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DBU-catalyzed condensation of acyldiazomethanes to aldehydes in water and a new approach to ethyl β-hydroxy α-arylacrylates

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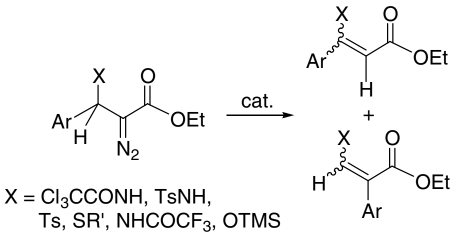
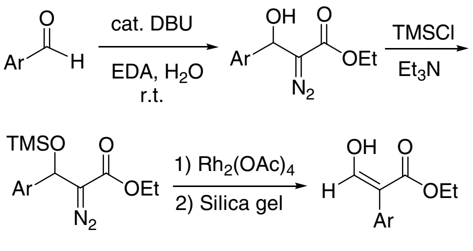
Abstract—DBU-catalyzed condensation of ethyl diazoacetate (EDA) with aldehydes in pure water afforded corresponding β-hydroxy α-diazo carbonyl compounds. The β-hydroxy group of the products was further converted into β-siloxy group. The Rh(II)-catalyzed reaction of the β-aryl β-siloxy α-diazo carbonyl compounds gave 1,2-aryl shift products predominantly. The three-step transformation constitutes an efficient synthesis of ethyl β-hydroxy α-arylacrylates.

α-Diazo carbonyl compounds have attracted a great attention because they can undergo diverse synthetically useful transformations.[1] Among them, β-hydroxy α-diazo carbonyl compounds[2] have been studied in some detail. A variety of β-substituted α-diazo carbonyl compounds can be prepared from them through simple nucleophilic substitution, and their Rh(II)-catalyzed reactions have been investigated. Although 1,2-hydrogen migration is a facile process,[3] 1,2-acetoxyl, 1,2-vinyl, and 1,2-acetylenyl migrations may become predominant depending on the substrates and reaction conditions.[4,5] In some cases, 1,2-alkyl migration[6] and 1,3-C–H insertion[4] are also possible. The change of migratory aptitude is attributed to the steric and electronic effects of non-migrating substituents.



On the other hand, Lewis acid-catalyzed reaction of β-hydroxy α-diazo carbonyl compounds afford 1,2-hydrogen migration products in a high yield, which constitutes an efficient synthesis of 1,3-dicarbonyl compounds from aldehydes and acyldiazomethanes. Various Lewis acids, including $Rh_2(OAc)_4$, $[(\eta^5\text{-}C_5H_5)Fe^+(CO)_2(THF)]\text{-}BF_4^-$, $ZnCl_2$, $SnCl_2$, BF_3, $GeCl_2$, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, and $SnCl_4$ have been reported to affect the transformation.[2,3] As a continuation of our investigation on β-hydroxy α-diazo carbonyl compounds, we report here (1) DBU-catalyzed condensation of EDA with aldehydes in water (2) predominant 1,2-aryl migration in $Rh_2(OAc)_4$-catalyzed reaction of β-aryl β-siloxy α-diazo carbonyl compounds. The overall three-step transformation is an efficient and green synthesis of β-hydroxy α-arylacrylates.



The nucleophilic addition of acyldiazomethane to carbonyl compound, which is a straightforward way to obtain β-hydroxy α-diazo carbonyl compounds, needs deprotonation of the acyldiazomethane. This is usually achieved by treating the diazo compound with a strong base, such as butyllithium, lithium diisopropylamide,

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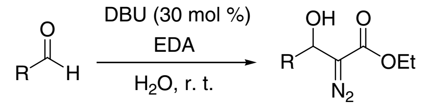
sodium hydride and potassium hydroxide.[2] Recently, it has been reported that the reaction can be catalyzed by phase-transfer reagents.[7] We have reported that DBU can efficiently catalyze nucleophilic condensation of acyldiazomethanes with aldehydes or imines in acetonitrile at room temperature.[8] Further investigation indicated that the DBU-catalyzed reaction could be efficiently carried out in water, as shown in Table 1.

