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New J. Chem.

ARTICLE

Barton decarboxylation under ultrasonic continuous flow

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Barton decarboxylation reaction was performed and optimized in ultrasonic continuous flow. Indeed, continuous flow was chosen to give access to bulkier syntheses, ultrasounds were used to enhance yields compared to simple heating. Various Barton adducts and reductive decarboxylated compounds were obtained in moderate to good yield (33% - 73%).

Introduction,

In the field of radical chemistry, Barton decarboxylation reaction[1–6] has a large presence. Recently, numerous reactions were published in this domain, especially for reactions on solid phase,[7] in tandem with addition,[8] as a step for carbasugar analogue,[9,10] and for the syntheses of high value compounds.[11–15] Among the recent advances in organic chemistry, alternative technologies such as continuous flows,[16,17] microwaves,[18,19] ultrasounds[20,21] and micellar catalysis[22] is expanding. In this regards, the number of publications of radical reactions in continuous flow is increasing,[23] mainly in material or polymer field,[24–28] but also in non-polymeric reactions domain.[29–34] In 2015, our group reported the first one-step Barton decarboxylation in batch without isolation of the *N*-hydroxy-2-thiopyridone ester. Both ultrasonic probe activation and micellar catalysis were optimized for the production of maleimide derivatives in water.[20] To the best of our knowledge, no Barton decarboxylation was described using ultrasonic irradiation in continuous flow. Consequently, the main purpose of the present work was to focus on Barton decarboxylation in continuous flow, using ultrasounds as alternative technique.

Results and discussion,

In the present work, a continuous flow system was used. All the reactants were dissolved in a mixture of dichloromethane-methanol and pumped into the system with an HPLC pump (0.5−20 mL.min^{-1}) at temperature below 35°C. Then the solution was entered into a tubular reactor (Teflon coil, 0.8 mm internal diameter, 40 m length and a total volume of 20.1 mL with an useful volume of 19.9 mL heated in an ultrasonic bath equipped with temperature (rt to 35°C), power (10% to 100% of 330 W) and frequency regulators (37 or 80 kHz). Then reaction termination was realized by cooling solution in a cooling bath (20°C). To maintain the reaction solution in liquid state, the pressure was set to 0.1 MPa by a back-pressure valve (Fig. 1). The reaction time was modified by varying the flow rate. The products were collected and yields of the target compounds were estimated by HPLC analysis with calibration curve. In our hands, the reaction was performed in non-degassed organic solvents in ultrasonic continuous flow. Indeed, it is well-known that ultrasounds can provide two distinct effects: (i) formation, growth, and collapse of cavitation bubbles in solution that brings energy and mechanical forces[35] and (ii) degassing.[36] In the present work, both parameters are envisioned to enhance yields of reaction by (i) bring the essential energy for the radical to be formed[37] and (ii) remove air oxygen and by-produced carbon dioxide from the solution. As a part of our continuing studies on the chemistry of Barton decarboxylation,[20] we have studied the “one-pot” conversion of hexanoic acid (**1a**) to substituted maleimide (**1**) as model reaction in continuous flow chemistry (Scheme 1).

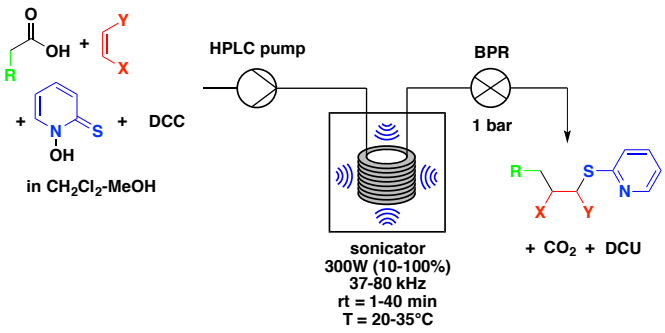

Fig. 1 General apparatus display.

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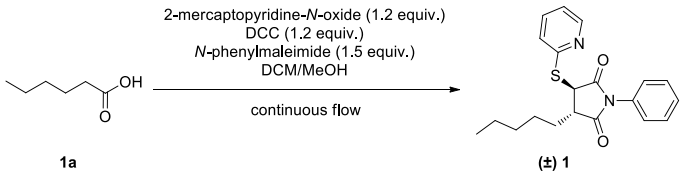
Electronic Supplementary Information (ESI) available: [Full experimental procedures, ^{1}H NMR, ^{13}C NMR]. See DOI: 10.1039/x0xx00000x

