Microwave-accelerated synthesis of benzyl 3,5-dimethyl-pyrrole-2-carboxylate

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Abstract

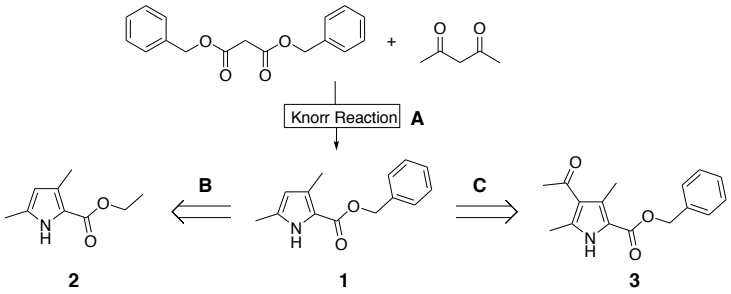
Benzyl 3,5-dimethyl-pyrrole-2-carboxylate, a very useful pyrrole in porphyrin and dipyrromethene synthesis, can be synthesized *via* the Knorr-type reaction, but in low yield. Alternative routes to benzyl 3,5-dimethyl-pyrrole-2-carboxylate have been developed involving the trans-esterification of ethyl 3,5-dimethyl-pyrrole-2-carboxylate and the de-acetylation of benzyl 4-acetyl-3,5-dimethyl-2-carboxylate, both precursors being easily obtained using the Knorr reaction. These traditional methods involve treatment of the known products with a strong basic solution or heating for extended periods which often leads to decomposition. The use of microwave energy to promote these two reactions proves to be an extremely efficient way to obtain benzyl 3,5-dimethyl-pyrrole-2-carboxylate quickly, in high yield, and in excellent purity with no need for recrystallization. Of particular note is the use of catalytic sodium methoxide in benzyl alcohol, rather than stoichiometric amounts of sodium benzoxide, to effect benzylation.

Introduction

The chemistry of substituted pyrroles is a challenging field that often relies on traditional reactions using harsh conditions, e.g. very high temperatures for extended periods of time, or highly acidic/caustic conditions. Many reactions for the synthesis (or functional group interconversion) of pyrroles were first introduced several decades ago, with little refinement having been reported since then. Benzyl 3,5-dimethyl-pyrrole-2-carboxylate **1** is a very useful precursor in the synthesis of functionalized pyrroles, dipyrromethenes and other multi-pyrrolic systems.[1-3] The β-free position allows for further substitution of the pyrrole. As well, porphyrins and dipyrromethenes made using this pyrrole can be substituted at this position. Pyrrole **1** can be synthesized *via* the Knorr-type

reaction[4] by reacting dibenzyl malonate with 2,4-pentanedione (Scheme 1) but the yields are typically low[5,6] (our group obtained 22 % of **1** on a 20 g, 0.07 mol scale of dibenzyl malonate).

Scheme 1 Synthetic (**A**) and retrosynthetic (**B** & **C**) pathways for **1**.



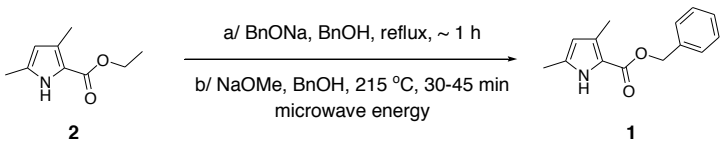
Alternative syntheses for benzyl 3,5-dimethyl-pyrrole-2-carboxylate **1** are also available, both involving transformations of other Knorr-type pyrroles: the trans-esterification of pyrrole **2** (Path **B**, Scheme 1) and the de-acetylation of benzyl 4-acetyl-3,5-dimethyl-pyrrole-2-carboxylate **3** (Path **C**, Scheme 1). Unlike for pyrrole **1**, the Knorr synthesis of ethyl 3,5-dimethyl-pyrrole-2-carboxylate **2**[7] and 4-acetyl-3,5-dimethyl-pyrrole-2-carboxylate **3**[8] gives good yields. Dibenzyl malonate, a precursor in the Knorr synthesis of **1** is around 70 times more expensive than diethyl malonate (a precursor in the Knorr synthesis of **2**) and around 10 times more expensive than benzyl acetoacetate (a precursor in the Knorr synthesis of **3**).

