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Solvent-Free Crossed Aldol Condensation of Cyclic Ketones with Aromatic Aldehydes Assisted by Microwave Irradiation

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Summary. A fast alumina-promoted crossed aldol-condensation reaction of aldehydes and cyclic ketones under microwave irradiation is described. This process is simple, efficient, and environmentally benign and proceeds in fairly high yield without any self-condensation.

Keywords. Alumina; Aldol reactions; Catalysts; Microwave irradiation; Cyclohexanone; Cyclopentanone.

Introduction

Due to the importance of α,α'-bis(substituted benzylidene)cycloalkanones as useful precursors for potentially bioactive pyrimidine derivatives, condensation of cycloalkanones with aldehydes to give the corresponding α,α'-bis(substituted benzylidene)cycloalkanones is of special interest [1].

Usually, this condensation can be performed using strong acid or base catalysts. However, the presence of strong acid or base often induces side reactions and thus gives the corresponding products in low yields [2]. Several metal complexes, such as Mn (II), Fe (II), Co (II), Ni (II), Cu (II), and Zn (II), have also been reported as catalysts for these reactions [3].

Among these metal complexes, Co (II)-bipyridyl is the most reactive one, but the yield of the condensation product starting from cyclopentanone and benzaldehyde is only 38%. Rh (III) porphyrin was also applied for this aldol condensation but similar to other metal complexes the yields of the reaction are low [4]. Cp_2TiPh_2 and anhydrous $RuCl_3$ have also been used to catalyze the crossed aldol condensation [5, 6]. Good yields of the products can only be obtained at high temperature

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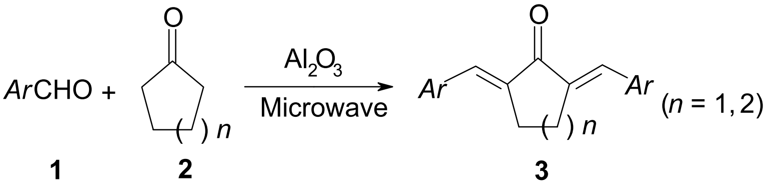

Scheme 1

in sealed tubes. The methods reported so far have serious limitations. There is a need to develop more convenient and efficient methods for this type reaction.

In recent years, microwave-assisted reactions have attracted great interest because of the simplicity of the process, enhanced reaction rates, and greater selectivity. Particularly, solvent-free reactions have gained popularity as they provide an opportunity to work with open vessels. This avoids the risks when working under high pressure conditions and provides an easy opportunity to scale-up the reaction. Thus microwave irradiation, which has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds under solvent-free conditions, is used to enhance the rates of many classical organic reactions [7–10].

Furthermore, microwave promoted solid-phase heterogeneous reactions are environmentally benign. Among the various heterogeneous catalysts alumina is attractive because it can be reused, it is environmentally compatible, its costs are low, it is non-toxic, and it is experimentally simple to apply [11–13].

We report here that acidic alumina efficiently catalyzes the crossed aldol condensation reaction between different cycloalkanones and aromatic aldehydes under microwave irradiation (Scheme 1).

Results and Discussions

Several classes of solids have commonly been used to catalyze organic transformations at their surface including alumina, silica gels, and clays. Acidic alumina, the material used commonly for column chromatography, is certainly one of the most interesting of these solids. Its surface properties allow many different organic transformations to occur [14–15].

We report here our results on the alumina catalyzed, fast, solvent-free condensations of cyclic ketones with different aromatic aldehydes under microwave irradiation (Table 1).

Green chemistry asks for the development of environmentally improved routes and the use of sustainable resources. The recovery and the reuse of the catalyst and the solvent is an important asset. After having separated the product by eluting with a suitable solvent such as CH_2Cl_2, the catalyst (Al_2O_3) could be recovered easily by drying at 100°C for several hours. Investigations using benzaldehyde and cyclopentanone as model substrates showed that the recovered alumina could be successfully reused several times. The recovered Al_2O_3 could be used five times and similar yields were obtained in all runs (Table 2, entry 5).

The aldol condensation of different substituted benzaldehydes and cyclopentanone were carried out in the presence of acidic, neutral, and basic alumina. The results are summarized in Table 3.

