Synthesis of 2-Cyclopentene-1-one Derivatives by Aldol Condensation

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Abstract

Aldol condensation of benzil and ketone with α-hydrogen atom in the presence of a solution of sodium hydroxide was carried out to afford some valuable 2-cyclopentene-1-one derivatives in 35~85 yield.

Keywords: 2-cyclopentene -1-one derivatives, benzil, aldol condensation, synthesis

Introduction

2-Cyclopenten-1-ones derivatives **(1)** are key and valuable intermediates in organic synthesis, and are widely applied as precursors for preparation of anti-viral[1], insecticides and antitumour drugs [2]. 2-Cyclopenten-1-ones derivatives comprising the cyclopentenone nucleus as inhibitors of the NF-B factor, with anti-inflammatory, anti-proliferative, immunosuppressive, cytoprotective and antiviral activity[3]. It is also found that the a,ß-unsatured carbonyl group in the cyclopentenone ring is the key structure necessary for NF-kB inhibition. However, some of the reported the synthesis of 2-cyclopenten-1-one derivatives suffer from certain drawbacks such as prolonged reaction time, unsatisfactory yield and complex product not to be separated easily[4]. Therefore, the discovery of simple and efficient procedures for the synthesis of 2-cyclopentene-1-one derivatives has gained considerable attention.

A useful carbon-carbon bond-forming reaction was known as the Aldol reaction or Aldol condensation[5,6].The reaction may occur between two molecules of aldehyde, two molecules of ketones or one molecule of aldehyde and a molecule of ketone[7,8]. In some cases, the products obtained from the Aldol addition can easily be converted (in situ) to important α,β-unsaturated carbonyl compounds, either thermally or under acidic or basic catalysis. Here we wish to develop a simple and inexpensive procedure for the synthesis of 2-cyclopentene-1-one derivatives by Aldol condensation of benzil **(2)** and ketone with α-hydrogen atom in the presence of a solution of sodium hydroxide (Scheme 1).

Our initial attempts to Aldol condensation of 4, 4´-dibromo-benzil (**2**, 1.5 mmol) and acetone (**3**, 10 mmol) in the presence of a solution of 10% sodium hydroxide in methanol (30 ml), and produced 2-cyclopentene-1-one **1** in 85% yield. The success of this reaction prompted us to examine the Aldol condensation of other benzils and ketones instead of 4, 4´-dibromo-benzil and acetone under the similar reaction conditions, and the results exhibited that the reaction can carry out smoothly and give the corresponding 2-cyclopentene-1-one derivatives in moderate to good yields (table 1). Table 1 shows the reactions of methyl isopropyl ketone and with benzil derivatives which have electron-donating groups (**1j** and **1m**) have higher yield than reactions with electron-withdrawing

groups on Para-position of benzil (**1c** and **1g**). These electron withdrawing groups accelerate benzil-benzilic acid rearrangement more than electron-donor groups, which lower the yield of aldol condensation reaction.

Material and Methods

In a typical procedure, a solution of 10% sodium hydroxide in methanol (30 ml) was dropwise added into a mixture of benzil (**2**, 1.5 mmol) and ketone (**3**, 10 mmol), then the reaction mixture was maintained under room temperture for the appropriate time (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water, and the resulting solid product was collected by filtration. The crude product was washed with water and ether, respectively, then gave the corresponding 2-cyclopentene-1-one derivatives **1**.

3,4-bis(*p*-bromophenyl)-4-hydroxy-2-cyclopentetne-1-one (**1a**): mp 234~236 °C, IR (KBr) (ν_{max}, cm^{-1}): 3363 (OH), 1685 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.77~2.96 (2H, CH_2), 5.92 (1H, s, OH), 6.83 (1H, s, CH), 7.43~7.52 (6H, dd, C_6H_5), 7.70~7.76 (2H, d, C_6H_5); ESI-MS *m/z* (%): 406 (M^+, 100), 408 (M^++2, 100), 405 (M-H^+, 100), 407 (M+2-H^+, 100).

3,4-bis(*p*-bromophenyl)-4-hydroxy-2-methyl-2-cyclopentetne-1-one (**1b**): mp 172~175 °C; IR (KBr) (ν_{max}, cm^{-1}): 3425 (OH), 1689 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.87 (3H, s, CH_3), 2.86-2.95 (2H, dd, CH_2), 5.62 (1H, s, OH), 7.35~7.60 (8H, m, C_6H_5); ESI-MS *m/z* (%): 420 (M^+, 65), 64 (M^++2, 66).

