Organic Process Research & Development

Technology Report

pubs.acs.org/OPRD

A Continuous Protodecarboxylation of Heteroaromatic Carboxylic Acids in Sulfolane.

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ABSTRACT: A versatile, scalable method for the decarboxylation of indole-2-carboxylic acids has been found. With one equivalent of DBU in sulfolane, indole-2-carboxylic acid derivatives were cleanly decarboxylated in a 316 stainless steel tube reactor at 300 °C within 20 min. The corresponding indole derivatives were obtained in good yields. It was also found that indole-2-carboxylic acid (**1**) can be decarboxylated in either pure sulfolane or sulfolane with 3% water at 300 °C within 20 min. (1) The decarboxylation with one equivalent of DBU could successfully be transferred to benzo[*b*]thiophene-2-carboxylic acid derivatives if a prolonged reaction time was used. (2) Picolinic acid could also be decarboxylated in sulfolane with 3% water, and thiophene-2-carboxylic acid was smoothly decarboxylated with DABCO instead of DBU. (3) Benzoic acid derivatives were either inert or decomposed under the reaction conditions.

INTRODUCTION

Decarboxylation constitutes an important and frequently desired transformation in living systems[1] as well as in the synthesis of diverse classes of bioactive organic and heterocyclic compounds as it confers a facile approach to modify the underlying carbon skeleton or introduction of radiolabeled species.[2] For instance, various pharmacologically and industrially important classes of compounds including indoles and benzothiophenes are frequently accessed through the decarboxylation of the respective carboxylic acids. A general versatile method for aromatic decarboxylation has yet to be reported. In general, aromatic decarboxylation is difficult due to the unstable intermediates that are formed during the course of the reaction. As a result, the methods available for decarboxylation all require forcing conditions.

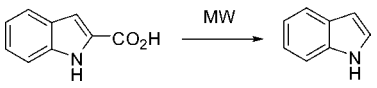
Prototypical methods include heating in the presence of a strong acid[3] and heating with a copper catalyst and quinoline.[4] The first method proceeds through ipso protonation of the aromatic ring and requires electron-rich systems and temperatures above 100 °C. In the copper/quinoline method the copper catalyst coordinates to the aromatic ring and helps to stabilize the anion that results upon loss of carbon dioxide. Again these reactions proceed only at high temperatures (>160 °C). Kozlowski et al.[5] have developed a palladium-catalyzed decarboxylation, utilizing trifluoroacetic acid as the proton source, that proceeds at <100 °C for substrates containing multiple methoxy groups. The method is not suitable, however, for heterocyclic carboxylic acids as two *o*-methoxy groups are necessary to obtain high yields.

Classical approaches to indoles including the Reissert,[6] Fischer,[7] and Rees-Moody[8] routes, all require subsequent removal of the 2-carboxyl function. In the case of indoles several procedures have been reported to effect this problematic transformation with varying degrees of efficiency. Problems encountered during the decarboxylation usually stem from decomposition of the product under prolonged thermolysis conditions and additional decomposition during purification. For these reasons it has become commonplace to remove the 2-carboxylic function in indoles by decarbonylation burdening the synthesis with additional steps and purifications.[9]

New approaches utilizing microwave technology for the decarboxylation have been reported.[5,9] The microwave energy heats the reactants directly, allowing for a rapid heatup even to temperatures well in excess of their normal boiling points, whereas conventional heating needs to heat the reactor walls that heats the reactants; in this, case no superheating is possible.

Jones and Chapman[9] found that heating of indole-2-carboxylate with Cu(I) and Cu(II) salts or Cu powder and quinoline for 12 min in the microwave oven gave a very clean decarboxylation. Since copper metal was observed to have plated out on the reaction vessel, the authors decided to try the decarboxylation without metal. They found from this experiment that heating indole-2-carboxylate with quinoline alone for 12 min in the microwave oven also afforded an almost quantitative yield of indole (Scheme 1). It was found that the thermolysis in an open vessel proved to be unsatisfactory as the mixture rapidly can reach 300 °C, leading to sublimation and vaporization of reactants and products. The authors obtained an isolated yield of 93% of indole when the reaction was run neat in quinoline on a 0.3 mmol scale. Attempts to scale up the process met with problems due to inefficient conduction of heat from the vessel lowering the yield to 70−80% on a 1 g scale. The authors commented that their method would be very useful on a scale <2 mmol.