Although highly successful, both the trans-esterification and the de-acetylation routes involve harsh conditions and often produce colored crude products.[9,10] Recrystallization of the crude materials gives clean products, but we wished to avoid using the harsh conditions that render this step essential. Recent reports on the use of microwave energy for the trans-esterification of ethyl esters[11] and the synthesis of pyrroles (via palladium-assisted transfer hydrogenation followed by the Paal-Knorr reaction or by reacting diones with primary amines)[12-14] led us to attempt the trans-esterification and de-acetylation pathways for the synthesis of benzyl 3,5-dimethyl-pyrrole-2-carboxylate **1** using microwave energy in order to improve conditions, yields and the purity of the crude products.

Result and discussion

Trans-esterification In the traditional trans-esterification[9] of **2** (Path **B**, Scheme 1), the pyrrole is dissolved in benzyl alcohol at reflux (bp = 205 °C) and a solution of sodium benzoxide, prepared from sodium and benzyl alcohol, is slowly added thereby producing ethanol vapor which lowers the temperature of the reaction mixture (Scheme 2). When the production of ethanol ceases, the temperature returns to 205 °C, announcing the completion of the reaction.

Scheme 2 Trans-esterification of pyrrole **2**: a/ traditional method; b/microwave method.



In practice, these temperatures are often difficult to monitor, and so an excess of sodium benzoxide is often used. Crystallization from methanol/water gives pyrrole **1**, but due to the solubility of benzyl alcohol in water and the solubility of pyrrole **1** in benzyl alcohol, low isolated yields of the desired product are often obtained. If the pyrrole-2-carboxylate ester is left in refluxing benzyl alcohol for too long the yields are further reduced, presumably due to decomposition. It has been reported that, for many reactions, the use of microwave energy to obtain high reaction temperatures is an excellent alternative to conventional heating methods.[15] Our new methodology for the trans-esterification of **2** is modeled after the traditional method for trans-esterification of pyrrole-2-carboxylate esters[9] previously described and the trans-esterification of ethyl esters to benzyl esters using microwave energy in open systems, reported by Loupy *et al*.[11] Their procedure for the trans-esterification of methyl esters is essentially solvent-free, using two equivalents of the alcohol corresponding to the desired ester functionality, and varying the equivalents of acid or base catalysts.

Our method for the trans-esterification of **2** using microwave energy involves stirring pyrrole **2** in benzyl alcohol in the presence of catalytic sodium methoxide in a round bottom flask linked to a condenser in the microwave (MARS 5, CEM) open to air (under atmospheric pressure). CAUTION: All chemical reactions utilizing microwave energy should be performed in a commercial unit designed for that purpose and incorporating temperature and pressure monitoring facilities. For this trans-esterification, the microwave unit is programmed at 600 W to reach 215 °C but the reaction mixture never attains this temperature because of the constant condensation of ethanol in the reaction flask. After 30 minutes (on a 1 g, 0.006 mol scale reaction) to 45 minutes (on a 15 g, 0.090 mol scale reaction), crystallization of the product is performed by the addition of ethanol/water or methanol/water.

The results of the two methods are compared in Table 1 and the yields prove to be very similar. However the traditional method[16] afforded product **1** as a coloured compound which turned red-brown over time. The microwave method proved to be easier as there is no need to prepare sodium benzoxide, no slow addition procedure, no handling of sodium metal and the reaction does not need to reach high temperatures which can take up to several hours using a heating bath, depending on the scale. The work-up and purification methods are the same for both procedures.

Table 1 Comparison of traditional synthesis of **1** with synthesis using microwave energy.

Entry	**Scale (g)**[a]	**Microwave method yield**[b]	**Traditional method yield**[b]
1	1.0	70 %	75 %
2	15.0	68 %	69 %

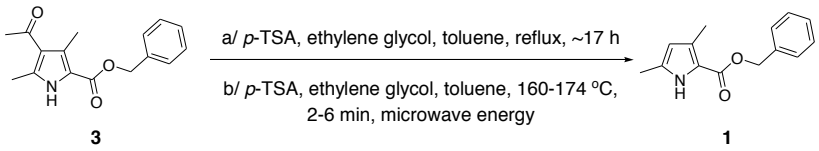
[a] amount of pyrrole **2**; [b] after crystallization.

