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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

A Facile Synthesis of $\alpha_{,\alpha}$ '-bis(Substituted Benzylidene) Cycloalkanones Catalyzed by KF/Al₂O₃ Under Ultrasound Irradiation

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To cite this article: Ji-Tai Li , Wen-Zhi Yang , Guo-Feng Chen & Tong-Shuang Li (2003) A Facile Synthesis of a, a'bis(Substituted Benzylidene) Cycloalkanones Catalyzed by KF/Al₂O₃ Under Ultrasound Irradiation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:15, 2619-2625, DOI: <u>10.1081/</u> <u>SCC-120021982</u>

To link to this article: <u>http://dx.doi.org/10.1081/SCC-120021982</u>

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SYNTHETIC COMMUNICATIONS[®] Vol. 33, No. 15, pp. 2619–2625, 2003

A Facile Synthesis of α,α'-bis(Substituted Benzylidene) Cycloalkanones Catalyzed by KF/Al₂O₃ Under Ultrasound Irradiation

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ABSTRACT

The condensation of the cyclopentanone or cyclohexanone with aromatic aldehydes catalyzed by KF/Al_2O_3 in MeOH under ultrasound irradiation, result the corresponding 2,5-*bis*(substituted benzylidene) cyclopentanones or 2,6-*bis*(substituted benzylidene) cyclohexanones in good yields.

Key Words: bis(Substituted benzylidene) cycloalkanone; Claisen-Schmidt condensation; Ultrasound; Supported catalyst.

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DOI: 10.1081/SCC-120021982 Copyright © 2003 by Marcel Dekker, Inc. 0039-7911 (Print); 1532-2432 (Online) www.dekker.com

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The α, α' -*bis*(substituted benzylidene) cycloalkanones are used as precursors to potentially bioactive pyrimidine derivatives,^[1] intermediates of agrochemical, pharmaceuticals, and perfumes.^[2] Preparation of α, α' -*bis*(substituted benzylidene) cycloalkanones is usually completed via Claisen-Schmidt condensation between cycloalkanones and aromatic aldehydes catalyzed by solid NaOH^[3–6] or NaOEt,^[7] using conventional heating method. It also has been reported that some compounds, such as *bis*(*p*-ethoxyphenyl)telluroxide (BMPTO),^[8] RuCl₃,^[9] SmI₃,^[10] Cp₂ZrH₂,^[11] TiCl₃(SO₃CF₃),^[12] were used as catalysts. But there were some shortcomings in terms of high cost, difficult preparation, and especially reaction conditions.

Ultrasound has been used more and more frequently in organic synthesis in recent three decades. Compared with traditional methods, this method is more convenient and easily controlled. Great many of organic reactions can be carried in higher yields, shorter reaction time or milder conditions under ultrasound irradiation. Our laboratory has reported the Claisen-Schmidt condensation of acetophenone with various aromatic aldehydes catalyzed by KF/Al₂O₃ under ultrasound irradiation, and the result are better than that under conventional heating condition.^[13] In connection with our on going work on KF/Al₂O₃—catalysis under ultrasound, herein we wish to report the condensation of cycloalkanones with aromatic aldehydes catalyzed by KF/Al₂O₃ in MeOH under ultrasound irradiation.

As reported previously, Claisen-Schmidt condensation of acetophenone with aromatic aldehydes catalyzed by KF/Al₂O₃, the best molar ratio of the catalyst to substrate is 0.8-1.^[13] In this article, the molar ratio of catalyst to cycloalkanone was 1:1. As shown in Table 1 and Sch. 1, the condensation of cyclopentanone or cyclohexanone with a variety of aromatic aldehydes afforded α, α' -bis(substituted benzylidene) cycloalkanones in good yields catalyzed by KF/Al₂O₃ in MeOH at 30-40°C for 0.5-2.5h under ultrasound irradiation. Meanwhile, we observed that KF/Al₂O₃ acted as an efficient catalyst for cross-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 95% EtOH, compounds 3a, 3c, 3d, 3h, and 3i were obtained with 60-90, 60-90, 60-90, 30-50, and 40-60% yields.^[6] While, the present method gave 3a, 3c, 3d, 3h, and 3i in 89, 92, 87, 80, and 73% yields respectively. The condensation of cyclopentanone (1) with furfural (2e) gave 96% yield (3e) catalyzed by KF/Al_2O_3 in 30 min under ultrasound irradiation, and the yield (3e) is higher than that obtained 85% yield catalyzed by KOH in 30 min under ultrasound.^[5]

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Entry	n = 0, Ar	Entry	n = 1, Ar
a	C ₆ H ₅ -	f	C_6H_{5-}
b	p-O ₂ NC ₆ H ₄ -	g	$p-O_2NC_6H_4-$
c	p-H ₃ COC ₆ H ₄ -	h	p-H ₃ COC ₆ H ₄ -
d	C ₆ H ₅ CH=CH-	i	C ₆ H ₅ CH=CH-
e	Furyl	j	Furyl

