

Cyclization of N-(3-Oxoalkyl)chloroacetamides Under Basic Conditions. Synthesis of *cis*-3,4-Epoxypiperidin-2-ones.

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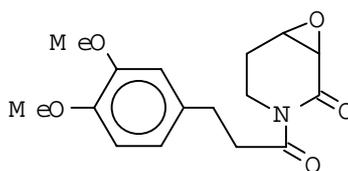
Abstract: It has been shown that N-(3-oxoalkyl)chloroacetamides (**1**) can be converted into *cis*-3,4-epoxypiperidin-2-ones (**2**) upon treatment with t-BuOK in a t-BuOH-C₆H₆ solution due to a resulting intramolecular Darzens reaction. It has been found that under kinetically controlled reaction conditions (NaOH/C₆H₆), besides the intramolecular Darzens reaction an intramolecular alkylation takes place.

Keywords: Darzens reaction, intramolecular cyclization, N-(3-oxoalkyl)chloroacetamides.

Introduction

cis-3,4-Epoxypiperidin-2-ones could be used as versatile building blocks in the synthesis of the biologically active functionalized piperidines by means of epoxide fragment modification. Such a moiety is found, for example, in the ant-repellent alkaloid Piplaroxide [1] (Scheme 1).

Scheme 1.



Known methods for synthesis of *cis*-3,4-epoxypiperidin-2-ones assume an oxidation of 5,6-dihydro-pyridin-2(1H)-ones [2] and cannot be considered as practical. Alternatively, the piperidine ring system could be assembled by cyclization of available acyclic precursors. In this manner, intramolecular cyclization of the corresponding α -functionalized N-(3-oxoalkyl)acetamides proceeding as Knoevenagel [3,4] or Wittig [5] reactions lead to 5,6-dihydropyridin-2(1H)-ones. To the best of our knowledge the intramolecular Darzens reaction of N-(3-oxoalkyl)chloroacetamides, which could make possible the preparation of *cis*-3,4-epoxypiperidin-2-ones, has not been investigated.

Results and Discussion

We have found that the treatment of compounds **1a-e** with potassium *t*-butoxide in a *t*-butanol and benzene mixture at 0°C afforded the corresponding *cis*-3,4-epoxypiperidin-2-ones **2a-e** in 10-71% yields (Table 1) as a result of an intramolecular Darzens reaction (Scheme 2). Besides the deprotonation of the α -carbamoyl position, the α -carbonyl position is deprotonated too and this causes, in the case of compounds **1c,d**, the formation of α,β -unsaturated ketones as a result of an E_{1cb} elimination that leads to decreased yields of the desired compounds **2c,d**. This complication does not occur in the reactions of the alkyl substituted N-(3-oxoalkyl)chloroacetamides **1a,b,e** under the same reaction conditions.

Use of a solvent mixture containing *t*-butanol provides a proton donating medium and as a result makes the deprotonation an equilibrium and therefore a thermodynamically controlled process. This kind of reaction conditions leads to formation of *cis*-3,4-epoxypiperidin-2-ones (**2**).

When the reaction is carried out in an aprotic medium (boiling benzene, NaOH powder) intramolecular alkylation of the α -carbonyl deprotonated intermediate occurs besides the Darzens reaction. Cyclization of compound **1b** under those conditions leads to an approximately 1:1 mixture of 4,6,6-trimethyl-3,4-epoxypiperidin-2-one (**2b**) and 4-acetyl-5,5-dimethylpyrrolidin-2-one (**3b**) (Scheme 2).

