

Facile Synthesis of Bis(arylmethylidene)cycloalkanones Mediated by Lithium Perchlorate under Solvent-Free Conditions

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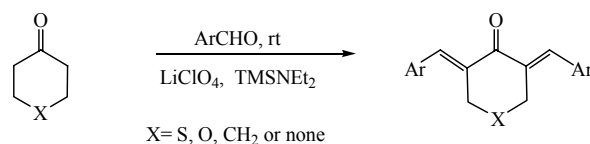
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Lithium perchlorate-mediated double crossed aldol condensations of a variety of aromatic aldehydes with cycloalkanones at room temperature in the presence of (trimethylsilyl)diethylamine and under solvent-free conditions are described. High to excellent yields of bis(arylmethylidene)cyclohexanones and bis(arylmethylidene)cyclopentanones are achieved within a few minutes in this facile one-pot procedure.

Keywords: Crossed aldol condensation, Bis(arylmethylidene)cycloalkanones, Lithium perchlorate, Solvent-free

INTRODUCTION

Bis(arylmethylidene)cycloalkanones are very important synthetic precursors for the synthesis of biologically active pyrimidine structures [1-2]. These compounds have gained lots of attention due to their uses as agrochemical, pharmaceutical and perfume intermediates and as liquid crystal polymer units [3-6]. Crossed aldol condensations have been employed for the synthesis of such structures [7]. In recent years many developments have widened the synthetic scope of bis(arylmethylidene)cycloalkanones by optimizing the reaction temperature, time, and yields of products [8-10]. Improvements have been achieved by application of KF-supported reagents under microwave mediation [11] and ultrasound irradiation [12]. Lewis acid catalysis using Yb(OTf)₃ [13], iodotrimethylsilane [14], TiCl₃(SO₃CF₃) [15], RuCl₃ [9], Pd/C-Me₃SiCl [16], SOCl₂ [17], and SmI₃ [18] or FeCl₃ [19] in ionic liquids are also employed. On the heterocyclic counterpart, we recently reported the room



Scheme 1

temperature synthesis of several novel bisarylmethylidenes of thiopyranones and pyranones (Scheme 1; X = S and X = O, respectively) [20] using lithium perchlorate LiClO₄ [21] and (trimethylsilyl)diethylamine (TMSNEt₂). We hereby would like to present the extension of these results to aldol condensation of homocyclic systems (X = CH₂ or none) under solvent-free conditions.

EXPERIMENTAL

General

Melting points are uncorrected. IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. ¹H and ¹³C NMR spectra were obtained on a Bruker AC 80

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MHz instrument as CDCl_3 solutions using TMS as internal standard reference. Reagents were purchased from commercial sources. Aldehydes were redistilled or recrystallized before use.

Typical Experimental Procedure

A mixture of the aldehyde (2 mmol), anhydrous LiClO_4 (2 mmol) and TMSNEt_2 (3 mmol) was stirred at room temperature under an inert atmosphere for 5 min. To this mixture was added cycloalkanone **1a** or **1b** (1 mmol) and the stirring was continued under the same conditions for another 2 min. At this stage, the product precipitated out immediately due to the relative insolubility of the non-polar products in the polar reaction medium. The reaction mixture was washed with 0.5 M hydrochloric acid solution and brine. The precipitates were recrystallized from ethyl acetate. Isolated yields of products were above 90%. Physical and spectral characterization of the products were confirmed by comparison with available literature data [12-14,19].

Selected Spectral Data

2,5-Dibenzylidenecyclopentanone (3a). M.p.: 186-187 °C (lit. [19]: 188-189 °C); ^1H NMR: δ (ppm) 3.12 (s, 4H), 7.35-7.62 (m, 12H); ^{13}C NMR (CDCl_3): δ (ppm) 22.6, 126.7, 127.5, 128.5, 133.2, 142.3, 144.5, 188.2.

