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Solvent-Free Crossed Aldol Condensation of Ketones with Aromatic Aldehydes Mediated by Magnesium Hydrogensulfate

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Summary. Crossed aldol condensations of ketones with aromatic aldehydes are carried out efficiently in the presence of magnesium hydrogensulfate under solvent-free conditions in good to excellent yield without the occurrence of any self-condensation. Similar reactions in solution do not proceed satisfactorily.

Keywords. Aldehydes; Aldol reactions; Ketones; Magnesium hydrogensulfate; Solid state.

Introduction

Aldol condensations and related reactions are important protocols for carbon–carbon bond formation and the synthesis of α,β-unsaturated carbonyl compounds. These reactions are always carried out in the presence of acids or bases [1–6]. The use of metal ions and organometallic compounds in aldol and crossed aldol condensations have also been reported [7–15]. Many of these methods, however, suffer from low yields or from the occurrence of self-condensation.

According to the presence of methylene units in many naturally occurring compounds and antibiotics as well as the use of α,α'-disubstituted benzylidene cycloalkanones as precursors for the synthesis of bioactive pyrimidine derivatives, the condensation of cyclopentanone and cyclohexanone with aldehydes and ketones is of considerable importance [16]. In continuation of our studies on the application of magnesium hydrogensulfate as a cheap and versatile reagent in organic synthesis [17–20] we report a simple, efficient, and selective method for the crossed aldol condensation of ketones with aromatic aldehydes under solvent-free conditions.

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Results and Discussion

Different types of cyclic and acyclic ketones were subjected to condensation with aromatic aldehydes in the absence of solvent; the results are summarized in Table 1. The cyclic ketones cyclopentanone and cyclohexanone were condensed with aromatic aldehydes in the presence of the reagent under neat conditions at 60°C (entries 1–5). Similar reactions were performed for acyclic ketones like acetophenone and 2-acetylnaphthalene (entries 6–10). The reactions were completed within 2–8 h with good to excellent yields; no self-condensation products could be detected. Attempted monocondensation from one side of cycloalkanones was not successful, and a mixture of mono- and di-aldol products were obtained. The reaction of aliphatic aldehydes with ketones did not proceed satisfactorily. When similar reactions were conducted in different solvents such as dichloromethane, toluene, or acetonitrile, product mixtures were obtained in poor yields.

In conclusion, the presented method is a very efficient and selective protocol for crossed aldol condensations of cyclic and linear ketones with aromatic aldehydes with a very cheap and stable reagent. In addition, it has the chemical and environmental advantages of solvent-free reactions [23]. There is no limitation with respect to the sequence of addition of starting materials or preforming of the enolate, which is essential for many other reported crossed condensations [24–27].

Experimental

Products were characterized by ^{1}H NMR, IR, and mass spectra and by comparison of their physical properties with those reported in the literature. ^{1}H NMR spectra were run on a Bruker Avance 500 spectrometer at 500 MHz. IR spectra were obtained using a Shimadzu 470 spectrophotometer. Mass spectra were recorded on a Shimadzu QP 1100 EX spectrometer. Melting points were determined in open capillaries with a Galenkamp melting point apparatus and are corrected. Reaction monitoring was accomplished by thin layer chromatography on silica gel polygram SIL G/UV 254 sheets. Yields refer to isolated products.

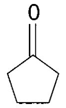
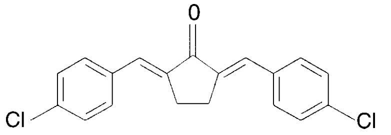
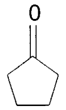
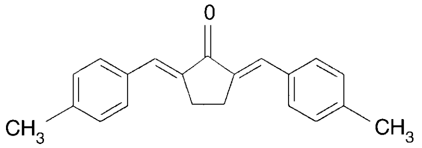
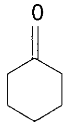
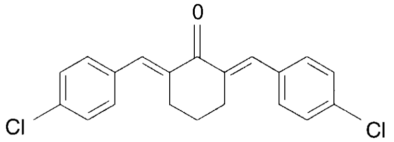
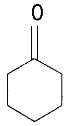
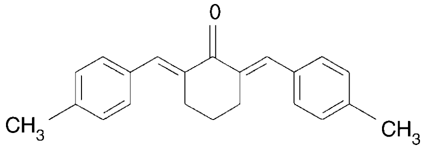
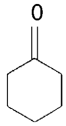
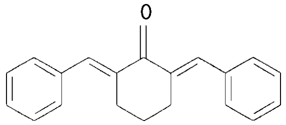
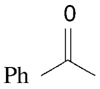
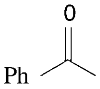
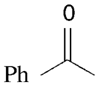
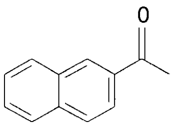
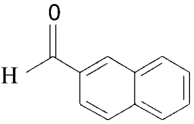
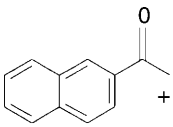
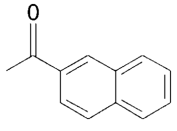
Preparation of magnesium hydrogensulfate

A 500 cm^3 suction flask was equipped with a constant-pressure dropping funnel. The gas outlet was conducted to a vacuum system through an adsorbing solution (H_2O) and an alkali trap. Anhydrous $MgCl_2$ (47.6 g, 0.5 mol) was charged in the flask, and concentrated H_2SO_4 (98.07 g, 1 mol) was added dropwise over a period of 30 min at room temperature. HCl gas was evolved immediately. After completion of the addition, the mixture was shaken for 30 min; meanwhile, the residual HCl was removed by suction. $Mg(HSO_4)_2$ was obtained as a white solid material (107 g).

