Chinese Chemical Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Solvent free synthesis of trifluoromethyl tertiary alcohols by cross Aldol reaction

Q1 Rui Tao, Xue-Jiao Yin, Ke-Hu Wang *, Yu-Zhuo Niu, Ya-Lin Wang, Dan-Feng Huang, Ying-Peng Su, Jin-Xian Wang, Yu-Lai Hu *, Ying Fu, Zheng-Yin Du

College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, China

ARTICLE INFO

Article history:
Received 10 January 2015
Received in revised form 13 March 2015
Accepted 24 March 2015
Available online xxx

Keywords:
Cross Aldol reaction
Grinding
Solvent free
Trifluoromethyl tertiary alcohols

ABSTRACT

Exceedingly fast preparation of trifluoromethyl tertiary alcohols has been accomplished from methyl ketones and trifluoromethyl ketones under solvent free conditions by cross Aldol reaction. The reaction was achieved in the presence of common inorganic base by grinding method at ambient temperature to give β-trifluoromethyl-β-hydroxyl ketones in high yields (up to 95%).

1. Introduction

Organic trifluoromethyl compounds are of increasing importance as pharmaceuticals, agrochemicals and functional materials [1]. Introduction of trifluoromethyl group into organic compounds usually induces dramatic consequences on their physical, chemical and biological properties [1,2]. Among trifluoromethylated compounds, trifluoromethyl tertiary alcohols are important intermediates or trifluoromethyl group building blocks in organic synthesis [3] and are desirable starting materials for preparing liquid crystals [4] and drugs such as Efavirenz (anti-HIV) [5].

Many methods for preparation of trifluoromethyl tertiary alcohols have been developed. Higashiyama's group reported the direct catalytic Aldol reaction of trifluoromethyl ketones with ketones to prepare trifluoromethyl tertiary alcohols using diethylzinc secondary amine complex as catalysts [6]. Organocatalytic Aldol addition of methyl ketones to aryl trifluoromethyl ketones afforded β-trifluoromethyl-β-hydroxyl ketones in good to excellent yield [7]. Although the above methods provided easy access to trifluoromethyl tertiary alcohols, it is still necessary to find more environment benign methods.

Solvent free organic reactions have attracted much research interest from the point of green chemistry in recent years. Many of solvent free organic reactions were reported to afford high conversions and yields in short reaction time at ambient temperature [8].

Our research group is engaged in green chemistry [9] and fluorine chemistry [10] for many years. Herein, we will report exceedingly fast preparation of trifluoromethyl tertiary alcohols from Aldol reaction between methyl ketones and trifluoromethyl ketones in high yields under solvent free conditions.

2. Experimental

All reactions were conducted in a 30 mL pear-shaped flask. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was carried out using Qingdao silica gel (230–400 mesh). Analytical thin layer chromatography (TLC) was done using Qingdao silica gel (silica gel GF254). TLC plates were analyzed by an exposure to ultraviolet (UV) light and/or in I_2. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 400 MHz and 100 MHz on Varian Mercury 400 plus instrument, respectively. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane (TMS) for ^{1}H NMR and chloroform for ^{13}C NMR. Coupling constants (J) are reported in Hertz (Hz). Melting points were uncorrected. Infrared spectra were recorded on an IR spectrometer (Perkin Elmer BX FT-IR), and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). The HRMS data were measured on MALDI-TOF type of instrument for the high-resolution mass spectra.

* Corresponding authors.
E-mail addresses: wangkh@nwnu.edu.cn (K.-H. Wang), huyl@nwnu.edu.cn (Y.-L. Hu).

http://dx.doi.org/10.1016/j.cclet.2015.04.015

2.1. Synthesis of β-trifluoromethyl-β-hydroxyl ketones 3

The mixture of trifluoroacetophenone (34.8 mg, 0.2 mmol) and acetophenone (24.0 mg, 0.2 mmol) was put into oven-dried, 30 mL pear-shaped flask at room temperature, and then lithium hydroxide powder (5.3 mg, 0.22 mmol) was added. The mixture was grinded and stirred in the flask at room temperature for 5–16 min, and then dissolved in water (5 mL) and ethyl acetate (5 mL). The organic phase was separated. Aqueous phase was extracted with ethyl acetate (3× 5 mL). The organic layer was combined, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as eluent to give the pure **3a**. Other target products were obtained in the same procedure.

