



DBU-promoted condensation of acyldiazomethanes to aldehydes and imines under catalytic conditions

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Received 29 October 2001; revised 3 December 2001; accepted 14 December 2001

Abstract—The condensation of acyldiazomethanes to aldehydes and imines can be promoted with catalytic amount of DBU. The condensation gives β -hydroxy α -diazo carbonyl compounds or β -amino α -diazo carbonyl compounds in high yields. © 2002 Elsevier Science Ltd. All rights reserved.

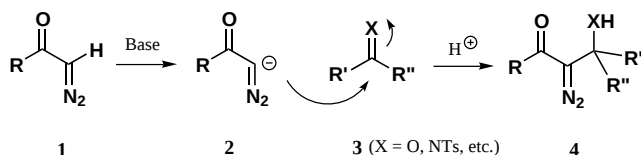
α -Diazo carbonyl compounds have attracted attention because these compounds can undergo diverse synthetically useful transformations.¹ For this purpose, the synthesis of α -diazo compounds is of great interest. α -Diazo carbonyl compounds are generally prepared by diazo transfer reactions of carbonyl compounds. In addition to these typical methods, they can also be obtained by condensation reactions of acyldiazomethanes with aldehydes, ketones and imines through nucleophilic addition (Scheme 1). This type of transformation is very useful because it can introduce a diazo group as well as a hydroxyl or an amino group in a single reaction step.

Nucleophilic addition of an acyldiazomethane to carbonyl compounds or imines requires deprotonation of the acyldiazomethane. This is usually achieved by treatment with a strong base, such as butyllithium,² lithium diisopropylamide (LDA),³ sodium hydride,⁴ potassium hydroxide,⁵ etc. The most widely employed base by far is LDA. The lithiated diazoesters and ketones can convert aldehydes and ketones into α -diazo- β -hydroxy carbonyl compounds, which can subsequently undergo

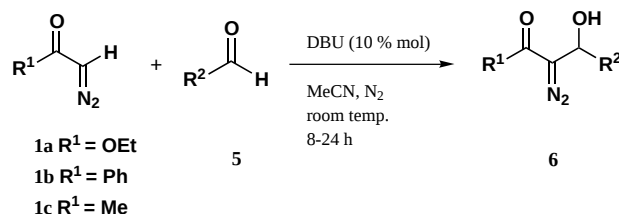
transformation to give β -dicarbonyl compounds.⁶ However, the deprotonation with LDA requires a low temperature and absolutely anhydrous conditions, and LDA is a very strong base, which may not be compatible with functional groups in the substrates. Here we report a milder deprotonation of acyldiazomethanes with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Nucleophilic condensation of acyldiazomethanes with aldehydes and imines can be promoted efficiently under catalytic conditions.

Thus, ethyl diazoacetate (**1a**, $R^1 = \text{OEt}$) (EDA) was dissolved and stirred with DBU (10 mol%) and various aldehydes in anhydrous MeCN at room temperature (Scheme 2).⁷

As shown by the data collected in Table 1, most aromatic aldehydes react efficiently to give the corresponding β -hydroxy α -diazo carbonyl compounds in high yields. As anticipated, the nucleophilic addition to an aromatic aldehyde with a strong electron-donating substituent, such as a *p*-methoxy group, is very slow, although the addition reaction did occur cleanly (entry 2). In addition to aromatic aldehydes, an α,β -unsaturated aldehyde (entry 8) and aliphatic aldehydes (entries



Scheme 1.



Scheme 2.

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Table 1. DBU-promoted condensation of acyldiazomethanes to aldehydes

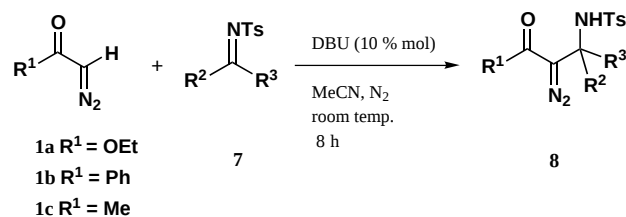
Entry	Acyldiazomethane R ¹	Aldehyde R ²	Reaction time (h)	Yield (%) ^a
1	OEt	C ₆ H ₅ -	8	78
2	OEt	<i>p</i> -MeOC ₆ H ₄ -	24	27 (81) ^b
3	OEt	<i>p</i> -PhC ₆ H ₄ -	8	58
4	OEt	<i>p</i> -FC ₆ H ₄ -	8	81
5	OEt	<i>m</i> -CF ₃ C ₆ H ₄ -	8	91
6	OEt	<i>m</i> -CNC ₆ H ₄ -	8	95
7	OEt	2,4-Cl ₂ C ₆ H ₃ -	8	92
8	OEt	<i>trans</i> -PhCH=CH-	8	59
9	OEt	CH ₃ (CH ₂) ₂ -	8	87
10	OEt	CH ₃ (CH ₂) ₃ -	8	78
11	OEt	CH ₃ (CH ₂) ₅ -	8	97
12	OEt	CH ₃ (CH ₂) ₁₀ -	8	64
13	C ₆ H ₅	<i>m</i> -CF ₃ C ₆ H ₄ -	24	82
14	C ₆ H ₅	<i>m</i> -NC-C ₆ H ₄ -	24	60
15	C ₆ H ₅	C ₆ H ₅ -	24	< 10
16	CH ₃	<i>m</i> -CF ₃ C ₆ H ₄ -	24	77
17	CH ₃	<i>m</i> -NC-C ₆ H ₄ -	24	65
18	CH ₃	C ₆ H ₅ -	24	< 10

^a Yields after column chromatographic purification.^b The yield is based on the recovered starting material.

