

Decarboxylation of Indole-2-carboxylic Acids: Improved Procedures

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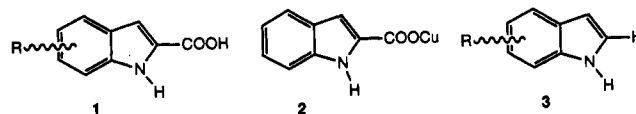
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Of the many synthetic avenues to 2-unsubstituted indoles available, classical approaches including the Reissert,¹ Fischer,² and Rees-Moody³ routes require subsequent removal of the 2-carboxyl function. Several procedures have been reported to effect this problematic transformation with widely ranging degrees of efficiency.^{4a-n} Problems encountered during the process usually stem from decomposition of the product under prolonged thermolysis conditions, and additional decomposition during purification of the crude product. For these reasons it has become commonplace to instead remove the carboxyl function at the indole-2-position by *decarbonylative* procedures,⁵ burdening any synthetic tree with additional steps.⁶ In connection with our studies on microwave-accelerated synthetic transformations,⁷ we reasoned that microwave-induced thermolysis of indole-2-carboxylate derivatives may allow decarboxylation to be accomplished with ease and now wish to report a successful protocol.

Results and Discussion

Inspection of the chemical literature suggested a variety of methods would be amenable for decarboxylation at the indole-2-position,⁴ however only one route gave an acceptable and reproducible yield in our hands, involving thermolysis of the indole-2-acid with copper chromite (25 mol % catalyst) in quinoline solution to give, in the case of 6-methoxyindole-2-carboxylate, a 65% yield of 6-methoxyindole (Table I, entry 2).^{4f,n} In an effort to improve this procedure using microwave thermolysis, several variants were examined, and eventually a quantitative

procedure was developed. Firstly, taking indole-2-carboxylate 1, (R = H) microwave thermolysis of a quinoline solution of the acid in a sealed tube in the presence of copper chromite gave a disappointingly low yield of the derived 2-unsubstituted indole (Table I, entry 3). Variation of the catalyst used in the process, however, had a marked beneficial effect (Table I entries 4-7). Copper(I) chloride proved to be an efficient catalyst, giving an 83% yield of indole with only 12 min of thermolysis. Using the copper(II) salt of the indolecarboxylate as catalyst,⁸ which presumably undergoes reduction to the copper(I) species 2 in quinoline,⁹ a 93% yield of decarboxylated indole was



recovered. Thermolysis was then attempted using copper powder as catalyst, and again an extremely clean decarboxylation ensued, giving a 94% yield of indole. Since copper metal was observed to have plated out on the reaction vessel, it was decided to attempt thermolysis in quinoline in the absence of a catalyst. *Near quantitative decarboxylation was achieved within 12 min, giving analytically pure indole on workup* (Table I, entry 8). Pyridine and triethylamine were found to be inferior to quinoline as solvents for the decarboxylation (entries 9, 10) and as expected, reducing the thermolysis time resulted in a lowering of yield of product (entries 11, 12). Conducting thermolyses in open tubes proved unsatisfactory (entry 13) since the internal temperature can approach 300 °C in a matter of minutes,^{7b} leading to sublimation and vaporization of reactants (CAUTION!). Since quantities of sublimed decarboxylated indole were recovered from the walls of the vessel, however, we attempted decarboxylation in the *absence of a solvent*.^{4d} Decarboxylation was successful, giving a 93% yield of indole on an analytical scale (0.3 mmol). Attempts to scale up the process, however, met with problems, presumably due to inefficient conduction of heat from the vessel, such that thermolysis of a 1-g sample gave yields of decarboxylated product which ranged from 70-80%. On the basis of the above results, a series of substituted indole-2-carboxylates were subjected to microwave thermolysis using quinoline as solvent (Table II). In all cases, near quantitative decarboxylation was achieved using a thermolysis time of 12 min, and the results were reproducible regardless of scale within the range studied (0.5-2 mmol).

The above methods offer high-yielding expeditious access to 2-unsubstituted indoles, useful in a variety of synthetic endeavors. The latter methods are noteworthy for their simplicity and efficiency since no derivitization of the carboxylate is required. It is anticipated that such protocol will find broad application in the small-scale (<2 mmol) decarboxylation of indoles, and as such the methodology is currently being exploited in these laboratories.

(8) The indole-2-carboxylate copper(II) salt, prepared by the method of Piers,⁴ could be dried and stored in a vacuum desiccator over phosphorus pentoxide for extended periods. It was also found, as expected that the copper(I) salts derived from any of the indole-2-carboxylates described herein could be used as catalysts for decarboxylation.