4,4,4-Trifluoro-3-hydroxy-1,3-diphenylbutan-1-one (**3a**) [6]: White solid, mp: 42–43 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, 2H, J = 7.6 Hz), 7.61–7.65 (m, 3H), 7.51 (t, 2H, J = 7.2 Hz), 7.28–7.37 (m, 3H), 6.62 (s, 1H), 4.27 (d, 1H, J = 17.2 Hz), 3.83 (d, 1H, J = 17.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 200.2, 143.1, 142.1, 138.4, 133.7, 133.1, 132.9, 132.8, 131.6, 130.5 (q, J = 285.0 Hz), 80.2 (q, J = 27.2 Hz), 46.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.01.

1-(2-Bromophenyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-1-one (**3b**) [7d]: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.62 (m, 3H), 7.26–7.35 (m, 5H), 7.18–7.19 (m, 1H), 5.36 (s, 1H), 3.96 (d, 1H, J = 17.2 Hz), 3.74 (d, 1H, J = 17.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4, 140.5, 137.1, 133.9, 132.6, 129.0, 128.8, 128.4, 127.6, 126.4, 124.4 (q, J = 283.5 Hz), 118.8, 76.6 (q, J = 29.1 Hz), 45.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.50.

1-(3-Bromophenyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-1-one (**3c**): Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.91 (d, 1H, J = 7.2 Hz), 7.83 (d, 1H, J = 7.6 Hz), 7.61 (d, 2H, J = 6.8 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.41–7.23 (m, 3H), 6.64 (s, 1H), 4.28 (d, 1H, J = 17.6 Hz), 3.80 (d, 1H, J = 17.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.1, 144.2, 143.0, 141.0, 136.0, 135.8, 133.0, 132.9, 132.2, 131.7, 130.5 (q, J = 285.2 Hz), 127.2, 80.2 (q, J = 27.4 Hz), 47.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.62. HRMS (ESI) Calcd. for $C_{16}H_{12}BrF_3O_2$ (M + Na): 394.9865, Found: 394.9870.

1-(4-Bromophenyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-1-one (**3d**) [3]: White solid, mp: 109–110 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, 2H, J = 7.6 Hz), 7.72 (d, 2H, J = 7.2 Hz), 7.61 (d, 2H, J = 6.8 Hz), 7.30–7.36 (m, 3H), 6.62 (s, 1H), 4.24 (d, 1H, J = 17.6 Hz), 3.79 (d, 1H, J = 17.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.4, 143.0, 141.2, 136.8, 135.3, 133.0, 132.9, 132.5, 131.6, 130.5 (q, J = 285.0 Hz), 80.2 (q, J = 27.3 Hz), 46.7. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.54.

1-(2-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-1-one (**3e**) [7d]: Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50–7.56 (m, 3H), 7.42 (s, 2H), 7.29–7.36 (m, 4H), 6.82 (s, 1H), 4.09 (d, 1H, J = 16.8 Hz), 3.65 (d, 1H, J = 16.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.0, 138.7, 136.9, 132.0, 130.1, 129.4, 129.2, 127.9, 127.7, 127.0, 126.5, 125.2 (q, J = 285.4 Hz), 75.0 (q, J = 27.4 Hz), 45.9. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.49.

4,4,4-Trifluoro-3-hydroxy-1-(3-nitrophenyl)-3-phenylbutan-1-one (**3f**): Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (s, 1H), 8.43 (d, 1H, J = 7.8 Hz), 8.33 (d, 1H, J = 7.2 Hz), 7.78 (t, 1H, J = 8.0 Hz), 7.61 (d, 2H, J = 6.8 Hz), 7.23–7.40 (m, 3H), 6.72 (s, 1H), 4.36 (d, 1H, J = 17.2 Hz), 3.88 (d, 1H, J = 17.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 198.8, 153.1, 143.5, 142.8, 139.5, 135.6, 133.1, 132.9, 132.5, 131.7, 130.6 (q, J = 284.8 Hz), 127.7, 80.2 (q, J = 27.7 Hz), 47.6. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.40. HRMS (ESI) Calcd. for $C_{16}H_{12}F_3NO_4$ (M + Na): 362.0611, Found: 362.0617.

