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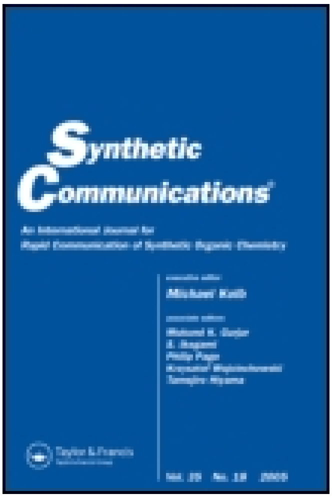

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Pyrrolidine-Catalyzed Condensation of Ethyl Diazoacetate to Aldehydes in Water

M. Lakshmi Kantam [a], L. Chakrapani [a], T. Ramani [a] & K. Rajender Reddy [a]

[a] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad, India

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PYRROLIDINE-CATALYZED CONDENSATION OF ETHYL DIAZOACETATE TO ALDEHYDES IN WATER

M. Lakshmi Kantam, L. Chakrapani, T. Ramani, and K. Rajender Reddy
Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad, India

A simple and convenient protocol for the synthesis of α-diazo carbonyl compounds from the condensation of ethyl diazoacetate to aldehydes in water was developed using pyrrolidine as a catalyst.

Keywords: Aldol-type reaction; α-diazo carbonyl compounds; ethyl diazoacetate; pyrrolidine; water

INTRODUCTION

α-Diazo carbonyl compounds are valuable intermediates for the synthesis of amino alcohols and amino acids.[1] Moreover, the carbene species generated from α-diazo carbonyl compounds are widely used in molecular insertion reactions to form a new carbon–carbon (C-C) and/or C-heteroatom bond.[2] Despite their tendency to convert into corresponding β-keto carbonyl compounds,[3] they are useful synthetic intermediates for many natural products.[4] These versatile α-diazo carbonyl compounds are generally prepared by the azido transfer reaction of carbonyl compounds. This can be usually achieved by treatment with a strong base, such as butyllithium, lithium diisopropylamide (LDA), sodium hydride or potassium hydroxide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and quartenary ammonium hydroxde under controlled conditions.[5] However, some of these methods involve the use of strong bases or expensive reagents and have poor yields of products. Moreover, the use of strong bases may not be compatible with functional groups in the substrates.

Catalytic transformations involving small organic molecules, known as organocatalysis, has attracted much interest in recent years.[6] These catalysts are environmentally more benign, as they do not involve metals. Though a number of these reactions have been performed in organic solvents, use of aqueous media is much more attractive because of environmental considerations. A number of organic reactions are now efficiently performed in water and display, in some cases, impressive rate accelerations, selectivity, new reactivity, and excellent yields.[7] Despite the

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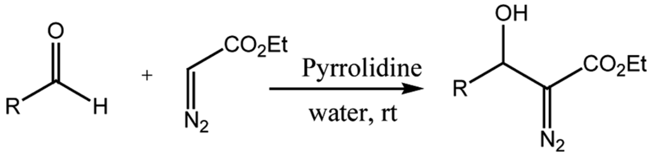
Address correspondence to M. Lakshmi Kantam, Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail: mlakshmi@iict.res.in



Scheme 1. Condensation of ethyl diazoacetate to aldehydes.

considerable progress made, the number of organocatalyzed reactions in pure water remains scarce, and there is a clear demand for new, direct, and efficient applications.

Pyrrolidine is a mild, readily available, and inexpensive organobase. Recently, the use of pyrrolidine and the pyrrolidine-derived organo catalysts was shown to be much more efficient for C-C bond-forming reactions.[8] Barbas and coworkers have shown that simple pyrrolidine can be utilized as an efficient catalyst for multicomponent reactions.[8] Recently, Chimni and Mahajan have reported pyrrolidine-catalyzed direct cross-aldol reaction of aromatic/heterocyclic aldehydes and ketones in water for the first time.[9] We have exploited further the advantage of pyrrolidine-catalyzed addition of ethyl diazoacetate (EDA) to various aromatic and heterocyclic aldehydes to yield diazo esters exclusively without any side products (Scheme 1).

