Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters

Tetrahedron Letters 46 (2005) 4057–4059

Synthesis of 2,3-benzoxepins by sequential cyclopropanation/ring-enlargement reactions of benzopyrylium triflates with diazoesters

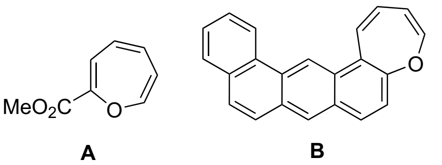
Sven Rotzoll,[a,b] Bettina Appel[b] and Peter Langer[a,*]

[a] *Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, D-18051 Rostock, Germany*
[b] *Institut für Chemie und Biochemie, Universität Greifswald, Soldmannstr. 16, D-17487 Greifswald, Germany*

Received 2 March 2005; revised 4 April 2005; accepted 5 April 2005
Available online 20 April 2005

Abstract—Functionalized 2,3-benzoxepins were prepared by cyclopropanation of benzopyrylium triflates with diazoesters and subsequent TFA-mediated ring enlargement.
© 2005 Elsevier Ltd. All rights reserved.

Oxepins and benzoxepins are of pharmacological relevance, since they play an important role in the biosynthesis and metabolism of mono- and polycyclic aromatic compounds.[1] For example, oxepin **A** has been isolated from cultures of the wood-rotting fungus *Phellinus tremulae*.[2] The 2,3-benzoxepin **B** represents a mammalian metabolite of dibenz[*a*,*j*]anthracene.[3]



A number of syntheses of oxepins have been reported, which include ring-enlargement reactions of pyran derivatives.[1] For example, 3-hexen-6-olides have been prepared by cyclopropanation of silyl ketene acetals of 5-pentanolides, to give oxabicyclo[4.1.0]heptanes, and subsequent ring enlargement.[4,5] The reaction of pyrylium salts with lithiated diazoesters has been reported to give 4-diazomethyl-4*H*-pyrans, which were transformed into oxepins by Pd(0)-catalyzed ring enlargement.[6] Very recently, Reddy et al. have reported the synthesis of benzoazepines by reaction of diazoesters with activated quinolines and isoquinolines.[7] Herein, we wish to report a convenient synthesis of functionalized 2,3-benzoxepins by cyclopropanation of benzopyrylium triflates[8,9] with diazoesters and subsequent TFA mediated ring enlargement.

Our first attempts to induce a cyclopropanation of chromone (**1a**) by copper(II) triflate catalyzed reaction with diazoester **2** failed.[10,11] We have found that the desired cyclopropane **3a** could be prepared in up to 71% yield by copper(II) triflate catalyzed reaction of **2** with benzopyrylium triflate **A**, which was generated in situ by reaction of **1a** with Me_3SiOTf[8,12] (Scheme 1). The presence of the copper salt was mandatory. Compound **3a** was obtained as a single diastereomer; the relative configuration was established by analysis of the coupling constants. Treatment of **3a** with trifluoroacetic acid (TFA) resulted in formation of the 2,3-benzoxepin **4a** via intermediates **B** and **C**.[13] 2,3-Benzoxepins, such as **4a**, generally reside in their oxepin form;[1] rearrangement of the latter to the corresponding naphthalene oxide would interrupt the aromaticity of the annulated benzene moiety.

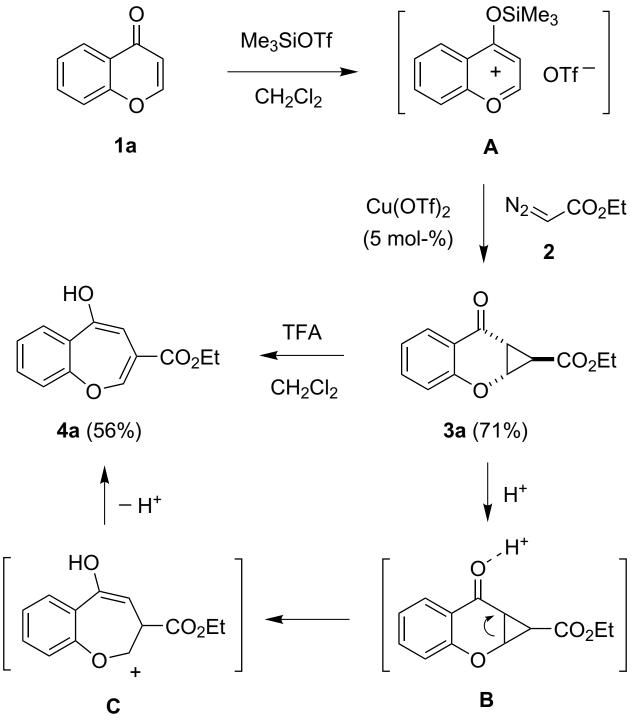
The preparative scope of our methodology was studied (Scheme 2, Table 1). The reaction of **2** with methyl-substituted chromones **1b** and **1c** afforded the cyclopropanes **3b** and **3c**, which were transformed into the 2,3-benzoxepins **4b** and **4c**, respectively. The 2,3-benzoxepins **4d**–**f** were prepared from the bromo-, chloro- and

