FAST AND CHEMOSELECTIVE *N*-DEBENZYLATION ROUTE TO CHIRAL 2-SUBSTITUTED THIOMORPHOLIN-3-ONES

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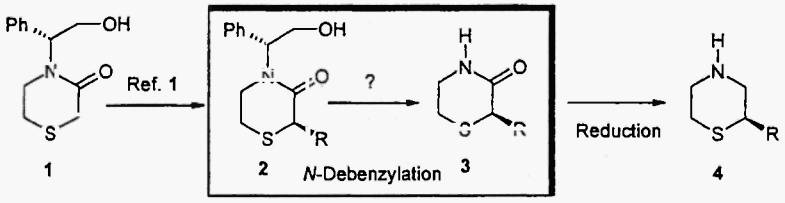
Abstract: Reaction time was found to be the critical parameter for the chemoselective *N*-debenzylation of thiomorpholin-3-one-derivatives with lithium in ammonia. This paper also reports the first preparation of a chiral 2-substituted thiomorpholine building block.

Introduction

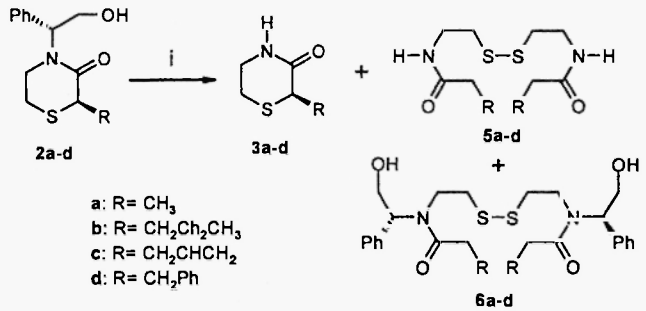
We have recently reported a general method for the diastereoselective alkylation of thiomorpholin-3-ones **1** (1). Our next objective was to cleave the chiral benzyl auxiliary to get a series of enantiomerically pure 2-substituted thiomorpholinones **3**. Final reduction of these compounds would yield the corresponding chiral thiomorpholines **4** (Scheme 1). To our surprise, a review of the literature revealed that such simple building blocks had only been prepared as their racemates (2,3). As the reduction of thiomorpholinone is already documented on racemic derivatives (2,4), our main task was therefore to develop a method for cleaving the *N*-benzyl group.



Scheme-1: N-debenzylation of thiomorpholin-3-ones

Results and Discussions

We had already reported the benzyl cleavage of thiomorpholinone **2d** using lithium in ammonia with an excellent yield (1). However, when the reaction was repeated on other analogues under the same conditions, the main products obtained were the disulfides **5a-c** (Scheme 2). This side-product also formed when the reaction was carried out with thiomorpholinone **2d** however to a much lesser extent (5 %). It is worth noting that the possible side-product **6a-d** resulting from a C-S bond cleavage but having still a benzyl group on were not detected. Considering this fact and the initial results on the benzyl derivative, it was thought that the *N*-debenzylation might occur quicker than the C-S bond cleavage. It was therefore decided to repeat the *N*-debenzylation and to evaluate the ratio of starting material/thiomorpholinone/disulfide. To our surprise, no starting material and no disulfide were detected on the crude NMR after a 5 minutes reaction time. The desired thiomorpholinones were all obtained in 80-90% yield after column chromatography.



Scheme 2: Reagents and conditions: (i) NH_3, Li (3 eq.), -78°C.

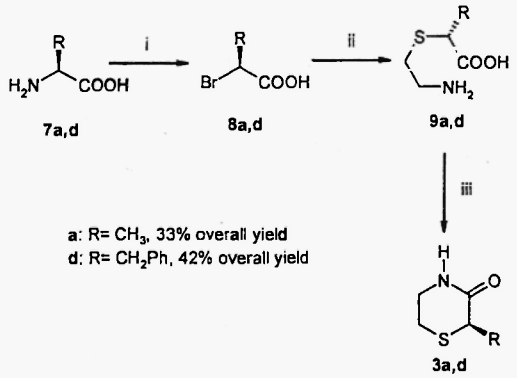
After 30 min, the ratio was completely reverse with the disulfide being the only product (Table 1, entry 1 to 3). However, when the thiomorpholinone **2d** was used, the main product was still the *N*-debenzylated compound **3d** (Table 1, entry 4). The reason for this difference in reactivity has not been identified yet.

