

Accessory Materials for:

Anchimeric Assistance in Hydrogen Atom Transfer to Bromine*

Anna K. Croft^{A,B} and Christopher J. Easton^{A,C}

^A Research School of Chemistry, Institute of Advanced Studies, The Australian National University,
Canberra, ACT 0200, Australia.

^B Current address: Department of Chemistry, University of Wales, Bangor, Gwynedd LL57 2UW, UK.

^C Author to whom correspondence should be addressed (e-mail: easton@rsc.anu.edu.au).

* Dedicated to Professor Lew Mander on the occasion of his 65th birthday.

Experimental

N-tert-Butyl-*O*-methyl-*N*^α-phthaloyltyrosinamide (**1h**)

To a solution of *O*-methyltyrosine^[1] (1.0 g, 5 mmol) in toluene (25 mL) was added triethylamine (0.5 g, 5 mmol) and freshly ground phthalic anhydride (0.8 g, 5 mmol). The mixture was heated at reflux for 3 h, then it was cooled and the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate, and the organic solution was washed with water, then it was dried and concentrated under reduced pressure, to give crude *N*-phthaloyl-*O*-methyltyrosine as a colourless powder (1.4 g, 87%); δ_{H} 3.49 (2H, d, *J* 8.4), 3.68 (3H, s), 5.13 (1H, t, *J* 8.4), 6.69 (2H, d, *J* 8.5), 7.05 (2H, d, *J* 8.5), 7.66 (2H, m) and 7.74 (2H, m). To a solution comprising a portion of the crude *N*-phthaloyl-*O*-methyltyrosine (0.41 g, 1.3 mmol) and triethylamine (0.13 g, 1.3 mmol) in dichloromethane (30 mL) was added ethyl chloroformate (0.14 g, 1.3 mmol). The mixture was stirred at room temperature for 10 min, then it was cooled to 0 °C. *tert*-Butylamine (92 mg, 1.3 mmol) was added, and that mixture was stirred at 0 °C for 15 min, before it was allowed to warm to room temperature and stirred for a further 30 min. The resultant suspension was filtered and the filtrate was washed with water, dried and concentrated under reduced pressure. Recrystallization of the residue from diethyl ether–dichloromethane–hexanes afforded the *title compound 1h* as a colourless powder (0.39 g, 81%) mp 138–143 °C (Found: C, 69.41; H, 6.33; N, 7.09. C₂₂H₂₄N₂O₄ requires C, 69.44; H, 6.36; N, 7.37%.); ν_{max} (cm⁻¹) 3311, 1775, 1755, 1716, 1658, 1610, 1552, 1513, 1302, 1252, 1222, 1174, 1118, 1088, 1036, 1014, 953, 873, 836 and 764; δ_{H} 1.31 (9H, s), 3.46 (2H, m), 3.70 (3H, s), 4.95 (1H, dd, *J* 6.8, 10.0), 5.89 (1H, br s), 6.73 (2H, d, *J* 8.5), 7.09 (2H, d, *J* 8.5), 7.70 (2H, m) and 7.79 (2H, m); *m/z* 380 (M⁺, 36%), 280 (49), 262 (21), 234 (40), 233 (100), 177 (43), 176 (69), 163 (31), 161 (67), 148 (15), 133 (36), 121 (83), 108 (59) and 104 (33).

N-tert-Butyl-*N*^α-phthaloyl-3,4-dimethoxyphenylalaninamide (**1j**)

The *title compound* was prepared from *N*-phthaloyl-3,4-dimethoxyphenylalanine,^[2] using the procedure described above for the synthesis of the amide **1h**. It was obtained as a colourless solid after recrystallization from dichloromethane–hexanes (0.58 g, 55%) mp 81–82 °C (Found: C, 64.61; H, 6.39; N, 6.28. C₂₃H₂₆N₂O₅·H₂O requires C, 64.46; H, 6.59; N, 6.54%.); ν_{max} (cm⁻¹) 3296, 1774, 1712, 1654, 1608, 1590, 1541, 1514, 1419, 1260, 1157, 1139, 1105, 1026, 964, 935, 885, 874, 795 and 766; δ_{H} 1.29 (9H, s), 3.44 (2H, m), 3.68 (3H, s), 3.74 (3H, s), 4.96 (1H, dd, *J* 6.7, 10.1), 5.99 (1H, s), 6.64 (1H, s),

6.68 (2H, s), 7.67 (2H, m) and 7.75 (2H, m); m/z 410 (M^+ , 41%), 310 (20), 264 (40), 263 (100), 206 (47), 191 (49), 151 (53), 138 (29) and 58 (31).