Scheme 2

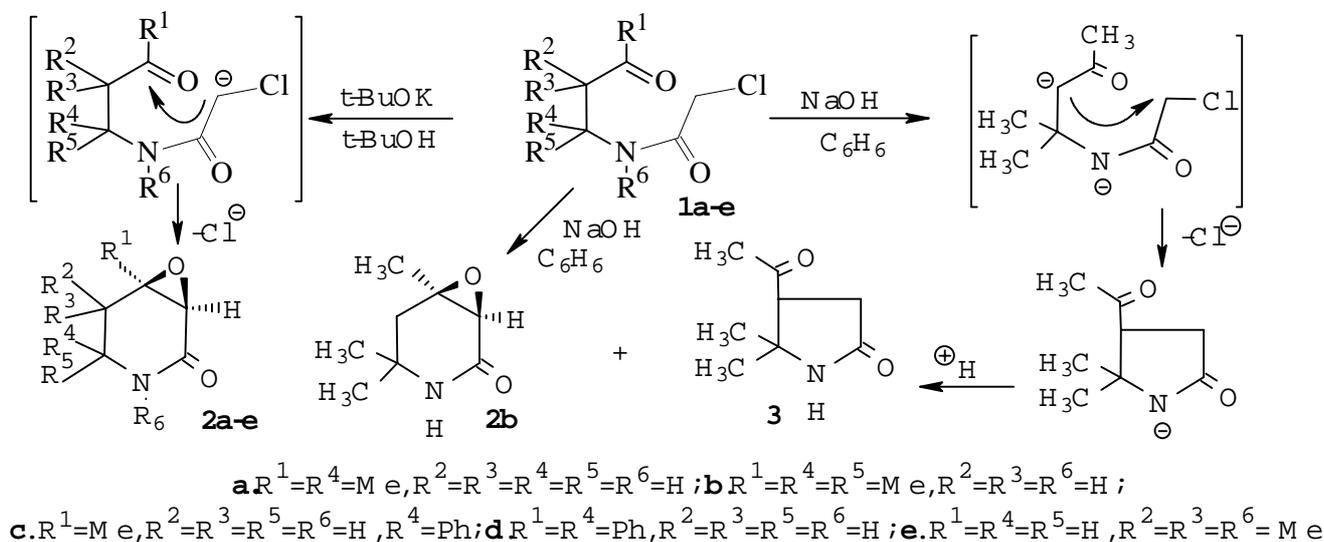


Table 1. Yields and Melting Points of Compounds **2a-e**, **3b**.

Compound	2a	2b	2c	2d	2e	3b
Yield, %	43	71 (28) ¹⁾	27	10	59	24 ¹⁾
m.p., °C ²⁾	130-131	181-182	>220(decomp)	>250(decomp)	77-78	93-95

¹⁾ yield in reaction with NaOH powder in benzene; ²⁾ sealed capillary, compounds sublimate

The structures of the obtained compounds were confirmed by their elemental analysis, IR, ¹H- and ¹³C-NMR spectroscopy. Both the signal multiplicities and chemical shift values in the NMR spectra of the *cis*-3,4-epoxypiperidin-2-ones (**2**) correspond completely to their structures. Long range spin-spin couplings confirmed by ¹H-¹H COSY spectroscopy are typical for protons with a W-arrangement (C₍₃₎-H and N-H, C₍₄₎-H and C₍₆₎-H_e).

Conclusions

It has been shown that N-(3-oxoalkyl)chloroacetamides undergo an intramolecular cyclization under the influence of bases via both intramolecular alkylation and intramolecular Darzens reactions. Despite the moderate and sometimes low yields of products observed, nevertheless the cyclization of N-(3-oxoalkyl)chloroacetamides can be proposed as a potentially useful method for the synthesis of *cis*-3,4-epoxypiperidin-2-ones because of the ready availability of the precursors.

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Experimental

General

¹H and ¹³C NMR spectra were obtained using a Bruker AC-200 NMR and were recorded at 200 and 50 MHz respectively, using CDCl₃ as solvent. IR spectra were recorded on a Specord-75IR spectrophotometer. Compounds **1a,b** (**a**, 25%, m.p. 42-43°C; **b**, 60 %, b.p. 110-115°C/7 mm Hg) have been obtained by acylation of the corresponding 1,3-aminoketones [7]; compounds **1c,d** (**c** 56%, m.p. 90-91°C; **d**, 81 %, m.p. 104-105°C) — by reaction of the α,β-unsaturated ketones and chloroacetonitrile [6]; compound **1e** (47%, b.p. 146-151°C/7 mm Hg) — by reaction of 2-methyl-1-propenyl (1,1,1-trimethylsilyl)ether with 1,3,5-trimethylhexahydro-1,3,5-triazene and ClCH₂COCl, in the presence of TiCl₄ [7].

Reaction of N-(3-oxoalkyl)chloroacetamides 1a-e with t-BuOK in t-BuOH-benzene media.

A solution of *t*-BuOK, freshly prepared from potassium (0.055 g, 1.4 mmol) and *t*-BuOH (5 mL) was added dropwise over 2 hours to a stirred solution of compound **1a-e** (1.4 mmol) in a mixture of benzene (5mL) and *t*-butanol (5 mL) at 0 °C. The reaction mixture was stirred for 6 hours at room temperature, poured into water (50 mL) and extracted with chloroform (3 x 15mL). The combined extracts were washed with water to pH~7, dried with MgSO₄ and concentrated in vacuo to give a residue which, after column chromatography on silica (eluent 3:1 CHCl₃-EtOAc), afforded the products **2a-e**.

Reaction of 2-chloro-N-(1,1-dimethyl-3-oxobutyl)acetamide 1b with sodium hydroxide in benzene.

Sodium hydroxide powder (0.25 g, 6.25 mmol) was added to a solution of compound **1b** (1.00 g, 5.2 mmol) in benzene, the resulting mixture was boiled for 1-2 min and then diluted with a 5 % aqueous solution of acetic acid. The organic layer was separated and the aqueous one was extracted with chloroform (2 x 10 mL). The combined organic extracts were dried with MgSO₄ and the solvent was removed in vacuo. The residue was chromatographed on silica, eluting first with 1:1 CHCl₃-EtOAc for the separation of **2b** and then with *i*-PrOH for separation of **3b**.

