(Z)- α -Haloacrylates: An Exceptionally Stereoselective Preparation via Cr(II)-Mediated Olefination of Aldehydes with Trihaloacetates

Supporting Information

D. K. Barma,[†] Abhijit Kundu,[†] Hongming Zhang,[‡] Charles Mioskowski,^{*,#} and J. R. Falck^{*,†}

[†]Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390-9038, [‡]Department of Chemistry, Southern Methodist University, Dallas, TX 75275, [#]Université Louis Pasteur de Strasbourg, Faculté de Pharmacie, Laboratoire de Synthèse Bio-Organique 74, route du Rhin 67 401 Illkirch, France

General. All reactions were maintained under an argon atmosphere. Anhydrous solvents were freshly distilled from sodium benzophenone ketyl, except for CH₂Cl₂, toluene and HMPA, which were distilled from CaH₂ under an argon atmosphere. Extracts were dried over anhydrous Na₂SO₄ and filtered prior to evaporation on a rotary evaporator under reduced pressure. ¹H and ¹³C NMR spectra were recorded in CDCl₃, unless otherwise stated, and are reported on the δ scale using tetramethylsilane as internal reference. Isomer ratios were determined by integration of the ¹H NMR spectrum of crude isolates. Elemental analyses were performed at Southern Methodist University, Dallas, Texas.

Methyl 2-chloro-5-phenylpent-2(Z)-enoate (5). TLC (SiO₂): 15% EtOAc/hexane, R_f ~ 0.75; ¹H NMR (400 MHz) δ 2.64-2.72 (m, 2H), 2.80 (t, 2H, J = 7.6 Hz), 3.81 (s, 3H), 7.01 (t, 1H, J = 7.2 Hz), 7.18-7.26 (m, 3H), 7.28-7.34 (m, 2H); ¹³C NMR (75 MHz) δ 31.20, 33.83, 53.25, 125.23, 126.52, 128.49, 128.75, 140.65, 141.66, 163.11; MS *m/z* 224 (M⁺), 226 (M⁺+2). Anal. calcd for C₁₂H₁₃ClO₂: C, 64.15; H, 5.83; found: C, 64.26; H, 5.90.

Methyl 2-chloro-4-phenylpent-2(Z)-enoate (8). TLC (SiO₂): 15% EtOAc/hexane, R_f ~ 0.70; ¹H NMR (300 MHz) δ 1.44 (d, 3H, J = 6.6 Hz), 3.81 (s, 3H), 4.35-4.15 (m, 1H), 7.06 (d, 1H, J = 9.6 Hz), 7.20-7.36 (m, 5H); ¹³C NMR (75 MHz) δ 20.10, 39.75, 53.29, 123.24, 127.13, 127.26, 128.98, 142.92, 146.15, 163.28; HRMS (CI, CH₄) calcd for C₁₂H₁₄ClO₂ (M⁺+1) *m/z* 225.0682, found 225.0686.

Methyl 2-chloro-3-(2,2-dimethyl-[1,3]dioxolan-4(S)-yl)prop-2(Z)-enoate (10).¹ TLC (SiO₂): 15% EtOAc/hexane, R_f ~ 0.65; ¹H NMR (300 MHz) δ 1.41 (s, 3H), 1.46 (s, 3H), 3.71 (dd, 1H, J = 6.6, 8.1 Hz), 3.85 (s, 3H), 4.30 (dd, 1H, J = 6.6, 8.4 Hz), 5.02 (dd, 1H, J = 6.6, 13.5 Hz), 7.12 (d, 1H, J = 6.9 Hz); ¹³C NMR (75 MHz) δ 25.71, 26.60, 53.53, 68.40, 73.52, 110.44, 125.63, 140.81, 162.33; HRMS (CI, CH₄) calcd for C₉H₁₄ClO₄ (M⁺+1) *m/z* 221.0581, found 221.0576.

Methyl 2-chloro-3-phenylprop-2(Z)-enoate (12).² TLC (SiO₂): 15% EtOAc/hexane, R_f ~ 0.70; ¹H NMR (300 MHz) δ 3.89 (s, 3H), 7.36-7.48 (m, 3H), 7.80-7.86 (m, 2H), 7.91 (s, 1H); ¹³C NMR (75 MHz) δ 53.55, 121.91, 128.72, 130.44, 130.83, 133.03, 137.42, 164.11; MS *m/z* 196 (M⁺), 198 (M⁺+2).

