

Catalytic Hunsdiecker Reaction of α,β -Unsaturated Carboxylic Acids: How Efficient Is the Catalyst?

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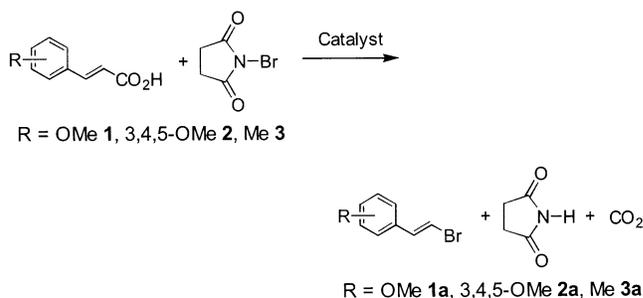
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Abstract: UV-vis spectrophotometry is utilized to measure the relative efficiency of lithium acetate, tetrabutylammonium trifluoroacetate, and triethylamine as catalysts for the conversion of 4-methoxycinnamic acid to 4-methoxy- β -bromostyrene. In acetonitrile-water as solvent, the efficiency order is lithium acetate > triethylamine > tetrabutylammonium trifluoroacetate. For triethylamine as catalyst, solvent-dependent order is acetonitrile-water > dichloromethane > acetonitrile. Using triethylamine as catalyst (5–20 mol %), cinnamic acids, and propiolic acids are converted to corresponding β -bromostyrenes and 1-halo-1-alkynes in 60–98% isolated yields within 1–5 min.

The decarboxylative halogenation of carboxylic acids is a synthetically useful route to organic halides. Various modifications of the classical Hunsdiecker reaction are testimony to the unabated interest of organic chemists in this reaction.¹ However, until recently, it remained a difficult task to adopt a synthetically meaningful Hunsdiecker strategy in acids bearing unsaturation directly at the C-terminus of the carboxyl group. Toward this, recent strategies developed are (a) oxidative halodecarboxylation including the green variation,^{2,3} (b) biscolidinehalogenium ion as a new Br⁺ or I⁺ source in additive-free halodecarboxylation,⁴ and (c) electrophilic halodecarboxylation catalyzed by either a metal salt such as lithium acetate,⁵ and manganese acetate,⁶ or a tetraalkylammonium salt.⁷ The latter is termed as the catalytic Hunsdiecker Reaction (hereafter CHR). Each of

SCHEME 1



the above protocols, within their limitations, is potential means to synthesize unsaturated organic halides in general and 1-halo-1-alkenes and 1-halo-1-alkynes in particular. Tokuda and co-workers⁸ have recently reported a microwave-induced version of CHR with lithium acetate as catalyst in acetonitrile-water, originally developed by us.⁵ Longer reaction time has been cited as one of the limitations of microwave-free CHR.^{3,8} Since in a bimolecular reaction reaction time is concentration dependent, efficiency judgment based on total reaction time becomes difficult at times unless one compares experiments performed under identical conditions. In view of this, we felt it appropriate to evaluate the comparative efficiency of the catalysts in the CHR of α,β -unsaturated acids and found UV-vis spectrophotometric methods to be the ideal probe. A delightful outcome of this study is the finding that triethylamine in dichloromethane or acetonitrile-water can also trigger CHR giving rise to high yields of products in short reaction time. The results of the above studies are presented in this paper.

To evaluate the effective rate of the reaction, initially ¹H NMR monitoring was attempted for the bromodecarboxylation of substituted cinnamic acids with *N*-bromosuccinimide in the presence of catalysts (Scheme 1). However, the method was found unsuitable due to difficulties associated with integrating overlapping peaks and very fast reaction in NMR-approachable concentration. For example, for a reaction with acid (10⁻² M), *N*-bromosuccinimide (10⁻² M), and catalyst (10⁻⁵ M), the total reaction time was less than 5 min. Henceforth, UV-vis spectrophotometry is attempted for reaction monitoring, for which 4-methoxycinnamic acid **1** is found to be the ideal substrate. Compound **1** and the corresponding β -bromostyrene **1a** show well-separated absorption maxima (Table 1). *N*-Bromosuccinimide and all catalysts are also transparent within the spectral region scanned (230–350 nm).