3,4-bis(*p*-bromophenyl)-5,5-dimethyl-4-hydroxy-2-cyclopentetne-1-one (**1c**): mp 199~201 °C; IR (KBr) (ν_{max}, cm^{-1}): 3272 (OH), 1693 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 0.58 (3H, s, CH_3), 1.23 (3H, s, CH_3), 5.43 (1H, s, OH), 6.78 (1H, s, CH), 7.50-7.68 (8H, dd, C_6H_5); ESI-MS *m/z* (%): 419 (M^+-CH_3, 100), 421(M^+-CH_3+2, 99),

3,4-bis(*p*-chlorophenyl)-5,5-dimethyl-4-hydroxy-2-cyclopentetne-1-one (1g): mp: 165~167 °C; IR (KBr) (ν_{max}, cm^{-1}): 3355 (OH), 1692 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 0.60 (3H, s, CH_3), 1.25 (3H, s, CH_3), 7.30~7.34 (4H, d, C_6H_5). 7.68~7.73 (4H, d, C_6H_5); ESI-MS *m/z* (%): 331(M^+-15,19).

3,4-bis(*p*-methylphenyl)-4-hydroxy-2-methyl-2-cyclopentetne-1-one (**1i**): mp 105~107 °C; IR (KBr) (ν_{max}, cm^{-1}): 3406 (OH), 1695 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (3H, s, CH_3), 2.23 (6H, s, CH_3), 2.73~2.90 (2H, CH_2), 5.10 (1H, s, OH), 7.10-7.13 (4H, d, C_6H_5), 7.28-7.31 (2H, d, C_6H_5); ESI-MS *m/z* (%): 292 (M^+, 80).

3,4-bis(p-methoxyphenyl)-4-hydroxy-2-cyclopentetne-1-one (1k): mp 220-222 °C;
IR (KBr)(ν_{max}, cm^{-1}): 3401 (OH), 1685 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.88 (1H, d, CH_2), 2.92(1H, d, CH_2), 3.72 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 5.29 (1H, s, OH), 6.65 (1H, s, CH), 6.85-6.88 (4H, d, C_6H_5), 7.43-7.46 (2H, d, C_6H_5), 7.82-7.84 (2H, d, C_6H_5); Calcd. for$C_{19}H_{18}O_4$: C, 73.55; H, 5.81 Found: C, 73.56; H, 5.78.

Conclusion

In conclusion, a simple, inexpensive and efficient methodology for the synthesis of 2-cyclopentene-1-one derivatives by Aldol condensation of benzil and ketone with α-hydrogen atom in the presence of sodium hydroxide was developed.

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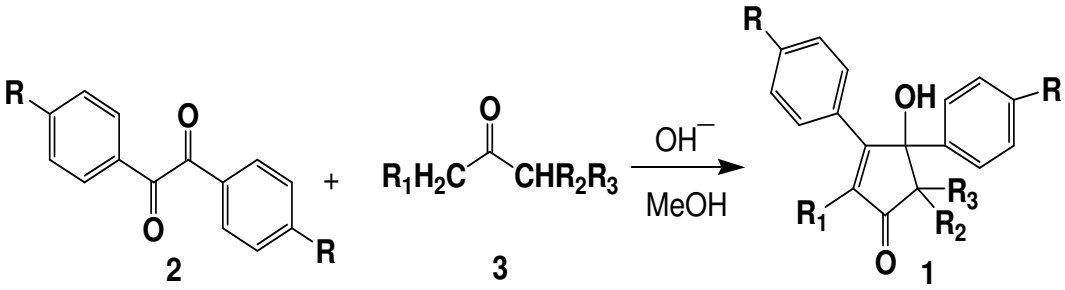

Scheme 1

Table-1: Synthesis of 2-Cyclopentene-1-one Derivatives by Aldol Condensation

Product[a]	R	R_1	R_2	R_3	Yield[b](%)	Time (h)
1a	Br	H	H	H	85	3.0
1b	Br	CH_3	H	H	45	6.0
1c	Br	H	CH_3	CH_3	52	4. 0
1d	Br	C_6H_5	H	H	58	2.5
1e	Cl	H	H	H	60	2.5
1f	Cl	CH_3	H	H	40	2.0
1g	Cl	H	CH_3	CH_3	47	6.0
1h	Me	H	H	H	40	3.5
1i	Me	CH_3	H	H	35	4.0
1j	Me	H	CH_3	CH_3	80	4.0
1k	OMe	H	H	H	42	2.5
1l	OMe	CH_3	H	H	47	3.0
1m	OMe	H	CH_3	CH_3	78	3.5

[a]All known compounds were characterized by comparing their spectral data with those reported; [b]Isolated yields.