Scheme 1. Microwave-assisted decarboxylation in quinoline or neat



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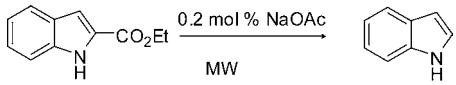
Received: May 11, 2012
Published: July 18, 2012

dx.doi.org/10.1021/op300125p | *Org. Process Res. Dev.* 2012, 16, 1449−1454

Sinha et al.[10] have found a new decarboxylation method during their search for alternative decarboxylation catalysts. They were attracted by the catalytic ability of basic ionic liquids as basic conditions have been known to favor the decarboxylation process. Consequently, **1** was irradiated with ionic liquid 1-butyl-3-methylimidazolium hydroxide [bmim]-OH under microwave conditions. The authors found that the expected indole (**2**) was obtained in 60% yield at the optimized temperature of 240 °C and thereafter screened a number of ionic liquids. From this study they found that the best ionic liquid was the neutral 1-hexyl-3-methylimidazolium bromide which increased the yield of indole (**2**) up to 79% at 240 °C. The yield could be further improved through the addition of a small amount of water to the ionic liquid (6 equiv in comparison to the substrate). The obtained yield of indole (**2**) was, after 15 min at 240 °C, 88%.

Trainer et al.[11] reported that in a simple procedure, indole-2-carboxylic acid (**1**) was quantitatively decarboxylated after 20 min at 255 °C in water in a microwave batch reactor. 2-Carbethoxyindole (**3**) could not be decarboxylated under these conditions. The authors found only the 2-indole carboxylic acid. They also found that an excess of base prohibits the decarboxylation of 2-carbethoxyindole (**3**). Changing the conditions from pure water or an excess of base to substoichiometric amounts of base *n*(0.2 mol %) in 0.05 M sodium acetate solutions gave within 60 min at 265 °C indole (**2**) in a 95% yield (Scheme 2). From their findings, the authors

Scheme 2. Microwave-assisted hydrolysis and decarboxylation in aqueous sodium hydroxide

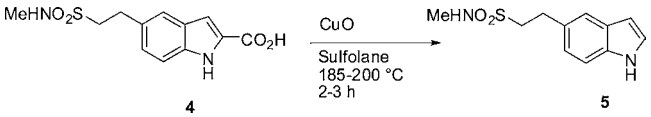


3 2

suggest that the decarboxylation is going through an arenium ion mechanism with H^+ as the electrophile and CO_2 as the leaving group. The authors back up their discussion with several references.

Rao et al.[12] reported the decarboxylation of indole derivative **4** with copper oxide in sulfolane at 185−200 °C with conventional heating to obtain **5** an intermediate for the synthesis of an active pharmaceutical ingredient (Scheme 3).

Scheme 3. Copper oxide-catalyzed decarboxylation in sulfolane



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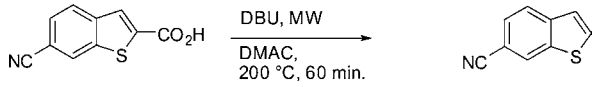
Allen[13] reported an improved decarboxylation method for substituted benzothiophenes by using microwave heating. They first developed a copper-mediated reaction in quinoline. The reaction was run on a 170 mmol scale in the CEM MARS microwave oven at 200 °C. Under these conditions they obtained an isolated yield of 6-cyano benzothiophene of 93% in comparison to 53% with conventional heating. The authors commented that, although the reaction was successful, the reaction mixture was heterogeneous and the workup problematic. To circumvent these problems the authors developed a new homogeneous decarboxylation method involving the use of an organic base, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), and a high-boiling polar aprotic solvent, *N*,*N*-dimethylacetamide (DMAC). Also for this method microwave heating was utilized. The decarboxylation was carried out at 200 °C for 1 h in a sealed microwave vessel (Scheme 4). The authors found

Scheme 4. DBU-promoted decarboxylation with microwave heating



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this method to be more convenient as both the base and the solvent could be easily washed away. Based on the substituents in the benzothiophene, yields between 54 and 100% were obtained.

The main obstacle with microwave technology is still the very limited scale-up possibilities; this limits the use of microwave heating for process development with the intention for large-scale manufacture. To mimic microwave heating with conventional heating, the fast heatup, and the ability for super heating, the amount of material heated has to be very small. One way of doing this is in a plug-flow tube reactor with pressure control. This reactor can be heated and cooled very rapidly to any temperature independent of the boiling point of the solvent.