4,4,4-Trifluoro-3-hydroxy-3-phenyl-1-(*p*-tolyl)butan-1-one (**3g**) [6]: White solid, mp: 72–73 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (d, 2H, J = 7.2 Hz), 7.59 (d, 2H, J = 6.8 Hz), 7.28–7.32 (m, 5H), 6.56 (s, 1H), 4.20 (d, 1H, J = 17.2 Hz,), 3.74 (d, 1H, J = 17.2 Hz,), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.9, 143.8, 138.0, 134.5, 129.2, 128.2, 127.8, 127.7, 126.5, 125.4 (q, J = 285.1 Hz), 75.2 (q, J = 27.3 Hz), 41.1, 21.1. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.53.

4,4,4-Trifluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylbutan-1-one (**3h**) [6]: White solid, mp: 90–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, 2H, J = 7.6 Hz), 7.58 (d, 2H, J = 6.8 Hz), 7.28–7.34 (m, 3H), 7.00 (d, 2H, J = 7.6 Hz), 6.56 (s, 1H), 4.15 (d, 1H, J = 17.2 Hz), 3.81 (s, 3H), 3.70 (d, 1H, J = 17.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.1, 163.4, 138.1, 130.6, 129.9, 127.8, 127.7, 126.5, 125.4 (q, J = 285.2 Hz), 113.8, 75.3 (q, J = 27.3 Hz), 55.6, 40.7. ^{19}F NMR (376 MHz, DMSO-d_6): δ −74.74.

4,4,4-Trifluoro-3-hydroxy-1-(2-hydroxyphenyl)-3-phenylbutan-1-one (**3i**) [11]: White solid, mp: 112–113 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 7.84 (d, 1H, J = 8.0 Hz), 7.61 (d, 2H, J = 6.8 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.30–7.35 (m, 3H), 6.94 (d, 2H, J = 7.2 Hz), 6.65 (s, 1H), 4.31 (d, 1H, J = 17.6 Hz), 3.86 (d, 1H, J = 17.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 200.0, 160.2, 138.1, 136.1, 131.0, 128.1, 128.0, 126.7, 125.6 (q, J = 285.5 Hz), 122.0, 119.4, 117.8, 75.3 (q, J = 27.0 Hz), 43.1. ^{19}F NMR (376 MHz, DMSO-d_6): δ −77.01.

1-([1,1′-Biphenyl]-4-yl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-1-one (**3j**): White solid, mp: 51–52 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 8.0 Hz), 7.72 (d, 2H, J = 7.2 Hz), 7.63 (d, 2H, J = 7.2 Hz), 7.49 (t, 2H, J = 7.2 Hz), 7.40–7.43 (m, 1H), 7.29–7.36 (m, 3H), 6.64 (s, 1H), 4.27 (d, 1H, J = 17.2 Hz), 3.83 (d, 1H, J = 17.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.9, 149.8, 143.9, 143.1, 140.9, 134.2, 133.9, 133.5, 132.9, 132.8, 132.1, 131.9, 131.6, 130.5 (q, J = 285.3 Hz), 80.3 (q, J = 27.3 Hz), 46.5. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.46. HRMS (ESI) Calcd. for $C_{22}H_{17}F_3O_2$ (M + Na): 393.1073, Found: 393.1078.

4,4,4-Trifluoro-3-hydroxy-1-(5-methylfuran-2-yl)-3-phenylbutan-1-one (**3k**): Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (d, 2H, J = 6.4 Hz), 7.51 (s, 1H), 7.34 (d, 3H, J = 7.6 Hz), 6.67 (s, 1H), 6.36 (s, 1H), 3.88 (d, 1H, J = 16.0 Hz), 3.51 (d, 1H, J = 16.0 Hz), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.6, 158.2, 150.9, 137.5, 128.0, 127.7, 126.5, 125.2 (q, J = 284.8 Hz), 121.5, 109.4, 75.2 (q, J = 27.5 Hz), 40.7, 13.5. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.34. HRMS (ESI) Calcd. for $C_{15}H_{13}F_3O_3$ (M + Na): 321.0709, Found: 321.0714.

