Supporting Information

Microwave-Enhanced Aminocarbonylations in Water

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EXPERIMENTAL SECTION	S2
Procedures	S2
Materials	S2
General procedure for aminocarbonylation in water	S3
Spectroscopic and analytical data for compounds 3p, 3s and 3z	S3
Appendix	S4
¹³C NMR and GC-MS chromatograms of compounds 3p, 3s and 3z	S4
¹³C NMR and GC-MS or LC chromatograms of compounds 3a-o, 3q,r, 3t-y and 4g	S11
REFERENCE:	S60

EXPERIMENTAL SECTION

Procedures

Analytical TLC was performed using Merck glass-backed 0.2 mm silica gel 60 F-254 plates. Visualization was done with UV light. NMR spectra were recorded for ^1H at 400 MHz, for ^{13}C NMR at 100 MHz at 25 °C. Chemical shifts for ^1H and ^{13}C were referenced to CHCl_3 and CDCl_3 for those samples with neat CDCl_3 as solvent, respectively. For those samples with CD_3OD as solvent chemical shifts were referenced to CD_2HOD (^1H) or CD_3OD (^{13}C). Low-resolution mass spectra were recorded in positive or negative ESI mode on a LC-MS instrument equipped with a reverse phase Chromolith SpeedROD RP-18e (4.6 x 50 mm) column eluted with 10:90 to 100:0 (0.05:99.5 $\text{HCOOH}:\text{CH}_3\text{CN}$):(0.05:99.5 $\text{HCOOH}:\text{H}_2\text{O}$). Alternatively, a GC-MS instrument equipped with a CP-Sil 8 CB capillary column (30 m x 0.25 mm, 0.25 μm) operating at an ionization energy of 70 eV was used. The oven temperature (GC) was 40-300 °C. Exact molecular masses were determined on a mass spectrometer equipped with an electrospray ion source. Microwave heated reactions were performed in a SmithSynthesizer from Biotage AB. Reaction temperatures were determined using the built-in, on-line IR-sensor. The specific temperature data for aqueous aminocarbonylation of aryl bromides was: 50 s ramp time (20-170 °C) and 550 s hold time at 170 °C.

Materials

All starting materials and reagents were commercially available and used as received. Herrmann's palladacycle, *trans*-di(μ -acetato)bis[*o*-tolylphosphino)benzyl]dipalladium (II), was purchased from Strem and $\text{Mo}(\text{CO})_6$ was obtained from Acros. Products **3a**¹, **3b**¹, **3f**¹, **3i**¹, **3j**¹, **3n**¹, **3c**², **3d**³, **3e**⁴, **3g**⁵, **3h**⁶, **3k**⁷, **3l**⁸, **3m**⁹, **3o**¹⁰, **3q**¹¹, **3r**¹², **3t**⁸, **3u**¹³, **3v**¹⁴, **3w**¹⁵, **3x**¹⁶, **3y**¹⁴ and **4g**¹⁷ have been previously reported and characterized. Compound **3p** is a new structure and compounds **3s** and **3z** are commercially available but without reported characterization

data. All known products gave satisfactory analytical and spectroscopic data corresponding to the reported literature values. Spectroscopic and analytical data are provided below for **3p**, **3s** and **3z**.

General procedure for aminocarbonylation in water

A 5 mL process vial was charged with **2** (1.0 mmol), Mo(CO)₆ (132 mg, 0.50 mmol), palladacycle (47 mg, 0.05 mmol), Na₂CO₃ (318 mg, 3.0 mmol), aryl bromide **1** (3.0 equiv) and water 2.0 mL. The vessel was exposed to microwave heating for 10 min at 170 °C. The reaction tube was thereafter cooled to room temperature and the mixture was extracted with ethyl acetate (6 mL × 3) and purified on silica gel (CH₂Cl₂, then EtOAc:Hexane) to give the corresponding amide **3**. Alternatively, after first being acidified with HCl aqueous solution to pH 2, the product mixture was extracted with EtOAc and purified on silica gel (EtOAc:Hexane) to give **4g**.

Spectroscopic and analytical data for compounds **3p**, **3s** and **3z**

Piperidin-1-yl-thiophen-3-methanone (**3p**)

According to the general procedure, compound **3p** was synthesized and purified on silica gel with CH₂Cl₂, then 35:65 EtOAc:Hexane, to give a colorless oil (148 mg, 76%). ¹H NMR (CDCl₃, 400 MHz): δ 1.30-1.70 (m, 6H), 3.40 (br s, 2H), 3.59 (br s, 2H), 7.10 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.24 (dd, *J* = 5.2, 3.2 Hz, 1H), 7.40 (dd, *J* = 3.2, 1.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 24.8, 25.9, 26.8, 43.5, 48.8, 125.9, 127.2, 137.1, 165.8; EI⁺-MS (*m/z*, relative intensity): 195 (M⁺, 45%); HRMS [M+H]⁺ Calcd for C₁₀H₁₄NOS: 196.0793. Found: 196.0796; Anal. Calcd for C₁₀H₁₃NOS: C, 61.5; H, 6.2; N, 7.2; Found: C, 61.2; H, 6.6; N, 7.2.

