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Reducing the Cost, Smell, and Toxicity of the Barton Reductive Decarboxylation: Chloroform as the Hydrogen Atom Source

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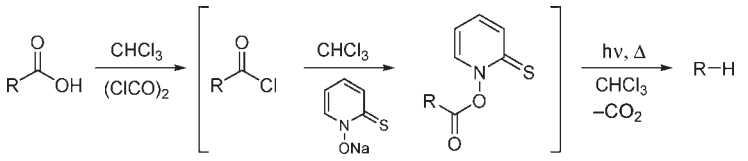
ABSTRACT



When used as solvent, chloroform was found to act as a hydrogen atom donor in Barton reductive decarboxylation reactions. Chloroform offers a substantial practical advantage over pre-existing hydrogen atom donors.

The Barton decarboxylation protocol is a powerful synthetic tool for converting alkyl carboxylic acid residues into a variety of different functionalities through the intermediacy of the corresponding alkyl radical.[1] Reductive decarboxylation is an important reaction subset, which can be performed in a variety of ways with the method of choice being that developed by Barton involving the homolytic decomposition of thiohydroxamic esters in the presence of a suitable hydrogen donor (H-donor).[2]

Under the Barton protocol, reductive decarboxylation to furnish the reduction product **2** is facilitated by mild photochemical decomposition of the corresponding thiohydroxamic ester (**3**), which can be obtained directly from an acid chloride **4** (or carboxylic acid **1**)[3] and the sodium salt of 1-hydroxypyridine-2(1*H*)-thione (**5**), in the presence of a suitable H-donor, originally tributyltin hydride or *tert*-butylthiol (Scheme 1).[1] This robust and broadly applicable reaction has one well-recognized shortcoming, namely that the said reducing agents are costly, highly toxic, and pungent, and their byproducts are often difficult to remove from the desired reaction products. To address these difficulties, innovative developments have been reported to address the issues with using organotin hydrides in particular.[4] However, these additional measures introduce further operational complexity and cost. The search for H-donor replacements[5] has seen the introduction of several alternative H-donors, including, tris(trimethylsilyl) silane,[6] germanim hydride,[7] hypophosphorous acid (and

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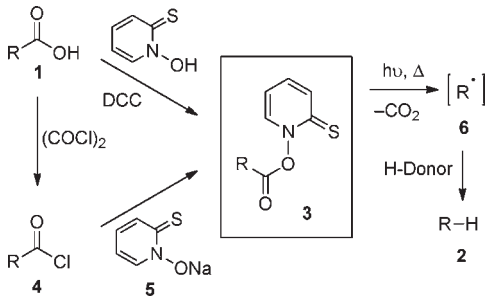
salts),[8] and tris(trimethylsilyl)methane.[9] Each of these H-donor replacements, however, brings their own limitations, including cost, availability, and toxicity. Despite the progress represented by these innovations, the availability of an H-donor that is effective, readily available, inexpensive, and easily removed from the final reaction products and with an acceptable toxicity profile is still lacking. Indeed, a reagent with these features would significantly enhance the attractiveness of the Barton reductive decarboxylation reaction. Herein we report on the utility of chloroform as such an H-donor.

Scheme 1. Barton Reductive Decarboxylation Reaction



Our chance observation that chloroform preferentially delivered hydrogen to 4-methoxycarbonyl-1-cubyl radical (Table 1, entry 5) under Barton conditions prompted a detailed investigation into its potential as a bona fide H-atom donor. While the original intent was to substitute the increasingly inaccessible carbon tetrachloride, an excellent Cl-atom donor under Barton conditions,[2e] with chloroform,[10] we were surprised to find that the major component isolated was methyl cubanecarboxylate, with only a trace of the corresponding chloride (methyl 4-chlorocubanecarboxylate) as observed by GPC.

Accordingly, we set out to explore the utility of chloroform, and other commonly used solvents, including nitromethane, as convenient H-donors for use in Barton reductive decarboxylation reactions.

While the mainstream free-radical literature has been somewhat silent on the synthetic utility of chloroform as an H-donor in the reduction of alkyl radicals, its behavior as a chain-transfer agent in the polymer literature has been well documented.[11]

