Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 259 (2006) 121–124
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Organic base catalyzed *O*-alkylation of phenols under solvent-free condition

Xiuli Bu, Huanwang Jing *, Li Wang, Tao Chang, Lili Jin, Yongmin Liang

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, Gansu 730000, China

Received 30 April 2006; received in revised form 31 May 2006; accepted 1 June 2006
Available online 20 July 2006

Abstract

Several phenyl ethers were prepared under solvent-free condition at room temperature with good to excellent yields by simply grinding the mixture of relevant phenol, alkyl bromide, anhydrous potassium carbonate and organic base as catalyst in a mortar. This method is easy to handle and provides also a convenient procedure for protecting phenols in organic synthesis.

Keywords: Phenols; *O*-Alkylations; Ethers; Organic base; Solid-state reaction

1. Introduction

Solid-state reaction is a green reaction and can be accelerated by heating, shaking, grinding of the reaction mixture and irradiation with ultrasound, which makes it a much ideal synthetic process. And it can avoid the environmental pollution, toxicity and flammability caused by solvents, and has been successfully applied to many kinds of reactions [1–6]. Hence, the investigation of solid-state reaction attracts much attention in recent decades [7,8]. The traditional methods for synthesis of phenyl ethers suffer a rigorous condition such as the strong base and high temperature via Williamson reaction [9–11]. Although a wide variety of procedures has been developed to prepare ethers, including the use of crown ethers [12,13], phase-transfer catalysis [14–16], ionic liquids [17,18], and microwave method and so on [19–24], few examples have been presented using solid-state reaction [25–27]. In this paper, we describe a very simple and convenient method to synthesize the phenyl ethers via the *O*-alkylation/etherification of phenols under solvent-free condition.

2. Experimental

2.1. Materials and facilities

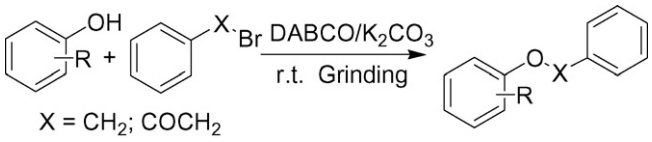
All melting points were determined on a XT-4 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with Bruker AM-400 spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Elemental analyses were determined with a Carioel elemental analyzer. MS spectra were measured with a ZAB-HS spectrometer. All phenols and other chemicals were purchased from Aldrich without further purification.

2.2. General procedure for synthesis of phenol ethers

The corresponding phenols (5 mmol), anhydrous K_2CO_3 (6.5 mmol), organic base (0.125 mmol) and alkyl bromides (5 mmol) were mixed in a mortar and grinded intermittently using a pestle. The mixture changed to mushy state within a proper reaction time and then solidified itself. TLC monitored the reaction. Once the reaction was completed, the crude products were purified by silica gel chromatography using hexane/ethyl acetate as eluent. All obtained compounds have been characterized by ^{1}H NMR, ^{13}C NMR, MS (FAB), and elemental analysis. The data are consistent with literatures.

* Corresponding author. Tel.: +86 931 891 2585; fax: +86 931 891 2582.
E-mail address: hwjing@lzu.edu.cn (H. Jing).

1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.06.009



Scheme 1. *O*-Alkylation of phenols under solvent-free condition.

3. Results and discussion

The alkylation reaction is an important transformation in organic synthesis whereas generally involving a rigorous condition such as the strong base and high temperature. Recently, we noticed that the *O*-alkylation reaction of phenols with *tert*-butyl halide could be easily carried out in the presence of liquid amines [28]. Hereby, we envisioned that organic bases, for example 1,4-diazabicyclo[2,2,2] octane (DABCO), would be efficient catalysts for the *O*-alkylation of phenols. Out of our expectation, the etherification reaction of phenols with phenacyl bromide was failed to be carried out under refluxed condition using DABCO as catalyst in THF or acetonitrile. Dramatically, this catalytic reaction took place very well in solid state at room temperature (Scheme 1).

3.1. The O-alkylation of phenols with phenacyl bromide

3.1.1. Synthesis of phenacyl ethers

The phenacyl bromide was firstly chosen as *O*-alkylation reagent. Then the mixture of phenol, phenacyl bromide, DABCO and anhydrous K_2CO_3 was grinded in a mortar. It was found that a new substance appeared several minutes later with the disappearance of reactants upon TLC plate. Other inorganic bases such as anhydrous Na_2CO_3, NaOH, and KOH having less activity can also be used in this reaction instead of anhydrous K_2CO_3. To further extend the scope of the reaction, several other substituted phenols were utilized as substrates in the reaction with phenacyl bromide in the presence of DABCO (Table 1).

