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LETTERS

Fluoride-Catalyzed Aldol Reaction of Ethyl Trimethylsilyldiazoacetate with Aldehydes Leading to Ethyl α-Diazo-β-Hydroxy Esters and Rhodium Catalyzed Decarboxylative Rearrangement of Diazo Urethanes Leading to β-Amino Acrylates

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Abstract: Ethyl trimethylsilyldiazoacetate reacts smoothly with a variety of aldehydes at 0 °C in the presence of a catalytic amount of tetrabutylammonium fluoride to produce α-diazo-β-hydroxy esters in good to excellent yields. The resulting α-diazo-β-hydroxy esters can be stereoselectively transformed, by a sequence of carbamation with *p*-toluenesulfonyl isocyanate and rhodium(II)-induced decarboxylative rearrangement, to α- or β-substituted β-(*p*-toluenesulfonylamino)acrylates depending upon migration aptitude of the substituents derived from the aldehydes.

When activated by a Lewis acid, α-diazo esters undergo aldol reaction with aldehydes to give the diazonium alkoxide betaine intermediates which are immediately followed by the 1,2-hydride migration with the concurrent elimination of nitrogen. This transformation leading to β-keto esters is especially effected by the action of tin(II) chloride and is known as the Roskamp homologation.[1-3] On the other hand, we have recently found that, in the reaction of α-diazo esters with aldehydes in the presence of a stoichiometric amount of trimethylsilyl trifluoromethanesulfonate, 1,2-nucleophilic rearrangement of the substituent derived from the aldehydes becomes favored to give α-formyl esters.[4] In the course of mechanistic study, we needed α-diazo-β-hydroxy esters. Although a known access to α-diazo-β-hydroxy esters involves the reaction of ethyl lithiodiazoacetate with aldehydes,[5] preparation of the lithiated reagent is not an easy process due to its extreme instability. We therefore planned to develop a new synthetic route by use of relatively stable ethyl trimethylsilyldiazoacetate.[6]

In the present communication, we would like to report a new catalytic route for the effective preparation of α-diazo-β-hydroxy esters by the reaction of ethyl trimethylsilyldiazoacetate with a variety of aldehydes in the presence of a catalytic amount of fluoride.[7] Novel derivatization of the α-diazo-β-hydroxy esters is also described.

Ethyl trimethylsilyldiazoacetate (**1**) was treated with benzaldehyde (**2a**) in diethyl ether in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF). With its catalytic loading of 10 mol% at 0 °C, ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (**3a**) was obtained in 80% yield (Table 1). Less catalytic loadings such as 2 and 0.5 mol% at the same temperature resulted in slow reaction rates leading to lower yields of **3a**. Although the reaction at room temperature using a smaller amount of TBAF (5 mol%) was completed in a short reaction time, this is not the conditions of optimization either. The best result was obtained when the reaction was performed at 0 °C in the presence of 5 mol% of TBAF for a few hours, the yield of **3a** being 83%.[8]

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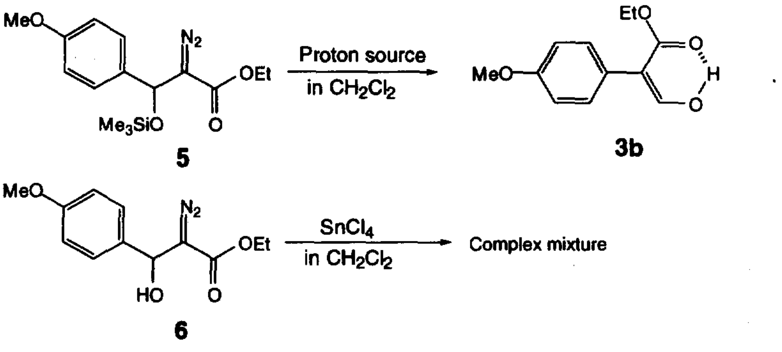
complex mixtures which contain a small amount of β-keto ester **4b**.



Scheme 3.

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9 A general procedure for the TMSOTf-catalyzed reaction: To a dichloromethane solution (5 ml) of TMSOTf (0.222 g, 1 mmol) and an aldehyde (1 mmol) was added ethyl diazoacetate (**1**, 1 mmol) dropwise at 0 °C. During the addition, nitrogen was evolved. After the nitrogen evolution was finished, a few drops of saturated aqueous $NaHCO_3$ were added. The dichloromethane solution was dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica gel with hexane - diethyl ether (8:1 v/v) to give a mixture of formyl ester **3** and b-keto ester **4**.

