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Niobium(V) chloride-catalyzed C–H insertion reactions of α-diazoesters: synthesis of β-keto esters

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Abstract—Aldehydes react readily with ethyl diazoacetate in the presence of 5 mol% of NbCl₅ in dichloromethane to produce the corresponding β -keto esters in good yields with high selectivity. This method is very useful for the preparation of β -keto esters from both electron-rich as well as electron-deficient aromatic aldehydes under mild reaction conditions. © 2004 Elsevier Ltd. All rights reserved.

1. Introduction

β-Keto esters are multicoupling reagents having an electrophilic carbonyl group and nucleophilic carbon which make them valuable intermediates for the synthesis of various biologically active compounds such as 3.4-dihydropyrimidinones, 4-alkyl or arylcoumarins, 1,4-dihydropyridines and many others.¹ They are versatile building blocks in the total synthesis of a variety of natural products such as thiolactomycin, trichodiene, polyoxamic acid, chokol, prostaglandin $PGF_{2\alpha}$, psuedotsugonoxide, syncarpic acid, diplodialide, and podophyllotoxin.^{2,3} Consequently, numerous methods have been developed for the preparation of β -keto esters.¹ Among them, one of the simple and most straight forward approaches for the synthesis of β -keto esters involves the acid catalyzed C-H insertion of ethyl diazoacetate into aldehydes.⁴ These C-H insertion reactions are chemoselective, which allow new carbon-carbon bond formation under mild conditions. Acid catalysts such as boron trifluoride etherate, tin(II) chloride, titanium(IV) chloride, triethyl oxonium tetrafluoroborate, and zinc(II) chloride have been reported for this conversion.^{5,6} However, many of these methods involve the use of strongly acidic reagents and harsh reaction conditions and the yields reported are far from satisfactory especially with aromatic aldehydes. Therefore, the development of mild and efficcient alternatives such as niobium(V) chloride would extend the scope and generality of the C–H insertion process of α -diazo esters. Recently, niobium chloride has emerged as an efficient Lewis acid catalyst in promoting various organic transformations such as Diels–Alder reaction, ringopening of epoxides, Mukaiyama aldol reaction and allylation of aldehydes, imines and *N*-acyliminium ions.⁷ In particular, niobium(V) chloride has advantages of low catalyst loading, moisture stability and ease of handling.⁸

In this article, we wish to describe a mild and efficient protocol for the preparation of β -keto esters through C–H insertion of ethyl diazoacetate with a range of aldehydes using niobium(V) chloride as catalyst (Scheme 1).

Accordingly, treatment of benzaldehyde with ethyl diazoacetate in the presence of 5 mol% NbCl₅ in dichloromethane afforded ethyl 3-oxo-3-phenylpropanoate **3a** in



R = aryl, alkyl, naphthyl, phenethyl, heterocyclic

Scheme 1.

Keywords: Transition metal catalysis; Carbene insertion; Diazo ester; β-Keto esters.

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85% yield. This remarkable catalytic activity of niobium(V) chloride provided the incentive for further study of reactions with other aromatic aldehydes. Interestingly, various aromatic aldehydes such as chloro-, nitro-, methoxy-, methyl-, cyano-, bromo-, trimethoxy-, naphthyl-derivatives reacted smoothly with ethyl diazoacetate under similar conditions to give the corresponding β-keto esters as the products of C–H insertion (entries **b**–**j**, Table 1). Aliphatic

aldehydes such as *n*-heptanal, cyclohexyl carboxaldehyde, and 3-phenyl propanal afforded the respective β -keto esters in high yields (entries **l**, **m**, and **n**, Table 1). This method also works well with acid sensitive substrates such as furfural (entry **k**, Table 1), which is known to polymerize under most of the reported conditions. In all cases, the reactions proceeded efficiently at room temperature. Both aromatic and aliphatic aldehydes underwent condensation to

Table 1. NbCl₅-catalyzed synthesis of β -keto esters from ethyl diazo acetate and aldehydes

Entry	Aldehyde 1	Product ^a 2	Time (h)	Yield (%) ^b
a	СНО	COOEt	3.0	85
b	СІСНО	COOEt	4.0	82
c	O2N CHO	O.N COOEt	4.5	78
d	MeO		3.5	76
e	Me		3.0	83
f	NC		3.5	90
g	Br	Br COOEt	4.5	86
h	CHO CHO	COOEt	4.0	79
i	MeO MeO OMe	MeO MeO MeO OMe	4.5	75
j	СНО	COOEt	5.0	82
k	Сно	COOEt	3.0	84
1	ССНО	COOEt	3.5	87
m	СНО	COOEt	3.5	85
n	СНО	COOEt	4.0	92
0	CHO N	COOEt	4.5	89
р	F CHO	COOEt	3.5	80

^a All the products were characterized by ¹H NMR, IR spectroscopy and mass spectroscopy.

