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Microwave assisted green synthesis of α,ά- bis(substituted-benzylidene) alkanones catalyzed by $NbCl_5$

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Abstract

The catalytic application of $NbCl_5$ as a heterogeneous catalyst was explored for the synthesis of α, ά- bis (substituted- benzylidene) alkanones under solvent-free conditions. The results showed that aldehydes bearing electron–releasing substituents on phenyl-ring favored the formation of product in good to excellent yields with reaction times ranging between 3 and 7 min. In addition, furfural, cinamaldehyde, thiophene-2-carbaldehyde and 5-methylthiophene-2-carbaldehyde were investigated in aldol reaction, and the results showed excellent yields. The microwave irradiation gave excellent yields at lower reaction time compared to room temperature (1.5-5 h) and thermal conditions (80 ^{0}C, 15-45 min). The microwave irradiation afforded selectively cross aldol products.

Keywords: Niobium pentachloride; solvent-free; aryl aldehyde; microwave irradiation.

Introduction

Aldol condensation is an important reaction in the biosynthesis of carbohydrates, and it is used for the synthesis of α, β–unsaturated ketones, which have great potential and valuable intermediates in organic synthesis [1]. This powerful C-C forming reaction is usually carried out in organic solvents between the active carbonyl and methylene groups to produce α, β–unsaturated carbonyl compounds in the presence of either a base or an acid. The corresponding products could be viewed as core structure of bioactive compounds, intermediates for agricultural, pharmaceuticals, perfumes and cytotoxic analogous [2]. Numerous methods are known to generate the aldol products over the last three decades. The conventional methods involve the use of strong acids or bases [3]. Recently, the use of heterogeneous catalysts such as polystyrene-supported sulfonic acid [4], BF_3-Et_2O [5], hydrotalcite [6], sulfamic acid [7], fluoroalkylated 1,4-disubstituted [1,2,3] triazole organocatalyst [8], silica chloride [9], NaOAc [10], a sulfonated carbon nanocage [11], sulfated zirconia [12] and cetyl trimethyl ammonium bromide [13] has been reported for the aldol condensation of cycloalkanones. Some of the above methods suffer from long reaction times, low yields, environmental pollution, side reactions, hazardous solvents and expensive catalysts. Therefore, we were encouraged to search for cleanly and efficiently heterogeneous catalyst for

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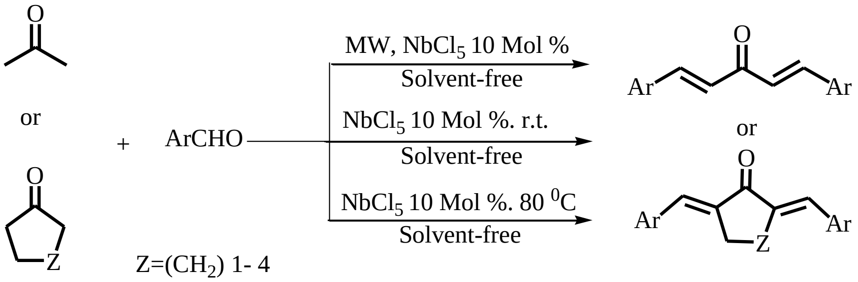
the aldol condensation reaction under environmentally friendly conditions in high yields and short reaction times.

On a different note, microwave irradiation which is used for the synthesis of organic compounds is one of the important techniques in green chemistry. The microwave technique has some benefits including accelerating the rate of reaction which reduces time from days and hours to minutes, increasing yields, improving reproducibility, reducing side reactions and making synthesis method easier than conventional heating [14].

Now, in continuation of our ongoing research on the application of heterogeneous catalyst in organic synthesis [15-19], we describe the catalytic activity of $NbCl_5$ under mechanical stirring and microwave irradiation conditions for green synthesis of α, ά-bis (substituted-benzylidene) alkanones (Scheme 1).



Scheme 1.

