Supporting Information

Increasing Rates and Scope of Reactions: Sluggish Amines in Microwave-Heated Aminocarbonylation Reactions under Air

Johan Wannberg and Mats Larhed*

Department of Organic Pharmaceutical Chemistry, Uppsala University, BMC, Box-574, SE-751 23 Uppsala, Sweden

mats@orgfarm.uu.se

S3-S7 Experimental Details

- S3   General Information
- S3   *N*-Benzoylpiperidine (**3a**)
- N*-phenyl-benzamide (**3b**)
- N*-((4-Methoxy)benzoyl)-piperidine (**3c**)
- S4   *N*-Benzyl-4-methoxy-benzamide (**3d**)
- 4-Methoxy-*N*-phenyl-benzamide (**3e**)
- N*-*tert*-Butyl-4-methoxy-benzamide (**3f**)
- N*-Benzyl-2-methyl-benzamide (**3g**)
- 2-Methyl-*N*-phenyl-benzamide (**3h**)
- N*-*tert*-Butyl-2-methyl-benzamide (**3i**)
- N*-Phenyl-4-trifluoromethyl-benzamide (**3l**)
- N*-*tert*-Butyl-4-trifluoromethyl-benzamide (**3m**)
- S5   Hippuric acid *tert*-butyl ester (**3n**)
- Hippuric acid (**3o**)
- S6   Bz-L-Leu-OH (**3p**)
- (DBU)₂Mo(CO)₄ (**6**)

S7-S8 References

Experimental Details

General The microwave reactions were performed in a SmithSynthesizer producing controlled irradiation at 2450 MHz with a power of 0-300 W. Reaction temperature and pressure were determined using the built-in on-line IR- and pressure sensors. ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz respectively. Chemical shifts are reported as values (ppm) and indirectly referenced to TMS via the residual solvent signal. GC-MS was performed with an instrument equipped with a mass selective detector (EI, 70 eV) and a HP-1 capillary column (25 m $\times$ 0.22 mm). The temperature gradient was 70-305 $^{\circ}\text{C}$. Flash column chromatography was performed on Silica gel 60 (0.040-0.063 mm). Precoated Silica gel F 254 plates and UV visualization were used for thin layer chromatography. The palladacycle **4** was made according to a literature procedure¹ and THF was freshly distilled over Na/benzophenone. All other chemicals were used as received.

All yields presented are isolated yields, >95 % pure (GC-MS or ^1H NMR).

N-Benzoylpiperidine (3a)² The title compound was obtained as a colorless oil in 81 % yield (61.4 mg) from **1a**.

N-Phenyl-benzamide (3b)³ The title compound was obtained as a white solid in 84 % yield (66.6 mg) from **1a**.

N-((4-Methoxy)benzoyl)-piperidine (3c)⁴ The title compound was obtained as a colorless oil in 88 % yield (77.3 mg) from **1b**.

***N*-Benzyl-4-methoxy-benzamide (3d)**³ The title compound was obtained as a white solid in 81 % yield (78.9 mg) from **1b** and in 92 % yield (88.9 mg) from **1c**.

4-Methoxy-*N*-phenyl-benzamide (3e)³ The title compound was obtained as a white solid in 87 % yield (79.5 mg) from **1b** and in 68 % yield (61.6 mg) from **1c**.

***N*-tert-Butyl-4-methoxy-benzamide (3f)**⁵ The title compound was obtained as a white solid in 44 % yield (36.2 mg) from **1c**.

***N*-Benzyl-2-methyl-benzamide (3g)**⁶ The title compound was obtained as a white solid in 83 % yield (75.0 mg) from **1d** and in 83 % yield (75.2 mg) from **1e**.

2-Methyl-*N*-phenyl-benzamide (3h)⁷ The title compound was obtained as a white solid in 84 % (70.9 mg, microwave heating) yield and 87 % (73.4 mg, conventional heating) yield from **1d** and in 85 % yield (71.7 mg) from **1e**.

***N*-tert-Butyl-2-methyl-benzamide (3i)**⁸ The title compound was obtained as a pale yellow solid in 53 % yield (40.8 mg) from **1d** and in 39 % yield (29.5 mg) from **1e**.