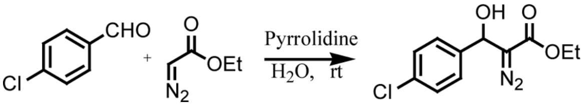
RESULTS AND DISCUSSION

Optimization of the reaction conditions was performed with 4-chlorobenzaldehyde. Initially, we examined the effects of various solvents. It was found that the nature of the solvent had a significant effect on the reaction. No formation of aldol-type product was observed when the reaction was conducted in nonpolar solvents, such as Et_2O, CH_2Cl_2, and $PhCH_3$ (Table 1, entries 1–3), or even in the polar solvents, such as MeOH and MeCN (Table 1, entries 4 and 5). Surprisingly, the rate of the reaction was accelerated in the presence of water, and very good conversions were observed when the reactions were carried out with a 1:1 mixture of $MeOH/H_2O$, $MeCN/H_2O$, and tetrahydrofuran $(THF)/H_2O$ (Table 1, entries 8–10). These results clearly indicate that water plays an important role in the activity of the catalyst. Later, we performed the reaction in pure water, in which greater yields were obtained in shorter reaction times (Table 1, entry 11).

Later, we examined the effect of various cyclic secondary amines, such as piperidine, morpholine, and proline for the present reaction. The results revealed that pyrrolidine was the most efficient catalyst, giving the products in greater yield, as shown in Table 2.

Under the optimized conditions, we performed the reaction of ethyl diazoacetate with a variety of structurally divergent aldehydes possessing a wide range of functional groups, and the results are summarized in Table 3. The aromatic aldehydes, having an electron-withdrawing substituent, gave the corresponding β-hydroxy-α-diazo carbonyl compounds in good yields (Table 3, entries 1–10),

Table 1. Screening of solvents for the addition of EDA to 4-chloro benzaldehyde[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	Ether	24	0
2	DCM	24	0
3	Toluene	24	0
4	MeCN	24	0
5	MeOH	24	0
6	THF	24	0
7	DME	24	0
8	MeOH/H_2O (1:1)	2	67
9	MeCN/H_2O (1:1)	2	70
10	THF/H_2O (1:1)	2	55
11	H_2O	2	89

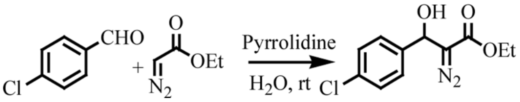
[a] All reactions were carried out with 30 mol% catalyst, aldehdye (0.5 mmol), EDA (0.55 mmol), solvent (2 mL).

[b] Isolated yields.

whereas the aromatic aldehydes with the electron-donating substituent gave greater yields after longer reaction times (Table 3, entry 11). In contrast, β-naphthaldehyde and cyclohexane carboxaldehyde provided lesser yields even after longer reaction times (Table 3, entries 12 and 13).

Later, we carried out the reactions with different heterocyclic aldehydes. The highly water-soluble pyridine aldehydes readily condensed with EDA to provide excellent yields in lesser reaction times. Reactions of aliphatic aldehydes and *trans*-cinnamaldehyde with EDA were unsuccessful under similar reaction conditions.

Table 2. Screening of different bases for the addition of EDA to 4-chlorobenzaldehyde[a]

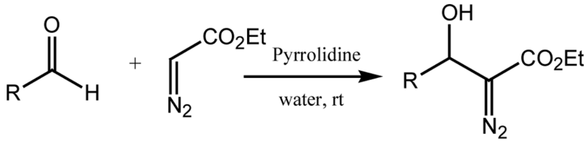


Entry	Base	Time (h)	Yield (%)[b]
1	pyrrolidine	2	89
2	piperidine	2	22
3	morpholine	18	12
4	proline	18	10

[a] All reactions were carried out with 30 mol% catalyst, aldehdye (0.5 mmol), EDA (0.55 mmol), H_2O (2 mL).

[b] Isolated yields.

Table 3. Pyrrolidine-catalyzed condensation of various aldehydes with ethyl diazoacetate[a]

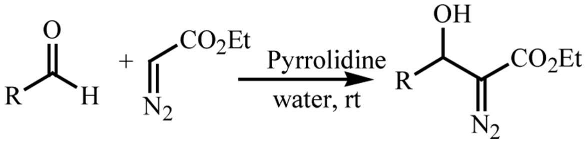


Entry	Substrate (R)	Time (h)	Yield (%)[b]
1	4-Cl-C_6H_4	2	89
2	4-CN-C_6H_4	<1	90
3	4-CF_3-C_6H_4	2	83
4	4-F-C_6H_4	3	80
5	3-NO_2-C_6H_4	1	80
6	4-Br-C_6H_4	2	65
7	4-NO_2-C_6H_4	<1	60
8	2-NO_2-C_6H_4	<1	71
9	C_6H_5	2	65
10	2-Cl-C_6H_4	2	50
11	4-CH_3-C_6H_4	12	80
12	2-Naphathyl	12	25
13	Cyclohexyl	12	40

[a] All reactions were carried out with 30 mol (%) catalyst, aldehyde (0.5 mmol), EDA (0.55 mmol), H_2O (2 mL).

