Selective β-Hydroxyethylation at the N-1 Position of a Pyrazolone: Synthesis of Benzyl 1-(β-Hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate

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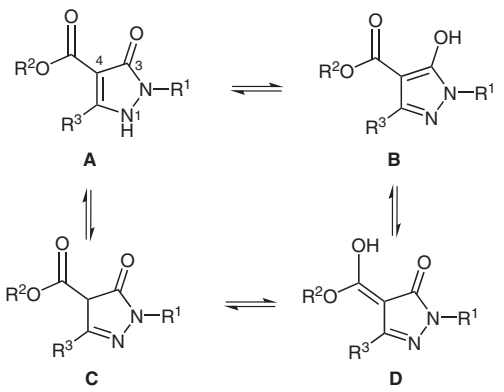
Dedicated to Robert E. Ireland on the occasion of his 79th birthday

Abstract: Selective 2-hydroxyethylation at the N-1 position of benzyl 5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate with epoxides was achieved using either $AlMe_3$ or $Mg(ClO_4)_2$ under mild conditions. The epoxide ring opening was both regioselective and stereospecific. Moderate to excellent yields were obtained from mono- and disubstituted epoxides with the exception of *cis*-dimethyl-2-butene oxide that gave only a trace amount of the product.

Key words: pyrazolones, pyrazole, epoxide, hydroxyethyl, selective, trimethylaluminum, magnesium perchlorate

Tautomerism in pyrazolones has been extensively studied.[1] For example, 3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate[2] can exist as tautomeric forms **A**, **B**, **C**, and **D** (Scheme 1). Not surprisingly, transformations at N-1, C-3–OH, and C-4 positions of pyrazolones are known[3] and often compete against one another. A perusal of the literature indicates that the majority of reactions involving 4-acyl-3-oxo-2,3-dihydro-1*H*-pyrazoles occur at the C3–OH. These include the Mitsunobu reactions,[4] methylations with CH_2N_2[5] or $TMSCHN_2$,[6] acylations,[7] and intramolecular cyclizations.[8] Alternatively, the C-3–OH is first activated using $POCl_3$ and subsequently displaced with other nucleophiles.[9]



Scheme 1

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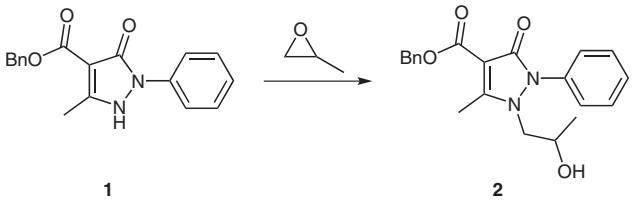
In contrast, only a few reactions are known to occur at the N-1 position of 4-acyl pyrazolones. For example, $(Me)_2SO_4$ (neat) at high temperature (140 °C) or MeOTs in the presence of K_2CO_3 promoted N-methylation.[10] Glycosylations under Lewis acid catalysis are also known to occur mainly at the N-1 position.[11] The sodium salts of 2-phenyl-5-methyl-3-pyrazolone and 2,5-diphenyl-3-pyrazolone have been reported to react with 2-chloroethyl alcohol under reflux to give mixtures of O- and N-hydroxyethyl derivatives.[12] Holzer et al. demonstrated that epichlorohydrin, when used as solvent, reacts with the sodium salt of 4-acylpyrazolones at the N-1 position in modest yields.[13] However, this reaction required high temperature (110 °C) and excess epichlorohydrin to achieve the N-1 versus O-3 selectivity. In our hands, the Holzer protocol only afforded trace amounts of products when benzyl 5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (**1**, Equation 1) was treated with either propylene oxide or epichlorohydrin. Given that epoxides are readily available and that the products derived from epoxide openings can be further transformed at the resulting hydroxyl group, a general procedure for coupling pyrazolones and epoxides at the N-1 position would serve as a valuable tool for accessing diverse set of pyrazolone derivatives.[14] Herein, we describe the development of mild conditions for the regioselective alkylation at the N-1 position of 4-carboxyl pyrazolones with epoxides.



