Preparation of γ,δ-unsaturated-β-ketoesters: Lewis acid-catalysed C-H insertion of ethyl diazoacetate into α,β-unsaturated aldehydes

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Abstract: The synthesis of γ,δ-unsaturated-β-keto esters was achieved by the Lewis acid-catalysed direct C-H insertion of an α-diazoester into various α,β-substituted-unsaturated aldehydes. C-H insertion of ethyl diazoacetate into alkyl- and aryl-substituted α,β-unsaturated aldehydes was performed under mild conditions to afford the corresponding γ,δ-unsaturated-β-keto esters in moderate to high yields as a mixture of keto/enol tautomers.
Keywords: γ,δ-Unsaturated-β-ketoesters, C-H insertion, ethyl diazoacetate

1. Introduction

β-Keto esters are important building blocks in organic synthesis and are used for the construction of a variety of biologically relevant molecules.[1a, 1b] They are excellent substrates for the synthesis of heterocyclic compounds including dihydroxypyridines, pyrroles, dihydropyrimidines, indoles, and quinolines.[2,3] As a subfamily of β-keto esters, γ,δ-unsaturated-β-keto esters are important intermediates in the preparation of enantiomerically pure γ,δ-unsaturated-β-hydroxy esters that act as chiral building blocks for the synthesis of many biologically active compounds and pharmaceutical products such as (-)-CP_2-disorazole C_1[4], turnagainolides A and B[5], epothilones[6] and seimatopolide A.[7]

Many methods have been developed for the synthesis of β-keto esters using strong bases or alkali metals, e.g. Claisen condensation,[8a-b] Blaise reaction,[9a-b] Dieckmann condensation.[10] Other methods include the Lewis acid-catalysed C-H insertion of α-diazoesters into aldehydes under mild conditions.[11a-d] In contrast, the synthesis of γ,δ-unsaturated-β-keto esters has traditionally been achieved using Wittig[12] and Horner-Wadsworth-Emmons (HWE) chemistry.[13a-b] Herein, we report a general process for the Lewis acid-catalysed C-H insertion of α-diazoesters into α,β-unsaturated aldehydes for the preparation of γ,δ-unsaturated-β-keto esters in moderate to high yields.

2. Results and discussion

Several Lewis acids, such as $BF_3{\cdot}OEt_2$, $MoOCl_4$, $SnCl_2$, $TiCl_4$, $NbCl_5$, and ZrCl, have been successfully utilised in the C-H insertion of α-diazoesters into aldehydes.[14a-f] However, only one, low yielding example involving an α,β-unsaturated aldehyde has previously been reported.[15] Accordingly, we conducted an initial screen to identify a suitable catalyst for

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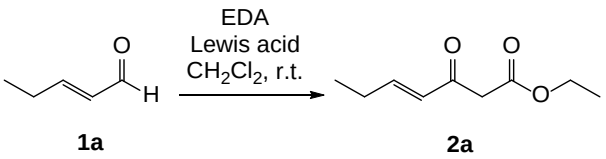
this transformation. Using *trans*-2-pentenal (**1a**) as our test substrate, a number of Lewis acids were examined for their ability to catalyse the C-H insertion of ethyl diazoacetate (EDA, Table 1). As the reaction of EDA with the Lewis acids was found to be exothermic, EDA was added at 0-5 °C before subsequent stirring at room temperature to avoid reagent degradation. CuI (Entries 1, 2), Ti(O-*i*Pr)$_4$ (Entries 3, 4), and Ce(SO$_4$)$_2$ (entries 5, 6) were each found to be ineffective catalysts. The addition of BF$_3$·OEt$_2$ (Entry 7) was accompanied by a vigorous reaction with the liberation of nitrogen gas, however, no product formation was observed. In contrast, CuBr$_2$ (Entry 8), TiCl$_4$ (Entry 9), PdCl$_2$ (Entry 10), and FeCl$_3$ (Entry 11) did effect the C-H insertion of EDA into *trans*-2-pentenal, but the conversions and yields were low even after prolonged reaction times. Both AlCl$_3$ (Entry 12) and NbCl$_5$ (Entry 13) resulted in complete conversion of the starting aldehyde. However, use of AlCl$_3$ afforded the target γ,δ-unsaturated-β-ketoester with a lower 52% yield in comparison to a 63% yield with NbCl$_5$. The reaction was further optimised by increasing the equivalents of EDA from 1.1 to 1.2 and the catalyst loading to 7 mol%, leading to an improved yield of 68% and a reduction in reaction time from 10 h to 8 h (Entry 14). Higher loadings were accompanied by a decreased yield (Entry 15).

