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RUTHENIUM-CATALYZED SYNTHESIS OF SUBSTITUTED 2-HYDROXYMORPHOLINES AND SUBSTITUTED MORPHOLINES

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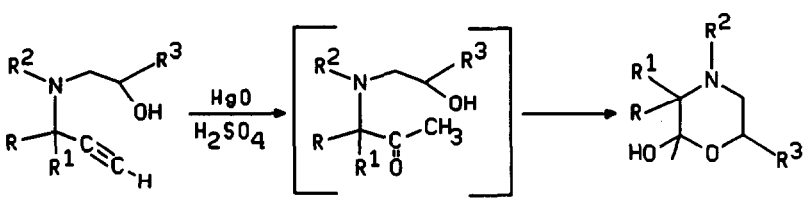
Summary: The reaction of primary amines with peroxides afforded substituted hydroxymorpholines which were then converted to substituted morpholines via dihydrooxazines as intermediates. The reaction appears to proceed through a ruthenium-catalyzed dehydrogenation-cyclization process.

Homogeneous catalysis using ruthenium complexes in organic synthesis has occupied the interests of chemists for the past decade and has been the subject of numerous and diverse investigations. In particular, ruthenium catalyzed alkylation of amines with alcohols has been shown to be an effective method for the preparation of tertiary amines[1-3]. Ruthenium complexes were also found to be effective catalysts for catalytic dehydrogenation[4-6]. For instance, Yoshikawa et. al.[4] have successfully dehydrogenated α,ω-diols to form lactones. In 1963, Dillard et. al.[7] reported that 2-hydroxymorpholines, which could be used as antimicrobial agents, could be prepared from hydroxyaminoacetylene via hydration-cyclization (Scheme I). We now report

Scheme I



that 2,4,6-trialkyl-2-hydroxymorpholines (1) can be produced from primary amines and epoxides via catalytic dehydrogenation-cyclization in which the corresponding dialkanolamines (2) and 2,4,6-trialkylmorpholines (3) are the major by-products.

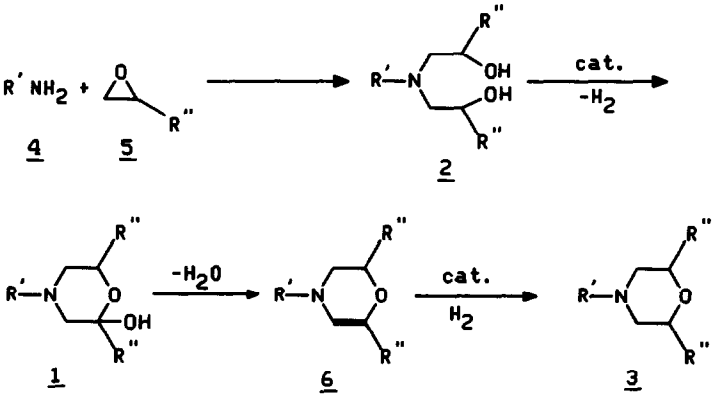
A representative procedure is presented for 4-*tert*-butyl-2,6-dimethyl-2-hydroxymorpholine (**1a**). A 300-ml stirred autoclave with Pyrex liner was charged with a mixture of *tert*-butylamine (**4a**, 14.6 g, 0.2 mol), propylene oxide (**5a**, 34.8 g, 0.6 mol), tributylphosphine (1.6 ml), ruthenium trichloride hydrate (0.52 g), and p-dioxane (20 ml). The reactor was sealed and purged of air. The reaction solution was heated to 180 °C, held at 180 °C for five hours, and then allowed to cool to room temperature. The solvent was removed at reduced pressure. The products were distilled to obtain **1a**[8] (52%) and N-*tert*-butyl-bis-(2-hydroxypropyl)amine (**2a**,12%). No detectable amount of 4-*tert*-butyl-2,6-dimethylmorpholine (**3a**) was obtained. The results of similarly reacting other amines with epoxides are summarized in Table 1.

