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An efficient synthesis of β-hydroxyethylpyrazoles from propylene and styrene oxide using Cs_2CO_3

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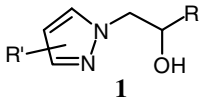
Abstract—Bases such as caesium carbonate efficiently catalyze the regioselective ring opening of propylene and styrene oxide with various substituted pyrazoles.

Pyrazole compounds have been used for a long time as ligands in transition metal complexes. The heterocyclic nucleus may coordinate directly to the metal via one or both of the vicinal nitrogen atoms or the metal may be bound to several pyrazole nitrogens in a polypyrazole system with a carbon or heteroatom linker. Since the pioneering work of Trofimenko[1] the enormous potential of polypyrazoles (boro, alkano, etc.) was recognized for organometallic chemistry and catalysis. In recent years there has been a growing interest in ligand systems that coordinate to the metal via chemically different coordination sites with variable bond strengths of the respective metal ligand bonds. SHOP (Shell Higher Olefin Process) catalysts for the oligomerization of alkenes[2] are a well known example of such hemilabile metal–ligand systems. In the pyrazole ring one nitrogen atom is easily alkylated giving access to systems that possess two and more (identical or different) heteroatoms. In a research project directed towards the development of new non-metallocene polymerization catalysts we became interested in heterocyclic pyrazole ligands that also contain functional groups, such as an OH, in a carbon side chain. We chose hydroxyethylpyrazoles **1** and we report here on the preparation of these type of pyrazoles. Considering that in these compounds both the pyrazole ring and also the carbon side chain is easily and selectively substituted with various aliphatic and aromatic groups, an important number of polysubstituted hydroxyethylpyrazoles may be envisaged.



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Several hydroxyalkylpyrazoles of type **1** are known, though no general applicable synthesis has been described.[3–10] The most general way would consist in the condensation of hydroxyethylhydrazines with the appropriate 1,3-dicarbonyl compounds. The parent hydroxyethylpyrazole **1** (R = R′ = H) was prepared in this way in 76% yield.[6] Another method for the introduction of the hydroxylated side chain consists in the α-lithiation of N-alkyl groups in pyrazoles followed by the electrophilc reaction with aldehydes or ketones.[7] However, the simplest and general way to β-aminoalcohol pyrazoles **1** consists in the nucleophilic attack of one pyrazole nitrogen to an oxirane functional group.

An epoxide ring is sufficiently reactive in order to be thermally cleaved even with the weakly basic pyrazole NH groups ($pK_a = 2.5$–4). Thus, following a patent application,[4] Elguero et al.[5] realized epoxide ring opening of styrene oxide with 3,5-dimethylpyrazole in refluxing xylene after 8 h reaction time according to path a (**3h**, $R_1 = R_2 = Me$).[11] With high-pressure conditions[8] or microwave activation[9] other methods were explored for the synthesis of, mainly, monosubstituted pyrazoles with a limited number of epoxides (styrene, cyclohexene, methylenecyclohexane, 1,1′-diphenyl-ethylene). All these conditions do not seem appropriate for larger scale

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preparations. In principle, there are two possible regioselective pathways but usually, a secondary alcohol of type **2** or **3** is obtained via substitution of the less substituted carbon in the epoxide in the noncatalyzed thermal reaction. This approach offers the opportunity to use directly the (non-negligible) pool of substituted pyrazoles.[12] In case of monosubstituted (R_1 or $R_2 = H$) or differently disubstituted pyrazoles ($R_1 \neq R_2$) 2 other regio isomers might be formed where the hydroxyethyl side-chain is vicinal or distant to one distinct substituent. In terms of ligand coordination, all four possible regio isomers induce a different sterical environment to the putative metal complex and, thus, each compound might be useful. We chose styrene and propylene oxide as convenient starting materials for the alcohol part.

1. Thermal conditions

We repeated the reaction described by Wolf and Flanigan[4] and Elguero et al.[5] with success and effectively, the unsubstituted as well as the dimethylated substrates (**3a**, $R_1 = R_2 = H$) and (**3h**, $R_1 = R_2 = Me$), respectively, were accessible via thermolysis of styrene oxide in moderate yields. Sometimes, better results were obtained on heating the pyrazole and **6** under neat reaction conditions without solvent. However, with monosubstituted pyrazoles, such as *tert*-butyl or *iso*-propylpyrazole only product mixtures were obtained in fairly moderate yields (30–50%). On the other side, thermolysis of propylene oxide **5** and unsubstituted pyrazole easily lead to 2-hydroxypropylpyrazole **2a** ($R_1 = R_2 = H$) in 66% yield at 60 °C (pressure tube, neat, excess of propylene oxide). On reacting other pyrazoles with **5** and **6** it became rapidly clear that the simple thermal ring opening was not a useful method for general application.

