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The Effect of Different Amine Bases in the Swern Oxidation of β-Amino Alcohols†

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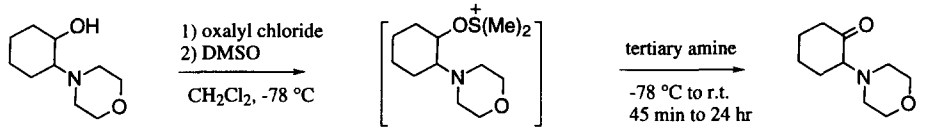
Abstract: Swern oxidation of β-amino alcohols containing tertiary amino groups afforded the corresponding α-amino carbonyl compounds in fair to excellent yield. Yields were dependent on the steric requirement of the amine base used for the reaction and were optimized by the use of *N*-methylpyrrolidine, *N*-ethylpiperidine, or triethylamine, depending on the β-amino alcohol substrate.

Oxidation of β–amino alcohols to the corresponding α–amino carbonyls is synthetically useful because the carbonyl group present in the amino carbonyl compounds readily undergoes homologation,[1] diastereoselective allyboration,[2] and asymmetric reduction.[3] β–Amino alcohols are difficult to oxidize with Jones reagent because the resulting α–amino carbonyl compounds form strong chelates with the chromium containing by-products.[4] Although protection of the amine moiety as an amide alleviates the chelation problem for primary and secondary amines, a practical approach is an oxidant having no cationic metal species. Swern oxidation[5] has been shown to be a favorable method for the oxidation of a few ^{t}BOC protected primary and secondary β–amino alcohols.[1,6] Even though Swern oxidation of selected *N,N*-dibenzyl β–amino alcohols has been documented, a systematic study of this non-metallic oxidation of β-amino alcohols containing tertiary amino groups has not been reported.[7]

For Swern oxidation of regular primary or secondary alcohols, the sterically hindered tertiary amine base *N,N*-diisopropylethylamine, Hunig's base, generally provides optimal carbonyl yield and minimum methylthiomethyl ether side-product.[5b] However, in our initial study of the oxidation of β–amino alcohols, Hunig's base did not furnish optimal yields. Oxidation of 1-(4-morpholino)-2-cyclohexanol (**1**) gave a mixture of the corresponding carbonyl **2** and recovered starting material, in a 3:2 ratio (eq 1).



1 **2** **(1)**

Altering the reaction conditions such as stoichiometry of the oxidant, molarity, and temperature, did not improve the yield of the product. However, extending the reaction time from 45 min to 24 h resulted in an increased albeit sporadic yield of **2**. We speculated that the steric requirement of the amine base was a key factor in the α-amino carbonyl yield. Consequently, we investigated the effect of the steric requirement of seven different amine bases in the Swern oxidation of two β-amino alcohol substrates (**table 1**). In several cases it was found that substituting a non-traditional amine base for the customary Hunig's base or triethylamine significantly increased the yields of the α–amino carbonyl products.

Table 1. The effect of the steric requirement of the amine base in Swern oxidation

tertiary amine base	% recovered[a] **1**	% yield[a] **2**	% recovered[a] **3**[b]	% yield[a] **4**[c]
N,N-diisopropylethylamine	33	65	80	17
triethylamine	24	68	28	70
N,N-diethylmethylamine	25	72	33	64
N-ethylpiperidine	5	93	64	33
N-methylpyrrolidine	42	57	11	89
DABCO	14	86	42	57
pyridine	98	1	85	14

[a] Yields determined by capillary gas chromatography, using internal standards.[8] [b] Compound **3** refers to 1-(1-piperidino)-2,2-dimethyl-propan-2-ol. [c] Compound **4** refers to 1-(1-piperidino)-2,2-dimethyl-propan-2-one.

For Swern oxidation of **1**, *N*-ethylpiperidine was determined to be the optimum amine base giving greater than 90% yield of **2**, a small amount of recovered starting material, and a trace of the methylthiomethyl ether of **1** as a side-product. Additionally, *N*-ethylpiperidine is less expensive than Hunig's base making the procedure economically attractive. For other β-amino alcohols, *N*-methylpyrrolidine afforded optimal yields of the α–amino carbonyl products. In general, it was observed that the sterically demanding Hunig's base did not produce α–amino carbonyl compounds in yields higher than 65%. Optimal yields were obtained by using a tertiary amine base whose steric requirement lies in between Hunig's base and DABCO. To investigate the generality of the reaction, we undertook a systematic study of the Swern oxidation of a wide variety of β-amino alcohols (**table 2**).[9, 10]

