Stereoselective Synthesis of (*E*)- α,β -Unsaturated Esters via Carbene-catalyzed Redox Esterification

Kirsten Zeitler*

*Institut für Organische Chemie, Universität Regensburg,
Universitätsstrasse 31, D-93053 Regensburg, Germany
kirsten.zeitler@chemie.uni-regensburg.de*

Supporting Information

List of Contents

General Methods	S1
General Procedures	S2
Experimental Data for unsaturated esters (Table 2/entries 1 to 12)	S3-S5
Exemplary GC/MS copies of starting material and crude reaction mixture (alkynal 6 $\rightarrow$ ethyl cinnamate 7/Table 1/entry 8 ; MS data and internal standard method)	S6-9
NMR experiment for alkynal 6 $\rightarrow$ ethyl cinnamate (start and final NMR and stacked plot)	S10
^1H and ^{13}C NMR spectra of products (Table 2/entries 1 to 12 ; Table 1/entry 12)	S12-S20

General Methods

NMR spectra were recorded on a Bruker Avance 300 (300.13 MHz) using the solvent peak as internal reference (CDCl_3 ; δ H 7.26; δ C 77.0). Mass spectra (MS) were recorded with a Finnigan MAT 95 or Varian MAT 311A. All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F₂₅₄; visualization was accomplished with UV light and/or staining with appropriate stains (anisaldehyde, vaniline, KMnO_4 or phosphomolybdic acid). GC/MS was performed on Agilent GC 6890. Standard flash chromatography procedures were followed (particle size 40–63 μm).

Dichloromethane was distilled from CaH_2 , and tetrahydrofuran was distilled from sodium/benzophenone. Other solvents (toluene, acetonitrile) were purchased at absolute quality and stored over molecular sieves. DIPEA and DBU were distilled from KOH. Triazolium salts were prepared according to reported protocols.¹ All reactions were carried out under an nitrogen atmosphere using oven-dried glassware.

¹ a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J.Org. Chem.* **2005**, *70*, 5725-5728. b) Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, 1292-1295.

General Procedures (representative reaction with phenylpropynal (6**) and ethanol)****General procedure A: Unsaturated Esters from Alkynals via Redox Esterification using DMAP/IMes·HCl**

To an oven-dried screw-capped, N₂-filled test tube was added IMes·HCl (6.8 mg, 0.020 mmol; 5 mol %), and suspended in 0.6 ml dry toluene. To this mixture was added sequentially aldehyde **6** (52 mg, 0.40 mmol; 1.0 equiv.) in 0.3 ml in dry toluene, ethanol (0.07 ml, 1.2 mmol, 3 equiv.) and finally DMAP (2.4 mg, 0.020 mmol; 5 mol %). After exchange of the septum with a screw cap, the sealed tube was stirred for 2 h at 60 °C.² The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford the unsaturated ester **7** as a slightly yellow oil (46 mg, 0.26 mmol; yield: 65%).

General procedure B: Unsaturated Esters from Alkynals via Redox Esterification using imidazole/IMes·HCl

To an oven-dried screw-capped, N₂-filled test tube was added IMes·HCl (6.8 mg, 0.020 mmol; 5 mol %), and suspended in 0.6 ml dry toluene. To this mixture was added sequentially aldehyde **6** (52 mg, 0.40 mmol; 1.0 equiv.) in 0.3 ml in dry toluene, ethanol (0.07 ml, 1.2 mmol, 3 equiv.) and finally imidazole (1.4 mg, 0.020 mmol; 5 mol %). After exchange of the septum with a screw cap, the sealed tube was stirred for 24 h at 110 °C. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford the unsaturated ester **7** as a clear oil (49 mg, 0.28 mmol; yield: 70%).

General procedure C: Unsaturated Esters from Alkynals via Redox Esterification using DIPEA/triazolium salt **5**

To an oven-dried screw-capped, N₂-filled test tube was added triazolium salt **5** (8.8 mg, 0.020 mmol; 5 mol %), and suspended in 0.6 ml dry THF. To this mixture was added sequentially aldehyde **6** (52 mg, 0.40 mmol; 1.0 equiv.) in 0.3 ml in dry THF, ethanol (0.07 ml, 1.2 mmol, 3 equiv.), 100 mg flame-dried Na₂SO₄ and finally DIPEA (6.6 μ l, 0.040 mmol; 10 mol %). After exchange of the septum with a screw cap, the sealed tube was stirred for 24 h at 60 °C. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford the unsaturated ester **7** as a yellow oil (44 mg, 0.25 mmol; yield: 63%).