Table-1: Ratio **3a-d/5a-d** obtained by *N*-debenzylation of **2a-d** after 5 and 30 min reaction time

Entry	Starting material	Ratio **3/5**	
		5 minutes	30 minutes
1	**2a**	100/0	0/100
2	**2b**	100/0	0/100
3	**2c**	100/0	0/100
4	**2d**	100/0	92/8

The structure of the resulting thiomorpholinones was also unambiguously confirmed by the preparation of product **3a** and **3d** using an alternative route (5) (Scheme 3). The bromoacids intermediates **8a,d** were obtained from corresponding aminoacids *via* a bromodeamination.

This reaction was followed by a coupling with cysteamine to give acids **9a,d**. Finally, ring closure gave the thiomorpholinones **3a,d** in enantiomerically pure form (6). The NMR spectra and the optical rotations were identical to these of the *N*-debenzylated products.

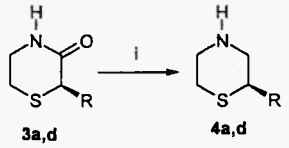


Reagents and conditions: (i) H_2SO_4 1N, KBr, $NaNO_2$, -10°C, 7h; (ii) cysteamine, MeOH, 24h; (iii) 1. *p*-toluene sulfonic acid 2. Na_2CO_3.

Scheme-3

Reductive cleavage of C-S bond (7-9) with metal in ammonia is a known reaction (see ref 7 for a detailed mechanism). To the best of our knowledge, these results are the first examples of a chemoselective *N*-debenzylation in the presence of a C-S bond with a metal in ammonia (10).

Finally, we have carried out the reduction of two thiomorpholinones using LAH and obtained the corresponding enantiomerically pure thiomorpholines **4a,d** (Scheme 4) (11). This is the first report on the preparation of such simple and potentially useful chiral building blocks.



Scheme-4: *Reagents and conditions*: (i) LAH, THF, 30h, rt.

Conclusions

In conclusion, we have developed a process for the selective cleavage of a benzyl group in the presence of a C-S bond using lithium in ammonia. This general method has allowed us to prepare new enantiomerically pure thiomorpholinones and thiomorpholines. The use of these new building blocks will be reported elsewhere.

Acknowledgments

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References

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6. **3a** $[\alpha]_D^{19}$ +45 (0.1, ethanol); **3d** $[\alpha]_D^{19}$ +34 (0.1, ethanol).
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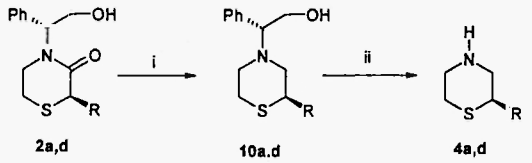
10. In a typical experiment, lithium (3 equiv.) was added to a solution of liquid ammonia (20 mL) at -78°C under a nitrogen atmosphere. A solution of thiomorpholin-3-ones derivatives **2a-d** (1 mmol) in THF (10 mL) was slowly added. The solution was stirred at -78°C for 5 min under a nitrogen atmosphere. The reaction was then quenched by addition of water (0.1 mL) and the mixture stirred at rt for 30 min. The solution was filtered and concentrated under reduced pressure. Purification was carried out by column chromatography to afford desired compound **3a-d** in 80-90% yield. **3a** $[\alpha]_D^{19}$ +45 (0.1, ethanol); **3b** $[\alpha]_D^{19}$ +48 (0.1, ethanol); **3c** $[\alpha]_D^{19}$ +40 (0.1, ethanol); **3d** $[\alpha]_D^{19}$ +34 (0.1, ethanol).

11. The preparation of compound **4a** was also carried out using an alternative route. $[\alpha]_D^{19}$ –17 (0.1, ethanol).



Reagents and conditions: (i) LAH, THF, 30h; (ii) Pd/C, H_2, MeOH, 24h.

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