Indian Journal of Chemistry
Vol. 45B, August 2006, pp. 1965-1967

Note

An efficient and practical procedure for synthesis of α,α′-bis(substituted benzylidene)cycloalkanones catalyzed by solid base SiO_2-OK

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Received 12 September 2005; accepted (revised) 4 April 2006

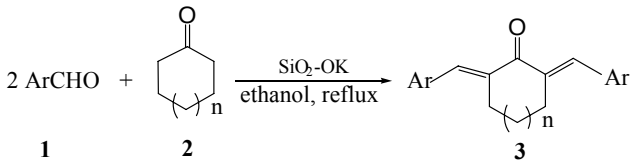
The condensation of cycloalkanones with aromatic aldehydes catalyzed by solid base SiO_2-OK in refluxing EtOH, result in the formation of the corresponding α,α′-bis(substituted benzylidene)cycloalkanones in good to excellent yields.

Keywords: α,α′-Bis(substituted benzylidene)cycloalkanone, cycloalkanones, aldehydes, SiO_2-OK, condensation

IPC Code: Int. Cl.[8] C07C

Owing to the importance of the methylene structural unit found in many naturally occurring compounds and antibiotics and the use of α,α′-bis(substituted benzylidene)cycloalkanones as precursors for synthesis of bioactive pyrimidine derivatives[1-2], the condensation of cycloalkanones with aromatic aldehydes is of special interest. Preparation of α,α′-bis(substituted benzylidene)cycloalkanones is usually carried out in the presence of strong acids or bases[3]. In these cases, many side reactions occurred. Recently, many methods for the synthesis of α,α′-bis(substituted benzylidene)cycloalkanones catalyzed by various catalysts have been reported[4-8]. They have their own merits, but there were some shortcomings in terms of high cost[7], long reaction time[8], low yields[3] and especially reaction conditions.

SiO_2-OK, which is a new type of solid base and has not been reported previously, provides some advantages such as efficiency, high activity, less corrosive, easy preparation and recyclability. Herein, is reported an efficient procedure for synthesis of α,α′-bis(substituted benzylidene)cycloalkanones with aromatic aldehydes and cycloalkanones catalyzed by SiO_2-OK (**Scheme I**).



1 **2** **3**

Scheme I

As shown in **Table I**, the condensation of cyclopentanone or cyclohexanone with a variety of aromatic aldehydes offered α,α′-bis(substituted benzylidene)cycloalkanones in good to excellent yields catalyzed by SiO_2-OK in ethanol at refluxing temperature.

The temperature plays an important role in the success of the reaction. For example, the condensation of cyclohexanone with 2,4-dichlorobenzaldehyde gave 98% yield of **3o** in 2.5 hr in refluxing ethanol, whereas the yield of **3o** obtained in 6 hr at rt is only 52%. Meanwhile, it was observed that SiO_2-OK acted as an efficient catalyst for crossed-aldol condensation reaction of cycloalkanones with aromatic aldehydes without occurrence of any self-condensation of ketones. In the classical condensation of aromatic aldehydes and cycloalkanones catalyzed by NaOH (aq) in EtOH, compounds **3a**, **3c**, **3h** and **3k** were obtained with 60-90, 60-90, 60-90, and 30-50% yields[3a] while the present method gave **3a**, **3c**, **3h**, and **3k** in 87, 91, 91 and 85% yields respectively.

To test the selectivity of the reaction, the reaction of 2,4-dichlorobenzaldehyde and cyclohexanone was chosen as a model reaction. When the mole ratios (2,4-dichloro-benzaldehyde/cyclohexanone) were 1:1, 1:2, 2:1, the reaction gave the same product α,α′-bis(2,4-dichlorobenzylidene)cycloalkanone (**3o**).

According to the results shown in **Table I**, the nature of the substituents on the aromatic ring had some effect on this conversion. Aromatic aldehydes carrying electron-withdrawing groups (-Cl, $-NO_2$) gave cleaner reactions with higher yields of **3** than aromatic aldehydes carrying electron-donating groups ($-CH_3$, $-OCH_3$). It is possible that electron-withdrawing groups in the aromatic ring increased the reactivity of aldehydes.