A subsequent solvent and temperature screen identified dichloromethane as the optimal reaction medium (Table 2, Entry 6). No reaction occurred in chloroform (Entry 4) while lower yields were observed in tetrahydrofuran (Entry 1), toluene (Entries 2, 3), and acetonitrile (Entry 4). For the reactions conducted in dichloromethane, lowering the temperature to either 0 °C (Entry 7) or -10 °C (Entry 8), or increasing the temperature to 40 °C (Entry 9) resulted in lower yields.

Table 1. Screening of suitable Lewis acids



1a **2a**

Entry	Lewis acid	Loading (mol%)	EDA (eq.)	Time (h)	Yield (%)
1	CuI	5	1.1	32	--
2	CuI	10	1.1	42	--
3	Ti(O-*i*Pr)$_4$	5	1.1	28	--
4	Ti(O-*i*Pr)$_4$	10	1.1	44	--
5	Ce(SO$_4$)$_2$	5	1.1	32	--
6	Ce(SO$_4$)$_2$	10	1.1	44	--
7	BF$_3$·OEt$_2$	5	1.1	24	--
8	CuBr$_2$	5	1.1	28	33
9	TiCl$_4$	5	1.1	24	44
10	PdCl$_2$	5	1.1	24	31
11	FeCl$_3$	5	1.1	24	27
12	AlCl$_3$	5	1.1	24	52
13	NbCl$_5$	5	1.1	10	63
14	NbCl$_5$	7	1.2	8	68
15	NbCl$_5$	10	1.2	8	59

Reagents and Conditions: *trans*-2-pentenal (0.9 mmol), CH$_2$Cl$_2$ (5 mL), r.t.

Table 2. Solvent and temperature study

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	THF	r.t.	16	54
2	Toluene	r.t.	18	59
3	Toluene	50	14	43
4	CHCl$_3$	r.t.	42	--
5	MeCN	r.t.	28	36
6	CH$_2$Cl$_2$	r.t.	8	68
7	CH$_2$Cl$_2$	-10	36	30
8	CH$_2$Cl$_2$	0	24	38
9	CH$_2$Cl$_2$	40	6	48

Reagents and Conditions: *trans*-2-Pentenal (0.9 mmol), EDA (1.08 mmol), NbCl$_5$ (7 mol%), solvent (5 mL).

A series of aliphatic and aromatic α,β-unsaturated aldehydes was next subjected to the C-H insertion reaction under the optimised conditions (Table 3). In general, it was found that longer reaction times were required for the complete conversion of α,β-unsaturated aldehydes compared to their saturated equivalents.[14e] Yields of the target γ,δ-unsaturated-β-keto esters were comparable regardless of the aldehyde chain length (Entries 1-12). The C-H insertion with aromatic aldehydes also afforded similar yields, albeit at the cost of longer reaction times (Entries 15-19). Noticeably higher yields were observed with electron-poor aromatic substrates (Entries 17-19) in contrast to aldehydes containing electron-rich rings (Entry 16). The presence of a methyl group at the γ- or δ-positions resulted in lower yields (Entries 10-12) most likely as a result of increased steric hindrance. β-Keto esters with more highly unsaturated side-chains were also tolerated under these conditions (Entry 12).

The mechanism is likely similar to that proposed by Yadav and co-workers whereby initial attack of the carbene species, generated from ethyl diazoacetate, on the aldehyde is followed by a 1,2-hydride shift and concomitant loss of nitrogen.[14e]

In conclusion, reaction conditions for the $NbCl_5$-catalysed C-H insertion of ethyl diazoacetate into α,β-unsaturated aldehydes were successfully optimised to produce γ,δ-unsaturated-β-keto esters in moderate to high yields. The outlined methodology tolerates both aliphatic, aromatic and unsaturated substrates equally well.

