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Organocatalytic direct aldol reaction between acetone and α-substituted β-keto esters

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Abstract

The organocatalytic aldol reaction between acetone and α-substituted β-keto esters is presented. The α-unsubstituted or α-chloro ethyl acetoacetates failed to react with acetone when L-proline was used as catalyst. L-Proline or other optically pure pyrrolidine derivatives catalyzed the direct aldol reaction of acetone and α-fluorinated β-keto esters affording δ-keto-β-hydroxy-α-fluoro esters in high yields. Both the α-fluoro- and α,α-difluoro-β-keto esters functioned as aldol acceptors in these reactions. High ee values, up to 83% coupled with low diastereoselectivities were obtained in the reaction of ethyl 2-fluoroacetoacetate. Our study revealed a novel extension of the scope of the organocatalytic direct aldol reaction catalyzed by chiral organic bases, being the first report in which an asymmetric organocatalytic fluoroketone–ketone aldol addition has been described.

Keywords: Acetone; Asymmetric; Direct aldol addition; Ethyl 2-fluoroacetoacetate; L-Proline

1. Introduction

Motivated by the increasing requirement for development of novel green methods that make use of easily available metal-free catalysts, the organocatalytic reactions presently are in the focus of organic synthesis research [1,2]. The need of optically pure fine chemicals used as chiral building blocks in the synthesis of pharmaceuticals led to the development of the asymmetric versions of many organocatalytic reactions [3]. Several types of organic reactions have been carried out with high enantiocontrol using chiral organic molecules as catalysts [3–13]. Due to the unique properties of fluorinated compounds the asymmetric catalytic synthesis of optically pure fluoro derivatives are of particular interest [14,15]. Among the methods applied with success for producing fluorine containing enantiomerically enriched compounds are the asymmetric organocatalytic fluorinations using special fluorinating agents [16–19], the enantioselective hydrogenations of fluorine containing prochiral compounds [20–25] and the enantioselective catalytic C–C bond forming reactions of fluorous starting materials [26–29].

In contrast to the vast literature on the enantioselective synthesis of fluorine containing fine chemicals, only a few reports can be found on aldol reactions of fluorinated compounds [29–32]. Furthermore, reports on the asymmetric aldol additions using ketones both as aldol acceptors and donors are scarce and so far limited on the use of pyruvates [30–35] or activated ketones, such as 1,3-dioxan-5-one derivatives, α-diketones, α-keto nitriles and α-keto lactames [36–39]. An interesting application of the reaction was the recently reported novel biomimetic preparation method of isotetronic acid by Dondoni and co-workers via the homoaldol reaction of pyruvates [33]. Our present study aimed the development of an organocatalytic approach for the enantioselective aldol reaction of β-keto esters with acetone. Here we present the results obtained in the direct aldol reactions of α-substituted β-keto esters catalyzed by L-proline and other optically pure pyrrolidine derivatives. We have focused our efforts on the aldol reaction of α-fluorinated β-keto esters and acetone, as a novel asymmetric catalytic method for obtaining optically enriched fluoro-hydroxy esters.

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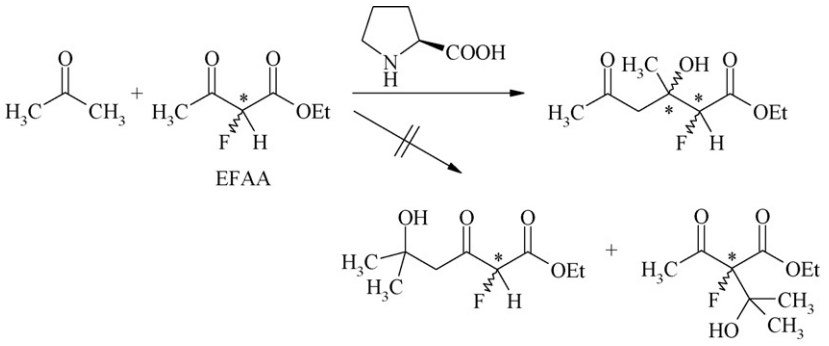


Scheme 1. Possible regioisomers in the enantioselective aldol reaction of acetone and ethyl 2-fluoroacetoacetate (EFAA).

