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Catalytic aldol-type reaction of aldehydes with ethyl diazoacetate using quarternary ammonium hydroxide as the base☆

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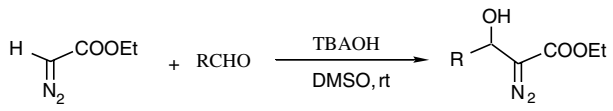
Abstract—The direct aldol-type condensation of aldehydes with ethyl diazoacetate (EDA) promoted by an organic base and non-metallic catalyst such as tetrabutylammonium hydroxide (TBAOH) gave β-hydroxy-α-diazocarbonyl compounds with moderate to excellent yields. Furthermore, the reactivity and scope of various phase-transfer catalysts as well as electronically divergent aldehydes are discussed.

α-Diazocarbonyl compounds have attracted attention because they undergo diverse synthetically useful transformations.[1] For this purpose, the synthesis of α-diazo compounds is of interest. Although the synthesis of diazocarbonyl compounds can be achieved by a number of routes,[2] one potentially attractive method is to carry out a substitution reaction on a readily available diazo compound. Such reactions, in which the diazo carbon reacts as nucleophile and the diazo group remains intact, are known. The nucleophilic addition of acyldiazomethane to carbonyl compounds requires deprotonation of the acyldiazomethane. This is usually achieved by treating with a strong base, such as butyllithium,[3] lithium diisopropylamide (LDA),[4] sodium hydride,[5] potassium hydroxide,[6] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[7] etc. However, the development of improved synthetic methods for the synthesis of α-diazocarbonyl compounds still remains an active ongoing research area. One of the most general and efficient methodologies these days is phase-transfer catalysis.[8] In continuation of our interest in developing novel synthetic methodologies, particularly for carbon–carbon and carbon–heteroatom bond formation,[9] we report that TBAOH (1.0 M solution in water), catalyzes aldol-type reactions of aldehydes with ethyl diazoacetate to give the corresponding β-hydroxy-α-diazocarbonyl compounds with moderate to excellent yields. To the best of our knowledge, there are no reports on this condensation using a phase-transfer catalyst with a non-metallic organic base (Scheme 1).[10]

The screening of several phase-transfer catalysts, allowed us to conclude that TBAOH was a suitable catalyst to affect this condensation of benzaldehyde with ethyl diazoacetate in DMSO at ambient temperature (Table 1). As seen in Table 1, the condensation product of benzaldehyde was acheived in 95% yield in 3 h. A typical procedure is as follows: EDA (1 mmol) was added to a solution of the base (TBAOH) (0.3 equiv) in DMSO (2 mL) at room temperature, and to this mixture was added benzaldehyde (1.2 equiv) over 15 min at room temperature. Isolation of the product by column chromatography afforded the expected product. Among the PTC's screened (Table 1), tetrabutyl ammonium hydroxide (TBAOH) (entry 4) and tetrabutyl ammonium fluoride (TBAF) (entry 5) gave promising yields in 3 h. Other PTC's, including benzyl triethylammonium chloride (BTEACl) (entry 1), benzyl triethylammonium bromide (BTEABr) (entry 2), cetyl trimethylammonium bromide (CTAB) (entry 3), tetrabutylammonium chloride (TBACl) (entry 6), tetrabutylammonium bromide (TBABr) (entry 7), tetrabutylammonium iodide (TBAI) (entry 8) and (*n*-hexyltrimethyl)ammonium bromide



Scheme 1.

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Table 1. Screening of PTC's for the addition of EDA to benzaldehyde over 24 h

Entry	PTC	Yield (%)[a]
1	BTEACl	0
2	BTEABr	0
3	CTAB	0
4	TBAOH	95[b]
5	TBAF	63[b]
6	TBACl	0
7	TBABr	0
8	TBAI	0
9	HTMABr	0

[a] Isolated yields.
[b] Reaction time was 3 h.

(HTMABr) (entry 9) gave no product even after stirring for 24 h.

Next, different solvents were screened (Table 2). As seen in Table 2, DMSO was the most appropriate and other solvents, such as acetonitrile, toluene, DMSO–water and water resulted in no reaction or considerably decreased yields of the products. A catalytic amount of TBAOH (0.3 equiv) was sufficient to afford the desired product in good yield. No significant improvements in yields were observed on increasing the catalyst loading.