RESULTS AND DISCUSSION

We have assembled and used a continuous reactor setup for process development and scale-up of high-pressure, high-temperature, continuous processes that has been used in various projects. The reactor consists of ISCO high-pressure syringe pumps, a mixing device (either micro mixer or T-joint), coiled tubing (stainless steel, PTFE, Hasteloy) coiled in a GC oven, and at the outlet of the reactor, a cooling zone, a pressure gauge, and a backpressure valve controlling the conditions to prevent evaporation or off gassing in the hot zone.

We have, in a way similar to that of Kappe et al.,[14] also looked at the potential to transfer processes that are run under microwave heating to continuous plug flow reactor protocols with convection heating. The microwave-assisted decarboxylation of indole-2-carboxylic acid from Jones and Chapman[9] is an interesting reaction as the reaction delivered indole in high yield under microwave heating in quinoline or neat. However, the reaction was found to be successful only on very small scale. The transfer to a tube reactor would be ideal as in this type of reactor there is a very small amount of reactants in the hot zone at any given time. In combination with the report of Sinha[10] on the decarboxylation of indole-2-carboxylic acid in an ionic liquid with a small amount of water and the process developed by Trainer[11] with a decarboxylation of the same substrate under high-temperature aqueous conditions, it seems possible to decarboxylate indole-2-carboxylic acid in solution in a tube reactor under various conditions. The microwave-mediated decarboxylation of the benzo[*b*]thiophene-2-carboxylic acid with 5 equiv of DBU in DMAC at 200 °C from Allen[13] is also interesting as part of this concept. On the basis of these reports we thought that it would be worthwhile to screen for a new protocol for the decarboxylation of indole-2-carboxylic acid and for other heteroaromatic and aromatic carboxylic acids in a tube

dx.doi.org/10.1021/op300125p | *Org. Process Res. Dev.* 2012, 16, 1449−1454

Table 1. Screen of base and solvent for the continuous decarboxylation of indole-2-carboxylic acid

entry	temperature, °C	amount base	solvent	conversion %	comment
1	300	5 equiv DBU	DMAC	99	polar impurities
2	300	5 equiv DABCO	DMAC	99	polar impurities
3	300	5 equiv DMAP	DMAC	47	polar impurities
4	300	5 equiv DBU	DMF	97	polar impurities
5	300	5 equiv DABCO	DMF	96	polar impurities
6	300	5 equiv DMAP	DMF	43	polar impurities
7	300	5 equiv DBU	NMP	99	polar impurities
8	300	5 equiv DBU	sulfolane	100	clean reaction
9	300	5 equiv DABCO	sulfolane	100	clean reaction
10	300	5 equiv DMAP	sulfolane	55	impurities

reactor. According to the reports, we believe that the use of amine bases such as DBU, 1,4-diazabicyclo[2.2.2.]octane (DABCO), and 4-dimethylaminopyridine (DMAP) in polar aprotic solvents such as DMAC, dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), and sulfolane at temperatures from 200 to 300 °C would be effective (see Table 1). Dimethylsulfoxide (DMSO) was ruled out due to its well-known instability at temperatures above 200 °C. The use of aqueous conditions in the same solvents would also be of interest.

The first test was with base in the selected solvents in the stainless steel tube reactor using indole-2-carboxylic acid (**1**) as substrate.

For the reactor setup we used in the front end a Teledyne Isco syringe pump 500 D with an internal pressure gauge. The reactor itself was a 2 m long 1/16 tube with an internal volume of 5.9 mL coiled to fit into the oven. At the outlet of the oven the reactor tube was fitted with a back pressure regulator prior to the product collecting flask. On the basis of our previous experiences we were confident that this methodology would be useful for the evaluation of the decarboxylation.

For the first test screen we decided to use the highest temperature, 300 °C, to see the stability of the mixture. The carboxylic acid (**1**) was dissolved in 10 volumes of solvent and 5 equiv of base at room temperature. For a good performance of the reaction in the tube reactor we needed a mixture of the preformed salt to remain homogeneous in the syringe pump at room temperature. The oven temperature was set at 300 °C. The rationale for the selection of this high temperature is that, if the bulk solution has a temperature of 200 °C in the reported procedure from Allen,[13] it may be that hot spots have a much higher temperature in the microwave oven. It was also reported by Jones and Chapman[9] that the temperature during the decarboxylation rapidly can reach 300 °C. Trainer[11] also used a high temperature (255 °C) for the decarboxylation. The flow was set to result in a residence time of 30 min in the hot zone. From this first screen we found that the best bases were DABCO and DBU. The best solvent was found to be sulfolane giving a cleaner reaction mixture than the other solvents with full conversion of the carboxylic acid (**1**). In the case of DMAP we did not reach complete conversion, merely 55% (entry 10, Table 1).