After optimization of the reaction conditions, it was concluded that the reaction could proceed effectively with 30 mol % DBU in water. As shown by the data collected in Table 1, the reaction proceeded well with a wide range of aldehydes. Most aromatic aldehydes reacted efficiently to afford the corresponding β-hydroxy α-diazo carbonyl compounds in moderate to good yields. As anticipated, the reaction with an aromatic aldehyde with a strong electron-donating substituent, such as a *p*-methoxy group, was very slow and gave products in only 40% yield after 3 days (Table 1, entry 8). It is worthwhile to note the reactions with aliphatic and propargylic aldehydes also proceeded well, although the yields were lower as compared with the reaction with aromatic aldehydes.

The Lewis acid-catalyzed reaction of β-hydroxy α-diazo carbonyl compounds has been known to give 1,2-hydrogen migration products. This has been developed into a useful approach to β-ketoesters. However, our recent study has demonstrated that the 1,2-migratory aptitude can be dramatically affected by the non-migrating group (bystander) in the β position. When the substituent in the β position is a bulky group, such as siloxy group, relatively bulkier aromatic group has preference over hydrogen to migrate. We have conceived that this can be utilized to design an efficient approach toward ethyl β-hydroxy α-arylacrylates, which are useful building blocks in organic synthesis.[10]

Table 1. DBU-catalyzed condensation of EDA to aldehydes in water[9]



1a-q **2a-q**

Entry	**1a–q**, R =	Reaction time[a] (h)	Product **2a–q**	Yield[b] (%)
1	**1a**, C_6H_5	24	**2a**	74
2	**1b**, *p*-FC_6H_4	24	**2b**	72
3	**1c**, *p*-ClC_6H_4	24	**2c**	77
4	**1d**, *p*-BrC_6H_4	24	**2d**	78
5	**1e**, *m*-BrC_6H_4	24	**2e**	85
6	**1f**, *o*-MeC_6H_4	24	**2f**	74
7	**1g**, *p*-MeC_6H_4	24	**2g**	61
8	**1h**, *p*-$MeOC_6H$	72	**2h**	40
9	**1i**, *m*-$MeOC_6H_4$	24	**2i**	75
10	**1j**, *m*-$F_3CC_6H_4$	24	**2j**	84
11	**1k**, 3,4-$Cl_2C_6H_3$	24	**2k**	69
12	**1l**, 3,5-$(MeO)_2C_6H_3$	24	**2l**	69
13	**1m**, 2-Furyl	24	**2m**	67
14	**1n**, H	168	**2n**	60
15	**1o**, CH_3	72	**2o**	43
16	**1p**, PhC≡C	3	**2p**	49
17	**1q**, $C_5H_{11}C$≡C	3	**2q**	43

[a] The reaction was carried out in water at room temperature with 30 mol % DBU.

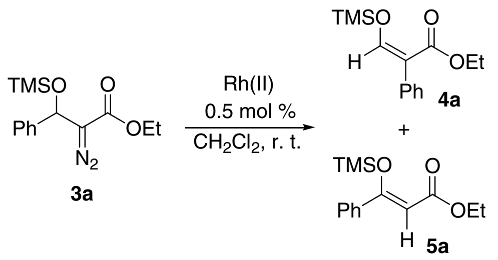
[b] Yields after silica gel column chromatographic purification.

The β-hydroxy group was converted to siloxy group in high yields to yield **3a–l** (for **1a–k**, 82–99%).[11] Then, Rh(II) catalysts were screened in order to find optimal reaction conditions. As shown in Table 2, the ratio for 1,2-hydrogen and 1,2-phenyl migration varies with the catalysts. The $Rh_2(OAc)_4$-catalyzed reaction gave the highest selectivity for 1,2-phenyl migration. It is worthwhile to note that Rh(II) catalysts with strong electron-withdrawing ligands, such as those in rhodium(II) trifluoracetate [$Rh_2(tfa)_4$] and rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$], favor 1,2-hydride migration. Removal of the TMS group by silica gel afforded the corresponding β-hydroxy α-phenylacrylate.

The scope of the $Rh_2(OAc)_4$-catalyzed was examined by β-siloxy diazo substrates **3a–l**. As shown in Table 3, β-hydroxy arylacrylates could be obtained in moderate to good yields for most substrates (Table 3, entries 1, 3–7). The minor products, which are from 1,2-hydrogen migration, could not be isolated in most cases, except for substrates **3h–j** (entries 8–10). When the aromatic substituent was *o*-methyl, only 1,2-hydrogen products could be isolated (entry 12). This may be due to the steric hindrance of the *ortho* methyl group, which prevents the approach of the aromatic ring to the carbene center. On the other hand, bulkier siloxy group, such as *tert*-butyldiphenylsiloxy (TBDPS), could further promote 1,2-aryl migration (entries 2 and 11).