With optimized experimental conditions for the reaction between benzaldehyde with EDA, the generality of this process was investigated for a wide range of aromatic, aliphatic and heterocyclic aldehydes; the results are illustrated in Table 3. In general, aldehydes with electron-withdrawing substituents reacted faster than those with electron-donating substituents (see entries 2–10). It is also worthwhile to note that good yields could be achieved with phenyl acetaldehyde (entry 11). α,β-Unsaturated aldehydes such as cinnamaldehyde (entry 12) also gave good yields of product. On the other hand, heterocyclic aldehydes did not give satisfactory yields even after stirring for 10–12 h (entries 14 and 15). Other aliphatic aldehydes such as cyclohexanecarboxaldehyde and butyraldehyde were also tolerated (entries 16 and 17). There were some limitations for the TBAOH catalyzed reaction. Aldehydes such as *N*,*N*-diethylbenzaldehyde, 4-hydroxybenzaldehyde, indole-3-carboxaldehyde and *N*-phthalimidoacetaldehyde were not tolerated under the present conditions. The reactions with aliphatic and aromatic ketones such as cyclohexanone and acetophenone were also found to be unsuccessful.

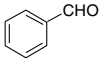
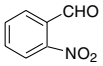
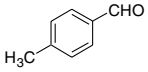
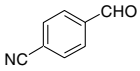
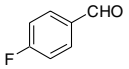
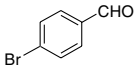
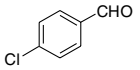
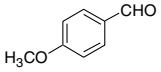
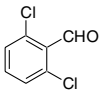
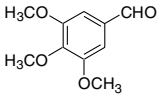
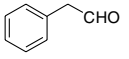
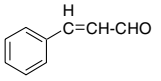
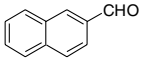
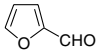
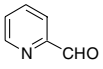
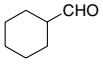
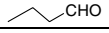
The mechanism of the present aldol-type reaction may involve the formation of a complex as depicted below

Table 2. Solvent effects on the reaction of EDA with benzaldehyde mediated by TBAOH

Solvent	Time (h)	Yield (%)[a]
DMSO	3	95
Water	5	28
DMSO–water	5	43
Acetonitrile	2	20
Toluene	3	0

[a] Isolated yields.

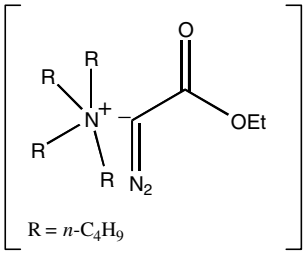
Table 3. TBAOH-catalyzed aldol-type reactions of aldehydes with ethyl diazoacetate

Entry	Aldehyde	Reaction time (h)	Yield[a]
1		3	95[3c,d]
2		1.5	88
3		3	74[3c]
4		2.5	85
5		2	77
6		4.5	58
7		4	68[3d]
8		3	72
9		6	70
10		6	65
11		8	85
12		4	78[3d]
13		3	85
14		10	55[3d]
15		12	47[3c]
16		3	80[3c]
17		4.5	85[3d]

[a] Isolated yields after column chromatography.

(Scheme 2) as a reactive intermediate and activation of the aldehyde group by the complex to furnish the corresponding β-hydroxy-α-diazo carbonyl compounds.

In conclusion, we have shown that commercially available phase-transfer catalysts such as TBAOH can catalyze the aldol-type condensation of electronically divergent aldehydes with EDA using DMSO as the solvent. Since the diazo group can be subjected to diverse transformations, there is a possibility that this reaction



Scheme 2. Possible reactive intermediate.

may be developed into a synthetically useful process, although further work is needed to expand the scope of the reaction.