---

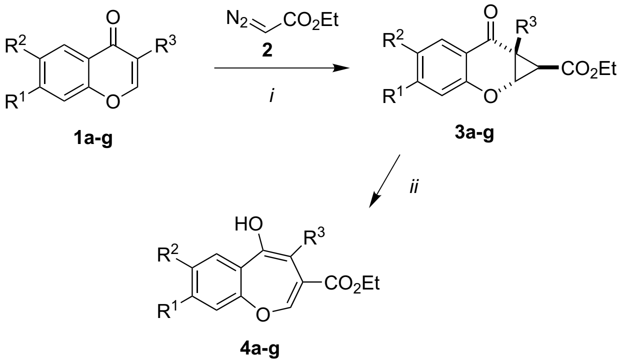
Keywords: Benzoxepins; Cyclizations; Diazo compounds; Pyrylium salts.

* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412; e-mail: peter.langer@uni-rostock.de

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.04.009



Scheme 1. Synthesis of 2,3-benzoxepin **4a**.



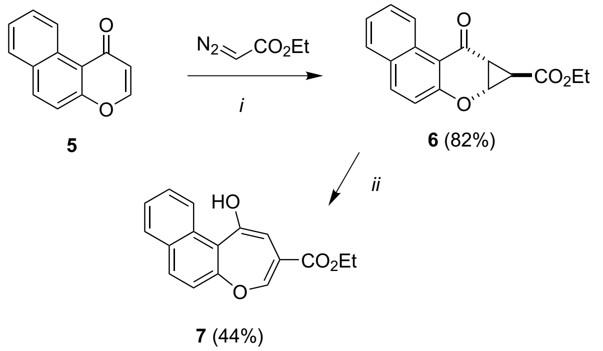
Scheme 2. Synthesis of benzoxepins **4a**–**g**. Reagents and conditions: (i) Me_3SiOTf, $Cu(OTf)_2$ (5 mol %), CH_2Cl_2; (ii) TFA, CH_2Cl_2.

Table 1. Products and yields

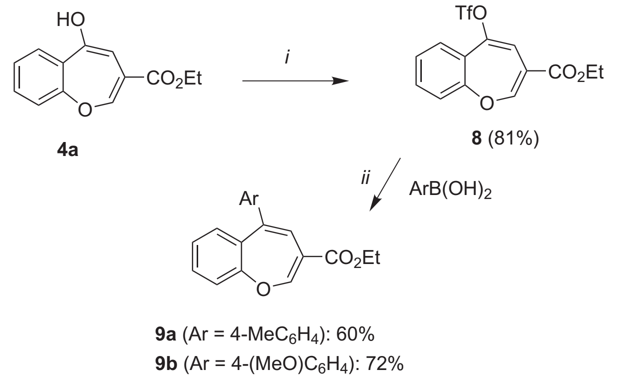
3, 4	R^1	R^2	R^3	% (**3**)[a]	% (**4**)[a]
a	H	H	H	71	56
b	Me	H	H	76	32 (56)
c	H	Me	H	69	27 (57)
d	H	Br	H	64	43 (54)
e	H	Cl	H	68	23 (32)
f	H	Ph	H	89	30 (65)
g	H	H	Me	64	41

[a] Yields of isolated products (in brackets: yields based on recovered starting material).

phenyl-substituted chromones **1d**–**f**. The reaction of **2** with 3-methylchromone (**1g**) gave the cyclopropane **3g**, which was transformed into the 2,3-benzoxepin **4g**.



Scheme 3. Synthesis of benzoxepin **7**. Reagents and conditions: (i) Me_3SiOTf, $Cu(OTf)_2$ (5 mol %), CH_2Cl_2; (ii) TFA, CH_2Cl_2.



