

Silver-Catalyzed Protodecarboxylation of
Heteroaromatic Carboxylic Acids[†]

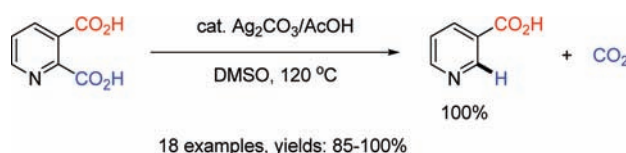
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ABSTRACT



A simple and highly efficient protodecarboxylation procedure for a variety of heteroaromatic carboxylic acids catalyzed by Ag_2CO_3 and AcOH in DMSO is described. This methodology can also perform the selective monoprotodecarboxylation of several aromatic dicarboxylic acids.

Decarboxylation reactions are important transformations in synthetic organic chemistry,¹ especially for the removal of carboxylate groups that were required as directing groups in other transformations² but are not part of the target molecules.³ Consequently, considerable effort has been directed to the study of the protodecarboxylation of aromatic carboxylic acids,⁴ which usually require the use of transition metals such as Cu,⁵ Hg,⁶ and Pd.⁷ Among the various methods, the use of Cu/quinoline systems is most widely

adopted following the seminal work by Shepard et al. on the protodecarboxylation of halofuroic acids promoted by stoichiometric Cu(0).^{5a,8} Subsequently, the protodecarboxylations of thenoic, furoic and indole-2-carboxylic acids were reported following similar procedures.^{5c,9} This methodology has recently been significantly improved by Goossen et al. with the development of a catalytic Cu(I)/phenanthroline/quinoline system.¹⁰ However, all of these methods suffer from the same problems, namely, the requirement for extremely high temperatures (170–200 °C), which limits substrate compatibility, and the difficulties in isolating the products from their high boiling point reaction solvents.

During the development of a Pd/Ag bimetallic system for mild direct arylations^{11a} and decarboxylative arylations of indoles,^{11b} we observed that Ag salts were able to promote the protodecarboxylation of aromatic carboxylic acids. As a result,

[†] Dedicated to the memory of Professor Keith Fagnou.

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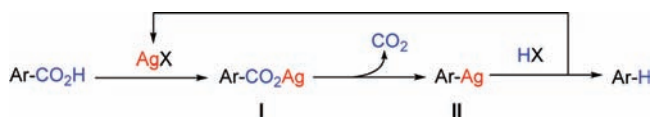
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we recently reported a method for the Ag-catalyzed protodecarboxylation of *ortho*-substituted benzoic acids that affords essentially quantitative yields at temperatures as low as 120 °C (i.e., 50–80 °C lower than the corresponding Cu-based methods).¹² This transformation is believed to proceed via silver arene **II**, which is subsequently protonated (Scheme 1).

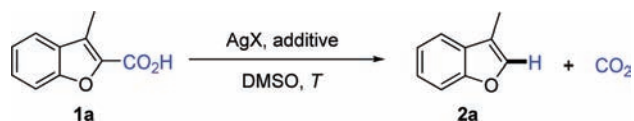
Scheme 1. Proposed Mechanism for the Ag-Catalyzed Protodecarboxylation of Benzoic Acids



The nature of the *ortho* substituent is extremely important, with only electron-withdrawing or alkoxy groups leading to protodecarboxylation.¹³ With the view to extending this protocol to heteroaromatic carboxylic acids, we hypothesized that the ring heteroatom could play the same role as the *ortho* substituent in our previous studies, activating a carboxylic acid at the α position. Herein, we report a new Ag-promoted protodecarboxylation protocol that affords excellent yields when applied to a wide range of heteroaromatic carboxylic acids. Further, we describe the extension of this protocol to the selective monodecarboxylation of dicarboxylic acids.

