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The preparation of α,α'-bis(substituted benzylidene) cycloalkanones

Li Hai-Ying, Yang Wen-Zhi*, Yang Jiang-Bin, Huang shun-sheng and Li Ji-Tai

College of Pharmacy, Hebei University, Baoding 071002, P.R.China

Claisen–Schmidt condensation of cyclopentanone or cyclohexanone with aromatic aldehydes catalysed by potassium fluoride supported on molecular sieve or potassium fluoride supported on alumina results 2,5-bis(substituted benzylidene) cyclopentanones or 2,6-bis(substituted benzylidene) cyclohexanones in 56–95% and 60–98% yields respectively in refluxed methanol.

Keywords: α,α'-bis(substituted benzylidene)cycloalkanones, Claisen–Schmidt condensation, potassium fluoride

Since α,α'-bis(substituted benzylidene) cycloalkanones are precursors for the synthesis of bioactive pyrimidine derivatives[1] and perfumes,[2] the condensation of cyclohexanone and cyclopentanone with aromatic aldehydes is of interest. The preparation of α,α'-bis(substituted benzylidene) cycloalkanones is usually achieved via a Claisen–Schmidt condensation between the cycloalkanone and aromatic aldehydes catalysed by solid NaOH[3-6] or NaOEt.[7] It also has been reported that some compounds, such as bis(p-ethoxyphenyl)telluroxide (BMPTO),[8] $RuCl_3$,[9] SmI_3,[10] Cp_2ZrH_2,[11] $TiCl_3(SO_3CF_3)$,[12] can be used as catalysts. There were some shortcomings in these methods in terms of high cost, difficult preparation and especially reaction conditions. Recently inorganic solid supports such as alumina, silica gel and montmorillonite have been used to give mild conditions, and a better yield. Our laboratory has reported the Claisen–Schmidt condensation of acetophenone with various aromatic aldehydes catalysed by KF/Al_2O_3 under ultrasound irradiation. The results were better than those under conventional heating condition.[13] We now report our results on the condensation reaction between cyclohexanone and aromatic aldehydes catalysed by potassium fluoride supported on inorganic solid supports (such as alumina, molecular sieve and kieselguhr).

We first examined the effect of different solid supports coated with KF on the reaction between cyclohexanone and benzaldehyde. As shown in Table 1, the best results were obtained with the mixture of composition cyclohexanone: benzaldehyde=1:2 catalysed by potassium fluoride supported on alumina or molecular sieve. Reaction temperature also significantly affected the yield and increasing the reaction temperature with either solid support coated with potassium fluoride enhanced the yield.

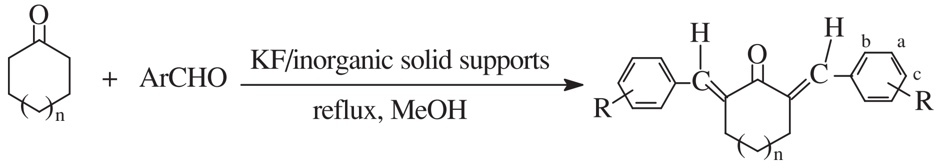
Table 1 Claisen–Schmidt condensation between cyclohexanone and benzaldehyde catalysed by using KF coated with different solid supports

Solid support	Methods	Time /h	Temperature /°C	Product yield/%
Kieselguhr	A	16	25	0
	B	8	64.6	65
Molecular sieve (5Å)	A	16	25	37
	B	8	64.6	90
Alumina	A	16	25	91
	B	8	64.6	93

Method A: The reaction was carried out using magnetic stirrer catalysed by KF-solid support in methanol.
Method B: The reaction was carried out using magnetic stirrer catalysed by KF-solid support in refluxing methanol
The molar ratio of cyclohexanone to catalyst (150mg mixture/mmol KF) was 1:1.

Taking the reaction of benzaldehyde with cyclopentanone as an example, the effect of the amount of KF-alumina on the condensation reaction was investigated. The yields were highly dependent on the amount of KF-alumina. The molar ratio of KF-alumina to substrate strongly affected the yield of products. The best molar ratio was 1.0–1.2 to give α,α'-dibenzylidenecyclohexanone in 93–95% yields. The ratio of 0.8 and 1.5 both led to a decrease in yields (78% and 77% respectively). In the absence of KF/Al_2O_3, the condensation did not take place.

The reaction solvent also plays an important role in this reaction. With the other reaction conditions fixed, the condensation of cyclohexanone with benzaldehyde catalysed by KF-alumina, the reaction was carried out under reflux for 8h, using as solvents:- ethanol, benzene, toluene, diethyl ether, petroleum ether (b.p.,60–90°C) and dichloromethane. The yields obtained were lower than that in refluxing methanol.



1 **2a-e** **3a-j**

Entry	*n* = 0, Ar	Entry	*n* = 1, Ar
a	C_6H_5-	f	C_6H_5-
b	*p*-ClC_6H_4-	g	*p*-ClC_6H_4-
c	*p*-$H_3COC_6H_4$-	h	*p*-$H_3COC_6H_4$-
d	$C_6H_5CH=CH$-	i	$C_6H_5CH=CH$-
e	Furyl	j	Furyl

Scheme 1

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* Correspondence. E-mail: yangwz@mail.hbu.edu.cn

Different attempts to selectively of mono-condense of benzaldehyde on one side of cyclohexanone were not successful. For example, we carried out the reaction in ratio (benzaldehyde /cyclohexanone) of 3:1 and 1:1 respectively. Both reactions provided the same product α,α′-dibenzylidenecyclohexanone and the yields based on the benzaldehyde obtained were 93% and 56% respectively. No α-benzylidenecyclohexanone was obtained.

