

Versatile One-Step One-Pot Direct Aldol Condensation Promoted by MgI_2

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A true one-step one-pot aldol-reaction procedure has been developed for the synthesis of β -hydroxy ketones and esters. The reaction can be run at room temperature by simply mixing four components in CH_2Cl_2 , with medium-to-high yields of aldol products obtained after regular workup. Mechanistically, the process probably proceeds *via* Mg-enolate formation of the ketone or ester component, followed by addition to the electrophilic aldehyde.

Introduction. – The development of new multicomponent-coupling processes for the construction of complex target molecules from simple starting materials has attracted much attention in recent years. Aldol reactions, *i.e.*, the condensation of a nucleophilic enolate with an electrophilic carbonyl compound, are considered to be among the most-powerful C,C-bond-forming reactions. The development of *direct* aldol reactions from unmodified ketones and aldehydes does not require the pre-conversion of a ketone or an ester to a more-reactive species (*e.g.*, an enol silyl ether or a ketene silyl acetal) and has, thus, attracted considerable attention.

Generally, direct aldol reactions fall into one out of two categories: 1) the carbonyl compound is first converted to its Li (or other metal) enolate by treatment with a strong base, typically lithium diisopropylamide (LDA) or a metal hexamethyldisilazide (MHMDS), followed by the addition of a carbonyl acceptor; or 2) the carbonyl compound is converted to its metal enolate under relatively mild conditions by treatment with a *Lewis* acid and a tertiary amine, followed by the reaction with the carbonyl acceptor. Both methods are *two-step* one-pot reactions, since the enolate needs to be formed before the addition of the carbonyl acceptor [1][2].

Recently, we found that MgI_2 is an excellent *Lewis* acid for C,C-bond-forming reactions in the synthesis of β -iodo *Baylis–Hillman* adducts [3]. We think that, in this process, MgI_2 serves both as a *Lewis* acid and an iodine source for a *Michael*-type addition in which an α,β -ethynyl ketone (or ester) is converted to an active ' β -iodo-allenolate' intermediate, which, in turn, reacts with aldehydes to yield β -iodo *Baylis–Hillman* adducts. Consequently, we were interested in testing whether MgI_2 , in the presence of a tertiary amine, would be a suitable reagent for the mild *in situ* formation of Mg enolates.

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Results and Discussion. – Generally, all reactions were carried out by simply adding a tertiary amine to a CH_2Cl_2 solution containing aldehyde, ketone (or ester), and MgI_2 at room temperature under N_2 atmosphere. This gave rise to the desired β -hydroxy adducts in moderate-to-high yields (*Table*). In a first attempt to condense benzaldehyde with acetophenone in the presence of $\text{EtN}(\text{i-Pr})_2$ and MgI_2 , product **1** was obtained in 85% yield after only 30 min (TLC monitoring). The yield of this reaction could be readily increased to 98% (*Entry 1* of the *Table*) by optimization of the reaction conditions.

Table. Direct, MgI_2 -Promoted Aldol Reaction of Various Ketones and Esters (Nucleophiles) with Aromatic Aldehydes (Electrophiles). Conditions: electrophile, 1 mmol; nucleophile, MgI_2 , and $\text{EtN}(\text{i-Pr})_2$, 1.2 mmol each; CH_2Cl_2 , r.t., 30 min; aqueous workup followed by flash chromatography.

Entry	R (nucleophile)	R' (electrophile)	Product	Isolated yield [%]
1	Ph	Ph	1	98
2	Ph	4-MeO-C ₆ H ₄	2	94
3	Ph	4-F-C ₆ H ₄	3	98
4	4-F-C ₆ H ₄	Ph	4	98
5	4-MeO-C ₆ H ₄	Ph	5	96
6	[1,1'-Biphenyl]-4-yl	Ph	6	98
7	Ph	Me-CH=CH	7	68
8	Ph	Et	8	70
9	Me	Ph	9	72
10	MeO	Ph	10	60
11	EtO	Ph	11	65
12	PhO	Ph	12	72

To find the optimum conditions, we varied the *Lewis* acid in the above model reaction between benzaldehyde and acetophenone, giving rise to 3-hydroxy-1,3-diphenylpropan-1-one (**1**). The following metal salts and organometallics were tested: $\text{Sn}(\text{OTf})_2$, SnCl_4 , TiCl_4 , $\text{Mg}(\text{OTf})_2$, MgBr_2 , MgCl_2 , $\text{Mg}(\text{ClO}_4)_2$, LiI , and MgI_2 ²⁾. However, except for MgBr_2 and MgI_2 , which afforded **1** in 71 and 98% yield, respectively, all other additives were found to be much less active or completely inert. Surprisingly, both TiCl_4 and $\text{Sn}(\text{OTf})_2$, common reagents for direct aldol reactions, failed to promote the condensation, offering only trace amounts (<5%) of the aldol product, even at a prolonged reaction time of 2 h at room temperature. This might be attributed to the propensity of these strong *Lewis* acids to form tight complexes with amines, which competes with enolate-intermediate production.