Scheme 4. Synthesis of benzoxepins **4a**–**g**. Reagents and conditions: (i) Tf_2O, pyridine, −78 to −10 °C; (ii) $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), dioxane, reflux.

The reaction of **2** with chromone **5**, prepared from 1-acetylnaphth-2-ol, afforded the cyclopropane **6** which was subsequently transformed into the benzoxepin **7** (Scheme 3).

The functionalization of the ring by Suzuki reactions was next studied. Benzoxepin **4a** was transformed into the triflate **8**. The Suzuki reaction of the latter with *p*-tolyl- and (*p*-methoxyphenyl)boronic acid afforded the benzoxepins **9a** and **9b** in good yields, respectively (Scheme 4).

In summary, we have reported the synthesis of functionalized 2,3-benzoxepins by cyclopropanation of benzopyrylium triflates with a diazoester and subsequent TFA mediated ring enlargement.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft and by the Landesforschungsschwerpunkt 'Neue Wirkstoffe und Screeningverfahren' is gratefully acknowledged.

References and notes

1. (a) Belen'kii, L. *Oxepanes and Oxepines*; Newkome, G. R. Ed.; Vol. 9, Chapter 9.02. In *Comprehensive Heterocyclic*

Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Elsevier Science, Oxford, 1996, p 45; (b) Boyd, D. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Oxepanes, Oxepines, Thiepanes and Thiepins; Newkome, G. R., Ed.; Elsevier Science: Oxford, 1984; Vol. 7, p 547, Part 5, Chapter 5.17.

2. Ayer, W. A.; Cruz, E. R. *Tetrahedron Lett.* **1993**, *34*, 1589.
3. Boyd, D. R.; O'Kane, G. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2079.
4. (a) Hirao, T.; Fujihara, Y.; Kurokawa, K.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1986**, *51*, 2830; (b) Fouque, E.; Rousseau, G.; Seyden-Penne, J. *J. Org. Chem.* **1990**, *55*, 4807.
5. For transformations of oxabicyclo[4.1.0]heptanes to oxepins, see: (a) Godet, J.-Y.; Pereyre, M. *Bull. Chim. Soc. Fr.* **1976**, 1105; (b) Tatsuoka, T.; Imao, K.; Suzuki, K.; Shibata, M.; Satoh, F.; Miyano, S.; Sumoto, K. *Heterocycles* **1990**, *30*, 749; (c) Sugita, Y.; Kawai, K.; Hosoya, H.; Yokoe, I. *Heterocycles* **1999**, *51*, 2029, and references cited therein.
6. Hoffmann, K.-L.; Maas, G.; Regitz, M. *J. Org. Chem.* **1987**, *52*, 3851.
7. Yadav, J. S.; Reddy, B. V. S.; Gupta, M. K.; Prabhakar, A.; Jagadeesh, B. *Chem. Commun.* **2004**, 2124.
8. For silyloxy-1-benzopyrylium triflates, see: Lee, Y.-G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K. *J. Org. Chem.* **1991**, *56*, 2058.
9. For reactions of benzopyrylium triflates with 1,3-bis-silyl enol ethers, see: (a) Langer, P.; Saleh, N. N. R.; Freifeld, I. *Chem. Commun.* **2002**, 168; (b) Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, *44*, 5133.
10. For the simple cyclopropanation of chromones by use of a sulfur ylide, see: Ghosh, C. K.; Sahana, S.; Ghosh, C. *Indian J. Chem.* **1996**, *35B*, 669.
11. For the cyclopropanation of coumarins, see: Bojilova, A.; Videnova, I.; Ivanov, C.; Rodios, N. A.; Terzis, A.; Raptopoulou, C. P. *Tetrahedron* **1994**, *50*, 13023.