^b Yield refers to the isolated pure producs after column chromatography.



Scheme 2.

yield the β -keto esters in good yields. The reaction probably proceeds through the activation of the aldehyde by complexation with niobium(V) followed by nucleophilic addition of EDA on the C=O group and subsequent 1,2-hydride shift with loss of N₂ resulting in the formation of β -keto ester **3** (Scheme 2).

The method is clean and the products are obtained in high yields with high selectivity. No side products such as glycidic esters were observed under the reaction conditions. Other side products like diethyl maleate and/or fumarate arising from carbene dimerization were not detected under these conditions. To determine the efficiency of this procedure, we have also performed the reactions with various other Lewis acids such as InCl₃, CeCl₃·7H₂O, TaCl₅ and GdCl₃. Among these catalysts, NbCl₅ was found to be the most effective catalyst for this conversion. In the absence of catalyst, no condensation was observed between aldehyde and ethyl diazoacetate. As solvent, dichloromethane appears to give the best results. Ketones such as acetophenone, cyclohexanone, and tetralone failed to undergo condensation with EDA. This is due to the lower reactivity of ketones in comparison with aldehydes. Other diazoesters such as diethyl diazomalonate and ethyl diazoacetoacetate did not yield any condensation product under the reaction conditions. The scope of this method is illustrated with respect to various aldehydes and ethyl diazoacetate and the results are presented in Table 1.

In summary, we describe a mild, convenient and efficient protocol for the preparation of β -keto esters via the C–H insertion of ethyl diazoacetate into aldehydes using NbCl₅ as novel catalyst. This method provides improved yields of β -keto esters including the less reactive aromatic substrates.

2. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ¹H NMR spectra were recorded on Gemini-200 spectrometer in CDCl₃ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV.

2.1. General procedure

A mixture of aldehyde (1 mmol), ethyl diazoacetate (1.2 mmol) and NbCl₅ (5 mol%) in dichloromethane (10 mL) was stirred at 27 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by

TLC, the reaction mixture was extracted with dichlomethane ($3 \times 10 \text{ mL}$). The combined organic extracts were dried over anhydrous Na₂SO₄, concentrated in vacuum and purified by column chromatography on silica gel (Merck, 100–200 mesh ethyl acetate–hexane, 1:9) to afford pure β -keto esters.

2.1.1. Ethyl 3-oxo-3-(2-pyridyl) propanoate (30). Pale yellow liquid, IR (neat): ν 3636, 3058, 2985, 2939, 1741, 1703, 1644, 1582, 1327, 1197, 1032, 791, 746, 648 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.64 (d, J=3.7 Hz, 1H), 8.04 (d, J=8.1 Hz, 1H), 7.84 (t, J=8.1 Hz, 1H), 7.47 (t, J=5.2 Hz, 1H), 4.16 (q, J=7.4, 14.1 Hz, 2H), 4.12 (s, 2H), 1.24 (t, J=7.4 Hz, 3H). EIMS: m/z (%): 193 (M⁺, 10), 148 (30), 121 (80), 106 (50), 78 (100), 51 (40). Anal. Calcd for C₁₀H₁₁NO₃ (193.201): C, 62.17; H, 5.74; N, 7.25. Found: C, 62.10; H, 5.69; N, 7.31%.

2.1.2. Ethyl 3-(4-flourophenyl)-3-oxopropanoate (3p). Brown oil, IR (neat) ν 3548, 3076, 2985, 1740, 1688, 1600, 1509, 1206, 1032, 845, 768, 569 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 7.98–7.95 (m, 2H), 7.16–7.11 (m, 2H), 4.18 (q, *J*=7.4, 14.1 Hz, 2H), 3.89 (s, 2H), 1.26 (t, *J*=7.4 Hz, 3H). EIMS: *m/z* (%): 210 (M⁺, 10), 166 (5), 124 (100), 96 (20). Anal. Calcd for C₁₁H₁₁FO₃ (210.203): C, 62.85; H, 5.27; F, 9.04. Found: C, 62.79; H, 5.32; F, 9.12%.

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