

Ammonium chloride catalyzed aldol condensation: a facile synthesis of α,α' -bis(substituted benzylidene) cycloalkanones

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Abstract

Introduction: Aldol condensation is a powerful tool for the formation of carbon-carbon bond in many classes of carbonyl compounds. This reaction is performed in the presence of acids, bases or different complexes of metal(II) ions as catalyst. According to importance of this reaction, efforts were done to achieve an efficient catalyst in order to improve aldol condensation.

Aims: The catalytic effect of ammonium chloride was determined in cross aldol condensation to afford the corresponding α,α' -bis(substituted benzylidene)cycloalkanones also, ammonium chloride with previously reported catalysts was compared in this reaction.

Materials and Methods: Aldol condensation of cyclopentanone and benzaldehyde in ethanol was selected as model reaction. In the absence of ammonium chloride no product was obtained either at room temperature or at reflux condition. Increasing the amount of catalyst, improve the yield of reaction (room temperature). Raising the temperature of the reaction (reflux condition) caused little amount of catalyst gave higher yields. Based on the experiments with the optimized condition, aldol condensation of cyclopentanone and cyclohexanone with aromatic aldehyde with electron donating and withdrawing groups was done.

Results: Ammonium chloride efficiently catalyzes cross aldol condensation of aromatic aldehydes with ketones to afford the corresponding α,α' -bis(substituted benzylidene)cycloalkanones in high yields. NH_4Cl compared with previously reported catalysts reflects the wide applicability and usefulness of the method.

Conclusion: NH_4Cl is an efficient and readily available reagent and inexpensive catalyst in cross aldol condensations of different ketones with various aromatic aldehydes to prepare the α,α' -bis(substituted benzylidene)cycloalkanones. The reaction is a green process avoiding the use of toxic solvents and acid liquids.

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Key Words: α,α' -Bis(substituted benzyldene)ketones, Cross aldol condensation, Ammonium chloride.

Introduction

Aldol condensation is a powerful tool for the formation of carbon-carbon bond in many classes of carbonyl compounds.^[1-4] Aldol condensation reactions in classical methods, they were performed in the presence of strong acids or bases.^[4,5] However traditional acid- or base-catalyzed reactions suffer from the reverse reaction,^[6] and also self-condensation of starting materials.⁷ In order to do these reactions under neutral conditions, some metal ions are used as catalyst or reagent.^[7-20] For example, the use of different complexes of metal(II) ions, such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) with different ligands have been used for aldol-condensations.^[8] Bis(*p*-methoxyphenyl) telluroxide and KF-Al₂O₃ have been used for cross-condensation of cycloalkanones with aromatic aldehydes under microwave irradiation.^[11,21] Anhydrous RuCl₃ and TiCl₃(SO₃CF₃) have also been used for this purpose under solvent-free conditions.^[12,22] The use of expensive and toxic reagents, long reaction times, low yields, and formation of a mixture of products are among the drawbacks of the reported methods. Recently, more attention has been paid to the synthesis of α,α' -bis(substituted benzyldene)cycloalkanones.^[23-27]

As part of our research on chemical transformations,^[28-30] In this paper, a process of aldol condensations of aldehydes and ketones catalyzed with ammonium chloride was studied.

Experimental

Reagents and methods

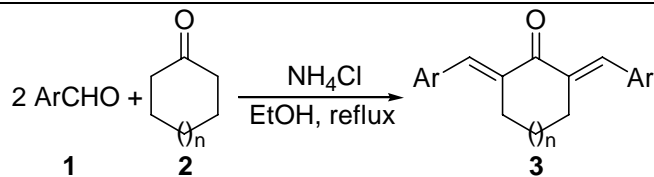
The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and Merck. All products are known compounds and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Bomem FT-IR-MB 100 spectrometer. ¹H NMR spectra was measured with a Bruker DRX-300 Avance spectrometer at 300 MHz using TMS as internal standard.

Procedure

A mixture of ketone (**2**, 1 mmol) and aromatic aldehyde (**1**, 2 mmol) was added to ethanol (5 ml) containing NH₄Cl (0.5 mmol). The solution was stirred at reflux condition for a period of time (Table 2) to complete the reaction (monitored by TLC). After cooling, the solid precipitated was isolated by filtration, rinsed with water and dried to give (**3**) with high purity.

Results and discussions

Due to the importance of using α,α' -bis(substituted benzyldene)cycloalkanones as precursors for the synthesis of bioactive pyrimidine derivatives,³¹ condensation of cycloalkanones with aldehydes is of special interest and cross-aldol condensation is an effective pathway for these preparations. Thus, we studied the cross-condensations of cyclopentanone and cyclohexanone with different aromatic aldehydes. The overall reaction is as shown in Scheme 1.



Scheme 1.