Table 1. Preparation of α,α'-bis(substituted benzylidene)cycloalkanones in solvent-free conditions under microwave irradiation

Entry	*Ar*	*n*	Time/sec	Products[a]	Alumina/g	Power/%	Isolated Yield/%	mp/°C
1	C_6H_5	1	60-60-60-60	**3a**	4	80	98	189 (Ref. [5] 188.5)
2	2-furyl	1	30-30-60-60	**3b**	4	100	92	164–166 (Ref. [16] 160–162)
3	*p*-$CH_3OC_6H_5$	1	30-30-60-60-60	**3c**	6.5	100	95	212 (Ref. [5] 212)
4	*m*-$CH_3OC_6H_5$	1	130-60-60-30	**3d**	4	100	95	144–146
5	*p*-BrC_6H_5	1	180-30	**3e**	3	60	99	251–253 (Ref. [5] 212)
6	*p*-$CH_3C_6H_5$	1	60-120-60-60	**3f**	5.5	80	98	233–235
7	$C_6H_5CH{=}CH$	1	60-120	**3g**	6.5	60	97	225 (Ref. [5] 223)
8	*m*-ClC_6H_5	1	120-120-60	**3h**	4	100	95	175–176 (Ref. [18] 177)
9	*o*-ClC_6H_5	1	120-120-60	**3i**	4	80	98	160–163
10	C_6H_5	2	180-30	**3j**	4.5	100	97	116–117 (Ref. [5] 116–117)
11	*p*-$CH_3OC_6H_5$	2	40-40-60	**3k**	8	100	94	205 (Ref. [5] 204)
12	*p*-$CH_3C_6H_5$	2	60-120-60-60	**3l**	6	100	89	167–169 (Ref. [5] 170)
13	*p*-BrC_6H_5	2	30-30-60-120-60	**3m**	3	80	96	163–165
14	*p*-$NO_2C_6H_5$	2	120-120-120-120	**3n**	6	100	87	159 (Ref. [5] 158.5)
15	*m*-ClC_6H_5	2	120-120-120-120	**3o**	4	80	72	105–107
16	$C_6H_5CH{=}CH$	2	120-30	**3p**	7	100	95	180 (Ref. [5] 179)
17	2-furyl	2	30-30-60-30	**3q**	2	100	98	143–145 (Ref. [16] 140–141)

[a] Products were characterized by ^1H NMR, ^{13}C NMR, IR, and by comparison of their physical properties with those reported in the literature

Table 2. Studies on the reuse of Al_2O_3

Round	Yield/%	Al_2O_3 recovered/%
1	92	99
2	90	98
3	88	98
4	88	99
5	86	98

Table 3. Condensation reaction of benzaldehyde and cyclopentanone in different alumina

Entry	Type of alumina	Time/min	Isolated yield/%
1	Acidic alumina	4 min	98
2	Neutral alumina	10 min	–
3	Basic alumina	10 min	10

Table 4. Comparison of some results obtained from using acidic alumina under MW irradiation, that listed in Table 1 (Method A), with other methods (Method B) [19] and (Method C) [16]

Entry	Product	Reaction time (yield/%)		
		Method A	Method B	Method C
1	**3a**	4 min (98)	6 h (92)	5 min (84.5)
6	**3f**	5 min (98)	6 h (90)	–
7	**3g**	3 min (97)	10 h (80)	5 min (93.4)
9	**3i**	5 min (98)	6 h (87)	–
10	**3j**	4 min (97)	6 h (90)	7 min (64.5)
12	**3l**	5 min (89)	6 h (94)	–
14	**3n**	8 min (87)	6 h (91)	7 min (71.4)
16	**3p**	2.5 min (95)	10 h (82)	7 min (71)

Only acidic alumina gave high yields of product under microwave irradiation (98%, Table 3, entry 1). When neutral alumina was used, the reaction could not be observed after 10 min microwave irradiation. Using basic alumina under similar conditions the desired product **3a** was obtained but in a disappointingly low yield (10%). Therefore acidic alumina was selected as solid catalyst for the subsequent reactions.

A comparison of our results with those reported in the literature clearly shows the advantage of using microwave irradiation in the presence of acidic alumina as catalyst (Table 4) [16, 19]. Employing our method (Method A) only 2.5–8 min were needed for almost complete transformation, whereas the condensation catalyzed by $FeCl_3 \cdot 6H_2O$ (Method B) [19] needs 6–10 hours. It has also been found that lower yields were obtained using acetonitrile as solvent and bis(p-methoxyphenyl)teluroxide (*BMPTO*) as catalyst under microwave irradiation (Method C) [16].

In summary, microwave-assisted solvent-free reactions were employed to synthesize α,α'-bis(benzylidene)cycloalkanone derivatives. The method not only offers substantial improvement in yield over conventional heating methods but also eliminates the use of hazardous solvents. Other advantages of this method include the fact that it is environmentally benign and an economical procedure. The short reaction time and the simplicity of the performance using a non-aqueous work-up are further advantages of our method.

Experimental

Melting points were measured on an Electro thermal 9100 apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 783 Infrared spectrophotometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-250 Avance spectrometer at 250 and 62.90 MHz, respectively. Aldehydes and ketones were obtained from Fluka (Buchs, Switzerland) and Merck and were used without further purification. An unmodified domestic household microwave oven (Philco, MTO8E29, 1250W) equipped with inverter technology, which provides a realistic control of the microwave power to the desired level (20–100%) was used for microwave heating. The MW oven was operated at reduced MW-power level of 60% (750 W), 80% (1000 W), and total power level 100% (1250 W).