Methyl 2-chloro-5-phenylpent-2(Z),4(E)-dienoate (14). TLC (SiO₂): 15% EtOAc/hexane, R_f ~ 0.72; mp 56-57°C; ¹H NMR (300 MHz) δ 3.86 (s, 3H), 7.00 (d, 1H, J = 15.9 Hz), 7.19 (dd, 1H, J = 10.8, 15.3 Hz), 7.30-7.40 (m, 3H), 7.46-7.54 (m, 2H), 7.62

(d, 1H, $J = 10.8$ Hz); ^{13}C NMR (75 MHz) δ 53.28, 122.35, 123.04, 127.73, 129.05, 129.74, 136.03, 138.23, 142.41, 163.67; HRMS (CI, CH_4) calcd for $\text{C}_{12}\text{H}_{12}\text{ClO}_2$ ($\text{M}^+ + 1$) m/z 223.0526, found 223.0530.

Methyl 2-chloro-3-(4-trifluoromethylphenyl)prop-2(Z)-enoate (16). TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.73$; mp 47-48°C; ^1H NMR (300 MHz) δ 3.93 (s, 3H), 7.68 (d, 2H, $J = 8.4$ Hz), 7.91 (d, 2H, $J = 8.4$ Hz), 7.93 (s, 1H); ^{13}C NMR (75 MHz) δ 54.22, 124.84, 126.01, 126.11, 131.27, 136.17, 136.87, 164.04; HRMS (CI, CH_4) calcd for $\text{C}_{11}\text{H}_9\text{ClF}_3\text{O}_2$ ($\text{M}^+ + 1$) m/z 265.0243, found 265.0243.

Methyl 2-chloro-3-(4-methoxyphenyl)prop-2(Z)-enoate (18).² TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.68$; ^1H NMR (300 MHz) δ 3.84 (s, 3H), 3.88 (s, 3H), 6.94 (d, 2H, $J = 8.7$ Hz), 7.85 (d, 2H, $J = 8.7$ Hz), 7.86 (s, 1H); ^{13}C NMR (75 MHz) δ 53.41, 55.53, 114.18, 119.30, 125.70, 132.91, 137.00, 161.34, 164.41; MS m/z 226 (M^+), 228 ($\text{M}^+ + 2$).

Methyl 2-bromo-3-(4-methoxyphenyl)prop-2(Z)-enoate (19). TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.69$; ^1H NMR (300 MHz) δ 3.84 (s, 3H), 3.88 (s, 3H), 6.94 (d, 2H, $J = 9.0$ Hz), 7.90 (d, 2H, $J = 9.0$ Hz), 8.17 (s, 1H); ^{13}C NMR (75 MHz) δ 53.41, 55.53, 114.18, 119.30, 125.70, 132.91, 137.00, 161.34, 164.41; HRMS (CI, CH_4) calcd for $\text{C}_{11}\text{H}_{12}\text{BrO}_3$ ($\text{M}^+ + 1$) m/z 270.9970, found 270.9966.

Methyl 2-chloro-3-(4-benzyloxy-3-methoxyphenyl)prop-2(Z)-enoate (22). TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.55$; mp 104-105°C; ^1H NMR (400 MHz) δ 3.89 (s, 3H), 3.93 (s, 3H), 5.21 (s, 2H), 6.91 (d, 1H, $J = 8.4$ Hz), 7.28-7.40 (m, 4H), 7.43 (d, 2H, $J = 7.2$ Hz), 7.57 (s, 1H), 7.84 (s, 1H); ^{13}C NMR (75 MHz) δ 53.46, 56.19, 70.92, 113.16, 113.73, 119.47, 125.42, 126.23, 127.37, 128.23, 128.84, 136.64, 137.15, 149.33, 150.23, 164.35; HRMS (CI, CH_4) calcd for $\text{C}_{18}\text{H}_{18}\text{ClO}_4$ ($\text{M}^+ + 1$) m/z 333.0894, found 333.0900.

Methyl 2-chloro-3-(3-bromophenyl)prop-2(Z)-enoate (24). TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.71$; mp 45-47°C; ^1H NMR (300 MHz) δ 3.91 (s, 3H), 7.30 (t, 1H, $J = 7.80$ Hz), 7.50-7.55 (m, 1H), 7.70-7.75 (m, 1H), 7.83 (s, 1H), 7.98 (t, 1H, $J = 1.8$ Hz); ^{13}C NMR (75 MHz) δ 53.70, 122.77, 123.40, 129.31, 130.21, 133.24, 133.30, 135.00, 135.76, 163.68. MS: m/z 274 (M^+), 276 ($\text{M}^+ + 2$); HRMS (CI, CH_4) calcd for $\text{C}_{10}\text{H}_9\text{BrClO}_2$ ($\text{M}^+ + 1$) m/z 274.9474, found 274.9476.

