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Perfluoroalkylated-pyridine catalyzed Aldol condensations of aldehydes and ketones in a fluorous biphasic system without fluorous solvent

Wen-Bin Yi *, Chun Cai

Chemical Engineering College, Nanjing University of Science and Technology, 200 Xlaolingwei, Nanjing 210094, China

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ABSTRACT

Aldol condensation of different ketones with various aromatic aldehydes proceeds efficiently in the presence of catalytic amount of perfluoroalkylated-pyridine in a fluorous biphasic system without fluorous solvent, which has prompted various concerns involving cost, solvent leaching, and environmental persistence. The catalyst can be recovered by simple cooling and precipitation and used again.

1. Introduction

Recently, reactions carried out in a fluorous biphasic system (FBS, Fig. 1) have become one of the most important methods for facile catalyst separation from the reaction mixture and recycling of the catalyst since FBS was introduced by Horváth and Rábai [1]. No catalyst recovery method is without potential drawbacks [2,3]. Accordingly, the fluorous solvent requirement in Fig. 1 has prompted various concerns involving cost, solvent leaching, and environmental persistence [4]. Small amounts of fluorous solvents are similarly found in the organic layers of fluorous/organic liquid/liquid biphase systems. This makes losses unavoidable upon phase separation. Therefore, the development of the strategy to eliminate the fluorous solvent requirement for fluorous catalysis is a topic of enormous importance.

Fluorous catalysis without fluorous solvent suggested that fluorous catalyst might be utilized under one-liquid-phase conditions involving ordinary organic solvents as shown in Fig. 2 [4]. The system would first be warmed to achieve monophasic reaction conditions. Subsequent cooling would precipitate the catalyst, and recovery would involve a simple liquid/solid phase separation [5]. The first example of the applicability of this concept to fluorous catalysis was introduced by Gladysz's group [4,6].

In the course of our extensive synthetic and physical investigations involving perfluoroalkylated-pyridines **1**–**3** (Fig. 3) [7–10], we noticed that **1** is very thermomorphic in less polar hydrocarbon solvents. On the other hand, the Aldol condensation is one of the most fundamental and important carbon–carbon bond-forming reactions. The reactions are usually catalyzed by strong acids or bases, and various Lewis acids [11]. Inspired by recent reports on the *N*-methylimidazole as a Lewis base catalyst for the Aldol condensation of trimethylsilyl enolate with aldehyde [12,13], we have applied the perfluoroalkylated-pyridines **1** catalyst to the Aldol condensation of ketones with aldehydes under FBS without fluorous solvent. It was exciting to find that rather high yields of the corresponding α,β-unsaturated ketones were obtained, and the fluorous catalyst is easily separated under fluorous-solvent-free conditions and can be reused several times without a significant loss of catalytic activity. We would like to report herein the work on this new application of the catalytic system.

2. Experimental

2.1. General remarks

Melting points were obtained with Shimadzu DSC-50 thermal analyzer. ^{1}H NMR and ^{19}F NMR spectra were characterized with a Bruker Advance RX300 spectrometer. IR spectra were recorded on a Bomen MB154S infrared analyzer. Mass spectra were recorded on a Saturn 2000GC/MS instrument. All fluorous solvents were purchased from Aldrich Co. Commercially available reagents were used without further purification.

* Corresponding author. Tel.: +86 25 84315514; fax: +86 25 84315030.
E-mail address: yiwenbin@mail.njust.edu.cn (W.-B. Yi).

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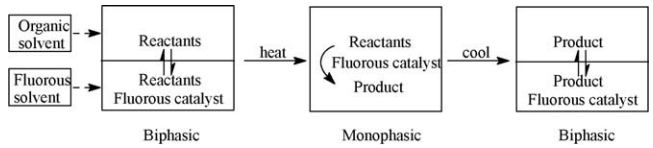

Fig. 1. Fluorous biphasic catalysis with fluorous solvent (the liquid/liquid FBS).

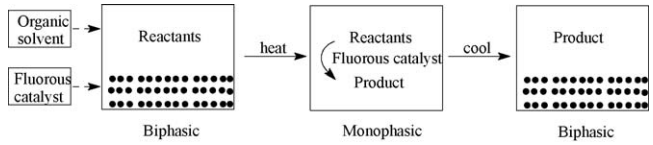

Fig. 2. Fluorous biphasic catalysis without fluorous solvent (the liquid/solid FBS).