2. Experimental

2.1. Materials

All reagents: ethyl acetoacetate (EAA, Fluka), ethyl 2-chloroacetoacetate (ECAA, Fluka), ethyl 2-fluoroacetoacetate (EFAA, Aldrich) and methyl 2,2-difluoro-oxopentanoate (MDFOP, Apollo Sci.) were obtained from commercial source and used as received. The catalysts L-proline, D-proline, L-prolinol and piperidine were Fluka products. High purity solvents were purchased from Scharlau Chemie S.A. and Fluka and were used without further purification.

2.2. General catalytic procedure

The specified amount of catalyst was dissolved or suspended in 5 mL solvent/acetone mixture (or only acetone), then 1 mmol β-keto ester was added and the mixture was stirred magnetically at room temperature. After the given reaction time the catalyst was removed from the mixture by treating with saturated NH_4Cl solution. The products were extracted with ethyl acetate, dried over Na_2SO_4, concentrated in vacuum and analyzed.

2.3. Product analysis

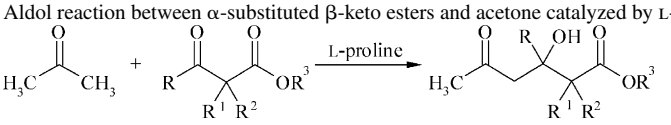
The products were identified by GC–MS (Agilent Techn. 6890N GC-5973 MSD) and NMR analysis (Bruker AVANCE DRX-500 spectrometer). Quantitative analysis, including enantiomeric separations were performed by gas chromatography (HP-5890 II-FID) on a HP-Chiral (30 m × 0.25 mm, J&W Sci. Inc.) chiral capillary column. The diastereomeric excess (de) and enantiomeric excess (ee) were calculated based on GC analysis using the formulae: de (%) = $100 \times |D_1 - D_2|/(D_1 + D_2)$, where D_1 and D_2 are the concentrations of the cross-aldol product diastereomers; ee (%) = $100 \times |E_1 - E_2|/(E_1 + E_2)$, where E_1 and E_2 are the concentrations of the enantiomers. The product resulted in the reaction of acetone and EFAA was purified by flash chromatography (eluent: hexane/methyl-*terc*-butyl ether 1/1). GC–MS, *m/z*(rel. int.): 191(1), 188(1), 168(2), 146(8), 121(13), 101(44), 78(13), 73(6), 59(8), 43(100), 29(11); ^{1}H NMR ($CDCl_3$, mixture of diastereomers), δ (ppm): 1.22–1.3 (m, 6H), 2.13–2.18 (s, 3H), 2.56–2.64 (dd, 1H, J = 17.4, 1.8 Hz), 2.84–2.92 (dd, 1H, J = 17.4, 1.8 Hz), 4.17–4.26 (m, 2H), 4.7–4.92 (d, 1H, J = 48.1 Hz); ^{13}C NMR ($CDCl_3$, mixture of diastereomers), δ (ppm): 14 (CH_2–CH_3), 23 and 24 (CH_3–C–OH), 31.3 and 31.6 (CH_3–C=O), 47.9–48.4 (O=C–CH_2), 61.5–61.8 (CH_3–CH_2–O), 72.0–72.8 (d, C–CH–F, J = 20.7 Hz), 91.0–93.3 (d, CH–F, J = 190 Hz), 167.5–168 (d, COO, J = 7.2 Hz), 209.4–209.8 (CH_3–C=O). The product resulted in the reaction of acetone and DMFOP: GC–MS, *m/z*(rel. int.): 195(10), 186(9), 167(4), 144(6), 115(49), 105(9), 97(6), 85(3), 73(3), 57(86), 43(100), 29(14).

