The Aldol-Grob Reaction: Regioselective Synthesis of (*E*)-Alkenes from Aldehydes and Ketones with Ytterbium Triflate Catalysis

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A simple, good yielding and solvent-free aldol-Grob reaction sequence, catalysed by $Yb(OTf)_3$ hydrate, affording (*E*)-alkenes regioselectively from aldehydes and ketones is described.

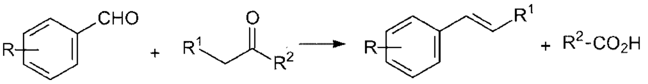
Introduction

The aldol condensation is one of the oldest organic reactions and has been extensively studied and applied many times during the last two centuries, especially for the formation of carbon-carbon bonds aimed towards the synthesis of a large number of biologically active compounds.[1] The initial product of this reaction is a β-hydroxycarbonyl compound, which, in turn, can be transformed either into an α,β-unsaturated carbonyl compound, via dehydration, or into an alkene by a mechanism similar to the Grob fragmentation[2] of *N*-halo-α-amino acids,[3] cyclobutanone hemiacetals[4] and β-hydroxy acetals[5] used for the synthesis of medium-sized carbocycles,[6] pharmaceuticals[7] and carbohydrates.[8]

In 1993 Sakai[9] and co-workers described a novel BF_3 etherate catalysed one-pot tandem aldol condensation-Grob fragmentation sequence. Recently Kabalka and coworkers[10] have published a more detailed study of the aldol-Grob reaction, incorporating the effect of different Lewis acids, solvents and substrate structure on the reaction pathway.[10] The aldol-Grob reaction has been applied successfully in the synthesis of some natural products and is the key step in the synthesis of sarmentosine,[11] pipercide and piperolein A,[12] three amide alkaloids extracted from *Piper sarmentosum* and *P. nigrum*.

During the last decade rare earth metal triflates have been found to be unique as Lewis acids in that they are water tolerant, recyclable catalysts that can effectively promote several carbon-carbon and carbon-heteroatom bond formation reactions. Very recently the use of lanthanide triflates in organic synthesis has been reviewed.[13]

As part of our ongoing studies to test the effectiveness of lanthanide triflates as catalysts of reactions carried out under solvent-free conditions,[14] we decided to investigate the use of $Yb(OTf)_3$ hydrate as a Lewis acid for the aldol-Grob reaction starting from differently substituted aromatic aldehydes and ketones in solvent-free conditions (Scheme 1).



Scheme 1

Results and Discussion

The reaction was carried out at 60 °C for 8 h using ketone (1.0 mmol) and aldehyde (1.0 mmol) in the presence of $Yb(OTf)_3$ hydrate (0.1 mmol). The results are summarised in Table 1.

The reaction is regioselective and gave only (*E*)-alkenes in good yields; the *E* geometry of the double bond was determined by coupling constants and the multiplicity of the olefinic proton signals, and by comparison of the NMR spectroscopic data with those previously reported.[10] The regioselectively giving exclusively *E* adducts may be explained by the mechanism proposed by Kabalka and coworkers.[10]

When other lanthanide triflates were used as catalysts under the same reaction conditions, a complex mixture of products was obtained and the desired product was recovered in less than 20% yield. Lower temperatures or shorter reaction times resulted in lower yields which were shown to be not significantly dependent on the position and electronic properties of the aryl substituent, except for nitro

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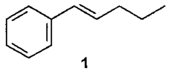
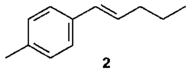
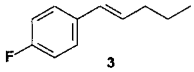
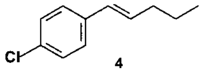
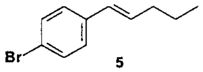
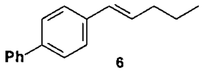
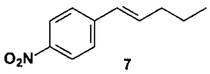
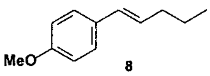
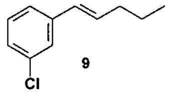
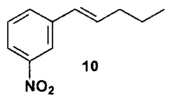
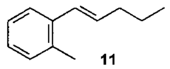
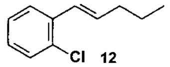
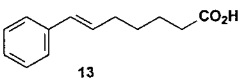
Table 1. Reaction between aldehydes and ketones catalysed by $Yb(OTf)_3$

Entry	Aldehyde	Ketone	Product	Yield (%)[a]
1	R = H	5-Nonanone	 **1**	89
2	R = p-CH_3	5-Nonanone	 **2**	91
3	R = p-F	5-Nonanone	 **3**	85
4	R = p-Cl	5-Nonanone	 **4**	83
5	R = p-Br	5-Nonanone	 **5**	71
6	R = p-Ph	5-Nonanone	 **6**	77
7	R = p-NO_2	5-Nonanone	 **7**	15
8	R = p-MeO	5-Nonanone	 **8**	11
9	R = m-Cl	5-Nonanone	 **9**	70
10	R = m-NO_2	5-Nonanone	 **10**	5
11	R = o-CH_3	5-Nonanone	 **11**	81
12	R = o-Cl	5-Nonanone	 **12**	78
13	R = H	2-Hexanone	**1**	82
14	R = p-CH_3	2-Hexanone	**2**	81
15	R = p-$N(CH_3)_2$	5-Nonanone	– (78)[b]	N.R.
16	n-Hexanal	5-Nonanone	– (81)[b]	N.R.
17	Cyclohexancarboxyaldehyde	5-Nonanone	–[c]	N.R.
18	R = p-F	2-Hexanone	**3**	81
19	R = p-Cl	2-Hexanone	**4**	77
20	R = H	7-Oxooctanoic acid	 **13**	68

[a] Isolated yield. [b] Yield of α,β-unsaturated ketone. [c] Starting material recovered in 90% yield.