The constraint of a one-pot reaction was to dissolve the starting reactants, target compounds and the by-products formed during the reaction. In our case, a mixture of dichloromethane (DCM) and MeOH was chosen, (i) DCM for the solubilization of all the reactants, for its good performances in literature[6,14,15,38] and to limit solvent-radical interactions; (ii) MeOH for the dissolution of dicyclohexylurea by-product of the esterification reaction (Table 1). First, the esterification reaction has been perform with 2-mercaptopyridine-*N*-oxide (1.2 equiv.), DCC (dicyclohexylcarbodiimide, 1.2 equiv.) and hexanoic acid (1.03 mmol) in a mixture of DCM-MeOH (4:1, v/v) at 35°C for a residence time of 20 minutes. Once the thiohydroxamic ester is formed, it reacts to form the corresponding decarboxylation adduct and the radical-trap (here *N*-phenylmaleimide, 1.5 equiv.) allows to form the adduct **±1**. It is noticeable that in our hands, compound **±1** was formed with a diastereroisomeric excess d.e = 100% for the *anti*-adduct. The presence of the *syn*-adduct was not observed using either NMR spectroscopies or HPLC. NOESY experiment was chosen to confirm this selectivity on compound **±1** and the cross peak between H^{o} (8.29 ppm) and H^{3} (3.23 ppm) indicated its *anti* configuration (Fig. 2).

Under these previous conditions (hexanoic acid (1.03 mmol), 2-mercaptopyridine-*N*-oxide (1.2 equiv.), DCC (dicyclohexylcarbodiimide, 1.2 equiv.) and *N*-phenylmaleimide (1.5 equiv.), DCM-MeOH, 4:1, v/v, 20 min at 35°C), solvent modulation was studied (Table 1).



Scheme 1 Continuous flow ultrasonic Barton decarboxylation for the synthesis of ±1

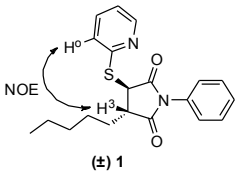


Fig. 2 NOESY experiment result

With a DCM-MeOH percentage lower than 70% (v/v), the yields of **±1** did not exceed 26% (Table 1, entries 1-4). Moreover, when the DCM/MeOH percentage was of 70 or 90% (v/v), the yields of **±1** were around 40% (Table 1, entries 5 and 7). The best yield of 53% was obtained when DCM-MeOH percentage of 80% (v/v) was used for the reaction (Table 1, entry 6). Then fixing the reactants equivalences, and DCM-MeOH to 80% (v/v) in a bath temperature of 35°C, the residence time was optimized (Fig. 3).

Table 1. Solvent modulation (total volume of 25 mL) for the Barton decarboxylation in continuous flow [a]

Entry	DCM-MeOH (%) (v/v)	Yield of **±1** (%)[b]
1	0	17
2	20	19
3	40	23
4	60	26
5	70	41
6	80	53
7	90	37

[a] Reagents and conditions: Without sonication, 2-mercaptopyridine-*N*-oxide (1.2 equiv.), DCC (1.2 equiv.), hexanoic acid (1.03 mmol), *N*-phenylmaleimide (1.5 equiv.), 35°C, residence time=20 min. [b] HPLC yields calculated *via* calibration curve with naphthalene as external standard.

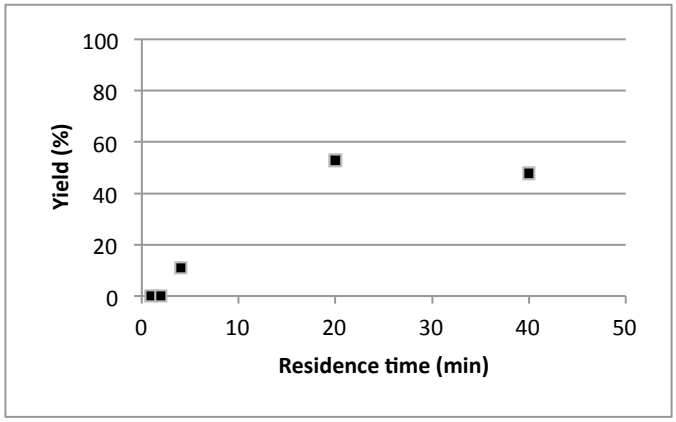


Fig. 3 Influence of the residence time on ±1 yield.

Residence time of 1, 2 or 4 min did not give the target compound ±1 with a yield upper than 10%. Herein we found that 20 min of

residence time gave 53% yield of ±1. But when this time was multiplied per two, the yield decreased to 48%, leading to the conclusion that 20 min was the best residence time for the reaction.