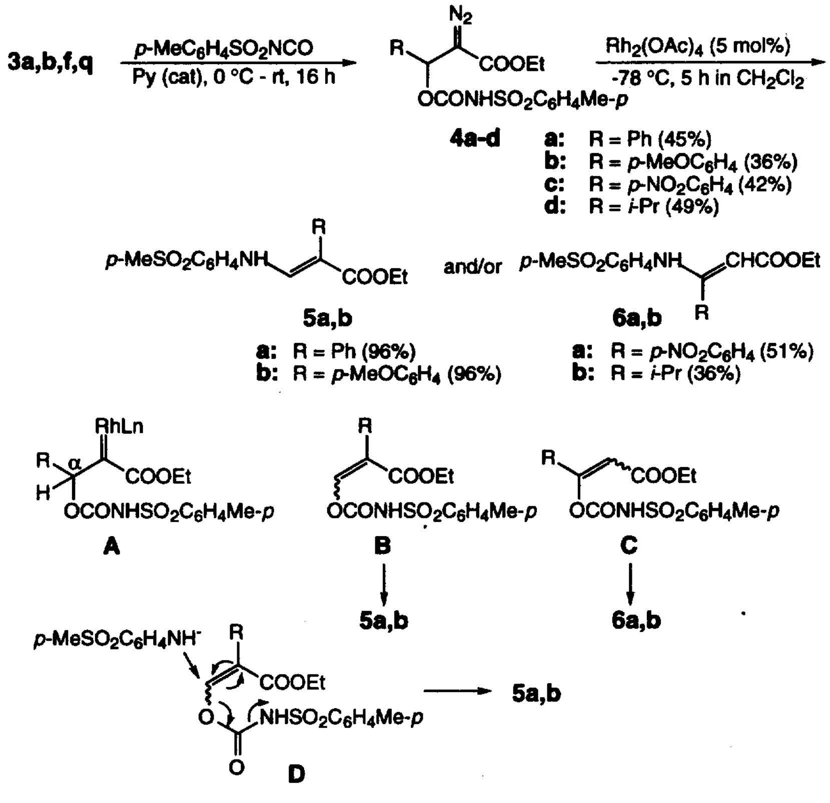
10 Roskamp describes that aromatic aldehydes are less reactive than aliphatic aldehydes (Ref. 5), reaction of benzaldehyde when catalyzed by $SnCl_2$ giving 50% yield of **4a**.

11 See Note 13 for the evidence for the reversibility of reaction of **1** with **2**.

12 When this reaction is performed in diethyl ether, the desilylated derivative of **5** is selectively formed (Kanemasa, S.; Araki, T.; Kanai, T.; Wada, E. Tetrahedron Lett. **1999**, *40*, 5059-5062.

13 *p*-Anisaldehyde is produced in 40% yield, indicating the possible reversibility of reaction of **1** with **2**.

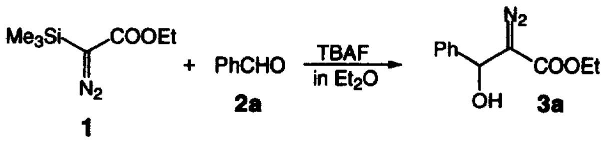
hydroxyl, and an ester functional group in addition to the functional group(s) derived from aldehydes. We therefore planned to generate metal carbenoid intermediates from **3** and utilize them for the delivery of functionality at this carbon by intramolecular insertion reaction. Therefore, the hydroxyl moiety of **3** was protected as carbamate by the reaction with *p*-toluenesulfonyl isocyanate as reactive isocyanate to produce carbamate **4a** (Scheme 2).[11,12] The resulting diazo carbamate **4a** smoothly reacted with a catalytic amount of rhodium(II) acetate at -78 °C.[13,14] The product **5a** obtained almost quantitatively as a single stereoisomer was determined as ethyl (*E*)-2-phenyl-3-(*p*-toluenesulfonylamino)acrylate on the basis of X-ray cryatallography as well as spectral data.[15] Diazo carbamate **4b** having an electron donating *p*-methoxyphenyl substituent underwent the same reaction producing a single isomer of **5b**. On the other hand, single isomers of cinnamic acid derivatives **6a,b** were produced, though stereochemistry unidentified, in the reactions of **4c,d** having less migratory ability such as *p*-nitrophenyl and isopropyl moieties.