Experimental

General

All chemicals were obtained from Merck and were used without further purification. Melting points were measured on Electro thermal 9100 apparatus. Microwave synthesizer (Microsynth, Microwave labstation, Milestone) was used for synthesis of products. IR spectra were recorded on a Perkin-Elmer 783 infrared spectrophotometer. ^{1}H and ^{13}C- NMR spectra were obtained with a Bruker at 250 and 62.9 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a GC-17A Shimadzu & MS-QP 5050 with DI at 7 0 e V.

General procedure for the synthesis of α, ά-bis (substituted-benzylidene) alkanones under microwave irradiations

Alkanone (1 mmol), aromatic aldehyde (2 mmol) and $NbCl_5$ (10 mol%) were taken in conical flask and mixed well. The prepared mixture was subjected to microwave irradiation at 180 W at appropriate times in cycles of 30 seconds. After completion, the reaction was quenched by the addition of saturated aq. $NaHCO_3$ solution and the product was extracted with ethyl acetate (3×15 mL). The organic layer was dried and concentrated under reduced pressure to obtain the crude product. The product was recrystallized from ethanol to afford the pure product which was characterized by ^{1}H &^{13}C-NMR, MS and IR spectroscopic analysis. All of the physical and spectroscopic data were compared with those reported in the literature.

General procedure for the synthesis of α, ά-bis (substituted-benzylidene) alkanones at room/thermal conditions

A mixture of alkanone (1 mmol), aromatic aldehyde (2 mmol) and NbCl$_5$ (10 mol%) was stirred at ambient/thermal (80 ^{0}C) conditions under solvent-free conditions. The progress of the reaction was monitored by thin layer chromatography. After completion, the reaction was quenched by the addition of saturated aq. NaHCO$_3$ solution and the product was extracted with ethyl acetate (3×15 mL). The organic layer was dried and concentrated under reduced pressure to obtain the crude product. The product was recrystallized from ethanol to afford the pure product which was characterized by ^{1}H &^{13}C-NMR, MS and IR spectroscopic analysis. All of the physical and spectroscopic data were compared with those reported in the literature.

Spectral data for selected products

Melting points were reported in the literature [20-23].

(2*E*, 5*E*)- 2,5- bis (4-methylbenzilidene) cyclopentanone (Table 1, Entry 4)

Yellow Solid; mp= 243-245^{o}C (lit^{20}. 244-246^{0}C); IR (KBr, νmax, cm^{-1}): 3079, 3030, 2941, 2882, 2841, 1695, 1631, 1591, 1581, 1551, 1501, 1381, 1278, 1245, 1171, 1125, 981, 811, ^{1}H-NMR (250MHz, CDCl$_3$): δ 2.41 (s, 6H), 3.10 (s, 4H), 7.25 (d, J= 7.5 Hz, 4H), 7.50 (d, J= 7.5 Hz, 4H), 7.58 (s, 2H), ^{13}C-NMR, (62.9 MHz, CDCl$_3$): δ 21.51, 26.51, 129.51, 130.81, 133.2, 133.8, 136.52, 139.72,196.41, MS: m/z (%) 290 (2.4, M^{+}+2), 277 (100), 263 (23), 247 (66), 199 (56), 184 (24), 167 (46), 153 (95), 145 (54), 128 (95), 115 (95), 102 (46), 91 (27), 77 (93).

(2*E*, 5*E*)- 2, 5- bis (2-nitrobenzylidene) cyclopentanone (Table 1, Entry 7)

Deep red Solid; mp= 160-162^{o}C (lit^{21}. 158-159^{0}C); IR (KBr, νmax, cm^{-1}): 3080, 3051, 2950, 2881, 1681, 1622, 1600, 1563, 1505, 1466, 1431, 1337, 1235, 1176, 981, 854, 773, 749, 733, 691, 662. ^{1}H-NMR (250MHz, CDCl$_3$): δ 2.88 (s, 4H), 7.58 (d, J= 7.8 Hz, 2H), 7.70 (m, 1H), 7.86 (s, 1H), 8.12 (d, J= 7.8 Hz, 1H). ^{13}C-NMR, (62.9 MHz, CDCl$_3$): δ 26.1, 125.0, 129.5, 130.5, 131.3, 132.2, 133.1, 140.0, 148.9, 194.5. MS: m/z (%) 350 (1, M^{+}), 304 (7, M-NO$_2$), 287 (100), 269 (2), 259 (5), 231 (7), 197 (8), 153 (18), 127 (47), 115 (39).