4,4,4-Trifluoro-3-hydroxy-3-phenyl-1-(pyridin-3-yl)butan-1-one (**3l**): Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (s, 1H), 8.75 (d, 1H, J = 4.0 Hz), 8.22 (d, 1H, J = 7.2 Hz), 7.59 (d, 2H, J = 6.8 Hz), 7.48–7.52 (m, 1H), 7.28–7.32 (m, 3H), 6.67 (s, 1H), 4.25 (d, 1H, J = 17.2 Hz), 3.83 (d, 1H, J = 17.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.7, 158.5, 154.4, 142.9, 140.7, 137.5, 133.0, 132.9, 131.6, 130.5 (q, J = 285.2 Hz), 128.8, 80.2 (q, J = 27.3 Hz), 47.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.36. HRMS (ESI) Calcd. for $C_{15}H_{12}F_3NO_2$ (M + H): 296.0893, Found: 296.0898.

1-(2,5-Dimethylthiophen-3-yl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-1-one (**3m**): Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59 (d, 2H, J = 7.2 Hz), 7.32–7.37 (m, 4H), 6.54 (s, 1H), 4.01 (d, 1H, J = 17.2 Hz), 3.57 (d, 1H, J = 17.2 Hz), 2.43 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.5, 151.5, 143.1, 141.0, 139.9, 132.9, 132.8, 131.9, 131.6, 130.4 (q, J = 285.5 Hz), 80.3 (q, J = 26.7 Hz), 49.0, 20.6, 19.7. ^{19}F NMR (376 MHz, DMSO-d_6): δ −74.87. HRMS (ESI) Calcd. for $C_{16}H_{15}F_3O_2S$ (M + H): 329.0818, Found: 329.0824.

4,4,4-Trifluoro-3-hydroxy-3-(4-nitrophenyl)-1-phenylbutan-1-one (**3n**): Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 2H, J = 8.0 Hz), 7.90–7.92 (m, 4H), 7.60–7.62 (m, 1H), 7.48–7.51 (m, 2H), 7.02 (s, 1H), 4.41 (d, 1H, J = 18.0 Hz), 3.94 (d, 1H, J = 18.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.1, 152.2, 151.0, 141.7, 138.5, 133.7, 133.1, 130.2 (q, J = 285.4 Hz), 127.9, 79.9 (q, J = 27.2 Hz), 46.8. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.40. HRMS (ESI) Calcd. for $C_{16}H_{12}F_3NO_4$ (M + H): 340.0791, Found: 340.0796.

Please cite this article in press as: R. Tao, et al., Solvent free synthesis of trifluoromethyl tertiary alcohols by cross Aldol reaction, Chin. Chem. Lett. (2015), http://dx.doi.org/10.1016/j.cclet.2015.04.015

3-(3-Bromophenyl)-4,4,4-trifluoro-3-hydroxy-1-phenylbutan-1-one (**3o**) [7d]: Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, 2H, J = 7.6 Hz), 7.82 (s, 1H), 7.61 (d, 2H, J = 5.6 Hz), 7.49–7.51 (m, 3H), 7.27–7.31 (m, 1H), 6.79 (s, 1H), 4.31 (d, 1H, J = 17.6 Hz), 3.83 (d, 1H, J = 17.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.4, 140.8, 136.8, 133.3, 130.6, 129.8, 129.3, 128.5, 128.0, 125.5, 125.1 (q, J = 285.2 Hz), 121.3, 74.5 (q, J = 27.3 Hz), 41.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.70.

3-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxy-1-phenylbutan-1-one (**3p**) [6]: White solid, mp: 71–73 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, 2H, J = 7.2 Hz), 7.64–7.66 (m, 3H), 7.50–7.53 (m, 2H), 7.42 (d, 2H, J = 7.2 Hz), 6.78 (s, 1H), 4.30 (d, 1H, J = 17.6 Hz), 3.86 (d, 1H, J = 17.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.5, 137.1, 136.8, 133.3, 132.6, 128.5, 128.4, 127.9, 127.6, 125.2 (q, J = 285.3 Hz), 74.6 (q, J = 27.8 Hz), 41.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.82.

4,4,4-Trifluoro-3-hydroxy-3-(4-methoxyphenyl)-1-phenylbutan-1-one (**3q**) [6]: White solid, mp: 71–72 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (d, 2H, J = 7.2 Hz,), 7.60–7.61 (m, 1H), 7.49–7.51 (m, 4H), 6.88 (d, 2H, J = 8.4 Hz), 6.51 (s, 1H), 4.18 (d, 1H, J = 17.2 Hz), 3.75 (d, 1H, J = 17.2 Hz), 3.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.4, 158.8, 137.0, 133.3, 129.7, 128.6, 128.0, 127.8, 125.4 (q, J = 284.8 Hz), 113.1, 74.9 (q, J = 27.5 Hz), 55.0, 41.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.84.

