# Lewis Acid-Catalyzed Reactions of Ethyl Diazoacetate with Aldehydes. Synthesis of α-Formyl Esters by a Sequence of Aldol Reaction and 1,2-Nucleophilic Rearrangement

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**Abstract:** Ethyl diazoacetate reacts with a variety of aldehydes in the presence of a Lewis acid catalyst to give either β-keto esters or α-formyl esters, the types of products mainly depending upon the nature of Lewis acid catalysts employed. Reactions catalyzed by Lewis acids such as $SnCl_2$ and $SnCl_4$ provide β-keto esters via nucleophilic 1,2-hydride migration, while those catalyzed by trimethylsilyl triflate give α-formyl esters via migration of the substituent of the aldehyde. Reaction mechanisms are discussed. © 1999 Elsevier Science Ltd. All rights reserved.
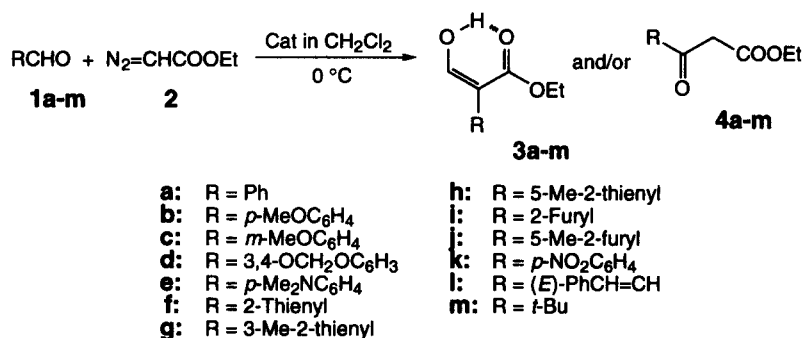
Stereo- and regiochemical control of 1,3-dipolar cycloaddition reactions by the aid of a Lewis acid now provides a powerful synthetic tool for the precise construction of stereochemically defined heterocyclic skeletons. Enhancement of reaction rate is responsible for the improvement of regio- and stereoselectivity of the reaction. However, investigations have been so far confined to the cycloaddition reactions of nitrone[1] and nitrile oxide.[2] In the course of our continuing study on the interaction of 1,3-dipoles with Lewis acids, we have focused our attention on diazo carbonyl 1,3-dipoles.[3] Boron trifluoride etherate-catalyzed reactions of diazo esters and ketones with cyclic ketones are known as useful ring enlargement or homologation methods giving β-keto esters,[4] and Roskamp and coworkers have recently extended this homologation to the reactions of aldehydes. The Roskamp reaction involves the interaction of a diazo ester with aldehydes in the presence of $SnCl_2$, the products being β-keto esters.[5,6] Later, effective catalysts of $TiCl_4$ and $ZrCl_4$ have been employed in the reactions using bulky aldehydes.[7]
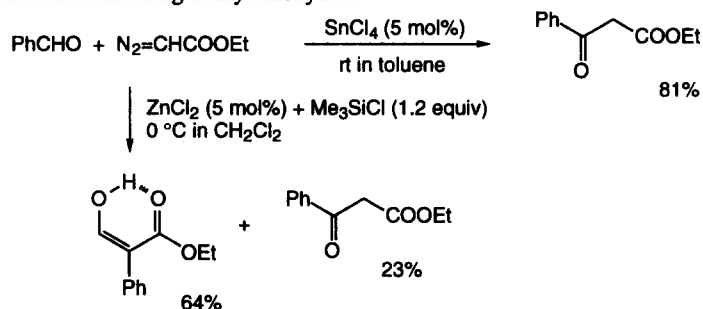


Recently Hossain and coworkers have reported the reaction of ethyl diazoacetate with aromatic aldehyde catalyzed by an iron Lewis acid [η⁵-(C₅H₅)Fe⁺(CO)₂(THF)]BF₄⁻.[8] α-Fomyl esters were produced as major products, but the selectivity to β-keto esters was not satisfactory. In this communication, we report a new feature of the Lewis acid catalyzed reactions of a diazo ester with aldehydes. In the Lewis acid-catalyzed reactions between benzaldehyde (1a) and ethyl diazoacetate (2), we have found that the reaction catalyzed by $SnCl_4$ (5 mol%) at room temperature in toluene gives ethyl benzoylacetate (4a) in 81% yield, while the

reaction catalyzed by a combination of $ZnCl_2$ (5 mol%) and chlorotrimethylsilane (1 equiv) in dichloro-methane produces a mixture of ethyl 3-oxo-2-phenylpropanoate (**3a**, 64%) and **4a** (23%). Benzoylacetate **4a** as β-keto ester is a product formed by the hydride rearrangement from the aldehyde carbon to the adjacent diazo carbon, while 3-oxo-2-phenylpropanoate **3a** as α-formyl ester is the one formed by the nucleophilic 1,2-rearrangement of phenyl group. Although the 1,2-hydride migration is known in the Roskamp reaction, to the best of our knowledge, the aryl migration is rare.

