Journal of Fluorine Chemistry 130 (2009) 484–487

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

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 Xiaolingwei, Nanjing 210094, China

ARTICLE INFO

Article history:
Received 23 December 2008
Received in revised form 1 February 2009
Accepted 20 February 2009
Available online 5 March 2009

Keywords:
Perfluoroalkylated-pyridine
Aldol condensation
Fluorous biphasic catalysis
Fluorous-solvent-free

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.

© 2009 Elsevier B.V. All rights reserved.

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).

0022-1139/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2009.02.013

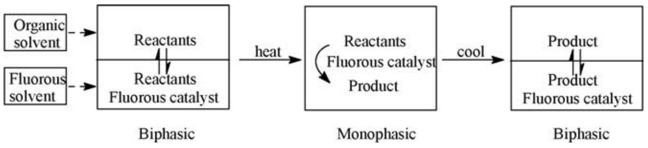


Fig. 1. Fluorous biphasic catalysis with fluorous solvent (the liquid/liquid FBS).

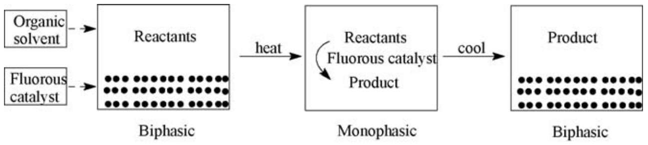


Fig. 2. Fluorous biphasic catalysis without fluorous solvent (the liquid/solid FBS).

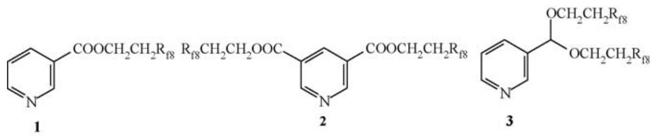


Fig. 3. Perfluoroalkylated-pyridines.

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^+).

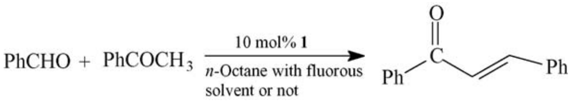
2.4. Typical procedure for catalyst recycling in a liquid/solid FBS

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**,

Table 1
The condensation of benzaldehyde with acetophenone in liquid/liquid or liquid/solid FBS[a]



Solvent	Yield (%)[b]				
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
n-Octane/perfluorodecalin	91	90	90	88	85
n-Octane	90	89	87	87	84

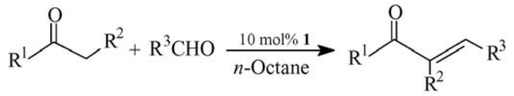
[a] The reaction condition: aldehyde, 4 mmol; ketone, 5 mmol; *n*-octane/perfluorodecalin, 3 mL/3 mL; *n*-octane, 6 mL; 80 °C.
[b] Isolated yield based on the aldehyde.

R_{f8} ($R_{f8} = C_8F_{17}$) pony tails give high fluorous phase affinities (coefficient for **1** was 92.1:7.9), allowing essentially quantitative recovery. Indeed, **2** was less thermomorphic than **1** and **3**. Between 0 and 80 °C, solubility of **1** in *n*-octane increased *ca.* 80-fold. The increase of **3** was 70-fold between 0 and 80 °C. However, **3** was liquid over the temperature range from −20 °C to 0 °C. Thus, it is impossible to recover fluorous catalyst by liquid/solid separation when using **2** and **3**.

The Aldol condensation of benzaldehyde with acetophenone was firstly investigated. The control experiment elucidated that no condensation product could be obtained in the absence of fluorous catalyst. Then, the condensation employing fluorous catalysis technology in the protocols of Figs. 1 and 2 was examined with perfluoroalkylated pyridine **1** catalyst (Table 1). In stage of liquid/liquid FBS, experiments were conducted in binary system perfluorodecalin/*n*-octane (1:1, v/v). Reactions proceeded under one-phase conditions at 80 °C. After 16 h, condensation product was obtained in 91% isolated yield. As summarized in Table 1, good yields were maintained for 3–5 cycles. The stage was set for the experimental sequence in liquid/solid FBS (Fig. 2). Benzaldehyde and acetophenone were combined in *n*-octane at room temperature. The sample was next warmed to 80 °C and became homogeneous. After stirring for 16 h, the reaction mixture was cooled. The catalyst **1** precipitated as a white solid. The solid was separated, washed with cold *n*-octane (0–3 °C), dried at vacuum and then reused for the next reaction. As would be expected, the fluorous catalyst can be reused several times without a significant loss of yield.

The problem on leaching in these catalyst recycling systems was studied. In the liquid/liquid FBS system, *ca.* 0.8% of ligand **1** and trace of perfluorodecalin (<1%) was found by GC–MS in organic layer. In fact, we also investigated the exact amount of ligand **1** in the recovered fluorous phase by GC, finding that 99.1% of ligand **1** retained in perfluorodecalin. As to the liquid/solid FBS case, the solubility data of **1** in *n*-octane predict catalyst leaching of *ca.* 1% percycle when liquid/solid phase separations are conducted at 0 °C according to the quantities in our previous report [7]. Based on ^{19}F NMR and GC–MS data, only trace of the catalyst (<0.6%) was found in separated organic layer. In addition, there were no significant differences between the IR spectra of the initial and recovered perfluoroalkylated pyridine, which may indicate that the fluorous catalyst is recovered unaltered after the condensation has taken place. These results suggest the robustness of the catalytic system for recycled use.