Scheme 2.

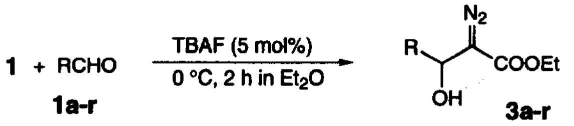
Possible reaction mechanism is shown in Scheme 2: rhodium complex **A** was probably formed as expected. However, 1,2-nucleophilic rearrangement of α-substituent was more favored than the expected insertion to the amide NH bond. The isomeric unsaturated carbamate, either **B** or **C**, was produced depending upon the relative migration aptitude between substituents H or R, and the following decarboxylation led to **5** and **6**. We believe this ready decarboxylation which occurred under mild reaction conditions should be catalyzed by a trace amount of *p*-toluenesulfonamide or its anion. The addition/elimination sequence of intermediates **B** and **C** as the migration products liberates *N*-*p*-

Table 1. TBAF-Catalyzed Aldol Reaction of Ethyl Trimethylsilyldiazoacetate (**1**) with Benzaldehyde (**2a**) Leading to the Formation of Ethyl 2-Diazo-3-hydroxy-3-phenylpropanoate (**3a**)



Entry	TBAF/mol%	Time/h	Temp/°C	Yield/%
1	10	20 min	0	80
2	2	4	0	48
3	0.5	4	0	3
4	5	2	0	83
5	5	20 min	rt	66

Under the same reaction conditions, a variety of aldehydes were employed and the results are summarized in Scheme 1. Aromatic aldehydes bearing electron-withdrawing groups (**1e-g**) are much better substrates than those bearing electron-donating ones (**1b-d**) because of the nucleophilic properties of the reacting species generated from diazo ester **1** and TBAF. Aromatic aldehyde having a highly acidic substituent such as *o*-formylbenzoic acid only led to the decomposition of **1**; poor yields were obtained in the reactions of salicylaldehyde (14%) and *p*-acetamidobenzaldehyde (20%). Although heteroaromatic aldehydes produced satisfactory yields of 2-diazo-3-hydroxypropanoates (**3h-l**), these products are less stable than the products of aromatic aldehydes. Diazo compounds are usually decomposed under acidic conditions through protonation at the diazo carbon. We believe that existence of hetero substituents close to the diazo moiety would accelerate the undesired protonation and, hence, decomposition. α,β-Unsaturated aldehydes **1m-o** resulted in the exclusive direct addition products **3m-o**, no formation of conjugate addition products being observed. Aliphatic aldehydes (**1p-r**) were also effective to give **3p-r**.



a: R = Ph (83%)
b: R = p-MeOC$_6$H$_4$ (60%)
c: R = o-MeOC$_6$H$_4$ (60%)
d: R = 3,4-OCH$_2$OC$_6$H$_3$ (48%)
e: R = p-BrC$_6$H$_4$ (98%)
f: R = p-NO$_2$C$_6$H$_4$ (99%)
g: R = o-NO$_2$C$_6$H$_4$ (97%)
h: R = 2-Thienyl (70%)
i: R = 3-Methyl-2-thienyl (57%)
j: R = 5-Methyl-2-thienyl (52%)
k: R = 2-Furyl (80%)
l: R = 2-Pyridyl (78%)
m: R = (E)-PhCH=CH (73%)
n: R = (E)-MeCH=CH (40%)
o: R = 1-Methylvinyl (49%)
p: R = t-Bu (50%)
q: R = i-Pr (90%)
r: R = n-C$_7$H$_{15}$ (76%)

Scheme 1.

Ketones are much less reactive than aldehydes toward α-diazo ester **1**. Even in the reaction with a highly electrophilic methyl ketone such as methyl pyruvate, the expected product, ethyl methyl 2-diazo-3-hydroxy-3-methylbutanedioate, was obtained only in 27% yield (TBAF: 10 mol%, at 0 °C, 4 h in Et$_2$O). Use of a Lewis acid to activate the methyl pyruvate was not effective.[9]

α-Diazo-β-hydroxy esters **3a-r** produced above are multi-functionalized compounds[10] having a diazo, a