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Poly(ethylene)glycol/$AlCl_3$ as a Green and Reusable System in the Synthesis of α,α'-bis(substituted-benzylidene) Cycloalkanones

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ABSTRACT

Aluminum chloride has been found to be a highly efficient catalyst for the aldol condensation of aldehydes and cycloketones in poly(ethylene)glycol 400 at room temperature. The reaction is very fast, clean and environmentally benign for the synthesis of a variety of α,α'-bis(substituted-benzylidene) cycloalkanones.

KEYWORDS

Aluminum chloride, poly(ethylene)glycol, α,α'-bis(substituted-benzylidene) cycloalkanones, aldol condensation.

Introduction

The α,α'-bis(substituted-benzylidene) cyclohexanones are very important materials used commonly as precursors of potentially bioactive pyrimidine derivatives,[1] organic materials for nonlinear optical applications,[2] cytotoxic analogues,[3] liquid crystalline polymers,[4] perfumes[5] and pharmaceutical applications, especially as HIV-1 integrase inhibitors.[6,7] Many of these methods suffer, however, from side reactions giving the corresponding products in low yields.[8,9] Recently some new kinds of Lewis acids have been used but in some cases the yields are less than 38 %.[10]

The usual synthetic procedures invariably use organic solvents as media to provide a homogeneous phase that allows for effective molecular interactions and to take the reaction to completion.

Organic solvents used are harmful and do not drive the reactions to total completion. However, the use of water as solvent is probably the most desirable approach. This is often not possible due to the hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions. In this paper we describe the use of a widely available polymer, poly(ethylene)glycol (PEG 400), as a recyclable, non-toxic, inexpensive and non-volatile solvent for the synthesis of α,α'-bis(substituted-benzylidene) cyclohexanones.

Results and Discussion

In continuation of our studies on the development of inexpensive and environmentally benign methodologies for organic reactions,[11] we reveal herein for the first time, the aluminum chloride-catalyzed aldol condensation of cyclohexanone and cyclopentanone with a variety of aldehydes using PEG 400 as the reaction medium (Scheme 1). The versatility of aluminum chloride and the environmentally benign nature of PEG encouraged us to couple them together and study their utility for the aldol condensation. Even though PEG has already been used as a solvent for these types of condensations,[12] to the best of our knowledge there are no literature reports on the aldol condensation of ketones with aldehydes under these conditions.

In a typical general experimental procedure, a solution of aldehyde (2 mmol) and ketone (1 mmol) in 2 mL of PEG in the presence of $AlCl_3$ (0.2 mmol) was stirred for 1.5–5 h, resulting in the formation of the corresponding α,α'-bis(substituted-benzylidene) cycloalkanones with good to excellent yields.

As $AlCl_3$ has not yet been used for these types of aldol condensations we decided to test it as a potential catalyst. We started with the aldol condensation between cyclohexanone and benzaldehyde, which has already been extensively used by other researchers but under different conditions.[13,14] Since green chemistry is currently an important and interesting aspect of organic synthesis, we initially decided to start with solvent-free conditions.

To study the required catalyst load we explored different reaction conditions under solvent-free conditions and the results are summarized in Table 1.

As indicated in Table 1, the best ratio of $AlCl_3$ to starting material is 0.2, but as the yields were poor, we decided to investigate the effect of different solvents on the reaction in an effort to increase the observed yields.

To reach this goal, we tested different solvents for the same aldol condensation reaction in the presence of 0.2 mmol $AlCl_3$ as catalyst.

Our results showed that this reaction is very solvent dependent. The results are summarized in Table 2.

As indicated in Table 2, this reaction does not work in ordinary solvents such as chloroform, dichloromethane, toluene and diethyl ether. The reaction also failed even with methanol and ethanol as solvent. It seems that low molar mass alcohols are

Table 1 Optimization of amount of $AlCl_3$ in the aldol condensation of cyclohexanone and benzaldehyde in solvent-free conditions at room temperature.