Acknowledgements

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10. Representative procedure. To a solution of TBAOH (1.0 M solution in water, 0.3 equiv) in DMSO (1 mL) was added EDA (1 mmol) at room temperature. Then, the aldehyde component (1.2 mmol) was added over 15 min to the reaction mixture, which was stirred at room temperature for the specified time (see Table 3). To the reaction mixture, saturated ammonium chloride solution (5 mL) was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and further purification by flash column chromatography using ethyl acetate–hexane (1:3), gave the corresponding β-hydroxy-α-diazo carbonyl compound. Most of the products are known and were determined by comparison of their physical data and spectral data with those reported in the literature. All new compounds gave satisfactory spectral data in accordance with their proposed structures.
Spectral data for new compounds:
Ethyl-3-hydroxy-2-diazo-3-(2-nitrophenyl)-propanoate (entry 2): Yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.2$ Hz, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 6.36 (s, 1H), 7.42–8.01 (m, 4H); Mass (EI): m/z (%) = 237 $(M-N_2)^+$; Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.82; H, 4.18; N, 15.84. Found: C, 49.75; H, 4.09; N, 15.93.
Ethyl-3-hydroxy-2-diazo-3-(4-cyanophenyl)-propanoate (entry 4): oil: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 7.2$ Hz, 3H), 4.25 (q, $J = 7.2$ Hz, 2H), 5.95 (s, 1H), 7.42–8.10 (m, 4H); Mass (EI): m/z (%) = 217 $(M-N_2)^+$; Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.61; H, 4.58; N, 17.21.
Ethyl-3-hydroxy-2-diazo-3-(4-fluorophenyl)-propanoate (entry 5): Yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H), 4.25 (q, $J = 7.2$ Hz, 2H), 6.05 (s, 1H), 6.98–7.66 (m, 4H); Mass (EI): m/z (%) = 238 (M^+); Anal. Calcd for $C_{11}H_{11}FN_2O_3$: C, 55.46; H, 4.65; N, 11.76. Found: C, 55.38; H, 4.71; N, 11.81.
Ethyl-3-hydroxy-2-diazo-3-(4-bromophenyl)-propanoate (entry 6): Yellow oil: FT IR (neat, cm^{-1}): ν 3452, 2985, 2102, 1749, 1698, 1371, 1219, 1021, 749; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.2$ Hz, 3H), 4.22 (q, $J = 7.2$ Hz,2H), 4.61 (s, 1H,), 5.82 (s, 1H), 7.22–7.78 (m, 4H). Mass (EI): m/z (%) = 271 $(M-N_2)^+$; Anal. Calcd for $C_{11}H_{11}BrN_2O_3$: C, 44.17; H, 3.71; N, 9.37. Found: C, 44.10; H, 3.55; N, 9.48.
Ethyl-3-hydroxy-2-diazo-3-(4-methoxyphenyl)-propanoate (entry 8): oil; FT IR (neat, cm^{-1}): ν 3435, 2981, 2107, 1757, 1696, 1327, 1217, 1168, 748; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (t, $J = 7.2$ Hz, 3H), 3.88 (s, 3H), 4.24 (q, $J = 7.2$ Hz, 2H), 5.79 (s, 1H), 6.94–6.98 (m, 2H), 7.76–7.79 (m, 2H). Mass (EI): m/z (%) = 250 (M^+); Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.64; H, 5.59; N, 11.07.
Ethyl-3-hydroxy-2-diazo-3-(2,6-dichlorophenyl)-propanoate (entry 9): Yellow oil: FT IR (neat, cm^{-1}): ν 3387, 2978, 2100, 1749, 1697, 1215, 1016, 752; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.2$ Hz, 3H), 3.45 (br s, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 6.45 (s, 1H), 7.15–7.38 (m, 3H). Mass (EI): m/z (%) = 261$(M-N_2)^+$; Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_3$: C, 45.70; H, 3.49; N, 9.69. Found: C, 45.58; H, 3.54; N, 9.85.
Ethyl-3-hydroxy-2-diazo-3-(3,4,5-trimethoxyphenyl)-propanoate (entry 10): oil: FT IR (neat, cm^{-1}): ν 3455, 2985, 2946, 2101, 1741, 1698, 1607, 1435, 1372, 1217, 1171, 745; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 7.2$ Hz, 3H),

3.24 (br s, 1H), 3.83 (s, 9H), 4.22 (q, $J = 7.2$ Hz, 2H), 5.78 (s, 1H), 6.58 (s, 1H), 7.08 (s, 1H). Mass (EI): m/z (%) = 310 (M^+); Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.21; H, 5.92; N, 8.97.

Ethyl 3-hydroxy-2-diazo-3-(2-naphthyl) propanoate (entry 13): oil: FT IR (neat, cm^{-1}): ν 3443, 2985, 2092, 1993, 1695, 1327, 1168; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3H), 2.93 (br s, 1H), 3.83 (s, 9H), 4.28 (q, $J = 7.2$ Hz, 2H), 5.98 (s, 1H), 7.29–8.31 (m, 7H). Mass (EI): m/z (%) = 270 (M^+); Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.42; H, 5.27; N, 10.45.