[b] Isolated yields.

Table 4. Pyrrolidine-catalyzed condensation of various heterocyclic aldehydes with ethyl diazoacetate[a]



Entry	Substrate (R)	Time (h)	Yield (%)[b]
1	4-Pyridyl	0.5	95
2	3-Pyridyl	<1	83
3	2-Pyridyl	6	50
4	2-Furfuryl	12	75
5	2-Thiophenyl	12	40

[a] All reactions were carried out with 30 mol (%) catalyst, aldehyde (0.5 mmol), EDA (0.55 mmol), H_2O (2 mL).

[b] Isolated yields.

CONCLUSION

In conclusion, we have demonstrated that pyrrolidine is a highly efficient catalyst for the aldol-type reaction of various aromatic and heterocyclic aldehydes with EDA to give β-hydroxy-α-diazo carbonyl compounds in excellent yields in water at room temperature.

EXPERIMENTAL

Typical Experimental Procedure for the Condensation of Ethyl Diazoacetate to Aldehydes

Water (2 mL), followed by aldehyde (0.5 mmol) and EDA (0.55 mmol), was added to a dried, 25-mL, round-bottomed flask charged with pyrrolidine (0.30 mmol, 21 mg) at room temperature. The reaction was monitored by thin-layer chromatography (TLC). The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and distilled to obtain the crude product. Coloumn chromatography of the crude product on silical gel (60–120 mesh) using a mixture of ethyl acetate and hexane in varying proportions as eluent gave the corresponding β-hydroxy-α-diazo carbonyl compound. All the products are known and were determined by comparison of their physical data and spectral data with those reported in the literature.

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REFERENCES

1. Doyle, M. P.; Mckervey, M. A. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998.
2. (a) Taber, D. F.; Petty, E. H. General route to highly functionalized cyclopentane derivatives by intramolecular C-H insertion. *J. Org. Chem.* **1982**, *47*, 4808–4809; (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. Highly selective insertion into aromatic C–H bonds in rhodium(II) triphenylacetate–catalysed decomposition of α-diazocarbonyl compounds. *J. Chem. Soc. Chem. Commun.* **1992**, 1508–1510; (c) Davies, M. J.; Moody, C. J.; Taylor, R. J. Rhodium carbenoid–mediated cyclizations, part 7: Synthesis and coupling reactions of 2-substituted 3-oxooxepanes. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 1–7; (d) Miller, D. J.; Moody, C. J. Synthetic applications of the O-H insertion reactions of carbenes and carbenoids derived from diazocarbonyl and related diazo compounds. *Tetrahedron* **1995**, *51*, 10811–101843; (e) Calter, M. A.; Sugathapala, P. M.; Zhu, C. Aldol cyclization reaction sequence for the synthesis of tetrahydrofurans. *Tetrahedron Lett.* **1997**, *38*, 3837–3840.
3. (a) Horton, D.; Philips, K. D. Synthesis of methyl 2-deoxy-2-diazo-D-*arabino*-hexonate, its behaviour on photolysis and thermolysis, and conversion into a pyrazole derivative. *Carbohydr. Res.* **1972**, *22*, 151–162; (b) Wenkert, E.; Ceccherelli, P.; Fugiel, R. A.

α-Diazo-β-hydroxycarboxylates. *J. Org. Chem.* **1978**, *43*, 3982–3983; (c) Taylor, K. G. Carbenes and carbenoids with neighboring heteroatoms. *Tetrahedron* **1982**, *38*, 2751–2772; (d) Nickon, A. New perspectives on carbene rearrangements: Migratory aptitudes, bystander assistance, and geminal efficiency. *Acc. Chem. Res.* **1993**, *26*, 84–89.