4,4,4-Trifluoro-3-hydroxy-1-phenyl-3-(*p*-tolyl)butan-1-one (**3r**) [6]: Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, 2H, J = 6.8 Hz), 7.62–7.63 (m, 1H), 7.50 (s, 4H), 7.14 (d, 2H, J = 7.2 Hz), 6.54 (s, 1H), 4.23 (d, 1H, J = 17.2 Hz), 3.77 (d, 1H, J = 17.2 Hz), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.2, 137.0, 134.9, 133.3, 128.6, 128.3, 128.0, 126.4, 125.4 (q, J = 285.0 Hz), 75.0 (q, J = 27.0 Hz), 41.2, 20.5. ^{19}F NMR (376 MHz, DMSO-d_6): δ −79.73.

4,4,4-Trifluoro-3-hydroxy-3-(naphthalen-1-yl)-1-phenylbutan-1-one (**3s**) [7d]: White solid, mp: 80–81 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.07 (d, 2H, J = 7.6 Hz), 7.97–8.02 (m, 2H), 7.74–7.75 (m, 2H), 7.66–7.52 (m, 4H), 7.46–7.48 (m, 1H), 6.99 (s, 1H), 4.88 (d, 1H, J = 18.4 Hz), 4.00 (d, 1H, J = 18.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.9, 136.8, 134.3, 133.4, 133.1, 131.9, 129.5, 128.6, 128.5, 127.9, 127.6, 126.7, 126.0 (q, J = 286.2 Hz), 125.3, 125.1, 124.4, 78.4 (q, J = 28.9 Hz), 43.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ −78.07.

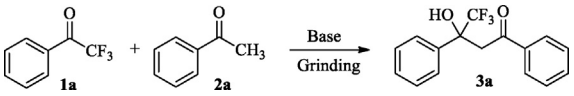
3. Results and discussion

Although many methods for preparation of trifluoromethyl organic compounds have been developed by using trifluoromethylation reagents, such as Togni reagent, Umemoto reagent, and Ruppert-Prakash reagent, trifluoromethyl group-containing building blocks still play important roles in preparation of trifluoromethyl compounds because of their easy commercial availability, low cost and stability [12]. The Aldol reaction using trifluoromethyl ketones were apparently a convergent method for preparation of trifluoromethyl tertiary alcohols. Thus, we firstly tried the Aldol reaction between trifluoroacetophenone **1a** and acetophenone **2a** in the presence of NaOH without any catalyst at room temperature under solvent free conditions to get β-trifluoromethyl-β-hydroxyl ketones. The reaction proceeded smoothly to generate Aldol product 4,4,4-trifluoro-3-hydroxy-1,3-diphenylbutan-1-one **3a** with the yield of 80%. However, if the ethanol was used as solvent, there was no reaction occurred. It was found that the reaction was exothermic under grinding condition with liquification of the reaction mixture, and then solidification of the product **3a** [13].

In order to improve the yields of the products, the reaction temperature was firstly examined. It was found that the temperature had great influence on the reaction. When the reaction was carried out at room temperature, the product **3a** could be obtained in 80% yield (Table 1, entry 1). Lowering reaction temperature would prolong the reaction time (Table 1, entry 2). However, the yield of **3a** was only 46% with the appearance of ethanol-insoluble solid when the reaction temperature was increased to 40 °C (Table 1, entry 3). The effects of reaction time were examined next. The results demonstrated that 5 min was enough for completion of the reaction (Table 1, entries 4–6). When the reaction time was prolonged, the yield of **3a** will not change too much. The choice of base was crucial to obtain good yields (Table 1, entries 7–14). A series of bases were tested, it was found that LiOH was the best base (Table 1, entry 7). Thus, the best result was achieved in the presence of LiOH at room temperature under solvent free conditions (Table 1, entry 7).

