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1-Haloalkynes from Propiolic Acids: A Novel Catalytic Halodecarboxylation Protocol

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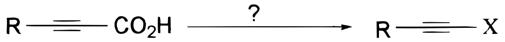
1-Haloalkynes are versatile intermediates in organic synthesis, the design of molecular materials,[1,2] and the preparation of biocidal agents.[3] Major synthetic routes[4] to 1-haloalkynes to date include (a) halogenation of metal acetylides or surrogates,[5] (b) dehydrohalogenation of 1,1-dihaloolefins,[6] and (c) oxidative halogenation of terminal alkynes.[7] A synthetically new entry envisaged by us was the halodecarboxylation of propiolic acid.



Berliner and co-workers found that aqueous bromination of phenylpropiolic acid afforded 11−18% of 1-bromophenyl acetylene among other products.[8] Further oxidative decarboxylation of phenylpropiolic acid with I_2/I_2O_5 in methanol/chloroform, with a 10:1:5 ratio of acid:I_2:I_2O_5, gave 1-iodophenyl acetylene and 2,2-diiodo-1-methoxyethynyl benzene in 73% and 27% yields, respectively.[9] However, the conversion was poor (<30%).

In light of the above, a strategy for the efficient transformation of phenylpropiolic acids to 1-haloacetylenes would be attractive. We delineate here a facile and bench-friendly protocol for the halodecarboxylation of propiolic acids containing aromatic or heteroaromatic groups, under the catalytic influence of tetrabutylammonium trifluoroacetate, TBATFA (Scheme 1).

The reaction of phenylpropiolic acid (1 mM) with *N*-iodosuccinimide (1.12 mM) and TBATFA (10 mol %) at ambient temperature was clean and complete in 0.25 h (TLC), leading to 1-iodophenylacetylene in 99% isolated yields (Table 1, entry a). The reaction has been extended to various ring-substituted phenylpropiolic acids (entries b−e) and naphthyl, anthracenyl, furyl, and thienyl propiolic acids (entries f−i). As can be seen from Table 1, except in the case of 2-furyl derivative (entry h), the yields of 1-iodoacetylenes are excellent to quantitative. The related bromodecarboxylation reactions of acid **1** with *N*-bromosuccinimide and catalytic TBATFA have been carried out successfully, giving rise to moderate to good yields of 1-bromoacetylenes (Table 1). Additionally, acids having enyne and bisalkyne functionalities (Scheme 2) gave the corresponding acetylenic halides **3** and **4** in poor to good yields. In control experiments, reaction of phenylpropiolic acid with *N*-bromosuccinimide in the absence of catalyst afforded <10% of the product. In sharp contrast, treatment of phenylpropiolic acids with *N*-chlorosuccinimide, under the present conditions, leads to total recovery of starting materials.

Scheme 1

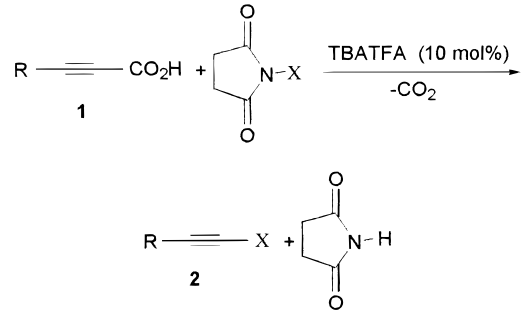
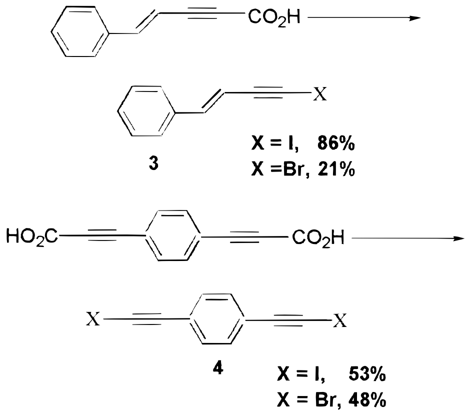


Table 1. TBATFA-Catalyzed Halodecarboxylation of R−C≡C-CO₂H (1) to R−C≡C−X (2) with *N*-Halosuccinimide

		X = I		X = Br	
entry	R	time (h)	yield (%)	time (h)	yield (%)
a	Ph	0.25	99	0.5	78
b	4-Me-C_6H_4	0.25	95	0.25	62
c	4-OMe-C_6H_4	0.25	85	0.25	53
d	4-Cl-C_6H_4	0.25	97	1	96
e	piperonyl	0.25	92	0.5	41
f	9-anthracenyl	0.25	86	1	41
g	1-naphthyl	0.25	97	0.5	31
h	2-furyl	0.25	67		
i	2-thienyl	0.25	84		

Scheme 2



On the Mechanism of Halodecarboxylation. Because the reaction was found to be unaffected in the presence of a nitrone radical trap, we believe that the