Spectral Data

2a: ¹H-NMR: 7.28 (1H, brs, NH); 3.52 (m, 1H, ³J=7.2, 6.9, 5.1 and 1.2 Hz, 6-H); 3.20 (1H, d, ⁴J=1.7 Hz, 3-H); 2.20 (1H, d.d, ²J=15.0 Hz, ³J=7.2 Hz, 5-H); 1.98 (1H, d.d, ²J 15.0 Hz, ³J=1.2 Hz, 5-H); 1.46 (3H, s, 4-CH₃); 1.35 (3H, d, ³J=6.9 Hz, 4-CH₃).

2b: ¹H-NMR: 7.17 (brs, 1H, NH), 3.20 (1H, d, ⁴J=1.7 Hz, 3-H), 2.09 (1H, d, ²J=14.9 Hz, ³J=7.2 Hz, 5-H), 1.92 (1H, d, ²J=14.9 Hz, 5-H), 1.45 (3H, s, 4-CH₃), 1.39 (3H, s, 6-CH₃), 1.25 (3H, s, 6-CH₃); ¹³C-NMR: 169.5, 60.3, 56.0, 51.1, 40.4, 32.1, 31.9, 21.4; IR (CHCl₃): 3410, 1690 cm⁻¹.

2c: ¹H-NMR: 7.37-7.22 (5H, m, 6-Ph). 6.36 (1H, brs, NH), 4.63 (1H, m.), 3.25 (1H, d, ⁴J=1.8 Hz, 3-H), 2.65-2.46 (2H, m, 5-H), 1.41 (3H, s, 4-CH₃).

2d: ¹H-NMR: 7.37-7.20 (10H, m, 4-Ph, 6-Ph), 6.36 (1H, brs, NH), 4.63 (1H, m.), 3.25 (1H, d, ⁴J=1.8 Hz, 3-H), 2.65-2.46 (2H, m, 5-H), 1.41 (3H, s, 4-CH₃).

2e: ¹H-NMR: 3.33 (1H, d, ²J=12.3 Hz, 6-H), 3.25 (1H, d, ³J=4.0 Hz, 3-H), 3.15 (1H, dd, ³J=4.0 Hz, ⁴J=1.7 Hz, 4-H), 2.94(3H, s, N-CH₃), 2.52 (1H, dd, ²J=12.3 Hz, ⁴J=1.7 Hz, 4-H), 1.18 (3H, s, 5-CH₃), 1.06 (3H, s, 5-CH₃).

3b: ¹H-NMR: 7.30 (brs, 1H, NH), 3.22 (1H, dd, ³J=9.7 and 8.5 Hz, 4-H), 2.94 (1H, dd, ²J=17.2 Hz, ³J=9.7 Hz, 3-H), 2.34 (1H, dd, ²J=17.2 Hz, ³J=8.5 Hz, 3-H), 2.25 (3H, s, CH₃CO), 1.56 (3H, s, 5-CH₃), 1.15 (3H, s, 5-CH₃); ¹³C-NMR: 205.3, 175.1, 58.0, 57.5, 32.7, 31.2, 30.2, 24.8; IR (CHCl₃): 3420, 3200, 1705, 1680 cm⁻¹.

References

1. Capron M. A.; Wiemer D. F. Piplaroxide, an ant-repellent piperidine epoxide from *Piper tuberculatum*. *J. Nat. Prod.*, **1996**, *59*, 794-795.
2. Marson Ch. M.; Grabowska U.; Fallah A.; Walsgrove T.; Eggleston D. S.; Baures P. W. Stereoselective Syntheses of 5,6-Dihydro-2(1H)-pyridinones in Polyphosphate Media. *J. Org. Chem.*, **1994**, *59*, 291-296.
3. Fisyuk A. S., Vorontsova M. A., Sagitullin R. S. A New Synthesis of 3-Phenyl-5,6-Dihydropyridin-2(1H)-ones. *Mendeleev Commun.*, **1993**, 249-251.
4. Fisyuk, A. S.; Vorontsova, M. A.; Ivanov, S. A. New synthesis of 3-aryl-5,6-dihydropyridin-2(1H)-ones. *Khim. Geterotsykl. Soedin.*, **1994**, *6*, 8115-8128.
5. Fisyuk A. S., Poendaev N. V., Bundel Y. G. A New Route for Synthesis of 5,6-Dihydropyridine-2(1H)-ones, Pyridones-2 and (4-Hydroxy-2-oxopiperidyl-3)pyridinium chlorides by Intramolecular Cyclization of N-3-Oxoalkylchloroacetamides Derivatives. *Mendeleev Commun.*, **1998**, 12-14.
6. Lora-Tamayo M., Madroñero R., Leipprand H. Beitrag zum chemischen Verhalten der 4H-1,3-Oxazine. *Chem. Ber.*, **1964**, *97*, 2244-2250.
7. Ikeda K., Terao Y., Sekiya M. New Syntheses of α -N-Alkylacetamidomethylated Carbonyl Compounds. *Chem. Pharm. Bull.*, **1981**, *29*, 1156-1159.

Sample Availability: Available from the authors.

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