



Pergamon

Tetrahedron Letters 41 (2000) 1381–1384

TETRAHEDRON  
LETTERS

## Synthesis of 8-substituted 5*H*,9*H*-6-oxa-7-aza-benzocyclononene-10,11-dione-11-*O*-methyloximes, a new [1,2]-oxazonine ring system<sup>1</sup>

Alfons Pascual,<sup>a,\*</sup> Hugo Ziegler,<sup>a</sup> Stephan Trah,<sup>a</sup> Peter Ertl<sup>b</sup> and Tammo Winkler<sup>c</sup>

<sup>a</sup>Research, Chemistry Projects, Novartis Crop Protection AG, CH-4002 Basel, Switzerland

<sup>b</sup>Research, Lead Discovery, Novartis Crop Protection AG, CH-4002 Basel, Switzerland

<sup>c</sup>Research Support, Novartis Crop Protection AG, CH-4002 Basel, Switzerland

Received 15 November 1999; accepted 13 December 1999

### Abstract

Reaction of (2-bromomethyl-phenyl)-methoxyimino-acetic acid methyl ester **4** with oximes **1** in the presence of NaH/DMF yields 8-substituted 5*H*,9*H*-6-oxa-7-aza-benzocyclononene-10,11-dione-11-*O*-methyloximes **3** together with the expected open chain compounds **2**. Some spectroscopic data as well as synthetic and mechanistic aspects of the formation of the novel compounds **3** are discussed. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* carbanions; cyclic ketones; cyclisation; deprotonation; oximes; substitution.

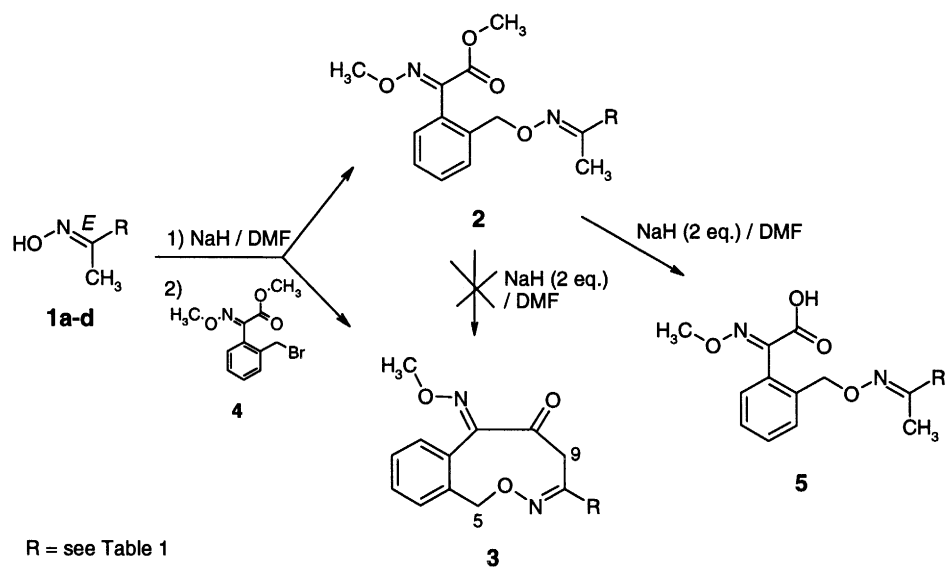
In the course of our research on pesticidal oxime ether compounds **2**,<sup>2</sup> we observed the unexpected formation of a new compound, to which the [1,2]-oxazonine ring structure **3** was assigned (Scheme 1). We report herein some examples of the synthesis of this novel heterocyclic system **3**, together with its spectroscopic characterisation as well as some considerations on the reaction mechanism and the ring conformation.

The reaction of oximes **1** (for R see Table 1) with the bromides **4** in the presence of 1.1 equiv. NaH in DMF usually yields the oxime ether derivatives **2** in good yields. In some cases, however, an additional compound was formed that was assigned the [1,2]-oxazonine structure **3** (see Table 1, entry **a**).<sup>3</sup> Increasing the amount of NaH favoured the formation of **3** (Table 1, entries **b–d**).

Compound **2** is not an intermediate in the formation of **3**, as shown by treatment of **2** with NaH in DMF, which resulted in slow cleavage of the ester group to the acid **5**. We suggest therefore that the oxime dianion is formed which reacts first with the ester group of **4**, followed by ring closure to **3**. Oxime dianions have been already described.<sup>4</sup>

The thiophene analogue **6** (Scheme 2) reacted similarly with the oxime **1e**.

\* Corresponding author. Fax: +41-616978529; e-mail: alfons.pascual@cp.novartis.com (A. Pascual)



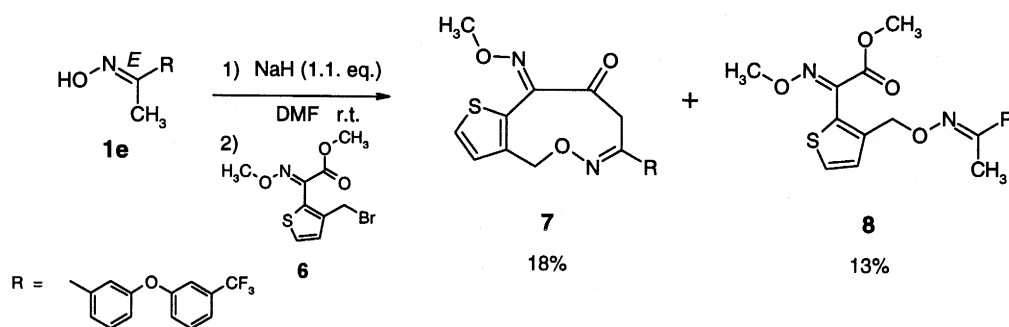
Scheme 1.

Table 1  
Reaction of bromide **4** with oximes **1a-d**

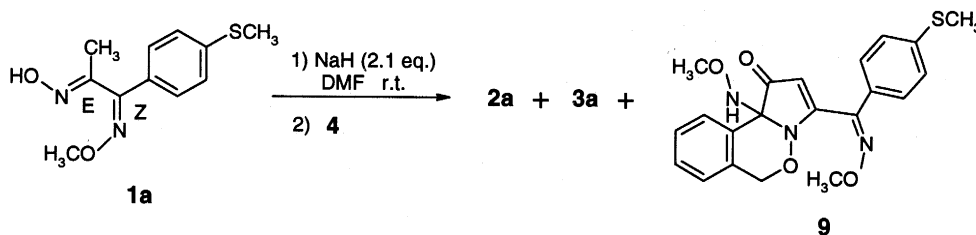
Compound	R	eq. NaH	% Yield of	
			<b>3</b>	<b>2</b>
<b>a</b>		1.1	36	26
<b>b</b>		1.2	--	64
		2.0	24	18
<b>c</b>		1.1	--	44
		2.1	32	traces
<b>d</b>		1.1	--	71
		2.1	34	--

Reaction of **1a** with 2.1 equiv. NaH resulted in the formation of an additional compound, to which the fused oxazine ring structure **9**<sup>5</sup> (Scheme 3) could be assigned with a heteronuclear multiple bond correlation. Interestingly, **3a** is not an intermediate in the formation of **9**, as shown by treating **3a** under the reaction conditions and with various acids and bases. Related structures like 9a-methoxy-3,9a-dihydro-4-oxa-4a-aza-fluoren-9-one have been described by Danishefsky and coworkers.<sup>6</sup>

The NMR spectra of **3** show exchange broadening for the two CH<sub>2</sub> groups at room temperature. At -50°C, they both split into an AB system (chemical shift values in CDCl<sub>3</sub> for **3d**: H<sub>9</sub> 4.24 and 3.60, H<sub>5</sub>



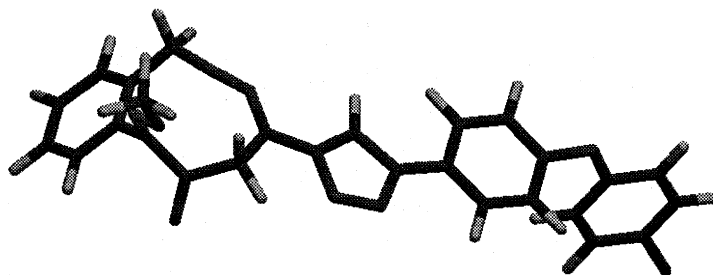
Scheme 2.



Scheme 3.

5.54 and 5.32 ppm). This shows that the nine-membered ring assumes a chiral conformation and that ring inversion is slow on the NMR time scale. The large chemical shift difference between the two protons H<sub>9</sub> (0.64 ppm) can then be explained by the chiral conformation and the proximity of the carbonyl and the isoxazolyl substituents.

This is borne out by a semiempirical AM1 calculation of the minimised conformation of **3d** (Fig. 1). It shows one of the two protons H<sub>9</sub> to be coplanar with the carbonyl group, an arrangement which introduces a strong downfield shift.<sup>7</sup> Thus, the observation of chirality strongly supports the nine-membered ring structure for **3**.

Figure 1. Minimised conformation of **3d**.

## References

1. Presented in part at the 17th International Congress of Heterocyclic Chemistry, Vienna University of Technology, August 1–6, 1999.
2. Farooq, S.; Trah, S.; Ziegler, H.; Zurflüh, R.; Pascual, A.; Szczepanski, H.; Hall, R. G. (Novartis). World Pat. Appl. WO 97/20809, 1997; Ziegler, H.; Trah, S.; Zurflüh, R.; Farooq, S. (Ciba-Geigy). World Pat. Appl. WO 95/18789, 1995.
3. As a typical experiment the synthesis of compound **3d** is described: NaH (0.24 g of an approximately 55% oil dispersion, 5.52 mmol) are suspended in DMF (5 ml). A solution of the oxime **1d** (1.00 g, 2.76 mmol) in DMF (5 ml) is added slowly at room temperature. After 2 h at room temperature, bromide **4** (0.79 g, 2.76 mmol) in DMF (5 ml) is added dropwise, and

stirring is continued at room temperature overnight. To the formed red solution, AcOH (1.5 ml) is added and after stirring for 5 min the solvents are evaporated. The residue is diluted with ethyl acetate, washed twice with water and once with saturated sodium chloride solution. After drying ( $\text{Na}_2\text{SO}_4$ ) and evaporating the solvent, the residue is purified by flash chromatography (hexane/ethyl acetate 9:1). 0.50 g (34%) of **3d** are obtained. Mp 164–166°C; EI-MS (70 eV): 536 (10), 535 ( $\text{M}^+$ , 32), 506 (17), 505 (46), 504 (12), 474 (10), 304 (36), 116 (100);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ; coupling constants given in Hz): 7.90 (part of an AA'BB'-system, 2H), 7.62 (part of an AA'BB'-system, 2H), 7.45–7.40 m (3H), 7.25–7.20 m (1H), 7.18 (part of an AA'BB'-system, 2H), 7.12 (part of an AA'BB'-system, 2H), 7.05 s (1H), 5.40 s (2H), 3.90 br s (2H), 3.79 s (3H). Physical data for new compounds **3a–c** and **7**: For **3a**: Mp 125–127°C;  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 7.68 (part of an AA'BB'-system, 2H), 7.42–7.39 m (3H), 7.27 m (1H), 7.21 (part of an AA'BB'-system, 2H), 5.28 s (2H), 4.02 s (3H), 3.88 s (3H), 3.71 s (2H), 2.49 s (3H);  $^{13}\text{C}$  NMR (250 MHz,  $\text{CDCl}_3$ ): see Fig. 2. For **3b**: Mp 92–96°C; FD-MS: 376 ( $\text{M}^+$ );  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 8.01 s (1H), 7.89 (part of an AA'BB'-system, 1H), 7.73 (part of an AA'BB'-system, 1H), 7.59 m (1H), 7.43–7.37, m (3H), 7.26–7.20 m (1H), 5.37 s (2H), 3.80 s (2H), 3.75 s (3H). For **3c**: Mp 129–130°C;  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 7.40–7.36 m (3H), 7.21 m (1H), 5.33 s (2H), 4.10 s (3H), 3.87 s (3H), 3.74 br s (2H), 2.51 s (3H). **7**: Mp 129–131°C; EI-MS (70 eV): 474 ( $\text{M}^+$ , 13), 445 (27), 444 (100), 413 (31), 412 (23), 277 (29), 263 (34), 122 (84);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 7.54 d (1H,  $J=6$  Hz), 7.52–7.35 m (5H), 7.30–7.25 m (1H), 7.20–7.06 m (2H), 6.85 d (1H,  $J=6$  Hz), 5.36 s (2H), 3.92 s (3H), 3.90 s (2H).

