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Acid catalyzed reactions of α,β-unsaturated aldehydes and ethyl diazoacetate

Bryan Branstetter and M. Mahmun Hossain*

Department of Chemistry and Biochemistry, University of Wisconsin, PO Box 413, Milwaukee, WI 53201, USA

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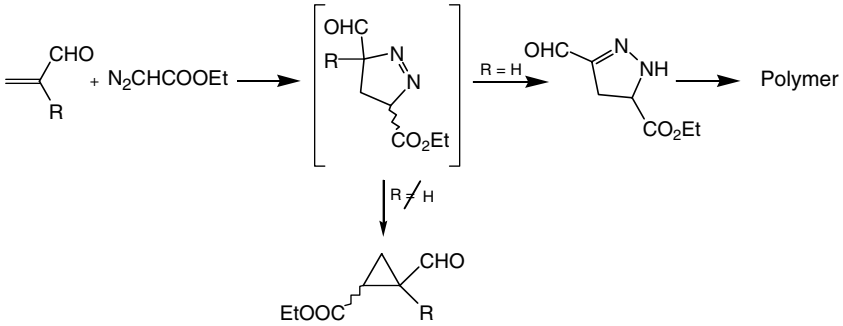
Abstract—The formation of cyclopropanes from α,β-unsaturated aldehydes and diazo compounds has been a rather challenging goal due to the extremely reactive aldehyde starter. Herein, our group reports the first formation of ethyl 2-formyl-1-cyclopropanecarboxylate in 100% yield from the acid catalyzed reaction between acrolein and ethyl diazoacetate (EDA).

1,3-Dipolar additions of diazo compounds to activated olefins or acetylenes have been extensively investigated[1] and are presently well understood;[2] in the case of unsaturated aldehydes unidentified polymers were formed. In 1978, Noels and co-workers found that the reaction between α,β-unsaturated aldehydes and diazoesters primarily created unstable 1,3-dipolar adducts (1-pyrazolines).[3] If the resulting pyrazoline had a proton geminal to the formyl group, tautomerization occurred to yield the highly favored 3-formyl-2-pyrazoline, which subsequently polymerized (Eq. 1). For example, when ethyl diazoacetate (EDA) was added to acrolein, the result was mostly polyacetals, which resulted from a polymerization through the formyl group of the 2-pyrazoline intermediate.[4] However, if the α,β-unsaturated aldehyde was substituted at the α position, cyclopropanation occurred through the 1-pyrazoline ring (Eq. 1).[3] For example, when EDA was added to α-chloroacrolein, a quantitative evolution of nitrogen took place and two isomeric cyclopropanes were obtained in almost equivalent yields.[3] In the case of β-substituted acroleins polymerization was observed similar to that of acrolein.[3]



(1)

In 2000, Aggarwal and co-workers studied the reaction of electron deficient alkenes in the presence of a catalytic amount of transition metal catalyst [$Rh_2(OAc)_4$ and $Cu(acac)_2$] and catalytic amounts of sulfide to produce cyclopropanes.[5,6] This cyclopropanation reaction was highly enantioselective, but did not work well with α,β-unsaturated aldehydes.

Our group has been actively studying the acid catalyzed reactions between aromatic aldehydes and EDA, which

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* Corresponding author. Tel.: +1 4142296698; fax: +1 4142295530; e-mail: mahmun@uwm.edu

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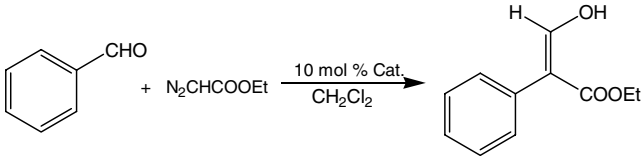
yield the highly versatile 3-hydroxy-2-arylacrylate (Eq. 2).[7] Due to the success of this reaction, we shifted our attention to the highly reactive unsaturated aldehydes (mainly acrolein and some of its derivatives). Herein, we report the first formation of ethyl 2-formyl-1-cyclopropanecarboxylate in very high yield from acrolein and EDA.