12. General procedure: To chromone **1** (2.0 mmol) and copper(II) triflate (0.1 mmol, 5 mol %) was added Me_3SiOTf (2.6 mmol) by syringe and the mixture was stirred for 30 min at 20 °C under inert atmosphere. To the mixture was added CH_2Cl_2 (10 mL) and, subsequently, a CH_2Cl_2 solution (5 mL) of **2** was slowly added at 0 °C. After stirring for 2–5 h (TLC control) the solution was poured into water, the organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel) to give a colourless oil. Starting with **1a** (292 mg, 2.0 mmol), Me_3SiOTf (578 mg, 2.6 mmol) and **2** (274 mg, 2.4 mmol), **3a** was obtained as a yellowish oil (327 mg, 71%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.27$ (t, $^{3}J = 7.2$ Hz, 3H, CH_3), 2.39 (dd, $^{3}J = 3.0$ Hz, $^{3}J = 4.8$ Hz, 1H, CH), 2.80 (dd, $^{3}J = 4.8$ Hz, $^{3}J = 6.9$ Hz, 1H, CH), 4.19 (q, $^{3}J = 7.2$ Hz, 2H, CH_2), 4.82 (dd, $^{3}J = 3.0$ Hz, $^{3}J = 6.9$ Hz, 1H, CH), 6.97 (dd, $^{3}J = 8.0$ Hz, $^{4}J = 1.0$ Hz, 1H, Ar), 7.08 (ddd, $^{3}J = 7.0$ Hz, $^{3}J = 8.0$ Hz, $^{4}J = 1.0$ Hz, 1H, Ar), 7.51 (ddd, $^{3}J = 7.0$ Hz, $^{3}J = 8.0$ Hz, $^{4}J = 2.0$ Hz, 1H, Ar), 7.88 (dd, $^{3}J = 8.0$ Hz, $^{4}J = 2.0$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 13.99$ (CH_3), 21.69 (CH), 32.92, 61.30 (CH), 61.60 (CH_2), 117.68 (CH, Ar), 118.42 (C, Ar), 122.36, 126.86, 135.99 (CH, Ar), 156.75 (C, Ar), 169.85, 185.94 (CO). IR (KBr): $\nu = 1726$ (s), 1682 (s), 1646 (w), 1610 (m), 1467 (m) cm^{-1}. UV (MeCN): λ ($\log \varepsilon$) = 216.19 (4.3) nm. MS (EI, 70 eV): *m*/*z* = 232 (M^+, 12), 187 (4), 175 (3), 121 (12), 28 (100).

13. General procedure: To a CH_2Cl_2 solution (10 mL) of **3** (1.4 mmol) was added TFA (1 mL) and a drop of water. The solution was stirred until the reaction was complete (TLC control). The solution was poured into an aqueous solution of hydrochloric acid (10%), the organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel) to give a colourless solid, mp = 173 °C. Starting with **3a** (327 mg, 1.4 mmol), CH_2Cl_2 (10 mL) and TFA (1 mL), **4a** was isolated as a colourless solid (183 mg, 56%). ^{1}H NMR ($CO(CD_3)_2$, 300 MHz) $\delta = 1.33$ (t, $^{3}J = 6.9$ Hz, 3H, CH_3), 4.30 (q, $^{3}J = 6.9$ Hz, 2H, CH_2), 6.96 (ddd, $^{3}J = 7.8$ Hz, $^{3}J = 8.1$ Hz, $^{4}J = 0.9$ Hz, 1H, Ar), 7.03 (dd, $^{3}J = 8.4$ Hz, $^{4}J = 0.9$ Hz, 1H, Ar), 7.19 (ddd, $^{3}J = 8.4$ Hz, $^{3}J = 8.1$ Hz, $^{4}J = 1.2$ Hz, 1H, Ar), 7.29 (d, $^{4}J = 0.8$ Hz, 1H, Ar), 7.77 (dd, $^{3}J = 7.8$ Hz, $^{4}J = 1.8$ Hz, 1H, Ar), 8.21 (d, $^{4}J = 0.8$ Hz, 1H, Ar), 9.26 (s, 1H, OH). ^{13}C NMR ($CO(CD_3)_2$, 75 MHz): $\delta_C = 14.63$ (CH_3), 60.85 (CH_2), 109.47 (CH), 116.99 (CH, Ar), 117.89 (C, Ar), 120.73 (CH, Ar), 122.27 (C), 126.44, 129.85 (CH, Ar), 146.86 (OCH), 152.89 (COH), 154.42 (*C*OAr), 163.49 (*C*OOEt). IR (KBr): $\tilde{\nu} = 3248$ (s), 3162 (w), 2981 (w), 1684 (s), 1611 (w) cm^{-1}. UV (MeCN): λ ($\log \varepsilon$) = 262.5 (4.2), 208.2 (4.5) nm. MS (EI, 70 eV): *m*/*z* = 232 (M^+, 27), 204 (5), 187 (4), 121 (8), 87 (9), 28 (100). HRMS (FT-ICR, API-ES): calcd for $C_{13}H_{13}O_4$ ($[M+H]^+$): 233.08139; found: 233.08249.