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TFA-Mediated Alkyne Hydration Reaction to Synthesize Methyl Ketones

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Trifluoroacetic acid efficiently promotes the hydration of terminal alkynes without the use of other catalysts to afford a wide variety of methyl ketones in good to excellent yields with perfect regioselectivities. This new procedure offers significant advantages over previous synthetic approaches, including brevity, mild reaction conditions, excellent yields and high functional group tolerance.

Keywords: Hydration, Terminal alkyne, Methyl ketone, Trifluoroacetic acid.

INTRODUCTION

The use of water as an inexpensive and environmentally friendly reagent in organic synthesis is an important topic and the hydration of alkynes is a typical example for converting alkynes into carbonyl compounds with a perfect atom economy[1,2]. The classical synthesis of ketones from hydration of alkynes employed a stoichiometric amount of mercury under strongly acidic conditions. Although this process offers very good yields, but it is not an environmentally benign and sustainable approach. The pollution problems associated with the handing and disposal of toxic mercury compounds limited its wide applications[3-5]. Over the past decades, alternative catalytic systems for the alkyne hydration reactions have been extensively explored. Among them, the transition-metal catalysts containing Ru[6,7], Rh[8], Au[9-12], Pt[13,14], Pd[15], Ir[16], Sn-W[17], Fe[18,19], Ag[20-22] and Co[23] have been used for the hydration of alkynes. However, the use of expensive metal-transition limits the exploitation of these methods. Therefore, a metal-free hydration of alkynes has been developed under acidic conditions including concentrated sulfuric acid[24] and catalytic Brønsted acid such as *p*-toluenesulfonic acid[25], trifluoromethanesulfonic acid or trifluoromethanesulfonimide[26]. Despite the advances of these methodologies, many of them require harsh conditions (large excess of strong acid, high temperature, high boiling point solvent) or are particularly limited to some substrates or low functional group compatibility and selectivity. New methodologies from simple substrates and environmentally benign reagents, with high efficiency, under mild conditions, are still a research field of undoubted current attention. Here we report a novel hydration of alkynes using trifluoroacetic acid (TFA) as solvent, without the use of other catalysts, which provides a synthetically practical and convenient process to give a wide variety of methyl ketones with perfect regioselectivities. The unstable enol trifluoroacetates were regarded as the important intermediates in this transformation (Fig. 1). It may be noted that this method is eco-friendly and economical, because it does not involve corrosive H_2SO_4 or any costly noble metal catalysts, especially the solvent TFA is easy to be recycle by distilling operation with medium boiling point (72.4 °C).

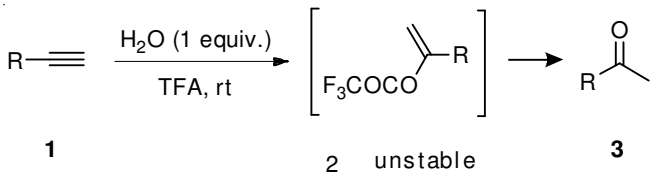


Fig. 1. Hydration reaction of terminal alkynes in trifluoroacetic acid

EXPERIMENTAL

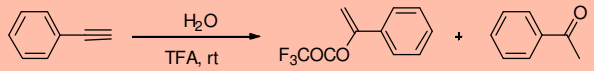
General procedure: A mixture of terminal alkyne (0.5 mmol) and water (1 equiv.) in TFA (1 mL) was stirred at room temperature for 2.5 h, after which TFA was distilled out for reuse. The residue was separated by column chromatography to give the pure sample.

^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.26 and 77 ppm, respectively, chloroform is solvent with TMS as the internal standard. Mass spectra were recorded on a GC-MS spectrometer at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter: 0.25 mm, length: 30 m). All the chemicals were purchased from Aldrich Chemicals.

