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Novel Approach to the Synthesis of (R,S)-Baclofen via PD(II)-Bipyridine–Catalyzed Conjugative Addition

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Abstract: Synthesis of (R,S)-baclofen is described starting from N-phthalimidoacetaldehyde. The key step in the synthesis was Pd(II)-bipyridine–catalyzed conjugative addition of 4-chloroboronic acid.

Keywords: Allylphthalimide, baclofen, N-phthalimidoacetaldehyde, ozonolysis, Pd(II)-bipy

Baclofen is a promising drug for the treatment of the paroxysmal pain of trigeminal neuralgia as well as spasticity of the spine without influencing sedation.[1,2] In this communication, we report a novel route for the synthesis of racemic baclofen.[3]

RESULTS AND DISCUSSION

Our synthesis commenced with the preparation of N-allyl phthalimide[4] **(1)** by condensing commercially available phthalic anhydride with allyl amine in the presence of triethylamine with toluene as solvent and azeotropic removal of water. Ozonolysis of **1** at $-78^{\circ}C$ in CH_2Cl_2-MeOH for 30 min gave N-phthalimidoacetaldehyde[5] **(2)**, which subsequently was treated with $Ph_3P{=}CHCOOEt$ to give the α,β-unsaturated ester **(4)**. The 1,4-conjugative addition of **4** with 4-chlorophenylboronicacid (3 equiv.) was optimized in the presence of $Pd(OAc)_2$ to give **5** in 82% yield.

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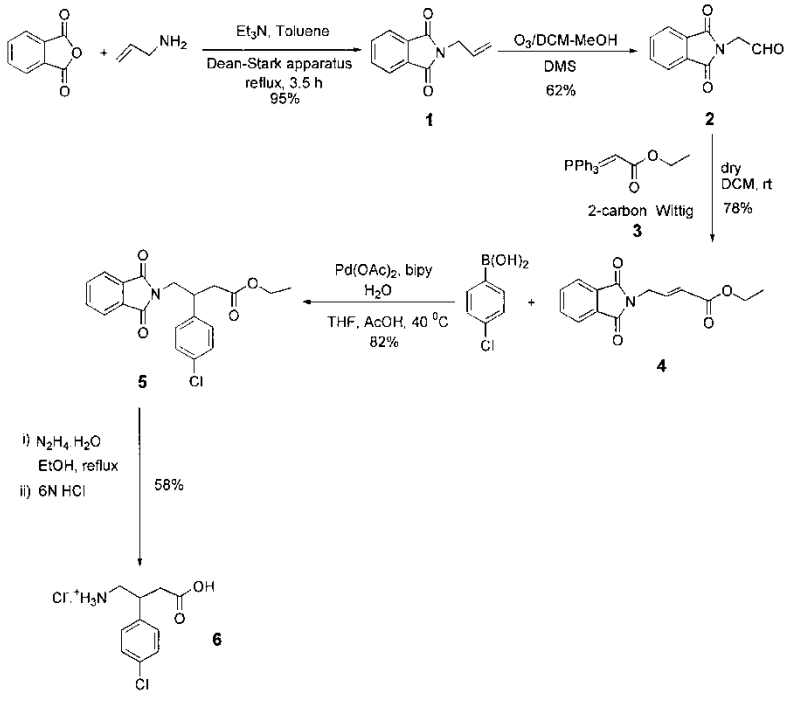
Among several bases utilized for the conjugate addition, the use of bipyridyl was by far the most efficient. The deprotection of **5** in 80% hydrazine hydrate in refluxing ethanol overnight, followed by acidification, gave the baclofen **(6)** in 22% overall yield. Baclofen **(6)** was also characterized by its HCl salt (Scheme 1).

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz, and 300 MHz, and chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Mass spectra were recorded in the form of m/z (intensity relative to base 100) on a VG 7070H micromass mass spectrometer at 200°C, 70 eV, with a trop current of 200 μA and 4 KV acceleration. Melting points have been recorded on an Electrothermal melting-point apparatus. IR spectra were recorded on a Perkin-Elmer 1620-F spectrophotometer. Analytical thin-layer chromatography (TLC) of all reactions was performed on Merck prepared plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100 ± 200 mesh). Reactions were routinely carried out under an atmosphere of nitrogen.



Scheme 1. Synthesis of (R,S)-baclofen.

N-Allylphthalimide (1)

Phthalic anhydride (7 g, 47.28 mmol), allyl amine (3.56 mL, 47.60 mmol), and triethyl amine (0.7 mL) in toluene (500 mL) were heated under reflux under a nitrogen atmosphere for 3.5 h with azeotropic removal of water. The solvent was removed under reduced pressure, diluted with ethyl acetate, washed with dil. HCl, dried over magnesium sulphate, and concentrated to give **1** (8.4 g, 95%); mp: 69–70°C (lit. mp: 68–70°C);[6] IR (KBr): 3022, 2921, 1773, 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.27 (d, 2H), 5.15–5.28 (dd, 2H), 5.67–5.89 (m, 1H), 7.70–7.81 (m, 2H), 7.82–7.88 (m, 2H); MS (EI): $m/z = 76$, 104, 130, 169, 187; ^{13}C NMR ($CDCl_3$): δ 40.0, 117.7, 123.3, 131.5, 132.1 134.0, 167.9; anal. calcd. for $C_{11}H_9NO_2$ (%): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.46; H, 5.00, N, 7.52.