² For a GC/MS of the crude reaction mixture see page S6 .

Experimental Data

Ethyl (*E*)-cinnamate³ (table 2/entry 1). following general procedure A:

yield 65%, slightly yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J = 15.9 Hz, 1H), 7.51-7.53 (m, 2H), 7.37-7.39 (m, 3H), 6.44 (d, J = 16.2 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.0, 144.6; 134.5, 130.2, 128.9, 128.1, 118.3, 60.5, 14.4; MS (CI) m/z (%) 194 (100) [M+NH₄]⁺, 178 (2), 177 (20) [M+H]⁺.

Methyl (*E*)-cinnamate⁴ (table 2/entry 2). following general procedure A:

yield 63%, colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, J = 15.9 Hz, 1H), 7.51-7.54 (m, 2H), 7.38-7.40 (m, 3H), 6.44 (d, J = 16.2 Hz, 1H), 3.81 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.4, 144.9; 134.3, 130.3, 128.9, 128.1, 117.8, 51.7; MS (CI) m/z (%) 180 (100) [M+NH₄]⁺, 164 (2), 163 (22) [M+H]⁺.

Benzyl (*E*)-cinnamate⁵ (table 2/entry 3). following general procedure A:

yield 55%, slightly yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, J = 15.9 Hz, 1H), 7.51-7.54 (m, 2H), 7.34-7.45 (m, 8H), 6.49 (d, J = 16.2 Hz, 1H), 5.26 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 166.8, 145.2; 136.1, 134.3, 130.4, 128.9, 128.6, 128.3, 128.3, 128.1, 117.9, 66.4; MS (EI) m/z (%) 238 (25) [M]⁺, 239 (3), 193 (49), 192 (87), 131 (85) [M-PhCH₂O]⁺, 103 (38), 91 (100), 77 (48), 65 (18).

isoPropyl (*E*)-cinnamate⁶ (table 2/entry 4). following general procedure C:

yield 38%, yellowish oil. ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J = 16.2 Hz, 1H), 7.51-7.54 (m, 2H), 7.37-7.40 (m, 3H), 6.42 (d, J = 15.9 Hz, 1H), 5.14 (sept, J = 6.3 Hz, 1H), 1.32 (d, J = 6.1 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5, 144.3; 134.5, 130.1, 128.8, 128.0, 118.8, 67.8, 21.9; MS (EI) m/z (%) 190 (40) [M]⁺, 175 (5), 147 (85), 131 (100), 103 (44), 91 (10), 77 (40).

Ethyl-3-naphthalen-2-yl-(*E*)-acrylate⁷ (table 2/entry 5). following general procedure A: yield 48%, slightly yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, J = 16.2 Hz, 1H), 7.79-7.88 (m, 4H),

³ Okamoto, K.; Akiyama, R.; Yoshida, H.; Yoshida, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 2125-2135.

⁴ Masllorens, J.; Moreno-Mañas, M.; Pia-Quintana, A.; Roglans, A. *Org. Lett.* **2003**, *5*, 1559-1562.

⁵ Crosignani, S.; White, P. D.; Steinauer, R.; Linclau, B. *Org. Lett.* **2003**, *5*, 853-856.

⁶ Shono, T.; Ishige, O.; Uyama, H.; Kashimura, S. *J. Org. Chem.* **1986**, *51*, 546-549.

⁷ Blakemore, P. R.; Ho, D. K. H.; Nap, W. M. *Org. Biomol. Chem.* **2005**, *3*, 1365-1368.

7.53-7.50 (m, 3H), 6.56 (d, J = 16.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.1, 144.6, 134.2, 133.3, 131.9, 129.9, 128.7, 128.5, 127.8, 127.2, 126.7, 123.5, 118.4, 60.5, 14.3; MS (EI) m/z (%) 226 (100) $[\text{M}]^+$, 198 (10), 181 (90), 153 (40), 152 (80), 76 (30).