Procedure for the Reaction of 1g–j and 4a–j with N-Bromosuccinimide

In a typical experiment, a mixture of the substrate **1g–j** or **4a–j** (2.0 mmol) and *N*-bromosuccinimide (2.2 mmol) in carbon tetrachloride (50 mL) was heated at reflux for 3 h while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool before it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the crude product, which was recrystallised from the solvent specified below.

Physical and Spectral Characteristics of 3h, 3j, 4b, 4h, 4j, and 6a–j

β -Bromo-N-tert-butyl-O-methyl-N $^{\alpha}$ -phthaloyltyrosinamide (3h)

Colourless crystals of a 1:1 mixture of diastereomers from ethyl acetate–hexanes, mp 124–137 °C (Found: C, 57.64; H, 5.34; N 5.80. $C_{22}H_{23}BrN_2O_4$ requires C, 57.63; H, 5.06; N, 6.11%.); ν_{max} (cm^{-1}) 3346, 1775, 1718, 1682, 1606, 1513, 1300, 1251, 1227, 1176, 1112, 1077, 1032, 880, 835 and 794; δ_H 1.04 (9H, s), 1.38 (9H, s), 3.66 (3H, s), 3.81 (3H, s), 5.21 (1H, d, J 11.9), 5.30 (1H, d, J 11.5), 5.94 (1H, br s), 6.05 (1H, d, J 11.5), 6.15 (1H, d, J 11.9), 6.41 (1H, br s), 6.71 (2H, d, J 8.8), 6.92 (2H, d, J 8.7), 7.28 (2H, d, J 8.8), 7.52 (2H, d, J 8.7), 7.66 (4H, m), 7.77 (2H, m) and 7.91 (2H, m); m/z 460 (M^+ , ^{81}Br , 0.9%), 458 (M^+ , ^{79}Br , 0.9), 379 (27), 378 (94), 321 (100), 306 (53), 280 (87), 279 (74), 278 (88), 264 (26), 260 (21), 233 (33) and 104 (62).

β -Bromo-N-tert-butyl-N $^{\alpha}$ -phthaloyl-3,4-dimethoxyphenylalaninamide (3j)

Colourless crystals of a 1:1 mixture of diastereomers from ethyl acetate–hexanes, mp 69–75 °C (Found: m/z 490.0926. $C_{23}H_{25}^{81}BrN_2O_5$ requires m/z 490.0926. Found: m/z 488.0924. $C_{23}H_{25}^{79}BrN_2O_5$ requires m/z 488.0946.); ν_{max} (cm^{-1}) 3354, 1775, 1717, 1604, 1516, 1263, 1142, 1101, 1025 and 876; δ_H 1.04 (9H, s), 1.38 (9H, s), 3.48 (3H, s), 3.78 (3H, s), 3.87 (3H, s), 3.93 (3H, s), 5.21 (1H, d, J 11.9), 5.32 (1H, d, J 11.4), 5.89 (1H, s), 5.99 (1H, d, J 11.4), 6.15 (1H, d, J 11.9), 6.48 (1H, s), 6.63 (1H, d, J 8.1), 6.87 (3H, m), 7.08 (1H, d, J 2.0), 7.16 (1H, dd, J 2.0, 8.2), 7.69 (6H, m) and 7.90 (2H, m); m/z 490 (M^+ , ^{81}Br , 1.2%), 488 (M^+ , ^{79}Br , 1.3), 408 (80), 351 (77), 336 (43), 318 (43), 316 (100), 263 (31), 176 (34), 162 (63) and 104 (70).

2-Phenylethyl Pentafluorobenzoate (4b)

Colourless plates from ethyl acetate–hexanes, mp 59–60 °C (Found: C, 57.01; H, 2.90. C₁₅H₉F₅O₂ requires C, 56.95; H, 2.87%); ν_{\max} (cm⁻¹) 1736, 1654, 1524, 1329, 1232, 1216, 1105 and 975; δ_{H} 3.08 (2H, t, *J* 6.9), 4.60 (2H, t, *J* 6.9) and 7.29 (5H, m); *m/z* 195 (34%), 167 (18), 117 (13), 104 (100) and 91 (38).

