Mendeleev Commun., 2012, **22**, 265–266

Mendeleev Communications

Regioselective formylation of 1-(2-oxiranylmethyl)-4,5,6,7-tetrahydroindole with DMF/$(COCl)_2$: the pyrrole *vs.* oxirane nucleophilicity

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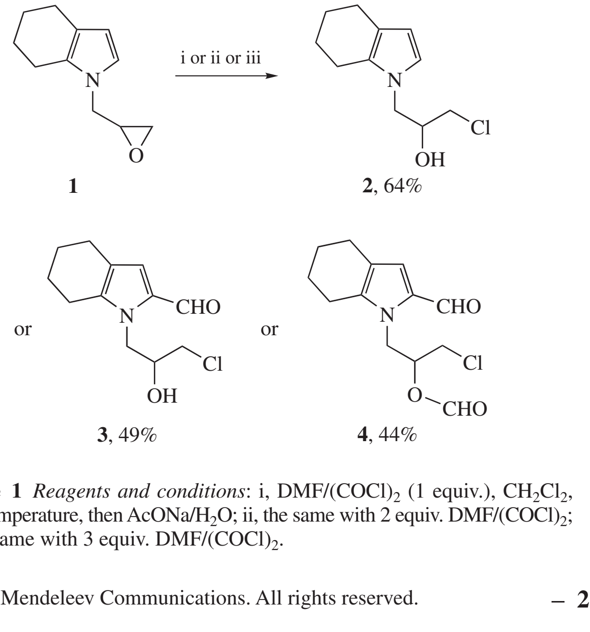
DOI: 10.1016/j.mencom.2012.09.013

Treatment of 1-(2-oxiranylmethyl)-4,5,6,7-tetrahydroindole with the DMF/$(COCl)_2$ reagent system in CH_2Cl_2 (room temperature, 40 min) starts oxirane opening to give 1-(3-chloro-2-hydroxypropyl)-4,5,6,7-tetrahydroindole followed by the formylation of the pyrrole ring to end up with the formation of 1-(3-chloro-2-formyloxypropyl)-4,5,6,7-tetrahydroindole-2-carboxaldehyde *via* the intermediate 1-(3-chloro-2-hydroxypropyl)-4,5,6,7-tetrahydroindole-2-carboxaldehyde.

Epoxy derivatives are valuable intermediates and monomers for hi-tech materials. Among them, 1-oxiranylmethylcarbazole is known to be applied to the design of the information storage and photosensitive devices.[1] Copolymers of 1-oxiranylmethylpyrroles exhibit electroconductivity and are prospective modificators of the Li/S rechargeable batteries.[3] Since recently, 1-(2-oxiranylmethyl)-4,5,6,7-tetrahydroindole **1** became available[4,5] and has been introduced into today laboratory work aiming on future industrial practice.

To gain a better understanding of the synthetic potential of compound **1**, we have studied its formylation with an original formylating reagent system, DMF/$(COCl)_2$ complex.[6] Here we briefly present major results of this study. From a fundamental point of view, in this reaction, a competition between the two nucleophilic sites (the pyrrole and the oxirane moieties) for the electrophilic attack by the complex DMF/$(COCl)_2$ or oxalyl chloride itself should be anticipated.

In fact, when equimolar ratio of compound **1** and the complex DMF/$(COCl)_2$ was allowed to contact in CH_2Cl_2 at room temperature for 40 min, the oxirane opening took place giving the 1-(3-chloro-2-hydroxypropyl) derivative **2** in 64% yield as the only product (Scheme 1). This evidences the oxirane moiety to be a preferred nucleophilic site [toward the system DMF/$(COCl)_2$] compared to the pyrrole ring.



Scheme 1 *Reagents and conditions*: i, DMF/$(COCl)_2$ (1 equiv.), CH_2Cl_2, room temperature, then AcONa/H_2O; ii, the same with 2 equiv. DMF/$(COCl)_2$; iii, the same with 3 equiv. DMF/$(COCl)_2$.

The second equivalent of the DMF/$(COCl)_2$ complex rendered the regioselective formylation of the pyrrole ring to afford aldehyde **3** (49% yield, GC-MS, ^{1}H NMR). Surprisingly, with three equivalents of complex DMF/$(COCl)_2$ further formylation of hydroxy group occurred producing compound **4** in 44% yield (see Scheme 1).[†]

The moderate yields of products **2**–**4** can be rationalized in view of susceptibility of epoxides towards acid catalyzed homopolymerization.[7]

The structure of diformylated compound **4** was unambiguously established by ^{1}H and ^{13}C NMR using 2D correlations.

[†] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 instrument (400.13 and 101.61 MHz, respectively) equipped with inverse gradient 5 mm probe in $CDCl_3$ with HMDS as internal standard. All 2D NMR spectra were recorded using standard gradient Bruker pulse programs. GC-MS characteristics were obtained on Shimadzu QP5050A.