RESULTS AND DISCUSSION

Table-1 summarizes the results of the reaction of phenylacetylene (**1a**) with water in presence of trifluoroacetic acid at room temperature. First, enol trifluoroacetate (**2a**) was afforded in high yield without additional water in 1 min. Acetophenone was formed in 11 % GC yield and water may come from trifluoroacetic acid solvent or air (Table-1, entry 1). We next examined the effects of using 1 equiv of water in different time (Table-1, entries 2-6). As the reaction time increased from 1 min to 2.5 h, the yield of **3a** increased gradually (Table-1, entries 2-5). For example, the reaction could afford acetophenone with 94 % isolated yield in 2.5 h (Table-1, entry 5). However, the longer time disfavored the reaction and the side-product 1,3-diphenyl but-2-en-1-one was generated from the aldol condensation reaction of acetophenone (Table-1, entry 6). Then the amount of water was surveyed, more water decreased the reaction yields (Table-1, entries 7-8). It is noteworthy that the reaction did not proceed well with co-solvent and it revealed the concentration of TFA was important for the transformation. After some attempts, we considered that the optimized reaction conditions are the following: **1a** (0.5 mmol) and water (1 equiv.) in trifluoroacetic acid (1 mL) at room temperature for 2.5 h (Table-1, entry 5).

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF ACETOPHENONE FROM PHENYLACETYLENE[a]



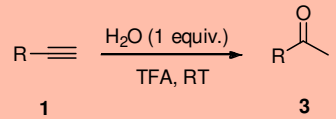
1a 2a 3a

Entry	H_2O	Time	GC yield (%) 2a	3a
1		1 min	85	11
2	1 equiv.	1 min	78	18
3	1 equiv.	0.5 h	43	54
4	1 equiv.	1.5 h	15	80
5	1 equiv.	2.5 h	3	96 (94)[b]
6	1 equiv.	3.0 h	3	91
7	3 equiv.	2.5 h	9	85
8	6 equiv.	2.5 h	11	78

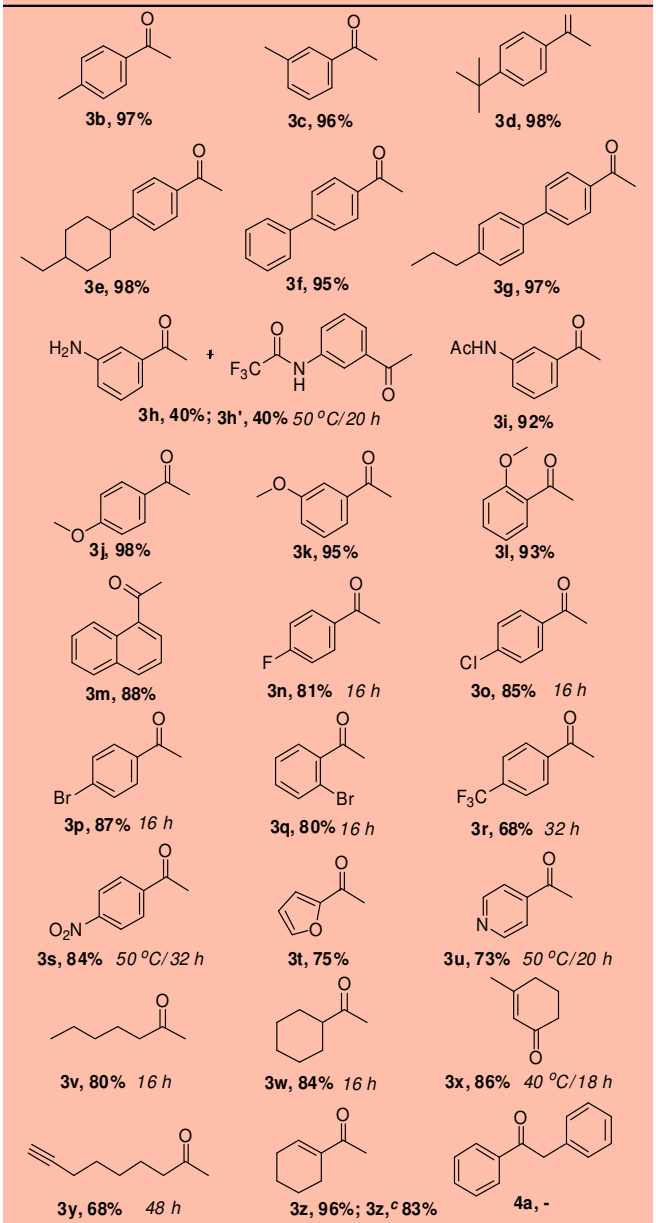
[a]Reaction conditions: phenylacetylene (0.5 mmol) and water in trifluoroacetic acid (1 mL) at room temperature. [b]Number in parentheses is isolated yield of **3a**