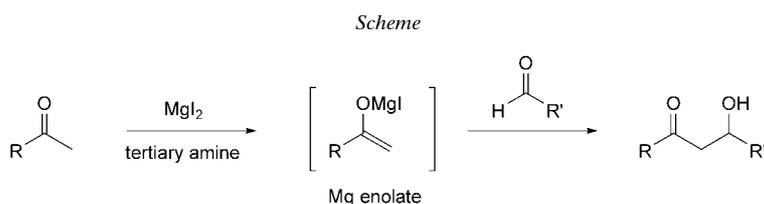
Upon varying the solvent, CH_2Cl_2 , benzene, and toluene gave the best results, in terms of yield, when benzaldehyde was used as the electrophile (30 min at r.t. to completion). In Et_2O or THF, the reaction required 10 h to go to completion; and after 30 min, only 10% of the desired product had been formed.

²⁾ Tf = Trifluoromethanesulfonyl

Both aromatic *and* aliphatic aldehydes were successfully used as electrophiles in the new one-pot reaction system. Especially high yields (94–98%) were obtained with aromatic aldehydes (*Table, Entries 1–6*). The somewhat lower yields (*ca.* 70%) for the condensation of aliphatic aldehydes (*Entries 7 and 8*) could be rationalized by side reactions arising from the self-condensation of acetophenone. This result indicates that aliphatic aldehydes are generally less active than aromatic ones in this new system.

Acetone also underwent the reaction with benzaldehyde, however, in lower yield (*Entry 9*). Esters were found to react with aldehydes as well, which gave rise to the corresponding β -hydroxy esters in yields of 60–72% (*Entries 10–12*). The new system, thus, may extend the scope to which esters are generally used as reaction substrates in aldol condensations.

A mechanistic working hypothesis of this new process is represented in the *Scheme*. The initial reaction step probably involves the formation of a Mg enolate, which reacts with aldehydes to form the classical aldol products.



Conclusions. – A true one-step one-pot aldol-reaction protocol has been successfully developed based on MgI_2 as a *Lewis* acid promoter. The reaction proceeds rapidly under mild conditions and provides β -hydroxy ketones and esters in medium-to-excellent yields (60–98%). The scope of the reaction and an extension of this new system to other applications will be published in due course.

Experimental Part

General. CH_2Cl_2 was freshly distilled from CaH under N_2 atmosphere. MgI_2 (98%) and all other chemicals were commercially available and used without further purification; the stoichiometrics were calculated based on the purities reported by the manufacturers. All reactions were conducted under N_2 gas in dry glassware equipped with a magnetic stirring bar. Flash chromatography (FC) was performed on *Silica Gel 60* (230–400 mesh; *Merck*). Infrared (IR) spectra were recorded on a *Shimadzu FT-IR-8400* spectrophotometer; in cm^{-1} . ^1H - and ^{13}C -NMR Spectra were recorded on a *Varian* spectrometer (at 500 and 125 MHz, resp.) in CDCl_3 ; chemical shifts δ in ppm rel. to Me_4Si (=0 ppm); coupling constant J in Hz Mass spectra were recorded on a *JEOL JMS-D300* mass spectrometer; in m/z . High-resolution (HR) mass spectra were recorded at the Mass Spectroscopy Laboratory at the *Crompton Corporation*.

Typical Procedure (see the *Table, Entry 1*). A 25-ml dry flask was loaded with CH_2Cl_2 (5.0 ml), benzaldehyde (1.0 equiv), acetophenone (1.2 equiv.), and MgI_2 (340.0 mg, 1.2 mmol). Under N_2 $\text{EtN}(\text{i-Pr})_2$ (0.23 ml, 1.3 mmol) was added dropwise *via* syringe, and the resulting mixture was stirred for 30 min at r.t. Then, the reaction was quenched with 2N HCl (4.0 ml), the org. solvent (CH_2Cl_2) was evaporated, and the aq. phase was extracted with AcOEt (8.0 ml). The org. layer was separated, and the aq. layer was re-extracted with AcOEt (2×8.0 ml). The combined org. layers were dried (MgSO_4) and concentrated, and the crude product (**1**) was purified by FC (hexane/AcOEt 10:1).

