The Clauson-Kaas pyrrole synthesis under microwave irradiation

Kelsey C. Miles, Sunshine M. Mays, Benjamin K. Southerland, Tyler J. Auvil, and Daniel M. Ketcha*

Department of Chemistry, Wright State University, Colonel Glenn Hwy, Dayton OH 45435, USA
E-mail: daniel.ketcha@wright.edu

Dedicated to the memory of Professor R.O. Hutchins

Abstract
The Clauson-Kaas pyrrole synthesis involving the reaction of primary amines with 2,5-dialkoxytetrahydrofurans is traditionally carried out in refluxing acetic acid (AcOH), whereas extension to less activated nitrogen nucleophiles often necessitates the use of acidic promoters. It is now reported that the preparation of N-substituted pyrroles can be effected under microwave conditions (10 min – 30 min) using acetic acid or water without additional catalysts.

Keywords: Clauson-Kaas, microwave-assisted, N-substituted pyrroles, green

Introduction

The reaction of primary amines with 2,5-dialkoxytetrahydrofurans in refluxing acetic acid (AcOH) to afford N-substituted pyrroles was first introduced by Clauson-Kaas in 1952.[1] The extension of this process to less nucleophilic nitrogen inputs such as amides[2,3] and sulfonamides[4] demonstrated the wide scope of this method, however longer reaction times were often required due to reduced reactivity. To overcome this impediment, a variety of acidic promoters such as phosphorus pentoxide,[5] thionyl chloride,[6] and 4-chloropyridinium hydrochloride[7] have been employed. Moreover, the successful application of microwave heating to the mechanistically related Paal-Knorr cyclizations of hexane-2,5-dione (neat,[9] in AcOH[10] or on MK10[11]) prompted examinations of the use of microwaves to expedite the Clauson-Kaas reaction.

Török[12] initially described the microwave assisted synthesis of pyrroles using montmorillonite K-10 under solvent-free conditions (2-6 min, 100 ^{o}C). However, while aromatic and primary aliphatic amines afforded practically quantitative yields of the expected pyrroles with no by-product formation, in the case of amides successive cyclocondensation processes were found to predominate affording the corresponding N-acylindoles and -carbazoles in addition to the desired pyrroles. These authors later reported that by lowering the reaction temperature to 80 ^{o}C

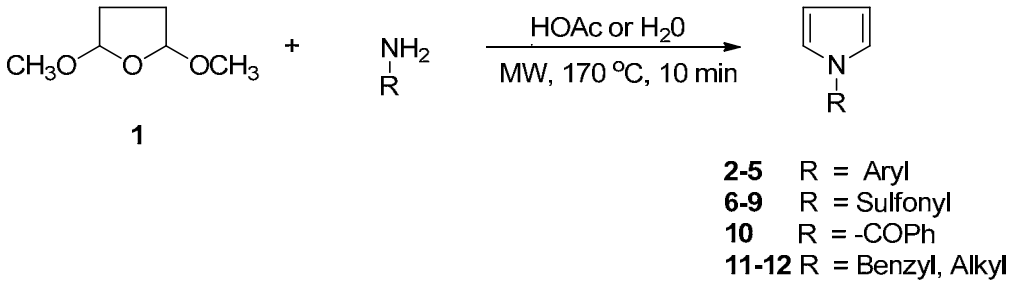
and employing 2 equiv of 2,5-dimethoxytetrahydrofuran (**1**), N-acylindoles could be obtained in high yields.[13] These same authors have found that in the case of primary sulfonamides using trifluoromethanesulfonic acid (triflic acid, TfOH),[14] selection of the appropriate sulfonamide / triflic acid ratio controls the nature of the heterocycle (pyrrole, indole, carbazole) produced via successive cyclization/annelation processes.