***N*-Phenyl-4-trifluoromethyl-benzamide (3l)**⁹ The title compound was obtained as a white solid in 86 % yield (91.5 mg) from **1f** and in 53 % yield (56.6 mg) from **1g**.

***N*-tert-Butyl-4-trifluoromethyl-benzamide (3m)** The title compound was obtained as a white solid in 35 % yield (34.7 mg) from **1g**. MS *m/z* (relative intensity, 70 eV) 245 (M^+ , 8),

230 (15), 190 (20), 173 (100), 145 (37); ^1H NMR (400 MHz, CDCl_3) 7.81 and 7.64 (AA'BB' system, 4H), 6.01 (br s, 1H), 1.47 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) 165.8, 139.3, 132.9 (q, $^2J_{\text{C-F}} = 33$ Hz), 127.3, 125.6 (q, $^3J_{\text{C-F}} = 4$ Hz), 125.2, 123.8 (q, $^1J_{\text{C-F}} = 273$ Hz), 52.1, 28.9 IR (neat, cm^{-1}) 3330 (NH), 1640 (C=O); Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{NO}$: C, 58.77; H, 5.75; N, 5.71. Found: C, 58.98; H, 5.83; N, 5.55.

Hippuric acid *tert*-butyl ester (3n)¹⁰ A 0.5-2.0 mL process vial was charged with iodobenzene (81.6 mg, 0.40 mmol), $\text{Pd}(\text{OAc})_2$ (9.0 mg, 0.040 mmol), $\text{Mo}(\text{CO})_6$ (0.106 g, 0.40 mmol), Glycine *tert*-butyl ester hydrochloride (201 mg, 1.2 mmol), DBU (0.36 mL, 2.4 mmol) and dry THF (1.0 mL). The vial was capped with a teflon septum under air and was irradiated with microwaves to 100 °C for 15 min. After cooling, the reaction mixture was filtered through a short celite pad and the solvent and excess DBU were removed under reduced pressure. The residue was purified by silica gel flash chromatography (1% MeOH in CHCl_3) to give the title compound as a white solid in 64 % yield (59.8 mg).

^1H NMR (400 MHz, CDCl_3) 7.77-7.83 (m, 2H), 7.38-7.52 (m, 3H), 6.70 (br s, 1H), 4.13 (d, $J = 4.8$ Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) 169.4, 167.4, 134.0, 131.8, 128.7, 127.1, 82.6, 42.6, 28.2; IR (neat, cm^{-1}) 3320, 1750, 1725.

Hippuric acid (3o)³ A 2.0-5.0 mL process vial was charged with iodobenzene (163 mg, 0.80 mmol), $\text{Pd}(\text{OAc})_2$ (18.0 mg, 0.080 mmol), $\text{Mo}(\text{CO})_6$ (211 mg, 0.80 mmol), glycine (180 mg, 2.4 mmol), DBU (0.72 mL, 4.8 mmol) and dry THF (2.0 mL). The vial was capped with a teflon septum and irradiated with microwaves to 100 °C for 15 minutes. After cooling, the reaction mixture was filtered through a short celite pad and the solvent and excess DBU were removed under reduced pressure. The residue was purified by preparative RP-LC-MS (on a 20×50 mm C8 column, using a 0-50% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient with 0.05 % HCOOH , using UV

(214, 254 nm) and MS (ESI) detection) to give the title compound as a white solid in 50 % yield (71.0 mg).

Bz-L-Leu-OH, 2-(S)-2-Benzoylamino-4-methyl-pentanoic acid (3p)¹¹ A 2.0-5.0 mL process vial was charged with iodobenzene (163 mg, 0.80 mmol), Pd(OAc)₂ (18.0 mg, 0.080 mmol), Mo(CO)₆ (211 mg, 0.80 mmol), L-leucine (315 mg, 2.4 mmol), DBU (0.72 mL, 4.8 mmol) and dry THF (2.0 mL). The vial was capped with a teflon septum and irradiated with microwaves to 100 °C for 15 minutes. After cooling, the reaction mixture was filtered through a short celite pad and the solvent and excess DBU were removed under reduced pressure. The residue was purified by preparative RP-LC-MS as above (**3o**) to give the title compound as a white solid in 46 % yield (85.7 mg).