Entry	Amount of $AlCl_3$/mmol	Time/min	Yield/%
1	0.0	60	no reaction
2	0.1	60	20
3	0.2	10	35
4	0.3	10	20
5	0.4	10	18

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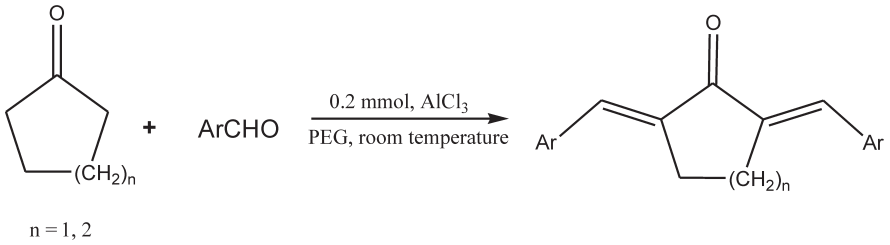

Scheme 1
The synthesis of α,α'-bis(substituted-benzylidene) cycloalkanones using $AlCl_3$ in PEG 400.

Table 2 Optimization of solvent in the aldol condensation of cyclohexanone and benzaldehyde with 0.2 mmol $AlCl_3$ as catalyst at room temperature.

Entry	Solvent	Time/h	Yield/%
1	PEG 400	14	90
2	EtOH	14	trace
3	MeOH	14	trace
4	ether	14	no reaction
5	toluene	14	no reaction
6	THF	14	no reaction
7	acetonitrile	14	trace

Table 4 Optimization of the temperature in the aldol condensation of cyclohexanone and benzaldehyde in PEG 400 as solvent and 0.2 mmol $AlCl_3$.[a]

Entry	T/°C	Yield after 0.5 h/%	Yield after 2.5 h/%
1	room temperature	0	trace
2	45	40	90
3	60	32	70
4	80	14	61

[a] Reaction conditions: benzaldehyde (2 mmol), cyclohexanone (1 mmol), $AlCl_3$ (0.2 mmol), PEG 400 (2 mL).

poor choices for solvents with $AlCl_3$ because they could readily react with the Lewis acid. Fortunately in the case of PEG 400 as solvent the yield is excellent (Table 2, entry 1). The optimum catalyst load when PEG 400 was used as solvent was also studied.

The results of the same aldol condensation with PEG 400 as solvent in the presence of different amounts of $AlCl_3$ as catalyst at room temperature are summarized in Table 3.

Our results showed that 0.2 mmol $AlCl_3$ as catalyst is the best concentration (Table 3, entry 3). These results are comparable with solvent-free conditions (Table 1, entry 3) but as indicated earlier, total yields in solvent-free conditions were low (Table 1, entries 1–5).

Finally, to study the effect of temperature we explored some reaction conditions for aldol condensation of cyclohexanone and benzaldehyde in the presence of 0.2 mmol $AlCl_3$ in PEG 400 as solvent. The results are summarized in Table 4.

As indicated in Table 4, increasing the temperature to 45 °C increases the obtained yield after 2.5 h (Table 4, entry 2). To study the scope of this procedure, the aldol condensations of a series of aldehydes with cyclohexanone and cyclopentanone at 45 °C have been studied. The results are summarized in Table 5.

As indicated in Table 5, the reaction works easily for a variety of aldehydes with both electron-donating and electron-withdrawing groups to give corresponding α,α'-bis(substituted-benzylidene) cyclohexanones in good to excellent yields.

Table 3 Optimization of the aldol condensation of cyclohexanone and benzaldehyde with $AlCl_3$ as catalyst in PEG 400[a] at room temperature.

Entry	$AlCl_3$/mmol	Time/h	Yield/%
1	0.0	14	0
2	0.1	14	55
3	0.2	14	90
4	0.3	14	85
5	0.4	14	60

[a] Reaction conditions: benzaldehyde (2 mmol), cyclohexanone (1 mmol), PEG 400 (2 mL).

It is important to note that it seems that aldehydes with electron-withdrawing groups at the *para* position (Table 5, entries 4, 6 and 12) react faster than aldehydes with electron-withdrawing groups at the *ortho* position (Table 5, entries 2, 3 and 11).

On the other hand, it seems that in the case of different ketones, cyclopentanone reacts faster than cyclohexanone (Table 5, entries 10–15). It is possible that the slightly more acidic protons of cyclopentanone *vs.* cyclohexanone might be the origin of this difference. It would be interesting to test the reaction on acyclic ketones as well, but it falls outside the scope of the current investigation. Table 6 compares the efficiency of our method with the efficiency of other published results of the same aldol reaction.

As indicated in Table 6, our method provides 92 % yield, which compares very well with other reported methods. The main advantages of our method are fast reaction time, clean and environmentally benign reagents with ease of separation of the product and reagents.