To test the selectivity of the reaction, we carried out the reaction in ratio (furural/cyclohexanone) of 2:1 and 1:1 (Entry 1j^c). Both the reaction provided the same product $\alpha_{\alpha}\alpha'$ -bis(fururylidene) cyclohexanone (3i). α -(fururylidene) cyclohexanone was not obtained. From these results we can deduce that the yields are, in general, similar or higher than these describe in the Lit.^[5,6,8,11] We also did the experiment catalyzed by KF/Al₂O₃ in the absence of ultrasound, the condensation of cyclohexanone (1) with furural (2j) was carried out in 87% (3j^d) yield using stirring. Compared with literature reported, the main advantages of the present procedure are minimally environmental pollution, cheap, and reusable catalvst,^[13] easier work-up, milder conditions, better yields, and shorter reaction time.

As shown in Sch. 2, a potential mechanism could account for the formation of α, α' -bis(substituted benzylidene) cycloalkanones: the surface of alumina coated with potassium fluoride provides a strong polar environment, which is favorable to many ionic and heterolytic reactions.

EXPERIMENTAL

Liquid aldehydes were purified by distillation prior to use. Melting points were uncorrected. Infrared spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ¹H NMR spectra were measured on VXR-300S (300 MHz) or Bruker AM-400S (400 MHz) spectrometer using TMS as internal standard and CDCl3 as solvent. Mass spectra were determined

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on a VG-7070E spectrometer (EI, 70 eV). Sonication was performed in a Shanghai Branson-CQX ultrasonic cleaner with a frequency of 25 kHz and a nominal power 500 W. The reaction flask was located in the maximum energy area in the cleaner, and the addition or removal of water controlled the temperature of the water bath.

Preparation of the Catalyst (KF-Al₂O₃)

The KF-Al₂O₃ was prepared by dissolving 20 g of KF in 80 mL of water and 30 g of neutral Al₂O₃. The mixture was stirred at $65-75^{\circ}$ C for 1 h. The water was removed under reduced pressure. The resulting free flowing powder was dried at 120°C for 4 h. The content of KF is about 30% (150 mg mixture/mmol KF).

General Procedure

A Pyrex flask (50 mL) was added aromatic aldehyde (1, 2 mmol), cycloalkanone (2, 1 mmol), MeOH (2 mL), and KF-Al₂O₃ (150 mg). The mixture was irradiated in the water bath of an ultrasonic cleaner at the temperature for the period as indicated in Table 2 (Sonication was

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continued until crystals were appeared or aldehyde was disappeared indicated by TLC). The mixture was dissolved in CH₂Cl₂. The catalyst was removed by filtration and washed with CH₂Cl₂. The solvent was evaporated under reduced pressure and the residue was crystallized with dichloromethane/ethanol to give α, α' -bis(substituted benzylidene) cycloalkanones or the residue chromatographed on a column of silica gel using light petroleum (b.p. 60–90°C)/dichloromethane as eluent. The authenticity of the products was established by comparing their melting points with literature and the data of IR, MS, and ¹H NMR spectra.

Table 2. Preparation of α, α' -*bis*(substituted benzylidene) cycloalkanones catalyzed by KF/Al₂O₃ in MeOH under ultrasound irradiation.

Entry	Mole ratio ^a	Time (min)/ temperature (°C)	Product yield ^b (%), (reported)	M.p. (°C) (reported)
a	2:1	40/30-35	89	195–196
			$(84.5),^{[8]}(69),^{[11]}(60-90)^{[6]}$	$(188.5)^{[9]}$
b	2:1	60/35-40	66	253-254
		100/05 10	(81)[6]	$(230-231)^{101}$
с	2:1	120/35-40	92 (52 5) ^[8] (52 60) ^[6]	220-221
			$(53.5),^{101}(60-90)^{101}$	$(210-211)^{10}$
d	2:1	60/35-40	87	224-225
		20125 10	$(93.4),^{to1}(71),^{tr1}(60-90)^{to1}$	(223)
e	2:1	30/35-40	96	1/0-1/1
			$(77.5),^{10},^{10},^{111},^{111},^{113},^{103}$	$(165)^{101}$
f	2:1	60/35-40	62	115–117
			$(64.5),^{[6]}(70),^{[11]}(50-80)^{[6]}$	$(116-117)^{191}$
g	2:1	150/35-40	60	208-210
			$(71.4)^{[8]}$	$(159)^{[8]}$
h	2:1	150/35-40	80	160–162
			$(69.5),^{[8]}(30-50)^{[6]}$	$(203-204)^{[8]}$
i	2:1	150/35-40	73	188–189
			$(71),^{[8]},^{[8]},^{[11]},^{[40-60)}$	$(179 - 180)^{[8]}$
j	2:1	30/35-40	94	145-146
			$(86)^{[8,11]}$	$(145)^{[8]}$
	1:1	30/35-40	93°	
	2:1	150/40	87 ^d	

^aThe mole ratio is aldehyde/cycloalkanone.