Methyl 2-chloro-3-(1,3-benzodioxol-5-yl)prop-2(Z)-enoate (26).³ TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.65$; mp 132-134°C; ^1H NMR (300 MHz) δ 3.89 (s, 3H), 6.03 (s, 2H), 6.86 (d, 1H, $J = 8.4$ Hz), 7.27 (dd, 1H, $J = 1.5, 7.2$ Hz), 7.59 (d, 1H, $J = 1.8$ Hz), 7.82 (s, 1H); MS m/z 240 (M^+), 242 ($\text{M}^+ + 2$).

Methyl 2-bromo-3-(1,3-benzodioxol-5-yl)prop-2(Z)-enoate (27).⁴ TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.48$; mp 107-108°C; ^1H NMR (300 MHz) δ 3.89 (s, 3H), 6.03 (s, 2H), 6.85 (d, 1H, $J = 8.1$ Hz), 7.28-7.32 (m, 1H), 7.65 (d, 1H, $J = 1.8$ Hz), 8.13 (s, 1H); ^{13}C NMR (75 MHz) δ 53.72, 101.87, 108.56, 109.67, 110.21, 127.28, 140.80, 147.89, 149.65, 164.26; MS m/z 284 (M^+), 288 ($\text{M}^+ + 2$).

Methyl 2-chloro-3-(4-dimethylaminophenyl)prop-2(Z)-enoate (29). TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.45$; mp 92-93°C; ^1H NMR (300 MHz) δ 3.04 (s, 6H), 3.87 (s, 3H), 6.68 (d, 2H, $J = 9.0$ Hz), 7.83 (s, 1H), 7.40 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR (75 MHz) δ 40.22, 53.29, 111.54, 116.14, 120.76, 133.11, 137.78, 151.70, 164.98; HRMS (CI, CH_4) calcd for $\text{C}_{12}\text{H}_{15}\text{ClNO}_2$ ($\text{M}^+ + 1$) m/z 240.0791, found 240.0794.

Methyl 2-chloro-3-(1-*H*-indol-2-yl)prop-2(Z)-enoate (31). TLC (SiO_2): 15% EtOAc/hexane, $R_f \sim 0.35$; mp 145-147°C; ^1H NMR (300 MHz) δ 3.92 (s, 3H), 7.20-7.36 (m, 2H), 7.44 (d, 1H, $J = 7.2$ Hz), 7.81 (d, 1H, $J = 7.5$ Hz), 8.31 (s, 1H), 8.32 (d, 1H, $J =$

4.2 Hz), 8.81 (bs, 1H); ^{13}C NMR (75 MHz) δ 53.30, 110.97, 111.79, 117.20, 118.60, 121.59, 123.67, 127.77, 128.76, 129.46, 135.43, 164.67; HRMS (CI, CH_4) calcd for $\text{C}_{12}\text{H}_{11}\text{ClNO}_2$ ($\text{M}^+ + 1$) m/z 236.0478, found 236.0481.

Methyl 2,2-dibromo-3-hydroxy-3-phenylpropanoate (33). TLC (SiO_2): 30% EtOAc/hexane, $R_f \sim 0.44$; mp 58–60°C; ^1H NMR (300 MHz) δ 3.45 (d, 1H, $J = 4.8$ Hz), 3.83 (s, 3H), 5.25 (d, 1H, $J = 4.8$ Hz), 7.27–7.32 (m, 3H), 7.49–7.53 (m, 2H); ^{13}C NMR (75 MHz) δ 54.97, 65.30, 78.92, 127.82, 129.30, 129.33, 136.28, 167.36; MS m/z 336 (M^+), 338 ($\text{M}^+ + 2$), 340 ($\text{M}^+ + 4$); HRMS (CI, CH_4) calcd for $\text{C}_{10}\text{H}_{11}\text{Br}_2\text{O}_3$ ($\text{M}^+ + 1$) m/z 336.9075, found 336.9077.