Using palmitic acid as a test vehicle the corresponding acid chloride was generated, dissolved in nitromethane, and exposed to the sodium salt of 1-hydroxypyridine-2(1*H*)-thione (**5**) to generate the Barton thiohydroxamic ester **3** (R = *n*-$C_{15}H_{31}$). Irradiation of the solution at reflux, with a tungsten lamp, afforded the reduced material **2** (R = *n*-$C_{15}H_{31}$), but only in 32% yield (Table 1, entry 1). When chloroform was used, instead of nitromethane, a dramatic increase in yield was observed (i.e., 86% isolated over two steps) (Table 1, entry 2). Together with this yield improvement, a practical advantage was also gained in that palmitoyl chloride could be generated in chloroform and used without purification in the next step. The Barton ester **3** (R = *n*-$C_{15}H_{31}$) was also obtained directly from the carboxylic acid using peptide coupling agents as has been previously reported.[3] In this case, the overall hydrocarbon yield fell to 72% (Table 1, entry 3), which is attributed to the efficiency of the coupling process rather than the inefficiency in the reductive decarboxylation step. These results are comparable, if not improvements, on the results obtained with classical H-donor sources such as *n*-Bu_3SnH, *t*-BuSH, and PhSH (Table 1, entries 4–6). Given the favorable results obtained using the acid chloride approach (Table 1, entry 2), this method was applied to a range of other substrates (Table 1). Both the adamantanyl and cubyl systems performed well (Table 1, entries 9 and 10), whereas 4-(methoxycarbonyl)cyclohexanecarboxylic acid afforded the methyl cyclohexanecarboxylate in only 48% yield (Table 1, entry 8). The decreased yield in this case was most likely a result of isolation difficulties rather than poor reactivity. Ketone functionality is well tolerated, and acid **1i** proceeds smoothly giving the product in 74% yield (Table 1, entry 14).[12] The two steroidal substrates (Table 1, entries 11 and 12) gave similar yields of product (i.e., 65 and 68%, respectively). In the case of entry 11, two minor byproducts, the alcohol **8** and aldehyde **7**, were isolated. These are presumably the result of extraneous oxygen acting on the radical intermediate. Slight oxidation was also apparent with diphenylacetic acid (Table 1, entry 15), which gave dimer **9** as the major product.

Aromatic carboxylic acids (i.e., Table 1, entry 15) were found not to undergo reductive decarboxylation under these conditions, but instead gave anhydrides. This finding is consistent with Barton's observations,[14] although Barton has demonstrated aromatic decarboxylative halogenation is possible with activated aromatic substrates.[15] Finally, our attempts to use this protocol to reduce α-amino acids led to complex, intractable, mixtures.

From a mechanistic perspective, the observed results can be rationalized in at least two ways. The first involves direct H-transfer from chloroform to the alkyl radical (**6**), thus furnishing the observed reduction product (**2**) and the

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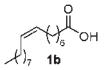
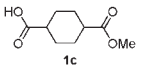
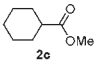
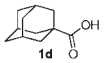
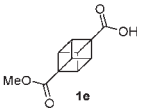
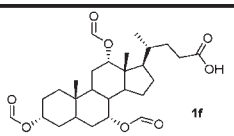
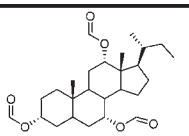
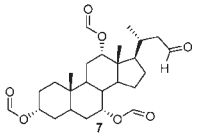
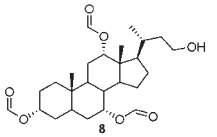
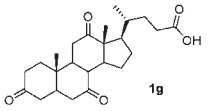
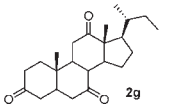
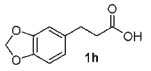
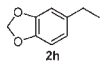
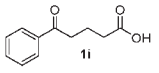
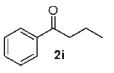
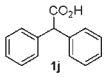
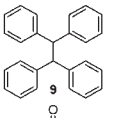
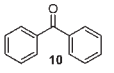
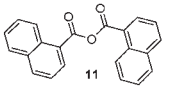
(15) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 4321.

Table 1. Examples of Barton Reductive Decarboxylations with Selected Substrates Using Chloroform As the H-Donor

entry	carboxylic acid	method[a]	product	yield (%)[g]
1	 1a	A[b]	 2a	32
2	 1a	A[c]	 2a	86
3	 1a	B[c]	 2a	66 (72)[h]
4	 1a	A[d]	 2a	72 ref [2a]
5	 1a	A[c]	 2a	72 ref [2a]
6	 1a	A[f]	 2a	85 ref [13]
7	 1b	A[c]	 2b	66
8	 1c	A[c]	 2c	48
9	 1d	A[c]	 2d	75
10	 1e	A[c]	 2e	82
11	 1f	A[c]	 2f	65
			 7	8
			 8	4
12	 1g	A[c]	 2g	68
13	 1h	A[c]	 2h	77
14	 1i	B[c]	 2i	74
15	 1j	A[e]	 9	51
			 10	12
16	 1k	A[e]	 11	64

[a] Method A: Conversion to acid chloride followed Barton decarboxylation. Method B: DCC coupling followed by Barton decarboxylation (see the Supporting Information). [b] Nitromethane as solvent. [c] Chloroform as solvent. [d] Benzene as solvent and *n*-Bu_3SnH as H-donor. [e] Benzene as solvent and *t*BuSH as H-donor. [f] CCl_4 as solvent and PhSH as H-donor. [g] Isolated yields. [h] Yield based on recovered starting material.

