Preparation of 4,5,6,7-tetrahydroindole alkaline salts and their reaction with chloromethyloxirane

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This paper is dedicated to Professor Alexander Pozharskii on the occasion of his 70th birthday

Abstract
N-Oxiranylmethyl-4,5,6,7-tetrahydroindole **3** has been synthesized in a yield of 68% by alkylation of 4,5,6,7-tetrahydroindole **1** with chloromethyloxirane **2.** The process was realized through reaction of the Na salt of **1**, prepared *in situ* from NaOH and **1** in toluene, with a 10-fold molar excess (relative to **1**) of **2** with azeotropic removal of water. Alkylation of 4,5,6,7-tetrahydroindole **1** with chloromethyloxirane **2** in the presence of alkaline metal hydroxides MOH (M = Na, K) proceeds with low efficiency (the yield does not exceed 25%).

Keywords: 4,5,6,7-Tetrahydroindole, Na and K salts of 4,5,6,7-tetrahydroindole, chloromethyloxirane, *N*-oxiranylmethyl-4,5,6,7-tetrahydroindole

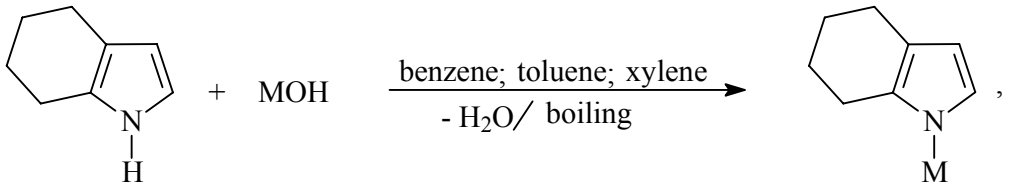
Introduction

Epoxy derivatives of heterocyclic compounds are valuable monomers for synthesizing advanced polymer materials. For instance, the polymers of *N*-oxiranylmethylcarbazole are used for storage and transmittance of information, and light sensitive devices.[1,2] The grafted copolymers of *N*-oxiranylmethyl pyrroles with polysiloxanes possess electroconductivity,[3] *N*-oxiranylmethyl derivatives of various heterocycles are useful for manufacturing of multifunctional molecular glasses.[4] Meanwhile, *N*-oxiranylmethyl derivatives of heterocycles are limited in number. Apart from *N*-oxiranylmethylcarbazole, the most explored in synthetic and applied aspects,[1,2,5-7] only few publications on synthesis and properties of oxiranylmethylpyrrole[3,8-10] and *N*-oxiranylmethylindole[11-13] are known. The reaction of ketoximes with acetylene in MOH/DMSO (M = alkaline metal) systems (Trofimov reaction)[14-17] has opened a technologically feasible

way[18] to 4,5,6,7-tetrahydroindole **1,** which can now be obtained from cyclohexanone oxime and acetylene, a multi-tonnage feedstock. Therefore, the development of industrially acceptable synthesis of *N*-oxiranylmethyl-4,5,6,7-tetrahydroindole **3** is timely.

Results and Discussion

In this work, the alkylation of the indole **1** with chloromethyloxirane **2** in the presence of alkaline metal hydroxides as well as the same alkylation of Na and K salts of **1** have been studied (Scheme 1a,b).



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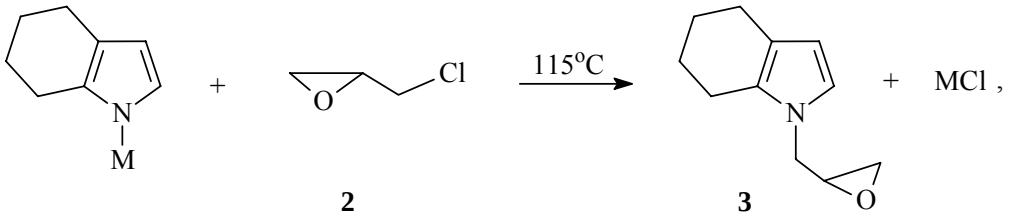
a)



2 **3**

M = Na, K

b)

Scheme 1

In the absence of bases, the indole **1** does not react with oxirane **2** even at temperatures up to 150 °C. In the presence of pyridine (1-2%) at the same temperature, resinification of the reaction mixture occurs, no target product **3** being detected. At low temperatures (20-36 °C, in Et_2O or no solvent, 2% of pyridine) the oxirane ring opening is also not observed. The interaction of the indole **1** with oxirane **2** in the presence of KOH in DMSO (1-3 equiv. of KOH, 90 °C, 0.25-3 h) also does not lead to the desired product **3**.

The efficiency of phase-transfer catalysis in the alkylation of functionalized alcohols with chloromethyloxirane has been exemplified by the synthesis of 1-(2-vinyloxyethoxy)-2,3-epoxypropan and the related species.[19] Phase-transfer catalysis (18 crown 6 as catalyst) was employed for the synthesis of *N*-oxyranylmethylpyrrole from pyrrole-K (prepared from KH and pyrrole in toluene) and chloromethyloxirane (40 °C, THF).[3] However, under phase-transfer

conitions (triethylbenzeneammonium chloride, 8 mass%, molar ratio of **1**:NaOH = 1:1.5-30, 50-80 °C, water, toluene), the target oxirane **3** was not obtained: the starting indole **1** and the oligomers of the oxirane **2** only were isolated.