The reaction of 1-(2-oxiranylmethyl)-4,5,6,7-tetrahydroindole **1** *with 3 equiv. of the complex DMF/*$(COCl)_2$. Oxalyl chloride (3.81 g, 30.0 mmol) was added dropwise (3–5 min) to DMF (2.19 g, 30.0 mmol) at ~0 °C (ice-cold water) and the white crystals formed were stirred for 15 min without cooling. Then CH_2Cl_2 (30 ml) was added, and a solution of 1-(2-oxiranylmethyl)-4,5,6,7-tetrahydroindole **1** (1.77 g, 10 mmol) in CH_2Cl_2 (15 ml) was added dropwise over 10 min at ambient temperature. The resulting mixture was stirred for 0.5 h at room temperature. Then a solution of NaOAc (9.85 g, 120 mmol) in H_2O (100 ml) was added and the stirring was continued for 0.5 h at room temperature. The lower organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 30 ml). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 30 ml) and H_2O (3 × 30 ml) and dried (K_2CO_3). The residue obtained after evaporation of the CH_2Cl_2 was purified on basic alumina (hexane–Et_2O, 2:1); this gave diformyl derivative **4** (1.18 g, 44%) as pale-yellow oil.

Compounds **2** and **3** were obtained in the same manner using 1 or 2 equiv. of the complex DMF/$(COCl)_2$, respectively.

1-(3-Chloro-2-hydroxypropyl)-4,5,6,7-tetrahydroindole **2**: yield 64%, yellow oil. ^{1}H NMR ($CDCl_3$) δ: 6.65 (d, 1H, H-2, ^3J 2.2 Hz), 6.11 (d, 1H, H-3, ^3J 2.2 Hz), 4.33 (dd, 1H, NCH_2, ^2J 13.8 Hz, ^3J 3.9 Hz), 4.21 (dd, 1H, NCH_2, ^2J 13.8 Hz, ^3J 8.4 Hz), 4.14–4.10 (m, 1H, OCH), 3.75–3.70 (m, 2H, CH_2Cl), 2.59–2.54 (m, 2H, 7-CH_2), 2.51–2.47 (m, 2H, 4-CH_2), 2.10 (br. s, 1H, OH), 1.87–1.82 (m, 2H, 6-CH_2), 1.82–1.78 (m, 2H, 5-CH_2).

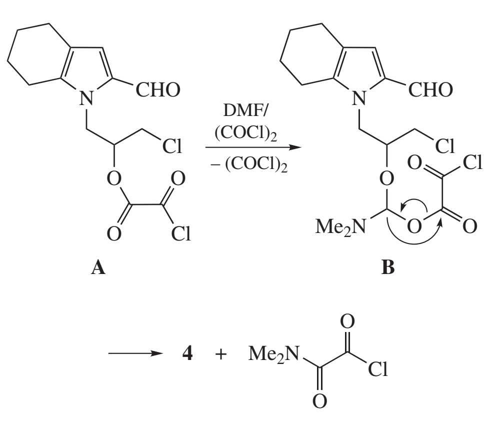
1-(3-Chloro-2-hydroxypropyl)-4,5,6,7-tetrahydroindole-2-carboxaldehyde **3**: yield 49%, yellow oil. ^{1}H NMR ($CDCl_3$) δ: 9.25 [s, 1H, C(O)H], 6.74 (s, 1H, H-3), 4.35 (dd, 1H, NCH_2, ^2J 13.2 Hz, ^3J 4.5 Hz), 4.26 (dd, 1H, NCH_2, ^2J 13.2 Hz, ^3J 7.3 Hz), 4.18–4.14 (m, 1H, OCH), 3.75–3.68 (m, 2H, CH_2Cl), 2.65–2.60 (m, 2H, 7-CH_2), 2.54–2.48 (m, 2H, 4-CH_2), 2.02 (br. s, 1H, OH), 1.84–1.78 (m, 2H, 6-CH_2), 1.76–1.72 (m, 2H, 5-CH_2).

In the ^{1}H NMR spectrum of compound **4**, main characteristic signals are singlet of aldehyde proton (9.38 ppm) and formate proton (8.03 ppm), and complex multiplets of N–CH$_2$ group protons (4.66 and 4.32 ppm), O–CH proton (5.49 ppm) and CH$_2$Cl protons (3.85 and 3.75 ppm). The assignment of ^{13}C signals, except for the quaternary carbons, was deduced from 2D HSQC experiment. The location of substituents was derived from analyses of ^{1}H-^{13}C correlations in 2D HMBC spectrum and confirmed by observed NOE in 2D NOESY experiment.[‡]

The observed ring-opening (according to Krasuski rule) deserves the special attention since under the acidic conditions, oxiranes react with acyl chlorides to form both expected regioisomers.[8] Particularly, oxalyl chloride gives with oxiranes ~1:1 isomeric mixtures,[9] which stands in contrast with our results.

Apparently, the intermediate ester **A**, a product of the oxalyl chloride oxirane opening, reacts with the third equivalent of this complex to deliver intermediate **B** which then decays to the diformylated derivative **4** and *N*,*N*-dimethyloxamoyl chloride (Scheme 2).

The new indole derivatives **2**–**4** may find a rewarding synthetic application, especially bearing in mind that their close analogues such as 1-(3-chloro-2-hydroxypropyl)indoles and 1-(3-chloro-2-hydroxypropyl)pyrrolidines were employed in the synthesis of the congeners of Pindolol – a nonselective beta-blocker with partial beta-adrenergic receptor agonist activity[10] and pharmacologicaly active 2*H*-pyrido[3,2-*b*][1,4]oxazin-3-ones.[11]



Scheme 2

This work was supported by the President of the Russian Federation (grant no. NSH-1550.2012.3 for leading scientific schools).

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Received: 23rd April 2012; Com. 12/3918

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[‡] Characteristic HMBC and NOESY correlations in compound **4**: