

A NOVEL MODIFICATION OF THE RITTER REACTION USING TRIMETHYLSILYL CYANIDE

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Abstract: A new modification of the Ritter reaction using trimethylsilyl cyanide (Me_3SiCN) is described, which converts alcohols to their corresponding formamides in high yields using a convenient procedure. The reaction conditions and mechanism are discussed. In some cases, new formamides are synthesized which cannot be prepared by the classical Ritter reaction. Copyright © 1996 Elsevier Science Ltd

The Ritter reaction¹ provides a useful method to convert alcohols or alkenes to amides by reaction with nitriles in the presence of sulfuric acid. The known reaction pathway involves the protonation of an appropriate alcohol or alkene generating a carbocation, which adds to the nitrile, followed by hydrolysis to the corresponding amide.

During the synthesis of an important tachykinin NK_3 antagonist and its analogs,² we needed multigram quantities of a key intermediate (2). The classical Ritter reaction³ of N-benzyl-4-hydroxy-4-phenylpiperidine (1) with NaCN, and concentrated sulfuric acid in acetic acid as solvent, gave the alkene (3) as major product (80%) instead of the expected formamide (2) (17%)⁴ (Scheme 1). However, reaction with acetonitrile under the same conditions gave the expected acetamide (4) in 95% yield. In view of this, we thought to try a more nucleophilic 'HCN' equivalent, such as trimethylsilyl cyanide (Me_3SiCN), in the Ritter type conversion of (1) to (2). This gave us the desired formamide (2) in good yield (70%). The alkene (3) under the same conditions was recovered with little formation of formamide product ((2) : (3) = 6 : 94). A thorough literature search showed no previous example of Me_3SiCN used in the Ritter type reaction. This encouraged us to further study this reagent in this novel application.

Scheme 1

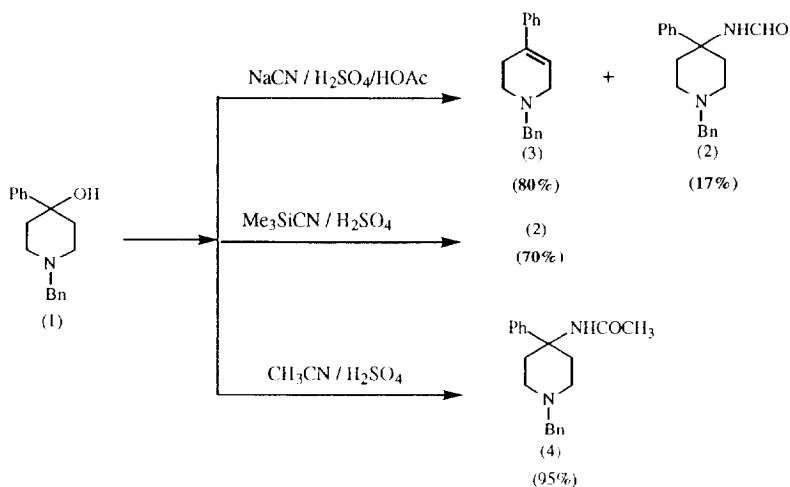


Table 1. Reaction of Alcohols with Me₃SiCN and H₂SO₄

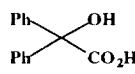
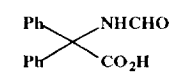
Entry	Reactant	Product*	Mp (°C)	% Yield
1			136 - 137	70
2			192 - 194 (dec.)	95
3			26 - 28	86
4			oil	88
5			121 - 122	94
6			98 - 100	71
7			oil	78
8			134 - 135	78
9			134 - 135	71
10			188 - 190	81
11			100 - 102	80
12			oil	34
13			oil	14
14			79 - 81	34
15		no reaction		0
16		no reaction		0

* All structures are consistent with ¹H NMR, ¹³C NMR, IR, MS and elemental analysis.

The reaction reported herein, involves a slow addition of concentrated sulfuric acid to a mixture of an alcohol and trimethylsilyl cyanide. Since the reaction with sulfuric acid is highly exothermic, the mixture of alcohol and Me_3SiCN is usually cooled in an ice bath under inert atmosphere. The reaction mixture is then warmed to ambient temperature. After the reaction is complete, the mixture is neutralized with NaOH , and the formamide product is purified by recrystallization or chromatography. The results are compiled in Table 1. These results show that better yields are obtained with substituents which stabilize the carbocation intermediate (entries 2, 5). Rearrangement products are observed (entry 12, 13), which also implies a carbocation intermediate in the reaction pathway. Secondary alcohols (entries 13, 14) give lower yields than tertiary alcohols, while no reaction is observed with primary alcohols (entries 15, 16). Pure silylated alcohols (ROSiMe_3) also give the expected formamides (entry 9).