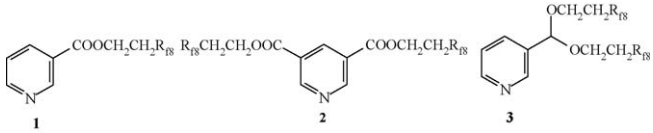

Fig. 3. Perfluoroalkylated-pyridines.

2.2. Typical procedure for Aldol condensation in a liquid/liquid FBS

The benzaldehyde (4 mmol) was slowly added into a mixture of **1** (227 mg, 0.4 mmol), *n*-octane (3 mL) and perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture, 3 mL) containing the acetophenone (5 mmol). The mixture was stirred at 80 °C for 16 h. The bottom fluorous layer was then separated (to be reused). The upper organic phase was washed with water (10 mL), 10% $NaHCO_3$ solution (10 mL) and water (10 mL ×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography (20% EtOAc in petroleum ether) to give the Aldol product.

2.3. Typical procedure for Aldol condensation in a liquid/solid FBS

The benzaldehyde (4 mmol) was slowly added into a mixture of **1** (227 mg, 0.4 mmol), *n*-octane (6 mL) and the acetophenone (5 mmol). After stirring at 80 °C for 16 h, the reaction mixture was cooled to 0 °C and the catalyst was separated (to be reused). The organic phase was washed with water (10 mL), 10% $NaHCO_3$ solution (10 mL) and water (10 mL ×2), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography (20% EtOAc in petroleum ether) to give the Aldol product.

Chalcone: A yellowish solid; m.p. 56–57 °C (lit. [14] 57–58 °C). IR (KBr) υ 3230, 2931, 1830, 1730, 1655, 1287, 753, 682 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 6.12 (d, *J* = 16.0 Hz, 1H), 7.25 (d, *J* = 16.0 Hz, 1H), 7.09–7.30 (m, 5H), 7.39–7.93 (m, 5H). MS (EI) *m/z* 207 (M^+).

4′-Methoxychalcone: A russety solid; m.p. 109–111 °C (lit. [14] 109–110 °C). IR (KBr) υ 3210, 2880, 1833, 1725, 1670, 1210, 856, 730 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 3.78 (s, 3H), 6.10 (d, *J* = 16.0 Hz, 1H), 7.24 (d, *J* = 16.0 Hz, 1H), 7.08–7.62 (m, 9H). MS (EI) *m/z* 238 (M^+).

4′-Nitrochalcone: A yellow solid; m.p. 151–153 °C (lit. [14] 151–152 °C). IR (KBr) υ 3010, 2895, 1708, 1680, 1642, 1468, 920, 837 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 6.33 (d, *J* = 16.1 Hz, 1H), 7.35 (d, *J* = 16.1 Hz, 1H), 7.14–7.38 (m, 5H), 7.49–8.24 (m, 4H). MS (EI) *m/z* 253 (M^+).

4-Chlorochalcone: A yellow solid; m.p. 114–115 °C (lit. [14] 114–117 °C). IR (KBr) υ 3080, 2908, 1780, 1712, 1650, 1205, 913, 748 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 6.20 (d, *J* = 16.0 Hz, 1H), 7.11 (d, *J* = 16.0 Hz, 1H), 6.24 (d, 2H), 7.10–7.34 (m, 4H), 7.36–8.02 (m, 5H). MS (EI) *m/z* 244 (M^++2), 242 (M^+).

4-Methylchalcone: A yellowish solid; m.p. 98 °C (lit. [14] 97–98 °C). IR (KBr) υ 3210, 2915, 1760, 1696, 1652, 1086, 942, 843, 722 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 2.32 (s, 3H), 6.01 (d, *J* = 16.4 Hz, 1H), 7.04 (d, *J* = 16.4 Hz, 1H), 7.06–7.36 (m, 4H), 7.38–7.83 (m, 5H). MS (EI) *m/z* 221 (M^+).