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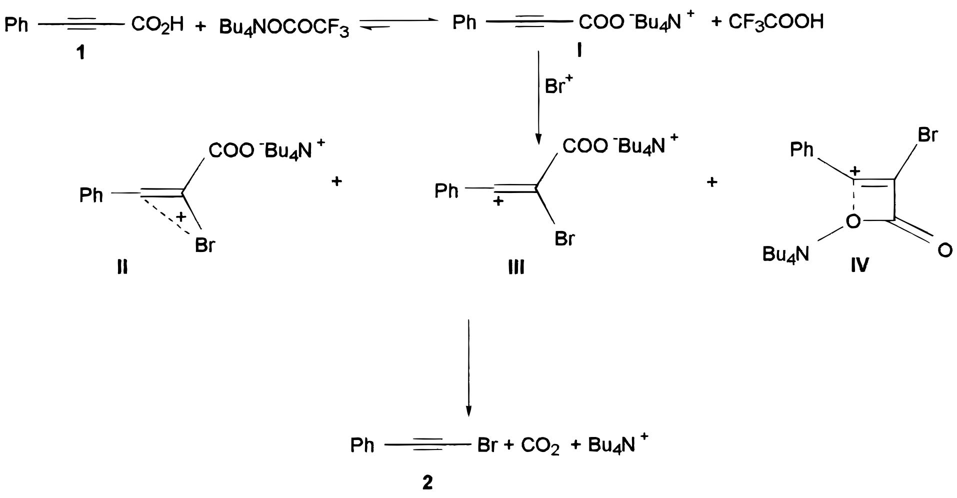
Scheme 3



halodecarboxylation proceeds by a ionic pathway. The pathways proposed here (Scheme 3) are based on earlier studies[8] and semiempirical (AM1) calculations carried out by us. AM1 calculations are carried out primarily to examine the geometry around $\pi_{C\equiv C}$ in various intermediate species and the energetics (ΔH_f, heat of formation) associated with them. For simplicity in calculation, ammoniumtetrafluoroacetate is preferred instead of TBATFA.

The pronounced catalytic effect of TBATFA suggests that the propiolate anion halodecarboxylates faster than acid. Because experiments are conducted in organic solvents, the anion is likely held as a tight-ion pair with tetrabutylammonium cation (**I** in Scheme 3). The HOMO of **I**, at an energy of −8.78 eV, shows higher orbital amplitude at the alkyne α-carbon (bound to carboxylate) compared to the β-carbon (bound to phenyl ring). The charge at the α-carbon is calculated to be −0.13 eV, compared to −0.12 eV at the β-carbon. The above observation strengthens the common notion that the incoming electrophile will preferentially attack the α-carbon of the $\pi_{C\equiv C}$ bond.

The plausibility of the formation of intermediates **II**, **III**, and **IV** has been analyzed. Stereoelectronically, intermediate **III** having an open-vinyl cation will be preferred over the weakly halo-bridging intermediate **II** or carboxylate-bridged intermediate **IV**. The heat of formation values (ΔH_f, kcal/mole) calculated for the intermediate **II** (159.23), **III** (159.20), and **IV** (157.74) are nearly similar. Thus, it is difficult to exclude one or the other on the basis of energetics alone. The minimized geometries of all of the intermediates show an expected increase in $C_\alpha-C_\beta$ bond length and a concomitant increase in C_α−COO bond length with respect to **I**. The calculated changes in heat of formation values in going from reactants to products are shown in Figure 1, taking the open-vinyl cation intermediate **III** as an example. Although entropy parameters need to be included to get a more clear free-energy profile of the reaction, Figure 1 provides a visualization useful in explaining the facile nature of the present halodecarboxylation reaction.

In conclusion, we have developed a synthetically attractive protocol for the transformation of propiolic acids to 1-halopropynes using readily available reagents. Current investigations in our laboratory are focused on making the halodecarboxylation route amenable to propiolic acids bearing alkyl substituents.

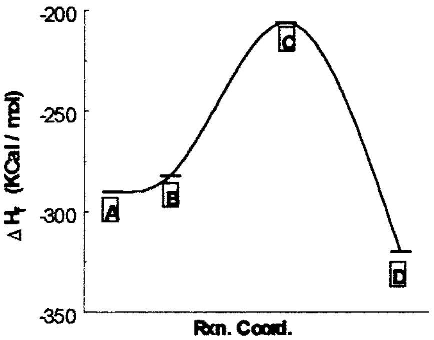


Figure 1. AM1-derived cumulative heats of formation of plausible species (refer to Scheme 3) in the bromodecarboxylation of phenylpropiolic acids. Speces A: **1** + $NH_4^+CF_3COO^-$ + NBS. Species B: **I** + CF_3COOH + NBS. Species C: **III** + CF_3COO^- + succinimide. Species D: **2** + CO_2 + $NH_4^+CF_3COO^-$ + succinimide. Tetrabutylammonium ion in intermediates **I** and **III** is substituted by ammonium ion for simplicity in calculation.

Experimental Section

General Procedure for the Halodecarboxylation of Propiolic Acids. Propiolic acid **1** (1 mM) was added to a solution of TBATFA (0.1 mM) in 3 mL of dichloroethane. After the mixture was stirred for 5 min at room temperature, *N*-halosuccinimide (1.12 mM) was added in portions. The progress of the reaction was monitored by TLC (eluent, *n*-hexane). After completion of the reaction, solvent was removed under reduced pressure, and the mixture was subjected to column chromatography (silica gel; eluent, *n*-hexane) to afford 1-haloalkynes.

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Supporting Information Available: Experimental procedure, product characterization data, AM1 derived optimized structures, orbital energy diagram and heat of formation values of intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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