In order to extend the scope of this method, the condensations of aromatic aldehydes with cycloalkanones in the presence of KF-molecular sieve and KF-alumina were successfully performed. The results are summarised in Table 2. As shown in Table 2 and Scheme 1, the condensation of cyclopentanone or cyclohexanone with a variety of aromatic aldehydes afforded α,α′-bis(substituted benzylidene) cycloalkanones in good yields catalysed by KF-alumina or KF-molecular sieve in refluxing methanol for 3–480 min. A good range of condensation reactions proceeded smoothly. Success of the reaction with cyclopentanone is remarkable. Meanwhile, we observed that KF-alumina or KF-molecular sieve 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 catalysed 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 94%, 86%, 93%, 98%, 60% and 94%, 94%, 87%, 56%, 63% yields respectively. When the aldehydes has an electron-donating –OH group reaction with cyclopentanone or cyclohexanone catalysed by KF- molecular sieve or KF-alumina under refluxing methanol, no reaction took place. From the Table 2, we can deduce that the yields are, in general, similar or higher than these described in the literatures.[5,6,8,11] Compared with literature reports, the main advantages of the present procedure are minimally environmental pollution, cheap and reusable catalyst,[13] easier work-up, milder conditions and better yields.

Experimental

Aromatic aldehydes were purified by distillation prior to use. Melting points were uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on Bruker AM-400S (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were determined on a VG-7070E spectrometer (EI, 70eV).

Preparation of the catalyst (KF-solid supports)

Anhydrous potassium fluoride (20 g) was dissolved in distilled water (80 ml) and mixed with solid supports (30g), such as neutral alumina, kieselguhr or Molecular sieve respectively. The mixture was stirred at 65–75°C for 1h. 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% (150mg mixture/mmol KF).

General procedure

The cycloalkanone (**1,** 1 mmol) and aromatic aldehydes (**2**, 2 mmol) are mixed with MeOH (2 ml). KF- inorganic solid support (150 mg) is added, and the mixture is refluxed for the period as indicated in Table 2 (Refluxing was continued until crystals were appeared or aldehyde was disappeared indicated by TLC). After cooling, the mixture was dissolved in CH_2Cl_2. The catalyst was removed by filtration and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure and the residue was crystallised with dichloromethane/ ethanol to give α,α′-dibenzylidenecycloalkanone. The authenticity of the products was established by comparing their melting points with the literature (see Table 2) and data of IR, MS and ^{1}H NMR spectra.

3c: Yellow platelets from ethanol; ν_{max} (KBr); 3080, 2850, 1680, 1590, 1490, 1430, 1400, 1370, 1300, 1245, 1190, 1023, 923, 830cm^{-1}; δ_H (400 MHz): 3.10 (4H, m, $-\mathbf{CH_2}-\mathbf{CH_2}$-), 3.88 (6H, s, $-O\mathbf{CH_3}$), 6.98 (4H, d, J=8.0 Hz, $\mathbf{H_a}$), 7.58 (2H, s, =C**H**-), 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).

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, $-CH_2CH_2CH_2-$), 2.94 (4H, m, $-CH_2CH_2CH_2-$), 3.86 (6H, s, $-OCH_3$), 6.95 (4H, d, J=8.7, Ha), 7.47 (4H, d, J=8.7 Hz, Hb), 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, $-CH_2CH_2CH_2-$), 2.83 (4H, m, $-CH_2CH_2CH_2-$), 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, Hc), 7.38 (4H, dd, J=7.6,7.2, Ha), 7.50 (2H, d, J=11.2, =CH–CH=CH–), 7.52 (4H, d, J=7.6, Hb) 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).

Table 2 Preparation of α,α′-bis(substituted benzylidene) cycloalkanones catalysed by KF-molecular sieve or KF-alumina in refluxed methanol

Entry	Method	Time/min	Product yield[a]/%, (Reported)	m.p./(°C) (Reported)
a	A	15	94 (84.5)[8], (69)[11], (60–90)[6]	190–191
	B	180	94	(188.5)[9]
b	A	3	98 (80)[14]	225–227
	B	80	95	(224–226)[14]
c	A	20	86 (53.5)[8], (60–90)[6]	220–221
	B	180	94	(210–211)[8]
d	A	20	93 (93.4)[8], (71)[11], (60–90)[6]	224–225
	B	120	87	(223)[9]
e	A	30	91 (77.5)[8], (67)[11], (85)[5]	165–167
	B	120	85	(165)[8]
f	A	480	93 (64.5)[8], (70)[11], (50–80)[6]	115–117
	B	480	90	(116–117)[9]
g	A	180	93 (81)[14]	147–148
	B	120	85	(146–147)[14]
h	A	480	98 (69.5)[8] (30–50)[6]	163–165
	B	480	56	(203–204)[8]
i	A	480	60 (71)[8], (84)[11], (40–60)[6]	186–188
	B	480	63	(179–180)[8]
j	A	40	92(86)[8,11]	145–146
	B	120	87	(145)[8]

[a]Isolated yield based on aromatic aldehydes

Method A: The reaction was carried out using magnetic stirrer catalysed by KF-alumina in refluxed methanol.

Method B: The reaction was carried out using magnetic stirrer catalysed by KF-molecular sieve in refluxed methanol.

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