Pergamon

Tetrahedron Letters 43 (2002) 7991–7994

TETRAHEDRON LETTERS

An easy and efficient method for the synthesis of hydroximoyl chloride from nitro olefin and silyl enol ether

Ming-Chung Yan, Zhijay Tu, Chunchi Lin and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei 116, Taiwan, ROC

Received 24 June 2002; revised 24 July 2002; accepted 26 July 2002

Abstract—Reactions of nitro olefin **1** with silyl enol ether **2** in the presence of $TiCl_4$ in CH_2Cl_2 at 0°C gave high yields of hydroximoyl chloride **3**. When the hydroximoyl chloride **3** was treated with Et_3N in the presence of dipolarophile, the corresponding 2-isoxazolines were obtained. © 2002 Elsevier Science Ltd. All rights reserved.

Nitrile oxides have contributed[1] significantly to modern organic synthesis among the known 1,3-dipoles over a long time, since they readily undergo a variety of 1,3-dipolar cycloaddition reactions. One of the most common methods for the generation of nitrile oxides is Huisgen's[2] base-induced dehydrohalogenation of hydroximoyl halides. Hence, hydroximoyl chlorides are precursors of nitrile oxides and have generated considerable interest in organic synthesis.

Although the utility of nitrile oxides in organic synthesis has been investigated extensively,[1] the synthesis of their precursors has not received much attention. There are only three methods for the preparations of hydroximoyl chlorides. Firstly, hydroximoyl chlorides can be prepared by chlorination of aldoximes.[3] Secondly, the intermediate nitronates, generated from 1,4-addition of various nucleophiles to nitro olefins, were slowly added to the ice cold concentrated hydrochloric acid, and then the corresponding hydroximoyl chlorides were obtained.[4] Thirdly, another method for the synthesis of hydroximoyl chlorides was from conjugated nitro alkenes by the reaction with $TiCl_4$.[5] Yoshikoshi,[6] Seebach,[7] Denmark,[8] and others[9] have reported the successful addition of lithium enolates, enol silanes, enol ethers, or enamines to nitro olefins. We, in fact, found that the third method,[5] by employing silyl enol ethers as nucleophiles, gave the corresponding hydroximoyl chlorides with the concomitant carbon–carbon bond formation in high yields and in one step (Eq. (1) and Table 1).

In the absence of $TiCl_4$, **1a** did not react with **2a**. When only 1 equiv. of **2a** was used in entry 1, α-chlorohydroximoyl chloride[5] was observed (15%) and the yield of the desired product **3a** was low (39%). It was manifest that the chloride anion also has opportunity to attack the intermediate **A** (Scheme 1). Increasing the amount of silyl enol ether can depress the opportunity of intermediate **A** trapped by chloride anion. When 2 equiv. of **2a** was used, α-chlorohydroximoyl chloride was not observed and only high yield of the hydroximoyl chloride **3a** was obtained (Table 1 and the general procedure was in Ref. 10). Danishefsky has reported that 1-methoxy-3-trimethylsilyloxy-1,3-butadiene can be used as an important reagent in Diels–Alder reactions,[11] and the similar result was also observed when **2e** reacted with **1a** through Diels–Alder route (Eq. (2)).[9c] In contrast, the reaction in entry 12 was proposed to proceed through ionic stepwise mechanism under the catalyst of $TiCl_4$. Slow addition of $TiCl_4$ was especially important in entry 12. When $TiCl_4$ was rapidly added, the yield of **3l** was low. However, in entries 1–11, the rate of the addition of $TiCl_4$ did not obviously affect the yields of **3**.

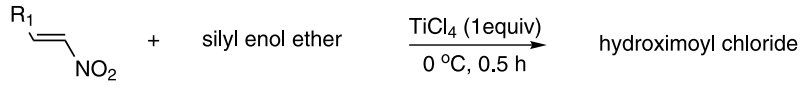
With a view to confirm that the corresponding nitrile oxides can be generated from hydroximoyl chlorides **3** with the keto group intact and also to investigate their cycloaddition reactions with dipolarophiles, the hydroximoyl chloride **3a**, prepared according to Table 1, was treated without isolation with Et_3N in the presence of diethyl maleate. In Eq. (3), the corresponding 2-isoxazoline **4** was successfully produced through intermolecular 1,3-dipolar cycloaddition.

A possible mechanism for the formation of hydroximoyl chlorides **3** is proposed in Scheme 1. Nitro olefin **1** activated with $TiCl_4$ forms the carbocationic interme-

* Corresponding author.