trichloromethyl radical (**14**), which then propagates the radical chain reaction through attack at the sulfur terminus of the thiohydroxamic ester (**3**), thereby furnishing the pyridyl sulfide coproduct (**15**) and a new alkyl radical **6** (path A). Available H-transfer rate constants (k_H) for chloroform from the work of Tuan and Gäumann[16] through the reaction of hexyl radicals with chloroform provided k_H of 4.8×10^3 M^{-1} s^{-1} at −10 °C, whereas the k_H for the adamantyl[10a] and *tert*-butyl[17] radicals at 25 °C were determined to be 2.9×10^3 M^{-1} s^{-1} and 2.54×10^2 M^{-1} s^{-1}, respectively. This data effectively places an upper limit for the k_H for chloroform with alkyl radicals at ca. 10^4 M^{-1} s^{-1} at the boiling point of chloroform (61 °C). Indeed, when viewed against well-established H-donors such as *n*-Bu_3SnH ($k_H = 4.9 \times 10^6$ M^{-1} s^{-1} at 50 °C)[2c] and *t*-BuSH ($k_H = 1 \times 10^7$ M^{-1} s^{-1} at 50 °C)[2c] the H-transfer potential of chloroform is less obvious.

An alternative scenario (path B), providing the same overall outcome, invokes the rapid H-transfer from chloroform to the 2-pyridiylthiyl radical (**12**), thereby generating 2-pyridinethiol (**13**). The thiol **13** would be a transient species that would be expected to deliver H to the alkyl radical (**6**) at a much greater rate consistent with the well-known ability of thiophenol to function as an effective H-donor to alkyl radicals (Scheme 2).[18,19]

Additionally, Newcomb and Kaplan[20] have previously determined the rate constant for the reaction of octyl

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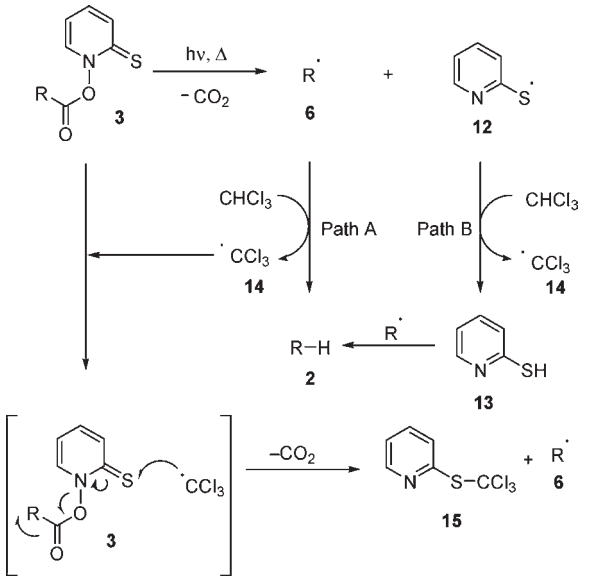
(17) Frith, P. G.; McLauchlan, K. A. *J. Chem. Soc., Faraday Trans. 2* **1976**, *72*, 87.
(18) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268.
(19) This suggested H-transfer between 2-pyridiylthyl radical and chloroform is consistent with the concept of polarity reversal catalysis developed by Roberts; see: Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.
(20) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.

Scheme 2. Speculative Mechanism for Barton Reductive Decarboxylation Using Chloroform as a H-Donor



radical with its precursor thiohydroxamic ester (**3**, R = octyl) to be ca. 4×10^6 M^{-1} s^{-1} at 80 °C, which effectively imposes a minimum reactivity for any H-donor to ensure minimal competition with self-trapping. This is a feature of all thiohydroxamic esters when decomposed homolytically in the absence of a radical trap.[1b]

The above analysis therefore places an upper limit on the effective tolerable concentration of the in situ formed thiohydroxamic ester (**3**) during a typical reductive decarboxylation reaction and is consistent with the way the reactions have been actually performed in this study, namely through the slow dropwise addition of an acid chloride to 1 equivalent of *N*-hydroxypyridine-2-thione, sodium salt. This protocol ensures a sufficiently low concentration of thiohydroxamic ester (**3**), which upon homolysis allows H-transfer to compete against self-trapping. Finally, the question of how H-transfer takes places, i.e., either through chloroform or through the in situ generated 2-pyridinethiol (**13**), or perhaps a combination of both, is still open and will require further mechanistic investigation.

In conclusion, we have presented a practical and cost-effective hydrogen atom source for performing Barton reductive decarboxylations. The procedure avoids the common toxic or miasmic conditions normally associated with this versatile reaction, and is amenable to academic and industrial applications. Theoretical calculations and further mechanistic studies are currently under investigation and will be reported in due course.

Acknowledgment. We thank CSIRO and the University of Queensland for financial support.

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