After optimization of the DCM-MeOH ratio (80 volume %) and residence time (20 min), temperature, sonication and reactant concentration were examined (Table 2). First, the mixture was not injected in the continuous flow coil, and was kept under stirring for 40 min at rt in the mixing flask. Compound **±1** was obtained in low yield (4%) (Table 2, entry 1), showing that the reaction nearly did not occur before entering the coil system. Moreover, it was noticeable that no methyl ester was observed in these conditions. Comparing 30°C to 35°C (Table 2, entries 2 and 3) led to the conclusion that 35°C was the best temperature to apply. Due to the boiling point of DCM, higher temperature than 35°C was not recommended. Fixing the reaction temperature at 35°C, applying a continuous 80 kHz ultrasound allowed the access to compound **±1** with a very good yield of 67% (Table 2, entry 4), increasing it by 14% compared to when the ultrasound is switched off.

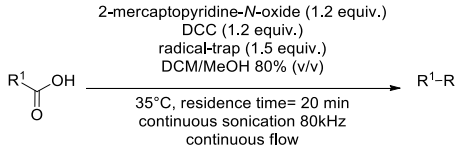
Table 2. Temperature, sonication and reactant concentration variations for the synthesis of ±1 in continuous flow[a]

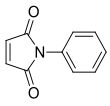
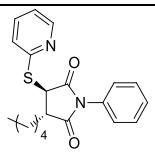
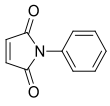
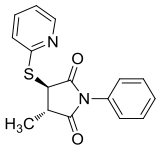
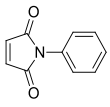
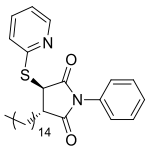
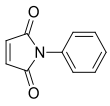
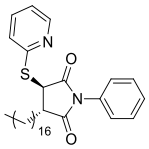
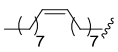
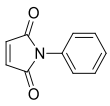
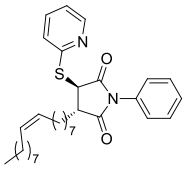
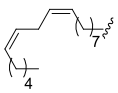
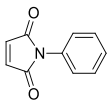
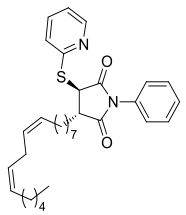
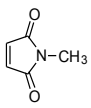
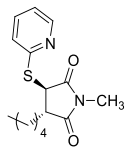
Entry	Ultrasound (kHz)[b]	**1a** (10^{-2} mol.L^{-1})	Temperature (°C)	**±1** Yield (%)[c]
1	-	4.1	r.t.	4[d]
2	-	4.1	30	28
3	-	4.1	35	53
4	80	4.1	35	67
5	80	17.2	35	38
6	80	8.6	35	45
7	80	2.0	35	39

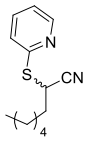
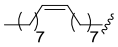
[a] Reagents and conditions: 2-Mercaptopyridine-*N*-oxide (1.2 equiv.), DCC (1.2 equiv.) hexanoic acid (1.03 mmol), *N*-phenylmaleimide (1.5 equiv.), residence time=20 min, DCM-MeOH 80% (v/v). [b] Continuous program. [c] HPLC yields obtained *via* calibration curve with naphthalene as external standard. [d] Keeping the solution in the mixing flask for 40 min, without injecting the solution in the continuous flow coil.