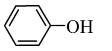
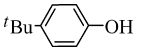
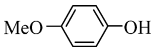
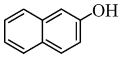
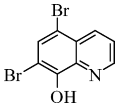
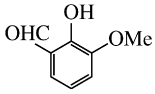
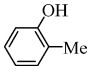
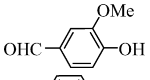
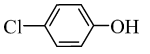
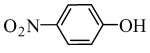
These experimental results exhibit that all investigated phenols can be smoothly converted to the corresponding ethers with excellent yield except for 4-nitrophenol which might be attributed to lower electron density of Nu^- (hydroxyl).

3.1.2. Characterization of new phenacyl ethers

*3.1.2.1. p-tert-Butylphenyl phenacyl ether (**2A**).* A white crystal; mp 67–68 °C. ^{1}H NMR ($CDCl_3$): $\delta = 8.03$ (dd, $J_1 = 1.5$ Hz, $J_2 = 8.7$ Hz, 2H), 7.63–7.48 (m, 3H), 7.34–7.25 (m, 2H), 6.93–6.81 (m, 2H), 5.27 (s, 2H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$): $\delta = 194.82$, 155.67, 134.48, 133.78, 128.74, 128.09, 126.27, 114.76, 114.20, 70.80, 34.00, 31.39. MS (FAB): *m/z* $[M]^+$ calcd for $C_{18}H_{20}O_2$: 268.3; found: 268.1. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.55; H, 7.52. Found: C, 80.23; H, 7.19.

*3.1.2.2. 5,7-Dibromo-8-phenacyloxyquinoline (**5A**).* A white crystal; mp 119–120 °C. ^{1}H NMR ($CDCl_3$): $\delta = 8.78$ (d, $J = 3.6$ Hz, 1H), 8.47 (d, $J = 9.0$ Hz, 1H), 8.05–8.01 (m, 4H), 7.61–7.46 (m, 4H), 5.85 (s, 2H). ^{13}C NMR (DMSO-d_6): $\delta = 193.95$, 150.92, 150.18, 149.69, 141.63, 135.59, 135.28, 134.38, 133.44, 133.07, 128.72, 127.75, 127.23, 123.53, 123.20, 114.56, 114.23, 75.79. MS (FAB): *m/z* $[M+H]^+$ calcd for $C_{17}H_{11}Br_2NO_2$: 422.1; found: 422.n Anal. Calcd for $C_{17}H_{11}Br_2NO_2$: C, 48.70; H, 2.65; N, 3.34. Found: C, 48.89; H, 2.46; N, 2.97.

Table 1
O-Alkylation of phenols with phenacyl bromide

Entry	Phenol	Time (min)	Yield[a] (%)	Conversion (%)
1		8	88	100
2		7	>99	100
3		6	99	100
4		9	94	100
5		10	96	100
6		9	99	100
7		8	>99	100
8		9	94	100
9		12	91	100
10		60	NR	NR

[a] Isolated yield.

*3.1.2.3. 3-Methoxy-2-phenacyloxybenzaldehyde (**6A**).* A white crystal; mp 84.5–85 °C. ^{1}H NMR ($CDCl_3$): $\delta = 10.65$ (s, 1H), 7.91 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, 2H), 7.61–7.42 (m, 4H), 7.26–7.11 (m, 2H), 5.50 (s, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 194.34$, 190.46, 151.84, 150.41, 134.47, 133.66, 129.69, 128.75, 127.70, 124.09, 119.32, 117.99, 74.78, 56.05. MS (FAB): *m/z* $[M]^+$ calcd for $C_{16}H_{14}O_4$: 271.3; found: 271.1. Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.09; H, 5.22. Found: C, 71.24; H, 4.84.

*3.1.2.4. 3-Methoxy-4-phenacyloxybenzaldehyde (**8A**).* A white crystal; mp 121–122 °C. ^{1}H NMR ($CDCl_3$): $\delta = 9.84$ (s, 1H), 8.02–7.99 (m, 2H), 7.67–7.28 (m, 5H), 6.86 (d, $J = 8.4$ Hz, 1 H), 5.50 (s, 2H), 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 193.03$, 190.84, 152.68, 149.84, 134.13, 130.85, 128.91, 127.92, 126.19, 112.41, 109.66, 71.05, 56.01. MS (FAB): *m/z* $[M]^+$ calcd for $C_{16}H_{14}O_4$: 271.3; found: 271.2 (M^+). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.09; H, 5.22. Found: C, 70.76; H, 5.07.