(entries 7 and 10), methoxy (entry 8) and dialkylamino (entry 15) substituted aldehydes, for which yields of the desired alkene decreased dramatically. As depicted by the reaction mechanism proposed by Kabalka and co-workers,[10] a destabilisation of the carbocationic intermediate by a nitro group and a complexation of the methoxy or amino group with the metal centre, diminishing its catalytic activity, may be invoked in these cases.

Using aliphatic aldehydes as substrates, no alkene was obtained and aldol condensation products (entry 16) or starting materials (entry 17) were recovered. This may indicate that a stabilized benzylic carbocation[10] is an intermediate also in the Yb(OTf)$_3$ catalysed aldol-Grob reaction.

In every reaction the corresponding carboxylic acid could be recovered in nearly quantitative yield. For example, pentanoic acid was obtained in 93% yield when 5-nonanone was condensed with benzaldehyde. The ketone symmetry does not affect the selectivity and yields of the process; in fact, the same alkene was obtained when using 5-nonanone or 2-hexanone as starting ketones, suggesting that Yb(OTf)$_3$ favours the formation of the more alkylated thermodynamically stable enolate and its subsequent addition to the aldehyde.

The best results were obtained using 0.1 equivalents of Yb(OTf)$_3$ hydrate. Higher loadings did not improve reaction times and yields and, moreover, the minimal quantity of catalyst employed in our process greatly disfavours the formation of styrenyl polymerisation by-products, deriving directly from the olefinic reaction products. It's also important to note that the addition of a few millilitres of CH_2Cl_2 to the reaction medium precipitated the catalyst allowing its simple recovery by filtration; the catalyst could therefore be recycled and used several times without appreciable loss of activity. The reaction to give alkene **1** was in fact repeated three times, washing the catalyst with CH_2Cl_2 and drying it at 70 °C for two hours after each run, with the following yields: 83%, 81% and 81%. Therefore the concomitant formation of a carboxylic acid as a reaction product, capable of rendering Yb(OTf)$_3$ ineffective as an aldol-Grob catalyst (by chelation), does not significantly affect its catalytic activity.

The absence of solvents seems to be crucial in driving the process to yield the aldol-Grob adduct, while the presence of solvents like THF, alcohols or water leads to the formation of only aldol condensation products (α,β-unsaturated ketones) and the use of dichloromethane, *n*-hexane or toluene greatly decreases the catalytic activity of Yb(OTf)$_3$; starting materials were recovered in almost quantitative yield.

Conclusions

In this paper we have shown that Yb(OTf)$_3$ hydrate is an effective catalyst in promoting the reaction between ketones and aromatic aldehydes, affording only (*E*)-alkenes. The main difference in our methodology compared to BF$_3$-catalysed reactions is the Lewis acid/substrate ratio, the optimal value of which was found to be 0.1:1; in the other cases a 1:1 ratio or even an excess of Lewis acid is needed to effectively promote the coupling reaction. Furthermore, product yields, easy workup procedure, absence of solvent, simple recovery, very high recyclability and easy handling of the catalyst are other important features of our methodology. Finally, the different reactivity of methylene- and methyl-derived enolates could allow the use of readily available methyl ketones.

Experimental Section

General Method: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 spectrometer operating at 200.1 and 50.53 MHz, respectively, in the Fourier transform mode. GC analyses and MS spectra were carried out with an HP 5890 gas chromatograph (dimethyl silicone column 12.5 m) equipped with an HP 5971 Mass Selective Detector. Flash column chromatography was performed on 0.040−0.063 mm (230−400 mesh ASTM) Merck silica gel. Elemental analysis was performed on a Carlo Erba Model 1106 elemental analyzer. All aldehydes and ketones, and Yb(OTf)$_3$ were purchased from Aldrich Chemical Co. and used without any purification.

General Procedure: Yb(OTf)$_3$ (0.1 mmol) was added to a mixture of aldehyde (1.0 mmol) and ketone (1.0 mmol) and stirring was continued at 60 °C for 8 h. CH_2Cl_2 (2 mL) was added at room temperature, the precipitated solid was collected and the filtrate was diluted with CH_2Cl_2 (20 mL) and washed twice with a 5% solution of $NaHCO_3$ (10 mL), dried over Na_2SO_4 and the solvents evaporated. The residue was purified by silica gel column chromatography, using *n*-hexane as eluent, to give the desired product. ^{1}H NMR, ^{13}C NMR and GC/MS data of compounds **1**, **2**, **4**, **5**, **7**, **8**, **9**, **10** and **12** were in full agreement with those reported previously.[10d]

(*E*)-1-phenyl-1-pentene (1): Yield: 130 mg (89%) (entry 1, Table 1). Yield: 120 mg (82%) (entry 13).