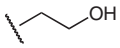
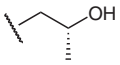
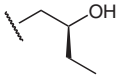
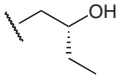
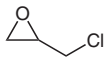
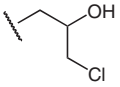
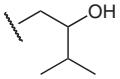
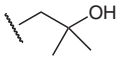
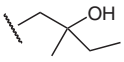
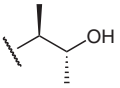
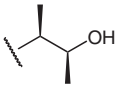
Equation 1

The fact that pyrazoles readily react with epoxides in the presence of a weak base (Cs_2CO_3),[15] whereas pyrazolones require harsh conditions (vide supra), suggests that the carbonyl groups in pyrazolones significantly decrease the nucleophilicity at the N-1 center. We reasoned that activation of the epoxide C–O bond might compensate for the weaker nucleophilicity of the pyrazolone nitrogen. In this regard, a variety of Lewis acids were screened for the re-

action of **1** with propylene oxide (Equation 1). For example, in the presence of various BF_3 (complexed with Et_2O, THF, AcOH) adducts in non-nucleophilic solvents ($CHCl_3$ or PhCl), the desired product **2** was indeed observed (less than 30% conversion by LC-MS). In general, extended reaction times or higher temperatures resulted in the formation of undesired byproducts. Only traces of product **2** were observed in the presence of trialkyl boranes. However, with $ZnMe_2$ a slow but steady reaction led to ca. 80% conversion after 2 days. Ultimately, we found that both Me_3Al (in PhMe or PhCl) and $Mg(ClO_4)_2$ (in MeCN or $CHCl_3$) promoted the complete conversion of **1** into **2** under mild conditions. For example, **2** was isolated in 96% yield after a mixture of **1** (0.31 g), $Mg(ClO_4)_2$ (10 equiv), and propylene oxide (10 equiv) was heated at 35 °C in MeCN for 3 hours.[16]

A number of epoxides were treated with **1** in the presence of either $Mg(ClO_4)_2$ (method A) or Me_3Al (method B). The results are shown in Table 1.[17] These transformations were highly regioselective for the N-1 position of the pyrazolone **1** and for the oxirane carbon bearing the least

Table 1 Reaction of Benzyl 5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**1**) with Various Epoxides[a]

Epoxide	Epoxide (equiv)	Method	Time (h)			Yield (%)
	>10	A[b]	16		**3**	92
	3 2	A[c] B	2 1.5		**4**	83 59
	5	A[d]	2		**5**	93
	5	A[c]	2		**6**	61
	3 1.5	A[c] B	4 1.5		**7**	87 54
	10 5 (*R*) 5 (*S*)	A[e] A[d] A[d]	2 48 48		**8a** **8b** **8c**	57 59 (*S*)[f] 58 (*R*)[f]
	5	B	48		**9**	42
	5	A[e]	72		**10**	30
	10	A[e]	2		**11**	73[g]
	10	A[e]	18		**12**	<5[g]

[a] Yields refer to isolated material. Method A: $Mg(ClO_4)_2$ (1 equiv) in $CHCl_3$ (35 °C).
[b] Method A: $Mg(ClO_4)_2$ (1 equiv) in $CHCl_3$ (35 °C); Method B: Me_3Al (5 equiv) in PhCl (0 °C to 23 °C).
[c] $Mg(ClO_4)_2$ (3 equiv) in MeCN (37 °C).
[d] $Mg(ClO_4)_2$ (3 equiv) in MeCN (50 °C[f]).
[e] $Mg(ClO_4)_2$ (5 equiv) in MeCN (50 °C[f]).
[f] The optical purity was determined to be >95% ee based on chiral HPLC analyses [Chiralpak AD-H (150 × 4.6 mm, 5 μm); isocratic CO_2 (80%)–MeOH (20%) at a flow rate of 4.0 mL/min (35 °C; outlet pressure of 120 bar)].
[g] Racemic material.