We decided to continue with DBU and DABCO in sulfolane due to the better impurity profile.

A residence time screen with 5 equiv DBU/DABCO in 10 volumes of sulfolane at 300 °C with residence times of 4, 7, and 15 min gave in all cases a complete conversion of the starting material (Table 2).

Table 2. Optimization of the continuous decarboxylation of indole-2-carboxylic acid[a]

entry	temperature, °C	amount base	residence time	conversion, %	comment
1	300	5 equiv DBU	15	complete	
2	300	5 equiv DBU	7	complete	
3	300	5 equiv DBU	4	complete	
4	300	5 equiv DABCO	15	complete	difficult to dissolve the salt
5	300	5 equiv DABCO	7	complete	difficult to dissolve the salt
6	300	5 equiv DABCO	4	complete	difficult to dissolve the salt

[a]All reactions were run in 10 volumes in sulfolane.

On the basis of the easier handling of the DBU salt of the carboxylic acid (**1**) we decided to continue with DBU as we did not see a difference in the impurity profile from the two different bases.

From the reaction at 300 °C and 7 min residence time with DBU we could isolate indole (**2**) in 83% yield after workup, addition of 1 N aqueous HCl, extraction of the product with MTBE, and crystallization from MTBE/hexane.

Reduction of the excess of DBU down to 1 equiv shows a small change in kinetics (Table 3 entry 3). The conversion of the starting material in this case is complete within 20 min (Table 3, entry 4). The reduction of sulfolane to 5 volumes gave also a complete conversion of (**1**) (entry 5). In three volumes the salt between 2-indole carboxylic acid and DBU is not more soluble at room temperature. The best conditions

Table 3. Optimization of the continuous decarboxylation with DBU of indole-2-carboxylic acid[a]

entry	temperature, °C	amount DBU, equiv	residence time, min	conversion, %	comment
1	300	5	7	complete	
2	300	3	7	complete	
3	300	1	7	90	
4	300	1	20	complete	
5	300	1	20	complete	5 volumes of sulfolane

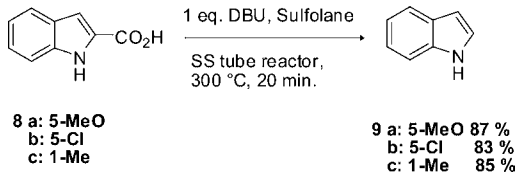
[a]All reactions were run in 10 volumes in sulfolane except entry 5.

dx.doi.org/10.1021/op300125p | *Org. Process Res. Dev.* 2012, 16, 1449−1454

from this evaluation was found to be to dissolve the indole-2-carboxylic in 5 volumes of sulfolane with 1 equiv of DBU and to pump the mixture through the 300 °C hot reactor with a residence time of 20 min in the reactor. The reactor is cleaned with one reactor volume of sulfolane, and the complete mixture is worked up through addition of 1 N hydrochloric acid and MTBE. The obtained crude product is purified through crystallization. After purification indole (**2**) was obtained in a yield of 84%.

Different indole-2-carboxylic acids gave under the same reaction conditions the corresponding indoles in good yields (Scheme 5).

Scheme 5. Decarboxylation of indole derivatives in sulfolane

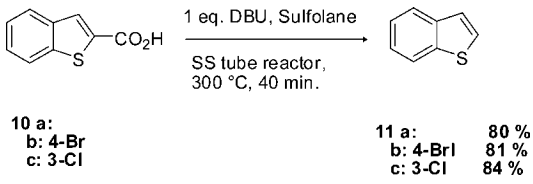


5-Methoxyindole-2-carboxylic acid (**8a**) was converted to 5-methoxyindole (**9a**) in a clean reaction giving the product (**9a**) in an isolated yield of 87%. 5-Chloroindole-2-carboxylic acid (**8b**) was also cleanly converted to 5-chloroindole (**9b**) in 83%. 1-Methylindole-2-carboxylic acid (**8c**) afforded in a clean reaction 1-methylindole (**9c**) in 85% yield.