3.2. The effect of organic base on the synthesis of 4-methoxyphenylphenacyl ether

The scope of the reaction was then investigated by using the 4-methoxyphenol as substrate with various organic bases. These

Table 2
O-Alkylation of 4-methoxyphenol with phenacyl bromide

Entry	Organic base	Time (min)	Yield[a] (%)	Conversion (%)
1	DABCO	6	99.0	100
2	DBU	8	94.5	100
3	DBN	8	96.7	100
4	DMAP	12	98.4	100
5	Pyridine	11	94.6	100
6	Picoline	12	97.2	100
7	Piperidine	13	92.9	100
8	PPh_3	16	95.1	100
9	None	35	92.7	100

[a] Isolated yield.

results were summarized in Table 2. It can be seen that DABCO has higher activity than other organic bases, which catalyze this C–O coupling reaction with excellent yield. Surprisingly, we found that this reaction can also took place slowly even without organic base as catalyst (entry 9). This might be attributed to the higher activeness of phenacyl bromide.

3.3. The effect of organic base on the synthesis of 4-methoxyphenylbenzyl ethers

To test the activity of other alkylating reagents, the less active benzyl bromide was selected to undergo this *O*-alkylation reaction. When the 4-methoxyphenol was used as substrate, it was found that the weak organic bases such as triphenylphosphine, picoline, and pyridine cannot catalyze this coupling reaction. But, the organic base DBU, DBN, DMAP and DABCO can catalyze this coupling reaction with different activity (Table 3). It can be seen that DABCO is the best catalyst in this *O*-alkylation reaction. The iodoethane was also tested in this *O*-alkylation reaction and shown no activity at all due to lower electrophilic reactivity.

3.4. DABCO catalyzed O-alkylation of phenols with benzyl bromide

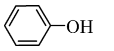
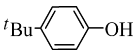
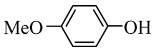
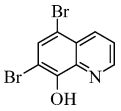
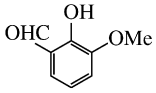
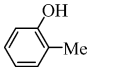
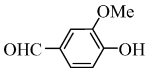
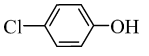
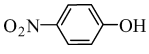
To further extend the scope of the reaction, several other phenols were utilized as substrates in the *O*-alkylation reaction with benzyl bromide in the presence of catalyst DABCO (Table 4). These results demonstrate that all investigated phenols can be smoothly converted to the corresponding ethers with excellent yield except for 4-nitrophenol, which might be attributed to lower electron density of Nu^- (hydroxyl). The blank experiment was also tested and shown no reaction occurred in the absence of DABCO.

Table 3
O-Alkylation of 4-methoxyphenol with benzyl bromide

Entry	Organic base	Time (min)	Yield[a] (%)
1	DABCO	40	85.0
2	DBU	42	75.3
3	DBN	50	73.3
4	DMAP	60	65.1
5	PPh_3/pyridine/picoline	60	0

[a] Isolated yield.

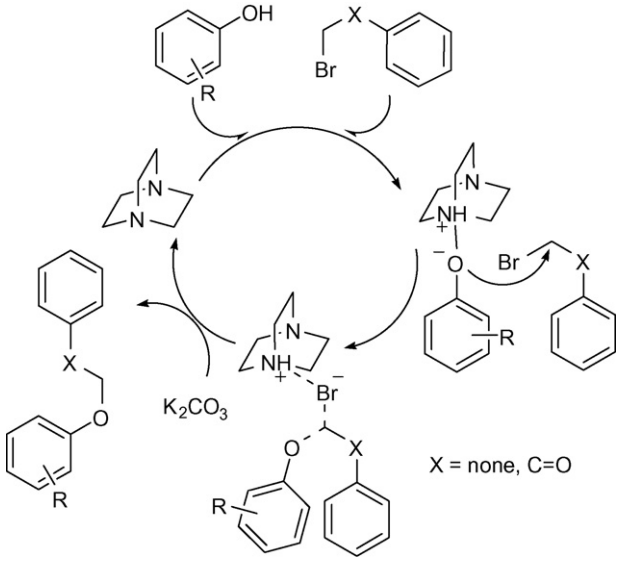
Table 4
O-Alkylation of phenols with benzyl bromide

Entry	Phenol	Time (min)	Yield[a] (%)	Conversion (%)
1		50	81	100
2		45	81	100
3		40	85	100
4		60	78	100
5		55	77	100
6		50	79	100
7		70	85	100
8		42	80	100
9		60	NR	NR

[a] Isolated yield.

3.5. Mechanism investigation

To investigate the mechanism of this catalytic *O*-alkylation/etherification reaction, the *N*-ylide of phenacyl-DABCO bromide was prepared and used to react with phenols. But the expected etherification products were not detected at all. These



Scheme 2. Proposed mechanism.

phenomena show that phenols are activated by organic bases in the etherification reaction instead of activation of alkyl bromides. The proposed mechanism of this *O*-alkylation reaction is depicted in Scheme 2.