However, concentrating **1a** from 4.1 to 17.2 or 8.6×10^{-2} mol.L^{-1}, as well as diluting it to 2.0×10^{-2} mol.L^{-1} decreased drastically the production of **±1** (Table 2, entries 5-7). In our hands, ultrasound activation as alternative technology permitted to improve the production of compound **±1** (67% *vs* 53%) (Table 2, entries 3 and 4) probably due to (i) the efficient formation of the radical species[35,37] and (ii) the remove air oxygen and by-produced carbon dioxide from the solution.[36] To conclude, the optimization of the reactions conditions leading to compound **±1** under ultrasonic continuous flow were as following: 2-mercaptopyridine-*N*-oxide (1.2 equiv.), DCC (1.2 equiv.) hexanoic acid (1.03 mmol at 4.1×10^{-2} mol.L^{-1}) in DCM-MeOH 80% (v/v), *N*-phenylmaleimide (1.5 equiv.) for a residence time of 20 min with 80 kHz continuous ultrasounds irradiation. With our optimized reaction conditions in hand, a range of saturated and unsaturated carboxylic acids and radical-traps having different structure such as *N*-phenylmaleimide, *N*-methylmaleimide, ethylacrylate and acrylonitrile in continuous flow was screened (Table 3). First, using *N*-phenylmaleimide as radical-trap, the variation of carboxylic acid reactant was examined (Table 3, entries 1-6). Saturated hexanoic, acetic, palmitic and stearic acids (**1a-4a**) were used giving access to short-chained (Table 3, entry 2) to long-chained (Table 3, entry 4) Barton adducts **±1** to **±4** in good yields from 49 to 73%. With hexanoic, palmitic and stearic acids (**1a**, **3a** and **4a**), compounds **±1**, **±3**, **±4** were obtained respectively with d.e. = 100%, whereas with acetic acid (**2a**), compound **±2** was obtained with d.e.= 86%. It seemed that steric hindrance should favor the diastereo differenciation of the radical addition. Natural unsaturated carboxylic acids were also used in the Barton decarboxylation (Table 3, entries 5 and 6). Using oleic and linoleic acids (**5a**) and (**6a**), Barton products **±5** and **±6** were obtained in good yields of 68 and 69%, respectively. Then, using hexanoic acid (**1a**), the radical-trap reactant varied to *N*-methylmaleimide (Table 3, entry 7) and gave access to the Barton adduct **±7** in 100% d.e. and 65% yield. It is clear that the *N*-aryl moiety did not influence the production of the pyrrolidine-2,5-dione compared with the *N*-alkyl moiety since the target compounds **±1** and **±7** were obtained in similar yields and identical d.e. (Table 3, entries 1 and 7). With ethylacrylate or acrylonitrile (Table 3, entries 8 and 9), compounds **±8** and **±9** were obtained in lower yields of 33 and 55%. As expected no enantiomeric excess was observed and a racemic mixture was purified. In these cases, the pentyl radical undergoes regiocontrolled addition to the most favored energetic position, which is controlled by orbital interactions[39] on the methylene of the ethylacrylate and acrylonitrile. Finally, chloroform was used either as *H*-donor and solvent (Table 3, entry 10) to give, from oleic acid (**5a**), (*Z*)-heptadec-8-ene (**10**) in 52% yield. It is well known in the literature that chloroform is a *bona fide* H-atom donor, and particularly when used as solvent, as it is a cost-effective hydrogen-atom donor for the Barton reductive decarboxylation.[40,41] In our hands, neither the corresponding chloroalkane nor the pyridylsulfide was observed, only unreacted Barton ester was recovered as by-product.

Table 3. Reactant modulation[a]



Entry	R^1	Reactant	Radical trap	R^1-R	Yields[b] (%)	d.e. (%)
1		**1a**		 **±1**	67	100
2		**2a**		 **±2**	49	86
3		**3a**		 **±3**	73	100
4		**4a**		 **±4**	72	100
5		**5a**		 **±5**	68	100
6		**6a**		 **±6**	69	100
7		**1a**		 **±7**	65	100
8		**1a**		c **±8**	33	-

9		**1a**		 **±9**	55	-
10		**5a**	chloroform[c]	 **10**	52	-

[a] Reagents and conditions: 2-Mercaptopyridine-*N*-oxide (1.2 equiv.), DCC (1.2 equiv.), carboxylic acid (1.03 mmol at 4.1×10^{-2} mol.L^{-1}) in DCM-MeOH 80% (v/v), *N*-phenylmaleimide (1.5 equiv.), residence time=20 min with 80 kHz continuous ultrasounds. [b] Isolated Yields [c] DCM was replaced by chloroform.

Conclusions

In conclusion, a "one-pot two steps" Barton decarboxylation reaction was performed in ultrasonic continuous flow for the first time. The impact of ultrasound technology in radical reaction was confirmed. The optimized method provided cyclic and linear scaffolds having maleimide, acrylate and acrylonitrile in 33-73% yields. For the maleimide derivatives, racemic *anti*-configuration (**±1** - **±7**) was obtained while for the acrylate and acrylonitrile derivatives (**±8** and **±9**), a 1,4- stereoselective addition was observed furnishing the racemic target compounds with a linear carbon atom chain. When $CHCl_3$ was used as solvent and radical-trap conventional alkane **10** was produced in 52% yield.

Experimental

Materials

All starting materials were used without purification. Flash column chromatography was performed on silica gel SiOH 40-60 µm. Mass spectrometry analyses were performed on a mass spectrometer equipped with an electrospray source (ESCI). The structures were assigned by aid of the following techniques: ^{1}H and ^{13}C NMR and if needed, HMBC and COSY H-H experiments. ^{1}H and ^{13}C NMR, HMBC and COSY H-H spectra were recorded on a 400 MHz instrument. Chemical shifts (δ) are quoted in ppm and are referenced to TMS as an internal standard. Coupling constants (*J*) are quoted in Hz, common splitting patterns and their abbreviations were s (singulet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), m (multiplet). Infrared spectra were measured on FT/IR instrument equipped with an ATR apparatus. Melting points were recorded without correction. High-resolution electrospray mass spectra (HR-ESI-MS) in the positive ion mode were obtained on a quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source.