We began our investigation with 3-methylbenzofuran-2-carboxylic acid (**1a**). Reaction of **1a** under the conditions previously established in this laboratory¹² afforded protodecarboxylation product **2a** in 85% yield together with 15% unreacted **1a** after 16 h (Table 1, entry 1). The yield of this

Table 1. Optimization of Protodecarboxylation of 3-Methylbenzofuran-2-carboxylic Acid (**1a**)^a



entry	temp (°C)	AgX (mol %)	additive (mol %)	yield (%) ^b
1	120	Ag ₂ CO ₃ (10)		85
2	130	Ag ₂ CO ₃ (10)		92
3	140	Ag ₂ CO ₃ (10)		95
4	140	Ag ₂ CO ₃ (10)	TFA (5)	100
5	140	Ag ₂ CO ₃ (10)	AcOH (5)	100
6	140	AgOAc (20)		86
7	140			0
8	140		AcOH (5)	0
9	120	Ag ₂ CO ₃ (10)	AcOH (5)	100
10	110	Ag ₂ CO ₃ (10)	AcOH (5)	89
11	100	Ag ₂ CO ₃ (10)	AcOH (5)	40
12	110	Ag ₂ CO ₃ (10)	AcOH (50)	96
13	100	Ag ₂ CO ₃ (10)	AcOH (50)	78

^a Reaction conditions: the reactions were carried out in a sealed vessel using 1.0 equiv of **1a** and the indicated amount of catalyst, in a 0.5 M DMSO solution for 16 h. ^b Yield of **2a** was determined by ¹H NMR analysis using an internal standard.

reaction could be enhanced moderately by increasing the reaction temperature (entries 2 and 3), though this was deemed an unsatisfactory solution. Suspecting that the inferior yields may be due to a less efficient protonation of the silver arene intermediate **II** by acid starting material **1a**, we examined the effect of introducing additional acid cocatalysts.^{7b} Gratifyingly, the use of 5% TFA was sufficient to afford quantitative conversion to product **2a** (entry 4). Further screening of milder acid additives revealed that AcOH gave similar results (entry 5), and it was chosen for later studies. Interestingly, replacing Ag₂CO₃ with AgOAc did not lead to any improvement in reactivity (entry 6). No reaction was observed in the absence of Ag₂CO₃ with or without AcOH (entries 7 and 8). The use of 5% AcOH and 10% Ag₂CO₃ enabled reduction of the reaction temperature to 120 °C maintaining quantitative formation of **2a** (entry 9). Subsequent attempts showed that the temperature can be further reduced to 110 °C, but 50 mol % AcOH is required to obtain a comparable yield (entries 10–13).¹⁴

With the conditions optimized (10% Ag₂CO₃ and 5% AcOH in 0.5 M DMSO at 120 °C), we explored the generality of this protocol toward other heteroaromatic carboxylic acids (Table 2). Initially, we explored a variety of heteroarenes bearing the carboxylic acid group α to the heteroatom. We were pleased to find that these conditions were compatible with a range of heterocycles such as benzofurans (**1a**), benzothiophenes (**1b**), quinolines (**1c**), isoquinolines (**1d**), pyridines (**1e**), furans (**1f,g**), thiophenes (**1h,i**), and thiazoles (**1j**), affording the corresponding decarboxylated heteroarenes **2** in excellent yields.¹⁵ In keeping with our hypothesis that the heteroatom plays an activating role, the presence of a heteroatom α to the carboxylate was found to be essential for the decarboxylation to proceed, as exemplified by benzofuran **1k**, which failed to react. On the other hand, carboxylic acids with β or γ heteroatoms, such as **1l** and **1m**, could also be activated for protodecarboxylation by using an *ortho* electron-withdrawing substituent, as reported in our previous communication.¹² This methodology is operationally simple, affording excellent yields of analytically pure product after an aqueous workup, without the need for further purification. Furthermore, it can be easily scaled; for example, **2g** was obtained in 88% yield when the reaction was carried out at a 5 g scale.

On the basis of the remarkable activating effect of α heteroatoms and *ortho* electron-withdrawing groups, we hypothesized that our methodology may be applied to the regioselective protodecarboxylation of aromatic com-

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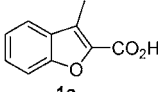
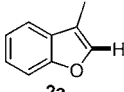
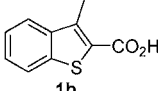
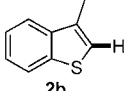
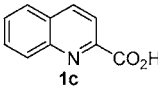
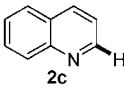
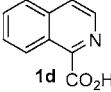
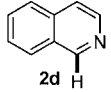
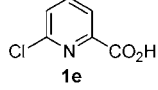
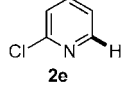
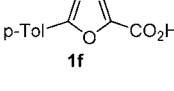
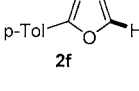
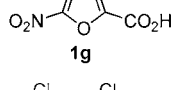
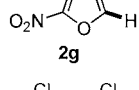
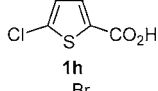
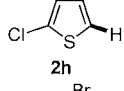
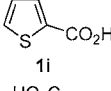



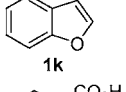

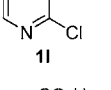



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(13) The origin of this selectivity is unclear at the moment, especially as the reaction seems to be activated by strongly electron-donating and -withdrawing groups, which may indicate that two different mechanisms are in place.