With the success in finding the optimum reaction conditions (Table-1, entry 5), the scope and the utility of this method with other terminal alkynes under the standard conditions were also investigated. As shown in Table-2, aromatic terminal alkynes with either an electron-donating or electron-withdrawing group on the benzene ring were able to generate the corresponding products in moderate to excellent yields (**3b-u**). Clearly, the electronic effect plays an important role, as electron-rich substituents on the benzene ring favored the transformation compared to the electron-deficient substituents (**3b-s**). The reaction conditions were compatible with alkyl, amino, alkyloxy, fluoro, chloro, bromo, trifluoromethyl and nitro groups (**3b-s**). Luckily, the unprotected amino and protected amino substituted substrates were efficient in the reaction conditions (**3h-i**). It should be pointed out that the

TABLE-2
TFA-MEDIATED SYNTHESIS OF METHYL KETONES FROM TERMINAL ALKYNES[a,b]



1 3



[a]Unless otherwise noted, the reactions were carried out with **1** (0.5 mmol), water (1 equiv.) and TFA (1 mL) at room temperature for 2.5 h. [b]Isolated yield. [c]The substrate was 1-ethynylcyclohexanol

carbon-halogen bonds were well tolerated and the products containing halogen were afforded smoothly. Especially the aryl bromides and aryl chlorides could be further functionalized (**3o-q**). The stronger electron-withdrawing group (nitro) on the benzene ring need higher temperature and longer time afford corresponding product in good yield (**3s**). Furthermore, heterocycle alkynes can be converted into the corresponding products in good yield as well (**3t-u**). Except for the aryl alkynes, the alkyl alkynes were also found to be suitable substrates for the standard conditions (**3v-z**). Interestingly, the conjugated enone

was formed in high yield from hepta-1-6-diyne (**3x**) and the mono hydrated product was afforded in moderate yield from nona-1,8-diyne (**3y**). Moreover, conjugated enyne allowed the addition of H_2O only at their carbon-carbon triple bond to give the corresponding enone and the ethynylcyclohexane bearing a hydroxyl group also formed the enone product (**3z**). Finally, the hydration of internal aromatic alkyne was evaluated. No reaction occurred with diphenylacetylene. So it is convenient for the selective hydration of terminal alkyne (**4a**).

On the basis of our experimental data and previous reports[27-29], a plausible reaction mechanism for the synthesis of methyl ketones is illustrated in Fig. 2. First, the alkenyl cation intermediate A was generated, followed by nucleophilic attack of CF_3COO- to produce enol trifluoroacetate **2**, which subsequently underwent successive hydrolysis and keto-enol tautomerism to form methyl ketone **3**.

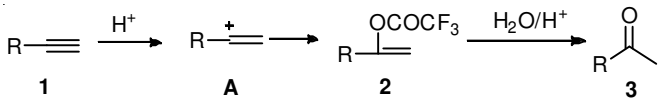


Fig. 2. Possible mechanism of TFA-mediated alkyne hydration reaction

Conclusion

In summary, we have presented an efficient, noble metal free and economical route for the hydration reaction of terminal alkynes. The results also indicated that the trifluoroacetic acid-mediated alkyne hydration reaction tolerated a variety of functional groups and had excellent selectivity. The proposed mechanism illustrated that enol trifluoroacetate may be the intermediate in this transformation. Further utilization of this procedure and understanding the mechanism will continue in our laboratory.