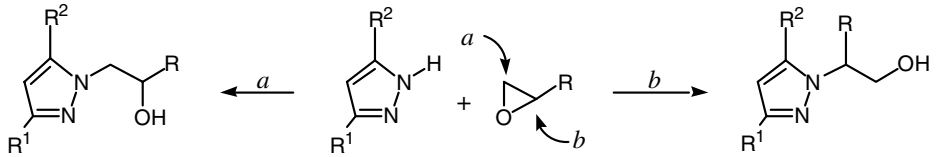
2. Catalytic conditions

The acid or base catalyzed ring opening of oxiranes by means of nitrogen-centered nucleophiles is a well known reaction. Azidohydrins[13] and aminohydrins[14] are easily prepared with high regioselectivities and a number of reaction conditions with base or Lewis acids are described. With strong bases, for example, it is possible to avoid drastic conditions but observe the regioselectivity of the uncatalyzed reaction and, thus, to transform internal and terminal epoxides into the corresponding β-amino alcohols.[15] Though primary and secondary amines have been used extensively, to our knowledge, the pyrazole nucleus was not transformed under these conditions. As mentioned before, the nucleophilic ring opening of unsymmetrical epoxides can occur at the secondary or tertiary oxirane carbon and gives rise to 2 (or 4) isomers. Having in mind to prepare selectively ring-substituted pyrazoles the efficient regiocontrol of both the epoxide ring-opening and pyrazole substitution was desired (Scheme 1).

Among several inorganic bases[16] that we tried it turned out that caesium carbonate[17,18] in trifluorotoluene[19] leads to the products from propylene and styrene oxide that we expected from the thermal reaction. The results with ten different pyrazoles are presented in Table 1. For example, we were pleased to observe that the transformation of most pyrazoles is quantitative and that the products **2h**,**a** and **3h**,**a** from, respectively, 1,3-dimethylpyrazole or unsubstituted pyrazole can be isolated in pure form and yields higher than 80% in multi gram quantities (Table 1, entries 1, 2, 15 and 16).

The transformation of styrene oxide required heating and we conducted the reaction in trifluorotoluene at reflux temperature (102 °C). More conveniently, propylene oxide reacts at room temperature and no solvent is necessary. The amount of base as well as reaction times were not optimized. As a good compromise we found that with styrene oxide 0.5 equiv of Cs_2CO_3 led to good and reproducible results within 16–22 h. With propylene oxide the basic catalyst could be reduced to 0.2 equiv. Different alkyl and aryl groups in the pyrazole ring are compatible with the reaction conditions; they do not influence the reactivity notably. It is noteworthy that the ring-opening of the epoxide is highly regioselective in nearly all cases. Pyrazole and disubstituted pyrazoles **4h**–**k** exclusively lead to the secondary amino alcohols **2** and **3**. However, with **4b**–**g** the substitution pattern of the pyrazole ring has a pronounced influence on the product ratio and only the *tert*-butyl and trifluoromethyl groups induce fairly good distand-selectivities (>80%; entries 5, 6, 9 and 10) in both series. Nevertheless, the different reaction products can be purified and separated chromatographically, though not all compounds were isolated in pure form.

The composition of the reaction mixture and the structure of the products are easily determined by proton and



2a-k R = Me
3a-k R = Ph

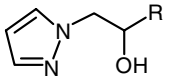
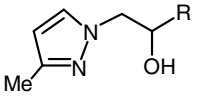
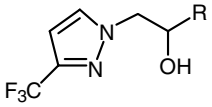
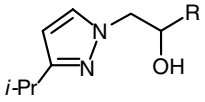
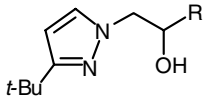
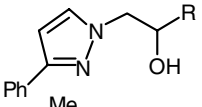
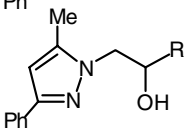
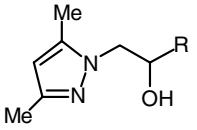
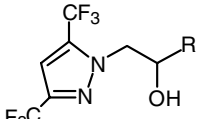
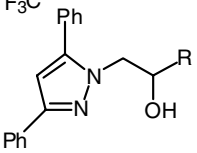
4a-k

5 R = Me
6 R = Ph

7 R = Me
8 R = Ph

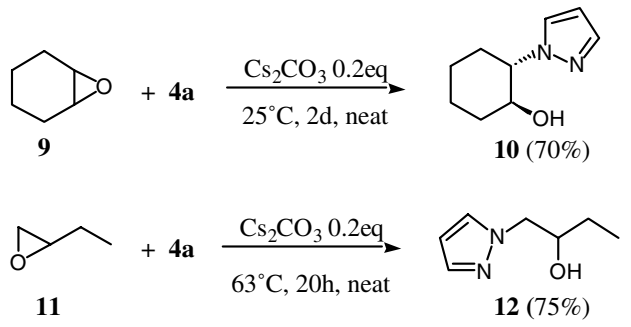
Scheme 1. Regiochemistry of the nucleophilic ring-opening of mono substituted oxiranes.