In order to demonstrate the efficiency and the applicability of the method, the reactions were performed with various methyl

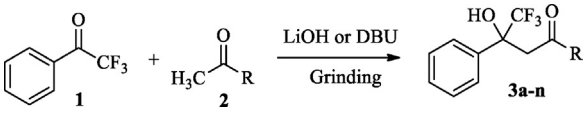
Table 1
Optimization of reaction conditions for the synthesis of **3a**.[a]



Entry	Base	Temp. (°C)	Time (min)	Yield (%)[b]
1	NaOH	r.t.	5	80
2	NaOH	0	30	77
3	NaOH	40	5	46
4	NaOH	r.t.	7	79
5	NaOH	r.t.	12	78
6	NaOH	r.t.	15	78
7	LiOH	r.t.	8	89
8	KOH	r.t.	4	65
9	Cs_2CO_3	r.t.	10	86
10	K_2CO_3	r.t.	20	56
11	Na_2CO_3	r.t.	20	Trace
12	$NaOCH_3$	r.t.	5	23
13	NEt_3	r.t.	20	Trace
14	DBU	r.t.	6	76

[a] Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.2 mmol), and base (0.22 mmol) was grinded under solvent free conditions.
[b] Yield of isolated product.

Table 2
Solvent free synthesis of β-trifluoromethyl-β-hydroxyl ketones from various methyl ketones.[a]

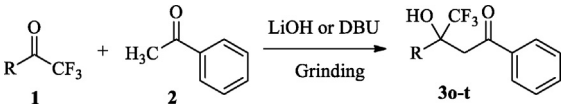


Entry	R	Products	Time (min)	Yield (%)[b]
1	C_6H_5	**3a**	8	89
2	2-BrC_6H_4	**3b**	8	91
3	3-BrC_6H_4	**3c**	8	84
4	4-BrC_6H_4	**3d**	10/20	79/73[c]
5	2-ClC_6H_4	**3e**	8	95
6	3-$NO_2C_6H_4$	**3f**	16	Trace/70[c]
7	4-MeC_6H_4	**3g**	8	87
8	4-$MeOC_6H_4$	**3h**	10	71
9	2-OHC_6H_4	**3i**	6	Trace/86[c]
10	4-PhC_6H_4	**3j**	10	Trace/67[c]
11	2-(5-Methyl-furanyl)	**3k**	8	87
12	3-Pyridinyl	**3l**	16	84
13	3-(2,5-Dimethyl-thiophthyl)	**3m**	16	63
14	C_2H_5		10	ND[d]
15	Cyclohexanone		8	ND[d]

[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2** (0.2 mmol), and LiOH (0.22 mmol) was grinded at room temperature under solvent free conditions.
[b] Yield of isolated product.
[c] DBU (0.22 mmol) was used as base instead of LiOH.
[d] No detected.

Please cite this article in press as: R. Tao, et al., Solvent free synthesis of trifluoromethyl tertiary alcohols by cross Aldol reaction, Chin. Chem. Lett. (2015), http://dx.doi.org/10.1016/j.cclet.2015.04.015

Table 3
Solvent free synthesis of β-trifluoromethyl-β-hydroxyl ketones from various trifluoromethyl ketones.[a]



1 2 3o-t

Entry	R	Products	Time (min)	Yield (%)[b]
1	4-$NO_2C_6H_4$	**3n**	10	Trace/83[c]
2	3-BrC_6H_4	**3o**	16	74
3	4-ClC_6H_4	**3p**	16	76
4	4-$MeOC_6H_4$	**3q**	8	88
5	4-MeC_6H_4	**3r**	16	80
6	1-Naphthyl	**3s**	8	71

[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2** (0.2 mmol), and LiOH (0.22 mmol) was grinded at room temperature under solvent free conditions.
[b] Yield of isolated products.
[c] DBU (0.22 mmol) was used as base instead of LiOH.

ketones and trifluoromethyl ketones under the optimized conditions. The results are summarized in Tables 2 and 3.

It showed that aromatic methyl ketones and trifluoromethyl ketones reacted smoothly affording the corresponding β-trifluoromethyl-β-hydroxyl ketones in good to excellent yields (63–95%). Aliphatic methyl ketones failed to give the desired products (Table 2, entries 14 and 15). This is due to the cross condensations between aliphatic methyl ketones to make the products very complex. The reactions of heterocyclic ketones with trifluoroacetophenone proceeded smoothly to furnish the products in good yields (Table 2, entries 11–13). The other trifluoromethyl ketones could also be converted to the corresponding products (Table 3). No obvious electronic effects of the ketones were observed.