N-Phthalimido Acetaldehyde (2)

Ozone gas was bubbled through a solution of N-allyl phthalimide (5 g, 26.73 mmol) and CH_2Cl_2/MeOH (9:1, 200 mL) at −78°C for 30 min until a blue color persisted. The mixture was purged with N_2 until the blue color disappeared at the same temperature. DMS (35 mL, 1.2 mol) was added, and the mixture was allowed to warm to room temperature and stirred for 16 h, at which point it was concentrated in vacuo. The residue was crystallized from DCM/hexane to give the desired compound **2** (3.13 g, 62%). Mp: 110–112°C (lit. mp: 111°C);[7] IR (KBr): 2931, 1777, 1716, 1613, 1466, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.56 (s, 2H), 7.71–7.80 (m, 2H), 7.82–7.91 (m, 2H), 9.63 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 47.36, 123.67, 131.12, 131.99, 134.35, 167.63, 193.0; MS (EI): $m/z = 50$, 63, 78, 104, 133, 160 (M-29), 161 (M-28); anal. calcd. for $C_{10}H_7NO_3$ (%): C, 63.49; H, 3.73; N, 7.40. Found: C, 63.54; H, 3.91; N, 7.32.

Ethyl-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)but-2-enote (4)

N-Phthalimido acetaldehyde (2.5 g, 13.23 mmol) **(2)** and $Ph_3P{=}CH\text{-}COOEt$ **(3)** (6.9 g, 19.84 mmol) in CH_2Cl_2 (60 mL) were stirred for 2.5 h at room temperature. The reaction mixture was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel by eluting with 1:3 of EtoAc/hexane to give **4** (2.67 g, 78%). Mp: 93–95°C (lit. mp: 94–96°C);[8] IR (KBr): 2923, 2361, 1773, 1714, 1389, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, $J = 6.1$ Hz, 3H), 4.05 (q, $J = 6.1$ Hz, 2H), 4.34 (d, $J = 5.5$ Hz, 2H), 5.77 (d, $J = 6.1$ Hz, 1H), 6.81 (m, 1H), 7.69–7.78 (m, 4H); MS (EI): $m/z = 58$, 76, 103, 142, 150, 186, 214, 259; ^{13}C NMR ($CDCl_3$): δ 13.9, 37.9, 60.2, 122.8, 123.2, 131.6, 134.0, 140.6, 165.2, 167.2; anal. calcd. for $C_{14}H_{13}NO_4$ (%): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.69; H, 5.13; N, 5.35.

Ethyl 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-(4-chlorophenyl) Butanoate (5)

4-chlorophenylboronic acid (3.6 g, 23.1 mmol), **4** (2 g, 7.7 mmol), $Pd(OAc)_2$ (86 mg, 0.385 mmol), bipyridine (0.24 g, 0.20 mmol), AcOH (7.5 mL), THF (4 mL), and H_2O (2.5 mL) under argon were heated at 40°C for 2 days.[9] The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel (EtOAc/petroleum ether, 1:20) to give **5** (2.35 g, 82%). Mp: 113–115°C (lit. mp: 114–116°C);[8] IR (KBr): 3433, 2968, 2925, 2852, 1773, 1708, 1397, 718, 672, 525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, $J = 7.1$ Hz, 3H), 2.69 (m, 2H), 3.79 (m, 1H), 3.91 (m, 4H), 7.23 (m, 4H), 7.70–7.76 (m, 4H); MS (FAB): $m/z = 76$, 103, 129, 157, 211, 298, 372 (M + 1); ^{13}C NMR ($CDCl_3$): δ 14.0, 38.5, 40.2, 42.9, 60.5, 123.3, 128.7, 129.1, 131.8, 133.0, 134.1, 138.9, 168.0, 171.1; anal. calcd. for $C_{20}H_{18}ClNO_4$ (%): C, 64.61; H, 4.88; N, 3.77. Found: C, 64.39; H, 4.87; N, 3.82.

4-Amino-3-(4-chlorophenyl)butyric Acid Hydrochloride (6) (Baclofen)

Compound **5** (2.0 g, 5.39 mmol), ethyl alcohol (75 mL), and 80% hydrazine hydrate (3 mL) were heated under reflux overnight. The mixture was left at room temperature for 10 h, and the solid was filtered and washed with ethanol (10 mL). To the filtrate, 6N Hcl (3.5 mL) was added and concentrated to half of its volume. The separated solid was filtered, and the filtrate was concentrated to furnish the desired compound **6** (0.74 g, 58%). Mp: 198–200°C (lit. mp: 195–197°C);[10] IR (KBr): 3000–2500, 1720, 1580, 1490, 1410, 1200, 1190, 1125, 1010, 950, 825 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.65–2.91 (AB part from ABX, $J_{AB} = 16.6$ Hz, $J_{AX} = 6.9$ Hz, $J_{BX} = 7.7$ Hz, 2H), 3.10–3.39 (AB part from ABX, $J_{AB} = 12.8$ Hz, $J_{AX} = 6.0$ Hz, $J_{BX} = 8.9$ Hz, 2H), 3.64–3.72 (m, 1H), 7.41–7.43 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.7, 48.5, 128.8, 128.9, 131.2, 141.8, 176.0; anal. calcd. for $C_{10}H_{12}ClNO_2$ (%): C, 56.21; H, 5.66; found: C, 56.15; H, 5.72; N, 6.54.

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