Most recently, a group from Wyeth reported an uncatalyzed microwave-assisted synthesis of pyrroles in water.[15] A variety of nitrogen inputs ranging from aromatic and heteroaromatic amines as well as sulfonamides afforded the corresponding pyrroles in excellent yields using the same microwave reaction conditions (150 °C, 30 min) using anywhere from 1.3 to 5.0 equivalents of 2,5-dimethoxytetrahydrofuran. Given the proclivity of sulfonamides to undergo successive annelations in the presence of excess tetrahydrofuran, this green variant of the Clauson-Kaas synthesis represents a substantial achievement, and prompts us to report on our own experiences in this arena.

Results and Discussion

We have, for some time now, been engaged in investigating the microwave-assisted Clauson-Kaas pyrrole synthesis.[16] Our initial attempts involved the use of bismuth(III) triflate in 1,2-dichloroethane as solvent at 170 ^{o}C.[16a] Although aryl amines underwent efficient condensation in the presence of 1 mol % of the metal triflate, benzylamine required 4 mol %. However, when benzamide or benzenesulfonamide were employed as substrates, we found that formation of indole and carbazole by-products were observed until we reduced the catalyst down to 1/12 mol %.

Given the capricious catalyst requirements in the case of bismuth triflate, we sought to simplify the process by employing AcOH [17] as both solvent and promoter.[16b] To that end, conducting the reaction of tetrahydrofuran **1** (1 – 1.3 equiv) with a variety of nitrogen derivatives in glacial acetic acid at 170 ^{o}C for 10 min led to the isolation of the appropriately N-substituted pyrroles **2-11** in good yields after simple filtration or column chromatography (Scheme 1). Because of this success with the relatively weak acid acetic acid, we considered that similar results might be obtained by simply employing water as the reaction medium.[16c] In the event, it was found that anilines (entries **2-5**) and sulfonamides **7-9** provided moderate to high yields of the corresponding pyrroles in high purity, albeit in lower yield than the analogous processes in AcOH (Table 1).



Scheme 1. Microwave-assisted pyrrole synthesis.

Whereas the N-arylpyrroles **2** and **3** were produced in comparable yields using either solvent system, in the case of *p*-nitroaniline reaction under standard conditions (170 °C / 10 min) in water resulted in the pyrrole **4** along with unreacted aniline. In order to drive this reaction to completion, the reaction time was extended to 30 min at which time starting material still remained. Unable to extract the *p*-nitroaniline from the pyrrole **4** using 10% hydrochloric acid, recrystallization from ethanol was employed to provide the purified sample in the reported isolated yield of 39%.

The relative reactivity of aniline versus sulfonamide as nucleophiles in this reaction is illustrated in the case of the dual functionalities present in sulfanilamide. When equal amounts of sulfanilamide and **1** were used, a pyrrole ring selectively formed on the aryl amino group yielding **5**.[18] When two equivalents of the tetrahydrofuran were employed, condensation occurred at both ends to produce the novel dipyrrole **9**.

Although benzamide was found to provide a good yield of the desired pyrrole **10** using AcOH, when the standard conditions (170 °C / 10 min) were employed using water no product was observed. Moreover, increasing the ratio of tetrahydrofuran to benzamide to 5:1 in water resulted in only 15% selectivity of the desired pyrrole along with the unreacted amide and a small amount of the corresponding indole (GC/MS). So as to minimize this successive annelation, the ratio was reduced to 1.3:1 whereupon conducting the reaction in water at 170 °C for 30 min led to a 12% isolated yield of the desired product **10** after column chromatography.

Extension to alkylamines in a water solvent system also proved difficult. In the case of benzylamine, the reaction in acetic acid resulted in a good yield of the pyrrole **11**; however, the reaction in water resulted in no pyrrole formation.

