COMMUNICATION

Synthesis of α-bromo-β-lactam *via* a novel catalytic Hunsdiecker like protocol† ‡

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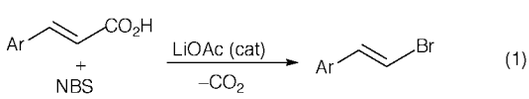
While α,β-unsaturated aromatic carboxylic acids, upon treatment with NBS and catalytic group-1 metal acetates, gives β-bromostyrenes, the corresponding reactions of α,β-unsaturated aromatic amides lead to α-bromo-β-lactams.

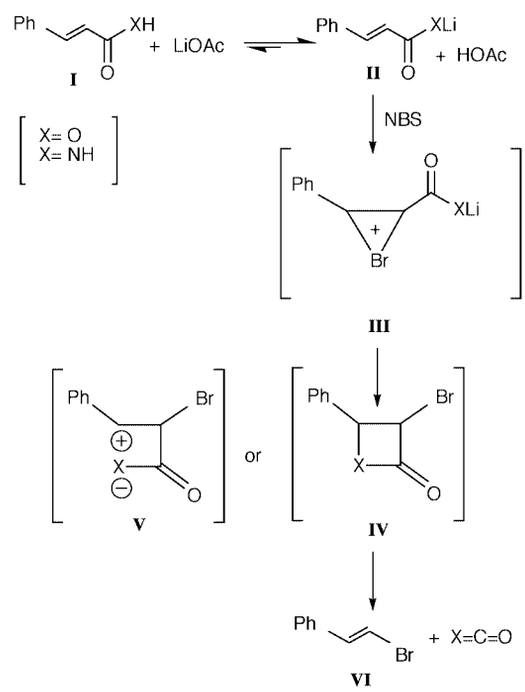
The halodecarboxylation of metal carboxylates, trivially known as the Hunsdiecker reaction, is of proven utility for the synthesis of various organic halides notably alkyl and aryl halides.[1] When we viewed this classical reaction from a synthetic organic chemist's perspective, the necessity to use stoichiometric metal carboxylates appeared against the dictum of atom-economy.[2] Keeping this in view, we have recently invoked a novel protocol[3] whereby a catalytic metal-salt pool is utilised in successfully mediating the Hunsdiecker reaction of α,β-unsaturated aromatic carboxylic acids [eqn. (1)].



(1)

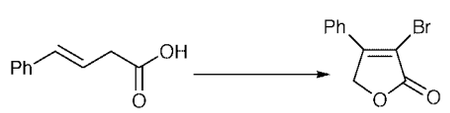
The major question that warranted further investigation is "What triggers the elimination of carbon dioxide?". No significant change in reaction time and yield of β-bromostyrene was observed for the reaction of cinnamic acid with NBS–LiOAc, in the presence of *N*-(*tert*-butyl)-α-phenyl nitrone as a radical trap, thereby suggesting an ionic pathway. Unfortunately, from *in situ* ^{1}H NMR monitoring at low temperature, no intermediate signal could be detected. A plausible halodecarboxylation pathway is depicted in Scheme 1, which is supported by insights derived from AM1 calculations[4] and a recent disclosure by Homsi *et al.*[5]

That the carboxylate anion halodecarboxylates faster than the acid itself, is evidenced by the pronounced catalytic effect of lithium acetate. Since experiments are conducted in organic solvent, we believe that the anion is held as a tight-ion pair with the lithium ion (**II** in Scheme 1). The regioselective attack of the bromonium ion at the α-carbon of $\pi_{C=C}$ in **II** may be due to the greater electron density in the HOMO of the α-carbon and greater negative charge (−0.164) compared to the β-carbon (−0.074). This argument gains further support from the optimised structure of **III** where the C_α–Br bond (1.95 Å, close to a Br–C_{sp3} bond) is significantly shorter than the C_β–Br bond (2.73 Å). A weakening of the C_α–COO bond in **III** (1.53 Å) compared to that in **II** (1.48 Å) indicates the elimination of carbon dioxide.



Scheme 1

The calculated heat of formation values of various intermediates in Scheme 1 suggest that α-bromo-β-lactone **IV** or its zwitterionic equivalent **V** is a much more likely intermediate in the Catalytic Hunsdiecker reaction (CHR). Formation of β-bromo-γ-lactone from the reaction of 4-phenylbut-3-enoic acid with NBS and catalytic NaOAc [eqn. (2)] provides indirect



(2)

experimental support for such a likelihood. It is noteworthy that thermal decomposition of β-lactones to the corresponding alkenes usually takes place at higher temperature.[6] However, the rate of decarboxylation is highly dependent on the nature of substituents and catalysts. For example in the presence of catalytic trifluoroacetic acid, α-*tert*-butyl-β-(4-methylphenyl)-propiolactone spontaneously decomposes at room temperature to yield the corresponding 1-*tert*-butyl-2-(4-methoxyphenyl)alkene.[7] Noyce *et al.* showed that 1-methyl-2-bromo-2-(4-chlorophenyl)propionic acid, upon treatment with either sodium hydride or silver oxide leads to a mixture of alkene and lactone in an 88:12 and 77:17 ratio respectively.[8] Also, β-phenylpropiolactone is known to be too reactive.[9] Asensio *et al.* showed that the zwitterionic intermediate of the type **V** is the preferred intermediate in the decarboxylation of lactones.[10]