Acknowledgments

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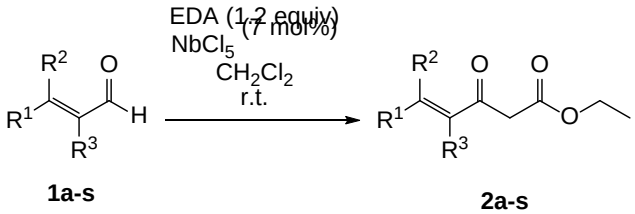
Table 3. Synthesis of γ,δ-unsaturated-β-ketoesters under optimised conditions[a]



Entry	Aldehyde	R^1	R^2	R^3	Product	Time (h)	Yield (%)	Keto:enol[b]
1	**1a**	CH_3CH_2	H	H	**2a**	8	68	60:40
2	**1b**	CH_3	H	H	**2b**	8	56[c]	68:32
3	**1c**	$CH_3(CH_2)_2$	H	H	**2c**	8	71	49:51
4	**1d**	$CH_3(CH_2)_3$	H	H	**2d**	8	72	59:41
5	**1e**	$CH_3(CH_2)_4$	H	H	**2e**	7.5	65	71:29

6	**1f**	$CH_3(CH_2)_5$	H	H	**2f**	8	63	50:50
7	**1g**	$CH_3(CH_2)_6$	H	H	**2g**	9.5	66	55:45
8	**1h**	$CH_3(CH_2)_7$	H	H	**2h**	10	60	49:51
9	**1i**	$CH_3(CH_2)_8$	H	H	**2i**	10	67	39:61
10	**1j**	CH_3CH_2	H	CH_3	**2j**	6.5	59	85:15
11	**1k**	$(CH_3)_2CH(CH_2)_2$	CH_3	H	**2k**	8	54	n.d.[c]
12	**1l**	Farnesal			**2l**	8	54	n.d.[c]
13	**1m**	$(CH_3)_2CH(CH_2)_2CH(CH_3)$	H	H	**2m**	6	67	45:55
14	**1n**	$C_6H_5(CH_2)_2$	H	H	**2n**	16	73	58:42
15	**1o**	C_6H_5	H	H	**2o**	5.5	69	49:51
16	**1p**	4-MeO-C_6H_4	H	H	**2p**	18	43	55:45
17	**1q**	2-NO_2-C_6H_4	H	H	**2q**	16	69	9:91
18	**1r**	3-NO_2-C_6H_4	H	H	**2r**	14	73	26:74
19	**1s**	4-NO_2-C_6H_4	H	H	**2s**	15	76	0:100

[a]Reagents and Conditions: α,β-Unsaturated aldehyde (0.9 mmol), EDA (1.08 mmol), $NbCl_5$ (7 mol %), CH_2Cl_2 (5 mL), r.t. See Ref 16 and Supporting Information for full experimental procedure and characterisation data.
[b]Keto:enol ratio determined by ^{1}H-NMR. [c]n.d.: not determined due to presence of (*E*)- and (*Z*)- isomers in starting material.

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16. $NbCl_5$ (0.063 mmol, 7 mol%) was added to a solution of the α,β-unsaturated aldehyde (0.9 mmol, 1.0 equiv) in anhydrous dichloromethane (5.0 mL) at 0 °C under an inert atmosphere. EDA (1.08 mmol, 1.2 equiv) was added over period of 10 minutes *via* syringe at 0 °C before stirring at room temperature until complete consumption of the aldehyde was evident by TLC. The solvent was removed *in vacuo* and the remaining residue was subjected to dry flash chromatography using a mixture of hexane and diethyl ether to afford the target γ,δ-unsaturated keto ester in moderate to high yields. Ethyl (*E*)-3-oxohept-4-enoate (**2a**): The title compound was isolated as a yellow oil in 68% yield as a mixture of keto-enol tautomers. ^{1}H-NMR (400MHz, $CDCl_3$) (mixture of keto-enol tautomers): δ 1.08 (m, 6H, CH_3), 1.24-1.33 (m, 6H, CH_3, ester), 2.20-2.30 (m, 4H, CH_2), 3.58 (s, 2H, α-CH_2, keto), 4.20 (m, CH_2, ester), 4.98 (s, 1H, α-CH enol), 5.79 (d, 1H, *J* = 15.6 Hz, CH), 6.16 (d, 1H, *J* = 15.6 Hz), 6.70 (m, 1H, CH), 6.94 (m, 1H, CH), 11.90 (d, *J* = 1.28 Hz, OH); ^{13}C-NMR (100MHz, $CDCl_3$) : δ 192.26, 173.03, 169.68, 167.47, 151.24, 142.39, 128.72, 123.43, 89.95, 61.31, 60.01, 46.93, 25.63, 22.63, 14.26, 14.07, 12.64, 12.05; ν_{maz}/(NaCl) cm^{-1}: 734, 802, 861, 979, 1031, 1097, 1159, 1203, 1376, 1670, 1737, 2884, 2943, 2983, 3446; HRMS (ESI+): Exact mass calc for $C_9H_{15}O_3$ ($M+H^+$) 171.1016 Found 171.1024.