Ethyl (E)-4-fluorocinnamate⁸ (table 2/entry 6). following general procedure A:

yield 46%, yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.65 (d, J = 15.9 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.07 (ps-t, J = 8.7 Hz, 2H), 6.36 (d, J = 16.2 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H);

^{13}C NMR (75 MHz, CDCl_3) δ 166.9, 163.8 (d, $^1J_{\text{CF}}$ = 250 Hz), 143.2, 130.7 (d, $^4J_{\text{CF}}$ = 3.7 Hz), 129.9 (d, $^3J_{\text{CF}}$ = 8.1 Hz), 118.0 (d, $^5J_{\text{CF}}$ = 2.2 Hz), 116.0 (d, $^2J_{\text{CF}}$ = 22.1 Hz), 60.5, 14.3; MS (EI) m/z (%) 194 (40) $[\text{M}]^+$, 166 (18), 149 (100), 121 (30), 101 (25).

Ethyl-3-thiophen-3-yl-(E)-acrylate⁹ (table 2/entry 7). following general procedure A:

yield 50%, yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, J = 15.9 Hz, 1H), 7.49 (dd, J = 3.0 Hz, J = 1.1 Hz, 1H), 7.34 (dd, J = 5.1 Hz, J = 3.1 Hz, 1H), 7.29 (dd, J = 5.2 Hz, J = 1.1 Hz, 1H), 6.26 (d, J = 15.9 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H);

^{13}C NMR (75 MHz, CDCl_3) δ 167.2, 138.0; 137.5, 128.0, 126.9, 125.1, 117.9, 60.4, 14.3; MS (EI) m/z (%) 182 (58) $[\text{M}]^+$, 153 (16), 137 (100), 110 (20), 109 (50), 65 (20).

Ethyl-3-benzo[1,3]dioxol-5-yl-(E)-acrylate¹⁰ (table 2/entry 8). following general procedure A: yield 60%, clear oil.

^1H NMR (300 MHz, CDCl_3) δ 7.59 (d, J = 15.9 Hz, 1H), 7.03-6.99 (m, 2H), 6.26 (d, J = 8.0 Hz, 1H), 6.26 (d, J = 15.9 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H);

^{13}C NMR (75 MHz, CDCl_3) δ 167.2, 149.5, 148.3, 144.3, 128.9, 124.4, 116.2, 108.5, 106.4, 101.5, 60.4, 14.3; MS (EI) m/z (%) 220 (100) $[\text{M}]^+$, 192 (15), 175 (75), 145 (50), 117 (25), 89 (30).

Ethyl-4,4-dimethyl-(E)-pent-2-enoate¹¹ (table 2/entry 9). following general procedure B: yield 90%, colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 6.97 (d, J = 15.9 Hz, 1H), 5.74 (d, J = 15.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.4, 159.1, 116.7, 60.2, 33.7, 28.7, 14.3; MS (CI) m/z (%) 191 (100) $[\text{M}+\text{NH}_4+\text{NH}_3]^+$, 174 (100) $[\text{M}+\text{NH}_4]^+$, 157 (17) $[\text{M}+\text{H}]^+$.

⁸ Masllorens, J.; Moreno-Manas, M.; Pia-Quintana, A.; Roglans, A. *Org. Lett.* **2003**, 5, 1559-1562.

⁹ Robinson, C. N.; Wiseman, L. J. J.; Slater, C. D. *Tetrahedron* **1989**, 45, 4103-4112.

¹⁰ Ranu, B. C.; Das, A.; Hajra, A. *Synthesis* **2003**, 1012-1014.

¹¹ Castalani, P.; Comasseto, J. V. *Tetrahedron* **2005**, 61, 2319-2326.

Ethyl-3-(4-acetyl-phenyl)-(E)-acrylate¹² (table 2/entry 10). following general procedure C: yield 66%, slightly yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 15.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 6.52 (d, J = 15.9 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.61, (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃)

δ 197.3, 166.5, 143.0, 138.8, 137.9, 133.0, 128.8, 128.3, 128.1, 118.3, 60.8, 26.7, 14.3; MS (CI) m/z (%) 238 (10), 236 (100) [M+NH₄]⁺, 219 (20) [M+H]⁺.

Ethyl (E)-4-nitrocinnamate⁸ (table 2/entry 11).following general procedure A: yield 41%, orange oil. ¹H NMR (300 MHz, CDCl₃) δ 8.25 (d, J = 8.8 Hz, 2H),

7.71 (d, J = 15.9 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 6.56 (d, J = 15.9 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); MS (CI) m/z (%) 239 (70)

[M+NH₄]⁺, 209 (35), 192 (100).