(2*E*, 6*E*)- 2, 6- bis (4-metoxybenzylidene) cyclohexanone (Table 1, Entry 14)Yellow Solid; mp= 202-204 ^{o}C (lit^{21}. 203-204^{0}C); IR (KBr, νmax, cm^{-1}): 3061, 3041, 2989, 2822, 1649, 1579, 1550, 14963, 1414, 1300, 1241, 1159, 1131, 1011, 961, 831. ^{1}H-NMR (250MHz, CDCl$_3$): δ 1.77 (m, 2H), 2.91 (t, 4H), 3.81 (s, 6H), 6.91 (d, J= 8.75 Hz, 4H), 7.43 (d, J= 8.75 Hz, 4H), 7.75 (s, 2H), ^{13}C-NMR, (62.9 MHz, CDCl$_3$): δ 23.1, 28.4, 55.2, 113.8, 128.8, 132.1, 134.4, 136.4, 159.8, 190.0. MS: m/z (%) 335 (11, M+1), 334 (100, M^{+}), 319 (11), 277 (20), 246 (18), 215 (8), 167 (10), 153 (25), 145 (16), 121 (32), 115 (53), 102 (63), 91 (44), 77 (69).

(2*E*, 6*E*)- 2, 6-bis (4-chlorobenzylidene) cyclohexanone (Table 1, Entry 16)

Yellow Solid; mp= 143-145 ^{o}C (lit^{21}. 147-148^{0}C); IR (KBr, νmax, cm^{-1}): 3099, 3031, 2951, 2881, 1664, 1599, 1567, 1480, 1401, 1395, 1260, 1155, 1141, 1121, 1086, 1001, 956, 828, 815, 790. ^{1}H-NMR (250MHz, CDCl$_3$): δ 1.81 (quin, J= 6.3 Hz, 2H), 2.90 (t, J=

6.3 Hz, 4H), 7.40 (m, 8H), 7.74 (s, 2H). ^{13}C-NMR, (62.9 MHz, $CDCl_3$): δ 22.7, 28.5, 128.6, 131.5, 134.2, 134.5, 135.7, 136.5, 189.8. MS: m/z (%) 342 (5, M^+), 344 (3, M+2), 346 (0.6, M+4), 309 (5), 307 (12), 281(4), 279 (14), 244 (16%, M-99), 215 (16), 168 (15), 151 (37), 127 (63), 114 (100).

(2*E*,6*E*)-2,6-bis(2-furylmethylene) cyclohexanone (Table 1, Entry 18)

Brown crystal; mp= 141-143 °C(lit[22]. 140-141^{0}C); IR (KBr, νmax, cm^{-1}): 3124, 2924, 1681. ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.78 (quin, J=6.2 Hz, 2H), 2.92 (t, J=6.2 Hz, 4H), 6.43–7.45(m, 8H). ^{13}C-NMR, (62.9 MHz, $CDCl_3$): δ 22.03, 28.35, 112.71, 116.42, 123.72, 144.91, 133.43, 153.14, 189.35.

(1*E*,4*E*)- 1, 5- bis (4-methylphenyl) penta-1,4-dien-3-one (Table 1, Entry 24)

Yellow Solid; mp= 146-148°C (lit[23]. 147-148^{0}C); IR (KBr, νmax, cm^{-1}): 3081, 3031, 2991, 2881, 1644, 1614, 1588, 1556, 1502, 1404, 1329, 1176, 1095, 988, 815. ^{1}H-NMR (250MHz, $CDCl_3$): δ 2.40 (s, 6H), 7.05 (d, J= 7.5 Hz, 2H), 7.22 (s, 4H), 7.53 (s, 4H), 7.72 (d, J= 7.5Hz, 2H). ^{13}C-NMR, (62.9 MHz, $CDCl_3$): δ 21.6, 124.7, 128.5, 129.6, 132.2, 140.8, 143.2, 189.1. MS: m/z (%) 262 (M^+, 10), 261 (100, M-1), 247 (79), 232 (8), 218 (18), 203 (13), 170 (15), 145 (23), 115 (33), 105 (14), 91 (21).