N-(3-Phenylpropyl)pentafluorobenzamide (4h)

Colourless powder from ethyl acetate–hexanes, mp 76–77 °C (Found: C, 58.30; H, 3.56; N, 4.12. C₁₆H₁₂F₅NO requires C, 58.34; H, 3.68; N, 4.26%); ν_{\max} (cm⁻¹) 3297, 1655, 1556, 1519, 1121, 1055 and 990; δ_{H} 1.97 (2H, tt, *J* 7.0, 7.6), 2.73 (2H, t, *J* 7.6), 3.51 (2H, dt, *J* 6.0, 7.0), 5.87 (1H, br) and 7.26 (5H, m); *m/z* 330 (M+H⁺, 15%), 329 (M⁺, 43), 226 (22), 225 (100), 207 (18), 206 (77), 196 (20), 195 (93), 177 (36), 167 (42), 118 (50), 117 (59), 105 (28), 104 (23), 103 (20), 92 (21) and 91 (54).

N-(4-Phenylbutyl)pentafluorobenzamide (4j)

Colourless powder from ethyl acetate–hexanes, mp 90–90.5 °C (Found: C, 59.55; H, 3.90; N, 3.97. C₁₇H₁₄F₅NO requires C, 59.46; H, 4.11; N, 4.08%); ν_{\max} (cm⁻¹) 3239, 3065, 1678, 1647, 1570, 1516, 1504, 1339, 1271, 1116, 1066 and 992; δ_{H} 1.67 (4H, m), 2.67 (2H, t, *J* 7.2), 3.49 (2H, dt, *J* 6.4, 6.6), 5.90 (1H, br) and 7.24 (5H, m); *m/z* 343 (M⁺, 50%), 252 (33), 239 (20), 225 (37), 224 (20), 220 (30), 206 (28), 204 (21), 195 (100), 167 (30), 132 (39), 117 (32), 104 (35) and 91 (66).

2-Bromo-2-phenylethyl Benzoate (6a)

Colourless plates from ethyl acetate–hexanes, mp 33–35 °C (Found: C, 59.04; H, 4.43. C₁₅H₁₃BrO₂ requires C, 59.21; H, 4.31%); ν_{\max} (cm⁻¹) 3063, 3037, 1722, 1601, 1582, 1493, 1451, 1382, 1352, 1315, 1269, 1205, 1176, 1109, 1070, 1026, 967, 762 and 710; δ_{H} 4.76 (1H, dd, *J* 6.7, 11.8), 4.85 (1H, dd, *J* 7.6, 11.8), 5.29 (1H, dd, *J* 6.7, 7.6), 7.45 (8H, m) and 8.01 (2H, m); *m/z* 305 (M–H⁺, ⁸¹Br, 2%), 303 (M–H⁺, ⁷⁹Br, 2), 225 (39), 184 (17), 182 (17), 105 (100), 104 (32), 103 (32) and 77 (41).

2-Bromo-2-phenylethyl Pentafluorobenzoate (6b)

Pale yellow solid from hexanes, mp 64–65 °C (Found: C, 45.36; H, 1.88%. C₁₅H₈BrF₅O₂ requires C, 45.60; H, 2.04%); ν_{\max} (cm⁻¹) 1749, 1716, 1649, 1525, 1499, 1325, 1218, 1009 and 974; δ_{H} 4.81 (1H, dd, *J* 7.4, 11.9), 4.89 (1H, dd, *J* 7.4, 11.8), 5.21 (1H, t, *J* 7.4) and 7.39 (5H, m); *m/z* 395 (M–H⁺, ⁸¹Br, 0.8%),

393 (M-H⁺, ⁷⁹Br, 0.8), 315 (35), 195 (100), 184 (12), 182 (12), 169 (16), 168 (16), 104 (40), 103 (38) and 77 (16).