N-Oxiranilmethylcarbazole was claimed to be obtained in 99% yield from carbazole and chloromethyloxirane in the presence of KOH using alkaline metal carbonates or sulfates to bind the evolving water (20 °C, 30 min).[5] But under these conditions, no reaction between the indole **1** and the oxirane **2** takes place.

Finally, we have managed to prepare the target oxirane **3** in 25% yield (based on the indole **1** consumed) upon heating (115 °C, 4 h) the reactants in the presence of an equimolar amount of NaOH: the conversion of the indole **1** was 33% (Table 1). At longer reaction time (11 h) the conversion of the indole **1** increases up to 94%, while the yield of oxirane **3** drops to 16% (Table 1).

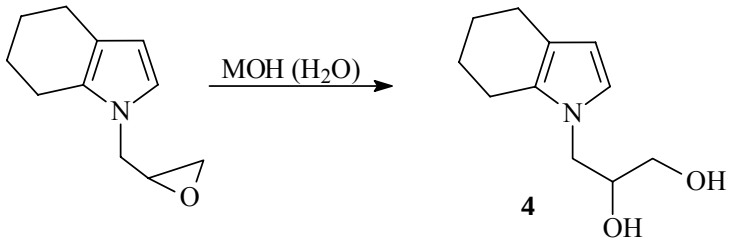
Table 1. Synthesis of oxirane **3** in the presence of MOH: effect of conditions

Molar ratio of indole **1**: MOH: oxirane **2**	MOH	T, °C	Time, h	Conversion of indole **1**, %	Yield of **3**, %
1:3:6[a]	KOH	20	1.0	7[b]	3[b]
1:3:6[a]	KOH	20	2	12[b]	8[b]
1:3:6[a]	KOH	20	24	15[b]	10[b]
1:1:10	NaOH	115	4	33	25
1:1:10	NaOH	115	11	94	16
1:1:1[c]	NaOH	90	4	48	19

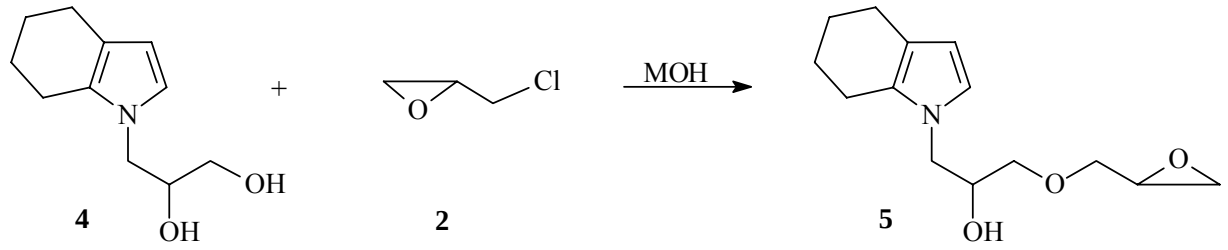
[a] addition of Na_2CO_3. [b] GLC. [c] reaction in toluene.

The low yields of the oxirane **3** are obviously caused by expected side reactions, such as those shown in Scheme 2:

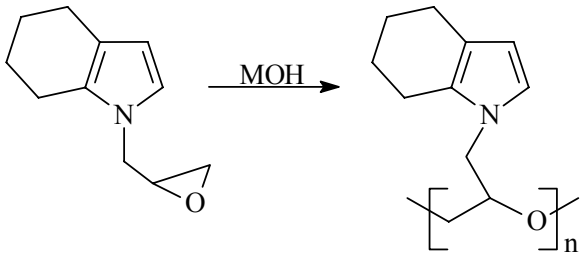
a) hydrolysis of the oxirane ring to the corresponding diol **4**;



b) further reactions of the diol **4** with the oxirane **2** to give the hydroxyoxirane **5** and higher similar oligomers;



c) the base catalyzed polymerization (copolymerization) of the target oxirane **3** as well as other side oxirane products of the type **5**.



Scheme 2

It is known that *N*-oxiranilmethylcarbazole is prepared from its Na or K salts and oxirane **2**, though the yield of the target product does not exceed 35%.[1,6] We have tried to apply this approach to the indole **1** (Scheme 1 a,b). Thus, using the Na or K salts of the indole **1** prepared by boiling of indole **1** with NaOH or KOH with simultaneous removal of water allowed us to synthesize the oxirane **3** in 47% yield (molar ratio of 1:NaOH = 1:1, for other conditions see Table 2).