3. Results and discussion

The work of Barbas and co-workers on the L-prolinol catalyzed asymmetric aldol reaction of fluoroacetone and aldehydes [29] and Jørgensen and co-workers' results obtained using α-keto esters as aldol acceptors [32], encouraged us to start a study on the enantioselective organocatalytic aldol reactions of unsubstituted and several α-substituted β-keto esters with acetone. Based on the achievements in the aldol reactions employing fluoroacetone [29], beside EAA we have studied the reaction of an α-fluoro (EFAA), an α,α-difluoro (MDFOP) and for comparison an α-chloro-β-keto ester (ECAA). Although, it was found that fluoroacetone acts as aldol donor in the L-proline catalyzed reactions with aldehydes [29], in the reaction α-fluoro-β-keto esters and acetone the outcome of the reaction was unknown. Thus, during the L-proline catalyzed reactions of these compounds and acetone the former substances could act either as aldol acceptors or as donors. The possible regioisomers that could form in the reaction of EFAA and acetone are shown in Scheme 1. However, in the L-proline catalyzed reaction the α-fluoro-β-keto ester (EFAA) acted exclusively as acceptor, only the corresponding cross-aldol addition product was formed during this reaction (see Scheme 1). As side product small amount of unsaturated dehydrated aldol compound was formed decreasing the selectivity. The self-aldol addition of acetone also occurred in some extent, leading to the formation of 4-hydroxy-4-methyl-2-pentanone and 4-methyl-3-penten-2-one.

The results of our initial attempts with the selected β-keto esters are presented in Table 1. The unsubstituted (EAA) and the α-chlorine substituted (ECAA) ethyl acetoacetates failed to react with acetone in presence of L-proline. On the contrary, both α-fluorinated compounds, i.e. EFAA and MDFOP gave aldol addition products in good yields. In the reactions of both

Table 1
Aldol reaction between α-substituted β-keto esters and acetone catalyzed by L-proline



Substrate				Reaction time (day)	Conversion (%)[a]	Selectivity (%)[a]	Stereoselectivities		
R	R^1	R^2	R^3				de (%)[a]	ee_1 (%)[a]	ee_2 (%)[a]
CH_3	H	H	CH_2CH_3	6	No aldol addition				
CH_3	Cl	H	CH_2CH_3	6	No aldol addition				
CH_3	F	H	CH_2CH_3	1	33	91	12	83	55
				6	78	97	11	81	53
CH_2CH_3	F	F	CH_3	2	40	92	–	26	–
				6	60	89	–	24	–

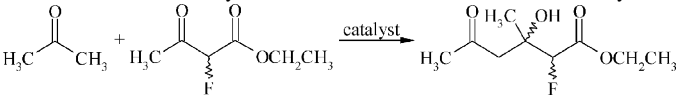
Reaction conditions: 5 mL DMSO/acetone, 1 mmol substrate, 0.2 mmol L-proline, room temperature.
[a] Conversions of the β-keto esters, selectivities of the cross-aldol products, diastereomeric excess (de) and enantiomeric excess (ee) determined by GC analysis.

fluorinated compounds acetone acted as aldol donor, thus, only one regioisomers were obtained in these reactions (see Table 1). Thus, one may assume that the α-fluorine atom has a crucial role in the reaction. Earlier studies have shown that during the direct aldol additions catalyzed by L-proline, the formation of the enamine condensation product of the aldol donor is the first step of the reaction [4,29,40,41]. In a second step this enamine intermediate reacted with the electrophiles present in the system. Obviously, in all of our reactions the formation of the enamine from acetone and L-proline occurred. However, the following step was highly dependent on the substrate structure. It is known that activation of the carbonyl group by α-fluorine atoms increases the electrophilic character of the carbonyl C atom. This activation seems to be necessary for obtaining cross-aldol products.

Although in the reaction of EFAA good ee were obtained, the diastereomeric excess was low, typically a 56/44 diastereomeric ratio was obtained. The identity of the diastereomers could be assumed on the bases of ^{1}H NMR analysis (see Section 2). The coupling constants $J(H_\alpha$-F) had the same values in both diastereomers, however, the chemical shifts δ (H_α) were different 4.78 and 4.85 ppm, respectively. According to the chemical shifts of the H_α observed for similar (α-fluoro-β-hydroxy esters) compounds the diastereomers having higher δ (H_α) values were proved to be the *syn*-fluoro-hydroxy derivatives [25,42]. Thus, the ^{1}H NMR analysis of our products showed that the *syn* diastereomers were formed in slight excess in the L-proline catalyzed aldol addition of acetone to EFAA.

