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Oxidation of carbamate-protected alkylhydrazines to the corresponding hydrazones under Swern conditions

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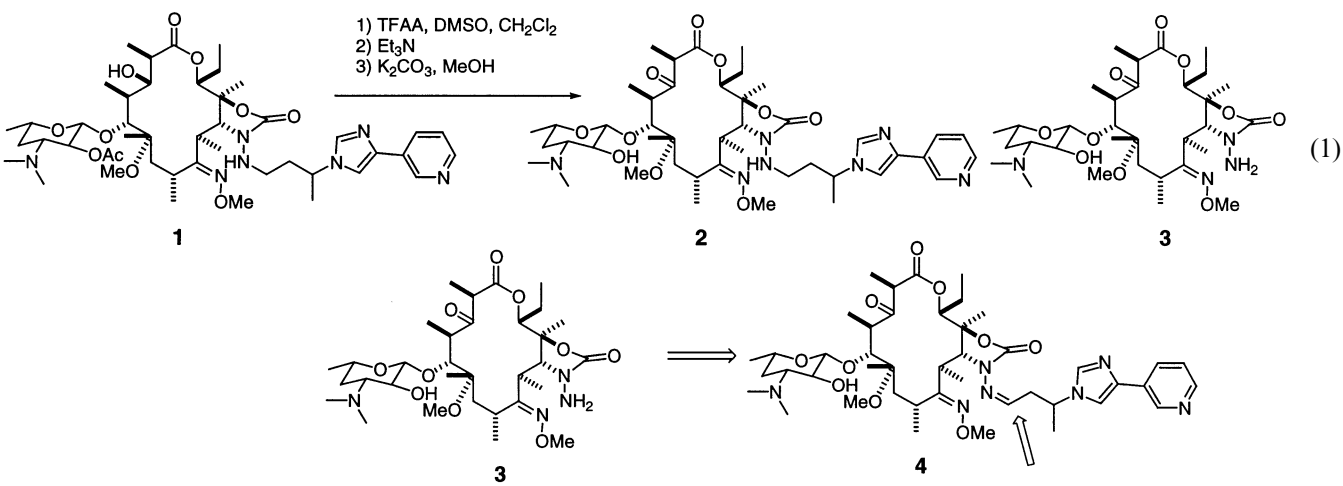
Abstract—Carbamate protected alkylhydrazines have been found to oxidize cleanly to the corresponding hydrazone under Swern conditions. The reaction works on hydrazines with primary, secondary, and branched alkyl groups.

In the course of scaling a synthesis of a novel macrolide antibiotic, the oxidation depicted in equation 1 was examined. Following the Swern oxidation[1] of the C-3 alcohol of **1** (reverse order of addition, run at −10°C), deprotection, and chromatography, the desired ketone **2** was found to contain 35% of a second macrolide that was determined to be structure **3**. Closer examination of the oxidation reaction showed formation of the hydrazone (**4**) of the desired **2**, which presumably hydrolyzed to the observed **3**, either in the deprotection or during reverse-phase chromatography. The initial impurity was identified by a series of LCMS experiments.[2] Repeating the oxidation at −80°C reduced this unwanted side reaction to less than 5%; however we were intrigued as to the generality of this reaction.

A literature search revealed few examples of the oxidation of unactivated hydrazines.[3,4] We therefore decided to synthesize a series of simpler hydrazines and examine this oxidation more closely. The starting hydrazines were synthesized from the corresponding aldehydes via hydrazone formation followed by reduction of the hydrazones with borane. This preparation provided authentic samples of the hydrazones with which to compare the oxidation products.



(1)

Keywords: hydrazine; hydrazone; oxidation; Swern oxidation.