(2)

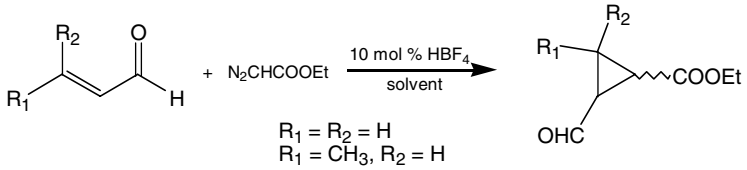
The first major difference in our reaction conditions, compared to the other cyclopropanation reactions discussed earlier, is the use of the Brønsted acid $HBF_4{\cdot}OEt_2$. In the past, reactions between acrolein and EDA were run at 0 °C in order to observe the formation of the 2-pyrazoline. Our first step was to run an acid catalyzed reaction between acrolein and EDA at 0 °C to compare results (Table 1, entry 1). The observed product did not match that of the 2-pyrazoline reported in the past. Instead, the observed product appeared to be polymeric in nature by ^1H and ^{13}C NMR. To investigate further, we decided to slow the reaction down by running at even colder temperatures (i.e., −78 °C). We have found in the past with aromatic aldehydes, EDA and $HBF_4{\cdot}OEt_2$ as catalyst, that better conversion to product was observed at −78 °C.[7]

When 1.0 equiv of acrolein and 10 mol % $HBF_4{\cdot}OEt_2$ were added to CH_2Cl_2 at −78 °C, and a solution of 1.2 equiv of EDA diluted in CH_2Cl_2 was added dropwise over 30 min, the result was quite surprising. After the reaction mixture was allowed to stir for 24 h at −78 °C, the mixture was pushed through a plug of silica gel and the resulting product was ethyl 2-formyl-1-cyclopropanecarboxylate in 100% yield, containing both cis- and trans-isomers (a ratio of 40:60).[8] This is the first report of a cyclopropane directly from acrolein and EDA (Table 1, entry 2).

After these exciting results, we wanted to see whether or not the solvent had any effect on formation of cyclopropane or selectivity between cis- and trans-isomers (Table 1, entries 3 and 4). When a polar coordinating solvent (such as ether) was used, the formation of ethyl 2-formyl-1-cyclopropanecarboxylate was again in 100% total isolated yield. Interestingly, under these conditions, the reaction favored the trans-isomer (entry 3). In the case of a non-polar solvent (such as pentane) the formation of cyclopropane decreased significantly (entry 4).

With this surprising result, we decided to try other α,β-unsaturated aldehydes. We chose mainly those substituted in the β position because the resulting cyclopropane would be substituted on all three carbons. Crotonaldehyde was the first β-substituted aldehyde subjected to our current reaction conditions and again we discovered the formation of ethyl 2-formyl-3-methylcyclopropane-1-carboxylate, in 60% yield (Table 1, entry 5). In 2000, Aggarwal and co-workers reported the formation of ethyl 2-formyl-3-methylcyclopropane-1-carboxylate in only 28% yield from crotonaldehyde and (ethoxycarbonylmethyl)sulfonium ylide, which was a mixture of two diastereomers.[5,6] Interestingly, only one of the two previously reported diastereomers was formed under our reaction conditions (1*RS*,2*RS*,3*SR*). This was confirmed by comparing ^1H and ^{13}C NMR values to previously reported values. In an attempt to increase the yield, the reaction was run at −100 °C; however, a decrease in yield was observed (Table 1, entry 6). Only one diastereomer was formed. Then, we ran the reaction in a polar solvent and non-polar solvent and the same phenomenon was observed as in the case with acrolein (Table 1, entries 7 and 8). When 3-methyl-2-butenal was reacted under the same conditions as acrolein, no cyclopropane was observed and the product

