Direct Aldol Reactions of Glyoxylic Acid Monohydrate with Ketones

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Abstract: The direct aldol reaction of various ketones with glyoxylic acid afforded the β−hydroxy carbonyl compounds in good yields and high regioselectivities.

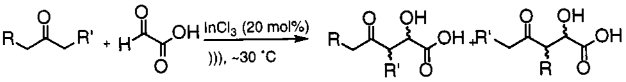
Key words: $InCl_3$, glyoxylic acid, α-hydroxy acid, direct aldol reaction, neat reaction

The aldol reaction is one of the most powerful tools for the construction of carbon-carbon bond[1]. Nature itself has made use of this reaction in the prebiotic biosynthesis of saccharides. In principle, the most classical and conventional aldol reactions which involve the mixed aldol reaction between a ketone containing α-hydrogen with an aldehyde in the presence of base or acid should be an useful method for the synthesis of complex molecules.[1] However, this type of aldol reaction has not been well exploited in organic synthesis due to the following reasons: 1) side-reactions such as self-condensation of the ketone or/and dimerization of the aldehyde can be a problem; 2) the harsh reaction conditions employed which usually require a strong base or acid make it unattractive for complex molecule synthesis which usually contain acid or base-labile functional groups; 3) byproducts such as α,β-unsaturated carbonyl compounds, dimers and polymers are usually formed together with the desired aldol addition product; 4) low regioselectivity was observed in most of these cases. Therefore, a new method which employed mild reaction conditions whilst able to overcome some if not all of the above problems is much sought after.

Recently, it has been reported that Zn-catalyst ($Zn(NO_3)_2{\cdot}6H_2O$ and α-amino acid ester)[2,] BCl_3[3] and $TiCl_4$[4,5] are useful catalysts to promote the direct aldol reaction. However, these reactions catalyzed by the latter two Lewis acids must be carried out under anhydrous condition because of their moisture sensitivities.

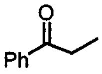
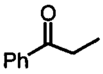
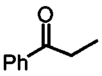
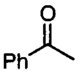
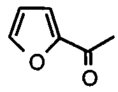
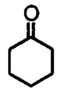
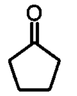
On the other hand, of special synthetic value among the many aldol reaction variants are the glyoxylic acid-aldol reaction which provide α-hydroxy acids which are of biological and synthetic importance.[6] However, in most of the cases, the aldol products were obtained in poor yields under very harsh reaction conditions.[6b,7]

In this article, we present the direct aldol reactions of glyoxylic acid monohydrate with aliphatic and aromatic ketones separately in the presence of $InCl_3$ under solvent-free condition (Scheme 1).[8]



Scheme 1

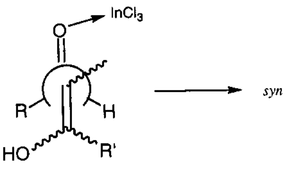
Table 1 Direct aldol reaction of glyoxylic acid with ketones

entry	Ketone	Condition	Yields (%)[a]	*syn*/*anti* [b]
1		))), 3 d	10	73:27
2		InCl3(20 mol%),))), 2 d	80	60:40
3		InCl3 (50 mol%),))), 3 d	95	59:41
4		InCl3 (20 mol%),))), 3 d	94	-
5		InCl3 (20 mol%),))), 3 d	91	-
6		InCl3 (20 mol%),))), 2 d	80	62:38
7		InCl3 (20 mol%),))), 4 d	95	71:29

a. Isolated yields. b. Determined by ^1H NMR and ^{13}C NMR analyses.[9,10]

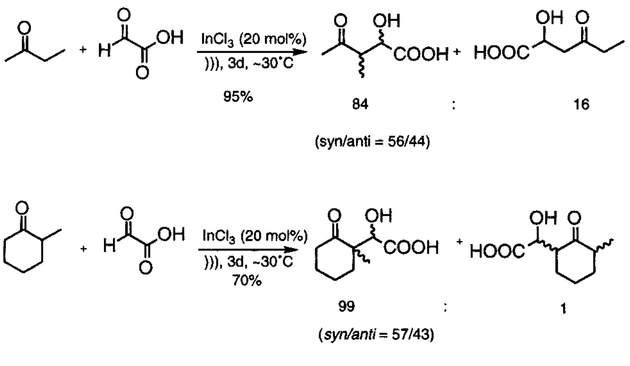
In our investigation, we found that $InCl_3$ can efficiently promote the direct aldol reaction of glyoxylic acid monohydrate under sonication. The results are shown in Table 1

As shown in Table 1, $InCl_3$ is essential for the success of the reactions with propiophenone (Table 1, entries 1, 2 and 3). In the presence of 20 mol% $InCl_3$ under sonication and neat condition, satisfactory yields were obtained in all cases. The diastereoselectivities were low to moderate and the *syn* products were predominant regardless of the geometry of the enols. The observed *syn* diastereoselectivities can be explained using an open-chain antiperiplanar transition state (Scheme 2).



Scheme 2

The regioselectivities of unsymmetrical ketones were high and the thermodynamically controlled product was obtained as the major product (Scheme 3).



Scheme 3

Generally, the direct aldol reactions of various ketones with glyoxylic acid are clean. The possible α,β-unsaturated acid resulted from the aldol condensation and double aldol reaction were not detected in most cases. The reactions proceeded smoothly under extremely mild conditions to give the corresponding α-hydroxyl acids in high yields with moderate diastereoselectivities and regioselectivities.[11] For unsymmetrical ketones, the thermodynamically controlling products were major products.

In summary, we have developed an easy approach to various α-hydroxy acids by the direct aldol reactions of various ketones with the commercially available hydrates of glyoxylic acid in the presence of indium trichloride under solvent-free conditions. Since the products of direct aldol reaction of ketones with glyoxylic acid are important and useful intermediates for natural products, we can expect that this simple, highly efficient, safe and environmentally friendly methodology will find wide application in industry.

A Typical Experimental Procedure:

Glyoxylic acid monohydrate (46 mg, 0.5 mmol), acetophenone (120 mg, 1mmol) and $InCl_3$ (24 mg, 0.1 mmol) were mixed and sonicated for 2-4 d (~ 30 °C). After normal acid-base workup, the pure aldol products were obtained in good yields. ^1H NMR (Acetone-d_6): δ 8.03-7.99 (m, 2H), 7.65-7.49 (m, 3H), 4.75 (t, J = 5.4 Hz, 1H), 3.50 (d, J = 5.4 Hz, 2H); ^{13}C NMR (Acetone-d_6): δ 198.60, 176.23, 138.61, 134.80, 130.24, 129.66, 68.42 44.06; FTIR (thin film) 1731.0, 1678.1 cm^{-1}; HRMS calcd. for $C_{10}H_{10}O_4$ 194.0579, found 194.0579.

References and Notes

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(11) The aldol product obtained was subjected to the same reaction condition for 3 d and no retro-aldol reaction was observed.

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