2,5-Bis-(4-chlorobenzylidene)-cyclopentanone (3d). M.p.: 226-227 °C (lit. [19]: 227-228 °C); ^1H NMR: δ (ppm)

3.01 (s, 4H), 7.30-7.45 (m, 10H); ^{13}C NMR: δ (ppm) 23.5, 128.9, 133.3, 143.6, 143.8, 187.9

2,5-Bis-(3-phenylallylidene)-cyclopentanone (3e). M.p.: 212-213 °C (lit. [19]: 213-214 °C); ^1H NMR: δ (ppm) 2.95 (s, 4H), 6.98-7.42 (m, 12H), 7.53 (d, $J = 7$ Hz, 4H); ^{13}C NMR: δ (ppm) 24.7, 127.7, 128.3, 134.9, 143.5, 147.5, 187.3.

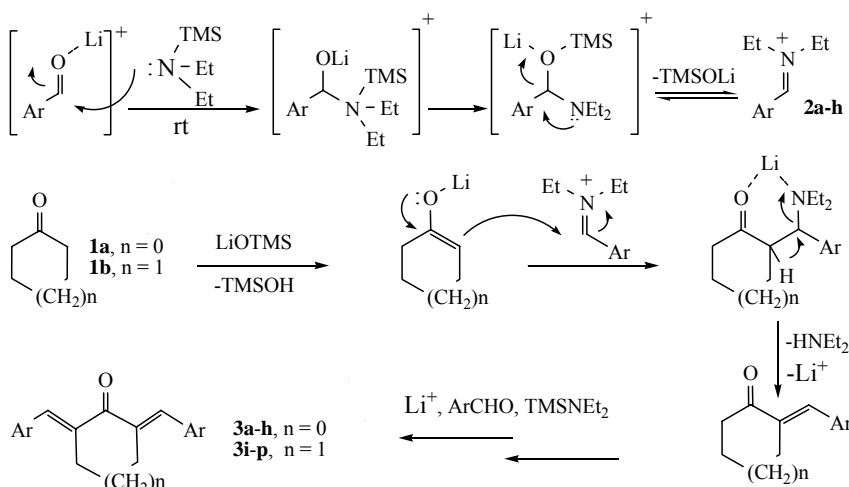
2,6-Dibenzylidenecyclohexanone (3i). M.p.: 113-114 °C (lit. [19]: 115-116 °C); ^1H NMR: δ (ppm) 1.76-1.83 (m, 2H), 2.96 (t, $J = 6.5$ Hz, 4H), 7.30-7.49 (m, 10H), 7.81 (s, 2H); ^{13}C NMR: δ (ppm) 27.8, 127.4, 128.5, 134.5, 141.6, 144.4, 187.2.

2,6-Bis-(4-methoxybenzylidene)-cyclohexanone (3j). M.p.: 159-160 °C (lit. [13]: 161-163 °C); ^1H NMR: δ (ppm) 1.73-1.80 (m, 2H), 2.88 (t, $J = 5.5$ Hz, 4H), 3.79 (s, 6H), 6.95, 7.50 (m, 8H), 7.78 (s, 2H); ^{13}C NMR: δ (ppm) 27.5, 56.1, 114.2, 127.1, 141.4, 144.2, 161.1, 187.5.

2,6-Bis-thiophen-2-yl-methylenecyclohexanone (3o). M.p.: 142-143 °C (lit. [13]: 142-143 °C); ^1H NMR: δ (ppm) 1.95-2.00 (m, 2H), 2.94 (t, $J = 5$ Hz, 4H), 7.16 (t, $J = 4$ Hz, 2H), 7.40 (d, $J = 2.5$ Hz, 2H), 7.54 (d, $J = 5$ Hz, 2H), 7.98 (s, 2H); ^{13}C NMR: δ (ppm) 27.4, 126.3, 127.9, 130.3, 136.5, 141.4, 150.5, 187.3.