Table 2. Oxidation of β–amino alcohols to the corresponding α–amino carbonyls

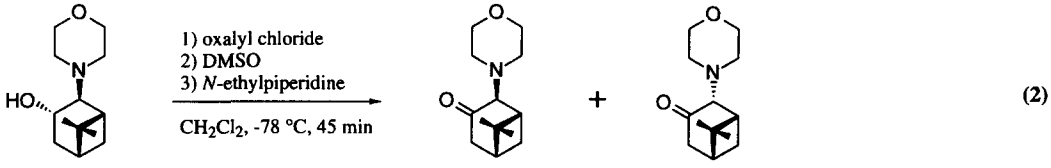
β–amino alcohol[a]	β–amino carbonyl[a]	yield[b]
1-(4-morpholino)-2-cyclohexanol (**1**)	1-(4-morpholino)-2-cyclohexanone (**2**)	93[h,c]
1-(1-piperidino)-2-phenylethanol	1-(1-piperidino)-2-phenylethylketone	86[g,c]
1-(*N,N*-methylbenzylamino)-phenylethan-2-ol	1-(*N,N*-methylbenzylamino)-phenylethyl-2-one	76[g,c]
1-(*N*-cyclohexylamino)-phenylethan-2-ol	1-(*N*-cyclohexylamino)-phenylethyl-2-one	65[g,d]
1-(1-piperidino)-2,2-dimethyl-propan-2-ol (**3**)	1-(1-piperidino)-2,2-dimethyl-propan-2-one (**4**)	89[i,c]
1-(1-piperidino)-5-hexene-2-ol	1-(1-piperidino)-5-hexene-2-one	88[g,c]
1-(4-morpholino)-heptan-2-ol	1-(4-morpholino)-heptan-2-one	87[g,c]
1-(1-pyrrolidino)-2-cyclohexanol	1-(1-pyrrolidino)-2-cyclohexanone	86[g,c]
1-(*N*-isopropylamino)-4-hexene-2-ol	1-(*N*-isopropylamino)-4-hexene-2-one	53[h,f]
1-(*N*-hexylamino)-2-cyclohexanol	1-(*N*-hexylamino)-2-cyclohexanone	51[h,f]
1-(*N*-hexylamino-*N*-^{t}BOC)-2-cyclohexanol	1-(N-hexylamino-*N*-^{t}BOC)-2-cyclohexanone	87[h,e]
1-(*N*-benzylamino)-2-cyclohexanol	1-(*N*-benzylamino)-2-cyclohexanone	52[g,f]
N-benzyl-*N*-methylethanol-amine	*N*-benzyl-*N*-methylethanal-amine	80[g,f]
2-(4-morpholino)-3-hydroxy-7-dimethyl bicyclo [3.1.1]heptane (**5**)	2-(4-morpholino)-3-oxo-7-dimethyl bicyclo[3.1.1] heptane (**6a, b**)	89[h,f]

[a] All materials were characterized by IR, 250 MHz ^{1}H-, ^{13}C-, and ^{13}C-dept 135 NMR. [b] Reactions done on 5 mmol scale; yields not optimized. [c] Isolated mass yield following short path distillation. [d] Isolated mass yield following recrystallization. [e] Isolated mass yield following flash chromatography on silica gel with 1 to 4 ratio of EtOAc:Hex. [f] Yield determined by capillary GC analysis of the crude product mixture. [g] Triethylamine. [h] *N*-ethylpiperidine. [i] *N*-methylpyrrolidine.

The oxidation of secondary amine β–amino alcohol 1-(*N*-cyclohexylamino)-phenylethyl-2-ol, provided the corresponding α-amino carbonyl as a solid, which was purified via recrystallization. However, the purification of the α-amino carbonyl products from other secondary amine β–amino alcohol substrates was thwarted by their rapid polymerization upon standing, even at 25 °C. Therefore, 1-(*N*-hexylamino)-2-cyclohexanol was protected[11] with ^{t}BOC to give the corresponding amide and subsequent Swern oxidation using the amine base *N*-ethylpiperidine, followed by purification using flash chromatography, furnished pure 1-(*N*-hexylamino-*N*-^{t}BOC)-2-cyclohexanone as a stable material in 87% isolated yield.

Unlike ordinary alcohol substrates, β–amino alcohols incorporate an amine moiety of moderate basicity which is potentially capable of disturbing the electrophilic sulfoxonium salt intermediate in the Swern oxidation. The results summarized in **table 2** indicate that the secondary and tertiary amine moieties of the β–amino alcohols did not interfere with the sulfoxonium salt intermediate, and that the difficulty in handling and purification of the products was due to the inherent nature of these secondary amine α-amino carbonyl compounds.