On the continued of study on the organic reaction catalyzed with ammonium chloride we found that it catalyzed aldol condensation of aromatic aldehydes with ketones. We started to study the aldol condensation catalyzed by NH_4Cl by examining the conditions required for the reaction involving cyclopentanone (1 mmol) and benzaldehyde (2 mmol) to afford adduct **3**. A summary of the results obtained is provided in Table 1. In the absence of NH_4Cl the desired α, α' -bis(substituted benzylidene)cyclopentanone (**3**) was not obtained and no reaction would take place even at high temperature (Table1, entries 1 and 2). On the other hand, **3** could be obtained in the presence of a catalytic amount of NH_4Cl . As shown in Table 1, the yield could not be improved further when the amount of NH_4Cl exceeded (Table 1, entries 3-7). At this point, this is not a very satisfactory result because excessive amount of catalyst was consumed. At this time, we began to increase the temperature of the reaction mixture. Based on the results obtained above, it was found that ethanol at reflux condition, gave the highest yield of the desired product (**3**).

Table1-Effect of catalyst for synthesis of α, α' -bis(substituted benzylidene)cyclopentanone under different reaction conditions.

Entry	NH_4Cl (mmol)	Reaction conditions	Time (h)	Yield (%)
1	0	r.t.	8	0
2	0	reflux	8	0
3	0.2	r.t.	5	11
4	0.4	r.t.	5	28
5	0.5	r.t.	5	59
6	0.6	r.t.	5	61
7	0.7	r.t.	5	62
8	0.2	reflux	5	80
9	0.5	reflux	5	93

The cross aldol condensation of cyclopentanone with benzaldehyde in the presence of NH_4Cl gave the aldol adduct in high yield. The results are summarized in Table 2. The data in Table 2 clearly show that the reaction of different cyclic ketones and aldehydes give the corresponding α, α' -bis(substituted benzylidene)cycloalkanones in excellent yield. Under these conditions, no self-condensation of the starting materials was observed.

Table 2- Synthesis of α,α' -bis(substituted benzyldene)ketones catalyzed by NH_4Cl in ethanol at reflux condition.

Entry ^a	Ar	n	Time (h)	Yield (%)	MP(°C) (lit.) ^{ref}	IR (cm ⁻¹)
1	C ₆ H ₅	0	5	93	189-190 (188-189) ³²	3053,1690, 1600,1446
2	C ₆ H ₅	1	5	91	115-116 (116-117) ³³	3030,1660, 1573,1465
3	Furyl	0	4.5	87	143-145 (143-144) ³⁴	3130,1680, 1625,1600
4	Furyl	1	4.5	89	164-165 (164-165) ³⁴	3148,1643, 1590-1546
5	<i>p</i> -CH ₃ O-C ₆ H ₄	0	3.5	89	210-212 (210-211) ³⁵	3029,1695, 1615,1595
6	<i>p</i> -CH ₃ O-C ₆ H ₄	1	3.5	89	202-203 (203-204) ³⁶	2937,1634, 1592,1450
7	<i>p</i> -Cl-C ₆ H ₄	1	3.5	90	144-145 (146-149) ³⁶	2928,1667, 1606,1452
8	<i>m</i> -NO ₂ -C ₆ H ₄	0	4	85	213-215 (214-215) ³⁷	2940,2922, 1659,1590
9	<i>o</i> -Br-C ₆ H ₄	1	4.5	81	142-144 (142-144) ³⁷	2938,2916, 1659,1600
10	C ₆ H ₄ -CH=CH	0	4	93	213-214 (215-216) ³⁸	3027, 1671, 1616, 1585
11	C ₆ H ₄ -CH=CH	1	4	92	177-178 (179-180) ³⁸	3050, 2900, 1690, 1600

^a All products were characterized by IR spectroscopic data and their mps compared with literature mps.

Our findings (Table 2) reflect the wide applicability and usefulness of the method. Some previously reported data on reaction conditions and the yield of product for preparation of α,α' -bis(substituted benzyldene)cyclopentanone (Table 2, entry 1) were compared with our results (Table 3). As one can see our results show a very good comparability with previously reported data in order to yields and reaction times.

Table 3- Comparison obtained results with reported previously data for synthesis of α,α' -bis(substituted benzyldene)cyclopentanone

Catalyst	Reaction condition	Time	Yield (%) ^{Ref.}
Bis(<i>p</i> -ethoxyphenyl)telluroxide	acetonitrile/MW	5 min	84.5 ¹¹
Yb(OTf) ₃	neat/ 90°C	6 h	92 ³⁹
SOCl ₂	EtOH/ 0°C	2 h	92 ⁴⁰
SmI ₂	[bmim]BF ₄ /N ₂ atm./r.t.	3 h	95 ⁴¹
<i>p</i> -toluene sulfonic acid	neat/MW	7 min	78 ⁴²
Iodotrimethylsilane	Acetonitrile/r.t.	1 h	92 ⁴³
Ammonium chloride	EtOH/reflux	5 h	93

Conclusions

In summary, NH_4Cl is an efficient and readily available reagent and inexpensive catalyst in cross aldol condensations of different ketones with various aromatic aldehydes to prepare the α,α' -bis(substituted benzyldiene)cycloalkanones. The reaction is a green process avoiding the use of toxic solvents and acid liquids.

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