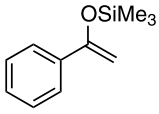
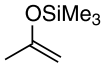
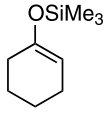
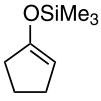
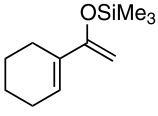
PII: S0040-4039(02)01616-7

Table 1. Preparation of hydroximoyl chlorides **3a**–**3l**



(1)

1 **2** **3**

entry	1 compd. no.	1 R_1	2	3 compd. no.	3 yield (%)[a]
1	**1a**	Ph		**3a**	90
2	**1b**	4-ClC_6H_4		**3b**	99
3	**1c**	4-MeC_6H_4	**2a**	**3c**	79
4	**1d**	2-thiophenyl		**3d**	99
5	**1e**	butyl		**3e**	67
6	**1a**	Ph		**3f**	96
7	**1b**	4-ClC_6H_4		**3g**	93
8	**1c**	4-MeC_6H_4	**2b**	**3h**	89
9	**1e**	butyl		**3i**	79
10	**1f**	H	 **2c**	**3j**	71
11	**1f**	H	 **2d**	**3k**	88
12	**1b**	4-ClC_6H_4	 **2e**	**3l**	67

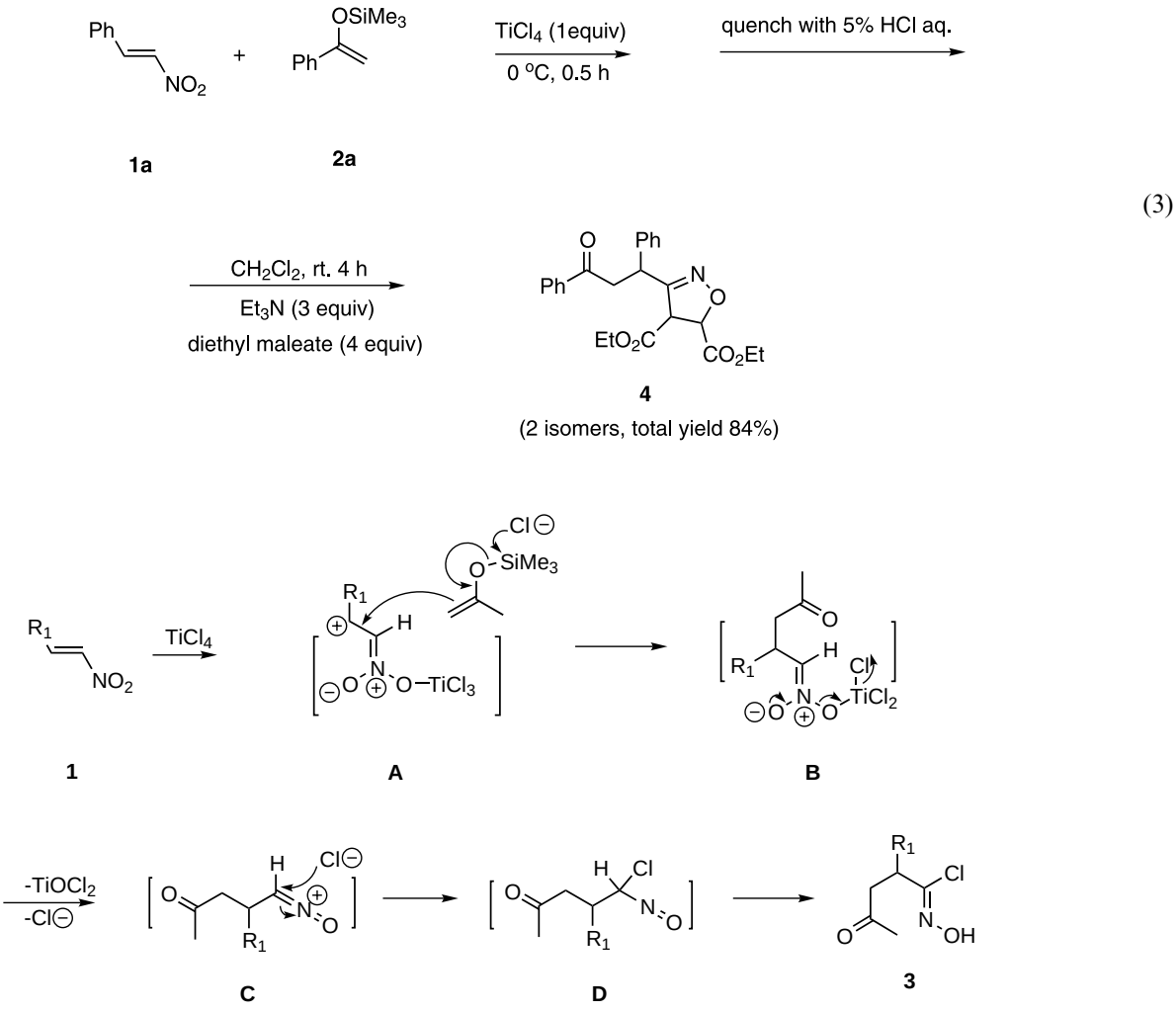
[a] All yields were obtained from ^{1}H-NMR with a known amount of DMF as an internal standard.

1a **2e**

(2)

diate **A**. The intermediate **A** was attacked by silyl enol ether to afford the intermediate **B**. After loss of $TiOCl_2$ and chloride ion from **B**, the intermediate **C** was generated. When the intermediate **C** was trapped by chloride ion, the α-chloronitroso intermediate **D** then isomerized to generate hydroximoyl chloride **3**.