4. Pellicciari, R.; Natalini, B.; Ceccheti, S.; Fringnelli, R. An efficient procedure for the regiospecific preparation of D-homo-steroid derivatives. *Steroids* **1987**, *49*, 433–441.
5. (a) Schollkopf, U.; Frasnelli, H.; Hoppe, D. Ethyl 2-oxazoline-5-carboxylate from ethyl isocyanoacetate and carbonyl compounds. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 300–301; (b) Moody, C. J.; Taylor, R. J. Rhodium carbenoid–mediated cyclizations: Use of ethyl lithiodiazoacetate in the preparation of ω-hydroxy-,-mercapto-, and -boc-amino-α-diazo-β-keto esters. *Tetrahedron Lett.* **1987**, *28*, 5351–5352; (c) Jiang, N.; Qu, Z.; Wang, J. 1,2-Aryl and 1,2-hydride migration in transition metal complex–catalyzed diazo decomposition: A novel approach to α-aryl-β-enamino esters. *Org. Lett.* **2001**, *3*, 2989–2992; (d) Wenkert, E.; McPherson, A. A. Condensations of acyldiazomethanes with aldehydes, ketones, and their derivatives. *J. Am. Chem. Soc.* **1972**, *94*, 8084–8090; (e) Jiang, N.; Wang, J. DBU-promoted condensation of acyldiazomethanes to aldehydes and imines under catalytic conditions. *Tetrahedron Lett.* **2002**, *43*, 1285–1287; (f) Wang, J.; Yao, W. Base-induced heterochiral dimerization of an oxiranyl carbaldimine: Stereoselective synthesis of a highly functionalized aziridine. *Org. Lett.* **2003**, *3*, 1527–1530; (g) Varala, R.; Ramu, E.; Sreelatha, N.; Rao, A. S. Catalytic aldol-type reaction of aldehydes with ethyl diazoacetate using quarternary ammonium hydroxide as the base. *Tetrahedron Lett.* **2006**, *47*, 877–880.
6. (a) Guillena, G.; Ramón, D. J. Enantioselective α-heterofunctionalisation of carbonyl compounds: Organocatalysis is the simplest approach. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492; (b) Dalko, P. I.; Moisan, L. In the golden age of organocatalysis. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (c) Duthaler, R. O. Proline-catalyzed asymmetric α-amination of aldehydes and ketones: An astonishingly simple access to optically active α-hydrazino carbonyl compounds. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (d) Jarvo, E. R.; Miller, S. J. Amino acids and peptides as asymmetric organocatalysts. *Tetrahedron* **2002**, *58*, 2481–2495; (e) Berkessel, A.; Gröger, H. (Eds.). *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
7. (a) Dickerson, T. J.; Janda, K. D. Aqueous aldol catalysis by a nicotine metabolite. *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221; (b) Cordova, A.; Notz, W.; Barbas, C. F. III. Direct organocatalytic aldol reactions in buffered aqueous media. *Chem. Commun.* **2002**, 3024–3025; (c) Reymond, J.-L.; Chen, Y. Catalytic, enantioselective aldol reaction with an artificial aldolase assembled from a primary amine and an antibody. *J. Org. Chem.* **1995**, *60*, 6970–6979; (d) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. Nornicotine aqueous aldol reactions: Synthetic and theoretical investigations into the origins of catalysis. *J. Org. Chem.* **2004**, *69*, 6603–6609.
8. (a) Ramachary, D. B.; Barbas III, C. F. Towards organo-click chemistry: Development of organocatalytic multicomponent reactions through combinations of aldol, Wittig, Knoevengel, Michael, Diels–Alder, and Huisgen cycloaddition reactions. *Chem. Eur. J.* **2004**, *10*, 5323–5331; (b) Ji, C.; Peng, Y.; Huang, C.; Wang, N.; Luo, Z.; Jiang, Y. An efficient method for direct aldol reactions catalyzed by pyrrolidine/catechol: The influence of cooperation of Brønsted acidity and hydrogen bond on the reaction. *J. Mol. Catal. A: Chem.* **2006**, *246*, 136–139; (c) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. Enantio- and diastereoselective Michael addition reactions of unmodified aldehydes and ketones with nitroolefins catalyzed by a pyrrolidine sulfonamide. *Chem. Eur. J.* **2006**, *12*, 4321–4322.
9. Chimni, S. S.; Mahajan, D. Electron deficiency of aldehydes controls the pyrrolidine-catalyzed direct cross-aldol reaction of aromatic/heterocyclic aldehydes and ketones in water. *Tetrahedron* **2005**, *61*, 5019–5025.