General procedure for the Barton decarboxylation under ultrasonic continuous flow

In a glass long-tube equipped with a stirring bar was placed the carboxylic acid (1.03 mmol), DCC (250 mg, 1.21 mmol, 1.2 equiv.), 2-mercaptopyridine-*N*-oxide (150 mg, 1.20 mmol, 1.2 equiv.), the radical-trap (1.5 equiv.), and 25 mL of mixture of DCM-MeOH 80% v/v. Then, the mixture was pumped (HPLC pump, 1 mL.min^{-1}) through a 20 mL Teflon coil (0.8 mm inner diameter) heated in an ultrasonic bath (35°C, 80 kHz). Then, the solvent was removed under vacuum, the crude product adsorbed on plug silica, and purified by flash chromatography (ethyl acetate-cyclohexane 0-20% v/v) with UV (254 and 280 nm) and ELSD (isopropanol) detectors.

3-Pentyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (±1)

Following general procedure for Barton decarboxylation, with hexanoic acid (120 mg, 1.03 mmol) and *N*-phenylmaleimide (268 mg, 1.5 mmol, 1.5 equiv.), 3-pentyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (**±1**) was obtained (245 mg, 67% yield) as a white solid (mp: 77-79°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.92 (t, *J* = 7.1 Hz, 3H, CH_3), 1.34-1.37 (m, 4H, CH_2), 1.53-1.60 (m, 2H, CH_2), 1.78-1.87 (m, 1H, CH_2), 2.04-2.12 (m, 1H, CH_2), 3.23 (dt, *J* = 8.6 and 5.2 Hz, 1H, CHCO), 3.92 (d, *J* = 5.6 Hz, 1H, CHS), 7.02 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.22 (d, *J* = 8.1 Hz, 1H, CHπ), 7.34-7.42 (m, 3H, CH_{ar}), 7.46-7.55 (m, 3H, CH_{ar}), 8.29 (ddd, *J* = 5.0, 1.8 and 1.0 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.0 (CH_3), 22.4 (CH_2), 26.1 (CH_2), 30.7 (CH_2), 31.6 (CH_2), 46.9 (CH), 47.2 (CHS), 120.2 (CHπ), 122.1 (CHπ), 126.4 (2 CH_{Ph}), 128.5 (CH_{Ph}), 129.1 (2 CH_{Ph}), 132.5 ($C_{Ph}N$), 136.6 (CHπ), 149.0 (CHπN), 156.1 (CπS), 174.4 (*C*OCHS), 177.4 (CO). ν_{max}/cm^{-1}: 1707 (C=O), 1389 (CH), 1173 (C-N). HRMS (ESI): found 355.1480; calculated 355.1480 for $C_{20}H_{23}N_2O_2S$.

3-Methyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (±2)

Following general procedure for Barton decarboxylation, with acetic acid (61 mg, 1.03 mmol) and *N*-phenylmaleimide (268 mg, 1.5 mmol, 1.5 equiv.), 3-methyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (**±2**) was obtained (145 mg, 49% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.56 (d, *J* = 7.4 Hz, 3H, CH_3), 3.32 (dt, *J* = 8.6 and 5.2 Hz, 1H, CHCO), 3.85 (d, *J* = 5.6 Hz, 1H, CHS), 7.04 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.24 (d, *J* = 8.1 Hz, 1H, CHπ), 7.36-7.42 (m, 3H, CH_{ar}),

7.46-7.56 (m, 3H, CH_{ar}), 8.29 (dd, *J* = 5.0, and 1.8 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.2 (CH_3), 42.5 (CH), 49.3 (CHS), 120.4 (CHπ), 122.4 (CHπ), 126.5 (2 CH_{Ph}), 128.6 (CH_{Ph}), 129.1 (2 CH_{Ph}), 132.6 ($C_{Ph}N$), 136.9 (CHπ), 149.0 (CHπN), 156.0 (CπS), 174.4 (*C*OCHS), 177.4 (CO). ν_{max}/cm^{-1}: 1710 (C=O), 1390 (CH), 1173 (C-N). HRMS (ESI): found 299.0855; calculated 299.0849 for $C_{16}H_{15}N_2O_2S$.

3-Pentadecyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (±3)