1-Hydroxy-1,3-diphenylpropan-1-one (1). Yield: 221.5 mg (98%). Colorless oil. IR (neat): 3477, 3061, 2975, 1679, 1601, 1576. ^1H -NMR (500 MHz, CDCl_3): 3.33 (*m*, 2 H); 3.68 (*d*, $J = 3.0$, OH); 5.32 (*m*, 1 H); 7.31 (*m*, 1 H); 7.39 (*m*, 2 H); 7.46 (*m*, 4 H); 7.59 (*m*, 1 H); 7.95 (*m*, 2 H). ^{13}C -NMR (125 MHz, CDCl_3): 47.3; 69.9; 125.6; 127.5;

128.1; 128.4; 128.6; 133.5; 136.4; 142.9; 200.0. CI-MS (CH_4): 226 (M^+). HR-MS: 226.0998 (M^+ ; $\text{C}_{15}\text{H}_{14}\text{O}_2^+$; calc. 226.0994).

3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (2). Yield: 240.6 mg (94%). Colorless oil. IR (neat): 3611, 3490, 3056, 1678, 1600. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.32 (*m*, 2 H); 3.60 (*d*, $J = 3.0$, OH); 3.78 (*s*, 3 H); 5.27 (*m*, 1 H); 6.88 (*m*, 2 H); 7.33 (*m*, 2 H); 7.44 (*m*, 2 H); 7.56 (*m*, 1 H); 7.93 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 47.2; 55.1; 69.5; 113.8; 126.9; 128.0; 128.5; 133.4; 135.1; 136.5; 158.9; 200.0. CI-MS (CH_4): 240 (M^+). HR-MS: 256.1095 (M^+ , $\text{C}_{16}\text{H}_{16}\text{O}_3^+$; calc. 256.1099).

3-(4-Fluorophenyl)-3-hydroxy-1-phenylpropan-1-one (3). Yield: 239.2 mg (98%). Colorless oil. IR (neat): 3622, 3002, 2901, 1678, 1678. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.33 (*m*, 2 H); 3.68 (*d*, $J = 3.0$, OH); 5.32 (*m*, 1 H); 7.04 (*m*, 2 H); 7.40 (*m*, 2 H); 7.46 (*m*, 2 H); 7.59 (*m*, 1 H); 7.93 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 47.3; 69.3; 115.2; 115.4; 127.3; 127.4; 128.1; 128.7; 133.7; 136.4; 138.6; 161.1; 163.1; 200.0. CI-MS (CH_4): 244 (M^+). HR-MS: 244.0903 (M^+ , $\text{C}_{15}\text{H}_{13}\text{FO}_2^+$; calc. 244.0900).

1-(4-Fluorophenyl)-3-hydroxy-3-phenylpropan-1-one (4). Yield: 239.3 mg (98%). Colorless oil. IR (neat): 3611, 2977, 2880, 1678, 1672. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.32 (*m*, 2 H); 3.59 (*d*, $J = 3.0$, OH); 5.32 (*m*, 1 H); 7.10 (*m*, 2 H); 7.28 (*m*, 1 H); 7.35 (*m*, 2 H); 7.41 (*m*, 2 H); 7.95 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 47.2; 69.9; 115.6; 115.8; 125.6; 127.6; 128.5; 130.7; 130.8; 132.9; 142.8; 164.9; 166.9; 198.3. CI-MS (CH_4): 244 (M^+). HR-MS: 244.0905 (M^+ , $\text{C}_{15}\text{H}_{13}\text{FO}_2^+$; calc. 244.0900).

3-Hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (5). Yield: 245.7 mg (96%). Colorless oil. IR (neat): 3609, 3483, 3064, 1678, 1598. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.28 (*m*, 2 H); 3.82 (*d*, $J = 3.0$); 3.83 (*s*, 3 H); 5.29 (*m*, 1 H); 6.90 (*m*, 2 H); 7.27 (*m*, 1 H); 7.35 (*m*, 2 H); 7.42 (*m*, 2 H); 7.90 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 46.8; 55.3; 70.0; 113.7; 125.6; 127.4; 128.4; 129.5; 130.4; 143.0; 163.8; 198.6. CI-MS (CH_4): 256 (M^+). HR-MS: 256.1103 (M^+ , $\text{C}_{16}\text{H}_{16}\text{O}_3^+$; calc. 256.1099).

1-[1,1'-Biphenyl]-4-yl-3-hydroxy-3-phenylpropan-1-one (6). Yield: 296.0 mg (98%). Yellowish oil. IR (neat): 3608, 2977, 1679, 1674, 1596, 1479. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.39 (*m*, 2 H); 3.63 (*d*, $J = 3.0$, OH); 5.36 (*m*, 1 H); 7.30 (*m*, 1 H); 7.39 (*m*, 3 H); 7.46 (*m*, 4 H); 7.61 (*m*, 2 H); 7.67 (*m*, 2 H); 8.01 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 47.3; 70.1; 125.7; 127.23; 127.28; 127.6; 128.3; 128.5; 128.7; 128.9; 135.2; 139.6; 142.9; 146.2; 199.7. CI-MS (CH_4): 302 (M^+). HR-MS: 302.1311 (M^+ , $\text{C}_{21}\text{H}_{18}\text{O}_2^+$; calc. 302.1307).