In summary, we have demonstrated that DBU can catalyze the condensation of EDA with aldehydes in water. Since water is the most cheap and environment-friendly solvent, this procedure is a convenient and green method to prepare β-hydroxy α-diazo carbonyl compounds. Converting the β-hydroxy to siloxy group enables the $Rh_2(OAc)_4$-catalyzed reaction to proceed with 1,2-aryl migration as the major pathway. The three-step transformation from aldehydes and EDA provides a new entry to β-hydroxy α-arylacrylate.

Table 2. Rh(II)-catalyzed reaction of **3a**[a]

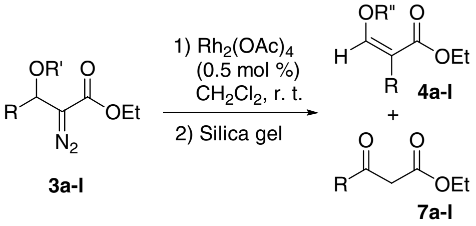


Entry	Catalyst	**4a**:**5a**[b]
1	$Rh_2(OAc)_4$	84:16
2	$Rh_2(O_2CCF_3)_4$	38:62
3	$Rh_2(O_2CC_3F_7)_4$	43:57
4	$Rh_2(O_2CC_7H_{15})_4$	81:19

[a] The reaction was carried out in CH_2Cl_2 at room temperature.

[b] Ratio determined by the ^1H NMR of the crude product.

Table 3. $Rh_2(OAc)_4$-catalyzed reaction of β-siloxy diazo substrates **3a**–**l**[12]



Entry	3a–l			Yield[a] (%)	
	R	R′	R″	4a–l	7a–l
1	**a**, C_6H_5	TMS	H	**a**, 80	**a**, —[b]
2	**b**, C_6H_5	TBDPS	TBDPS	**b**, 92	**b**, —
3	**c**, *p*-FC_6H_4	TMS	H	**c**, 80	**c**, —
4	**d**, *p*-PhC_6H_4	TMS	H	**d**, 85	**d**, —
5	**e**, *p*-$MeOC_6H_4$	TMS	H	**e**, 70	**e**, —
6	**f**, 2-Furyl	TMS	H	**f**, 76	**f**, —
7	**g**, *p*-$CH_3C_6H_4$	TMS	H	**g**, 81	**g**, —
8	**h**, *p*-BrC_6H_4	TMS	H	**h**, 74	**h**, 12
9	**i**, *p*-ClC_6H_4	TMS	H	**i**, 77	**i**, 14
10	**j**, *m*-BrC_6H_4	TMS	H	**j**, 47	**j**, 28
11	**k**, *m*-BrC_6H_4	TBDPS	TBDPS	**k**, 78	**k**, —
12	**l**, *o*-$CH_3C_6H_4$	TMS	H	**l**, —[b]	**l**, 97

[a] Yields after silica gel column chromatographic purification.

[b] No product could be isolated.

Acknowledgements

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9. *General procedure for DBU-promoted reactions of* **1a**–**q** *in water*. To a stirring solution of water (1 mL) containing EDA (1.2 mmol) and aldehyde (1 mmol), DBU (30 mol %) was added. The reaction mixture was stirred at room temperature until completion of the reaction. Usual workup afforded the pure **2a**–**q**.
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11. *General procedure for the conversion of β-hydroxy diazo compounds to the corresponding β-siloxy diazo compounds*. In a flamed three-necked round-bottomed flask, β-hydroxy-α-diazo compound (1.0 mmol) was dissolved in CH_2Cl_2 (5 mL). Triethylamine (3.0 mmol) was added to the solution at 0 °C for 5 min. Then $R^1R^2R^3SiCl$ (1.1 mmol) was added via syringe at 0 °C. The mixture was allowed to stir for 2 h between 0 °C and room temperature. Usual workup afforded the pure β-siloxy diazo compounds.
12. *General procedure for $Rh_2(OAc)_4$-catalyzed reaction of* **3a**–**l**. To a stirring solution of anhydrous CH_2Cl_2 (10 mL) containing $Rh_2(OAc)_4$ (0.5 mol %) was added diazo compound **4a**–**l** (1.0 mmol). The reaction mixture was stirred at room temperature. When the diazo compound disappeared as indicated by TLC, the solvent was removed under reduced pressure to give a crude residue, which was purified by silica gel column chromatography.