Following general procedure for Barton decarboxylation, with palmitic acid (264 mg, 1.03 mmol) and *N*-phenylmaleimide (268 mg, 1.5 mmol, 1.5 equiv.), 3-pentadecyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (**±3**) was obtained (372 mg, 73% yield) as a white solid (mp: 68-71°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.80 (t, *J* = 6.9 Hz, 3H, CH_3), 1.18-1.36 (m, 24H, CH_2), 1.50 (quin, *J* = 7.4 Hz, 2H, CH_2), 1.70-1.77 (m, 1H, CH_2), 2.96-2.03 (m, 1H, CH_2), 3.13 (dt, *J* = 8.8 and 5.1 Hz, 1H, CHCO), 3.86 (d, *J* = 5.6 Hz, 1H, CHS), 6.95 (dd, *J* = 6.7 and 5.0 Hz, 1H, CHπ), 7.17 (d, *J* = 8.1 Hz, 1H, CHπ), 7.27-7.34 (m, 3H, CH_{ar}), 7.39-7.49 (m, 3H, CH_{ar}), 8.22 (d, *J* = 4.5 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1 (CH_3), 22.7 (CH_2), 26.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.7 (CH_2), 31.9 (CH_2), 46.9 (CH), 47.2 (CHS), 120.3 (CHπ), 122.2 (CHπ), 126.4 (2 CH_{Ph}), 128.5 (CH_{Ph}), 129.1 (2 CH_{Ph}), 132.5 ($C_{Ph}N$), 136.8 (CHπ), 148.9 (CHπN), 156.0 (CπS), 174.4 (*C*OCHS), 177.3 (CO). ν_{max}/cm^{-1}: 1708 (C=O), 1387 (CH), 1173 (C-N). HRMS (ESI): found 495.3047; calculated 495.3045 for $C_{30}H_{43}N_2O_2S$.

3-Heptadecyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (±4)

Following general procedure for Barton decarboxylation, with stearic acid (292 mg, 1.03 mmol) and *N*-phenylmaleimide (268 mg, 1.5 mmol, 1.5 equiv.), 3-heptadecyl-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (**±4**) was obtained (375 mg, 72% yield) as a white solid (mp: 85-86°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.26 (bs, 28H, CH_2), 1.56 (quin, *J* = 7.5 Hz, 2H, CH_2), 1.78-1.87 (m, 1H, CH_2), 2.04-2.13 (m, 1H, CH_2), 3.23 (dt, *J* = 8.7 and 5.2 Hz, 1H, CHCO), 3.95 (d, *J* = 5.6 Hz, 1H, CHS), 7.03 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.24 (dt, *J* = 8.1 and 0.9 Hz, 1H, CHπ), 7.34-7.42 (m, 3H, CH_{ar}), 7.46-7.56 (m, 3H, CH_{ar}), 8.30 (ddd, *J* = 5.0, 1.8 and 1.0 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1 (CH_3), 22.7 (CH_2), 26.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (2 CH_2), 29.7 (5 CH_2), 30.8 (CH_2), 31.9 (CH_2), 46.9 (CH), 47.2 (CHS), 120.3 (CHπ), 122.3 (CHπ), 126.4 (2 CH_{Ph}), 128.5 (CH_{Ph}), 129.1 (2 CH_{Ph}), 132.5 ($C_{Ph}N$), 136.8 (CHπ), 148.9 (CHπN), 156.0 (CπS), 174.4 (*C*OCHS), 177.3 (CO). ν_{max}/cm^{-1}: 1708 (C=O), 1388 (CH), 1169 (C-N). HRMS (ESI): found 523.3363; calculated 523.3359 for $C_{32}H_{47}N_2O_2S$ and found 545.3198; calculated 545.3177 for $C_{32}H_{46}N_2O_2SNa$.

(*Z*)-3-(Heptadec-8-en-1-yl)-1-phenyl-4-(pyridin-2-ylthio)-pyrrolidine-2,5-dione (±5)

Following general procedure for Barton decarboxylation, with oleic acid (290 mg, 1.03 mmol) and *N*-phenylmaleimide (268 mg, 1.5 mmol, 1.5 equiv.), (*Z*)-3-(heptadec-8-en-1-yl)-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (**±5**) was obtained (356 mg, 68% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.27-1.31 (m, 22H, CH_2), 1.56 (quin, *J* = 7.4 Hz, 2H, CH_2), 1.77-1.87 (m, 1H, CH_2), 2.01-2.05 (m, 1H, CH_2), 3.23 (dt, *J* = 8.7 and 5.2 Hz, 1H, CHCO), 3.91 (d, *J* = 5.7 Hz, 1H, CHS), 5.35 (dt, *J* = 5.7 and 3.5 Hz, 2H, CH), 7.01 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.23 (dt, *J* = 8.1 and 0.9 Hz, 1H, CHπ), 7.35-7.41 (m, 3H, CH_{ar}), 7.46-7.55 (m, 3H, CH_{ar}), 8.29 (ddd, *J* = 4.9, 1.8 and 0.9 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1 (CH_3), 22.7 (CH_2), 26.5 (CH_2), 27.1 (CH_2), 27.2 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (2 CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 30.7 (CH_2), 31.9 (CH_2), 46.9 (CH), 47.1 (CHS), 120.2 (CHπ), 122.1 (CHπ), 126.4 (2 CH_{Ph}), 128.4 (CH_{Ph}), 129.1 (2 CH_{Ph}), 129.7 (CH), 130.0 (CH), 132.5 ($C_{Ph}N$), 136.6 (CHπ), 149.0 (CHπN), 156.0 (CπS), 174.3 (*C*OCHS), 177.3 (CO). ν_{max}/cm^{-1}: 1717 (C=O), 1384 (CH), 1179 (C-N). HRMS (ESI): found 521.3221; calculated 521.3202 for $C_{32}H_{45}N_2O_2S$.

