Mercuric Triflate-TMU Catalyzed Hydration of Terminal Alkyne to give Methyl Ketone under Mild Conditions

Mugio Nishizawa,* Mariusz Skwarczynski, Hiroshi Imagawa, and Takumichi Sugihara
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514

(Received September 5, 2001; CL-010871)

Herein developed mercuric triflate-TMU catalyzed hydration of terminal alkyne is a mild procedure to give methyl ketone in excellent yield with high chemoselectivity. By using 0.05 eq of $Hg(OTf)_2{\cdot}(TMU)_2$ and 3 eq of water, hydration takes place at a reasonable rate in acetonitrile.

Hydration of terminal alkyne to give methyl ketone is an important and fundamental functional group transformation. The conventional standard procedure is heating an aqueous methanol solution of alkyne in the presence of HgO and sulfuric acid.[1] Most other methods also require a significant quantity of $HgSO_4$,[2] $Hg(OAc)_2$,[3] or sometimes $FeCl_3$.[4] Heating with a catalytic amount of $NaAuCl_4$,[5] $PdCl_2$,[6] $RhCl_3$,[7] or $PtCl_2$,[8] has also been reported; however, the results were not always satisfactory enough to be realized as new standard procedure. We have developed an efficient olefin cyclization agent, mercuric triflate,[9] and applied it to the syntheses of a variety of polycyclic natural products.[10] The efficiency of this reagent for oxymercuration was also shown by the total synthesis of gelsemine by Sketchamp,[11] and the scope and limitation of the latter reaction were elucidated by us.[12] We have also described novel mercuric triflate-catalyzed condensation of ketone and homoallyl alcohol.[13] Herein we would like to describe that the mercuric triflate-*N*,*N*,*N*',*N*'-tetramethylurea (TMU) complex is a highly effective catalyst for the hydration of terminal alkyne to give methyl ketones under very mild conditions.

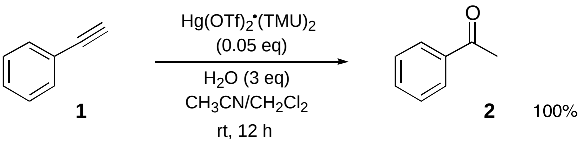

Figure 1.

Upon treatment of phenylacetylene (**1**) with 0.05 eq of mercuric triflate and TMU (0.1 eq) in CH_3CN and CH_2Cl_2 in the presence of 3 eq of water at room temperature for 12 h acetophenone (**2**) was obtained in quantitative yield. The quantity of CH_2Cl_2 was ajusted to make the mixture a nearly homogeneous solution.[14] 3-Phenylpropyne (**3**) also afforded benzyl methyl ketone (**4**) in quantitative yield under the same conditions. Terminal alkyne with a long alkyl chain such as **5**, which required longer reaction period due to its low solubility, still afforded **6** in high yield. A hydroxyl group on the remote position like **7** did not cause any trouble to give **8** in 95% yield. The aldehyde of **9**, double bond of **11**, and acetoxy group of **13** did not interfere with the reaction to give ketones **10**, **12**, and **14**, respectively, in excellent yields. The THP protecting group of **15** was partially cleaved under the reaction conditions and afforded **16** and **17** in 54% and 46% yield, respectively. The acetal group of **18** was not stable enough and produced keto acetal **19** together with keto aldehyde **20** in 68% and 27% yield, respectively. The benzyl

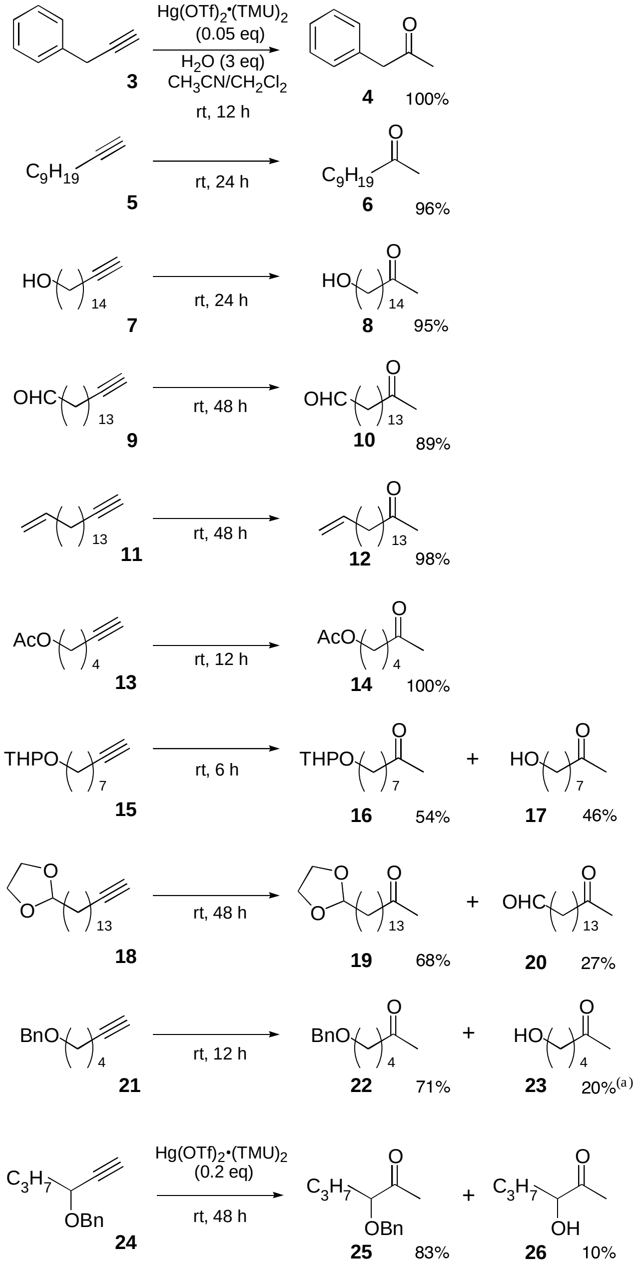

Figure 2. $Hg(OTf)_2{\cdot}(TMU)_2$ catalyzed hydration of terminal alkyne. (a) Exist as a 3:1 mixture of keto alcohol **23** and its hemiacetal.