substituents.[18] In general, the reactions proceeded more efficiently with less-hindered epoxides, such as propylene oxide and monosubstituted epoxides (i.e., **3**–**6**). The synthesis of **7** illustrates that alkylchlorides are well tolerated under these conditions. Notably, the epoxide ring-opening processes were highly stereospecific. This was demonstrated by the high optical purities (>95% ee) obtained from the reactions of (*R*)- and (*S*)-2-isopropyloxirane (**8b**,**c**). For geminal disubstituted epoxides, prolonged reaction times were required and the yields were modest (i.e. **9** and **10**). There were significant rate differences in the reactions of vicinal disubstituted epoxides: *trans*-2-butene oxide was converted into **11** in 2 hours with 73% yield, whereas the *cis*-isomer afforded only trace amounts of **12** after 18 hours.

Many reactions of epoxide opening involve the use of aluminum reagents. For example, dialkylaluminum amides formed in situ from trialkylaluminum and amines react with epoxides to give β-amino alcohols.[19] The examples described herein required the use of excess Me_3Al relative to the pyrazolone, indicating that activation of the epoxide may be the rate-limiting step.[20] This is further supported by the fact that the use of a bulkier trialkyl aluminum such as $(i\text{-Bu})_3Al$, or epoxides bearing geminal substituents, led to longer reaction times. Similarly, facile aminolysis of epoxides by alkyl amines in the presence of $Mg(ClO_4)_2$ was ascribed to the activation of the epoxide.[21] The dramatic rate difference observed between *cis*- and *trans*-2-butene oxide is in agreement with coordination of Al or Mg to the oxygen atom with concomitant nucleophilic attack by the pyrazolone nitrogen from the opposite face of the oxirane plane, thus rendering this process highly stereospecific.

In summary, a simple and efficient method for installing β-hydroxyethyl groups to the N-1 position of 5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate has been developed. Under theses conditions, various substituted epoxides were coupled with modest to excellent yields. It is anticipated that this methodology will be applicable to other pyrazolones.

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References and Notes

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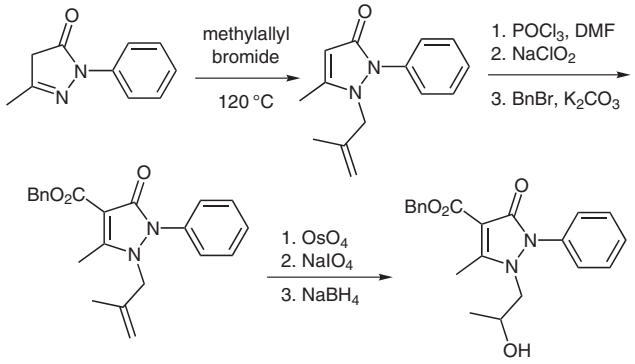
(16) The structure of **2** was confirmed based on an alternative synthesis in ca. 10% overall yield (Scheme 2).

(17) **General Procedures for Method A**
To a stirring suspension of **1** (15.0 g, 49 mmol) in dry MeCN (100 mL) at 0 °C was added $Mg(ClO_4)_2$ (33 g, 146 mmol) in 3 portions over 1 min. After the reaction temperature returned to 0 °C, the epoxide was added. The flask was equipped with a reflux condenser and was heated for the specified time and temperature. The solution was then concentrated under reduced pressure, dissolved in $CHCl_3$ (100 mL), chilled to 10 °C, and quenched with ice-cold water (200 mL). The resulting biphasic solutions were stirred for 1 h and separated. The aqueous layer was extracted with $CHCl_3$ (2 × 50 mL), and the combined organic



Scheme 2

layers were washed with NH_4Cl (sat.), dried over $MgSO_4$, and concentrated. The crude product was purified on SiO_2 (120 g) chromatography eluting with a gradient of 1–2.5% of MeOH–CH_2Cl_2.

