

A Nitro-Hunsdiecker Reaction: From Unsaturated Carboxylic Acids to Nitrostyrenes and Nitroarenes

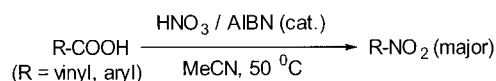
Jaya Prakash Das, Pradipta Sinha, and Sujit Roy*

Organometallics and Catalysis Laboratory, Chemistry Department,
Indian Institute of Technology, Kharagpur 721302, India

sroy@chem.iitkgp.ernet.in

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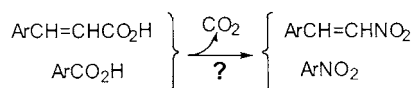
ABSTRACT



The nitrodecarboxylation of aromatic α,β -unsaturated carboxylic acids and ring-activated benzoic acids can be achieved using nitric acid (3 equiv) and catalytic AIBN (2 mol %) in MeCN. From the effect of various additives, the nitrodecarboxylation is postulated to involve the generation of an acyloxy radical RCO_2^\cdot by a NO_3^\cdot radical followed by attack of a NO_2^\cdot radical.

β -Nitrostyrenes are versatile building blocks in organic synthesis.^{1,2} They are generally prepared by the condensation of aldehydes with nitroalkanes, the Henry reaction, or by the nitration of styrenes. Our recent success in catalytic halodecarboxylation reaction of unsaturated carboxylic acids³ prompted us to find a gateway into nitrostyrenes and nitroarenes via the nitrodecarboxylation reaction (Scheme 1).

Scheme 1



Bachman et al. showed that under high dilution conditions, acyl nitrates, RC(=O)ONO_2 , could be generated from aliphatic carboxylic acids with little or no danger of explosion. Nitrodecarboxylation of acylnitrates was accomplished satisfactorily at the optimum temperature range

of 270–300 °C to provide nitroalkenes in good yields.⁴ However, under similar conditions, aromatic carboxylic acids gave 11–23% of nitroarenes. More recently, nitrodecarboxylation of benzoic acids with N_2O_5 – HNO_3 , AcOH – HNO_3 , and NO_2X – HNO_3 is reported.^{5,6}

Prior to 1960, the reaction of styrenes and acrylic acids was carried out by a wide variety of nitrating agents.⁷ Rationalization of the reactions was complicated by diverse distribution of products. Subsequent literature is testimony to the reagent-selective product formation in the nitration of styrenes. Only in a few cases are β -nitrostyrenes obtained as the major or minor products.⁸ To our knowledge, in no case is a nitrodecarboxylation observed. This has now been realized in the case of aromatic α,β -unsaturated carboxylic acids using nitric acid (3 equiv) and catalytic azobisisobutyronitrile (AIBN).

Taking 4-methoxycinnamic acid **1** as the model substrate, we carried out a number of optimization experiments. Comparison of data, particularly for the first 1 h of the

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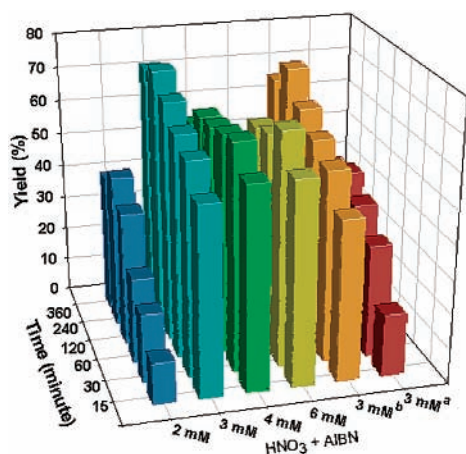


Figure 1. Nitrodecarboxylation of 4-methoxycinnamic acid **1**: effect of nitric acid concentration on the yield of β -nitrostyrene **2**. (a) In the presence of oxygen; (b) without AIBN.

reaction, provided meaningful insight into the mechanistic course of the reaction. Reaction of **1** with 2 equiv of nitric acid and additives such as acetic acid, sulfuric acid, or nitronium salts afforded negligible yield of nitrodecarboxylated product. In sharp contrast, facile nitrodecarboxylation occurred once the nitric acid concentration was raised to 3 equiv or when catalytic AIBN was added in acetonitrile as the solvent at 40–60 °C and under an inert atmosphere, giving rise to the corresponding β -nitrostyrene **2** and 4-methoxybenzaldehyde **2a**. Henceforth, reactions were carried out using 1 mM **1** in MeCN (2 mL) at the optimized temperature of 50 °C and monitored for **2** and **2a** by GC at regular time intervals for 6 h.⁹ Major observations are summarized in Figures 1–4.