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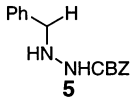
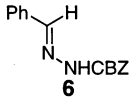
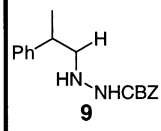
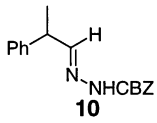
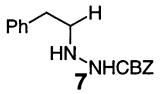
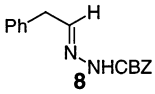
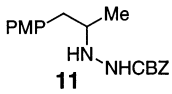
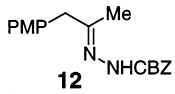
Table 1.[a]

Starting Material	Product	Isolated Yield	Starting Material	Product	Isolated Yield
 **5**	 **6**	87	 **9**	 **10**	84
 **7**	 **8**	80	 **11**	 **12**	76

[a] Reactions were carried out using 2:1 CH_2Cl_2:DMSO as solvent and 2.2 equivalents of TFAA at −10°C, 1 h, followed by triethylamine. For details see Ref. 5.

These oxidations turned out to be remarkably facile, with yields ranging from 76 to 87%. The reaction can be run at temperatures between −78 and −10°C with no notable difference on yield or purity (Table 1).[5] A SO_3–pyridine oxidation[6] on compound **5** also provided hydrazone **6**, albeit in lower yield (55%). Primary, secondary, and branched alkylhydrazines all underwent oxidation under the conditions described without significant differences in the yield.

This is the first example of which we are aware of the oxidation of an otherwise unactivated hydrazine to the corresponding hydrazone using a sulfur-based oxidation system.

References

1. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
2. The impurity was identified by LCMS, and the crude reaction mixture was then treated with aqueous acetic acid and the hydrolysis was monitored by LCMS. The impurity tentatively assigned as the hydrazone based on molecular weight disappeared with simultaneous growth of impurity **3** and pyridylimidazole (identified by mass and independent synthesis). The corresponding aldehyde had previously been demonstrated to undergo retro-Michael reaction under the conditions employed to yield pyridylimidazole and crotonaldehyde (unpublished results of T. Kaneko and W. McMillen). These results convinced us of the presence of the hydrazone in the oxidation reaction and led us to undertake this study.
3. Unactivated hydrazines are hydrazines that do not contain additional functionality alpha to the hydrazine that would facilitate oxidation at that carbon, such as aromatic rings, electron withdrawing groups, or the like. (a) With monochloroamine: Ferrizol, M.; Gazet, J.; Cohen-Adad, M.-T. *Bull. Soc. Chim. Fr. I* **1984**, 180–188; (b) with $KMnO_4$: Sucrow, W.; Grosz, K.-P. *Chem. Ber.* **1976**, *109*, 2154–2158; (c) via elimination of a TMS hydrazine: West, R.; Ishikawa, M. *J. Am. Chem. Soc.* **1967**, *89*, 4981–4984.
4. Oxidation of activated hydrazines: (a) with $KMnO_4$: Bailey, J. R.; Read, W. T. *J. Am. Chem. Soc.* **1914**, *36*, 1747–1766; (b) with HNO_3 and H_2SO_4: Cugnon de Sevricourt, M.; Robba, M. *J. Heterocycl. Chem.* **1977**, *14*, 777–780; (c) with bromine: Grundmann, C.; Schroeder, H.; Ratz, R. *J. Org. Chem.* **1958**, *23*, 1522.
5. A typical procedure is as follows: A solution of **5** (0.25 g, 1.0 mmol) in CH_2Cl_2 (1 mL) and DMSO (0.5 mL) was cooled to −10°C, and TFAA (0.31 mL, 2.2 mmol) was added dropwise. The solution turned bright yellow. After 1 h, triethylamine (0.54 mL, 3.9 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 2 h. The reaction was partitioned between 2 mL EtOAc and 2 mL brine. The brine layer was extracted two more times with 2 mL of EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and filtered. The solution was concentrated to provide **6** as a thick oil (0.22 g, 0.87 mmol, 87%). The material was identical in all aspects (^1H NMR, ^{13}C NMR, UV, TLC) to the authentic sample made from benzaldehyde and benzyl carbazate. ^1H NMR (400 MHz, d_4-MeOH) δ 5.23 (2H, s), 7.30–7.44 (7H, m), 7.67–7.72 (2H, m), 7.95 (1H, s); ^{13}C NMR (100.5 MHz, d_4-MeOH) 67.7, 127.0, 128.0, 128.1, 128.4, 128.5, 129.8, 133.9.
6. Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.