In order to investigate the recyclability of polyethylene glycol (it is immiscible with ether) the crude reaction mixture was extracted with ether and the retained PEG phase was reused. We used the extracted PEG three times and the yield reduced each time (92 %, 85 % and 75 %). For the fourth time, the yield was 60 %. An approximately 5 % mass loss of PEG was observed during each cycle.

In summary, a new and highly efficient condition for the synthesis of α,α'-bis(substituted-benzylidene) cycloalkanones *via* the condensation reaction of cyclohexanone and cyclopentanone in the presence of $AlCl_3$ in PEG as a green and reusable solvent is reported. This protocol also describes a very fast, user-friendly, low cost procedure and a greener method for a wide range of these reactions.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer model 783 spectrophotometer (Waltham, MA, USA). The NMR spectra were obtained on a Bruker AMX-300 (300 MHz) spectrometer (Ettlingen, Germany). The solvent was $CDCl_3$. Tetramethylsilane (TMS) was used as internal reference.

Table 5 Preparation of α,α'-bis(substituted-benzylidene) cycloalkanones catalyzed by $AlCl_3$ (0.2 mmol) in PEG 400 at 45 °C.

Entry	Ar	*n*	Time/h	Yield/% [a]	M.p./ºC (found)	M.p./°C (reported)
1	-C_6H_5	2	2.5	92	113–115	116–117 [15]
2	2-Cl-C_6H_4	2	4	93	102–106	102–104 [15]
3	2-NO_2-C_6H_4	2	5	81	155–157	158–159 [17]
4	4-Cl-C_6H_4	2	3.5	91	145–147	147–148 [15]
5	4-Br-C_6H_4	2	1.5	75	163–165	163–164 [18]
6	4-NO_2-C_6H_4	2	3	87	160–162	162–163 [15]
7	4-Me-C_6H_4	2	2	89	163–165	164–165 [16]
8	4-MeO-C_6H_4	2	2	85	159–161	161–163 [16]
9	2-Naphthyl	2	2	90	198–200	199–202 [17]
10	-C_6H_5	1	2	94	188–189	188–189 [17]
11	2-Cl-C_6H_4	1	2	78	160–161	154–156 [15]
12	4-Cl-C_6H_4	1	1.5	88	225–226	228–229 [15]
13	4-NO_2-C_6H_4	1	2	96	230–231	229–230 [15]
14	4-Me-C_6H_4	1	2	92	239–241	242–243 [15]
15	4-MeO-C_6H_4	1	1.5	86	209–210	211–212 [15]
16	4-CN-C_6H_4	2	0.75	94	208–211	–

[a] Isolated yield.

Table 6 Comparison of results using $AlCl_3$/PEG with those obtained by other workers for the synthesis of 2,6-dibenzylidenecyclohexanone.

Conditions	T/°C	Time/h	Yield/%	Ref.
$AlCl_3$/PEG	45	2.5	92	–
EtOH/solid KOH	0–30	6	91	17
TCT	90	0.33	90	15
NaOAc/HOAc	120	7	86	18
NKC-90 resin/$CHCl_3$	reflux	4	86	19
I_2/CH_2Cl_2	room temperature	4.5	92	20

General Procedure for the Preparation of α,α'-bis(substituted-benzylidene) Cycloalkanones

A mixture of aldehyde (2 mmol), ketone (1 mmol) and $AlCl_3$ (0.2 mmol) in PEG (2 mL) was stirred at 45 °C for an appropriate time. After completion of the reaction (monitored by TLC), the reaction mixture was cooled in a dry ice-acetone bath to precipitate the PEG 400 and the organic products were extracted with ether. The ether layer was washed with water (2 mL) and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to give the crude product. The resulting crude product was recrystallized from ethanol. This procedure was used for all compounds reported in Table 5.

All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR, and were identified by the comparison of the spectral data with those reported in the literature.

New Compound Characterization

α,α'-bis(4-cyano-benzylidene) cyclohexanone (Table 5, entry 16)

M.p. 208–211 °C. IR (KBr): ν_{max}: 2223, 1666, 1577, 1500, 1139 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 7.75 (2H, sbr), 7.70 (4H, dbr, J = 8.20 Hz), 7.53 (4H, dbr, J = 8.35 Hz), 2.91 (4H, m), 1.83 ppm (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.29, 140.20, 138.23, 135.22, 135.18, 132.14, 130.57, 118.51, 112.00, 28.30, 22.56 ppm. Anal. calc. for $C_{22}H_{16}N_2O$; C 81.49, H 4.93, N 8.63 %, found: C 81.10, H 4.88, N 8.56 %.

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