On the basis of the reports from Arun K. Sinha et al.[10] and from Robert W. Trainer et al.[11] that aqueous conditions for the decarboxylation, either with small amounts water or in water as solvent, we decided to investigate if it would be possible to run the reaction without base and instead add a small amount of water. A mixture of 3% water in sulfolane is commercially available, and in comparison to pure sulfolane the mixture is a liquid at room temperature.[15] The mixture has a melting point of 10 °C, but addition of more water lowers the melting point even further. Indole-2-carboxylic acid (**1**) dissolves readily in the 3% mixture. When the reaction mixture is heated for 20 min at 300 °C a complete conversion of the acid (**1**) takes place. Indole (**2**) was obtained through this method in 84%. Also in anhydrous sulfolane indole-2-carboxylic acid (**1**) is decarboxylated under the same reaction conditions giving indole (**2**) in 81%.

Being successful with the decarboxylation of indole-2-carboxylic acids with three different methods, we turned our attention to the decarboxylation of benzo[*b*]thiophene-2-carboxylic acid (**10a**) to benzo[*b*]thiophene (**11a**) (Scheme 6). As Allen et al.[13] have reported that the decarboxylation takes place with 5 equiv of DBU in DMAC under microwave heating at 200 °C, we started the investigation with 1 equiv of DBU in sulfolane at 300 °C for a continuous protocol. The conversion of the acid was after 20 min residence time 80% in a clean reaction. At 310 °C we obtained 95% conversion, and at 320 °C the conversion was complete. If the reaction was run at 300 °C with a residence time of 40, min the reaction was also complete. In this case we obtained after workup benzo[*b*]-thiophene (**11a**) in a yield of 80%. With 2 equiv of DBU, the reaction was complete after 20 min at 300 °C.

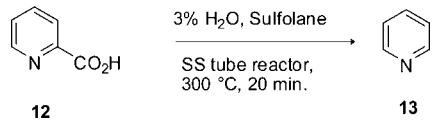
Scheme 6. Decarboxylation of benzo[*b*]thiophene derivatives in sulfolane



In addition, the decarboxylation of 4-bromo benzo[*b*]-thiophene-2-carboxylic (**10b**) acid worked well, giving the 4-bromo-benzo[*b*]thiophene (**11b**) in 81% yield. The conversion of 3-chloro-benzo[*b*]thiophene-2-carboxylic acid (**10c**) to 3-chloro-benzo[*b*]thiophene (**11c**) (84%) also went smoothly.

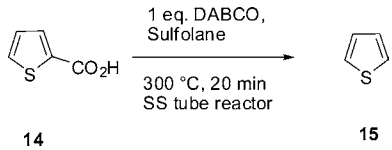
Picolinic acid (**12**) was only to 50% converted to pyridine (**13**) with 1 equiv of DBU in sulfolane at 300 °C after 20 min (Scheme 7). In sulfolane with 3% water without DBU the conversion was complete, and pyridine could be isolated in 75% yield.

Scheme 7. Decarboxylation of picolinic acid in sulfolane



The decarboxylation of thiophene-2-carboxylic acid (**14**) failed with 1 equiv of DBU in sulfolane; at 300 °C after 20 min only 5% conversion was obtained. With more harsh conditions, no product and no starting material could be detected. The method with 3% water in sulfolane did also not give any conversion of the carboxylic acid. As we changed the base to DABCO we surprisingly obtained a complete conversion (Scheme 8) with an isolated yield of 73% from thiophene (**15**).

Scheme 8. Decarboxylation of thiophene-2-carboxylic acid in sulfolane



With benzoic acid derivatives either no conversion as in the case of benzoic acid, 5-chlorobenzoic acid, or nahphthoic acid was observed. 5-Methoxybenzoic acid gave undefined mixtures of products containing some phenol.

CONCLUSION

In conclusion we have found a scalable, versatile, continuous process for the decarboxylation of heterocyclic carboxylic acids with 1 equiv of either DBU or DABCO in sulfolane at 300 °C. In some cases no base is needed.

EXERIMENTAL SECTION

All solvents were purchased as anhydrous and used as received. All reagents were used as received. All manipulations were performed under nitrogen atmosphere. Reactions were monitored with reversed phase HPLC on a Waters instrument with a photodiode array detector using a Waters Sunfire (4.8 mm × 50 mm C8, 3.5 μm). The mobile phase (water/acetonitrile/phosphoric acid (0.1%), 85:5:10 in 0 min to 0:90:10 in 3.3 min; 3.3 min to 0:90:10 in 5.0 min; 0:90:10 in 5 min to 85:5:10 in 5.1 min with a flow rate of 3.0 mL/min. The