[α]_D²³ –10.3 °, litt. [α]_D²⁰ –10.0±1° (c=1 in MeOH).

(DBU)₂Mo(CO)₄ (6) To a 2.0-5.0 mL process vial charged with Mo(CO)₆ (264 mg, 1.0 mmol) was added DBU (1.5 mL, 10 mmol). The vial was capped with a Teflon septum under air and the mixture was irradiated with microwaves to 100 °C until constant pressure was reached (~30 s). After cooling, the yellow mixture was poured into 50 mL isohexane and a yellow solid precipitated. The precipitate was filtered, washed with additional isohexane and dried at 50 °C under reduced pressure (remaining Mo(CO)₆ was thereby removed by sublimation). The resulting yellow powder (60 %, 311 mg) was subjected to analytical LC-MS, IR, ¹³C NMR, HRMS and combustion elemental analysis. The poor solubility and stability of the complex in common organic solvents prevented standard MS and NMR analysis. The results do however indicate that the complex is relatively pure in solid form with a molecular composition consistent with **6** and the CO-signals from IR are consistent with a *cis*-disubstituted octahedral metal-carbonyl complex (*cis*-L₂M(CO)₄).¹²⁻¹⁵ HRMS

produced an ion with the isotopic pattern of Mo and a mass consistent with a loss from **6** of one DBU fragment. Decomposition prohibited NMR analysis.

IR (neat, cm^{-1}) 1990, 1865, 1840, 1800 (CO), 1585 (C=N); Anal. Calcd for $\text{C}_{22}\text{H}_{32}\text{MoN}_4\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 50.67; H, 6.38; N, 10.74. Found: C, 50.4; H, 6.5; N, 10.9. HRMS (FAB+) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{MoN}_2\text{O}_4$ 362.0167, found (M-DBU)⁺ 362.0168, (M-DBU-CO)⁺ 334.

References for the Supporting Information Section

- (1) Herrmann, W. A.; Brossmer, C.; Reisinger, C. P.; Riermeier, T. H.; Ofele, K.; Beller, M. *Chemistry-a European Journal* **1997**, *3*, 1357-1364.
- (2) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523-528.
- (3) Kang, Y.-J.; Chung, H.-A.; Kim, J.-J.; Yoon, Y.-J. *Synthesis* **2002**, 733-738.
- (4) Howarth, N. M.; Malpass, J. R.; Smith, C. R. *Tetrahedron* **1998**, *54*, 10899-10914.
- (5) Paredes, R.; Bastos, H.; Montoya, R.; Chavez, A. L.; Dolbier, W. R.; Burkholder, C. R. *Tetrahedron* **1988**, *44*, 6821-6830.
- (6) Agwada, V. C. *J. Chem. Eng. Data* **1982**, *27*, 479-481.
- (7) Suezawa, H.; Hirota, M.; Yuzuri, T.; Hamada, Y.; Takeuchi, I.; Sugiura, M. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2335-2340.
- (8) Houlihan, W. J.; Cheon, S. H.; Parrino, V. A.; Handley, D. A.; Larson, D. A. *J. Med. Chem.* **1993**, *36*, 3098-3102.
- (9) Nongkunsarn, P.; Ramsden, C. A. *Tetrahedron* **1997**, *53*, 3805-3830.
- (10) Vollmar, A.; Dunn, M. S. *J. Org. Chem.* **1960**, *25*, 387-390.
- (11) Barton, D. H. R.; Ferreira, J. A. *Tetrahedron* **1996**, *52*, 9367-9386.

- (12) Orgel, L. E. *Inorg. Chem.* **1962**, *1*, 25-29.
- (13) Cotton, F. A.; Kraihanzel, C. S. *J. Am. Chem. Soc.* **1962**, *84*, 4432-4438.
- (14) Kraihanzel, C. S.; Cotton, F. A. *Inorg. Chem.* **1963**, *2*, 533-540.
- (15) Bodner, G. M. *Inorg. Chem.* **1975**, *14*, 2694-2699.