Table 1. Reactions of Primary Amines with Epoxides

Entry	Amine	Epoxide	Temp. (°C)	Yield (%)		
				1	2	3
1	**4a**	**5a**	180	52	12	<1
2	**4b**	**5a**	165	32	50	<1
3	**4c**	**5a**	180	17	25	43
4	**4a**	**5b**	180	61	30	<1
5	**4a**	**5a**	220	14	8	54

The results show that reaction of **4a** with **5a** produced mostly **1**. With the less hindered *n*-propylamine (**4c**), the yield of **1** is decreased and the yield of **3** is increased dramatically (entries 3 and 1, Table 1). The reaction of **4a** with 1,2-epoxybutane (**5b**) also gives a good yield of **1** (entry 4, Table 1). However, the reaction produces more **3** when it is carried out at higher temperature (compare entries 1 and 5, Table 1). These results suggest that decreasing the steric hindrance of the amine or increasing the temperature of the reaction results in a change of the product distribution. For less hindered amines or at higher temperatures, the reaction proceeds to form **3** to a greater extent. On the other hand, more hindered amines or lower temperatures produce a greater proportion of **1**. In addition, **1** was formed highly diastereoselectively, and no other diastereoisomer was observed. Interestingly, **3** was produced much less diastereoselectively. In the reaction of **4c** with **5a** at 180 °C, the **3** was obtained with a methyl *cis/trans* ratio of about 7/4 (entry 3, Table 1). Moreover, in the reaction of **4a** with **5a** at 220 °C, the **3** was obtained with a methyl *cis/trans* ratio of about 1/1 (entry 1, Table 1). Apparently, **1** is the precursor of the corresponding **3**. Hence, Scheme II is suggested as the reaction pathway.

Scheme II



R'=*t*-Bu, *i*-Pr, *n*-Pr, Me, *n*-Bu; R"=Me, Et.
2a: R'=*t*-Bu, R"=Me; **2b**: R'=*i*-Pr, R"=Me; **2d**: R'=Me, R"=Me; **2e**: R'=*n*-Bu, R"=Me.

Since we suggest that 3,4-dihydro-2H-1,4-oxazine (**6**) is the intermediate in the conversion of **1** to **3**, isolation of the intermediate **6** was attempted. Blum et. al.[9] have shown the ruthenium-catalyzed transfer hydrogenation of α,β-unsaturated ketones using carbinols as the hydrogen donors. Thus, if **6** does indeed act as the intermediate, we should be able to isolate it by employing an α,β-unsaturated ketone to scavenge hydrogen. Therefore, *trans*-4-phenyl-3-buten-2-one (**7**) was employed as a trapping agent in the reaction. Not surprisingly, in all cases, **6** was obtained; the results are given in Table 2. These results may provide some

Table 2. The Preparation of 6 from 2 and 7

Entry	Dialkanol-amine	Mole Ratio of H Acceptor/Reactant	Temp. (°C)	Yield of **6** (%)
1	**2a**	1.8	220	56
2	**2b**	2.1	220	57
3	**2d**	1.0	180	65
4	**2e**	1.8	180	51

support for the proposed reaction pathway. It is, of course, also possible that **3** is produced through another reaction pathway, and the α,β-unsaturated ketone somehow inhibits the process. However, we feel this is less probable. In a typical experiment, a mixture of N-methyl-bis-(2-hydroxypropyl)amine (**2d**, 75 g, 0.51 mol), **7** (75 g, 0.51 mol), ruthenium trichloride hydrate (0.626 g, 12.3 mmol), triphenylphosphine (2 g, 17.6 mmol),

and tetraethylene glycol dimethyl ether (30 g) was added to a 250-ml 3-neck flask connected with a fractional distillation column. The reaction was heated to 180 °C under nitrogen, and the products were distilled. The products (organic layer) were then fractionally redistilled to obtain 3,4-dihydro-2,4,6-trimethyl-2H-1,4-oxazine[10] (**6d**, 65%).

References and Notes

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8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.13 (d, J=6.3 Hz, 3H), 1.38 (s, 3H), 1.88 (apparent t, 1H), 2.10 (d, J=10.8 Hz, 1H), 2.78 - 2.88 (m, 2H), 3.96 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.0, 25.4, 25.9, 52.7, 53.0, 55.3, 65.4, 93.2.
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10. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.26 (d, J=5.7 Hz, 3H), 1.75 (s, 3H), 2.46 (s, 3H), 2.55 (d, J=8.6 Hz, 1H), 2.90 (dm, 1H), 4.05 (m, 1H), 4.98 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.8, 19.0, 43.2, 56.0, 68.8, 112.4, 134.0.

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