Finally, condensations of acid sensitive amino acids and esters with **1** are typically conducted by heating in acetic acid in the presence of sodium acetate and often afford products of poor quality due to decomposition processes.[19] To ameliorate this problem, Jefford[20] introduced the use of a two phase system involving aqueous acetic acid/dichloroethane for the case of amino acids and a water/dichloroethane system for amino ester hydrochlorides, wherein the acid-sensitive pyrrole products are removed from the aqueous layer upon formation. More recently,[21] an alternate protocol was formulated which involves an initial mild aqueous hydrolysis (2 h, reflux) of 2,5-dimethoxytetahydron **1** to the presumably more activated 2-5-

dihydroxytetrahydrofuran derivative. The solution is then cooled to room temperature whereupon dichloromethane is added followed by the amine and 1 equiv of acetic acid and sodium acetate to form a buffer ~ pH 5. In the case of amine hydrochlorides, it was found that no acetic acid was required and 2 equiv of sodium acetate can be employed as buffer. We now find condensation of 4-aminobutyrate hydrochloride with **1** can be effected in aqueous sodium acetate, thereby precluding the need for a two phase system and/or prior hydrolysis of the tetrahydrofuran. Due to the expected acid sensitivity of this representative model for amino ester hydrochlorides, the reaction was heated for 10 min at 120 °C rather than 170 °C to afford an 81% yield of the alkyl pyrrole **12**. In the absence of the acetate buffer, attempted condensation of the amine hydrochloride in water alone under these conditions led to extensive degradation.

Table 1. Compounds and yields

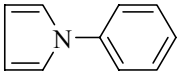
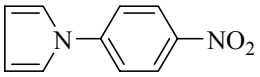
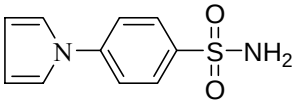
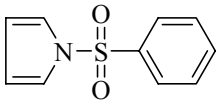
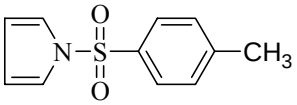
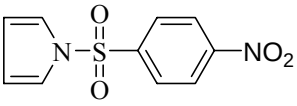
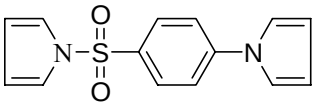
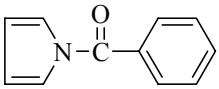
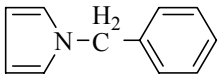
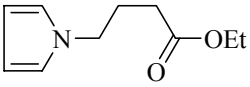
#	Compound	Solvent	Yield (%)
2		AcOH	70
		H_2O	63
3		AcOH	77
		H_2O	65
4		AcOH	92
		H_2O	39 [a]
5		AcOH	92
6		AcOH	96
		H_2O	70
7		AcOH	86
		H_2O	45
8		AcOH	79
		H_2O	74
		H_2O	12 [a]

Table 1. Continued

#	Compound	Solvent	Yield (%)
9		AcOH	59 [b]
10		AcOH	73
11		AcOH	86
12		1M NaOAc	81 [c]

All reaction were irradiated at 170 °C for 10 min and used 1:1 to 1.3:1 ratio of tetrahydrofuran to nitrogen input unless indicated otherwise.

[a] irradiated for 30 min.

[b] 2 equivalents of tetrahydrofuran used.

[c] irradiated at 120 °C.

Conclusions

An examination of the scope and limitations of the microwave-assisted Clauson-Kass pyrrole synthesis under green conditions[24] using either acetic acid or water in the absence of promoters has been detailed.[25] The reaction is successful for all common nitrogen inputs in the case of acetic acid, whereas benzamide and benzylamine are resistant to cyclocondensation under aqueous conditions. In the case of an amino acid ester hydrochloride, reaction to afford the pyrrole can be accomplished without the need for the biphasic conditions normally employed to effect such reactions.