N-sec-Butyl-4-methyl-benzamide (**3s**)

According to the general procedure, compound **3s** was synthesized and purified on silica gel with CH₂Cl₂, then 30:70 EtOAc:Hexane, to give a white solid (142 mg, 74%). ¹H NMR (CDCl₃, 400 MHz): δ 0.90 (t, J = 7.6 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.45-1.58 (m, 2H), 2.33 (s, 3H), 4.05 (m, 1H), 6.30 (br s, 1H), 7.13 (apparent d, J = 8.0 Hz, 2H), 7.65 (apparent d, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 10.5, 20.5, 21.4, 29.7, 47.0, 126.9, 129.0, 132.2, 141.4, 166.9; EI⁺-MS (m/z , relative intensity): 191 (M⁺, 20%); HRMS [M+H]⁺ Calcd for C₁₂H₁₈NO: 192.1396. Found: 192.1388.

Azocan-1-yl-*p*-tolyl-methanone (**3z**)

According to the general procedure, compound **3z** was synthesized and purified on silica gel with CH₂Cl₂, then 30:70 EtOAc:Hexane to give a white solid (162 mg, 70%). ¹H NMR (CDCl₃, 400 MHz): δ 1.50-1.62 (m, 8H), 1.78-1.88 (m, 2H), 2.33 (s, 3H), 3.24-3.34 (m, 2H), 3.58 (t, J = 6.4 Hz, 2H), 7.15 (apparent d, J = 8.0 Hz, 2H), 7.23 (apparent d, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 21.3, 24.0, 25.5, 26.3, 26.5, 26.9, 46.6, 51.1, 126.3, 129.0, 134.8, 138.8, 171.5; EI⁺-MS (m/z , relative intensity): 231 (M⁺, 20%); HRMS [M+H]⁺ Calcd for C₁₅H₂₂NO: 232.1694. Found: 232.1701.

Appendix

¹³C NMR and GC-MS chromatograms of compounds **3p**, **3s** and **3z**

Piperidin-1-yl-thiophen-3-methanone (3p)

Chromatogram Plot

File: i:\wu_thiopiperidine 3-11-2005.sms

Sample: wu_ThioPiperidine

Scan Range: 1 - 1312 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 19:33

N-*sec*-Butyl-4-methyl-benzamide (3s)

Chromatogram Plot

File: h:\wu_2_aminobutyltolu.sms

Sample: wu_2_AminobutylToly

Scan Range: 1 - 1342 Time Range: 0.00 - 12.98 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 03/03/05 11:33

Azocan-1-yl-*p*-tolyl-methanone (3z)

Chromatogram Plot

File: i:\wu_octatoly 3-11-2005.sms

Sample: wu_OctaToly

Scan Range: 1 - 1308 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 19:52

**¹³C NMR and GC-MS or LC chromatograms of compounds 3a-o, 3q,r, 3t-y and
4g**

***N*-Butyl-4-methoxy-benzamide (3a)**

Chromatogram Plot

File: i:\wu_meophbutyl 3-11-2005.sms

Sample: wu_MeOPhButyl

Scan Range: 1 - 1310 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 20:50

***N*-Butyl-4-methyl-benzamide (3b)**

Chromatogram Plot

File: h:\wu_tolcarbobotyl_n.sms

Sample: wu_TolCarboButyl_n

Scan Range: 1 - 1348 Time Range: 0.00 - 12.99 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 01/19/05 18:47

***N*-Butyl-2-methyl-benzamide (3c)**

Chromatogram Plot

File: i:\wu_o-methylphbutyl 3-11-2005.sms

Sample: wu_o-MetylPhButyl

Scan Range: 1 - 1310 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 20:31

N-Butyl-benzamide (3d)

Chromatogram Plot

File: i:\wu_phbutyl 3-11-2005.sms

Sample: wu_PhButyl

Scan Range: 1 - 1309 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 20:12

***N*-Butyl-4-fluoro-benzamide (3e)**

Chromatogram Plot

File: i:\wu_fphbutyl 3-11-2005.sms

Sample: wu_FPhButyl

Scan Range: 1 - 1313 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 21:09

***N*-Butyl-4-trifluoromethyl-benzamide (3f)**

Chromatogram Plot

File: i:\wu_cf3phbutyl 3-11-2005.sms

Sample: wu_CF3PhButyl

Scan Range: 1 - 1311 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 21:29

Naphthalene-1-carboxylic acid butylamide (3g)