In the $ZnCl_2$/chlorotrimethylsilane-catalyzed reaction, one equivalent amount of chlorotrimethylsilane is needed for the completion of reaction. Although the catalytic activity of $ZnCl_2$ alone is very low and chlorotrimethylsilane has no catalytic activity, their combination shows sufficient catalytic activity so that the reaction is smoothly completed even at -78 °C. However, in the reaction catalyzed by $SnCl_4$, addition of chlorotrimethylsilane does not alter the reaction mode, **4a** being obtained in 72% yield as the single product. We assumed that $ZnCl_2$ would serve to activate chlorotrimethylsilane to generate a powerful silyl-type Lewis acid. Accordingly, we employed trimethylsilyl trifluoromethanesulfonate instead of the combination of $ZnCl_2$/chlorotrimethylsilane. Scheme 1 and Table 1 summarize the results obtained. The reactions catalyzed by $ZnCl_2$/chlorotrimethylsilane (catalyst A) and trimethylsilyl trifluoromethanesulfonate (catalyst B) are compared.[9]

RCHO + $N_2$=CHCOOEt $\xrightarrow[\text{0 °C}]{\text{Cat in }CH_2Cl_2}$

**1a-m**    **2**

**3a-m**    and/or    **4a-m**

| a: | R = Ph | h: | R = 5-Me-2-thienyl |
|---|---|---|---|
| b: | R = p-MeOC₆H₄ | i: | R = 2-Furyl |
| c: | R = m-MeOC₆H₄ | j: | R = 5-Me-2-furyl |
| d: | R = 3,4-OCH₂OC₆H₃ | k: | R = p-NO₂C₆H₄ |
| e: | R = p-Me₂NC₆H₄ | l: | R = (E)-PhCH=CH |
| f: | R = 2-Thienyl | m: | R = t-Bu |
| g: | R = 3-Me-2-thienyl | | |

**Scheme 1.**

Aromatic aldehydes having electron donating substituent(s) and electron rich heteroaromatic aldehydes gave better yields of α-formyl esters **3** than those having electron withdrawing substituent(s) and aliphatic aldehydes. Thus high migratory aptitude of aldehyde substituents is responsible for the successful production of α-formyl esters **3**. Electron poor aromatic aldehydes **1k, l** produced only poor yields of β-keto esters **4k, l**, and aliphatic aldehyde **1m** resulted in the formation of complex mixtures. This tendency is opposite to that observed in the Roskamp reactions where aliphatic aldehydes preferred the formation of β-keto esters **4** in good yields.[10] Although the $ZnCl_2$/chlorotrimethylsilane catalyzed reaction of p-N,N-dimethylaminobenz-aldehyde **1e** led to no trace of **3e**, the trimethylsilyl trifluoromethanesulfonate catalyzed reaction using the same substrate gave a satisfactory yield of **3e** (entry 9). The basic amino substituent deactivated the catalyst $ZnCl_2$ by coordination. Except for this particular case, two catalyst systems (A and B) showed similar results. Therefore, some other reactions in the presence of trimethylsilyl trifluoromethanesulfonate have been examined. However, aldehydes having a basic substituent such as 2-pyrrolyl, 1-methyl-2-pyrrolyl, 2-pyridyl, and 4-methylpyridyl led to either the formation of complex mixture or the recovery of ethyl diazoacetate.

Aldehydes can be activated by coordination of the trimethylsilyl trifluoromethanesulfonate catalyst so that the diazo ester adds to the carbonyl carbon to give diazonium silyloxy intermediates A through a linear transition structure (Scheme 2). The β-substituent R derived from aldehydes migrates from the backside of the diazonium group producing α-formyl esters **3**, this migration being especially facile when R has a high

migratory aptitude.