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‡ Synthetic details for **1** and **2**, spectral characteristics of compounds **2a**–**g**, AM1 derived optimised structures of **I**–**V** and heats of formation are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/1999/2435, otherwise available from BLDSC (SUPPL. NO. 57602, pp. 11) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

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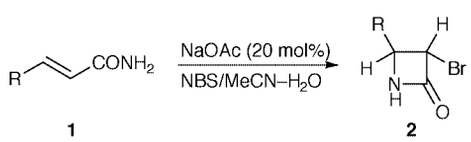
Most recently Homsi *et al*. isolated α-bromo-β-lactones from the reaction of 1,2- or 2,2-disubstituted α,β-unsaturated acids.[5]

Henceforth, we sought to look into the hypothetical CHR of α,β-unsaturated amides (Scheme 1, X = NH).[11] From a comparison of the heat of formation values for various intermediates associated with the acid and corresponding amide, the following facts appeared rather striking to us.

(i) In the CHR of the acid, the fully decarboxylated product **VI** is energetically favoured over the α-bromo-β-lactone intermediate **IV** or its zwitterionic equivalent **V** (X = O) by 22.4 kcal mol^{-1}.

(ii) In the hypothetical CHR of the amide, **VI** is energetically favored over the α-bromo-β-lactam intermediate **IV** or its zwitterionic equivalent **V** (X = NH) by only 0.6 kcal mol^{-1}.

The obvious question, therefore, is "Can we terminate CHR of amide at the α-bromo-β-lactam stage?". Indeed we were delighted when the reaction of 4-methylcinnamide **1a** (1 mM) with NBS (2 mM) and catalytic LiOAc (20 mol% with respect to the amide) in acetonitrile–water (3 mL, 97:3 v/v) and at ambient temperature afforded the corresponding α-bromo-β-lactam **2a** in 35% isolated yield. The yield was improved to 46% by using catalytic NaOAc (Scheme 2). The reaction has been



1 **2**

No.	R	Time/h	Yield (%)
2a	4-MeC_6H_4	3.5	46
2b	4-$OMeC_6H_4$	2.5	54
2c	4-ClC_6H_4	2.5	55
2d	Ph	24	20
2e	1-Naphthyl	4	52
2f	9-Phenanthrenyl	4	53
2g	3-Thienyl	1	48

Scheme 2

further extended to substituted cinnamides as well as to analogous 1-naphthyl, 9-phenanthrenyl and 3-thienyl derivatives to afford the α-bromo-β-lactams **2b**–**2g** in 20–55% yields. In all cases, only the *trans*-isomer was formed. Uncatalysed reactions, on the other hand, showed <5% conversion.

α-Halo-β-lactams are versatile synthons in constructing a wide variety of functionalised lactams.[12] Major transformations directed at the C_α-halogen centre include reduction, metallation, alkylation, allylation and replacement by azide. Notable routes to α-halo-β-lactams are cycloaddition of haloketenes to imines[13] and thermal decomposition of (*N*-dihaloacetylpiperidine)phenyl mercury.[14] More recently, Quiclet-Sire *et al*. demonstrated a nickel promoted radical cyclisation route.[15] In addition to the above, the present 4-*endo-trig* cyclisation protocol stands as a promising new entry for the synthesis of α-bromo-β-lactams. The recent synthesis of halolactams from α,β-unsaturated *N*-sulfonamides is particularly relevant in the present context.[5]

In conclusion, our quest for the intermediate in the catalytic Hunsdiecker reaction led us to engineer a new route to α-bromo-β-lactams. Yield optimization and further assessment of the synthetic utility of the invented protocol towards β-lactam antibiotics is in progress.

Experimental

Typical procedure for the preparation of α-bromo-β-lactam 2a

Amide **1a** (1 mM) was added to a solution of NaOAc (0.2 mM) in acetonitrile–water (3 mL, 97:3 v/v). After the mixture was stirred for 5 min at room temperature, *N*-bromosuccinimide (2 mM) was added in portions. The progress of the reaction was monitored by TLC (eluent ethyl acetate–hexane). After completion of the reaction, the solvent was removed under reduced pressure and the mixture was subjected to column chromatography (silica gel, eluent ethyl acetate–hexane) to afford α-bromo-β-(4-methylphenyl)propiolactam **2a**. TLC (silica gel, ethyl acetate–hexane 20%), R_f = 0.33; mp 123–124 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 4.5 (t, 1H, J = 2.4 Hz), 4.76 (d, 1H, J = 2.4 Hz), 6.44 (br, 1H), 7.18 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 164.49, 138.81, 134.36, 129.68, 125.55, 62.24, 51.27, 21.19; IR (KBr) cm^{-1}: 1123 (m), 1723 (vs), 2908 (m); EIMS *m*/*z* (rel intensity): 239 (M^+, 5%), 196 (68%), 160 (42%), 132 (12%), 117 (100%), 91 (70%), 77 (15%), 65 (39%), 39 (48%); Anal. Calcd. for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.19; N, 5.84. Found: C, 49.71; H, 3.98; N, 5.79.

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