N-(2-Bromo-2-phenylethyl)acetamide (**6c**)

Pale yellow oil (Found *m/z* 243.0083. C₁₀H₁₂⁸¹BrNO requires *m/z* 243.0082. Found *m/z* 241.0099. C₁₀H₁₂⁷⁹BrNO requires *m/z* 241.0102); δ_H 1.99 (3H, s), 3.86 (2H, m), 5.09 (1H, dd, *J* 5.9, 8.7), 6.17 (1H, br) and 7.33 (5H, m); *m/z* 243 (M⁺, ⁸¹Br, 21%), 241 (M⁺, ⁷⁹Br, 27), 163 (65), 121 (50), 119 (91), 117 (92) 104 (100) and 91 (51).

N-(2-Bromo-2-phenylethyl)trifluoroacetamide (**6d**)

Colourless powder from ethyl acetate–hexanes, mp 87–88 °C (subl.) (Found: C, 40.39; H, 2.85; N, 4.45. C₁₀H₉BrF₃NO requires C, 40.68; H, 3.07; N 4.75%); ν_{max} (cm⁻¹) 3311, 2722, 1702, 1562, 1208, 1168, 1054, 954 and 764; δ_H 3.95 (2H, m), 5.08 (1H, dd, *J* 5.7, 8.8), 6.79 (1H, br) and 7.37 (5H, m); *m/z* 296 (M-H⁺, ⁸¹Br, 0.8%), 294 (M-H⁺, ⁷⁹Br, 0.8), 216 (100), 198 (16), 184 (36), 182 (36), 171 (47), 169 (45), 119 (21), 104 (35), 103 (56) and 77 (22).

N-(2-Bromo-2-phenylethyl)benzamide (**6e**)

Pale yellow oil; δ_H 4.02 (2H, m), 5.23 (1H, dd, *J* 5.6, 8.9), 6.22 (1H, br), 7.27 (8H, m) and 7.72 (2H, m). Attempted isolation of this material by chromatography on silica, eluting with ethyl acetate–hexanes, instead afforded 2,5-diphenyl-Δ²-1,3-oxazoline (**7**) as a colourless oil, with physical and spectral characteristics consistent with those reported.^[3]

N-(2-Bromo-2-phenylethyl)pentafluorobenzamide (**6f**)

Colourless needles from ethyl acetate–hexanes, mp 138–139 °C (Found: C, 45.90; H, 2.44; N, 3.85. C₁₅H₉BrF₅NO requires C, 45.80; H, 2.31; N, 3.56%); ν_{max} (cm⁻¹) 3289, 1664, 1559, 1526, 1342, 1264, 1201, 1128, 1056, 992 and 914; δ_H 3.88 (2H, m), 5.15 (1H, dd, *J* 6.5, 8.2), 5.92 (1H, br) and 7.34 (5H, m); *m/z* 395 (M⁺, ⁸¹Br, 0.5%), 394 (0.6), 393 (1), 392 (0.5), 391 (0.6), 315 (18), 314 (72), 313 (20), 224 (20), 207 (72), 195 (100), 184 (12), 182 (12), 167 (23) and 104 (20).

N-(3-Bromo-3-phenylpropyl)benzamide (**6g**)

Pale yellow oil (Found *m/z* 319.0399. C₁₆H₁₆⁸¹BrNO requires *m/z* 319.0394); δ_H 2.54 (2H, m), 3.62 (2H, m), 5.07 (1H, t, *J* 7.4), 6.53 (1H, br), 7.40 (8H, m) and 7.71 (2H, m); *m/z* 319 (M⁺, ⁸¹Br, 1.6%), 317

(M⁺, ⁷⁹Br, 1.6), 238 (32), 237 (42), 146 (30), 105 (100) 104 (66) and 77 (61).

N-(3-Bromo-3-phenylpropyl)pentafluorobenzamide (**6h**)

Colourless needles from carbon tetrachloride–hexanes, mp 112–113 °C (Found: C, 47.44; H, 2.55; N, 3.73. C₁₆H₁₁BrF₅NO requires C, 47.18; H 2.72; N, 3.44%); ν_{\max} (cm⁻¹) 3317, 1664, 1547, 1519, 1329, 1247, 1230, 1116, 1092, 1067, 1040, 984, 794, 762 and 694; δ_{H} 2.48 (2H, dt, *J* 6.9, 6.6), 3.53 (1H, m), 3.65 (1H, m), 5.02 (1H, t, *J* 6.9), 6.65 (1H, br) and 7.35 (5H, m); *m/z* 327 (35%), 236 (46), 195 (92), 167 (39), 118 (26), 117 (32), 116 (43), 115 (34), 105 (49), 104 (100), 103 (29), 78 (25) and 77 (34).