To summarize, microwave-accelerated trans-esterification uses cheap easily prepared ethyl 3,5-dimethyl-pyrrole-2-carboxylate **2**, and is a quick, easy and clean method to produce pyrrole **1** in

good yields. The method does not require the preparation of sodium benzoxide and instead uses catalytic sodium methoxide which is commercially available as a powder.

De-acetylation The traditional manner to de-acetylate benzyl 4-acetyl-3,5-dimethyl-2-carboxylate **3** (Path **B**, Scheme 1) involves heating the pyrrole in a mixture of ethylene glycol and toluene with a catalytic amount of *para*-toluene sulfonic acid[10] (Scheme 3). The reaction is typically heated to reflux overnight (depending on the scale it can require several days) followed by a methanol/water recrystallization. Given our success with using microwave energy for the trans-esterification of **2** and the ready availability of pyrrole **3**, we decided to use microwave energy for the de-acetylation reaction, thus enabling us to perhaps perform the same reaction in a reduced time.

Scheme 3 De-acetylation of pyrrole **3**: a/ traditional method; b/ microwave method.



3 **1**

The initial de-acetylation of **3** using microwave energy was modeled after the literature methods for de-acetylation of the same pyrrole using traditional heating methods.[10] The reactions were performed in a sealed 100 mL, Quartz, QXP, vessel with different ratios of ethylene glycol and toluene (Table 2).

Table 2 Initial conditions and yields of the de-acetylation performed in the microwave.

Entry	Scale [a] (g)	Time	Temperature (°C)	Ratio [b]	Yield
1	0.8	2 x 1 min	160	1.2:1	80 %
2	1.0	6 min	160	1.2:1	78 %

3	4.9	6 min	174	1:0	0 %[c]
4	1.0	6 min	160	1:6	89 %
5[d]	1.0 g	17 h	140	1:6	79 %
6	15.0 g	6 min	160	1:5.5	84 %
7[d]	15.0 g	26 h	140	1:5.5	87 %

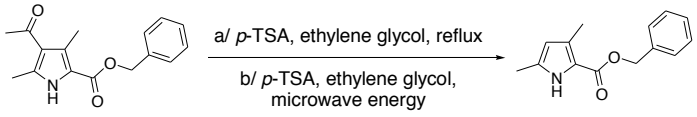
[a] amount of pyrrole **3** used, [b] ratio of volume of ethylene glycol:toluene, [c] due to polymerization; [d] traditional method.

It was shown that by increasing the reaction time (Entries 1 and 2, Table 2) the yields were not significantly enhanced. In the pressurized vessel, and under more concentrated conditions, exposure to high temperature (Entry 3) in the absence of toluene promoted polymerization and no benzyl 3,5-dimethyl-pyrrole-2-carboxylate **1** was recovered. However, changing the ratio of ethylene glycol and toluene from 1.2:1 to 1:6 (Entry 4) improved the yields. The traditional method[16] and the method that uses microwave energy were compared on different scales (1 g scale: Entry 4 and 5; and 15 g scale: Entry 6 and 7 Table 2) and even though the yields are very similar, the reaction time (traditional ~ 17-26 hours) was reduced to a few minutes by using microwave energy, with excellent isolated yields (Entry 4, 89 %).

Solvent-free de-acetylation. We had previously noticed that the exposure of benzyl 3,5-dimethyl-pyrrole-2-carboxylate **1** to high temperature when evaporating the toluene under reduced pressure over an extended period of time in a water bath (heating bath) lead to decomposition of the product. Consequently, the traditional method was performed without toluene (Scheme 4, **a**). The results of the solvent-free de-acetylation were successful: 15 min for 1 g scale (69 % yield), and 30 min for 10 g scale (75 % yield) and the product was easily crystallized upon cooling and addition of water. This idea led us to perform the reaction without toluene using microwave energy, with the power,

temperature and reaction time being varied (Table 3 and Scheme 4, **b**). This time the reaction was conducted using a round bottom flask and a condenser at atmospheric pressure. The reactions were monitored by TLC and the product was recrystallized using methanol/water.

Scheme 4 Solvent-free de-acetylation of pyrrole **3** to pyrrole **1**: a/ traditional method, b/ microwave method.



3 **1**

Table 3 Optimization of the solvent-free de-acetylation of **3** in the microwave.