4. Conclusions

In conclusion, the *O*-alkylation of phenols was achieved in up to 100% yield for phenacyl bromide and up to 85% yield for benzyl bromide, respectively. To the best of our knowledge, this Williamson reaction under solvent-free condition at room temperature is not reported till now. This catalytic grinding method is easy to handle and provides also a convenient procedure for protecting phenols in organic synthesis [29–31]. Apart from these good results, the new phenacyl ethers would be potential precursors of substituted benzofurans according to Ref. [3]. This investigation is now undergoing in our laboratory.

Acknowledgment

We are grateful for the financial support of the Natural Science Foundation of China (NSFC QT program 20021001) and Natural Science Foundation of Gansu Province (3ZS041-A25-008).

References

[1] K. Tanaka, F. Toda, Chem. Rev. 100 (2000) 1025.
[2] N.J. Coville, C. Lin, J. Organomet. Chem. 571 (1998) 149.
[3] H.M. Meshram, K.C. Sekhar, Y.S.S. Ganesh, J.S. Yadav, Synlett (2000) 1270.
[4] J.A. Seijas, M.P. Vazquez-Tato, M.M. Martinez, B. Pacios-Lopez, Synthesis (2001) 999.
[5] J. Marquie, A. Laporterie, J. Dubac, N. Roques, Synlett (2001) 493.
[6] S.-J. Jeon, H. Li, P.J. Walsh, J. Am. Chem. Soc. 127 (2005) 16416.
[7] K. Tanaka, Solvent-Free Organic Synthesis, Wiley/VCH, Weinheim, 2003.
[8] F. Toda, Organic Solid State Reactions, Springer, New York, 2005.
[9] A.W. Williamson, J. Chem. Soc. 4 (1852) 229.
[10] O.C. Dermer, Chem. Rev. 14 (1934) 385.
[11] J.-P. Mazaleyrat, M. Wakselman, J. Org. Chem. 61 (1996) 2695.
[12] S.K. Banerjee, B.D. Gupta, K. Singh, J. Chem. Soc., Chem. Commun. 14 (1982) 815.
[13] M. Lissel, S. Schimidt, B. Neumann, Synthesis 5 (1986) 382.
[14] C.M. Starks, C. Liotta, Phase Transfer Catalysis, Academic Press, New York, 1978, p. 128.
[15] W.P. Weber, G.W. Gokel, Phase Transfer Catalysis in Organic Synthesis, Springer, New York, 1977, p. 73.
[16] D.G. Yadav, S.V. Lande, Appl. Catal. A: Gen. 287 (2005) 0267.
[17] A. Loupy, J. Sansoulet, F. Vaziri-Zand, Bull. Soc. Chim. Fr. 6 (1987) 1027.
[18] M. Badri, J.-J. Brunet, Tetrahedron Lett. 33 (1992) 4435.
[19] J.C. Lee, J.Y. Yuk, S.H. Cho, Synth. Commun. 25 (1995) 1367.
[20] T. Ando, J. Yamawaki, T. Kawate, S. Sumi, Bull. Chem. Soc. Jpn. 55 (1982) 2504.
[21] F. Camps, J. Coll, J.M. Moretó, Synthesis (1982) 186.
[22] J.D. Godfrey Jr., R.H. Mueller, T.C. Sedergran, N. Soundararajan, V.J. Colandrea, Tetrahedron Lett. 35 (1994) 6405.
[23] B. Jurssić, Tetrahedron 44 (1988) 6677.
[24] G.A. Krafft, W.R. Sutton, R.T. Cummings, J. Am. Chem. Soc. 110 (1988) 301.
[25] F. Toda, K. Okuda, J. Chem. Soc., Chem. Commun. 17 (1991) 1212.
[26] F. Toda, H. Takumi, M. Akehi, J. Chem. Soc., Chem. Commun. 18 (1990) 1270.
[27] M. Rohr, C. Geyer, R. Wandeler, M.S. Svhneider, E.F. Murphy, A. Baiker, Green Chem. 3 (2001) 123.
[28] H. Masada, Y. Oishi, Chem. Lett. (1978) 57.
[29] J.B. Hendrickson, C. Kandall, Tetrahedron Lett. (1970) 343.
[30] W.L. Mendelson, M. Holmes, J. Dougherty, Synth. Commun. 26 (1996) 593.
[31] N.R. Kolecha, S.V. Ley, S. Mantegani, Synlett (1992) 395.