The spectral profile during the bromodecarboxylation of **1** to **1a** in the presence of excess *N*-bromosuccinimide (2–6.5 equiv) and catalytic lithium acetate and triethyl-

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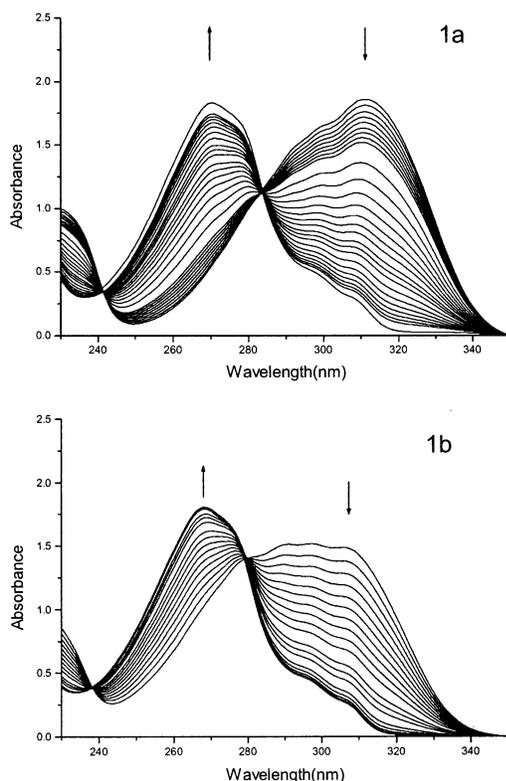
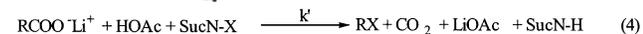
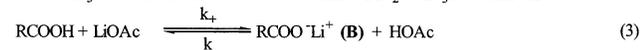
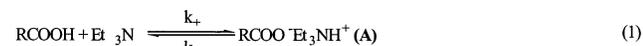
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TABLE 1. UV Spectral Data for Cinnamic Acid **1** and Unsaturated Bromide **1a** in Various Solvents

MeCN		MeCN–H ₂ O (97:3 v/v)			CH ₂ Cl ₂	
acid	bromide	acid	bromide	acid	bromide	
λ_{nm}	(log ϵ)	λ_{nm}	(log ϵ)	λ_{nm}	(log ϵ)	(log ϵ)
306	4.335	3.553	3.06	4.301	3.620	312 4.314 3.306
299	4.328	3.728	298	4.300	3.767	299 4.257 3.715
292	4.318	3.828	292	4.294	3.829	292 4.209 3.816
268	3.991	4.379	268	3.921	4.314	270 3.733 4.295

**FIGURE 1.** Spectral profile during the bromodecarboxylation of 4-OMeC₆H₄CH=CHCO₂H, **1**, to 4-OMeC₆H₄CH=CHBr, **1a**: (a) Et₃N as catalyst in CH₂Cl₂; (b) LiOAc as catalyst in MeCN–H₂O (97:3 v/v).**SCHEME 2**

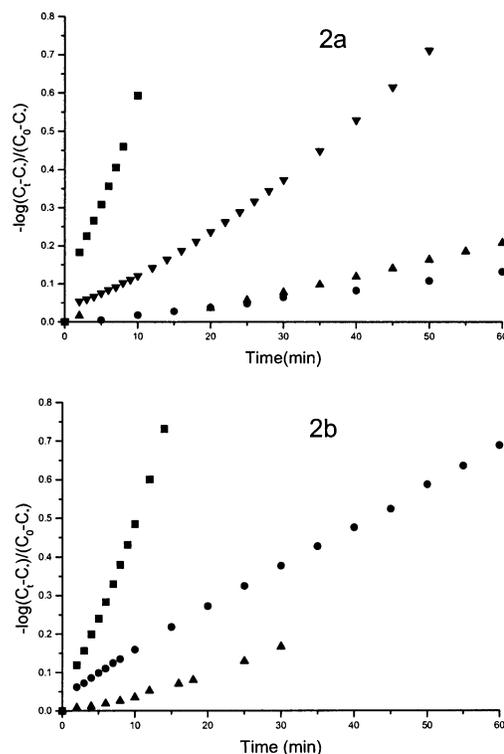
$$d[\text{RCOOH}]/dt = k_+[\text{cat}][\text{RCOOH}] = k_{\text{obs}}[\text{RCOOH}] \quad (5)$$

$$k_{\text{obs}} = k_+[\text{cat}]^n \quad (6)$$

$$\text{cat} = \text{LiOAc}, \text{Et}_3\text{N}, \text{R}_4\text{N}^+ \text{X}^-$$

amine are shown in Figure 1a,b. The presence of isobestic points is noteworthy and well supports our original view that decarboxylation reaction may involve fewer intermediates.^{5,7}

An ionic mechanism, proposed earlier by us and supported by semiempirical calculations, assumes the carboxylate anion or the corresponding lithium or alkylammonium salts to be the key reactive intermediate (Scheme 2, eqs 1–4).^{5–7} Applying steady-state approxi-

