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Characterization and Synthesis of Some α, β-unsaturated Ester Derivatives from Aliphatic Aldehydes

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Abstract

Ethyl diazoacetate compound is useful synthetic intermediates for α, β-unsaturated ester in organic synthesis but, due to its toxicity and unpredictable explosive behaviour, its unique reactivity has not been fully exploited and the use on large scale has been avoided. We have developed a reliable method that generates EDA compound *in situ*. Our approach is based on the Wittig reaction, which utilizes EDA as diazo precursors. In the presence of $Cu(OTf)_2$, we found that diazo compounds can be cleanly converted to alkenyl compounds under mild reaction conditions and in a narrow range of solvents. These diazo compounds can then be induced to react directly with aldehydes to synthesize olefin. We have shown the usefulness of this chemistry in a number of different transformations, such as Wittig olefination reactions chemistry as applied toward the synthesis of more complicated molecules.

Keywords: α, β-unsaturated ester; Acryclic acid ethyl ester; Aliphatic aldehyde; Cu(II) triflate; Triphenylphosphine.

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1. Introduction

Carbon-carbon bond formation is a common reaction in organic chemistry. Wittig reaction variants are widely used for the synthesis of α, β-unsaturated esters from aldehydes is very common carbon-carbon bond forming reaction, especially catalytic asymmetric multicomponent reactions (CAMCRs), in which three or more reactants are combined in a single chemical step stereoselectively, have received considerable attention [1-3]. In most cases the problem with their unsatisfactory atom economy resulting in significant bye-product formation. Horner-Wadsworth-Emmons reaction is an alternative modified approach suggested by different research groups, such as Cynthia Burnell-Curty Research group have focused on the development of new synthetic methods using stannylenes and germylenes. With regard to stannylenes, they have found that acetals may

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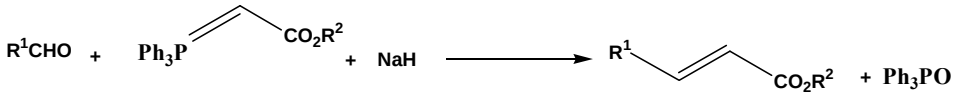
be selectively hydrolyzed to aldehydes under mildly basic conditions in the presence of tin(II) chloride [4 -9]. In addition, Knoevenagel reaction is the decarboxylative alternative methodology for the synthesis of α, β-unsaturated esters from aldehydes using malonate half ester, but it is seldom used [10].



Scheme 1

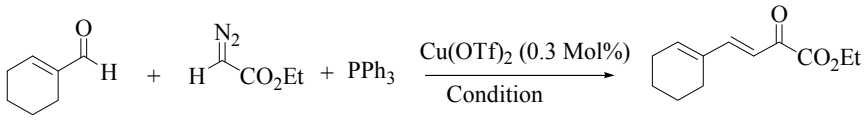
Although, phosphorous based reagents are expensive but the corresponding half-esters of malonates can be obtained from inexpensive dialkylmalonate (scheme 1). Furthermore, by the reaction with enolizable aldehydes, α, β-unsaturated esters (or their mixtures) are not commonly obtained, most importantly, in this method (*E*) vs (*Z*) selectivity varies [11-13]. In this context Benjamin *et al.* [14-15] explored the synthesis of α, β-unsaturated esters from malonate half esters with aldehyde and carried out the reaction in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP, 10 mol %) at room temperature which provided the corresponding unsaturated esters with the remarkable result. To produce olefin the reaction of carbonyl compounds with diazo reagents, in most cases, diazoacetate derivatives, a number of transition metal complexes derived from Mo, Re, Fe, Ru, Co, and Ir are used significantly as catalyst [16 -26]. Recently a research group reported [27] the formation of esters from the reaction of carbonyl compounds with diazoacetate using lanthanide triflates as catalyst. Among the various metal triflates copper (II) triflate [$Cu(OTf)_2$], plays an indispensable role in the discovery of novel and improved reaction process. [$Cu(OTf)_2$], has long been known to promote elimination reactions, oxidative coupling reactions and reactions of diazocompounds [28]. In our previous study, we report the formation of α, β-unsaturated esters from aldehydes by using copper triflates as catalyst in the reaction between ethyl diazoacetate (EDA) and carbonyl compounds especially various aromatic aldehydes [9]. In the present work, a series of aliphatic Acryclic acid ethyl ester derivatives were evaluated and compared against aromatic acryclic acid ethyl ester.

As a part of our ongoing studies to search for new carbon-carbon bond formation processes using diazo compounds, our future studies will focus on exploring the full scope of this reaction to other carbonyl compounds.