Table 2
Perfluoroalkylated pyridine **1** catalyzed Aldol condensation in liquid/solid FBS[a]



Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]
1	4-CH_3OPh	H	Ph	16	72
2	4-NO_2Ph	H	Ph	16	95
3	Ph	H	4-ClPh	16	91
4	Ph	H	4-CH_3Ph	16	79
5	Ph	H	4-CH_3OPh	16	68
6	Ph	H	4-NO_2Ph	16	96
7	$(CH_2)_6$		Ph	8	94
8	$(CH_2)_6$		4-CH_3OPh	12	93
9	$(CH_2)_6$		4-NO_2Ph	16	96
10	$(CH_2)_5$		4-CH_3OPh	12	92
11	$(CH_2)_5$		4-NO_2Ph	16	97
12	CH_3	H	C_3H_7	24	4[c]
13	CH_3	CH_3	C_3H_7	24	6[c]
14	CH_3	H	C_4H_9	24	3[c]

[a] The reaction condition: aldehyde, 4 mmol; ketone, 5 mmol; cycloalkanone 2.5 mmol; *n*-octane, 6 mL; 80 °C.
[b] Isolated yield based on the aldehyde.
[c] Yields calculated by GC.

From these observations it was revealed that using perfluoroalkylated pyridine **1** as fluorous catalyst the technology of liquid/solid FBS (Fig. 2) can be considered the most attractive alternative to existing traditional liquid/liquid FBS (Fig. 1). Next, we applied the strategy in Fig. 2 to other Aldol condensations. The results were summarized in Table 2. The condensation products were isolated and identified as α,β-unsaturated ketones, and no side-reactions were observed. Based on ^1H NMR and GC–MS data, the reaction was found to give the *E*-stereoisomer as the sole product. In general, reactions between aromatic aldehydes and ketones gave good results, but not those of aliphatic compounds. The condensations of *p*-substituted benzaldehyde with *p*-substituted acetophenones yielded the corresponding chalcones and the product yields were remarkably affected by the substituent groups of either aldehydes or ketones: reactants having electron-withdrawing substituents gave high yields and those having electron-donating ones gave low yields. The cross-condensations of cyclopentanone and cyclohexanone with different aromatic aldehydes were finished within 8–16 h and excellent yields (92–97%) of α,α′-bis(substituted) benzylidene cyclopentanones and cyclohexanones were obtained, regardless of the kind of substituent group on benzaldehyde. However, the catalyst **1** system appeared to show no catalytic activity for the condensation of the aliphatic ketones such as acetone and 2-butanone with the aliphatic aldehydes, butanal and pentanal under the conditions described in Table 2.

4. Conclusion

In conclusion the perfluoroalkylated pyridine **1** was found to be highly efficient for Aldol condensation under fluorous-solvent-free conditions. The catalyst can be applied under homogeneous conditions at elevated temperatures and efficiently recovered by simple liquid/solid phase separation at lower temperature. The simple procedures as well as easy recovery and reuse of this novel catalytic system are expected to contribute to the development of more benign method for catalyst recovery—"fluorous catalysis without fluorous solvents"—that removes many objections to be organic/fluorous liquid/liquid FBS.

Acknowledgments

We thank the Nature and Science Foundation of Jiangsu Province (BK2007592) and the National Defense Committee of Science and Technology of China (40406020301) for financial support.

References

[1] T.H. Horváth, J. Rábai, Science 266 (1994) 72–76.
[2] J.A. Gladysz, Pure Appl. Chem. 73 (2001) 1319–1324.
[3] J.A. Gladysz, Chem. Rev. 102 (2002) 3215–3216.
[4] M. Wende, J.A. Gladysz, J. Am. Chem. Soc. 125 (2003) 5861–5872.
[5] V.K. Dioumaev, R.M. Bullock, Nature 424 (2003) 530–532.
[6] M. Wende, R. Meier, J.A. Gladysz, J. Am. Chem. Soc. 123 (2001) 11490–11491.
[7] W.B. Yi, C. Cai, Catal. Commun. 9 (2008) 1291–1296.
[8] W.B. Yi, C. Cai, X. Wang, Eur. J. Org. Chem. (2007) 3445–3448.
[9] W.B. Yi, C. Cai, X. Wang, J. Mol. Catal. A: Chem. 274 (2007) 68–71.
[10] W.B. Yi, C. Cai, X. Wang, J. Fluorine Chem. 128 (2007) 919–924.
[11] R.L. Reeves, in: S. Patai (Ed.), Chemistry of Carbonyl Group, Wiley, New York, 1966, pp. 580–593.
[12] R. Srivastava, J. Mol. Catal. A: Chem. 264 (2007) 146–152.
[13] H. Hagiwara, H. Inoguchi, M. Fukushima, T. Hoshi, T. Suzuki, Tetrahedron Lett. 47 (2006) 5371–5373.
[14] K. Watanabe, A. Imazawa, Bull. Chem. Soc. Jpn. 55 (1982) 3208–3211.
[15] M. Zheng, L.C. Wang, J.G. Shao, Q. Zhong, Synth. Commun. 27 (1997) 351–354.
[16] T. Nishimura, Y. Maeda, N. Kakiuchi, S. Uemura, J. Chem. Soc., Perkin Trans. 1 (2000) 4301–4305.
[17] C. Rocaboy, F. Hampel, J.A. Gladysz, J. Org. Chem. 67 (2002) 6863–6870.
[18] J. Nishikido, M. Kamishima, H. Matsuzawa, K. Mikami, Tetrahedron 58 (2002) 8345–8349.