Table 1. Regioselective preparation of various hydroxyethylpyrazoles from propylene oxide **5**[a] and styrene oxide **6**[b] in the presence of Cs_2CO_3

Entry	Pyrazole	Products[c] **2** and **3**		Side products (isomers)[d]	Isolated yield(%)[e]
1	Pyrazole **4a**		Quant		**2a** R = Me, 95%[f]
2			Quant		**3a** R = Ph, 80%
3	3-Methyl-pyrazole **4b**		60%	40%	**2b** R = Me, 70%[g]
4			40%	60%[h]	**3b** R = Ph, 95%[g]
5	Trifluoromethyl-pyrazole **4c**		80%	20%	**2c** R = Me, 60%
6			>90%	5–10%	**3c** R = Ph, 80%[g]
7	3-*iso*-Propylpyrazole **4d**		65%	35%	**2d** R = Me, 70%[g]
8			60%	40%	**3d** R = Ph, 50%
9	3-*tertio*-Butylpyrazole **4e**		90%	5–10%	**2e** R = Me, 85%[g]
10			90%	5–10%	**3e** R = Ph, 61%
11	3-Phenylpyrazole **4f**		80%	20%	**2f** R = Me, 88%[g]
12			70%	30%	**3f** R = Ph, 90%[g]
13	5-Methyl-3-phenylpyrazole **4g**		80%	20%[h]	**2g** R = Me, 75%
14			80%	20%[h]	**3g** R = Ph, 60%
15	3,5-Dimethylpyrazole **4h**		Quant	—	**2h** R = Me, 89%[f]
16			Quant	—	**3h** R = Ph, 85%[f]
17	3,5-Bis-trifluoro-methyl-yl-pyrazole **4i**		Quant	—	**2i** R = Me, 70%
18			Quant	—	**3i** R = Ph, 75%
19	3,5-Diphenyl-pyrazole **4k**		Quant	—	**2k** R = Me, 95%
20			Quant	—	**3k** R = Ph, 90%

[a] Propylene oxide (1 mL), pyrazole (1 mmol), Cs_2CO_3 (0.2 mmol), rt (25 °C), 16–22 h without solvent in a small flask.
[b] Styrene oxide (2 mmol), pyrazole (1 mmol), Cs_2CO_3 (0.5 mmol), trifluorotoluene (5 mL), reflux (102 °C), 16–18 h.
[c] Analysis of the crude reaction product by ^1H NMR after filtration and evaporation of the solvent.
[d] Generally not characterized; mainly compounds **2** and **3** R_1 = H, R_2 = substituent.
[e] Flash chromatography: ether or ethylacetate/petroleum ether, mixtures or crystallization from petroleum ether/ether.
[f] 50 mmol scale.
[g] The mixture was not separated.
[h] Three isomers.

carbon NMR analysis.[20,21] Several characteristic signals confirm the presence of the β-amino alcohol side chain with the secondary OH group. The respective ^{13}C signals for CH–OH (**2h**, 67.4 and **3i**, 74.0 ppm) and CH_2–N (**2h**, 54.9 and **3i**, 56.2 ppm) agree well with the ABM pattern (**2h**, 4.06, 3.88, 3.73 and **3i**, 5.26, 4.43, 4.14 ppm) in the 1H NMR spectrum. In the compounds from propylene oxide the doublet ($J = 6$ Hz) of the methyl group (**2h**, 1.13 ppm) is a useful indicator of an effective ring-opening of the epoxide. The N-substitution of unsymmetrical pyrazoles may occur at both nitrogen atoms and mixtures of isomers were obtained with camphorpyrazole[8a] or menthylpyrazole.[22] However, in many cases substitution takes place at the least hindered nitrogen with respect to the pyrazole substituent[23] and consequently the 3-substituted substrates **2** and **3** (R_1 = substitutent, R_2 = H) are the main products. In the case of 5-methyl 3-phenylpyrazole **4g**[24] the structure is confirmed by NOESY experiments and it should be noted that the regioselective epoxide cleavage is comparable to the reaction of the monosubstituted 3-phenylpyrazole **4f**.



Scheme 2.

In order to check the broader generality of our reactions we also submitted an internal epoxide and another aliphatic terminal oxirane to our reaction conditions. Cyclohexene oxide **9** as well as 1,2-epoxybutane **11** were easily tansformed into the β-hydroxyalkylpyrazole derivatives **10**[25] and **12**, respectively, in good yields and excellent regioselectivities (Scheme 2).