Chromatogram Plot

File: i:\wu_naphthabutyl 3-11-2005.sms

Sample: wu_NaphthaButyl

Scan Range: 1 - 1306 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 18:35

Thiophene-1-carboxylic acid butylamide (3h)

Chromatogram Plot

File: i:\wu_thiophenebutyl 3-14-2005.sms

Sample: wu_ThiopheneButyl

Scan Range: 1 - 1296 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/14/05 19:30

(4-Methoxy-phenyl)-piperidin-1-yl-methanone (3i)

Chromatogram Plot

File: i:\wu_meophipiperadine 3-9-2005.sms

Sample: wu_MeOPhPiperadine

Scan Range: 1 - 1306 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/09/05 13:32

(4-Methyl-phenyl)-piperidin-1-yl-methanone (3j)

Chromatogram Plot

File: i:\wu_tolypiperidine 3-11-2005.sms

Sample: wu_TolyPiperidine

Scan Range: 1 - 1312 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 19:14

(2-Methyl-phenyl)-piperidin-1-yl-methanone (3k)

Chromatogram Plot

File: i:\wu_o-mephipiperidine 3-11-2005.sms

Sample: wu_o-MePhPiperidine

Scan Range: 1 - 1307 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 18:54

Phenyl-piperidin-1-yl-methanone (3l)

Chromatogram Plot

File: h:\wu_phpiperidine.sms

Sample: wu_PhPiperidine

Scan Range: 1 - 1316 Time Range: 0.00 - 12.98 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 03/06/05 22:22

(4-Fluoro-phenyl)-piperidin-1-yl-methanone (3m)

Chromatogram Plot

File: i:\wu_fphpiperadine 3-9-2005.sms

Sample: wu_FPhPiperadine

Scan Range: 1 - 1308 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/09/05 12:54

(4-Trifluoromethyl-phenyl)-piperidin-1-yl-methanone (3n)

Chromatogram Plot

File: i:\wucf3phpiperidine 3-7-2005.sms

Sample: wuCF3PhPiperidine

Scan Range: 1 - 1304 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/07/05 20:25

Naphthalene-1-yl-piperidin-1-yl-methanone (3o)

Chromatogram Plot

File: i:\wu_naphthalenpipera 3-9-2005.sms

Sample: wu_NaphthalenPipera

Scan Range: 1 - 1308 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/09/05 13:13

***N*-Hexyl-4-methyl-benzamide (3q)**

Chromatogram Plot

File: h:\wu_hexyltolyltoly.sms

Sample: wu_HexylToly

Scan Range: 1 - 1337 Time Range: 0.00 - 12.99 min.

Sample Notes: today

Operator: Operator

Date: 03/03/05 15:51

***N*-Isobutyl-4-methyl-benzamide (3r)**

Chromatogram Plot

File: h:\wu_isobutyltolu001.sms

Sample: wu_IsobutylToly

Scan Range: 1 - 1312 Time Range: 0.00 - 12.98 min.

Sample Notes: today

Operator: Operator

Date: 03/03/05 10:27

***N*-tert-Butyl-4-methyl-benzamide (3t)**

Chromatogram Plot

File: h:\wu_tbutyltoly.sms

Sample: wu_tButylToly

Scan Range: 1 - 1340 Time Range: 0.00 - 12.99 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 03/01/05 11:31

***N*-Cyclohexyl-4-methyl-benzamide (3u)**

Chromatogram Plot

File: h:\wu_cyclohexyltolu.sms

Sample: wu_CyclohexylToly

Scan Range: 1 - 1338 Time Range: 0.00 - 12.99 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 03/03/05 11:11

***N*-Benzyl-4-methyl-benzamide (3v)**

Chromatogram Plot

File: h:\wu_benzyltoly.sms

Sample: wu_BenzylToly

Scan Range: 1 - 1338 Time Range: 0.00 - 12.99 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 03/03/05 15:29

***N,N*-Dibutyl-4-methyl-benzamide (3w)**

Chromatogram Plot

File: i:\wu_dinbutyltolyl 3-11-2005.sms

Sample: wu_dinButylToly

Scan Range: 1 - 1311 Time Range: 0.00 - 12.99 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 22:26

Pyrrolidin-1-yl-*p*-tolyl-methanone (3x)

Chromatogram Plot

File: i:\wu_tolypyrro 3-11-2005.sms

Sample: wu_TolyPyrro

Scan Range: 1 - 1313 Time Range: 0.00 - 12.98 min.

Sample Notes: Routine

Operator: Org Farm Kemi

Date: 03/11/05 18:16

Morpholin-4-yl-*p*-tolyl-methanone (3y)

Chromatogram Plot

File: h:\wu_mortoly.sms

Sample: wu_MorToly

Scan Range: 1 - 1325 Time Range: 0.00 - 12.99 min.

Sample Notes: ROUTINE

Operator: Operator

Date: 03/01/05 10:56

Naphthalene-1-carboxylic acid (4g)

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