Table 2. Synthesis of the oxirane **3** *via* Na salt of indole **1**: effect of conditions (NaOH, 10-fold molar excess of chloromethyloxirane, 115 °C)

Synthesis of salt[a]			Synthesis of the oxirane **3**[b]	
Molar ratio of indole **1**:NaOH	Solvent	T, °C	Conversion of indole **1**, %	Yield of oxirane **3**, %
1:1	Toluene	110	50	47
1:1.5	Toluene	110	55	54
1:3	Toluene	110	64	68
1:5	Toluene	110	90	7
1:1	Benzene	80	40	44
1:1	Benzene	80	52[d]	45
1:3	*p*-Xylene	138	85	58
1:3[c]	Toluene	110	74	46
1:3[c]	*p*-Xylene	138	78	48

[a] reaction time 18 h. [b]115 °C, reaction time 4 h. [c] reaction with KOH. [d] reaction time 9 h.

Under the same conditions, but with 3-fold excess of NaOH, the yield increases up to 68% (Table 2). Further increase of the amount of NaOH (up to 5-fold molar excess) results in a sharp decrease of the oxirane **2** yield (to 7%), with a consequent increasing to 90% of the amount of side products and the conversion of the starting indole **1** reaching 90%. The preparation of Na salts of **1** both in boiling benzene (80 °C) or *p*-xylene (138 °C) does not give any preparative advantages (the yields are 44 and 58%, respectively, Table 2). With KOH, under the best conditions found for NaOH (Table 2), the yield of the oxirane **3** equals 46%. The structure of the oxirane **3** was confirmed by ^{1}H, ^{13}C NMR and IR techniques (see Experimental Section).

In conclusion, the first practical and useful synthesis of previously unknown *N*-oxiranylmethyl-4,5,6,7-tetrahydroinole in 68% yield based on alkylation of its Na salt with chloromethyloxirane has been developed. Since 4,5,6,7-tetrahydroindole is now becoming available,[18] the new epoxy monomer may find a wide application, particularly as a modifier of special epoxy materials and building block for synthesis of novel indole compounds.

Experimental Section

General Procedures. IR spectra were recorded on a Bruker IFS-25 spectrometer. NMR spectra were run on a Bruker DPX 400 instrument [400.13 (^{1}H) MHz, 101.6 MHz (^{13}C)] in $CDCl_3$ using HMDS as an internal standard. The initial 4,5,6,7-tetrahydroindole **1** was synthesized in 97% yield from cyclohexanone oxime and acetylene under atmospheric pressure by the procedure described in patent.[18] The alkylation was monitored by GLC chromatography (Agilent 6890N

chromatograph). To a sample (1 ml) was added Et_2O (3 ml), the residue and resin was removed, then toluene (0.1 ml) was added as an internal standard and the solution obtained was analyzed.

1-Oxiranylmethyl-4,5,6,7-tetrahydroindole (3). 4,5,6,7-Tetrahydroindole **1** (3.62 g, 0.03 mol) and powdered NaOH (3.60 g, 0.09 mol) was boiled in toluene (100 ml) for 18 h with stirring and equipped with a Dean-Stark trap, and the water distilled was collected. Toluene was distilled off in vacuum, to a dark-brown viscous residue (sodium salt of indole) was added chloromethyloxyrane **2** (27.63 g, 0.30 mol) and the mixture was boiled at 115°C for 4 h under stirring. The excess **2** was removed under atmospheric pressure. To the residue was added toluene (20 ml) under stirring, the mixture was filtered off, the solvent was removed, and the mixture was fractionally distilled at 90-110 °C (1 mm Hg) to give 2.28 g (68% yield) of indole **3.** Unreacted 4,5,6,7-tetrahydroindole (1.32 g) was recovered from the reaction mixture. After repeat distillation **(**105-108°C, 1 mm Hg) indole **3 –** is an oily light-yellowish liquid with slight odour, n_D^{20} 1.5308, d_4^{20} 1.1637. Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found, %: C, 74.91; H, 8.06; N, 8.17. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.61 d (1H, H-2 J_{2-3} 2.2 Hz), 6.00 d (1H, H-3 J_{2-3} 2.2 Hz), 4.06-3.89 m (2H, N-CH_2), 3.22 m (1H, CH), 2.84 dd (1H, CH_2, ^{2}J 5.0 Hz, ^{3}J 3.9 Hz) and 2.53 dd (1H, CH_2, ^{2}J 5.0 Hz, ^{3}J=2.4 Hz), 2.56-2.60 m (4H, H-4, H-7), 1.70-1.89 m (4H, H-5, H-6). ^{13}C NMR ($CDCl_3$, δ, ppm) 127.7 (C-7a), 119.2 (C-3a), 117.5 (C-2), 106.8 (C-3), 51.2 (NCH_2), 47.7 (CHO), 45.30 (CH_2O), 23.5, 23.3, 23.1, 21.7 (C-4, C-5, C-6, C-7). IR (cm^{-1}): 3092, 3053, 2994, 2926, 2849, 1579, 1519, 1487, 1460, 1442, 1415, 1398, 1369, 1324, 1298, 1259, 1237, 1198, 1175, 1137, 1107, 1073, 1057, 1034, 1003, 975, 952, 914, 851, 834, 803, 761, 707, 690, 637, 609, 598, 518, 498, 464, 438.

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