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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[1]

Alfons Pascual,[a,*] Hugo Ziegler,[a] Stephan Trah,[a] Peter Ertl [b] and Tammo Winkler [c]

[a]*Research, Chemistry Projects, Novartis Crop Protection AG, CH-4002 Basel, Switzerland*
[b]*Research, Lead Discovery, Novartis Crop Protection AG, CH-4002 Basel, Switzerland*
[c]*Research Support, Novartis Crop Protection AG, CH-4002 Basel, Switzerland*

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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.

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

In the course of our research on pesticidal oxime ether compounds **2**,[2] 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**).[3] 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.[4]

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)

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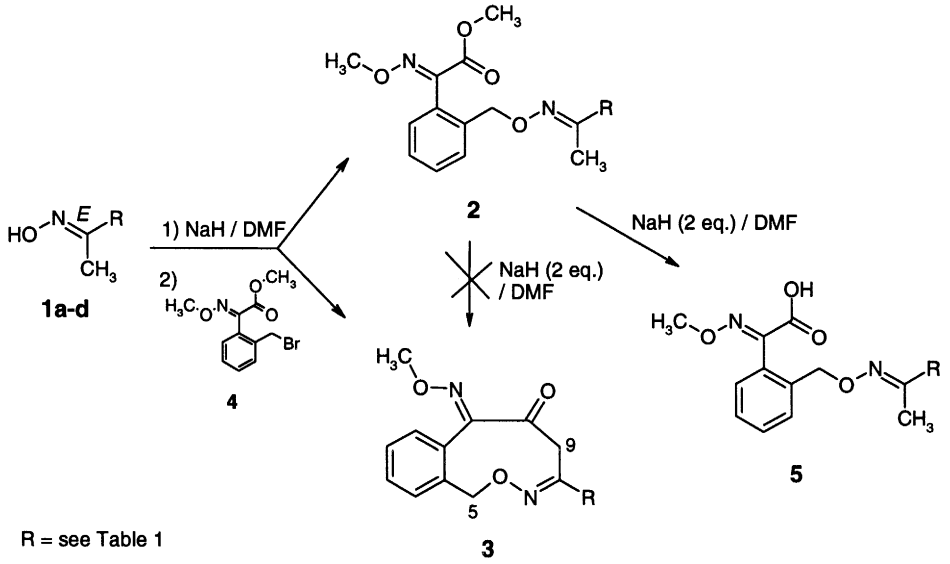
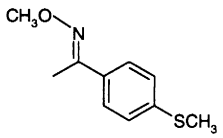
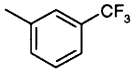
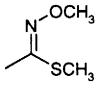
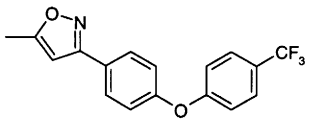


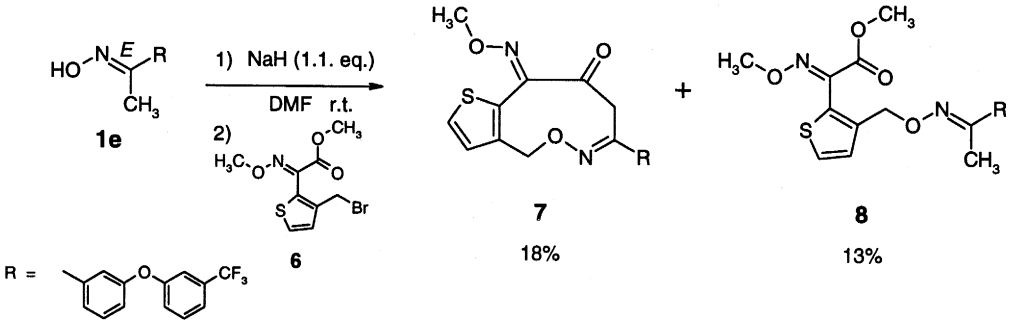
Scheme 1.