General procedure

Ketone (4 mmol), aromatic aldehyde (4–8 mmol), and $Mg(HSO_4)_2$ (8 mmol) were placed in a mortar and mixed. The mixture was heated in an oven at 60°C for 2–8 h. For monitoring of the reaction progress, a sample of the reaction mixture was added to a few drops of CH_2Cl_2, and the solution was subjected to TLC after insoluble $Mg(HSO_4)_2$ had settled down. After completion of the reaction, 40 cm^3 CH_2Cl_2 were added, the mixture was filtered over a sintered glass funnel, and the residue was washed with 2×10 cm^3 CH_2Cl_2. The solvent was evaporated, and the remaining solid was purified on a short silica gel column (eluent: CCl_4:$CH_2Cl_2 = 3:2$) or by recrystallization from EtOH.

Table 1. Crossed aldol condensation of ketones with aromatic aldehydes mediated by Mg(HSO$_4$)$_2$ at 60°C under solvent-free conditions

Entry	Starting materials	Time/h	Yield/%[a]	Product[b]	m.p./°C
1	 + 4-C1C$_6$H$_4$CHO	8	82		225
2	 + 4-CH$_3$C$_6$H$_4$CHO	5	86		218–220 [11]
3	 + 4-ClC$_6$H$_4$CHO	7	93		144–146 [21]
4	 + 4-CH$_3$C$_6$H$_4$CHO	3	95		167–169 [22]
5	 + C$_6$H$_5$CHO	2.5	88		115 [13]
6	 + 4-ClC$_6$H$_4$CHO	5	93	4-ClC$_6$H$_4$CH=CHCOPh	107–109
7	 + 4-CH$_3$C$_6$H$_4$CHO	4	91	4-CH$_3$C$_6$H$_4$CH=CHCOPh	96–98 [15]
8	 + C$_6$H$_5$CHO	7	93	C$_6$H$_5$CH=CHCOPh	54–56 [15]
9	 + 4-ClC$_6$H$_4$CHO	3	92	4-ClC$_6$H$_4$CH=CH 	163–165
10	 + 4-CH$_3$C$_6$H$_4$CHO	2	96	4-CH$_3$C$_6$H$_4$CH=CH 	142–143

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[a] Isolated yield; [b] Products were characterized by ^{1}H NMR, IR, and mass spectra and by comparison of their physical properties with those reported in the literature

Condensation of cyclohexanone and 4-chlorobenzaldehyde as a typical example

Cyclohexanone (0.4 g, 4 mmol), 4-chlorobenzaldehyde (1.14 g, 8 mmol), and $Mg(HSO_4)_2$ (1.74 g, 8 mmol) were placed in a mortar and mixed. The mixture was heated in an oven at 60°C for 7 h without any further agitation. The progress of the reaction was monitored by TLC (eluent: CCl_4:CH_2Cl_2 = 3:2). After completion of the reaction, 40 cm^3 CH_2Cl_2 were added, and the mixture was filtered. The solvent was evaporated, and the crude material was recrystallized from EtOH affording the pure product in 93% yield; m.p.: 144–146°C (Ref. [21]: 147–148°C).

Selected spectroscopic data of products (Table 1)

Entry 1: m.p.: 225°C; IR (KBr): $\nu = 3010$ (w), 2920 (m), 1688 (s), 1618 (s), 1584 (s), 1481 (s), 1101 (s), 820 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.12$ (4H, s), 7.28–7.56 (10H, m) ppm; MS (EI, 70 eV): $m/z = 332$ (M + 4), 330 (M + 2), 328 (M^+), 293, 150, 129, 115 (100%), 89, 63.

Entry 6: m.p.: 107–109°C; IR (KBr): $\nu = 3010$ (w), 1651 (s), 1599 (s), 1213 (s), 1026 (s), 836 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.28$–8.05 (11H, m) ppm; MS (EI, 70 eV): $m/z = 244$ (M + 2), 242 (M^+), 207, 179, 137, 105, 77 (100%), 51.

Entry 9: m.p.: 163–165°C; IR (KBr): $\nu = 3010$ (w), 1655 (s), 1600 (s), 1588 (s), 1173 (s), 977 (s), 827 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.29$–8.14 (13H, m) ppm; MS (EI, 70 eV): $m/z = 294$ (M + 2), 292 (M^+, 100%), 257, 229, 180, 155, 127, 101, 75.

Entry 10: m.p.: 142–143°C; IR (KBr): $\nu = 3011$ (w), 2910 (w), 1649 (s), 1600 (s), 1554 (m), 1174 (s), 978 (s), 805 (s), 746 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.37$ (3H, s), 7.27–8.13 (13H, m) ppm; MS (EI, 70 eV): $m/z = 272$ (M^+, 100%), 257, 229, 180, 155, 127, 91.

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