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Titanium isopropoxide as efficient catalyst for the aza-Baylis-Hillman reaction. Selective formation of α-methylene-β-amino acid derivatives

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Supporting Information

Characterization data for the compounds in Table 2 (melting points are uncorrected).

Methyl α-methylene-β-[(p-toluenesulfonyl)amino]-3-(2-furanyl)propionate (3a). Mp 91-92 °C; 1H-NMR (400 MHz, CDCl3) δ 2.40 (s, 3H), 3.67 (s, 3H), 5.38 (d, J = 9.3 Hz, 1H), 5.65 (d, J = 9.3 Hz, 1H), 5.84 (s, 1H), 6.05 (dt, J = 3.3 and 0.9 Hz, 1H), 6.21 (dd, J = 3.3 and 1.8 Hz, 1H), 6.23 (s, 1H), 7.21 (dd, J = 1.8 and 0.9 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H); 13C-NMR (100 MHz, CDCl3) δ 21.73, 52.31, 53.82, 107.64, 110.77, 127.41, 128.59, 129.68, 137.07, 137.76, 142.50, 143.61, 151.41, 165.79; MS (MALDI-TOF) (m/z) 373.943 (MK⁺) 357.987 (MNa⁺). Anal. Calcd for C16H17NO5S: C, 57.30; H, 5.11; N, 4.18. Found: C, 56.97; H, 5.05; N, 4.07.

Methyl α-methylene-β-[(p-toluenesulfonyl)amino]-3-(2-pyridyl)propionate (3b). Work-up as reported for 1 followed by a short column on silica gel to separate the product from the alcohol adduct. Eluent pentane:ethyl acetate 2:1, Rf 0.25 Mp 85-86 °C; 1H-NMR (400 MHz, CDCl3) δ 2.36 (s, 3H), 3.64 (s, 3H), 5.38 (d, J = 8.0 Hz, 1H), 5.87 (s, 1H), 6.25 (s, 1H), 6.51 (d, J = 8.1 Hz, 1H), 7.11 (ddd, J = 7.5, 4.9 and 1.2 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 8.1 Hz, 1H), 7.54 (dt, J = 7.7 and 1.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 8.43 (ddd, J = 4.8, 1.8 and 1.0 Hz, 1H); 13C-NMR (100 MHz, CDCl3) δ 21.63, 52.12, 58.57, 122.20, 122.73, 127.38, 128.37, 129.56, 136.85, 137.59, 139.05, 143.39, 148.93, 157.09, 166.06; MS (MALDI-TOF) (m/z) 385.059 (MK⁺) 369.073 (MNa⁺) 347.090 (MH⁺). Anal. Calcd for C17H18N2O4S: C, 58.94; H, 5.24; N, 8.09. Found: C, 58.76; H, 5.24; N, 7.96.

Methyl α-methylene-β-[(p-toluenesulfonyl)amino]-3-(3-chlorophenyl)propionate (3c). Work-up as reported for 1 followed by a short column on silica gel to separate the product
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from the alcohol adduct. Eluent pentane:ethyl acetate 3:1, Rf 0.3 Mp 121-122 °C; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.41 (s, 3H), 3.62 (s, 3H), 5.27 (d, \(J = 9.2\) Hz, 1H), 5.75 (d, \(J = 9.2\) Hz, 1H), 5.81 (s, 1H), 6.23 (s, 1H), 7.04-7.10 (m, 1H), 7.15-7.20 (m, 2H), 7.20-7.25 (m, 2H), 7.66 (d, \(J = 8.4\) Hz, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.70, 52.31, 58.85, 124.79, 126.95, 127.35, 128.08, 128.60, 129.74, 129.99, 134.65, 137.64, 138.12, 140.86, 143.81, 165.73; MS (MALDI-TOF) (m/z) 418.011 (MK\(^+\)) 402.042 (MNa\(^+\)). Anal. Calcd for C\(_{18}\)H\(_{18}\)ClNO\(_4\)S: C, 56.91; H, 4.78; N, 3.69. Found: C, 56.76; H, 4.81; N, 3.72.