4-Methoxychalcone: A russety solid; m.p. 75–76 °C (lit. [14] 75–77 °C). IR (KBr) υ 3303, 2979, 1830, 1722, 1660, 1185, 929, 815 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 3.72 (s, 3H), 5.96 (d, *J* = 16.0 Hz, 1H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.92–7.21 (m, 4H), 7.32–7.99 (m, 5H). MS (EI) *m/z* 238 (M^+).

4-Nitrochalcone: A brown solid; m.p. 158–159 °C (lit. [14] 158–160 °C). IR (KBr) υ 3235, 2908, 1872, 1673, 1660, 1476, 923, 834 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 6.35 (d, *J* = 16.1 Hz, 1H), 7.40 (d, *J* = 16.1 Hz, 1H), 7.36–7.68 (m, 3H), 7.70–8.32 (m, 4H). MS (EI) *m/z* 252 (M^+).

2,6-Dibenzylidenecyclohexanone: A yellow solid; m.p. 116 °C (lit. [15] 116–117 °C). IR (KBr) υ 3020, 2922, 1664, 1612, 1570, 1269, 1138, 768, 689 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 1.75–1.86 (m, 2H), 2.94 (t, *J* = 6.4 Hz, 4H), 7.28–7.46 (m, 10H), 7.80 (s, 2H). MS (EI) *m/z* 273 (M^+).

2,6-Di(p-methoxybenzylidene)cyclohexanone: A yellow solid; m.p. 202–204 °C (lit. [15] 203–204 °C). IR (KBr) υ 3022, 2920, 1658, 1606, 1568, 1265, 1140, 780, 687 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 1.80–1.84 (m, 2H), 2.96 (t, *J* = 6.0 Hz, 4H), 3.85 (s, 6H), 6.92–7.38 (m, 8H), 7.79 (s, 2H). MS (EI) *m/z* 333 (M^+).

2,6-Di(p-nitrobenzylidene)cyclohexanone: A russety solid; m.p. 158 °C (lit. [15] 159 °C). IR (KBr) υ 3086, 2933, 1670, 1612, 1581, 1525, 1340, 805 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 1.86–1.92 (m, 2H), 2.99 (t, *J* = 5.6 Hz, 4H), 7.60–8.24 (m, 8H), 8.32 (s, 2H). MS (EI) *m/z* 363 (M^+).

2,6-Di(p-methoxybenzylidene)cyclopentanone: A green solid; m.p. 211–212 °C (lit. [15] 210–211 °C). IR (KBr) υ 2965, 2840, 1649, 1592, 1506, 1247, 1025, 830 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 3.11 (t, 4H), 3.86 (s, 6H), 6.96–7.59 (m, 8H), 7.60 (s, 2H). MS (EI) *m/z* 319 (M^+).

2,6-Di(p-nitrobenzylidene)cyclopentanone: A russety solid; m.p. 230–233 °C (lit. [15] 230–231 °C). IR (KBr) υ 3108, 2850, 1708, 1600, 1525, 1344, 821 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 3.06 (t, 4H), 7.61–8.13 (m, 8H), 8.28 (s, 2H). MS (EI) *m/z* 349 (M^+).

2.4. Typical procedure for catalyst recycling in a liquid/solid FBS

After the reaction as described above, the mixture was allowed to stand at 0 °C for *ca.* 1 h without stirring, and the upper organic phase was separated using a pipette. The solid obtained was washed with cold *n*-octane (0–3 °C) and dried at room temperature for 12 h in vacuum. The resulting catalyst was ready for further runs: The aldehyde (4 mmol), *n*-octane (6 mL) and the ketone (5 mmol) were added to **1** (227 mg, 0.4 mmol) and the mixture was stirred at 80 °C.

3. Results and discussion

Perfluorinated pyridine **1** was prepared according to the method described by Uemura and co-workers [16]. **1** was soluble in perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture), perfluoromethylcyclohexane ($CF_3C_6F_{11}$) and perfluorotoluene ($CF_3C_6F_5$). It also showed significant solubility in ether, THF, $CHCl_3$ and CH_2Cl_2. However, **1** appeared to be very poorly soluble in *n*-octane, *n*-hexane and toluene at room temperature. Quantitative data on fluorous phase affinities were sought. The perfluorodecalin/toluene partition coefficients were determined by GC according the previously reported method [17,18]. These reflect *relative* as opposed to *absolute* solubilities. In perfluoroalkylated-pyridines **1**,