group of **21** was also partially cleaved affording an equilibrium mixture of keto alcohol **23** and its hemiacetal in 20% yield along with major product **22** in 71% yield. Hydrolysis of **24** is a slow reaction and it required 48 h even by using 0.2 eq of catalyst to give ketone **25** (83% yield) along with keto alcohol **26** in 10% yield.

When the reaction of 6-acetoxyhexyne (**13**) with 0.05 eq of $Hg(OTf)_2 \cdot (TMU)_2$ and 3 eq of H_2O in CD_3CN was monitored by 400 MHz NMR, we detected only the decrease of the starting **13** and increase of ketone **14**, reflecting the slow but very clean reaction. Thus the procedure is simple enough to apply to medium scale synthesis. Following is a challenge to prepare unstable benzyl methyl ketone (**4**) in a gram scale by using 1 mol% of catalyst. A solution of $Hg(OTf)_2 \cdot (TMU)_2$ prepared by mixing HgO (40 mg, 0.19 mmol) and Tf_2O (52 mg, 0.19 mmol), and then TMU (43 mg, 0.38 mmol) in acetonitrile (10 mL) was added to 3-phenyl-1-propyne (**3**) (2.15 g, 19 mmol). After addition of H_2O (1 g, 57 mmol) and then dichloromethane (4 mL), the resulting nearly-homogeneous mixture was stirred at room temperature for 24 h. An aqueous sodium hydrogenecarbonate-sodium chloride solution was added and the organic material were extracted with ethyl acetate. Dried and concentrated material was purified through short pass column chromatography on silica gel by using hexane and ethyl acetate to give **4** (2.42 g, 97% yield).

This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) ''Exploitation of Multi-Element Cyclic Molecules'' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

1 G. W. Stacy and R. A. Mikulec, *Org. Syn.*, Coll. Vol. IV, 13 (1963).

2 H. Schick, B. Roatsch, S. Schramm, H. -D. Gilsing, M. Ramm, and E. Grundemann, *J. Org. Chem.*, **61**, 5788 (1996).

3 S. Janardhanam, A. Balakumar, K. Rajagopalan, L. S. Bai, K. Ravikumar, and S. S. Rajan, *Synth. Commun.*, **23**, 297 (1993).

4 J. P. Damiano and M. Postel, *J. Organomet. Chem.*, **522**, 303 (1996).

5 Y. Fukuda and K. Uchimoto, *J. Org. Chem.*, **56**, 3729 (1991).

6 Y. Fukuda, H. Shiragami, K. Uchimoto, and H. Nozaki, *J. Org. Chem,*. **56**, 5816 (1991).

7 J. Blum, H. Huminer, and H. Alper, *J. Mol. Catl.*, **75**, 153 (1992).

8 P. W. Jennings, J. W. Hartman, and W. C. Hiscox, *Inorg. Chim. Acta*, **222**, 317 (1994).

9 Mercuric triflate is instantaneously prepared *in situ* by mixing yellow mercuric oxide and triflic anhydride in CH_3CN at room temperature. see M. Nishizawa, E. Morikuni, K. Asoh, Y. Kan, K. Uenoyama, and H. Imagawa, *Synlett*, **1995**, 169.

10 a) M. Nishizawa, H. Takenaka, and Y. Hayashi, *J. Org. Chem.*, **51**, 806 (1986). b) M. Nishizawa, H. Yamada, and Y. Hayashi, *J. Org. Chem.*, **52**, 4878 (1987). c) M. Nishizawa, H. Takao, Y. Iwamoto, H. Yamada, and H. Imagawa, *Synlett*, **1998**, 76. d) M. Nishizawa, H. Imagawa, I. Hyodo, M. Takeji, E. Morikuni, K. Asoh, and H. Yamada, *Tetrahedron Lett.*, **39**, 389 (1989).

11 N. J. Newcombe, F. Ya, R. J. Vijn, H. Hiemstra, and W. N. Speckamp, *J. Chem. Soc., Chem. Commun.*, **1994**, 767.

12 H. Imagawa, T. Shigaraki, T. Suzuki, H. Takao, H. Yamada, T. Sugihara, and M. Nishizawa, *Chem. Pharm. Bull.*, **46**, 1341 (1998); M. Nishizawa, T. Kashima, M. Sakakibara, A. Wakabayashi, K. Takahashi, H. Takao, H. Imagawa, and T. Sugihara, *Heterocycles*, **54**, 629 (2001).

13 M. Nishizawa, T. Shigaraki, H. Takao, H. Imagawa, and T. Sugihara, *Tetrahedron Lett.*, **40**, 1153 (1999).

14 The addition of a large quantity of CH_2Cl_2 caused $Hg(OTf)_2$ to precipitate.