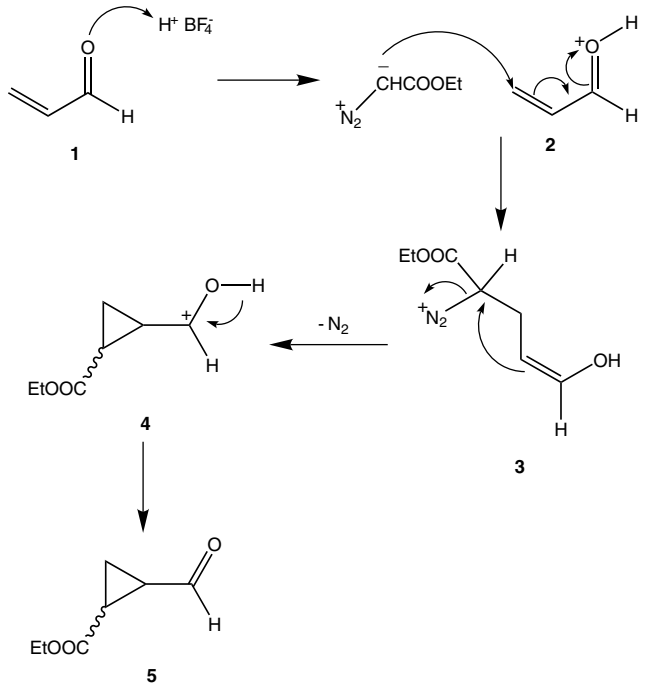
Table 1. Acid-catalyzed reactions of α,β-aldehyde in the presence of EDA[a]



$R_1 = R_2 = H$
$R_1 = CH_3, R_2 = H$

Entry	Substrate	Solvent	*T* (°C)	% Yield (cis vs trans)[b]
1	Acrolein	CH_2Cl_2	0	0[c]
2	Acrolein	CH_2Cl_2	−78	100 (40:60)
3	Acrolein	Ether	−78	100 (30:70)
4	Acrolein	Pentane	−78	61 (45:55)
5	Crotonaldehyde	CH_2Cl_2	−78	60
6	Crotonaldehyde	CH_2Cl_2	−100	42
7	Crotonaldehyde	Pentane	−78	15
8	Crotonaldehyde	Ether	−78	60

[a] EDA (1.2 equiv) was added dropwise over 30 min.
[b] Ratio determined by ^1H NMR.
[c] Unidentified polymeric substance was isolated.



Scheme 1. Proposed mechanism for acid catalyzed cyclopropanation.

appeared to be polymeric. This reaction is currently under investigation to try and gain an understanding of what precisely is taking place.

Although the mechanistic details of this reaction are not fully studied, based on our experimental data, we proposed the mechanism outlined in Scheme 1. We believe upon protonation of the carbonyl oxygen, the aldehyde undergoes a 1,4 addition reaction with EDA to form the intermediate **3**. The resulting intermediate **3** can then cyclize upon loss of nitrogen and form the cyclopropane ring. Lack of any polymeric product from the reaction of acrolein and EDA and observation of no 1-pyrazoline intermediate by NMR at −78 °C, may suggest it is most likely that the reaction does not proceed through a pyrazoline intermediate (Eq. 1).

In conclusion, our group reports the first formation of ethyl 2-formylcyclopropanecarboxylate from the acid-catalyzed reaction of acrolein and EDA in 100% total yield. Our reaction scheme is an extremely inexpensive and efficient route to cyclopropanes and requires no use of a transition metal catalyst or sulfide. In the case of crotonaldehyde our reaction appears to be selective towards only one diastereomer, whereas the sulfide catalyzed reaction reported the formation of two diastereomers. Our group is interested in cyclopropanes because they are an important structural component to many biologically active compounds, for example pyrethroid acids, which have been recently been approved in USA for use as insecticides.

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8. General procedure for acid-catalyzed reactions of α,β unsaturated aldehydes: for each experiment, 200 mg of aldehyde was dissolved in 15–20 mL of freshly distilled dichloromethane under nitrogen. A 0.1 equiv sample of the appropriate acid catalyst was added and then the reaction mixture was stirred. Ethyl diazoacetate (1.2 equiv; EDA) was diluted in 4 mL of freshly distilled dichloromethane and drawn into a gas-tight syringe. The diluted EDA was then added dropwise via a syringe pump over 30–40 min, unless otherwise noted. The reaction mixture was allowed to stir for an additional 24–26 h. The reaction mixture was then filtered through a silica or alumina plug and the solvent removed by rotary evaporation. Products were isolated by column chromatography and identified by comparing the spectra to known ^{1}H NMR. ^{1}H and ^{13}C NMR and elemental analysis were applied to characterize new compounds.