Entry	Scale[a] (g)	Power (W)	Set temperature (°C)	Maximum temperature reached (°C)	Reaction time	Isolated Yield
1	1.0	600	100	>200	2 min	76 %
2	1.0	300	100	150	2 min	83 %
3	1.0	300	80	95	4 min	87 %
4	1.0	225	100	130	2 min	84 %
5	1.0	150	100	115	2 min	91 %
6	15.0	300	100	100	12 min	93 %
7	1.0	360	100	100	6 min	96 %
8	30.0	360	100	100	8 min	99 %
9	50.0	360	100	100	8 min	98 %

[a] amount of pyrrole **3** used.

Our initial attempt evidently utilized a higher power than necessary since, despite the set temperature of 100 °C, the temperature overshot to >200 °C. It was observed that exposure to such high temperature (Entry 1, Table 3) gives slightly lower yields than de-acetylation in toluene In order to avoid excess temperature jumps, it is recommended that the optimization process begins by using a low power, increasing it as necessary to achieve completion of the reaction. The power was

decreased (Entry 2) leading to increased yields. As the maximum temperature reached was still very high (150 °C) the set temperature was lowered to 80 °C (Entry 3). This change resulted in an increased reaction time of four minutes and so the temperature was fixed at 100 °C for the following experiments. The power was decreased to 225 W (Entry 4), which resulted in a slight increase of the yield compared to Entry 2. The power was finally set to 150 W (Entry 5), which led to a maximum temperature closer to 100 °C and our best yield recorded 91 % for the 1 g scale de-acetylation reaction. The reaction was also performed on scales of 30 g and 50 g (Entry 8 and 9, respectively, Table 3). The results were excellent with reaction times not exceeding eight minutes and yields close to 100 %. It was not necessary to further purify the crystals by recrystallization as high quality platelets are formed originally.

The color of the product was one of the reasons we tried to improve our methodology and by varying the power and temperature we observed that the lower the power, the longer the reaction time but the more white the crystals (e.g. Entry 1 gives grey crystals and Entry 6 gives white crystals).

Conclusion

We have improved the two major ways of obtaining benzyl 3,5-dimethyl-pyrrole-2-carboxylate **1** by using microwave energy: this results in a significant decrease in the reaction times and cleaner products are obtained, compared to conventional heating methods. The trans-esterification of pyrrole **2** and the de-acetylation of **3** use readily available reagents, and require no special equipment save the microwave unit itself. Either of these routes can produce a significant quantity of benzyl 3,5-dimethyl-pyrrole-2-carboxylate (**1**) quickly and cleanly. The mechanism(s) for the enhanced reactivity and product purity are under investigation.

Experimental

General method All reagents were used as supplied unless otherwise stated. Dichloromethane was distilled prior to use. Pyrroles **2** and **3** were prepared and purified according to literature procedure.[7,8] The results obtained following the traditional methods were performed using the Macdonald and Lide method for the trans-esterification[9] and the Smith method for the de-acetylation.[10] Thin layer chromatography was performed with ultra pure silica gel pre-coated aluminum plates (0.25 mm thick) with a 3:7 ethyl acetate: hexanes solution as eluent with visualization by UV light (254 nm) and stain (vanillin). ^{1}H and ^{13}C NMR, the chemical shifts are reported in part per million (ppm) and *J* values are quoted in Hertz. Melting points were determined using a Fisher-Johns melting point apparatus. **General microwave information** All the microwave reactions were conducted in a CEM brand MARS 5® industrial microwave. Microwave reactions for the trans-esterification and the optimized de-acetylation were performed in an open glass round bottom flask connected to a condenser and equipped with a RTP-300 Plus temperature probe. Microwave reactions for the initial de-acetylation were performed in a 100 mL, QXP, quartz-lined vessel sealed with a bolt, perpendicular to the cap, tightened to a torque of 50 Nm. It was equipped with a RTP-300 Plus temperature probe and an ESP-1500 Plus pressure probe. CAUTION: All chemical reactions utilizing microwave energy should be performed in a commercial unit designed for that purpose and incorporating temperature and pressure monitoring facilities.