The much lower ee values obtained in the reaction of MDFOP indicated that beside the activation effect of the fluorine atom, the steric effect of the α-substituent also has important role in obtaining high enantioselectivity. In the reaction of the compound bearing two fluorine atoms in α position (MDFOP) the enantiodiscrimination between the two faces of the molecule was less accentuated. EFAA with one α-fluorine atom due to the steric differences of the two substituents in α position (H and

Table 2
Effect of solvent and catalyst structure on the aldol reaction between ethyl 2-fluoroacetoacetate (EFAA) and acetone



Catalyst (mol%)	Solvent	Reaction time (day)	Conversion (%)[a]	Selectivity (%)[a]	Stereoselectivities		
					de (%)[a]	ee_{anti} (%)[a,b]	ee_{syn} (%)[a,b]
L-Proline (20)	DMSO/acetone 4/1	1	33	91	12	83	55
		3	60	97	11	82	54
		6	78	97	11	81	53
L-Proline (20)	$CHCl_3$/acetone 4/1	4	15	90	18	83	27
L-Proline (20)	acetone	4	52	98	15	79	38
D-Proline (20)	DMSO/acetone 4/1	6	68	97	3	81[c]	56[c]
L-Prolinol (20)	DMSO/acetone 4/1	1	19	72	10	22[c]	24[c]
		4	40	86	12	22[c]	26[c]
Piperidine (30)	DMSO/acetone 4/1	3	15	99	20	–	–

Reaction conditions: 5 mL solvent, 1 mmol EFAA, room temperature.
[a] Conversions of the EFAA, aldol product selectivity, de and ee determined by GC analysis.
[b] Identification of the excess enantiomers are in progress; ee_{anti} and ee_{syn} the enantiomeric excesses of the assumed *anti* and *syn* diastereomers.
[c] The excess enantiomers had opposite configuration in comparison with those obtained in the reactions catalyzed by L-proline.

F) favored a preferential attack from one side of the carbonyl group.

The good ee values obtained in the reaction of EFAA encouraged us to continue our study using this substrate and examining the effect of the solvent and the catalysts structure (see Table 2).

The best results were obtained in the frequently used DMSO/acetone 4/1 solvent mixture [3–5]. Using $CHCl_3$/acetone low yields were obtained possibly due to the lower solubility of L-proline in $CHCl_3$, while in neat acetone the conversion was only slightly lower than that obtained in DMSO/acetone but the ee values decreased. Using D-proline as catalyst similar results were obtained as with L-proline, except the opposite enantiomers were formed in excess, as expected based on previous direct aldol addition studies [9]. Surprisingly, when L-prolinol was used as catalyst the sense of the enantiomeric induction was also opposite to that obtained with L-proline. However, in this reaction L-prolinol was a much less stereoselective catalyst, lower ee values being obtained. The use of the achiral cyclic secondary amine, piperidine also afforded the same aldol adduct, interestingly in the highest diastereomeric excess and obviously lacking any enantioselection.

To sum up our results, the scope of the asymmetric organocatalytic aldol reaction has been extended to ketone-α-fluoro-β-keto ester aldol addition. It has been shown that this unprecedented reaction can be carried out with readily available chiral amine catalysts, obtaining good enantioselectivities in the reaction of the α-monofluorinated compounds. However, lower ee values could be obtained in case of an α,α-difluoro-β-keto ester. Interesting inversion of enantioselection has been observed by replacing the L-proline catalyst with L-prolinol. Although, in this novel example of the asymmetric direct aldol addition the good enantioselectivity values were coupled with rather low diastereoselectivities, our results opened a novel research direction in this highly studied area of the stereochemical organic synthesis.

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