9–12) can also react efficiently under the same conditions. However, the reaction with ketones was found to be too slow to be practically useful.

For benzoyldiazomethane (**1b**, R = Ph) and acetyldiazomethane (**1c**, R = Me), the reactivity toward the aldehydes is lower compared to that of EDA (**1a**) under identical condition (entries 15, 18). Nevertheless, for these diazomethane derivatives, the reaction with the aromatic aldehydes bearing electron-withdrawing substituents still works well (entries 13, 14, 16 and 17).

To the best of our knowledge, there has been no report on the deprotonation of acyldiazomethanes by DBU and the subsequent nucleophilic addition under catalytic conditions. Since DBU is a much weaker base than LDA or NaH, the nucleophilic addition can be efficiently performed with a catalytic amount of this base suggesting that the acidity of the proton attached to the diazo carbon of the acyldiazomethane is much

**Scheme 3.**

greater than generally believed. It may be possible that other types of acyldiazomethane anion reactions can also be catalytically promoted by DBU. A closely related reaction is the nucleophilic addition of an acyldiazomethane anion to *N*-tosyl protected aromatic imines. We found that this reaction can also be efficiently promoted by catalytic amounts of DBU (Scheme 3). The aromatic imines are found to be more reactive toward the acyldiazomethane anion compared

Table 2. DBU-promoted condensation of acyldiazomethanes to imines

Entry	Acyldiazomethane		Imine		Reaction time (h)	Yield (%) ^a
	R ¹	R ²	R ³			
1	OEt	<i>o</i> -MeC ₆ H ₅ -	H	8	77	
2	OEt	<i>m</i> -BrC ₆ H ₄ -	H	8	64	
3	OEt	<i>trans</i> -PhCH=CH-	H	8	53	
4	OEt	C ₆ H ₅ -	Me	8	< 20	
5	OEt	<i>p</i> -Me ₂ NC ₆ H ₄ -	H	8	86	
6	C ₆ H ₅	<i>m</i> -CF ₃ C ₆ H ₄ -	H	8	64	
7	C ₆ H ₅	<i>m</i> -MeOC ₆ H ₄ -	H	8	73	
8	C ₆ H ₅	C ₆ H ₅ -	H	8	76	
9	CH ₃	<i>m</i> -CF ₃ C ₆ H ₄ -	H	8	72	
10	CH ₃	<i>p</i> -MeOC ₆ H ₄ -	H	8	81	
11	CH ₃	C ₆ H ₅ -	H	8	57	

^a Yields after column chromatographic purification.

to the corresponding aldehydes (Table 2). For benzoyldiazomethane (**1b**, R=Ph) and acetyldiazomethane (**1c**, R=Me), the reaction with *N*-tosyl benzaldimine gave the expected products in moderate yields (entries 7 and 10). The condensation with imines gave α -amino- β -diazo carbonyl compounds, which can subsequently be transformed to α -aryl β -enamino esters by transition metal-catalyzed or acid-catalyzed diazo decomposition.⁴ In conclusion, we have demonstrated that the condensation of acyldiazomethanes with aldehydes and imines can be promoted with catalytic quantities of DBU. The reaction conditions are mild and should be compatible with functional groups in the substrates.

Acknowledgements

The project is generously supported by Natural Science Foundation of China (Grant No. 29972002). Ms. Xiaoyu Xing performed part of the experimental work.

References

1. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998.
2. (a) Schollkopf, U.; Frasnelli, H.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1970**, 9, 300; (b) Schollkopf, U.; Banhidai, B.; Frasnelli, H.; Meyer, R.; Beckhaus, H. *Liebigs Ann. Chem.* **1974**, 1767.
3. (a) Pellicciari, R.; Natalini, B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1882; (b) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1991**, 118, 1; (c) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1987**, 28, 5351.
4. Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, 3, 2989.
5. (a) Wenkert, E.; McPherson, A. A. *J. Am. Chem. Soc.* **1972**, 94, 8084; (b) Burkoth, T. L. *Tetrahedron Lett.* **1979**, 57, 5049; (c) Woolsey, N. F.; Khalil, M. H. *J. Org. Chem.* **1972**, 37, 2405.
6. For examples, see: (a) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959; (b) Ye, T.; McKervey, M. A. *Tetrahedron* **1992**, 48, 8007.
7. **A typical procedure.** To a solution of ethyl diazoacetate (1.2 mmol) in anhydrous CH₃CN (5 mL), at room temperature under N₂, was added successively a solution of DBU (0.1 mmol) in anhydrous CH₃CN (1 mL) and aldehyde or imine (1 mmol) in anhydrous CH₃CN (4 mL) via syringe. After stirring at room temperature for 8–24 h, the reaction was quenched with saturated aqueous NaHCO₃ and then extracted with CH₂Cl₂ (20 mL). The solvent was removed by evaporation under reduced pressure and the crude product was purified by flash chromatography to give β -hydroxy α -diazo carbonyl compounds or β -amino- α -diazo carbonyl compounds. The structures of the products were confirmed by IR and ¹H NMR (200 MHz) measurements.