**Table 1. Lewis Acid Catalyzed Reactions of Ethyl Diazoacetate with Aldehydes[a]**

| Entry | 1 (R of RCHO) | Catalyst[b] | 3 (Yield/%)[c] | | 4 (Yield/%)[c] | | Reference | |
|---|---|---|---|---|---|---|---|---|
| 1 | 1a (Ph) | A | 3a | 67 | 4a | 23 | 4a | 50[d], 81[f] |
| 2 | | B | 3a | 64 | 4a | 23 | 3a+4a | 70+19[e] |
| 3 | 1b (p-MeOC₆H₄) | A | 3b | 70 | 4b | 0 | 3b+4b | 60+20[e] |
| 4 | | B | 3b | 72 | 4b | 0 | | |
| 5 | 1c (m-MeOC₆H₄) | A | 3c | 61 | 4c | 21 | | |
| 6 | | B | 3c | 48 | 4c | 26 | | |
| 7 | 1d (3,4-OCH₂OC₆H₃) | A | 3d | 71 | 4d | 0 | 4d | 35[d] |
| 8 | | B | 3d | 42 | 4d | 20 | | |
| 9 | 1e (p-Me₂NC₆H₄) | A | 3e | 72 | 4e | 0 | | |
| 10 | | B | 3e | + | 4e | + | | |
| 11 | 1f (2-Thienyl) | A | 3f | 61 | 4f | 0 | | |
| 12 | 1g (3-Me-2-thienyl) | A | 3g | 90 | 4g | 0 | | |
| 13 | 1h (5-Me-2-thienyl) | A | 3h | 81 | 4h | 0 | | |
| 14 | 1i (2-Furyl) | A | 3i | 51 | 4i | 0 | | |
| 15 | 1j (5-Me-2-furyl) | A | 3j | 87 | 4j | 0 | | |
| 16 | 1k (p-NO₂C₆H₄) | A | 3k | 0 | 4k | 27 | 4k | 83[e] |
| 17 | 1l ((E)-PhCH=CH) | A | 3l | 0 | 4l | 14 | | |
| 18 | 1m (t-Bu) | A | 3m | 0 | 4m | 0 | 4m | 65[d] |

[a]All the reactions were performed in dichloromethane at 0 °C for 30 min. [b]A: Trimethylsilyl triflate (1 equiv), B: ZnCl₂ (5 mol%) and chlorotrimethylsilane (1 equiv). [c]Yield of isolated products. [d]Reported products (yields) under Roskamp's conditions (Ref. 5). [e]Reported products (yields) under Hossain's conditions (Ref. 8). [f]The present result by use of SnCl₄ as catalyst.

On the other hand, in the Roskamp reactions (catalyst: $SnCl_2$) as well as our $SnCl_4$ catalyzed reaction, metallic halide-type Lewis acid catalysts are used. We propose that the reaction proceeds through a chelation transition state **B** to form intermediate **C**, where the aldehyde substituent R should occupy the equatorial position. When the diazonium group occupies the axial position in this reversible aldol reaction,[11] a smooth hydride migration with the removal of nitrogen takes place.
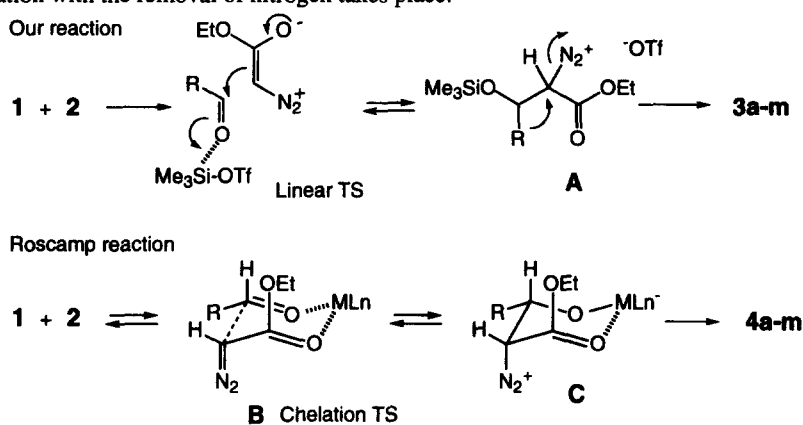


**Scheme 2.**

A model precursor **5** of intermediate **A** is easily obtained by reaction of ethyl 2-trimethylsilyldiazoacetate with p-anisaldehyde in benzene in the presence of a catalytic amount of fluoride.[12] Protonation of **5** with p-toluenesulfonic acid gives intermediate **A** which then undergoes the migration of p-methoxyphenyl nucleophilic substituent to give α-formyl ester **3b** in 50% yield.[13] Thus, the reaction mechanism was confirmed. On the other hand, treatment of desilylated derivative **6** with $SnCl_4$ led to the formation of

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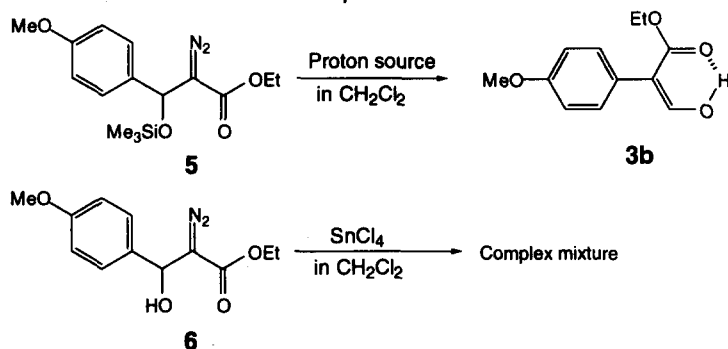


**Scheme 3.**

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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$_2$SO$_4$ 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**.