^bIsolated yield based on aromatic aldehydes.

^cThe ratio of furural to cyclohexanone is 1:1.

 $^{\rm d} The$ reaction was carried out using magnetic stirrer catalyzed by KF/Al_2O_3 without ultrasound irradiation.

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3b. Yellow platelets from dichloromethane/ethanol. ν_{max} (KBr): 3080, 1680, 1610, 1520, 1350, 1260, 1190, 870, 820, 770 cm⁻¹. $\delta_{\rm H}$ (400 MHz): 3.22 (4H, m, $-CH_2-CH_2-$), 7.67 (2H, s, =CH-), 7.76 (4H, d, J = 8.0 Hz, H_b), 8.33 (4H, d, J = 8.0 Hz, H_a) ppm. m/z (%): 350 (M+, 15), 304 (15), 303 (46), 228 (13), 126 (43), 115 (100), 77 (32), 51 (15), 40 (96).

3c. Yellow platelets from ethanol. ν_{max} (KBr): 3080, 2850, 1680, 1590, 1490, 1430, 1400, 1370, 1300, 1245, 1190, 1023, 923, 830 cm⁻¹. δ_{H} (400 MHz): 3.10 (4H, m, $-\text{CH}_2\text{-CH}_2\text{-}$), 3.88 (6H, s, $-\text{OCH}_3$), 6.98 (4H, d, J = 8.0 Hz, \mathbf{H}_a), 7.58 (2H, s, =CH-), 7.59 (4H, d, J = 8.0 Hz, \mathbf{H}_b) ppm. m/z (%): 320 (M+, 60), 305 (10), 289 (23), 160 (25), 146 (50), 131 (48), 121 (63), 115 (34), 103 (75), 91 (30), 77 (31), 40 (100).

3g. Yellow platelets from dichloromethane/ethanol. ν_{max} (KBr): 3100, 1680, 1590, 1520, 1490, 1350, 860, 810 cm⁻¹. $\delta_{\rm H}$ (300 MHz): 1.86 (2H, m, -CH₂CH₂CH₂-), 2.95 (4H, m, -CH₂CH₂CH₂-), 7.60 (4H, d, J=8.7, H_b), 7.80 (2H, s, =CH-), 8.28 (4H, d, J=8.7 Hz, H_a) ppm. m/z (%): 364 (M+, 6), 348 (30), 318 (15), 290 (19), 245 (11), 216 (28), 168 (19), 153 (20), 128 (50), 115 (71), 103 (42), 91 (29), 77 (45), 65 (80), 55 (8), 51 (23), 40 (100).

3h. Yellow needles from ethanol. ν_{max} (KBr): 2850, 1670, 1590, 1240, 1150–1101, 1018, 930, 828 cm⁻¹. δ_{H} (300 MHz): 1.76 (2H, m, -CH₂CH₂CH₂-), 2.94 (4H, m, -CH₂CH₂CH₂-), 3.86 (6H, s, -OCH₃), 6.95 (4H, d, J = 8.7, H_a), 7.47 (4H, d, J = 8.7 Hz, H_b), 7.78 (2H, s, =CH–) ppm. m/z (%): 334 (M+, 19), 306 (15), 270 (11), 200 (11), 172 (11), 160 (15), 147 (62), 131 (47), 121 (55), 115 (40), 103 (100), 91 (38), 77 (38), 55 (9), 40 (15).

3i. Yellow platelets from dichloromethane/ethanol. ν_{max} (KBr): 3050, 2890, 1605, 1590, 1580, 1455, 1295, 1240, 1160, 990–910, 750, 700 cm⁻¹. δ_{H} (400 MHz): 1.91 (2H, m, -CH₂CH₂CH₂–), 2.83 (4H, m, -CH₂CH₂CH₂–), 7.00 (2H, d, J=15.6, =CH-CH=CH–), 7.10 (2H, dd, J=15.6, 11.2, =CH-CH=CH–), 7.32 (2H, t, J=7.2, H_e), 7.38 (4H, dd, J=7.6,7.2, H_a), 7.50 (2H, d, J=11.2, =CH-CH=CH–), 7.52 (4H, d, J=7.6, H_b) ppm. m/z (%): 326 (M+, 38), 249 (9), 235 (30), 178 (21), 165 (13), 141 (32), 128 (32), 115 (53), 91 (100), 77 (17), 65 (11), 40 (68).

ACKNOWLEDGMENT

NSFC (29872011) and NSF of Hebei Province supported the project (203107).

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Received in Japan September 21, 2002



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