Results and discussion

The condensation of benzaldehyde (2 mmol) and cyclopentanone (1 mmol) were attempted in the presence of $NbCl_5$ under microwave irradiations and solvent-free conditions. First, we confirmed that the reaction did not proceed at all in the absence of catalyst (Table 1, Entry 1). In order to determine the optimum conditions for the synthesis of α, ά- bis (substituted-benzylidene) alkanone, variations in molar ratios of reagents and the irradiation time and power level of microwave set-up were investigated. After some experimentation, we found a set of conditions that generally provided products in good yield. The optimum conditions for aldol condensation are as follows: $NbCl_5$ (10 mol%) under solvent-free conditions at room temperature and thermal conditions, $NbCl_5$ (10 mol%), and MW power (40%) under solvent-free conditions for microwave irradiation. Under the optimal reaction conditions, we investigated the reaction of aryl aldehydes substituted by either electron-withdrawing or electron–donating groups with ketones to get the corresponding α, ά- bis(substituted-benzylidene) alkanone. The results showed that aldehydes bearing electron–donating substituents on phenyl-ring favored the formation of product (85-95%) with reaction times ranging between 3 and 4.5 min. (Table 1, Entries 4, 9, 11, 12, 14). In contrast, aldehydes bearing electron–withdrawing groups gave lower yields (53-75%) with longer reaction time (7 min). (Table 1, Entries 5, 6, 7, 15, 16, 17). In the case of 2-nitrobenzaldehyde (Entry 17), low yield (53%) may be due to the steric effects of nitro-group. Encouraged by the obtained results, several acyclic ketones were treated with aryl aldehydes to yield the corresponding products. It was found that acyclic ketones took longer time and lower yields compared to 5&6 membered cycloketones (Table 1, Entries 24-28). Also, furfural, cinamaldehyde, thiophene-2-carbaldehyde and 5- methylthiophene-2-carbaldehyde were investigated in aldol reaction (Table 1, Entries 18-21). The results showed excellent yields.

Also, the reactions were carried out at room and thermal (80 ^{0}C) conditions. As the results show in Table 1, the yields are in accordance with the microwave irradiations, but the time is 1.5-5 h at room temperature and 15-45 min in thermal conditions. Finally, 7&8 memberd cycloketones showed low yields and a long reaction time (Table 1, Entries 22& 23). A proposed mechanism for aldol condensation reaction catalyzed by $NbCl_5$ was illustrated in figure 1. Under conditions of $NbCl_5$, the enol tautomer of the ketone that functions as the nucleophilic attack to the activated carbonyl group of aldehyde and c-c bond formation was occurrd (step 1). The second step consists of the elimination of water to form the carbon-carbon double bond. By repeating the steps 1 and 2, the corresponding product was synthesized.

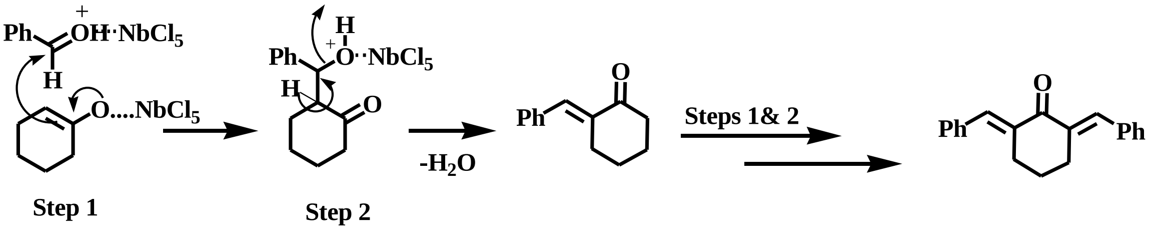


Figure 1. Plausible mechanism for aldol condensation reaction catalyzed by $NbCl_5$

Table 1. $NbCl_5$ catalyzed condensation of aromatic aldehydes with cyclic and non-cyclic ketones