2. Experiments, Results and Discussion

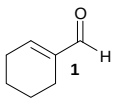
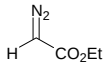
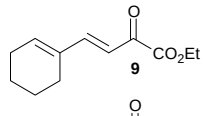
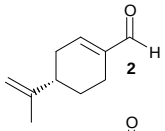
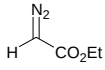
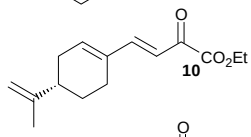
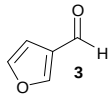
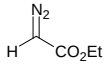
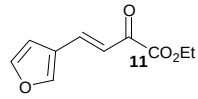
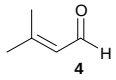
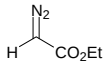
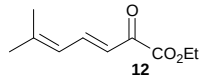
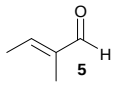
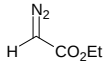
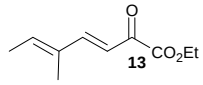
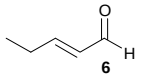
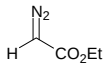
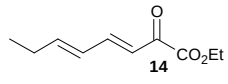
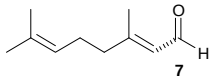
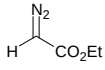
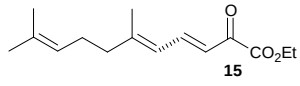
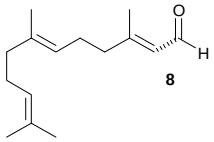
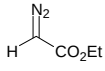
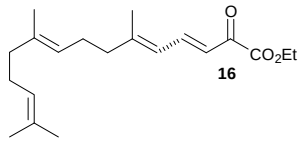
Our early studies mainly focused on the allyl aldehydes to give α, β-unsaturated esters in excellent yields. The common reaction of aliphatic aldehyde was used as a model system for optimization of the reaction conditions using cupper(II) triflate was first examined under standard methods (0.30 mol% catalyst, refluxing in $CHCl_3$, 0.5 equiv EDA for 7hr) (scheme 2). A complete series of reaction was achieved with entry **1-8** under the same

conditions. Product yields and measured enantio selectivities from these reactions are presented in Table 1. High product yields are obtained in each case, and especially **1** was the highest achieved.



Scheme 2

Table 1. Some aliphatic aldehydes (entry 1 to 8) have been treated in the same condition and gave corresponding α,β-unsaturated ester.

Entry	Aldehydes	Ethyl diazoacetate	Unsaturated Ester	Yield (%)
1				94
2				67
3				83
4				79
5				82
6				51
7				80
8				60

Catalyst: $Cu(OTf)_2$ (0.3 Mol %)

The reaction of aldehyde and ethylyl diazoacetate gave the corresponding conjugated ester derivatives 9-16 entry in above Table 1. Initially a variety of reactions were tested in

presence of copper (II) triflate conditions, employing different solvents such as chloroform, dichloromethane, tetrahydrofuran with different aldehyde at room temperature to elevated temperature. But the best results were obtained when the reaction was carried out in chloroform at 70^0 C (Table 2).

Table 2. Yields of products with different solvents using $Cu(OTf)_2$.

Catalyst (eq)	Condition	Yield (%)
$Cu(OTf)_2$ (0.3)	CH_2Cl_2, r.t	0
$Cu(OTf)_2$ (0.3)	$CHCl_3$, r.t	0
$Cu(OTf)_2$ (0.3)	PhF, r.t	0
$Cu(OTf)_2$ (0.3)	THF, r.t	0
$Cu(OTf)_2$ (0.3)	$CHCl_3$, 70^0 C	73

We propose that the reason for the low reactivity of compound **6 (**yield 5l %) at the electronically not favored aliphatic site of aldehyde is that the carbonyl group is very sterically unfair and unable to approach this site for reaction. In order to design systems capable of clean reactions at C=O sites, the site would need to be electronically activated while the rest of the molecule must have no activated sites or the sites would need to be sterically protected. No alkyl group next to double bond occurred, presumably because the electrons are delocalized into the double bond and are not sufficiently activating the carbonyl group. One obvious system would be 1-cyclohexenyl-acetaldehyde (**1**) as the cyclohexene group would activate the site and sterically favor the carbonyl group. $Cu(OTf)_2$ catalyzed the decomposition of ethyl diazoacetate at 70°C resulting in efficient C=O activation generating **9** in 94% yield. In order to explore the scope of this reaction, the effect of temperature and the substituent on the aldehyde compound was examined and the results are summarized in Table 1. In the case of compound **2**, which has para-propene substituted, an efficient reaction was obtained at 67% yield and the next compound **3** was improved (yield 83 %) on the adding aromatic ring. In the case of 5,9,13-Trimethyl-tetradeca-2,4,8,12-tetraenyl substitution of aldehyde (**8**) lowering the yields of **16** was obtained at 60% only, while in the case of rest of the compounds would generate steadily good yield.