In conclusion, this method is an easy and general route for the synthesis of hydroximoyl chlorides with keto group intact. This methodology has several advantages over the traditional preparative methods of hydroximoyl chlorides from aldoximes by chlorination.[3] The keto group and hydroximoyl chloride function can be



Scheme 1.

introduced in a single step while the traditional method[3] needs multi steps. The reaction condition is mild and all starting materials are commercially available or easily prepared. The reaction time is short and the reaction temperature (0°C) can be easily attained. In addition, the fact that aliphatic nitro alkenes participated in this reaction considerably broadens its scope.

Acknowledgements

Financial support to this work by the National Science Council of the Republic of China is gratefully acknowledged.

References

1. (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410; (b) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719; (c) Esipenko, A. A.; Samarai, L. I. *Russ. Chem. Rev.* **1993**, *62*, 1097.
2. Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345.
3. (a) Chiang, Y. H. *J. Org. Chem.* **1971**, *36*, 2146; (b) Rheinbold, H. *Leibigs Ann. Chem.* **1927**, *451*, 161; (c) Peake, C. J.; Strickland, H. *Synth. Commun.* **1986**, *16*, 763; (d) Liu, K. C.; Shelton, B. R.; How, R. K. *J. Org. Chem.* **1980**, *45*, 3916; (e) Kim, J. N.; Ryu, E. K. *J. Org. Chem.* **1992**, *57*, 6649.
4. (a) Yao, C. F.; Chen, W. C.; Lin, Y. M. *Tetrahedron Lett.* **1996**, *37*, 6339; (b) Yao, C. F.; Yang, C. S.; Fang, H. Y. *Tetrahedron Lett.* **1997**, *38*, 6419; (c) Yao, C. F.; Kao, K. H.; Liu, J. T.; Chu, C. M.; Wang, Y.; Chen, W. C.; Lin, W. W.; Yan, M. C.; Liu, J. Y.; Chuang, M. C.; Shiue, J. L. *Tetrahedron* **1998**, *54*, 791; (d) Kao, K. H.; Yang, C. S.; Liu, J. T.; Lin, W. W.; Fang, H. Y.; Yao, C. F.; Chen, C. *Tetrahedron* **1998**, *54*, 13997; (e) Liu, J. T.; Lin, W. W.; Jang, J. J.; Liu, J. Y.; Yan, M. C.; Kao, K. H.; Wang, Y.; Yao, C. F. *Tetrahedron* **1999**, *55*, 7115.
5. Kumaran, G.; Kulkarni, G. H. *J. Org. Chem.* **1997**, *62*, 1516.
6. (a) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284; (b) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149; (c) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *Org. Synth.* **1990**, *7*, 414.

7. (a) Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 836; (b) Seebach, D.; Brook, M. A. *Helv. Chim. Acta* **1985**, *68*, 319; (c) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413; (d) Seebach, D.; Lyapkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1829.
8. (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857; (b) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859; (c) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853.
9. (a) Cory, R. M.; Anderson, P. C.; Bailey, M. D.; McLaren, F. R.; Renneboog, R. M.; Yamamoto, B. R. *Can. J. Chem.* **1985**, *63*, 2618; (b) Cory, R. M.; Anderson, P. C.; McLaren, F. R.; Yamamoto, B. R. *J. Chem. Soc., Chem. Commun.* **1981**, 73; (c) Richter, F.; Otto, H. H. *Tetrahedron Lett.* **1987**, *28*, 2945.
10. The solution of 1 mmol of nitro olefin **1b** and 2 mmol of silyl enol ether **2b** in 5 mL dry CH_2Cl_2 was cooled to 0°C and 1 mmol of titanium tetrachloride in 5 mL CH_2Cl_2 was slowly added to the solution. After stirring for 0.5 h at 0°C, the solution was added to the 5% ice cold aqueous HCl solution and extracted with CH_2Cl_2. After evaporation CH_2Cl_2, the corresponding hydroximoyl chloride **3g** was obtained. The purification of hydroximoyl chloride **3g** was carried out by flash column chromatography (we use CH_2Cl_2 as eluent and a column with a short package (about 4 cm height) of silica gel, because hydroximoyl chlorides were unstable in silica gel).
3g: Colorless solid. Mp 110–112°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br, 1H), 7.31 (d, $J=8.4$ Hz, 2H), 7.20 (d, $J=8.4$ Hz, 2H), 4.32 (dd, $J=8.4$, 6.0 Hz, 1H), 3.32 (dd, $J=8.8$, 8.4 Hz, 1H), 2.79 (dd, $J=8.8$, 6.0 Hz, 1H). 2.15 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.22, 142.18, 137.02, 133.71, 129.34, 129.05, 47.45, 46.85, 30.27 MS m/z (relative intensity) 259 (M^+, 40), 242 (60), 216 (62), 166 (100). HRMS calcd for $C_{11}H_{11}NO_2Cl_2$ (M^+) 259.0177, found 259.0191.
11. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.