Ethyl-3-(4-formyl-phenyl)-(E)-acrylate¹³ (table 2/entry 12). following general procedure A: yield 18%, yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 10.0 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 16.2 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 6.52 (d, J = 15.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 191.5,

166.4, 142.8, 140.1, 137.1, 133.4, 130.2, 129.5, 128.5, 121.5, 60.8, 14.3; MS (CI) m/z (%) 224 (30), 222 (100) [M+NH₄]⁺, 205 (38) [M+H]⁺, 159 (10).

Sideproduct: (3,3-Diethoxy-prop-1-ynyl)-benzene¹⁴ (table 1/entry 12).

¹H NMR (300 MHz, CDCl₃) δ 7.47-7.50 (m, 2H), 7.30-7.34 (m, 3H), 5.50 (s, 1H), 3.78-3.88 (m, 2H), 3.61-3.71 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 131.9, 128.8, 128.2, 121.9, 91.8, 85.2, 84.3, 60.9, 15.1; MS (CI)

m/z (%) 221 (30) [M+NH₄]⁺, 159 (100) [M+H-C₂H₅OH]⁺, 130 (15).

¹² Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034-6035.

¹³ Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

¹⁴ Poncini, L. *J. Org. Chem.* **1984**, *49*, 2031-2032.

Exemplary GC/MS

Starting material phenylpropynal (**6**)

crude reaction mixture (**table 1/entry 8**)¹⁵

¹⁵ Peak at 12.49 min corresponds to side product 3,3-diethoxy-1-propynyl-benzene; peak at 18.12 min corresponds to (Z)-9-Octadecenamide (solvent impurity).

GC Yield Determination (internal standard)

Calibration

Data Path : C:\MSDCHEM\1\DATA\Zeitler\
 Data File : G0190_00.D
 Acq On : 21 Dec 2005 11:09
 Operator : R. Vasold
 Sample : Eichung
 Misc : K290 + KK265c + Tracer [0.25 + 0.25 + 0.50 mg]
 ALS Vial : 1 Sample Multiplier: 1

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	5.566	419	435	437	BV 2	49812	1738077	0.47%	0.191%
2	5.588	437	439	476	VB	48015	2944867	0.79%	0.324%
3	9.726	1152	1163	1179	BV	12139592	220996464	59.47%	24.335%
4	10.595	1310	1315	1326	VV 2	30468	532838	0.14%	0.059%
5	10.869	1356	1363	1370	BB	31042	394057	0.11%	0.043%
6	11.384	1422	1453	1481	BV	7506052	371599669	100.00%	40.915%
7	11.572	1481	1486	1496	VB	134762	1726167	0.46%	0.190%
8	11.950	1546	1552	1562	BV 2	44131	595676	0.16%	0.066%
9	12.075	1562	1574	1588	VV	16926972	301355055	81.10%	33.184%
10	12.207	1588	1597	1611	VB 5	27859	695349	0.19%	0.077%
11	12.492	1638	1647	1655	BB	514530	5564954	1.50%	0.613%

Reaction mixture

Data Path : C:\MSDCHEM\1\DATA\Zeitler\
 Data File : G0190_02.D
 Acq On : 21 Dec 2005 12:14
 Operator : R. Vasold
 Sample : K357 + Tracer
 Misc : K357 [0,5 mg/ml + 0.5 mg/ml Tracer]
 ALS Vial : 3 Sample Multiplier: 1

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	3.999	139	161	265	BV	1419897	230093486	59.35%	33.470%
2	9.703	1152	1159	1174	BB 2	42593	813533	0.21%	0.118%
3	11.372	1423	1451	1481	BV	7869336	387668850	100.00%	56.391%
4	11.944	1542	1551	1562	BV	106797	1324090	0.34%	0.193%
5	12.052	1562	1570	1588	FB	5278788	65547018	16.91%	9.535%
6	12.492	1638	1647	1654	BV	94679	1051417	0.27%	0.153%
7	17.653	2543	2550	2563	BV	29689	447603	0.12%	0.065%
8	18.322	2662	2667	2677	BV	36333	518088	0.13%	0.075%

NMR Experiment

Stacked Plot

NMR direct after DMAP addition (d^8 -toluene)

NMR after full conversion

^1H and ^{13}C NMR spectra of products