**Methyl α-methylene-β-[(p-toluenesulfonyl)amino]-3-(3-nitrophenyl)propionate** (3d).

Work-up as reported for 1 followed by a short column on silica gel to separate the product from the alcohol adduct. Eluent pentane:ethyl acetate 3:1, Rf 0.35 Mp 110-111 °C; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.40 (s, 3H), 3.63 (s, 3H), 5.38 (d, \(J = 9.4\) Hz, 1H), 5.87 (s, 1H), 6.05 (d, \(J = 9.4\) Hz, 2H), 7.23 (d, \(J = 8.5\) Hz, 2H), 7.44 (t, \(J = 8.1\) Hz, 1H), 7.61 (app. dquint, \(J = 7.7\) and 0.9 Hz, 1H), 7.66 (d, \(J = 8.4\) Hz, 2H), 7.94 (d, \(J = 2\) Hz, 1H), 8.06 (ddd, \(J = 8.1, 2.2\) and 1.1 Hz, 1H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.69, 52.49, 58.85, 121.70, 122.89, 127.29, 129.42, 129.74, 129.84, 132.84, 137.45, 137.63, 141.10, 144.05, 148.38, 165.54; MS (MALDI-TOF) (m/z) 429.112 (MK\(^+\)) 413.127 (MNa\(^+\)). Anal. Calcd for C\(_{18}\)H\(_{18}\)N\(_2\)O\(_6\)S: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.18; H, 4.77; N, 7.10.

**Methyl α-methylene-β-[(p-toluenesulfonyl)amino]-3-(4-nitrophenyl)propionate** (3e).

Mp 103-104 °C; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.41 (s, 3H), 3.62 (s, 3H), 5.37 (d, \(J = 9.5\) Hz, 1H), 5.82 (s, 1H), 5.97 (d, \(J = 9.6\) Hz, 1H), 6.24 (s, 1H), 7.25 (d, \(J = 8.6\) Hz, 2H), 7.40 (d, \(J = 9.0\) Hz, 2H), 7.67 (d, \(J = 8.4\) Hz, 2H), 8.09 (d, \(J = 8.9\) Hz, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.70, 52.47, 59.04, 123.86, 127.31, 127.61, 129.32, 129.82, 137.57, 137.70, 144.06, 146.16, 147.53, 165.54; MS (MALDI-TOF) 429.054 (MK\(^+\)) 413.082 (MNa\(^+\)).

**Methyl α-methylene-β-[(p-toluenesulfonyl)amino]-3-naphthylpropionate** (3f).

Mp 139-140 °C; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.34 (s, 3H), 3.58 (s, 3H), 5.48 (d, \(J = 8.8\) Hz, 1H), 5.81 (d, \(J = 8.9\) Hz, 1H), 5.90 (s, 1H), 6.27 (s, 1H), 7.16 (d, \(J = 8.6\) Hz, 2H), 7.23 (dd, \(J = 8.5\) and 1.9 Hz, 1H), 7.41-7.45 (m, 2H), 7.54 (d, \(J = 1.3\) Hz, 1H), 7.65-7.70 (m, 4H) 7.75 (dd, \(J = 6.0\) and 3.5 Hz, 1H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.65, 52.25, 59.31, 124.58, 125.73, 126.41, 126.44, 127.40, 127.71, 128.17, 128.23, 128.63, 129.65, 132.91, 133.23, 135.99,
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137.72, 138.69, 143.62, 165.98; MS (MALDI-TOF) (m/z) 434.045 (MK⁺) 418.093 (MNa⁺).
Anal. Calcd for C₂₂H₂₁NO₄S: C, 66.82; H, 5.35; N, 3.54. Found: C, 66.65; H, 5.41; N, 3.54.

Methyl α-methylene-β-[p-(toluenesulfonyl)amino]-3-(4-methoxyphenyl)propionate (3g).
Mp 117-118 °C; ¹H-NMR (400 MHz, CDCl₃) δ 2.42 (s, 3H), 3.61 (s, 3H), 3.75 (s, 3H), 5.25 (d, J = 8.6 Hz, 1H), 5.53 (d, J = 8.6 Hz, 1H), 5.83 (s, 1H), 6.21 (s, 1H), 6.75 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 21.74, 52.20, 55.45, 58.71, 114.14, 127.45, 127.68, 127.92, 129.70, 130.85, 137.73, 138.88, 143.58, 159.31, 166.06; MS (MALDI-TOF) (m/z) 414.051 (MK⁺) 398.070 (MNa⁺). Anal. Calcd for C₁₉H₂₁NO₅S: C, 60.78; H, 5.64; N, 3.73. Found: C, 60.90; H, 5.70; N, 3.92.