Experimental Section

General. Melting points were determined via the use of open capillaries with an Electrothermal melting point apparatus and are reported uncorrected. Elemental analyses were performed by

Midwest Microlab, Indianapolis, IN. Elemental analysis results are within +0.4% of the theoretical values. The ^{1}H and ^{13}C NMR data were obtained on a Bruker Avance 300 MHz NMR in $CDCl_3$ solution unless otherwise indicated. Chemical shifts for proton NMR are reported in δ (ppm) downfield from tetramethylsilane as an internal standard and ^{13}C NMR shifts are calibrated on the $CDCl_3$ resonance at 77.23 ppm unless otherwise stated. Coupling constants (*J*) are in Hz. The following abbreviations are used to describe peak patterns where appropriate: s, singlet; d, doublet, dd, double doublet; t, triplet; q, quartet; dt, double triplet; m, multiplet. GC/MS measurements were performed using Hewlett-Packard 6890 Series GC with auto injection and mass fragments are reported a mass per charge, *m/z*. The GC was coupled with a mass spectrometer with Hewlett-Packard 5973 mass selective detector/quadrupole system. High resolution mass spectra (HRMS) were obtained at the University of Cincinnati Mass Spectrometry Facility was taken on a Thermo Scientific LTQ-FT consisting of a linear ion trap and FT-ICR (Fourier transform ion cyclotron resonance mass spectrometer). Flash column (Silica Gel, Premium Rf, 200-400 mesh, Sorbent Technologies) and thin layer chromatography (TLC) were performed on silica gel with indicated solvent systems. All microwave reactions were performed in a monomode Biotage Emery's Creator 300 Watt system with sample absorption set to "normal".

1-Phenyl-1*H*-pyrrole (2). To a 2-5 mL microwave vial charged with glacial acetic acid (4 mL) a magnetic stir bar was added aniline (182 μL, 2.00 mmol) and 2,5-dimethoxytetrahydrofuran **1** (258 μL, 2.00 mmol). The reaction vessel was sealed and heated under microwave irradiation for 10 min at 170 ^{o} C with a pre-stirring of 20 sec. After cooling, the reaction vessel was uncapped, the vial contents poured onto a beaker of ice (*ca* 25 mL) and the resulting light brown solid was collected by vacuum filtration and washed with cold water to yield pure **2**: (0.20 g, 70%); mp 56-58 ^{o}C (lit.[2] mp 61-62 ^{o}C); R_f 0.85 (DCM); GC/MS *m/z* 143 (M^+, 100%), 115, 77, 51; ^{1}H NMR δ: 7.38 (m, 4H), 7.22 (m, 1H), 7.08 (apparent t, *J* = 2.2 Hz, 2H), 6.34 (apparent t, *J* = 2.2 Hz, 2H); ^{13}C NMR δ: 140.8, 129.6, 125.6, 120.6, 119.4, 110.5.
Following the same procedure with deionized water (4 mL) instead of acetic acid yielded **2** (0.18 g, 63%).
1-(4-Methoxyphenyl)-1*H*-pyrrole (3). To a 2-5 mL microwave vial charged with glacial acetic acid (3 mL) a magnetic stir bar was added *p*-anisidine (0.185 g, 1.50 mmol) and 2,5-dimethoxytetrahydrofuran **1** (194 μL, 1.50 mmol). The reaction vessel was sealed and heated under microwave irradiation for 10 min at 170 ^{o} C with a pre-stirring of 20 sec. After cooling, the reaction vessel was uncapped, the vial contents poured onto a beaker of ice (*ca* 25 mL) and the resulting light brown solid was collected by vacuum filtration and washed with cold water to yield pure **3**: (0.20 g, 77%); mp 110–113 °C; lit.[2] mp 111–113 °C; R_f 0.67 (1:1 EtOAc:Hex); MS (*m/z*) 173 (M^+), 158 (100%), 130, 103, 77; ^{1}H NMR δ: 7.34 (d, *J* = 8.8 Hz, 2H), 7.04 (2H, m), 6.97 (d, *J* = 8.8 Hz, 2H), 6.25 (apparent t, *J* = 2.2 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR δ: 157.7, 134.6, 122.2, 119.7, 114.7, 109.9, 55.6.

Following the same procedure with deionized water (3 mL) instead of acetic acid yielded **3** (0.17 g, 65%) after recrystallization in MeOH/H_2O.