SiO_2-OK can be reused after simple heating at 120°C for 2 hr. The catalyst could be reused 6 times

Table I—Condensation of aromatic aldehydes with cycloalkanones catalyzed by SiO_2-OK

Entry	Ar	n	Product	Time (hr)	Yield (%)[a]	m.p. (°C) Found	Reported
1	C_6H_5 **1a**	0	**3a**	3.0	87	189-90	188-89 (Ref. 8)
2	4-$CH_3C_6H_4$ **1b**	0	**3b**	3.5	94	234-35	235-36 (Ref. 3)
3	4-$CH_3OC_6H_4$ **1c**	0	**3c**	4.0	91	211-13	211-12 (Ref. 6)
4	2-ClC_6H_4 **1d**	0	**3d**	2.5	98	159-60	
5	3-ClC_6H_4 **1e**	0	**3e**	3.0	96	180-82	
6	4-ClC_6H_4 **1f**	0	**3f**	3.0	96	221-22	223-24 (Ref. 7)
7	2,4-$Cl_2C_6H_3$ **1g**	0	**3g**	1.5	98	205-07	206-08 (Ref. 6)
8	C_6H_5CH=CH **1h**	0	**3h**	4.5	91	217-18	215-16 (Ref. 7)
9	C_6H_5 **1i**	1	**3i**	3.5	89	118-19	116-17 (Ref. 5)
10	4-$CH_3C_6H_4$ **1j**	1	**3j**	4.0	84	173-74	172-73 (Ref. 7)
11	4-$CH_3OC_6H_4$ **1k**	1	**3k**	4.0	85	161-63	160-62 (Ref. 6)
12	2-ClC_6H_4 **1l**	1	**3l**	3.0	86	114-15	
13	4-ClC_6H_4 **1m**	1	**3m**	3.0	88	148-50	149-51 (Ref. 6)
14	3-$NO_2C_6H_4$ **1n**	1	**3n**	2.5	92	192-93	189-91 (Ref. 9)
15	2,4-$Cl_2C_6H_3$ **1o**	1	**3o**	2.5	98	163-64	163-64 (Ref. 6)

[a]Isolated yield, based on the cyclokanones

Table II—Reuse of the catalyst for the synthesis of **3o**

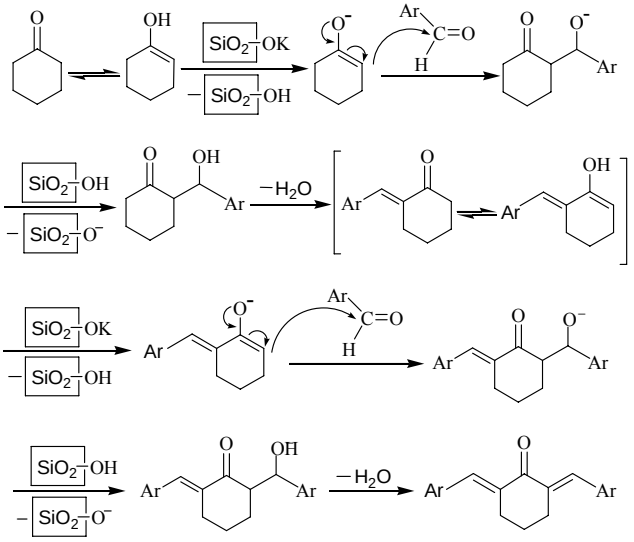
Entry	1	2	3	4	5	6
Yield (%)*	98	98	97	96	95	94

*Isolated yield, based on the cyclohexanone

for the synthesis of **3o** without significant loss of activity. The results are summarized in **Table II**.

As shown in **Scheme II**, the following possible mechanism was proposed to account for the formation of α,α′-bis(substituted benzylidene)cycloalkanones.

To conclude, a practical and highly efficient procedure for the synthesis of α,α′-bis(substituted benzylidene)cycloalkanones catalyzed by SiO_2-OK in refluxing ethanol has been described. The main advantages of the present procedure are minimal effluent generation, cost effectiveness, recyclability, easier work-up, shorter reaction time, and higher yields.



Scheme II

Experimental Section

Liquid aldehydes and cycloalkanones were purified by distillation before use. IR spectra were recorded on a Bio-Rad FIS-40 spectrometer (KBr). ^1H NMR spectra were measured on an AVANCE-400 spectrometer using TMS as internal standard and $CDCl_3$ as solvent.

Preparation of SiO_2-OK. The SiO_2-OK was prepared by dissolving 27.6 g (0.2 mole) of K_2CO_3 in ethanol-water solution and 100 g of silica gel. The mixture was stirred at rt for 1~2 hr. The solvent was removed under reduced pressure. Then the powder obtained was activated at 1000°C for 4 hr, and finally stored in a desiccator for subsequent use.

