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LETTERS

Is Metal Necessary in the Hunsdiecker-Borodin Reaction?[#]

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ABSTRACT: The tetrabutylammonium trifluoroacetate (TBATFA) catalyzed conversion of α,β-unsaturated carboxylic acids to the corresponding halides with N-halosuccinimides in dichloroethane is reported as the first example of a metal-free catalytic version of the title reaction. The methodology was further employed for a facile synthesis of piperine.

In 1861 Borodin[1] and in 1942 Hunsdiecker[2] demonstrated that silver carboxylates, when reacted with bromine at elevated temperature, undergo facile bromodecarboxylation to afford the corresponding alkyl bromides. In the intervening years the reaction has been further modified to include carboxylates of Hg(II), Pb(IV) and Tl(I) and molecular halogen or halide.[3-7] This halodecarboxylation reaction, recently renamed[8] the Hunsdiecker-Borodin-Cristol-Firth reaction, is of proven utility for the synthesis of various organic halides notably alkyl (1°,2°,3°) and aryl halides. When we viewed this classical reaction from a synthetic organic chemists perspective; the necessity to use stoichiometric metal carboxylate appeared against the dictum of *atom-economy*.[9] Other limitations include: (a) necessity to use high temperature; (b) the toxicity/hazard related to molecular bromine and salts of Hg, Tl, Pb, Ag and (c) very poor yields[10] in cases of substrates such as α,β-unsaturated carboxylic acids. We have recently invoked a novel protocol whereby a catalytic metal-salt pool is utilized in mediating a one-pot Hunsdiecker synthesis from *in-situ* generated metal carboxylates.[11] The questions that warrant further investigations are: (i) what triggers the elimination of carbondioxide, a carboxylate ion promoted decarboxylation or via an intermediate α-halo-β-lactone and (ii) what is the role of the metal in terms of soft-hard, covalent-ionic and steric-electronic relationships? While working on these issues, we discovered a novel metal free version of the title reaction of α,β-unsaturated carboxylic acids, under the aegis of TBATFA and we wish to delineate the same herein. α,β-Unsaturated carboxylic acids were chosen as key substrates owing to their low reactivity in classical Hunsdiecker reaction.

Thus reaction of cinnamic acid (8 mM) with NBS (11.5 mM) and TBATFA (1.6 mM) in dichloroethane (16 mL) at ambient temperature for 6 h furnished after work-up, β-bromostyrene in 73% isolated yield (Table 1, entry 1).[12] In contrast, the uncatalysed reaction showed only 14% conversion. The methodology was extended to bromo, chloro and iododecarboxylation of various substituted cinnamic acids **1** with NBS, NCS and NIS (scheme 1). Excellent yields of corresponding halides **2** were obtained which are

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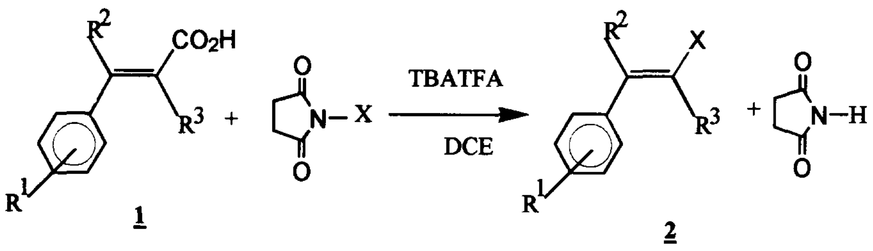
best compared to all previous Hunsdiecker strategies. Acids bearing electron donating substituents are particularly reactive (entry 4 - 10) compared to those having electron withdrawing groups (entry 11, 12).

Table 1: Conversion of α,β-unsaturated carboxylic acids to β-halostyrenes



entry	R1	R2	R3	X	time (h)	yield (%)[a]
1	H	H	H	Br	6 R	73
2				Cl	16	78
3				I	20	18[b]
4	4-OMe	H	H	Br	2	94
5				Cl	6	87
6				I	4	74
7	4-OMe	H	Me	Br	4	96
8				Cl	7	93[c]
9				I	4	73[d]
10	4-Me	H	H	Br	5	90
11	H	H	Ph	Br	27	51[e]
12	4-Cl	H	H	Br	13	21[f]