General Procedure for Method B

To a stirring suspension of **1** (5.0 g, 16 mmol) in chlorobenzene (25 mL) at 0 °C was added a solution of Me_3Al (2.0 M in toluene, 24 mL, 49 mmol) under nitrogen. To the resulting clear solution was added the epoxide, and the mixture was stirred at 23 °C. The reaction was monitored by LCMS and more epoxide was added if the reaction stalled. Upon completion, the mixture was diluted with THF (100 mL), quenched with $Na_2SO_4 \cdot 10H_2O$ (6 g), and stirred for 24 h. The salts were removed by filtration (glass frit) and washed with EtOAc (100 mL). The filtrate was washed with HCl (1 N, 20 mL) and NH_4Cl (sat., 20 mL), dried over $MgSO_4$, and concentrated. The crude product was purified on SiO_2 (40 g) chromatography eluting with 25–75% of EtOAc in hexane.

(18) All compounds were characterized by ^1H NMR and LC-MS to be >95% pure except for **3** that was further derivatized via the mesylate. Selected ^1H NMR [(400 MHz, $CHCl_3$-d_1), δ in ppm] data are provided for compounds listed in Table 1:
Compound **4**: 0.95 (d, *J* = 6.26 Hz, 3 H), 2.65 (s, 3 H), 3.38 (dd, *J* = 14.87, 1.76 Hz, 1 H), 3.43 (s, 1 H), 3.65 (dd, *J* = 14.97, 9.88 Hz, 1 H), 3.94–4.05 (m, 1 H), 5.23 (s, 2 H), 7.20–7.39 (m, 5 H) 7.39–7.49 (m, 5 H).
Compounds **5** and **6**: 0.74 (t, *J* = 7.43 Hz, 3 H), 1.18–1.37 (m, 2 H), 2.67 (s, 3 H), 3.55 (d, *J* = 13.30 Hz, 1 H), 3.61–3.77 (m, 2 H), 5.27 (d, *J* = 3.52 Hz, 2 H), 7.27–7.39 (m, 5 H), 7.41–7.51 (m, 5 H).
Compound **7**: 2.68 (s, 3 H), 3.21–3.34 (m, 2 H), 3.65–3.78 (m, 1 H), 3.80–3.90 (m, 1 H), 4.02–4.12 (m, 1 H), 5.16–5.31 (m, 2 H), 5.73 (br s, 1 H), 7.28–7.35 (m, 5 H), 7.36–7.51 (m, 5 H).
Compound **8**: 0.68 (d, *J* = 6.85 Hz, 3 H), 0.74 (d, *J* = 6.85 Hz, 3 H), 1.49 (dd, *J* = 12.81, 6.75 Hz, 1 H), 2.67 (s, 3 H), 3.25 (br s, 1 H), 3.46–3.53 (m, 1 H), 3.58–3.64 (m, 1 H), 3.70–3.80 (m, 1 H), 5.29 (q, *J* = 12.78 Hz, 2 H), 7.28–7.41 (m, 6 H), 7.42–7.50 (m, 4 H).
Compound **9**: 0.95 (s, 6 H), 2.65 (s, 3 H), 3.77 (s, 2 H), 4.79 (s, 1 H), 5.21 (s, 2 H), 7.23 (d, *J* = 7.43 Hz, 2 H), 7.27–7.33 (m, 1 H), 7.37 (q, *J* = 7.50 Hz, 3 H), 7.42–7.47 (m, 2 H), 7.50 (t, *J* = 7.73 Hz, 2 H).
Compound **10**: 0.74 (t, *J* = 7.53 Hz, 3 H), 0.82–0.93 (m, 1 H), 1.02 (s, 3 H), 1.23–1.43 (m, 2 H), 2.72 (s, 3 H), 3.68–3.89 (m, 2 H), 5.30–5.33 (m, 2 H), 7.21–7.27 (m, 3 H), 7.29–7.37 (m, 3 H), 7.42–7.53 (m, 4 H).
Compound **11**: 1.05 (d, *J* = 6.1 Hz, 3 H), 1.41 (d, *J* = 7.2 Hz, 3 H), 2.12 (d, *J* = 3.3 Hz, 1 H), 3.75–3.85 (m, 1 H), 2.70 (s, 3 H), 3.87–3.97 (m, 1 H), 5.29 (s, 2 H), 7.22–7.29 (m, 3 H), 7.29–7.35 (m, 2 H), 7.35–7.42 (m, 1 H), 7.42–7.51 (m, 4 H).

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