tert-Butyl α-methylene-β-[p-(toluenesulfonyl)amino]-3-phenylpropionate (3h).
¹H-NMR (400 MHz, CDCl₃) δ 1.29 (s, 9H), 2.40 (s, 3H), 5.26 (d, J = 9.1 Hz, 1H), 5.63 (d, J = 9.1 Hz, 1H), 5.66 (s, 1H), 6.1 (s, 1H), 7.13–7.25 (m, 7H), 7.68 (d, J = 8.4 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 21.69, 28.01, 59.39, 82.04, 126.59, 127.17, 127.40, 127.76, 128.64, 129.68, 138.03, 139.24, 140.12, 143.48, 167.77.

N-(2-cyano-1-phenyl-2-propenyl)-4-methyl-benzenesulfonamide (3i). Work-up as reported for 1 followed by a short column on silica gel to separate the product from the alcohol adduct. Eluent pentane:ethyl acetate 5:1, Rᵣ 0.2 ¹H-NMR (400 MHz, CDCl₃) δ 2.43 (s, 3H), 5.06 (d, J = 7.2 Hz, 1H), 5.11 (d, J = 7.2 Hz, 1H), 6.00 (d, J = 1.1 Hz, 1H), 6.06 (d, J = 1.3 Hz, 1H), 7.08-7.12 (m, 2H), 7.25-7.33 (m, 5H), 7.70 (d, J = 8.4 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 21.70, 59.89, 116.87, 123.56, 127.05, 127.40, 129.12, 129.32, 129.88, 131.98, 136.22, 136.95, 144.13.

N-(2-phenylsulfone-1-phenyl-2-propenyl)-4-methyl-benzenesulfonamide (3j). Work-up as reported for 1 followed by a short column on silica gel to separate the product from the by-product 4. Eluent pentane:ethyl acetate 3:1, Rᵣ 0.3 Mp 152-153 °C; ¹H-NMR (400 MHz, CDCl₃) δ 2.43 (s, 3H), 5.25 (d, J = 6.8 Hz, 1H), 5.40 (d, J = 6.8 Hz, 1H), 6.03 (t, J = 1.1 Hz, 1H), 6.49 (d, J = 1.0 Hz, 1H), 6.87 (d, J = 7.5 Hz, 2H), 7.02-7.14 (m, 3H), 7.25 (d, J = 8.5 Hz,

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1 Kündig, E. P.; Xu, L. H.; Schnell, B. Synlett 1994, 413.
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2H), 7.23-7.33 (m, 2H), 7.43-7.51 (m, 3H), 7.57 (d, J = 8.4 Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 21.79, 57.95, 127.26, 127.58, 128.18, 128.52, 128.80, 128.84, 129.08, 129.85, 133.48, 136.20, 136.90, 139.48, 143.98, 149.69; MS (MALDI-TOF) (m/z) 466.140 (MK$^+$) 450.146 (MNa$^+$).

**Methyl α-methylene-β-[(4-nitrobenzenesulfonyl)amino]-3-phenylpropionate (3k).** Compound precipitated during the acidic work-up. Recrystallized in diethyl ether. Pale yellow crystals; Mp 139-140 °C $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.64 (s, 3H), 5.41 (d, J = 9.2 Hz, 1H), 5.82 (s, 1H), 6.11 (d, J = 9.1 Hz, 1H), 6.23 (s, 1H), 7.12-7.25 (m, 5H), 7.93 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 52.46, 59.88, 124.27, 126.59, 128.30, 128.37, 128.55, 128.92, 137.98, 138.46, 146.73, 150.06, 165.93; MS (MALDI-TOF) (m/z) 414.846 (MK$^+$) 398.905 (MNa$^+$) 376.964 (MH$^+$). Anal. Calcd for C$_{17}$H$_{16}$N$_2$O$_6$S: C, 54.25; H, 4.28; N, 7.44. Found: C, 54.43; H, 4.29; N, 7.39.