**FIGURE 2.** Plot of $-\log [(C_t - C_0)/(C_0 - C_\infty)]$ versus time (min). **2a**: ■, LiOAc as catalyst in MeCN–H₂O; ●, TBATFA as catalyst in MeCN; ▲, TBATFA as catalyst in CH₂Cl₂; ▼, TBATFA as catalyst in MeCN–H₂O. **2b**: ■, Et₃N as catalyst in MeCN–H₂O; ●, Et₃N as catalyst in CH₂Cl₂; ▲, Et₃N as catalyst in MeCN.**TABLE 2.** Rate Data for Different Catalysts and Solvent Combinations

catalyst	solvent	$K_{\text{obs}} \times 10^5 \text{ (s}^{-1}\text{)}$	K_+ (rel rate) (s ⁻¹)
Et ₃ N	CH ₂ Cl ₂	42	4.6
	MeCN	21	2.3
	MeCN–H ₂ O (97:3)	192	21.3
LiOAc	MeCN–H ₂ O (97:3)	209	23.2
TBATFA	CH ₂ Cl ₂	13	1.4
	MeCN	9	1
	MeCN–H ₂ O (97:3)	44	4.8

mation⁹ to **A** or **B** and under the condition $[\text{SucN-X}] > [\text{RCOOH}]$, the rate law reduces to the expression shown in eqs 5 and 6, Scheme 2).

The pseudo first-order rate plots for the conversion of **1** to **1a** against various catalysts are shown in Figure 2a,b, where $C = [\mathbf{1}]$. It is evident that the goodness of fit at longer reaction time is poor. Therefore the first-order rate constant values k_{obs} are evaluated for the early part of the reaction only. The k_{obs} values are average of two runs and are within $\pm 5\%$ accuracy. From the data (Table 2) the following conclusions are drawn: (a) lithium acetate is the best catalyst of all, (b) efficiency of tetrabutylammonium trifluoroacetate (TBATFA) is 1 order of magnitude less than that of lithium acetate, and (c) triethylamine is a catalyst having remarkable solvent-

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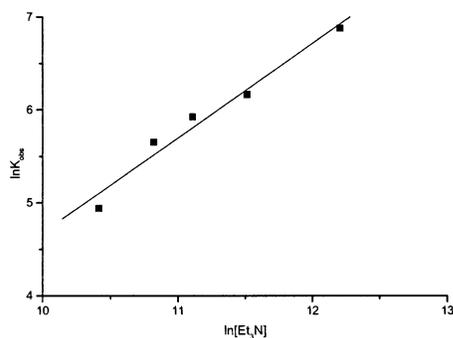


FIGURE 3. Plot of $\ln k_{\text{obs}}$ versus $\ln [\text{Et}_3\text{N}]$.

dependent efficiency. The efficiency of triethylamine in dichloromethane and acetonitrile–water (97:3 v/v) is nearly 2- and 10-fold, respectively, as compared to that in acetonitrile. A plot of $\log k_{\text{obs}}$ vs $\log [\text{Et}_3\text{N}]$ is found to be linear with a slope of 1.02, which establishes that the reaction is first order with respect to catalyst (Figure 3).

On the basis of the above studies, it remained an important task for us to evaluate how good is the efficiency assignment of a catalyst based on markers such as reaction time and isolated yield. The reactions of substituted cinnamic acids **1–7** and propiolic acids **8–12** is carried out using triethylamine as catalyst. Triethylamine is chosen as it is a new catalyst in CHR and also offers varied efficiency with respect to solvents.

The reaction of 4-methoxy cinnamic acid **1** (1 mM) with *N*-bromosuccinimide (1.2 mM) and triethylamine (0.05 mM) in dichloromethane (3 mL) is stirred at ambient temperature for 5 min (Table 3, method A) and immediately worked up. Isolation by column chromatography leads to the corresponding β -bromostyrene **1a** in 90% yield (Table 3). Changing the solvent from dichloromethane to acetonitrile–water (97:3 v/v) reduces the overall reaction time to 1–2 min (method B) without the loss of overall isolated yield. Note that the reaction time and yields are comparable to those under microwave assistance (method C). Similar reactions of substituted cinnamic acids **2–5**, bearing electron donating group either in aromatic ring or in the alkene appendage, with *N*-halosuccinimide by method A or B provides the corresponding β -halostyrenes in 60–98% isolated yields. We believe that the true advantage of microwave assistance lies for reactions of cinnamic acids bearing electron withdrawing groups, as in the case of acid **5**.