Benzyl 3,5-dimethyl-pyrrole-2-carboxylate 1 *via* trans-esterification of ethyl 3,5-dimethyl-pyrrole-2-carboxylate 2 (Entry 1, Table 1) Sodium methoxide (0.48 g, 8.97 mmol) was added to a solution of pyrrole **2** (1 g, 5.98 mmol) in benzyl alcohol (7.5 mL, 71.8 mmol) and the flask was equipped with a stirrer bar, a condenser and the temperature probe. The reaction mixture was exposed to 600 W for 30 minutes reaching a final temperature of 200 °C (set temperature of the program: 215 °C), allowed to cool for about 10 minutes and water added to dissolve the excess sodium methoxide. The aqueous phase was extracted with DCM (3 x 30 mL) and the combined extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and

concentrated under reduced pressure. Methanol was added (15 mL), followed by a 50/50 water/methanol mixture (30 mL). Water was then slowly added until the pyrrole crystallized (~ 8 mL). The flask was kept in the freezer for 24 hours and the resulting white crystals were filtered, rinsed with water and dried in a vacuum oven at room temperature over night to give pyrrole **1** as flat white crystals (0.96 g, 70 %).

Benzyl 3,5-dimethyl-pyrrole-2-carboxylate 1 *via* initial de-acetylation of ethyl 3,5-dimethyl-pyrrole-2-carboxylate 3 (Entry 3, Table 2) Pyrrole 3 (1.07 g, 3.93 mmol) and *para*-toluene sulfonic acid (49 mg, 0.26 mmol) were weighed in a QXP vessel to which was added ethylene glycol (2.5 mL, 44.8 mmol) and toluene (15.5 mL). The vessel was then equipped with a stirrer bar, the temperature probe and the pressure probe of the microwave and exposed to 600 W for 6 minutes at 160 °C. The reaction mixture was then allowed to cool to room temperature, cautiously unsealed and water (20 mL) added. The aqueous phase was extracted with DCM (3 x 30 mL) and the combined organics were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Water (40 mL) was added to the crude product in benzyl alcohol (15 mL) and the mixture was heated to approximately 60 °C to dissolve the pyrrole after which ethanol (40 mL) was added. The flask was set aside to cool, resulting in the crystallization of the product which was filtered, rinsed with water and left to air-dry to afford pyrrole **1** as white flaky crystals (0.80 g, 89 %).

Benzyl 3,5-dimethyl-pyrrole-2-carboxylate 1 *via* optimized de-acetylation of ethyl 3,5-dimethyl-pyrrole-2-carboxylate 3 (Entry 5, Table 4) *Para*-toluene sulfonic acid (49 mg, 0.26 mmol), pyrrole 3 (1 g, 3.69 mmol) and ethylene glycol (7.5 mL, 0.13 mol) were poured into a round bottomed flask equipped with a stirrer bar, a condenser and the temperature probe. The reaction mixture was exposed to 150 W for 2 minutes reaching a maximum temperature of 115 °C (set target temperature of the program: 100 °C). The reaction mixture was then allowed to cool (~10 minutes) and water was then added resulting in the formation of sticky flat crystals. They were dissolved, as

they were very hard to collect, and the two phases were separated. The aqueous phase was extracted with DCM (3 x 30 mL) and the combined organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Hot methanol was added (20 mL) to dissolve the resulting solid then water was added until the pyrrole crystallized (~ 5 mL). The flask was kept in the freezer for 24 hours and the resulting white crystals were filtered, rinsed with water and dried in a vacuum oven at room temperature overnight to produce pyrrole 1 as flat white crystals (0.77 g, 91 %).The large-scale reactions (15, 30 and 50 g) did not require an aqueous work-up: when water was added to the reaction mixture, the product crystallized out. Filtration followed by rinsing of the crystals with water and then drying in a vacuum oven at room temperature overnight gave the isolated pure pyrrole **1**. Further re-crystallization was possible following the small scale procedure in order to obtain flatter and shinier crystals. **Data** mp: 102 °C (Lit. 102-103 °C)[17]; R_f 0.80 (1:1 ethyl acetate:hexanes); δ_H (250 MHz; $CDCl_3$)[18] 8.67 (1H, bs, N*H*), 7.42-7.30 (5H, m, Ar*H*), 5.80 (1H, d, *J* = 2.8 Hz, C*H*=), 5.29 (2H, s, CH_2OCO), 2.32 (3H, s, CH_3), 2.23 (3H, s, CH_3); δ_C (126 MHz; $CDCl_3$) 161.3 (C), 136.6 (C), 132.7 (C), 127.7 (C), 128.6 (CH= x 2), 128.1 (CH= x 3), 117.4 (C), 111.6 (CH=), 65.5 (CH_2), 13.1 (CH_3), 12.9 (CH_3); m/z [EI^+] 229.1 (M^+, 100 %).

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