RESULTS AND DISCUSSION

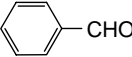
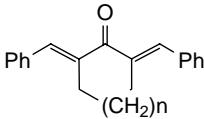
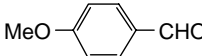
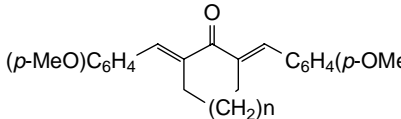
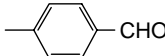
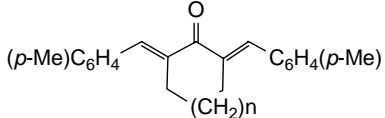
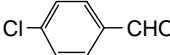
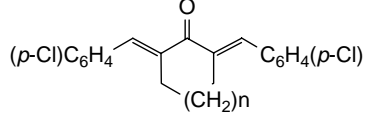
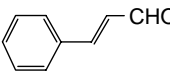
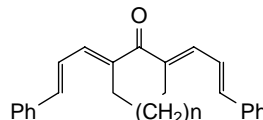
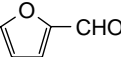
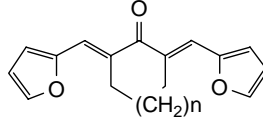
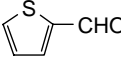
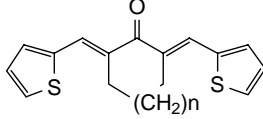
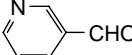
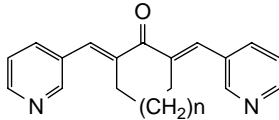
In the present work, a one-pot synthetic pathway for double condensation of ketones **1a-b** with aromatic aldehydes in the presence of TMSNEt_2 and LiClO_4 at room temperature



Scheme 2

Facile Synthesis of Bis(arylmethylidene)cycloalkanones

Table 1. Reactions of Cycloalkanones with Aldehydes in the Presence of TMSNEt₂ and LiClO₄

Entry	Aldehyde	Product	M.p. (°C) (reported)	Yield (%) ^a
1			3a: n = 0: 186-187 (188-189) 3i: n = 1: 113-114 (115-116)	97 94
2			3b: n = 0: 214-215 (211-212) 3j: n = 1: 159-160 (161-163)	98 92
3			3c: n = 0: 240-241 (244-245) 3k: n = 1: 161-162 (163-164)	94 93
4			3d: n = 0: 226-227 (227-228) 3l: n = 1: 141-142 (144-145)	92 96
5			3e: n = 0: 212-213 (213-214) 3m: n = 1: 175-176 (177-178)	90 95
6			3f: n = 0: 160-161 (163-164) 3n: n = 1: 142-143 (145-146)	99 98
7			3g: n = 0: 174-175 (176-178) 3o: n = 1: 142-143 (142-143)	99 97
8			3h: n = 0: 222-223 (222-224) 3p: n = 1: 130-131	92 86

^aIsolated yields.

is described (Scheme 2). This strategy represents the first report on the synthesis of the title structures using iminium ions under solvent free conditions.

Mechanistically, we envisage that treatment of benzaldehyde with TMSNEt₂ and anhydrous LiClO₄ at room temperature facilitated in situ formation of the corresponding

iminium salt **2a**, due to the Lewis acidity of the lithium ion and the high polarity of the reaction medium [21]. Subsequent addition of ketone **1a** to the reaction mixture resulted in quantitative conversion of **1a** into the double crossed aldol condensed product **3a** within a few minutes at room temperature (Table 1, entry 1, n = 0). In order to test the

chemoselectivity of the reaction, parallel experiments were carried out using different ketone/benzaldehyde ratios of 1:1 and 1:2. In both cases the same product **3a** was formed in comparable yields. Other control experiments were run to clarify the role of the various reactants. A test reaction conducted in the absence of TMSNEt₂ gave no product. Omission of LiClO₄ from the reaction medium also led to complete recovery of the unreacted starting materials. The generality of the method was demonstrated by the synthesis of similar products **3b-h** using other aromatic aldehydes under the same conditions (entries 2-8, n = 0). All the reactions proceeded rapidly at room temperature and complete conversions were observed within a few minutes. Use of ketone **1b** in a series of experiments similar to those carried out for **1a** resulted in the formation of bis(arylmethylidene)cyclohexanones **3i-p** (entries 1-8, n = 1) in excellent yields.

Under the above conditions, all reactions proceeded cleanly and none of the other side products which are normally observed under classical conditions were detected. The present one-pot protocol involves mild reaction conditions, high efficiency, short reaction times, high product yields, and use of commercially available materials.

In conclusion, we have reported a general and efficient solvent free synthetic protocol for the preparation of 2,6-bis(arylmethylidene)cycloalkanones at room temperature. The generality of this versatile reaction makes it an attractive addition to the known methods.

ACKNOWLEDGMENTS

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