General Procedure

Ketone (1 mmol), aromatic aldehyde (2 mmol), and 2–7 g of acidic alumina (Table 1) were added in a Pyrex beaker (20 cm^3). The mixture was stirred for 30 s until a free flowing powder was obtained. The whole mixture was then irradiated in the microwave oven for appropriate times. The sample was thoroughly mixed outside for 30 s and again irradiated for another time period. This intermittent heating-stirring cycle was repeated for the total irradiation time as required to complete the reaction (TLC, Table 1). The reaction mixture was then eluted with CH_2Cl_2 (20 cm^3) and the extract was dried over Na_2SO_4 and the solvent was evaporated to leave the crude product which was further purified by recrystallization from ethanol.

3d: Yellow crystal, yield 95%, mp 212°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.04$ (s, $2CH_2$), 3.78 (s, $2OCH_3$), 6.37–7.49 (m, $6CH_{furyl}$), 7.38 (s, CH_{vinyl}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 26.93$ (CH_2), 55.70 (OMe), 115.48, 116.38, 123.69, 130.10, 134.21 (5CH), 137.51, 137.92, 160 (3C), 190.01 (C=O) ppm; IR (KBr): $\bar{\nu} = 3020$ (=C-H_{Str}), 2995 (C-H_{Str}), 2915 (C-H_{Str}), 1780 (C=O) cm^{-1}.

3i: Yellow crystal, yield 98%, mp 159–167°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.92$ (s, $2CH_2$), 6.90–7.85 (m, $8CH_{arom}$), 8.17 (s, $2CH_{vinyl}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 26.93$ (CH_2), 127.00, 130.43, 130.50, 130.60 (4CH), 134.23, 136.44, 137.50 (3C), 139.68 (CH), 191.01 (C=O) ppm; IR (KBr): $\bar{\nu} = 3020$ (=C-H_{Str}), 2920 (C-H_{Str}), 1780 (C=O) cm^{-1}.

3k: Yellow crystal, yield 97%, mp 205°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.82$ (quin, $J = 5.7$ Hz, CH_2), 2.93 (t, $J = 5.7$ Hz, $2CH_2$), 3.86 (s, $2OCH_3$), 6.95 (d, J = 8.6 Hz, $4CH_{arom}$), 8.10 (s, CH_{vinyl}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.43$ (CH_2), 28.92 (CH_2), 55.70 (OMe), 114.29 (CH), 129.13 (C), 132.63 (CH), 134.73 (C), 136.89 (CH), 160.31(C), 190.55 (C=O) ppm; IR (KBr): $\bar{\nu} = 3020$ (=C-H_{Str}), 2910 (C-H_{Str}), 1650 (C=O) cm^{-1}.

3m: Yellow crystal, yield 97%, mp 164°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.69$ (quin, $J = 6.2$ Hz, CH_2), 2.78 (t, $J = 6.2$ Hz, $2CH_{2\ allyl}$), 7.22–7.61 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.55$ (CH_2), 30.15 ($CH_{2\ allyl}$), 124.73 (C-Br), 133.41 (CH meta to Br), 133.57 (C ortho to Br), 136.48 (C_{ipso}), 137.60 (CH_{vinyl}), 138.27 (*C*=CH), 191.53 (C=O) ppm; IR (KBr): $\bar{\nu} = 3020$ (C-H_{Str}), 2920 (C-H_{Str}), 2820 (C-H_{Str}), 1720 (C=O), 1600 (C=C), 830 (C-H_{OOP}) cm^{-1}.

3o: Yellow crystal, yield 72%, mp 106°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.83$ (quin, $J = 6.5$ Hz, CH_2), 2.91 (t, $J = 6.5$ Hz, $2CH_2$), 7.34–7.44 (m, 8H), 7.72 (s, CH_{vinyl}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.15$ (CH_2), 28.72 ($2CH_{2\ allyl}$), 128.88, 128.99, 130.05, 130.29, 134.73, 135.96 (6C), 137.43 (=CH_{vinyl}), 138.01 (*C*=CH), 190.04 (C=O) ppm; IR (KBr): $\bar{\nu} = 3050$ (C-H_{Str}), 2935 (C-H_{Str}), 2860 (C-H_{Str}), 2830 (C-H_{Str}), 1720 (C=O) cm^{-1}.

3q: Brown crystal, yield 98%, mp 145°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.79$ (quin, $J = 6.2$ Hz, CH_2), 2.91 (t, $J = 6.2$ Hz, $2CH_2$), 6.42–7.46 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 22.04$ (CH_2), 28.36 ($2CH_2$), 112.70, 116.43, 123.73, 144.90 (4CH), 133.42, 153.15 (2C), 189.34 (C=O) ppm; IR (KBr): $\bar{\nu} = 3125$ (C-H_{Str}), 2925 (C-H_{Str}), 1680 (C=O) cm^{-1}.

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