3-((8*Z*,11*Z*)-Heptadeca-8,11-dien-1-yl)-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (±6)

Following general procedure for Barton decarboxylation, with linoleic acid (288 mg, 1.03 mmol) and *N*-phenylmaleimide (268 mg, 1.5 mmol, 1.5 equiv.), 3-((8*Z*,11*Z*)-heptadeca-8,11-dien-1-yl)-1-phenyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (**±6**) was obtained (369 mg, 69% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 1.29-1.37 (m, 14H, CH_2), 1.55 (quin, *J* = 7.2 Hz, 2H, CH_2), 1.76-1.86 (m, 1H, CH_2), 2.06 (q, *J* = 6.8 Hz, 5H, CH_2), 2.78 (t, *J* = 6.3 Hz, 2H, CH_2), 3.23 (dt, *J* = 8.7 and 5.2 Hz, 1H, CHCO), 3.89 (d, *J* = 5.7 Hz, 1H, CHS), 5.30-5.43 (m, 4H, CH), 6.98 (ddd, *J* = 7.3, 5.0 and 0.8 Hz, 1H, CHπ), 7.19 (d, *J* = 8.1 Hz, 1H, CHπ), 7.34-7.40 (m, 3H, CH_{ar}), 7.44-7.52 (m, 3H, CH_{ar}), 8.27 (ddd, *J* = 4.9, 1.7 and 1.0 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.0 (CH_3), 22.4 (CH_2), 25.5 (CH_2), 26.4 (CH_2), 27.1 (2 CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 30.6 (CH_2), 31.4 (CH_2), 46.8 (CH), 47.0 (CHS), 120.1 (CHπ), 121.9 (CHπ), 126.3 (2 CH_{Ph}), 127.8 (CH), 127.9 (CH), 128.3 (CH_{Ph}), 128.9 (2 CH_{Ph}), 129.9 (CH), 130.1 (CH), 132.5 ($C_{Ph}N$), 136.5 (CHπ), 148.9 (CHπN), 155.9 (CπS), 174.2 (*C*OCHS), 177.2 (CO). ν_{max}/cm^{-1}: 1717 (C=O), 1382 (CH), 1179 (C-N). HRMS (ESI): found 519.3052; calculated 519.3046 for $C_{32}H_{43}N_2O_2S$.

3-Pentyl-1-methyl-4-(pyridin-2-ylthio)pyrrolidine-2,5-dione (±7)

Following general procedure for Barton decarboxylation, with hexanoic acid (120 mg, 1.03 mmol) and *N*-methylmaleimide (166 mg, 1.5 mmol, 1.5 equiv.), 3-pentyl-1-methyl-4-(pyridin-2-

ylthio)pyrrolidine-2,5-dione (**±7**) was obtained (189 mg, 65% yield) as white solid (mp: 66-68°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.89 (t, *J* = 7.1 Hz, 3H, CH_3), 1.32-1.37 (m, 4H, CH_2), 1.43-1.50 (m, 2H, CH_2), 1.69-1.73 (m, 1H, CH_2), 1.95-1.98 (m, 1H, CH_2), 3.05 (m, 1H, CHCO), 3.09 (s, 3H, CH_3), 3.97 (d, *J* = 5.6 Hz, 1H, CHS), 7.00 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.22 (d, *J* = 8.1 Hz, 1H, CHπ), 7.52 (dd, *J* = 8.0 and 1.8 Hz, 1H, CHπ), 8.24 (dd, *J* = 5.0, 1.8 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 13.9 (CH_3), 22.4 (CH_2), 25.3 (CH_2), 26.1 (CH_3), 30.4 (CH_2), 31.5 (CH_2), 46.5 (CH), 47.5 (CHS), 120.2 (CHπ), 122.2 (CHπ), 136.6 (CHπ), 149.0 (CHπN), 155.9 (CπS), 175.6 (*C*OCHS), 178.5 (CO). ν_{max}/cm^{-1}: 1707 (C=O), 1389 (CH). HRMS (ESI): found 293.1312; calculated 293.1318 for $C_{15}H_{21}N_2O_2S$.