ACKNOWLEDGEMENTS

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REFERENCES

1. F. Alonso, I.P. Beletskaya and M. Yus, *Chem. Rev*., **104**, 3079 (2004).
2. L. Hintermann and A. Labonne, *Synthesis*, 1121 (2007).
3. M. Kutscheroff, *Ber. Dtsch. Chem. Ges*, **14**, 1540 (1881).
4. B. Neumann and H. Schneider, *Angew. Chem*., **33**, 189 (1920).
5. W.L. Budde and R.E. Dessy, *J. Am. Chem. Soc*., **85**, 3964 (1963).
6. J. Halpern, B.R. James and A.L.W. Kemp, *J. Am. Chem. Soc*., **83**, 4097 (1961).
7. M.M.T. Khan, S.B. Halligudi and S. Shukla, *J. Mol. Catal*., **58**, 299 (1990).
8. B.R. James and G.L. Rempel, *J. Am. Chem. Soc*., **91**, 863 (1969).
9. R. Casado, M. Contel, M. Laguna, P. Romero and S. Sanz, *J. Am. Chem. Soc*., **125**, 11925 (2003).
10. N. Marion, R.S. Ramón and S.P. Nolan, *J. Am. Chem. Soc*., **131**, 448 (2009).
11. D. Wang, R. Cai, S. Sharma, J. Jirak, S.K. Thummanapelli, N.G. Akhmedov, H. Zhang, X. Liu, J.L. Petersen and X. Shi, *J. Am. Chem. Soc*., **134**, 9012 (2012).
12. E. Mizushima, K. Sato, T. Hayashi and M. Tanaka, *Angew. Chem. Int. Ed*., **41**, 4563 (2002).
13. J.W. Hartman, W.C. Hiscox and P.W. Jennings, *J. Org. Chem*., **58**, 7613 (1993).
14. W. Baidossi, M. Lahav and J. Blum, *J. Org. Chem*., **62**, 669 (1997).
15. K. Imi, K. Imai and K. Utimoto, *Tetrahedron Lett*., **28**, 3127 (1987).
16. H. Kanemitsu, K. Uehara, S. Fukuzumi and S. Ogo, *J. Am. Chem. Soc*., **130**, 17141 (2008).
17. X. Jin, T. Oishi, K. Yamaguchi and N. Mizuno, *Chem. Eur. J.*, **17**, 1261 (2011).
18. X.-F. Wu, D. Bezier and C. Darcel, *Adv. Synth. Catal*., **351**, 367 (2009).
19. J.R. Cabrero-Antonino, A. Leyva-Pérez and A. Corma, *Chem. Eur. J.*, **18**, 11107 (2012).
20. M.B.T. Thuong, A. Mann and A. Wagner, *Chem. Commun.*, **48**, 434 (2011).
21. B. Rao, W. Zhang, L. Hu and M. Luo, *Green Chem*., **14**, 3436 (2012).
22. Z.-W. Chen, D.-N. Ye, Y.-P. Qian, M. Ye and L.-X. Liu, *Tetrahedron*, **69**, 6116 (2013).
23. T. Tachinami, T. Nishimura, R. Ushimaru, R. Noyori and H. Naka, *J. Am. Chem. Soc*., **135**, 50 (2013).
24. A.D. Allen, Y. Chiang, A.J. Kresge and T.T. Tidwell, *J. Org. Chem*., **47**, 775 (1982). (and references cited therein).
25. T. Suchimoto, T. Joya, E. Shirakawa and Y. Kawakami, *Synlett*, 1777 (2000).
26. N. Olive, E. Thomas, J.-F. Peyrat, M. Alami and J.-D. Brion, *Synlett*, 2175 (2004).
27. D.S. Noyce and K.E. DeBruin, *J. Am. Chem. Soc*., **90**, 372 (1968).
28. D.S. Noyce and M.D. Schiavelli, *J. Am. Chem. Soc*., **90**, 1020 (1968).
29. Z. Chen, J. Li, H. Jiang, S. Zhu, Y. Li and C. Qi, *Org. Lett*., **12**, 3262 (2010).