The triethylamine-catalyzed CHR has been successfully extended to propiolic acids. The reaction of phenylpropionic acid **8** (1 mM) with *N*-bromosuccinimide (1–2 mM) and triethylamine (0.2 mM) in dichloromethane (method A) leads to 1-bromophenylacetylene **8a** in 92% isolated yield. Once again, changing the solvent to acetonitrile–water (method B) reduces the overall reaction time to 1–2 min without the loss of overall isolated yield. The reaction has been extended to various ring-substituted phenylpropionic acids **9–11** leading to 85–92% isolated yields of corresponding 1-haloalkynes. Thieryl and naphthyl propiolic acids **12** and **13** provide the corresponding 1-haloacetylenes **12a**, **12c**, and **13a** in 85–94% isolated yields. Note that the reaction time and yields are independent of substituents on the aromatic side chain. Furthermore, the yields of products are found

TABLE 3. Decarboxylative Halogenation of Unsaturated Acids with Triethylamine as Catalyst

no.	acid	halide		isolated yield ^a (%)		
		X	no.	method A	method B	method C
1		Br	1a	90	90	91
		Cl	1b	89		77
		I	1c	70		
2		Br	2a	98	97	88
		Cl	2b	60		
		I	2c	75		
3		Br	3a	97		
		Cl	3b	90		
4		Br	4a	70	67	
5		Br	5a	15		54
6		Br	6a	60		84
7		Br	7a	86	80	
		I	7c	60		
8		Br	8a	92	90	90
		I	8c	97		
9		Br	9a	92	89	
10		I	10c	91		
11		Br	11a	85		
		I	11c	90		
12		Br	12a	85		
		I	12c	90		
13		Br	13a	94		94

^a Method A: solvent = dichloromethane; reaction time 5 min. Method B: solvent = acetonitrile–water (97:3 v/v); reaction time 1–2 min. Method C: solvent = acetonitrile–water (97:3 v/v); microwave, 260 W; reaction time 1 min.

to be similar to that of reactions carried out under microwave assistance (method C).

In conclusion the present study offered for the first time a quantitation of catalyst efficiency in Hunsdiecker Reaction. The study further highlights the importance of solvents in influencing the catalytic activity. It may also be emphasized that exogenous influence of other conditions, such as microwave should be judged on a case to case basis.

Experimental Section

General Remarks. General experimental procedures including instrumentation are as described previously.^{5–7} Triethylamine was refluxed with solid potassium hydroxide and distilled. Dichloromethane and acetonitrile were refluxed over phosphorus pentoxide, and distilled. *N*-Bromosuccinimide and *N*-chlorosuccinimide were recrystallized from water prior to use. *N*-Iodosuccinimide was used as received.

General Procedure for the Synthesis of α,β -Unsaturated Halides by Method A. Triethylamine (7 μL) was added to a solution of α,β -unsaturated aromatic carboxylic acid (1 mM) in

dichloromethane (3 mL). After the mixture was stirred for 5 min at room temperature, *N*-halosuccinimide (1.2 mM) was added. The solution was stirred for 5 min, and solvent was removed under reduced pressure. The mixture was subjected to column chromatography over silica gel (60–120 mesh, eluent 1% ethyl acetate in hexane) to afford the β -halostyrenes. The products were fully characterized by spectroscopy and by comparison with authentic samples.^{5–7}

General Procedure for the Synthesis of 1-Haloalkynes by Method A. Triethylamine (28 μ L) was added to a solution of substituted propiolic acid (1 mM) in 3 mL dichloromethane. After the mixture was stirred for 5 min at room temperature, *N*-halosuccinimide (1.2 mM) was added. After 5 min, solvent was removed under reduced pressure, and the mixture was subjected to column chromatography (silica gel 60–120 mesh, eluent 1% ethyl acetate–hexane) to afford 1-haloalkynes. The latter were fully characterized by spectroscopy and by comparison with authentic samples.^{5–7}

General Procedure for Kinetic Study. Kinetic measurements were recorded on a Shimadzu spectrophotometer model

UV-1601PC, with external thermostat. Spectrophotometric grade solvents were used for kinetic study. Stock solutions of **1** (10^{-2} M), NBS (10^{-2} M), and triethylamine (10^{-3} M) were prepared in respective solvents. Using appropriate amounts of the above solutions, the reaction mixture was prepared in a quartz cuvette so that the final concentrations of acid, NBS and triethylamine were 10^{-4} , 0.2×10^{-2} , and 10^{-5} M, respectively. The cuvette was thermostated at 28.0 ± 0.2 °C and UV scanning (230–350 nm) was done at an interval of 1 min for first 10 minutes and thereafter at 2–5 min intervals until the end of the reaction. The absorption maximum was recorded at two different wavelengths corresponding to the λ_{max} of acid and halide at different time intervals. The pseudo first-order rate plot was derived from the calculated concentration of acid. The k_{obs} values are average of two runs and are within $\pm 5\%$ accuracy.

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