In the course of the experiment, we found that when both methyl ketones and trifluoromethyl ketones were liquid, the solid base LiOH was the best suitable base to obtain the corresponding products **3** in excellent yields. For example, 1-(4-bromophenyl)ethanone reacted with trifluoroacetophenone smoothly to afford the corresponding compound **3d** with the yield of 79% when LiOH was used as base. Liquid organic base such as DBU could also been used in the reaction to obtain reasonable yield of **3d** (73%, Table 2, entry 4). If methyl ketones or trifluoromethyl ketones were solid, liquid base such as DBU must be used in order to obtain good yields (Table 2, entries 6, 9, and 10; Table 3, entry 1).

4. Conclusion

In conclusion, β-trifluoromethyl-β-hydroxyl ketones were successfully synthesized from cross Aldol reaction of methyl ketones and trifluoromethyl ketones under solvent free conditions. The reaction could be achieved smoothly with various aromatic methyl ketones, even with some heterocyclic and aliphatic ketone. The features of this procedure are mild conditions, high yields, operational simplicity, and the environmental friendliness.

Acknowledgments

Q3 We are thankful for the financial support from the National Natural Science Foundation of China (No. 21262031), Bioactive Product Engineering Research Center for Gansu Distinctive Plants, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University.

References

[1] (a) R. Filler, Y. Kobayashi, L.M. Yagupolskii, Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993;
(b) R.E. Banks, B.E. Smart, C.J. Tatlow, Organofluorine Chemistry: Principles and Comercial Applications, Springer, New York, 1994, pp. 237–262;
(c) T. Hiyama, Organofluorin Compounds: Chemistry and Application, Springer, Berlin, 2000, pp. 183–234;
(d) W.P. Gu, J.H. Lin, J.C. Xiao, Direct N-gem-difluorocyclopropylation of nitroheterocycles by utilizing gem-difluorocyclopropyl tosylate, Chin. Chem. Lett. 25 (2014) 24–28.
[2] (a) K. Müller, C. Faeh, F. Diederich, Fluorine in pharmaceuticals: looking beyond intuition, Science 317 (2007) 1881–1886;
(b) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Fluorine in medicinal chemistry, Chem. Soc. Rev. 37 (2008) 320–330;
(c) W.K. Hagmann, The many roles for fluorine in medicinal chemistry, J. Med. Chem. 51 (2008) 4359–4369.
[3] H. Kawai, S. Okusu, E. Tokunaga, N. Shibata, Enantioselective synthesis of 5-trifluoromethyl-2-isoxazolines and their N-oxides by [hydroxy(tosyloxy)iodo] benzene-mediated oxidative N–O coupling, Eur. J. Org. Chem. 29 (2013) 6506–6509.
[4] P.V. Ramachandran, Asymmetric Fluoroorganic Chemistry: synthesis, Application and Future Directions, ACS, Washington, 1999, pp. 255–269.
[5] (a) J. Ren, J. Milton, K.L. Weaver, S.A. Short, D.I. Stuart, D.K. Stammers, Structural basis for the resilience of efavirenz (DMP-266) to drug resistance mutations in HIV-1 reverse transcriptase, Structure 8 (2000) 1089–1094;
(b) O.S. Pedersen, E.B. Pedersen, The flourishing syntheses of non-nucleoside reverse transcriptase inhibitors, Synthesis 4 (2000) 479–495.
[6] S. Sasaki, K. Kikuchi, T. Yamuchi, K. Higashiyama, Direct Aldol reaction of trifluoromethyl ketones with ketone catalyzed by Et_2Zn and secondary amines, Synlett 10 (2011) 1431–1434.
[7] (a) L.H. Qiu, Z.X. Shen, C.Q. Shi, Y.H. Liu, Y.W. Zhang, Proline catalyzed asymmetric Aldol reaction between methyl ketones and 1-aryl-2 2,2-trifluoroethanones, Chin. J. Chem. 23 (2005) 584–588;
(b) N. Duangdee, W. Harnying, G. Rulli, et al., Highly enantioselective organocatalytic trifluoromethyl carbinol synthesis – a caveat on reaction times and product isolation, J. Am. Chem. Soc. 134 (2012) 11196–11205;