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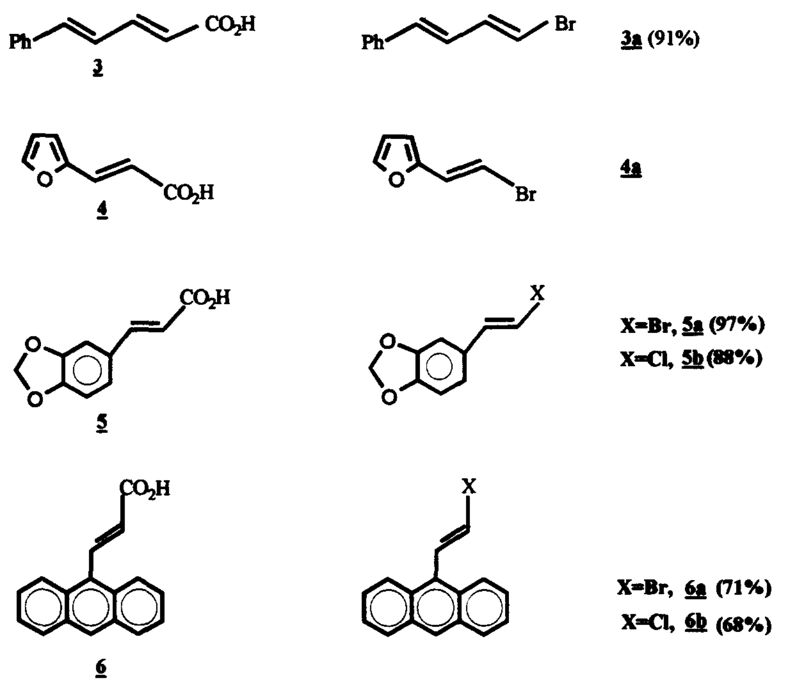
[a] isolated yield w.r.t. acid; [b] rapid decomposition was observed during chromatography; [c] cis:trans 1:1; [d] cis:trans 11:89; [e] acid recovered 20%; [f] acid recovered 40%.

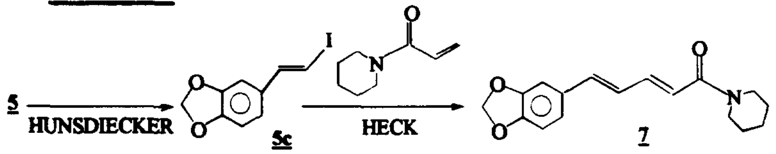
To further investigate the generality of our protocol, various precursors containing α,β-unsaturated carboxyic appendage were chosen (Chart 1). Dienoic acid 3 afforded the corresponding bromide 3a in excellent yield. Onl the other hand, furylacrylic acid 4 gave rise to the desired Hunsdiecker product 4a (vide NMR) along with uncharacterized products. Both piperonal derivative 5 and 9-anthracenyl acrylic acid 6 underwent very facile bromo and chloro decarboxylation giving rise to the corresponding halides 5a, 5b and 6a, 6b respectively.

CHART 1



High yielding conversions in the above examples enthused us to undertake a short synthesis of the natural product piperine. The strategy comprises of coupling the catalytic Hunsdiecker reaction with conventional Heck reaction. Reaction of 5 with NIS under our protocol afforded 5c in 73% yield, the latter was coupled with 1- acryloxy piperidine under Heck conditions to afford piperine 7 in 38% isolated yield.[13] It may be noted that all earlier syntheses of piperine involved rigorous multistep protocol.[14,15]

CHART 2



In conclusion, we have been successful in extending the Hunsdiecker synthesis from stoichiometric metal carboxylate protocol to a one-pot catalytic metal-free version. We have also utilized our strategy in combination with Heck reaction towards a simple and affordable synthesis of piperine. In the future, we hope to elaborate these results and provide examples of the catalytic Hunsdiecker reaction on substrates other than α,β-unsaturated carboxylic acids.

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10. Typical yield 18% from silver cinnamate/bromine, Johnson, R.J.; Ingham, R.K.; *Chem. Rev.* **1956,** *56*, 219; improved yield in oxidative halo decarboxylation using *stoichiometric* PhIO/NBS/acid/60°C h, Graven, A.; Jorgensen, K.A.; Dahl, S.; Stanczak, A.; *J. Org. Chem.* **1994,** *59*, 3543.
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12. Work-up involves solvent removal under reduced pressure and product purification by column chromatography (silica-gel 60-120 mesh, hexane/ethylacetate). For reactions with NIS, nitrogen blanket and dark conditions were employed. All compounds were fully characterized by ^{1}H NMR (200 MHz), EIMS (70 eV), FTIR and by comparison with authentic samples wherever possible.
13. Typical procedure: Pipereonyl acryl iodide **5c** (1 mM), palladium acetate (10 mol%), triphenylphosphine(30 mol%), lithium chloride (20 mol%), dry triethylamine (3 mM) and dry acetonitrile (2 mL) were taken in a schlenk flask equipped with reflux condenser. The mixture was allowed to stirr for 10 minutes at ambient temperature and under nitrogen, then 1-acryloxy piperidine (2 mM) in acetonitrile (1 mL) was added dropwise and the mixture was stirred at 70°-80°C for 18h. Following solvent removal under reduced pressure, the material was taken in ether, washed with water and brine solution and then dried over anhydrous $MgSO_4$. Pure piperine was isolated in 38% yield via preparative TLC (MERCK Kieselgel 60 F254, eluent hexane/ethylacetate: 9/1). This product was spectroscopically identical to reported literature (ref. 14, 15).
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