In summary, caesium carbonate is a good catalyst for the regioselective ring-opening of terminal epoxides under very mild reaction conditions. Propylene oxide reacts at room temperature whereas styrene oxide requires refluxing temperature in trifluorotoluene as solvent. The transformation is general and preparatively useful; the observed regioselectivities, with respect the ring substitution of the pyrazole, but also the generation of secondary alcohols are acceptable and these type substrates have already found an application as ligands in metal catalyzed reactions.[26]

Acknowledgements

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20. Typical procedure with propylene oxide: the pyrazole (1 mmol), propylene oxide (1 mL) and Cs_2CO_3 (72 mg, 0.2 mmol) are stirred for the indicated time at room temperature. The propylene oxide is evaporated and the residue taken up in dichloromethane (1 mL) and stirred with brine (1–2 × 0.2 mL). The organic solution is separated from the aqueous phase, and dried over $MgSO_4$. After filtration the solvent is evaporated. Often, the product is pure enough for further use, however, it can be purified with flash chromatography or by recrystallization (petroleum ether/ether or petroleum ether/ethylacetate mixtures). *1-(3,5-Dimethylpyrazol-1-yl)-propan-2-ol* (**2h**): Mp 51–52 °C (petroleum ether/ether). Found: C, 62.17; H, 8.98; N, 18.01. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31%; H, 9.15%; N, 18.17%. ^{1}H NMR: $\delta = 5.73$ (s, 1H), 4.06 (m, 2H), 3.88 (dd, $J = 4$, 14 Hz, 1H), 3.73 (dd, $J = 8$, 14 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 1.13 (d, $J = 6$ Hz, 3H). ^{13}C NMR $\delta = 148.1$, 139.99, 105.23, 54.94, 20.62, 13.74, 11.4.
21. Typical procedure with styrene oxide: a mixture of the pyrazole (1 mmol), styrene oxide (240 mg, 2 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol) in trifluorotoluene is stirred and refluxed (102 °C) during (in general) one night. After cooling the reaction mixture is filtered and the residue extracted with ether or dichloromethane (5–10 mL). The combined solutions are dried over $MgSO_4$, filtered and the solvent evaporated. Excess styrene can be evaporated at 50–60 °C under 0.1 mm high vacuum. Often, the product is pure enough for further use, however, it can be purified with flash chromatography or by recrystallization (petroleum ether/ether or petroleum ether/ethylacetate mixtures). *2-(3,5-Diphenyl-1-pyrazolyl)-1-phenylethanol* (**3k**): Mp 85 °C (pentane/toluene). Found: C, 81.06; H, 5.97; N, 8.20. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15%; H, 5.92%; N, 8.23%. ^{1}H NMR: $\delta = 7.94$–7.99 (m, 2H), 7.29–7.52 (m, 13H), 6.67 (s, 1H), 5.4 (br, 1H), 5.26 (dd, $J = 4$, 8 Hz, 1H),

4.43 (dd, $J = 4$, 14 Hz, 1H), 4.3 (dd, $J = 8$, 14 Hz, 1H). ^{13}C NMR $\delta = 151.56$, 146.6, 141.29, 133.32, 130.47, 129.5, 129.25, 129.16, 129.11, 128.9, 128.49, 128.29, 126.4, 126.13, 103.8, 74.01, 56.16.

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24. (a) Compound **3g**: (R_1 = Ph, R_2 = Me) 1H NMR: $\delta = 7.7$–7.8 (m, 2H), 7.20–7.40 (m, 8H), 6.2 (d, $J = 0.8$ Hz, 1H), 5.08 (dd, $J = 3.6$, 7.2 Hz, 1H), 4.9 (s, 1H), 4.14 (dd, $J = 3.6$, 13.8 Hz, 1H), 4.03 (dd, $J = 7.2$, 13.8 Hz, 1H). ^{13}C NMR $\delta = 148.5$, 145.6, 131.0, 129.4, 129.0, 126.3, 125.8, 106.1, 67.4, 55.7, 20.5, 13.8; (b) The regioisomer **8g** (R_1 = Ph, R_2 = Me) was prepared in the presence of $SnCl_4$ ^{1}H NMR: $\delta = 7.73$–7.76 (m, 2H), 7.15–7.34 (m, 2H), 6.98–7.01 (m, 2H), 6.32 (s, 1H), 5.21–5.24 (m, 1H), 4.1–4.4 (m, 3H), 1.99 (s, 3H). ^{13}C NMR $\delta = 150.2$, 140.9, 138.1, 133.3, 128.7, 128.6, 127.9, 127.6, 126.52, 125.5, 103.2, 65.8, 64.1, 11.1 ppm.
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