The best ratio of the reactants was determined, and the results are listed in Table 2. A large excess of Me_3SiCN and sulfuric acid does not increase the yield. We found the optimum ratio is alcohol : Me_3SiCN : H_2SO_4 = 1 : 2 : 3. When solid alcohols are used, the reaction mixture may become too thick to stir. In this situation, HOAc may be added as a solvent, and this does not lower the yields.⁵

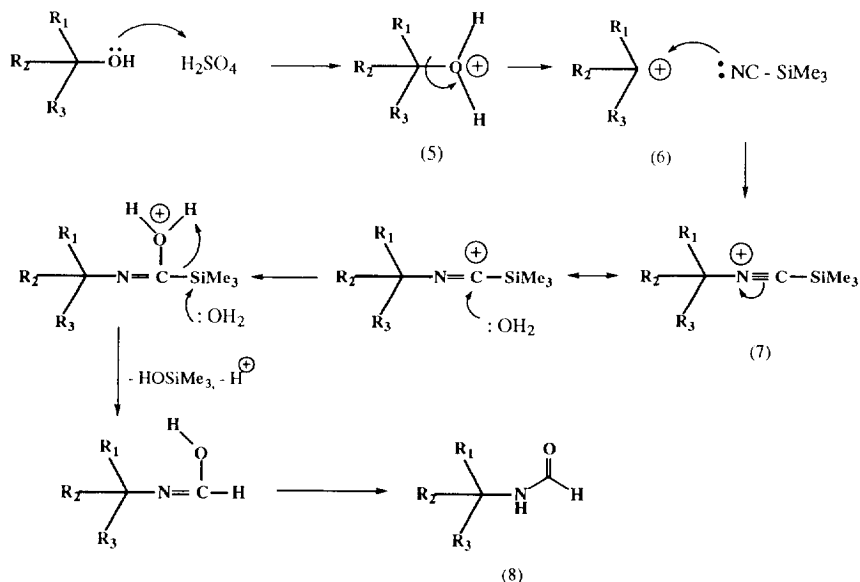
Table 2

	+ Me_3SiCN	+ H_2SO_4	\longrightarrow	
mmols	mmols	mmols		yield%
10	50	115		94
10	50	60		94
10	40	50		93
10	30	40		95
10	20	30		95
10	10	20		79

The mechanism of the reaction is proposed in Scheme 2. The protonation of the alcohol OH group with H_2SO_4 , followed by loss of water gives the carbocation (6). Me_3SiCN reacts quickly with the carbocation to form intermediate (7), which is then hydrolyzed to the formamide (8).

General Procedure: To a mixture of alcohol (10 mmol) and trimethylsilyl cyanide (20 mmol), cooled to -15°C in an ice-salt bath, under nitrogen, is added concentrated sulfuric acid (30 mmol) dropwise with vigorous stirring (caution: highly exothermic). After the addition, the cold bath is removed and the mixture is stirred at ambient temperature for 18 hrs. The mixture is then poured onto ice, and neutralized with 50% NaOH solution to $\text{pH} \sim 7$. The aqueous is extracted with $t\text{BuOMe}$ or CHCl_3 , and the combined organic extracts are washed with brine, and dried over MgSO_4 . The crude product is purified by recrystallization (solid) or flash chromatography (oil).

Scheme 2



In summary, we have developed a novel modification for the Ritter reaction using Me_3SiCN , which provides a convenient and useful way to convert tertiary and secondary alcohols to the corresponding formamides. The ease of handling of Me_3SiCN would also facilitate in the rapid synthesis of combinatorial libraries of formamides. Further study of the reagent with alkenes and other functional groups is currently on-going in our laboratory.

References and Notes

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- Recently Taylor and co-workers (Taylor, G. M.; Baker, S. J.; Gedndy, A.; Pearson, D. J.; Sibley, G. E. *Tetrahedron Lett.* **1996**, *37*, 1297.) have reported predominant alkene formation in the Ritter reaction of N-benzyl-3-hydroxy-3-methylpiperidine. Our experiment with $\text{Me}_3\text{SiCN}/\text{H}_2\text{SO}_4$ also produced the alkene as the sole product.
- Usually the same volume of HOAc as H_2SO_4 was used. In entry 2, 97% yield was obtained with HIOAc as solvent, and 76% yield in entry 6.

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