3-Hydroxy-1-phenylhex-4-en-1-one (7). Yield: 129.2 mg (68%). Colorless oil. IR (neat): 3437, 2919, 1714, 1445. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.70 (*m*, 3 H); 3.17 (*m*, 2 H); 3.28 (*d*, $J = 3.0$, OH); 4.70 (*m*, 1 H); 5.59 (*m*, 1 H); 5.78 (*m*, 1 H); 7.46 (*m*, 2 H); 7.57 (*m*, 1 H); 7.94 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 17.6; 45.1; 68.6; 127.0; 128.0; 128.5; 132.0; 133.4; 136.6; 200.2. CI-MS (CH_4): 190 (M^+). HR-MS: 190.0990 (M^+ , $\text{C}_{12}\text{H}_{14}\text{O}_2^+$; calc. 190.0994).

1-Phenyl-3-hydroxypentan-1-one (8). Yield: 124.6 mg (70%). Colorless oil. IR (neat): 3435, 3011, 2889, 1713, 1443. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.01 (*t*, $J = 7.5$, 3 H); 1.60 (*m*, 2 H); 3.03 (*dd*, $J = 17.5$, 9.5, 1 H); 3.17 (*dd*, $J = 18.0$, 3.0, 1 H); 3.32 (*d*, $J = 3.0$, OH); 4.14 (*m*, 1 H); 7.46 (*m*, 2 H); 7.57 (*m*, 1 H); 7.95 (*m*, 2 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 9.9; 29.3; 44.5; 69.0; 128.0; 128.5; 133.4; 136.7; 200.9. CI-MS (CH_4): 178 (M^+). HR-MS: 178.0990 (M^+ , $\text{C}_{11}\text{H}_{14}\text{O}_2^+$; calc. 178.0994).

4-Hydroxy-4-phenylbutan-2-one (9). Yield: 118.0 mg (72%). Colorless oil. IR (neat): 3424, 3061, 2961, 1712, 1604. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.16 (*s*, 3 H); 2.77 (*dd*, $J = 17.5$, 3.3, 1 H); 2.87 (*dd*, $J = 17.5$, 9.0, 1 H); 3.47 (*d*, $J = 3.1$, 1 H); 5.12 (*m*, 1 H); 7.26–7.34 (*m*, 5 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 30.7; 51.8; 125.4; 127.5; 128.5; 142.7; 209.0.

Methyl 3-Hydroxy-3-phenylpropanoate (10). Yield: 108.0 mg (60%). Colorless oil. IR (neat): 3450, 3061, 2953, 1732, 1604. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.71 (*dd*, $J = 16.5$, 4.1, 1 H); 2.77 (*dd*, $J = 16.5$, 6.2, 1 H); 3.30 (*d*, $J = 3.3$, OH); 3.69 (*s*, 3 H); 5.12 (*m*, 1 H); 7.20–7.40 (*m*, 5 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 43.2; 52.1; 70.2; 125.6; 127.9; 128.6; 142.5; 172.9. HR-MS: 180.0788 (M^+ , $\text{C}_{10}\text{H}_{12}\text{O}_3^+$; calc. 180.0786).

Ethyl 3-Hydroxy-3-phenylpropanoate (11). Yield: 126.1 mg (65%). Colorless oil. IR (neat): 3438, 3060, 2976, 1719, 1490. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.27 (*t*, $J = 7.2$, 3 H); 2.71 (*dd*, $J = 16.5$, 2.6, 1 H); 2.77 (*dd*, $J = 16.5$, 6.3, 1 H); 3.32 (*d*, $J = 3.3$, OH); 4.19 (*q*, $J = 7.2$, 2 H); 5.15 (*m*, 1 H); 7.26–7.38 (*m*, 5 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 14.1; 43.4; 61.0; 70.4; 125.6; 127.9; 128.5; 142.4; 172.6. HR-MS: 194.0940 (M^+ , $\text{C}_{11}\text{H}_{14}\text{O}_3^+$; calc. 194.0943).

Phenyl 3-Hydroxy-3-phenylpropanoate (12). Yield: 174.0 mg (72%). Colorless oil. IR (neat): 3610, 3019, 1747, 1496. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.87–3.08 (*m*, 2 H); 3.09 (*d*, $J = 3.4$, OH); 5.24 (*m*, 1 H); 7.06 (*d*, $J = 7.1$, 2 H); 7.14–7.48 (*m*, 8 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 174.2; 150.6; 141.5; 129.6; 128.4; 128.1; 126.4; 126.2; 121.4; 74.6; 47.

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