

An Efficient and Mild Preparation of Vinyl Diazo Carbonyl Compounds

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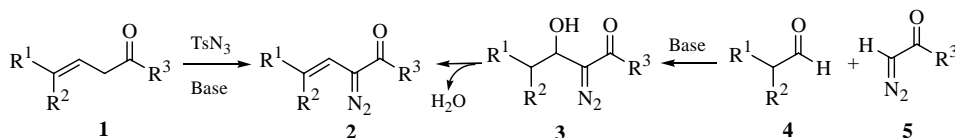
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Abstract: The combination of $(\text{CF}_3\text{CO})_2\text{O}/\text{Et}_3\text{N}$ is found to be a mild and efficient dehydration condition for β -hydroxy- α -diazo compounds.

Keywords: Diazo compounds, dehydration, synthesis.

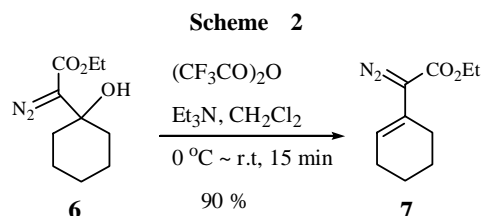
The organic synthesis based on the reaction of α -diazo carbonyl compounds have been extensively explored in recent years¹. Among the various α -diazo carbonyl compounds, the vinyl diazo carbonyl compounds have received significant attention because their unique combination of functional groups². For example, Davies *et al.* have extensively explored the chemistry of Rh(II)-stabilized vinyl carbenoids³. The preparation of these useful diazo compounds is generally achieved by the diazo transfer reaction to β , γ -unsaturated carbonyl compounds (**1** to **2**, **Scheme 1**)⁴. The obvious drawback of this approach is that several steps are needed to prepare β , γ -unsaturated carbonyl compounds. An alternative approach is the condensation of acyldiazomethanes to aldehyde, followed by dehydration (**3** to **2**, **Scheme 1**)⁵. Because the diazo group is relatively labile, the usual dehydration condition (for example, excess phosphorus oxychloride and pyridine as solvent) may not be compatible with the stability of the vinyl diazo compounds. Consequently, this approach has not been widely used in the preparation of vinyl diazo compounds. Here we report a mild and efficient dehydration procedure, which may be applied to some types of vinyl diazo carbonyl compounds.

Scheme 1



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The condensation of acyldiazomethanes to aldehydes or ketones can be easily achieved by established procedures with either DBU or LDA as base^{5,6}. The yields of the condensation reactions are generally high. With the β -hydroxy diazo carbonyl compounds in hand, we proceeded to investigate the dehydration reaction. Since our previous study shows that the combination of $(\text{CF}_3\text{CO})_2\text{O}$ and Et_3N is an efficient and mild dehydration reagent for the hydroxyl compounds bearing diazo group^{7,8}, we first tested this condition for the α -diazo- β -hydroxy ester **6**. Thus, the solution of **6** and $(\text{CF}_3\text{CO})_2\text{O}$ (2 eq.) and Et_3N (2.5 eq) in CH_2Cl_2 was stirred at room temperature for 15 min. The vinyl diazo compound **7** was obtained in 90 % yield after usual work up and silica gel column purification. As a comparison, it was reported that the same α -diazo- β -hydroxy ester **6** was treated with phosphorus oxychloride and Et_3N in CH_2Cl_2 at 0 °C to room temperature for 12 h, the vinyl diazo compound **7** was obtained in 64 % isolated yield².



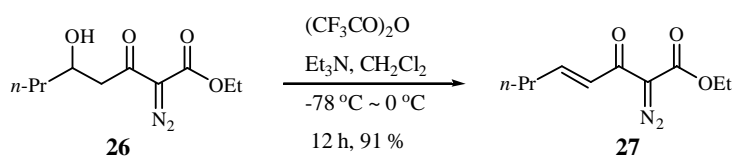
This dehydration condition was further applied to other α -diazo- β -hydroxy ester compounds. The dehydration was found to be efficient and the reaction is completed within 1 h at room temperature for the most substrates. It is known that the vinyl diazo compounds are rather labile and readily cyclize to 3*H*-pyrazoles⁹. We found that the vinyl diazo compounds derived from aldehydes with our condition are relatively stable. The product could be purified by silicagel column chromatography, and could be stored at refrigerator for long time (**Table 1**, entries 1-5). However, the vinyl diazo compounds derived from ketone are not stable and easily cyclize to 3*H*-pyrazoles during the work up and column purification (**Table 1**, entries, 6, 7). For cyclic compounds, the stability of the vinyl diazo compounds depends on the size of the cyclic substituent. The vinyl diazo compound **7**, which has a six-membered ring substituent, is quite stable, while the five- and seven-membered counterparts **20** and **24** are unstable. For **20** and **24**, the isolated pure diazo compounds cyclize to 3*H*-pyrazoles during the usual work up. Therefore, it is not possible to obtain these diazo compound in pure form under normal condition. This situation is obviously due to the inherent instability of these diazo compounds.

Overall, the combination of $(\text{CF}_3\text{CO})_2\text{O}$ and Et_3N in CH_2Cl_2 is an efficient and mild dehydration reagent. The vinyl diazo carbonyl compounds could be obtained under this condition from the dehydration of α -diazo- β -hydroxy carbonyl compounds, providing the vinyl diazo products are inherently stable enough to the usual work up and purification. This dehydration condition is superior in terms of reaction time, the ease of work up and the yields. It can also be applied to other hydroxyl compounds bearing diazo group. For example, **26** was effectively dehydrated to give **27** in 91 % yield (**Scheme 3**).

Table 1 Dehydration of the α -diazo- β -hydroxy carbonyl compounds with $(\text{CF}_3\text{CO})\text{O}/\text{Et}_3\text{N}^{10}$

Entry	α -diazo- β -hydroxy compounds	product	reaction time	yield ^a %
1	8a R = OEt	9a R = OEt	1 h	89
2	8b R = Me	9b R = Me	1 h	82
3	8c R = Ph	9c R = Ph	1 h	65
4			1 h	53
5			1 h	70
6			20 min	79
7			1 h	95
		17 90 : 10 18		
8			10 min	98
10	6 n = 2	7 100 : 0	15 min	90
11	23 n = 3	24 55 : 45 ^b	20 min	99
		21 22 25		

^aIsolated yield after column chromatography. ^bThe isolated pure **20** and **24** hanged to **21** and **25** during evaporation.

Scheme 3

Acknowledgments

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References and Notes

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10. General procedure for the dehydration reaction: In a flamed two-necked round-bottom flask, α -diazo- β -hydroxy compound (1.0 mmol) was dissolved in CH_2Cl_2 (5 mL). Stirring at 20 °C, Et_3N (2.5 eq) and $(\text{CF}_3\text{CO})_2\text{O}$ (2 eq) was added successively with syringe (note: it is necessary to use water bath to maintain the room temperature during the addition of the Et_3N and $(\text{CF}_3\text{CO})_2\text{O}$). The mixture was allowed to stir for another 10 minutes to 1 hour. Concentrated under reduced pressure with rotovapor. The residue was subjected to silica gel chromatography (petroleum ether: acetone = 15 : 1) for purification.

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