Entry	**Z(CH2)**	**Ar**	**Time/Yield**[a]		
			r.t (h)/yield	**80^{0}C(min)/yield**	**Microwave (min)/yield**
1	1	C6H5	**----**	**-----**	**-----**
2	1	*o*-CH3C6H5	3.5/88	30/91	4.5/90
3	1	*m*-CH3 C6H5	1.5/91	15/92	3/90
4	1	*p*-CH3 C6H5	1.5/92	15/95	3/95
5	1	*o*-Cl C6H5	5/78	45/80	7/80
6	1	*p*-Cl C6H5	5/85	46/85	7/85
7	1	*o*-NO2 C6H5	4.5/55	42/57	7/57
8	1	*o*-CH3O C6H5	1.5/90	15/91	3/90
9	1	*p*-CH3O C6H5	1.5/94	15/95	3/95
10	2	*o*-CH3 C6H5	2/89	17/91	3/90
11	2	*m*-CH3 C6H5	2/94	17/95	3/95
12	2	*p*-CH3 C6H5	1.5/95	15/95	3/95
13	2	*o*-CH3O C6H5	3/84	20/85	3.5/85
14	2	*p*-CH3O C6H5	2/90	17/90	3/90

15	2	*m*-Cl C6H5	5/80	45/80	7/80
16	2	*p*-Cl C6H5	5/84	45/85	7/85
17	2	*o*-NO2 C6H5	5/53	45/53	7/53
18	2	2-furyl	1.5/90	15/91	3/90
19	2	C6H5CH=CH	1.5/91	15/93	3/93
20	2	2-thienyl	2/88	17/90	3/89
21	2	5-methyl-2-thienyl	1/90	12/95	2/95
22	3	C_6H_5	12/30	200/30	----
23	4	C_6H_5	24/10	500/10	-----
24	acetone	$\mathbf{C_6H_5}$	5/50	45/51	7/50
25	"	*p*-CH3 C6H5	5/72	45/75	7/75
26	"	*o*-CH3O C6H5	5/73	45/75	7/75
27	"	*p*-CH3O C6H5	5/79	45/82	7/80
28	"	*o*-NO2 C6H5	5/54	45/56	7/55

[a] The products were isolated and characterized by MS, IR spectroscopy, ^{1}H and ^{13}C- NMR.

We compared the efficiency of $NbCl_5$ with previously reported results (Table 2). Our reaction conditions showed a shorter reaction time than all the other conditions and gave high yields of the desired products (Table 2, Entry 16).

Table 2. Comparison of the efficiency of $NbCl_5$ with different catalysts

Entry	Catalyst/Solvent	T(^{0}C)	Time (min)	Yield (%)	Ref.
1	Sulfamic acid/solvent-free	80	150-1440	94	7
2	Fluoroalkylated 1,4-disubstituted [1,2,3]triazole organocatalyst/EtOH	reflux	600-1200	96	8
3	Silica chloride/solvent-free	100-110	120-900	95	9
4	NaOAc/ glacial AcOH	120	180-480	93	10
5	Sulfonated carbon nanocage/solvent-free	70	30-120	92	11

6	Sulfated zirconia/solvent-free	170	240-360	96	12
7	Cetyl trimethyl ammonium bromide/ H_2O	60	360-480	98	13
8	$RuCl_3$/water	120	360	95	21
9	I_2/CH_2Cl_2	r. t.	270	89	24
10	$Yb(OPf)_3$/ perfluorodecalin	120	480	92	25
11	animal bone meal(ABM)/ H_2O	reflux	75	76	26
12	ACOH/Acetate	120	480	95	27
13	$FeCl_3\cdot 6H_2O$/ ([bmim][BF4])	80	360	90	28
14	NBS/EtOH	80	960	92	29
15	H^+Catalyst/H_2O	100	120	95	30
16	$NbCl_5$/MW/solvent-free	-----	3	95	This work

Conclusion

In summary, we have described a green and efficient method for the synthesis of α, ά- bis (substituted-benzylidene) alkanone derivatives catalyzed by $NbCl_5$ under microwave irradiations and solvent-free conditions. The advantages of this procedure include easily work up, mild reaction conditions as well as reduced solvent waste and good to excellent yields.

Acknowledgments

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