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PREPARATION OF CHIRAL 5,6-TRANS-DISUBSTITUTED PHENANTHROLINES FROM PHENANTHROLINE-5,6-EPOXIDE

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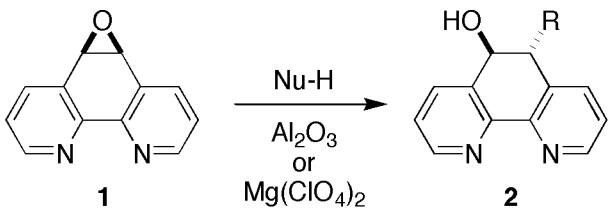
Abstract – A new preparative route to chiral aminoalcohol derivatives of 5,6-dihydro-1,10-phenanthroline is described. Ring opening of 1,10-phenanthroline-5,6-epoxide (**1**) with a variety of nitrogen nucleophiles was accomplished using magnesium perchlorate as an effective Lewis acid and compared to reactions catalyzed by alumina.

1,10-Phenanthroline[1-3] and its congeners have found numerous applications as versatile ligands; recent examples include their use in asymmetric catalysis[4] and bioaffinity assays.[5] An increased interest in applying 1,10-phenanthroline templates in molecular recognition processes has resulted in renewed preparative efforts towards functionalized phenanthroline ligands.

In connection with our study of phenanthroline substituent effects on catalytic activity, we explored functionalization in the 5- and 6-positions. To date, direct methods for the halogenation,[6-8] nitration,[9,10] and oxidation[11-14] at C_5/C_6 have been described. However, the preparation of phenanthroline derivatives with stereogenic centers in the B-ring is uncommon.[15] We herewith report a practical method for the synthesis of known and new chiral 5,6-dihydrophenanthrolines derived from ring opening reactions of epoxide **1** with a variety of nitrogen nucleophiles (aniline, 2-bromo-, 2-chloro-, and 2-cyanoaniline, 2- and 4-ethylaniline, benzylamine, and sodium azide), as outlined in Scheme 1.



Previously, Moody and co-workers[11] reported reactions of epoxide (**1**) with aniline derivatives pre-adsorbed on basic alumina. While alumina is well precedented as a catalyst for epoxide opening,[16] this method could not be used with 2-cyano- and 2-haloanilines. The authors suggested steric congestion as a reason and, instead, employed more reactive aluminum amide derivatives[17] of these anilines.

While searching for practical methods to new aminoalcohol derivatives (**2**), we employed alumina in reactions of (**1**) with known and new nucleophiles. Using basic alumina (activated Brockmann I) and excess aniline, compound (**2a**) was obtained in variable yields (24-30%).[11] The results improved significantly when more active alumina[18] was employed (Method A). In contrast to previous reports,[11] we found that alumina did catalyze reactions with sterically demanding (Entry 11) and electron-deficient ortho-substituted (Entries 5, 7, 9) anilines. However, the use of alumina has some disadvantages because reactions require excess nucleophile, 3-4 equivalents, and thorough quenching with methanol for complete product recovery. The reactions are also moisture-sensitive, since water deactivates alumina, and often require purification by column chromatography to remove excess amines. We therefore explored other methods and found that magnesium perchlorate[19] is an efficient Lewis acid for ring opening of phenanthroline-5,6-epoxide (**1**). Reactions with 1.0-1.3 equivalents of nitrogen nucleophile in refluxing acetonitrile cleanly gave the corresponding amino alcohols in very good yields and most products could be purified by a single recrystallization (Method B). Moreover, these conditions did not promote side reactions, *i.e.* dehydration, and were suitable for sterically hindered and electronically deactivated ortho-substituted anilines (Entries 6, 8, 10, 12). Method B also extended to nucleophiles such as sodium azide (Entry 15) and benzylamine (Entry 4), which has a significantly higher pK_a value than anilines. Sodium azide could not be used with the alumina method due to poor solubility in dichloromethane.

All compounds were characterized by relevant spectroscopic methods and gave data that were consistent with expected or reported values. Most products were isolated as air-stable solids with sharp melting points. It is interesting to note that products (**2a**) and (**2g**), derived from aniline and 4-ethylaniline, respectively, melt above 200° C. In contrast, aminoalcohols (**2c**-**f**), that contain 2-anilino substituents, have a significantly lower melting point (130-155° C).

In conclusion, we have prepared new chiral 5,6-dihydrophenanthroline amino- and azidoalcohols (**2**) as potential ligands in very good yields, comparing the use of alumina with magnesium perchlorate as catalysts for epoxide opening. This is the first report describing the application of

magnesium perchlorate catalysis to heterocyclic substrate (**1**). Use of either alumina or magnesium catalysis yielded products efficiently with a variety of anilines, benzylamine and sodium azide.

Table 1. Chiral aminoalcohol derivatives (**2a-h**) obtained from 1,10-phenanthroline-5,6-epoxide (**1**).

Entry	Nucleophile	Conditions [a]	Product (R =)	Yield % [b]	Melting Points °C
1	Aniline	Method A	**2a** (NH-C_6H_5)	85 (98) [c]	210 (lit. 206)[c]
2		Method B		86	
3	Benzylamine	Method A	**2b** (NH-$CH_2C_6H_5$)	85	(oil)
4		Method B		87	
5	2-Bromoaniline	Method A	**2c** (NH-2-Br-C_6H_4)	88 (76) [c]	130 (lit. 128) [c]
6		Method B		83	
7	2-Chloroaniline	Method A	**2d** (NH-2-Cl-C_6H_4)	65	155
8		Method B		86	
9	2-Cyanoaniline	Method A	**2e** (NH-2-CN-C_6H_4)	51	149 (lit. 130-131) [c]
10		Method B		73	
11	2-Ethylaniline	Method A	**2f** (NH-2-Et-C_6H_4)	86	146
12		Method B		97	
13	4-Ethylaniline	Method A	**2g** (NH-4-Et-C_6H_4)	83	208
14		Method B		78	
15	Sodium azide	Method B	**2h** (N_3)	87 (73) [d]	83 (lit. 99-100) [e]

[a] Method A: Epoxide (**1**) (0.255 mmol), nucleophile (3-4 eq.), Al_2O_3 (86 eq.),[18] CH_2Cl_2, 25° C, 24-48 h. Method B: Epoxide (**1**) (0.255 mmol), nucleophile (1.0-1.3 eq.), $Mg(ClO_4)_2$ (1.5 eq.), CH_3CN, 80° C, 24-72 h.

[b] Isolated yields after column chromatography or recrystallization. Literature yields are reported in parentheses. All products were characterized by ^1H, ^{13}C NMR, IR and MS spectoscopy.

[c] Reference 11.

[d] Prepared with sodium azide in acetone / water.[20]

[e] Azido alcohol (**2h**) was isolated as hemihydrate.[20]

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