In order to further explore the utility of Swern oxidation, a representative β–amino alcohol containing an epimerizable steriogenic center[12] was included in our study. Accordingly, amino alcohol **5** was oxidized using the representative Swern procedure. Under extended exposure to basic conditions, steric repulsion from the nopinone bridgehead *gem*-dimethyl moiety was expected to induce **6a** to undergo epimerization at C-2, giving the thermodynamic product **6b**. However, Swern oxidition of β–amino alcohol **5** using the amine base *N*-ethylpiperidine gave the sterioisomers **6a** and **6b**, in a ratio of 98:2 (eq. 2).



5 6a (98%) 6b (2%) (2)

This result clearly shows that these oxidation conditions cause a minimal degree of epimerization of sensitive α–amino carbonyl sterogenic centers. In contrast, oxidation of **5** using Jones reagent, followed by basic work-up gives up to 20% epimerization at C-2.[13]

In summary, it was found that Swern oxidation promotes the conversion of β-amino alcohols to the corresponding α–amino carbonyls in fair to excellent yield, provided that an appropriate tertiary amine base is used. Neither the secondary nor the tertiary amine moieties in β-amino alcohols such as 1-(*N*-hexylamino)-2-cyclohexanol or 1-(*N*-pyrolidino)-2-cyclohexanol, interfered with the electrophilic sulfoxonium salt intermediate of the Swern oxidation. However, in some cases, the secondary amine moiety may cause difficulty during purification of the products, due to the inherent nature of the secondary amine α-amino carbonyl compounds. In such cases, β-amino alcohol substrates with secondary amine moieties require protection of the amine group prior to oxidation. The reaction conditions described herein are favorable when sensitive optically active amino alcohol substrates are to be oxidized. For example, minimal epimerization was seen in the Swern oxidation of β-amino alcohol **5**. Because this oxidation procedure utilizes low temperatures, a non-aqueous solvent system, and a short reaction time, the conditions are comparatively mild. Consequently, Swern oxidation is a generally applicable method for the oxidation of β-amino alcohols, and is an attractive alternative to Jones oxidation.

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† Dedicated to professor H. C. Brown on the occasion of his 85th birthday.

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8. Samples of pure α-amino ketones to be used as GC standards were obtained by reoxidation of the crude reaction mixture. For example, **1** was Swern oxidized to give 93% of **2** and 5% recovered **1**, plus a trace of side products. The crude mixture was reoxidized, and upon short path distillation furnished 99% pure 1-(4-morpholino)-2-cyclohexanone (**2**).
9. *N*-benzyl-*N*-methylethanol-amine was purchased from Aldrich and used as received. β-amino alcohol **5** was prepared by hydroboration of the morpholino enamine of (1*R*, 5*S*)-(+)-nopinone. All other β–amino alcohol substrates were prepared by known methods, from commercially available epoxides and amines: Harris, E.; Fisher, B.; Beardsley, D.; Lee, L.; Goralski, C.T.; Nicholson, L.W.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7746.
10. **General procedure for the Swern oxidation of 1-(4-morpholino)-2-cyclohexanol:** All operations were carried out with oven dried glassware, cooled under a stream of dry nitrogen.[14] A 100-mL round bottom flask containing a magnetic stir-bar was charged with dry CH_2Cl_2 (20 mL). Oxalyl chloride (0.6 mL, 7 mmol) was added and the solution cooled to -78 °C. Dimethyl sulfoxide (0.8 mL, 11 mmol) was added dropwise over 10 min. After 10 min, a 1 M solution of 1-(4-morpholino)-2-cyclohexanol (0.93g, 5 mmol) in dry CH_2Cl_2 was added dropwise over 10 min. *N*-ethylpiperidine (3.4 mL, 25 mmol) was added dropwise and the reaction stirred for an additional 45 min. The cooling bath was removed and the reaction mixture was allowed to reach 0 °C. The solution was poured over crushed ice containing 3 M HCl (5 mL), and the organic layer was extracted with dilute aqueous HCl (3 x 10 mL). The combined aqueous portions were cooled to 0 °C, and basified with solid NaOH (4.5 g). Ether extraction (4 x 15 mL) of the basic aqueous portion, followed by drying ($MgSO_4$) and evaporation of the combined orgainc portions, gave the α-amino ketone and *N*-ethylpiperidine mixture. The *N*-ethylpiperidine was evaporated (25 °C, 0.3 Torr), and the crude product was purified by short path distillation to yield 1-(4-morpholino)-2-cyclohexanone as a colorless oil: 0.85g, 92% yield; bp 65 °C (0.3 Torr).
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