(14) Longer reaction times did not improve the yield.

(15) However, indoles and pyrroles were found to be unsuitable for protodecarboxylation under these reaction conditions.

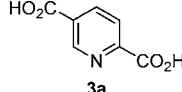
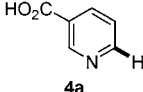
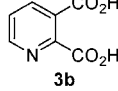
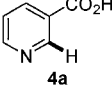
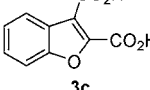
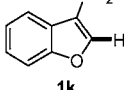
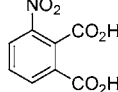
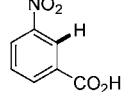
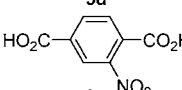
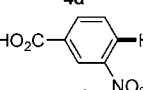
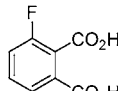
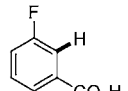
Table 2. Protodecarboxylation of Heteroaromatic Carboxylic Acids **1a–m**^a

entry	acid	product	yield (%) ^b
1			88
2			100
3 ^c			90
4			92
5 ^{c,d}			97
6 ^e			82
7			88
8			91
9 ^d			100
10 ^d			100
11			0
12 ^{c,d}			91
13 ^d			100

^a Unless otherwise noted, all reactions were carried out with 10 mol % Ag₂CO₃, 5 mol % AcOH, and 1.0 equiv of acid in a 0.5 M DMSO solution at 120 °C for 16 h. ^b Yields of isolated pure material. ^c The reaction was carried out at 140 °C. ^d This product was found to be volatile. The reaction was carried out in a sealed vessel, and the yield was determined by ¹H NMR analysis using an internal standard. ^e No AcOH was used.

pounds bearing more than one carboxylic acid, which would be of great value in the synthesis of natural

Table 3. Selective Monoprotodecarboxylation of Aromatic Dicarboxylic Acids **3a–f**^a

entry	diacid	product	yield (%) ^b
1 ^{c,d}			100
2 ^c			100
3 ^d			85
4			93
5			92
6			86

^a Unless otherwise noted, all reactions were carried out with 10 mol % Ag₂CO₃, 5 mol % AcOH, and 1.0 equiv of acid in a 0.5 M DMSO solution at 120 °C for 16 h. ^b Yields of isolated pure material. ^c Yield was determined by ¹H NMR analysis using an internal standard. ^d The reaction was carried out at 140 °C.

products.² Gratifyingly, when diacids **3a–f** were subjected to the above conditions (Table 3), complete regioselectivity was obtained affording monoacids **4a–f** in good to excellent yields. In every case, only the carboxylic acid α to a heteroatom (**3a–c**) or *ortho* to an appropriate substituent (**3d–f**) was removed, leaving the other carboxylate intact. It is noteworthy that adjacent carboxylic acid groups do not activate each other for protodecarboxylation (entries 2 and 3; 5 and 6). As a comparison, a test reaction was carried out using the Cu₂O/phenanthroline/quinoline protocol^{10a} on dicarboxylic acid **3d**, which afforded nitrobenzene as the only observed product in 47% yield as determined by ¹H NMR.

In summary, we have developed a mild and operationally simple procedure for the Ag-catalyzed protodecarboxylation of a range of heteroaromatic carboxylic acids, which is believed to proceed via organosilver intermediates. Under these conditions, selective monoprotodecarboxylation of aromatic and heteroaromatic dicarboxylic acids was also accomplished by exploiting the activating effects of *ortho* substituents or α heteroatoms. Current investigations are directed toward further decreasing the temperature required in order to accommodate thermally unstable substrates.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of **2b**, **2g**, **1k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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