This induction is in agreement with our published model [29] that predicts that the product would be formed. The absolute structure of the other products is assigned assuming a similar effect. Very efficient reactions were also obtained with the even more electron-rich aromatic system **11**. Once again, reaction of ethyl diazoacetate with **8** at 70°C resulted in very less effective C=C insertion to form product **16** in only 60% yield. The demonstration that **EDA** with a very electron-rich aromatic ring is an appropriate substrate how steric factor effects the aromatic ring from reaction with the carbonyl group.

When the reaction was conducted with an excess of EDA (2 equiv.), the product was obtained in 83% yield.

In order to determine the C=O activation into aldehyde site required the presence of a strong electrondonating group in the left position; the reaction was extended to high product. Moreover, treatment of EDA with formaldehyde in a Cu (II) catalyzed reaction afforded no product and also the reaction did not progress without PPh_3. In case of the nonattendance or lack of catalyst, the reaction afforded azine as main product while the reaction mixture was stirred for 2 days.

The expected structures of the products have been established by the spectral data (IR, ^{1}H-NMR). The ^{1}H NMR spectra of the compounds 9-16 were not identical, but the characteristic spectra of two double bond hydrogen of those compounds were similar in all cases. Two geminal protons appeared nearly at 7.24 ~7.60 ppm as doublets and the coupling constant was about 15.8Hz and 6.12~6.14 ppm was for nearest proton, while the other protons appeared in the aromatic and aliphatic regions, respectively.

Experimental Section

General method

1H NMR spectra were run at 300 MHz with the sample solvent being $CDCl_3$ unless otherwise noted. IR spectra were obtained using a Nicolet Impact series 420 IR Spectrometer as KBr pellet or sodium chloride plate. Column chromatography was carried out on silica gel 60 (230–400) meshes.

Thin layer chromatography (TLC) plate made by Merck (aluminum 5554) was used and visualized by UV lamp (254-365nm). The color can be determined by dipping into the solution of 300ml MeOH, 9.0g Vanillin and 1.5ml H_2SO_4 (98%) and then burning by heat gun. All commercial reagents purchased from Aldrich Sigma (American) and Junsei (Japanese), were used without further purification.

General Procedure

A mixture of aldehyde (1.0 mmol) and the appropriate ethyl diazo acetate(2mmol) was taken in a well-dried RB flask under nitrogen atmosphere. The reaction mixture was stirred in the presence of $Cu(OTf)_2$ (0.3mmol) and chloroform (7ml) at 70^0 C for 7-10h duration to obtain a clear crude product. Then the crude product was purified by column chromatography (hexane-EtOAc) on silica gel to give corresponding α, β-unsaturated ester(**9-16**).

3-Cyclohex-1-enyl-acrylic acid ethyl ester (9)

1H NMR (300 MHz, $CDCl_3$): δ= 7.26 (d, *J* = 15.8Hz, 1H), 6.14 (t, *J* = 4.1Hz, 1H), 5.35 (d, *J* = 15.8Hz, 1H), 4.18 (q, *J* = 7.1Hz, 2H), 2.19-2.10 (m, 4H), 1.71-1.55 (m, 4H) 1.27 (t, *J* = 7.1Hz, 3H).

IR (neat):2932, 1717, 1630, 1451, 1306, 1267, 1165, 1036, 982, 833 cm^{-1}.

3-(4-Isopropenyl-cyclohex-1-enyl)-acrylic acid ethyl ester (10)
1H NMR (300 MHz, CDCl3): δ= 7.28 (d, *J* = 15.8Hz, 1H), 6.16 (q, *J* = 2.8Hz, 1H), 5.75 (d, *J* = 15.8Hz, 1H), 4.73-4.70 (m, 2H), 4.18 (q, *J*= 7.1Hz, 2H), 2.35-2.10 (m, 5H), 1.93-1.87 (m, 1H), 1.73 (s, 3H), 1.52-1.46 (m, 1H), 1.27 (t, *J* = 7.1Hz, 3H).
IR (neat): 2980, 2928, 1715, 1632, 1449, 1368, 1304, 1165, 1040, 982, 889, 820 cm^{-1}.

3-Furan-3-yl-acrylic acid ethyl ester (11)
1H NMR (300 MHz, CDCl3): δ= 7.62 (s, 1H), 7.55 (d, *J* =15.8Hz, 1H), 7.40 (s, 1H), 6.56 (s, 1H), 6.30 (d, *J* = 15.8Hz, 1H), 4.22 (q, *J* = 7.1Hz, 2H), 1.30 (t, *J* = 7.1Hz, 3H).
IR (neat): 2984, 2932, 1715,
1645, 1368, 1314, 1267, 1221, 1179, 1155, 1038, 978, 872, 799 cm^{-1}.