(c) N. Hara, R. Tamura, Y. Funahashi, S. Nakamura, N-(heteroarenesulfonyl) prolinamides-catalyzed Aldol reaction between acetone and aryl trihalomethyl ketones, Org. Lett. 13 (2011) 1662–1665;
(d) Y. Zheng, H.Y. Xiong, J. Nie, M.Q. Hua, J.A. Ma, Biomimetic catalytic enantioselective decarboxylative Aldol reaction of β-keto acids with trifluoromethyl ketones, Chem. Commun. 48 (2012) 4308–4310.
[8] (a) M.A.P. Martins, C.P. Frizzo, D.N. Moreira, L. Buriol, P. Machado, Solvent-free heterocyclic synthesis, Chem. Rev. 109 (2009) 4140–4182;
(b) G. Choudhary, R. Krishna Peddinti, An expeditious, highly efficient, catalyst-free and solvent-free synthesis of nitroamines and nitrosulfides by Michael addition, Green Chem. 13 (2011) 276–282;
(c) A. Kumar, S. Sharma, A grinding-induced catalyst- and solvent-free synthesis of highly functionalized 1,4-dihydropyridines via a domino multicomponent reaction, Green Chem. 13 (2011) 2017–2020;
(d) D. Wang, J. Li, N. Li, T. Gao, S. Hou, B. Chen, An efficient approach to homocoupling of terminal alkynes: solvent-free synthesis of 1,3-diynes using catalytic Cu (II) and base, Green Chem. 12 (2010) 45–48;
(e) B.R. Vaddula, R.S. Varma, J. Leazer, Mixing with microwaves: solvent-free and catalyst-free synthesis of pyrazoles and diazepines, Tetrahedron Lett. 54 (2013) 1538–1541;
(f) J. Yang, N. Li, S. Li, W. Wang, L. Li, A. Wang, X. Wang, Synthesis of diesel and jet fuel range alkanes with furfural and ketones from lignocellulose under solvent free conditions, Green Chem. 16 (2014) 4879–4884;
(g) S. Yan, Y. Chen, L. Liu, N. He, J. Lin, Three-component solvent-free synthesis of highly substituted bicyclic pyridines containing a ring-junction nitrogen, Green Chem. 12 (2010) 2043–2052;
(h) Y.H. Ma, G. Wu, N. Jiang, et al., Microwave-assisted, facile, rapid and solvent-free one pot two-component synthesis of some special acylals, Chin. Chem. Lett. 26 (2015) 81–84.
[9] (a) H.W. Zhan, J.X. Wang, X.T. Wang, Solvent- and catalyst-free synthesis of dihydropyrimidinthiones in one-pot under focused microwave irradiation conditions, Chin. Chem. Lett. 19 (2008) 1183–1185;
(b) X.Q. Men, T.J. Meng, J.X. Wang, L. Xin, Pd(II) catalyzed addition reaction of benzylzinc bromides or allylzinc iodines with aromatic aldehydes, Chin. J. Org. Chem. 27 (2007) 272–275 (in Chinese);
(c) J.X. Wang, N. An, Solvent-free synthesis of 1 4-bis(3-aryl-3-oxo-3-propenyl)-benzenes under grind condition, J. Northw. Norm. Univ. (Nat. Sci.) 47 (2011) 59–62 (in Chinese).
[10] J. Xu, Y. Hu, D. Huang, et al., Thiourea-catalyzed enantioselective fluorination of β-keto esters, Adv. Synth. Catal. 354 (2012) 515–526.
[11] V.Y. Sosnovskikh, I.S. Ovsyannikov, I.A. Aleksandrova, Ketone–ketone condensation with the participation of polyhaloalkyl phenyl ketones, Zh. Org. Khim. 28 (1992) 518–526.
[12] J. Nie, H.C. Guo, D. Cahard, J.A. Ma, Asymmetric construction of stereogenic carbon centers featuring a trifluoromethyl group from prochiral trifluoromethylated substrates, Chem. Rev. 111 (2011) 455–529.
[13] (a) G. Rothenberg, A.P. Downie, C.L. Raston, J.L. Scott, Understanding solid/solid organic reactions, J. Am. Chem. Soc. 123 (2001) 8701–8708;
(b) T. Friščić, W. Jones, Recent advances in understanding the mechanism of cocrystal formation via grinding, Cryst. Growth Des. 9 (2009) 1621–1637;
(c) P.R. Patil, K.P.R. Kartha, Application of ball milling technology to carbohydrate reactions: I. Regioselective primary hydroxyl protection of hexosides and nucleoside by planetary ball milling, J. Carbohydr. Chem. 27 (2008) 279–293.