Ethyl 2-(pyridin-2-ylthio)octanoate (±8)

Following general procedure for Barton decarboxylation, with hexanoic acid (120 mg, 1.03 mmol) and ethyl arcrylate (0.16 mL, 1.54 mmol, 1.5 equiv.), ethyl 2-(pyridin-2-ylthio)octanoate (**±8**) was obtained (92 mg, 33% yield) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.89 (t, *J* = 7.1 Hz, 3H, CH_3), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3), 1.32-1.37 (m, 6H, CH_2), 1.43-1.50 (m, 2H, CH_2), 1.69-1.73 (m, 1H, CH_2), 1.95-1.98 (m, 1H, CH_2), 3.05 (m, 1H, CHCO), 4.16-4.19 (ddt, *J* = 7.7, 4.1 and 2.9 Hz, 2H, CH_2), 4.52 (t, *J* = 7.3 Hz, 1H, CHS), 6.97 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.21 (d, *J* = 8.1 Hz, 1H, CHπ), 7.47 (dd, *J* = 8.0 and 1.8 Hz, 1H, CHπ), 8.39 (dd, *J* = 5.0, 1.8 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.07 (CH_3), 14.17 (CH_3), 22.4 (CH_2), 22.5 (CH_2), 27.1 (CH_2), 28.8 (CH_2), 31.5 (CH_2), 46.8 (CH_2), 61.2 (CHS), 119.8 (CHπ), 122.3 (CHπ), 136.1 (CHπ), 149.2 (CHπN), 157.6 (CπS), 172.7 (*C*OCHS). ν_{max}/cm^{-1}: 1752 (C=O), 1055 (C-O), 1410 (CH). HRMS (ESI): found 282.1525; calculated 282.1522 for $C_{15}H_{24}NO_2S$.

2-(Pyridin-2-ylthio)octanenitrile (±9)

Following general procedure for Barton decarboxylation, with hexanoic acid (120 mg, 1.03 mmol) and acrylonitrile (0.01 mL, 1.54 mmol, 1.5 equiv.), 2-(pyridin-2-ylthio)octanenitrile (**±9**) was obtained (128 mg, 55% yield) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, *J* = 7.1 Hz, 3H, CH_3), 1.32-1.37 (m, 6H, CH_2), 1.69-1.73 (m, 2H, CH_2), 1.95-1.98 (m, 2H, CH_2), 3.05 (m, 1H, CHCO), 4.85 (t, *J* = 7.3 Hz, 1H, CHS), 7.06 (ddd, *J* = 7.4, 5.0 and 1.0 Hz, 1H, CHπ), 7.18 (d, *J* = 8.1 Hz, 1H, CHπ), 7.55 (dd, *J* = 8.0 and 1.8 Hz, 1H, CHπ), 8.47 (dd, *J* = 5.0, 1.8 Hz, 1H, CHπ). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.07 (CH_3), 22.4 (CH_2), 27.1 (CH_2), 28.5 (CH_2), 31.3 (CH_2), 31.4 (CH_2), 32.2 (CHS), 119.9 (CHπ), 120.6 (CN), 122.4 (CHπ), 136.6 (CHπ), 149.7 (CHπN), 154.9 (CπS). ν_{max}/cm^{-1}: 2250 (CN), 1395 (CH). HRMS (ESI): found 235.1265; calculated 235.1263 for $C_{13}H_{19}N_2S$.

Heptadec-8-ene (10)

Following the general procedure for Barton decarboxylation with oleic acid (290 mg, 1.03 mmol) in $CHCl_3$ (25 mL), 2-(pyridin-2-ylthio)octanenitrile (**±9**) was obtained (124 mg, 52% yield) as colourless oil. Analyses are consistent with the literature.[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.88 (t, *J* = 7.1 Hz, 6H, CH_3), 1.25-1.28 (m, 22H, CH_2), 2.02 (d, J = 5.6 Hz, 4H, CH_2), 5.35 (t, J = 4.5 Hz, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.14 (CH_3), 22.70 (CH_2), 26.92 (CH_2), 27.24 (CH_2), 29.26 (CH_2), 29.31 (CH_2), 29.35 (CH_2), 29.56 (CH_2), 29.73 (CH_2), 29.81 (CH_2), 30.19 (CH_2), 31.92 (CH_2), 31.94 (CH_2), 129.91 (CH).

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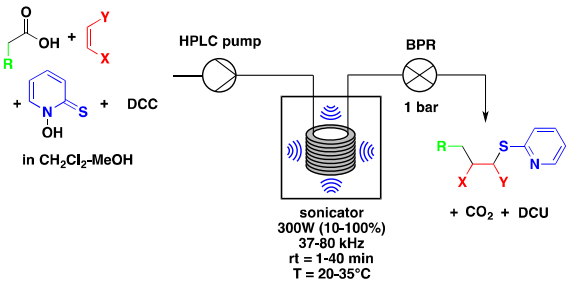
Graphical abstract



Barton decarboxylation was performed in ultrasonic continuous flow for bulkier syntheses and enhanced yields compared to conventional heating.