N-(4-Bromo-4-phenylbutyl)benzamide (**6i**)

Pale yellow oil; δ_{H} 1.74 (2H, m), 2.28 (2H, m), 3.47 (2H, m), 5.00 (1H, t, *J* 7.4), 6.41 (1H, br), 7.35 (8H, m) and 7.74 (2H, m). Attempted isolation of this material by chromatography on silica, eluting with ethyl acetate–hexanes, instead afforded 1-benzoyl-2-phenylpyrrolidine (**8**) as a pale yellow oil, with physical and spectral characteristics consistent with those reported.^[4]

N-(4-Bromo-4-phenylbutyl)pentafluorobenzamide (**6j**)

Yellow oil (Found *m/z* 423.0081. C₁₇H₁₃⁸¹BrF₅NO requires *m/z* 423.0099. Found *m/z* 421.0094. C₁₇H₁₃⁷⁹BrF₅NO requires *m/z* 421.0101.); δ_{H} 1.69 (2H, m), 2.24 (2H, m), 3.45 (2H, m), 4.98 (1H, dd, *J* 6.4, 8.4), 6.41 (1H, br) and 7.34 (5H, m); *m/z* 423 (M⁺, ⁸¹Br, 1.2%), 421 (M⁺, ⁷⁹Br, 1.3), 343 (30), 342 (63), 341 (33), 294 (16), 224 (23), 196 (21) 195 (100), 167 (36), 132 (23), 131 (58), 130 (53), 129 (30), 118 (20), 117 (42), 116 (21), 115 (33), 104 (36) and 91 (49).

Procedure for Determining the Relative Rates of Reaction of 1a–j and 4a–j with N-Bromosuccinimide

Mixtures of two of the substrates **1a–j** and **4a–j** (1 mmol each), *N*-bromosuccinimide (0.7 mmol) and *N*-*tert*-butylbenzamide (0.2 mmol) in carbon tetrachloride were heated at reflux while being irradiated with a 250 W mercury lamp. Aliquots were removed at intervals of 0.5 h, and they were cooled and filtered. The filtrates were analysed by ¹H NMR spectroscopy, using the *N*-*tert*-butylbenzamide as an inert internal standard, to determine the proportions of the remaining substrates **1a–j** and **4a–j** and the corresponding products **3a–j** and **6a–j**. For any two substrates X and Y, the ratio of the rates of reaction was measured by comparing the concentration of each substrate after reaction (*t* = 1) relative to the original (*t* = 0) concentration of that substrate according to the equation:

$$k_X/k_Y = \ln([X]_{t=1}/[X]_{t=0})/\ln([Y]_{t=1}/[Y]_{t=0})$$

Various mixtures of the substrates **1a–j** and **4a–j** were studied including **1b** and **1g**, **1b** and **1i**, **1g** and **1h**, **1i** and **1j**, **1h** and **1j**, **4a** and **4b**, **4c** and **4d**, **4e** and **4f**, **4g** and **4h**, **4i** and **4j**, **4a** and **4c**, **4b** and **4d**, **4c** and **4f**, **4e** and **4h**, and **4e** and **4j**.

References

- [1] N. Izumiya, A. Nagamatsu, *Bull. Chem. Soc. Jpn.* **1952**, *25*, 265–267.
- [2] W. J. Gensler, A. L. Bluhm, *J. Org. Chem.* **1956**, *21*, 336–339.
- [3] (a) L. N. Pridgen, L. B. Kilmer, R. L. Webb, *J. Org. Chem.* **1982**, *47*, 1985–1989. (b) O. Tsuge, S. Kanemasa, K. Matsuda, *J. Org. Chem.* **1986**, *51*, 1997–2004. (c) H. Stamm, R. Falkenstein, *Chem. Ber.* **1990**, *123*, 2227–2230. (d) H. Vorbrüggen, K. Krolikiewicz, *Tetrahedron* **1993**, *49*, 9353–9372.
- [4] T. Mizoguchi, *Chem. Pharm. Bull.* **1961**, *9*, 818–826.