) A. Rosales, R. E. Estévez, J. M. Cuerva and J. E. Oltra, *Angew. Chem., Int. Ed.*, 2005, **44**, 319–322; (*b*) A. F. Petri, A. Bayer and M. E. Maier, *Angew. Chem., Int. Ed.*, 2004, **43**, 5821–5823; (*c*) F. Hilli, J. M. White and M. A. Rizzacasa, *Org. Lett.*, 2004, **6**, 1289–1292; (*d*) S. M. Kühnert and M. E. Maier, *Org. Lett.*, 2002, **4**, 643–646.
4 For recent examples, see: (*a*) A. Basak, S. K. Roy and S. Mandal, *Angew. Chem., Int. Ed.*, 2005, **44**, 132–135; (*b*) H. Bieräugel, T. P. Jansen, H. E. Schoemaker, H. Hiemstra and J. H. van Maarseveen, *Org. Lett.*, 2002, **4**, 2673–2674; (*c*) A. Sudau, W. Münch, J. W. Bats and U. Nubbemeyer, *Chem. Eur. J.*, 2001, **7**, 611–621; (*d*) D. M. Hodgson and L. A. Robinson, *Chem. Commun.*, 1999, 309–310.
5 For a review of the relevant literature, see: V. Cere, F. Peri, S. Pollicino and A. Antonio, *J. Chem. Soc., Perkin Trans. 1*, 1998, 977–979.
6 (*a*) H. Neukirch, A. Guerriero and M. D'Ambrosio, *Eur. J. Org. Chem.*, 2003, 3969–3975; (*b*) H. Neukirch, N. C. Kaneider, C. J. Wiedermann, A. Guerriero and M. D'Ambrosio, *Bioorg. Med. Chem.*, 2003, **11**, 1503–1510; (*c*) D. M. Hodgson and I. D. Cameron, *Org. Lett.*, 2001, **3**, 441–444.
7 P. Müller, D. Riegert and G. Bernardelli, *Helv. Chim. Acta*, 2004, **87**, 227–239.
8 A. F. Khlebnikov, M. S. Novikov and R. R. Kostikov, *Russ. Chem. Rev.*, 2005, **74**, 171–192.
9 For a review of the relevant literature, see: (*a*) A. F. Khlebnikov, T. Yu. Nikiforova, M. S. Novikov and R. R. Kostikov, *Russ. J. Org. Chem.*, 1997, **33**, 885–895; (*b*) A. F. Khlebnikov, T. Yu. Nikiforova, M. S. Novikov and R. R. Kostikov, *Synthesis*, 1997, 677–680; (*c*) M. K. Meilahn, D. K. Olsen, W. J. Brittain and R. T. Anders, *J. Org. Chem.*, 1978, **43**, 1346–1350.
10 R. R. Kostikov, A. F. Khlebnikov and K. A. Ogloblin, *Chem. Heterocycl. Compd.*, 1978, 37–41.
11 J. Iqbal and A. Shukla, *Tetrahedron*, 1991, **47**, 8753–8766.
12 N. Furukawa and S. Sato, *Top. Curr. Chem.*, 1999, **205**, 90–129.