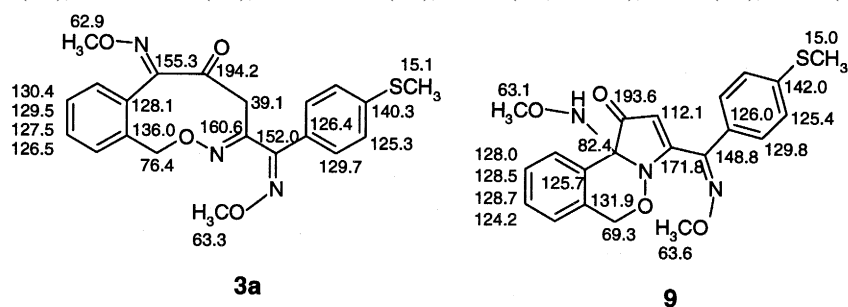


Figure 2.  $^{13}\text{C}$  NMR data for **3a** and **9**.

- Livingston, M. J.; Chick, M. F.; Shealy, E. O.; Beam, C. F. *J. Heterocycl. Chem.* **1982**, *19*, 215.
- Isolation of compound **9**: NaH (0.96 g, 22.0 mmol), **1a** (2.50 g, 10.5 mmol), and **4** (3.00 g, 10.5 mmol) are reacted as shown for **3d**. After work-up, the residue is filtered on silica gel (ethyl acetate). The first fraction is separated by flash chromatography (ethyl acetate:hexane 1:4) to give, in the order of elution, traces of **1a**, compound **3a** (0.14 g, 3%), **2a** (0.19 g, 4%) and compound **9** (0.11 g, 3%) as resin. Physical data for **9**: ESI-MS: 412.19 ( $\text{M}^+$ );  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 7.92 (part of an AA'BB'-system, 1H), 7.69 (part of an AA'BB'-system, 2H), 7.40–7.27 m (4H), 7.03 (part of an AA'BB'-system, 1H), 6.16 s ( $\text{D}_2\text{O}$  exch., 1H), 5.81 s (1H), 5.05 d (1H,  $J=15$  Hz), 4.69 d (1H,  $J=15$  Hz), 4.09 s (3H), 3.66 s (3H), 2.52 s (3H);  $^{13}\text{C}$  NMR (250 MHz,  $\text{CDCl}_3$ ): see Fig. 2. The second fraction from the filtration contains the acid **5** (2.00 g, 45%).
- McClure, K. F.; Benbow, J. W.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 8185; Benbow, J. W.; McClure, K. F.; Danishefsky, S. *J. Am. Chem. Soc.* **1993**, *113*, 12 305.
- Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon, Oxford, 2nd ed., 1969, p. 88