1-(4-Nitrophenyl)-1*H*-pyrrole (4). To a 2-5 mL microwave vial charged with glacial acetic acid (3 mL) a magnetic stir bar was added *p*-nitroaniline (0.207 g, 1.50 mmol) and 2,5-dimethoxytetrahydrofuran **1** (194 µL, 1.50 mmol). The reaction vessel was sealed and heated under microwave irradiation for 10 min at 170 ^{o} C with a pre-stirring of 20 sec. After cooling, the reaction vessel was uncapped, the vial contents poured onto a beaker of ice (*ca* 25 mL) and the resulting brownish yellow solid was collected by vacuum filtration and washed with cold water to yield pure **4**: (0.26 g, 92%); mp 181-185 °C; lit.[2] mp 180-181 °C; R_f 0.87 (1:1 EtOAc:Hex); MS (*m/z*) 188 (M^+, 100 %) 141, 115; ^{1}H NMR (Acetone-d_6) δ: 8.35 (dd, *J* = 8.8 Hz, 2.3 Hz, 2H), 7.85 (dd, *J* = 8.8, 2.3 Hz, 2H), 7.48 (dd, *J* = 4.4, 2.4 Hz, 2H), 6.40 (dd, *J* = 4.4, 2.4 Hz, 2H); ^{13}C NMR (Acetone-d_6) δ: 146.1, 145.5, 126.3, 120.1 (2C), 113.1.

The same procedure was used with an increase of reaction time to 30 min and with deionized water (4 mL) instead of acetic acid to afford **4** (0.11 g, 39%) after recrystallization from EtOH/H_2O.

(4-Pyrrol-1-ylphenyl)sulfonamide (5). To a 2-5 mL microwave vial charged with glacial acetic acid (4 mL) a magnetic stir bar was added sulfanilamide (0.344 g, 2.00 mmol) and 2,5-dimethoxytetrahydrofuran **1** (258 µL, 2.00 mmol). The reaction vessel was sealed and heated under microwave irradiation for 10 min at 170 ^{o} C with a pre-stirring of 20 sec. After cooling, the reaction vessel was uncapped, the vial contents poured onto a beaker of ice (*ca* 25 mL) and the resulting light brown solid was collected by vacuum filtration to yield pure **5**: (0.41 g, 92%); mp 247-250 °C; lit.[22] mp 246-247 °C; R_f 0.37 (1:1 EtOAc: Hex); GC/MS *m/z* 222 (M+, 100%), 142; ^{1}H NMR δ: 7.98 (dt, *J* = 8.8 Hz, 2.2 Hz, 2H), 7.74 (dt, *J* = 8.8 Hz, 2.2 Hz, 2H), 7.39 (apparent t, *J* = 2.3 Hz, 2H), 6.61 (s, 2H), 6.35 (apparent t, *J* = 2.3 Hz, 2H); ^{13}C NMR δ: 143.9, 141.6, 128.8, 120.2, 119.9, 112.3.

1-(Phenylsulfonyl)-1*H*-pyrrole (6). The procedure for pyrrole **2** was followed with benzenesulfonamide (0.340 g, 2.16 mmol), 2,5-dimethoxytetrahydrofuran **1** (266 µL, 2.06 mmol), and glacial acetic acid (4 mL) and a stir bar. The resulting light brown solid was vacuum filtered and yielded pure **6**: (0.41 g, 96%); mp 89-90 °C; lit.[4] mp 87-87 °C; R_f 0.50 (60% EtOAc: Hex); GC/MS *m/z* 207 (M+), 141, 77 (100%). Identical to a sample previously prepared in the laboratory by the sulfonylation of pyrrole by the method of Ottoni.[23]

The same procedure was used with an increase of reaction time to 30 min and with deionized water (4mL) instead of acetic acid. The crude mixture was purified by column chromatography on silica gel (60:40 EtOAc:Hex) to afford pure **6**: (0.30 g, 70%).