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Table I. Thermolytic Decarboxylation of Indole-2-carboxylic Acids 1 To Form Indoles 3

entry	substituent	thermolysis/ time, min	solvent	catalyst (%)	% yield of 3
1	1, R = H	thermal/24	quinoline	CuO-Cr ₂ O ₃ (25)	53
2	1, R = 6-MeO	thermal/24	quinoline	CuO-Cr ₂ O ₃ (25)	65
3	1, R = H	microwave/12	quinoline	CuO-Cr ₂ O ₃ (5)	3
4	1, R = H	microwave/12	quinoline	CuCl (5)	83
5	1, R = 6-MeO	microwave/12	quinoline	Cu(II) salt of 2 (5)	93
6	1, R = 6-MeO	microwave/12	quinoline	Cu(II) salt of 2 (10)	93
7	1, R = H	microwave/12	quinoline	Cu powder (7)	94
8	1, R = H	microwave/12	quinoline	-	95
9	1, R = H	microwave/12	triethylamine	-	36
10	1, R = H	microwave/12	pyridine	-	60
11	1, R = H	microwave/10	quinoline	-	63
12	1, R = H	microwave/6	quinoline	-	37
13	1, R = H	microwave/12	quinoline	-(open tube)	<15
14	1, R = H	microwave/12	no solvent	-	70-83

Table II. Microwave-Accelerated Decarboxylation of Indole-2-carboxylates 1 to Form 3

entry	indole 1	thermolysis time, min	% yield of 3
1	R = H	12/quinoline	95
2	R = 4-MeO	12/quinoline	97
3	R = 6-MeO	12/quinoline	99
4	R = 5-MeO	12/quinoline	100
5	R = 5-F	12/quinoline	96
6	R = 6-F	12/quinoline	91

Experimental Section

Indole-2-carboxylates used in this study were derived from the corresponding indole 2-methyl esters, prepared using the azidocinnamate indole route.³ For all microwave thermolyses reported herein, an unmodified commercial (600 W) oven was used.^{7b} The following procedures are representative:

Conventional Decarboxylation of 6-Methoxyindole-2-carboxylate: 6-Methoxyindole-2-carboxylic acid (0.1338 g, 0.70 mmol), copper chromite (barium-promoted) (0.06 g, 0.17 mmol), and triply distilled quinoline (10 mL) were placed under nitrogen in a 25 mL round-bottom flask fitted with a reflux condenser. The flask was lowered into an oil bath preheated to 220 °C. The nitrogen line was removed and a microbubbler attached. The reaction mixture was heated until gas evolution stopped (24 min). The nitrogen line was reattached, and the mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate (75 mL) and washed with HCl (1% 3 × 300 mL). The acid washes were then extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (2 × 75 mL) and NaOH (0.1 M 3 × 50 mL). The NaOH washes were extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (2 × 50 mL), and the solvent was evaporated. The compound was purified by flash chromatography on silica (1:1 ether/hexanes) to yield 6-methoxyindole (0.067 g, 65%) as light yellow crystals, mp 90–91 °C (lit.¹⁰ mp 91–92 °C).

Microwave-Accelerated Decarboxylation of 5-Methoxyindole-2-carboxylate. A suspension of 5-methoxyindole-2-carboxylic acid (0.247 g, 1.293 mmol) in redistilled quinoline (1.5 mL) was placed in a glass tube (3/4-in. heavy wall borosilicate

tubing) with a tapered end. The mixture was placed under vacuum and sealed.¹¹ The tube was packed in vermiculite (35 g) in a glass beaker (250 mL) and subjected to microwave heating for 12 min (2450 MHz, 600 W). Upon cooling, the tube was opened, and the entire contents were diluted with ethyl acetate (35 mL). The solution was washed with HCl (1%, 5 × 75 mL), and then the combined washes were extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with water (2 × 75 mL) and then NaOH (0.1 M, 5 × 50 mL). After extraction of the base washings with ethyl acetate (2 × 25 mL), the combined organic extracts were washed with water (2 × 50 mL) and then filtered through a silica gel plug, and the solvent was evaporated. The crude product was then azeotroped with benzene (2 × 50 mL) and then dried under vacuum to give 5-methoxyindole (0.190 g, 100%) as a colorless solid, mp 56–57 °C (lit.^{4a} mp 55 °C) homogeneous and identical to a commercial sample as verified by 300-MHz ¹H NMR and capillary GC analysis.¹²

General Procedure for Microwave-Accelerated Decarboxylation in the Absence of Solvent. Using the same tubes, indole-2-carboxylic acid (0.0528 g, 0.328 mmol) was decarboxylated (12 min, 600 W). On cooling, the walls of the tube were washed with ethyl acetate (20 mL), and the solution was concentrated to dryness to yield indole (0.0357 g, 93%).

General Procedure for Microwave-Accelerated Decarboxylation Using Copper Metal. Using the same tubes, and the same-purity quinoline (1 mL), but with the addition of copper metal (powdered, 200 mesh) (0.0058 g, 0.09 mmol, 7 mol %), indole-2-carboxylic acid (0.2058 g, 1.28 mmol) was decarboxylated (12 min, 600 W) to yield indole (0.1406 g, 94%).

General Procedure for Microwave-Accelerated Decarboxylation Using the Derived Copper(II) Salt. The copper(II) salt of indole-2-carboxylate was prepared according to the method of Piers.⁴ As a solution in triply distilled quinoline (1 mL), 6-methoxyindole-2-carboxylic acid (0.0573 g, 0.30 mmol) was decarboxylated (12 min, 600 W) in the presence of the copper(II) salt of indole-2-carboxylate (0.0060 g, 0.0156 mmol, 5 mol %) in a sealed tube to yield 6-methoxyindole (0.0410 g, 93%) and indole (0.0014 g, 4%).

(11) Alternatively, a reusable sealed tube (Chem Glass part no AF-009001) can be used.^{7b}

(12) All product yields reported are based on purified indoles which were homogenous (¹H, ¹³C NMR, GC, mp) and spectroscopically identical with commercially available samples.

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