General procedure for the synthesis of α,α′-bis(substituted benzylidene)cycloalkanone. A solution of aromatic aldehyde **1** (2.00 mmole) and cycloalkanone **2** (1.00 mmole) in ethanol was heated under reflux in the presence of a catalytic amount of SiO_2-OK (100 mg) for a period of time required to complete the reaction. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to rt and SiO_2-OK was filtered off. The catalyst was washed with CH_2Cl_2

(2×5 mL) and then the organic layer was washed twice with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to obtain the crude solid product. Drying and recrystallization from ethanol afforded the pure products **3**.

Selected spectral data of some products are given below:

3a. IR (KBr): 1707, 1601, 1568, 1447, 1250, 1179, 932, 764 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.60 (2H, s, =CH–), 7.45-7.35 (10H, m, ArH), 3.13 (4H, s, -CH_2CH_2-).

3c. IR (KBr): 2962, 2841, 1694, 1595, 1506, 1253, 1027, 834 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.58 (2H, s, =CH-), 7.56-6.96 (8H, m, ArH), 3.86 (6H, s, -OCH_3), 3.09 (4H, s, -CH_2CH_2-).

3d. IR (KBr): 2929, 1671, 1637, 1595, 1415, 1130, 786 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.95 (2H, s, =CH-), 7.58-7.28 (8H, m, ArH), 3.03 (4H, s, -CH_2CH_2-).

3e. IR (KBr): 2924, 1623, 1254, 1179, 672 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.60 (2H, s, =CH-), 7.55-7.28 (8H, m, ArH), 3.15 (4H, s, -CH_2CH_2-).

3g. IR (KBr): 3071, 2910, 1688, 1614, 1576, 1463, 1182, 812 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.84 (2H, s, =CH-), 7.49-7.28 (6H, m, ArH), 2.98 (4H, s, -CH_2CH_2-).

3k. IR (KBr): 2938, 1658, 1593, 1556, 1249, 831 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.77 (2H, s, =CH-), 7.47-6.94 (8H, m, ArH), 2.94 (4H, t, -C*H*$_2$CH$_2$C*H*$_2$-), 1.83-1.80 (2H, m, -CH$_2$C*H*$_2$CH$_2$-).

3l. IR (KBr): 2952, 1662, 1609, 1527 1347, 1168, 896, 807, 719 cm^{-1}; ^1H NMR($CDCl_3$): δ 8.34 (2H, s, =CH-), 8.23 (2H, d, *J*= 5.9 Hz, ArH), 7.83 (2H, s, ArH), 7.78 (2H, d, *J* =7.3 Hz, ArH), 7.63 (2H, t, *J*=7.3Hz, ArH), 2.99 (4H, m, -C*H*$_2$CH$_2$C*H*$_2$-), 1.86-176(2H, m, -CH$_2$C*H*$_2$CH$_2$-).

3m. IR (KBr): 2930, 1665, 1606, 1576, 1262, 828 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.73 (2H, s, =CH-), 7.41-7.36 (8H, m, ArH), 2.89 (4H, t, -C*H*$_2$CH$_2$C*H*$_2$-), 1.84-1.78 (2H, m, -CH$_2$C*H*$_2$CH$_2$-).

3n. IR (KBr): 2952, 1662, 1609, 1527 1347, 1168, 896, 807, 719 cm^{-1}; ^1H NMR($CDCl_3$): δ 8.34 (2H, s, =CH-), 8.23 (2H, d, *J* = 5.9 Hz, ArH), 7.83 (2H, s, ArH), 7.78 (2H, d, *J* = 7.3 Hz, ArH), 7.63 (2H, t, *J* = 7.3Hz, ArH), 2.99 (4H, m, -C*H*$_2$CH$_2$C*H*$_2$-), 1.89 (2H, m, -CH$_2$C*H*$_2$CH$_2$-).

3o. IR (KBr): 3093, 2967, 1658, 1595, 1575, 1464, 1138, 827 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.83 (2H, s, =CH-), 7.47-7.26 (6H, m, ArH), 2.75 (4H, t, -C*H*$_2$CH$_2$C*H*$_2$-), 1.88 (2H, m, -CH$_2$C*H*$_2$CH$_2$-).

Acknowledgement

The project was supported by National Natural Science Foundation of China (Grant nos. 29872011 and 29572039), Educational Ministry of China, Educational Department of Hebei Province (Grant no.990104), and Science and Technology Commission of Hebei province.

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