1-(*p*-Toluenesulfonyl)-1*H*-pyrrole (7). The procedure for pyrrole **2** was followed with toluenesulfonamide (0.323 g, 1.89 mmol), 2,5-dimethoxytetrahydrofuran **1** (266 µL, 2.06 mmol), and glacial acetic acid (4 mL) and a stir bar. The resulting light brown solid was vacuum filtered and yielded pure **7**: (0.36 g, 86%); mp 99-102 °C; lit.[4] mp 100-101 °C; R_f 0.64 (1:1 EtOAc: Hex); GC/MS *m/z* 221 (M+), 155, 91 (100%); ^{1}H NMR δ: 7.74 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* =

8.2 Hz, 2H), 7.15 (apparent t, *J* = 2.3 Hz, 2H), 6.26 (apparent t, *J* = 2.3 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR δ: 144.9, 136.2, 130.0, 126.8, 120.7, 113.5, 21.6.

Following the same procedure with deionized water (4 mL) instead of acetic acid and yielded pure **7**: (0.19 g, 45%).

1-(4-Nitrophenylsulfonyl)-1*H*-pyrrole (8). The procedure for pyrrole **2** was followed with 4-nitrobenzenesulfonamide (0.323 g, 1.60 mmol), 2,5-dimethoxytetrahydrofuran **1** (266 μL, 2.06 mmol), and glacial acetic acid (4 mL) and a stir bar. The resulting light brown solid was vacuum filtered and yielded pure **8**: (0.32 g, 79%); mp 137-139 °C; lit.[4] mp 135-136 °C; R_f 0.67 (1:1 EtOAc: Hex); GC/MS *m/z* 252 (M+, 100%), 186, 122; ^{1}H NMR δ : 8.34 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.17 (apparent t, *J* = 2.2 Hz, 2H), 6.36 (apparent t, *J* = 2.2 Hz, 2H); ^{13}C NMR δ: 150.6, 144.4, 128.1, 124.6, 121.0, 114.8.

Following the same procedure with deionized water (4 mL) instead of acetic acid and yielded pure **8**: (0.30 g, 74%).

(4-Pyrrol-1-ylphenyl)-1-phenylsulfonylpyrrole (9). The procedure for pyrrole **2** was followed with sulfanilamide (0.345 g, 2.00 mmol), 2,5-dimethoxytetrahydrofuran **1** (516 μL, 4.00 mmol), and glacial acetic acid (4 mL) and a stir bar. The resulting light brown solid was collected by vacuum filtration to afford **9** (0.32 g, 59%) with 92% selectivity determined by GC/MS. Recrystallization in MeOH afforded analytical sample (0.074 g); mp 152-154 °C; R_f 0.65 (1:1 EtOAc: Hex); GC/MS *m/z* 272 (M+), 142 (100%); ^{1}H NMR δ: 7.92 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.49 (dt, *J* = 8.8 Hz, 2.0 Hz, 2H), *7*.20 (apparent t, *J* = 2.2 Hz, 2H), 7.13 (apparent t, *J* = 2.2 Hz, 2H), 6.41 (apparent t, *J* = 2.2 Hz, 2H), 6.34 (apparent t, *J* = 2.2 Hz, 2H); ^{13}C NMR δ: 144.58, 135.12, 128.75, 120.77, 119.87, 118.97, 113.85, 112.30; Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.18; H, 4.64; N, 10.01. HRMS *m/z* calcd for $C_{14}H_{12}N_2O_2S$: 273.06922. Found: 273.06925.