Methyl 2,2-dichloro-3-hydroxy-5-phenylpentanoate (34). TLC (SiO_2): 20% EtOAc/hexane, $R_f \sim 0.26$; mp 53–54°C; ^1H NMR (400 MHz) δ 1.91–2.01 (m, 1H), 2.16–2.24 (m, 1H), 2.66 (d, 1H, $J = 6.4$ Hz), 2.71–2.78 (m, 1H), 2.94–3.01 (m, 1H), 3.88 (s, 3H), 4.19–4.23 (m, 1H), 7.21–7.32 (m, 5H); ^{13}C NMR (75 MHz) δ 32.00, 32.76, 54.73, 76.68, 86.65, 126.37, 128.67, 128.72, 141.14, 166.56; MS m/z 276 (M^+), 278 ($\text{M}^+ + 2$), 230 ($\text{M}^+ + 4$); HRMS (CI, CH_4) calcd for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{O}_3$ ($\text{M}^+ + 1$) m/z 277.0398, found 277.0392.

Methyl 2,2-dichloro-3-hydroxy-5-phenylpent-4(E)-enoate (35). TLC (SiO_2): 20% EtOAc/hexane, $R_f \sim 0.27$; mp 45–47°C; ^1H NMR (400 MHz) δ 2.90 (d, 1H, $J = 6.6$ Hz), 3.92 (s, 3H), 4.96 (t, 1H, $J = 6.0$ Hz), 6.35 (dd, 1H, $J = 15.6, 6.3$ Hz), 6.82 (d, 1H, $J = 15.6$ Hz), 7.28–7.44 (m, 5H); ^{13}C NMR (75 MHz) δ 54.84, 78.31, 85.88, 123.24, 127.08, 128.70, 128.88, 135.96, 136.31, 166.27; MS m/z 274 (M^+), 276 ($\text{M}^+ + 2$), 278 ($\text{M}^+ + 4$); HRMS (CI, CH_4) calcd for $\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{O}_3$ ($\text{M}^+ + 1$) m/z 275.0242, found 275.0245.

Methyl 2,2-dichloro-3-(2,2-dimethyl-[1,3]dioxolan-4(R)-yl)-3-hydroxypropanoate (36: major isomer). TLC (SiO_2): 50% EtOAc/hexane, $R_f \sim 0.70$; mp 102–103°C; ^1H NMR (400 MHz) δ 1.30 (s, 3H), 1.35 (s, 3H), 3.09 (d, 1H, $J = 5.1$ Hz), 3.86 (s, 3H), 4.07–4.18 (m, 2H), 4.24–4.33 (m, 2H); ^{13}C NMR (75 MHz) δ 25.05, 26.25, 54.61, 66.80, 75.36, 78.00, 87.05, 110.14, 165.59; HRMS (CI, CH_4) calcd for $\text{C}_9\text{H}_{15}\text{Cl}_2\text{O}_5$ ($\text{M}^+ + 1$) m/z 273.0296, found 273.0297.

36 (minor isomer). TLC (SiO_2): 50% EtOAc/hexane, $R_f \sim 0.77$; mp 34–35°C; ^1H NMR (400 MHz) δ 1.39 (s, 3H), 1.42 (s, 3H), 3.42 (d, 1H, $J = 9.3$ Hz), 3.85–3.91 (m, 4H), 4.16–4.22 (m, 2H), 4.51–4.56 (m, 1H); ^{13}C NMR (75 MHz) δ 25.83, 26.17, 54.82, 68.07, 72.94, 76.18, 84.89, 110.71, 165.64; MS m/z 272 (M^+), 274 ($\text{M}^+ + 2$), 276 ($\text{M}^+ + 4$); HRMS (CI, CH_4) calcd for $\text{C}_9\text{H}_{15}\text{Cl}_2\text{O}_5$ ($\text{M}^+ + 1$) m/z 273.0296, found 273.0299.

References

- (1) Hayon, A. F.; Fehrentz, J. A.; Chapleur, Y.; Castro, B. *Bull. Soc. Chim. Fr.* **1983**, 207–210.
- (2) Kruper, W. J., Jr.; Emmons, A. H. *J. Org. Chem.* **1991**, 56, 3323–3329.
- (3) Dhoubhadel, S. P. *J. Indian Chem. Soc.* **1976**, 53, 951–952.
- (4) Sai, H.; Ogiku, T.; Nishitani, T.; Hiramatsu, H.; Horikawa, H.; Iwasaki, T. *Synthesis* **1995**, 582–586.
- (5) Timmler, H.; Wegler, R. *Chem. Ber.* **1967**, 10, 2362–2366.