5-Methyl-hexa-2, 4-dienoic acid ethyl ester (12)
1H NMR (300 MHz, CDCl3): δ = 7.53 (dd, *J* = 11.6, 15.2Hz, 1H), 5.96(d, *J* = 11.6Hz, 1H), 5.74 (d, *J* = 15.2Hz, 1H), 4.17 (q, *J* = 7.1Hz, 2H), 1.87 (s, 3H), 1.85 (s, 3H), 1.27 (t, *J* = 7.1Hz, 3H).
IR (neat): 2980, 2932, 1713, 1640, 1447, 1368, 1306, 1277, 1213, 1140, 1040, 992,882 cm^{-1}.

4-Methyl-hexa-2,4-dienoic acid ethyl ester (13)
1H NMR (300 MHz, CDCl3): δ = 7.30 (d, *J* = 15.7Hz, 1H), 5.95 (q, *J* = 7.0Hz, 1H), 5.76 (d, *J* = 15.7Hz, 1H), 4.18 (q, *J* = 7.1Hz, 2H), 1.79(d, *J* = 7.0Hz, 3H), 1.74 (t, *J* = 1.0Hz, 3H), 1.28 (t, *J* = 7.1Hz, 3H).
IR (neat): 2982, 2928, 1715, 1622, 1447, 1368, 1302, 1175, 1038, 982,820 cm^{-1}.

Hepta-2,4-dienoic acid ethyl ester (14)
1H NMR (300 MHz, CDCl3): δ= 7.24-7.16 (m, 1H), 6.12-6.08 (m, 2H), 5.72 (d, *J* = 15.3Hz, 1H), 4.14(q, *J* = 7.1Hz, 2H), 2.18-2.08 (m, 2H), 1.22 (t, *J* = 7.1Hz, 3H), 0.98 (t, *J* = 7.4Hz, 3H).
IR (neat): 2970, 1715, 1644, 1618, 1462, 1367, 1302, 1186, 1142, 1001, 876 cm^{-1}.

5,9-Dimethyl-deca-2,4,8-trienoic acid ethyl ester (15)
1H NMR (300 MHz, CDCl3): δ= 7.60-7.49 (m, 1H), 5.96 (d, *J* =11.6Hz, 1H), 5.75 (dd, *J* = 7.8, 15.2Hz, 1H), 5.10-5.02 (m, 1H), 4.18 (d, *J* = 7.1, 1.2Hz, 2H), 2.29 (t, *J* = 7.2Hz, 1H), 2.12 (d, *J* = 3.1Hz, 2H),
2.02, (s, 1H), 1.87-1.85 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.27 (t, *J* = 7.1Hz, 3H).
IR (neat): 2926, 2857, 1715, 1636, 1649, 1368, 1275, 1152, 1038, 980, 887 cm^{-1}.

5, 9,13-Trimethyl-tetradeca-2,4,8,12-tetraenoic acid ethyl ester (16)
1H NMR (300 MHz, CDCl3): δ = 7.60-7.48 (m, 1H), 5.96 (d, *J* = 11.6Hz, 1H), 5.74 (dd, *J* = 6.5, 15.2Hz, 1H), 5.09-5.04 (m, 2H), 4.21-4.12 (m, 2H), 2.32-2.23 (m, 1H), 2.17-2.12 (m, 3H), 2.01-1.95 (m, 4H)

1.87-1.85 (m, 3H), 1.66 (s, 3H), 1.58 (s, 6H), 1.27 (t, J = 7.1Hz, 3H).
IR (neat): 2967, 2926, 1715, 1447, 1368, 1275, 1148, 1030, 980, 887, 822 cm^{-1}.

3. Conclusions

We have demonstrated that effective C=O activation of aldehyde groups can be achieved as long as the olefin is least substituted. The aromatic ring and aliphatic group substituted compounds are more reactive than that of olefin compounds. Furthermore, the reaction between EDA and carbonyl compounds are catalyzed well by copper triflate catalysts and proves to be a fairly good catalyst. In addition, a salient feature of copper (II) triflate is its inherent stability in aqueous solvents that open the door to environmental chemistry [30]. In addition, the electrophilic attack is accomplished by the copper (II) carbonyl intermediates. Thus, the C=O activation strategy we have presented herein offers exciting new options for the synthesis of α, β-unsaturated compounds as illustrated in the very concise route to acryclic acid ethyl ester.

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