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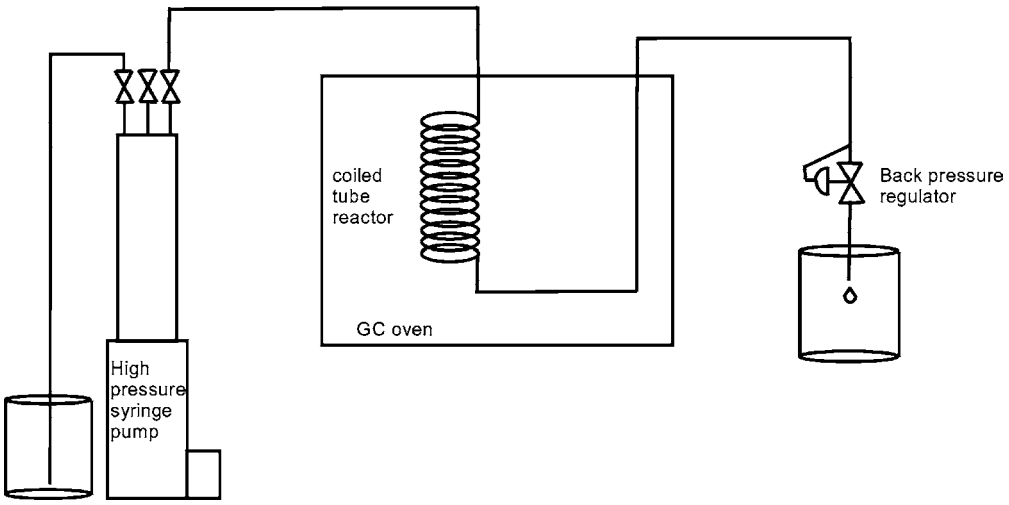

Figure 1. Schematic description of the continuous tube reactor setup.

spectral data for all obtained products were identical to those of commercial samples.

The reactor setup (see Figure 1): Connect the pump containing an internal pressure gauge with the coiled tube reactor at the front end. Connect the back end of the coiled 316 stainless steel reactor (internal volume 15.8 mL) to a T-joint. To the T-joint is a pressure gauge connected at one end and to the other is connected a back-pressure regulator prior to the outlet into the collection flask. Insert the coiled reactor part into the GC-oven.

Example for the Decarboxylation of Indole-2-carboxylic Acid. Indole-2-carboxylic acid (16.16 G, 100 mmol) was dissolved in sulfolane (160 mL). DBU (15.2 g, 100 mmol) was added. The mixture was filled into the syringe pump. The temperature in the oven was set to 300 °C. The pump was started with a flow rate of 0.8 mL/min. As the pump became empty, it was refilled with 16 mL of sulfolane, and the pumping was continued. At the end, a sample was collected to verify that the complete reaction mixture had been removed from the reactor. The pump was stopped, and 1 equivalent of 1 N hydrochloric acid (100 mL) and MTBE ether (150 mL) were added to the collected solution. The phases were separated, and the aqueous phase was extracted twice with MTBE ether (50 mL). The combined organic phases were washed twice with water (50 mL). The solvent was removed through vacuum distillation in the rotary evaporator. The crude product was redissolved in one volume of MTBE, and hexane was slowly added under stirring until the product started to crystallize. The mixture was cooled in the freezer overnight to complete the crystallization. The product was filtered off and washed with hexane. The product was dried in vacuum; 9.8 g of indole (84%) was obtained. According to HPLC the purity of the crystalline product was 99.3%. Spectroscopic data were in accordance with reported data.

Example for the Decarboxylation of Thiophene-2-carboxylic acid. Thiophene-2-carboxylic acid (12.82 G, 100 mmol) was dissolved in sulfolane (160 mL). DABCO (11.2 G, 100 mmol) was added. The mixture was filled into the syringe pump. The temperature in the oven was set to 300 °C. The pump was started with a flow rate of 0.8 mL/min. As the pump became empty, it was refilled with 16 mL of sulfolane and the pumping continued. At the end, a sample was collected to verify that the complete reaction mixture had been removed from the reactor. The pump was stopped, and 1 equiv of 1 N hydrochloric acid (100 mL) and MTBE (150 mL) were added to the collected solution. The phases were separated, and the aqueous phase was extracted twice with MTBE (50 mL). The combined organic phases were washed twice with water (50 mL). The solvent was removed through distillation in a distillation setup. After removal of the MTBE, the product was distilled; boiling point = 84 °C. From the distillation, 6.1 g of thiophene (73%) was obtained. According to HPLC the purity of the isolated product was 98.5%. Spectroscopic data were in accordance with reported data.

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Notes

The authors declare no competing financial interest.

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