Phenyl(1*H*-pyrrol-1-yl)methanone (10). To a 20 mL microwave vial was added benzamide (2.035 g, 16.80 mmol), 2,5-dimethoxytetrahydrofuran **1** (2.27 mL, 17.6 mmol), and glacial acetic acid (15 mL) with a stir bar. The vial was capped and subjected to microwave irradiation for 10 min at 170 °C. The vial was cooled with compressed air and decapped. The dark brown organic material was extracted from H_2O with DCM (3 x 50 mL), dried over Na_2SO_4, and concentrated via rotary evaporation. The crude mixture was purified by column chromatography on silica gel (70:30 Hex:DCM) to afford a yellow oil, **10**: (2.1 g, 73%); R_f 0.27 (70:30 Hex:DCM); GC/MS (*m/z*) 171 (M^+, 100 %) 105, 77; ^{1}H NMR δ: 7.66 (dt, *J* = 7.0 Hz, 1.4 Hz, 2H), 7.52 (tt, *J* = 7.4 Hz, 1.3 Hz 1H), 7.42 (tt, *J* = 7.4 Hz, 1.5 Hz, 2H), 7.20 (apparent t, *J* = 2.3 Hz, 2H), 6.26 (apparent t, *J* = 2.3 Hz, 2H); ^{13}C NMR δ: 167.70, 133.30, 132.25, 129.49, 121.30, 113.14.

The same procedure was used with benzamide (0.182 g, 1.50 mmol), 2,5-dimethoxytetrahydrofuran **1** (252 μL, 1.95 mmol), and an increase of reaction time to 30 min. The crude mixture was purified by column chromatography on silica gel (70:30 EtOAc:Hex) to afford pure **10**: (0.03 g, 12%).

1-Benzyl-1*H*-pyrrole (11). The procedure for compound **10** was followed but with benzylamine (1.850 g, 16.90 mmol), 2,5-dimethoxytetrahydrofuran **1** (2.00 mL, 15.5 mmol) by pipette, and

acetic acid (15 mL) to afford a colorless oil, **11**: (2.1 g, 86%); R_f 0.52 (70:30 Hex:DCM); GC/MS (*m/z*) 157 (M^+), 91(100%); ^{1}H NMR δ: 6.99 – 7.25 (m, 2H), 6.58 (t, *J* = 2.1 Hz, 2H), 6.10 (t, *J* = 2.1 Hz, 2H), 4.95 (s, 2H); ^{13}C NMR δ: 138.3, 128.8, 127.7, 127.1, 121.2, 108.6, 53.4.

Ethyl 4-(pyrrol-1-yl)butanoate (12). To a 2-5 mL microwave vial was added ethyl 4-aminobutyrate hydrochloride (0.255 g, 1.52 mmol), 2,5-dimethoxytetrahydrofuran **1** (194 μL, 1.50 mmol) by pipette, and 1M sodium acetate (3 mL) with a stir bar. The vial was capped and subjected to microwave irradiation for 10 min at 120 °C with a pre-stirring of 20 sec. The vial was cooled via compressed air and decapped. The aqueous layer was extracted with DCM and the combined organic layers were washed successively with 3M HCl (2 x 10 mL), and brine (1 x 10 mL). The product was dried over Na_2SO_4 and evaporated down under high power vacuum to afford a yellow oil, **12**: (0.22 g, 81%): R_f 0.20 (3:17 Hex: EtOAc); MS (*m/z*) 181 (M^+, 100 %) 136, 94; ^{1}H NMR δ: 6.54 (t, *J* = 2.1 Hz, 2H), 6.02 (t, *J* =2.1 Hz, 2H), 3.97 – 4.06 (m, 2H), 3.83 (t, *J* = 6.8 Hz, 2H), 2.15 (t, *J* = 7.1, 2H), 1.96 (quintet, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ: 172.8, 120.6, 108.2, 60.5, 48.5, 31.0, 26.8, 14.2.