(*E*)-1-(4-methylphenyl)-1-pentene (2): Yield: 145 mg (91%) (entry 2). Yield: 130 mg (81%) (entry 2).

(*E*)-1-(4-fluorophenyl)-1-pentene (3): Yield: 140 mg (85%) (entry 3). Yield: 135 mg (81%) (entry 18). Colourless oil. ^{1}H NMR: $\delta = 0.98$ (t, $J = 7.1$ Hz, 3 H), 1.52−1.74 (m, 2 H), 2.15−2.27 (m, 2 H), 6.11−6.23 (m, 1 H), 6.48 (d, $J = 12.0$ Hz, 1 H), 7.08−7.48 (m, 4 H) ppm. ^{13}C NMR: $\delta = 13.7$, 22.5, 36.1, 115.0, 127.2, 127.3, 128.7, 130.6, 134.1, 152.5 ppm. MS (EI): *m*/*z* (%) = 164 (33), 135 (100), 122 (27), 115 (25), 109 (27). $C_{11}H_{13}F$ (164.2): calcd. C 80.45, H 7.98; found C 80.47, H 7.96.

(*E*)-1-(4-chlorophenyl)-1-pentene (4): Yield: 150 mg (83%) (entry 4). Yield: 140 mg (83%) (entry 19).

(*E*)-1-(4-bromophenyl)-1-pentene (5): Yield: 160 mg (71%).

(*E*)-1-(4-phenylphenyl)-1-pentene (6): Yield: 170 mg (77%). colourless oil. ^{1}H NMR: $\delta = 1.02$ (t, $J = 7.0$ Hz, 3 H), 1.51−1.82 (m, 2 H), 2.22−2.34 (m, 2 H), 6.27−6.35 (m, 1 H), 6.49 (d, $J = 12.5$ Hz, 1 H), 7.32−7.74 (m, 9 H) ppm. ^{13}C NMR: $\delta = 13.8$, 22.6, 35.2, 126.3, 126.9, 127.1, 127.2, 128.8, 129.3, 131.2, 137.0, 139.5, 140.9 ppm. MS (EI): *m*/*z* (%) = 222 (84), 193 (100), 178 (93), 165 (36), 152 (16), 115 (16). $C_{17}H_{18}$ (222.3): calcd. C 91.84, H 8.16; found C 91.85, H 8.15.

(*E*)-1-(4-nitrophenyl)-1-pentene (7): Yield: 30 mg (15%).

(*E*)-1-(4-methoxyphenyl)-1-pentene (8): Yield: 20 mg (11%).

(*E*)-1-(3-chlorophenyl)-1-pentene (9): Yield: 125 mg (70%).

(*E*)-1-(3-nitrophenyl)-1-pentene (10): Yield: 10 mg (5%).

(*E*)-1-(2-methylphenyl)-1-pentene (11): Yield: 130 mg (81%). Colourless oil. ^{1}H NMR: $\delta = 1.08$ (t, $J = 7.0$ Hz, 3 H), 1.51−1.68 (m, 2 H), 2.17−2.32 (m, 2 H), 2.42 (s, 3 H), 6.07−6.19 (m, 1 H), 6.68 (d, $J = 12.3$ Hz, 1 H), 7.25 (m, 3 H), 7.12−7.54 (m, 1 H) ppm. ^{13}C NMR: $\delta = 13.8$, 19.8, 22.6, 35.4, 125.5, 126.0, 126.8, 127.8, 130.2, 132.4, 134.9, 137.1 ppm. MS (EI): *m*/*z* (%) = 160 (46), 131

(100), 115 (16), 91 (16). $C_{12}H_{16}$ (160.2): calcd. C 89.94, H 10.06; found C 89.92, H 10.08.

(*E*)-1-(2-chlorophenyl)-1-pentene (12): Yield: 140 mg (78%).

(*E*)-7-Phenyl-6-heptenoic acid (13): Yield: 140 mg (68%). White solid. m.p. 93−94 °C. ^{1}H NMR: δ = 1.44−1.61 (m, 4 H), 2.12−2.25 (m, 2 H), 2.32 (t, *J* = 6.9 Hz, 2 H), 6.12−6.19 (m, 1 H), 6.32 (d, *J* = 12.5 Hz, 1 H), 7.25−7.37 (m, 5 H) ppm. ^{13}C NMR: δ = 23.4, 26.6, 32.7, 33.4, 126.2, 128.4, 128.5, 129.0, 131.9, 135.4, 177.2 ppm. MS (EI) (as methyl ester): *m*/*z* (%) = 218 (34), 186 (65), 169 (11), 158 (12), 143 (12), 130 (40), 117 (100), 104 (36), 91 (36). $C_{13}H_{16}O_2$ (204.2): calcd. C 76.44, H 7.90; found C 76.46, H 7.89.

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