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

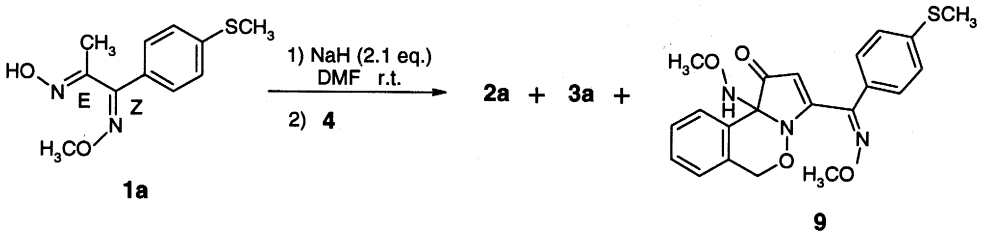
Compound	R	eq. NaH	% Yield of **3**	% Yield of **2**
a		1.1	36	26
b		1.2	--	64
		2.0	24	18
c		1.1	--	44
		2.1	32	traces
d		1.1	--	71
		2.1	34	--

Reaction of **1a** with 2.1 equiv. NaH resulted in the formation of an additional compound, to which the fused oxazine ring structure **9**[5] (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.[6]

The NMR spectra of **3** show exchange broadening for the two CH_2 groups at room temperature. At −50°C, they both split into an AB system (chemical shift values in $CDCl_3$ for **3d**: H_9 4.24 and 3.60, H_5



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_9 (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_9 to be coplanar with the carbonyl group, an arrangement which introduces a strong downfield shift.[7] Thus, the observation of chirality strongly supports the nine-membered ring structure for **3**.

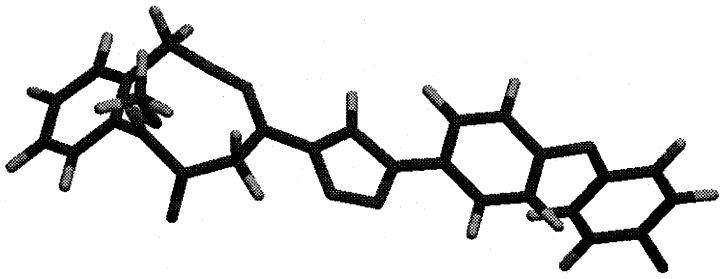


Figure 1. Minimised conformation of **3d**.

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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 (Na_2SO_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 (M^+, 32), 506 (17), 505 (46), 504 (12), 474 (10), 304 (36), 116 (100); ^{1}H NMR (250 MHz, $CDCl_3$; 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}H NMR (250 MHz, $CDCl_3$): 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}C NMR (250 MHz, $CDCl_3$): see Fig. 2. For **3b**: Mp 92–96°C; FD-MS: 376 (M^+); ^{1}H NMR (250 MHz, $CDCl_3$): 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}H NMR (250 MHz, $CDCl_3$): 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 (M^+, 13), 445 (27), 444 (100), 413 (31), 412 (23), 277 (29), 263 (34), 122 (84); ^{1}H NMR (250 MHz, $CDCl_3$): 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).

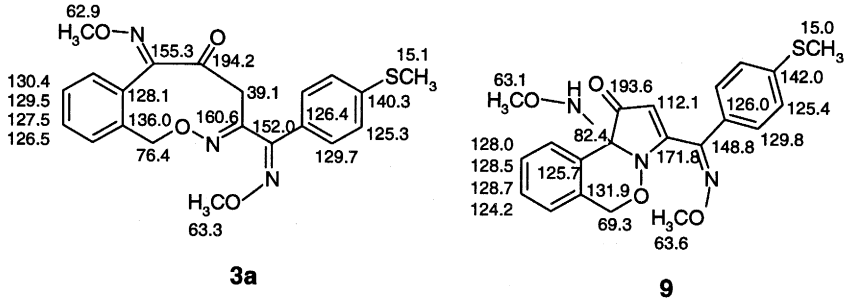

Figure 2. ^{13}C NMR data for **3a** and **9**.

4. Livingston, M. J.; Chick, M. F.; Shealy, E. O.; Beam, C. F. *J. Heterocycl. Chem.* **1982**, *19*, 215.
5. 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 (M^+); ^{1}H NMR (250 MHz, $CDCl_3$): 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 (D_2O 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}C NMR (250 MHz, $CDCl_3$): see Fig. 2. The second fraction from the filtration contains the acid **5** (2.00 g, 45%).
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7. Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon, Oxford, 2nd ed., 1969, p. 88