Acknowledgements

National Science Foundation – Course, Curriculum, and Laboratory Improvement (CCLI) – Instructional Materials Development (DUE-0127240), Procter & Gamble Fund, Curriculum Development Grant for Rapid Transfer of Knowledge and Technology

References and Notes

1. (a) Clauson-Kaas, N.; Tyle, Z. *Acta Chem. Scand.* **1952**, *6*, 667. (b) Elming, N.; Clauson-Kaas, N. *Acta Chem. Scand*. **1952**, *6*, 867.
2. Gross, H. *Chem. Ber.* **1962**, *95*, 2270.
3. Menger, F. M.; Donohoe, J. A. *J. Am. Chem. Soc*. **1973**, *95*, 432.
4. Wasley, J. W. F.; Chan, K. *Synth. Commun*. **1973**, *3*, 303.
5. Fang, Y.; Leysen, D.; Ottenheijm, H. C. J. *Synth. Commun*. **1995**, *25*, 1857.
6. Ekkati, A. R.; Bates, D. K. *Synthesis* **2003**, 1959.
7. Cardinaud, I.; Gueiffier, A.; Debouzy, J. C.; Milhared, J.-C.; Chapat, J.-P. *Heterocycles* **1993**, *36*, 2513.
8. Zuo, B.; Chen, J.; Liu, M.; Ding, J.; Wu, H.; Su, W. *J. Chem. Res.* **2009**, 14.
9. Danks, T. N. *Tetrahedron Lett*. **1999**, *40*, 3957.
10. Werner, S.; Iyer, P. S. *Synlett* **2005**, 1405.
11. Abid, M.; Spaeth, A.; Török, B. *Adv. Synth. Catal*. **2006**, *348*, 2191.
12. Abid, M.; Landge, S. M.; Török, B. *Org. Prep. Proced. Int*. **2006**, *38*, 495.
13. Abid, M.; Paolis, O. D.; Török, B. *Synlett* **2008**, 410.

14. Abid, M.; Teixeira, L.; Török, B. *Tetrahedron Lett.* **2007**, *48*, 4047.
15. Wilson, M. A.; Filzen, G.; Welmaker S. G.; *Tetrahedron Lett.* **2009**, *50*, 4807.
16. (a) Ketcha, D. M.; Southerland, B. K.; Marketwala, N; Freeman, T. *233rd ACS National Meeting, Chicago, IL, March 25-29,* **2007**, ORGN-201. (b) Mays, S. M.; Southerland, B. K.; VanNess, B. G.; Ketcha, D. M. *235th ACS National Meeting, New Orleans, LA, April 6-10,* **2008**, CHED – 550.(c) Miles, K. C.; Ketcha, D. M. *237th ACS National Meeting, Salt Lake City, UT, March 22-26,* **2009**, CHED-797.
17. Lui, K.; Lu, H.; Hou, L.; Qi, Z.; Teixeira, C.; Barbault, F.; Fan, B.; Liu, S.; Jiang, S.; Xie, L. *J. Med. Chem.* **2008**, *51*, 7843.
18. Llobet, A.; Masllorens, E.; Rodriguez, M.; Roglans, A.; Benet-Bucholz, J. *Eur. J. Inorg. Chem*. **2004**, 1601.
19. Kashima, C.; Maruyama, T.; Harada, K.; Hibi, S.; Omote, Y. *J. Chem. Res. (S)* **1988**, 62.
20. Jefford, C. W.; de Villedon de Naide, F.; Sienkiewicz, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1069.
21. Gourlay, B. S.; Molesworth, P. P.; Ryan, J. H.; Smith, J. A. *Tetrahedron Lett*. **2006**, *47*, 799.
22. Mehltretter, C. L. *J. Am. Chem. Soc*. **1947**, *69*, 2133.
23. Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915.
24. For reviews on aqueous microwave chemistry, see: (a) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546. (b) Dallinger, D.; Kappe, C.O. *Chem. Rev*. **2007**, *107*, 2563. (c) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists*; VCH, Weinheim, 2008.
25. Note added in proof: in order to provide a comparison of the relative effectiveness of microwave irradiation over the corresponding thermal conditions, the reaction of entry **2** (AcOH) was repeated in an oil bath at 170 ^{o}C for 10 min using a sealed heavy wall pressure vessel (Chemglass, CG-1880-40). The resulting pyrrole was isolated yield after chromatography in 51% yield.