A combination of 3 mM nitric acid along with 0.02 mM AIBN (2%) provided the highest yield of **2** (75% after 4 h)

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(9) **GC Monitoring for Nitrodecarboxylation of 4-Methoxycinnamic Acid 1**. Nitric acid (21.35 M, 0.15 mL, 3 mM) was added to a stirred solution of **1** (178 mg, 1 mM) in MeCN (2 mL) at room temperature under an argon atmosphere. To this reaction mixture was added AIBN (3.3 mg, 2 mol %), and the mixture was stirred at 50 °C. An aliquot of 0.2 mL was taken out at different time intervals and quenched with ice-cold water (0.2 mL) followed by triethylamine (0.03 mL), and a known amount of β -nitrostyrene solution in chloroform (0.134 M) was added as a reference. The organic layer was separated and directly used for GC analysis. The yield of 4-methoxynitrostyrene **2** was found to be 75% after 4 h. It was also isolated by column chromatography in 68% yield.

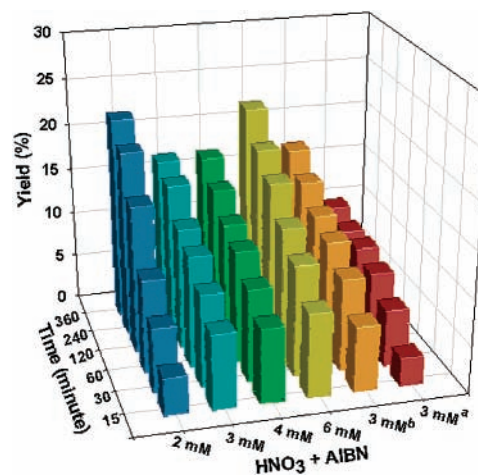


Figure 2. Nitrodecarboxylation of 4-methoxycinnamic acid **1**: effect of nitric acid concentration on the yield of 4-methoxybenzaldehyde **2a**. (a) In the presence of oxygen; (b) without AIBN.

along with **2a** (16%) (Figures 1 and 2). The marked effect of nitric acid concentration becomes obvious if one compares the data for the first 30 min of reaction. Thus, for nitric acid concentrations of 2, 3, 4, and 6 mM, the yields of **2** were 12, 55, 59, and 59, respectively, after 15 min. With 3 mM nitric acid but under an oxygen atmosphere, the yield of **2** sharply decreased to 18%. A control experiment confirmed the formation of aldehyde **2a** to be due to the oxidative decomposition of **2** by nitric acid.

The effect of other additives in the nitrodecarboxylation was tested with 3 mM nitric acid in acetonitrile at 50 °C (Figures 3 and 4). While lithium nitrate sharply decreased the yield of **2** (15 min, 8%; 30 min, 20%), silver nitrate remained noninfluential. Note that nitrate salts are known to have a marked effect on nitration reactions proceeding via ionic pathways.^{7,10} As stated earlier, AIBN was found to

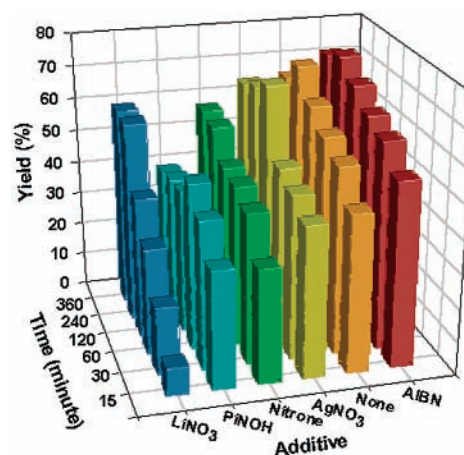


Figure 3. Nitrodecarboxylation of 4-methoxycinnamic acid **1**: effect of additives on the yield of β -nitrostyrene **2**.

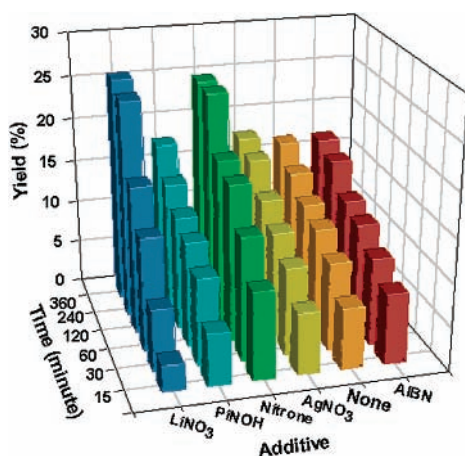


Figure 4. Nitrodecarboxylation of 4-methoxycinnamic acid **1**: effect of additives on the yield of 4-methoxybenzaldehyde **2a**.

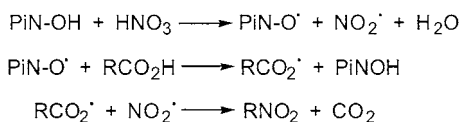
catalyze the nitrodecarboxylation reaction, while a nitron radical trap (*N*- α -diphenyl nitron) significantly retarded the nitrodecarboxylation. Curiously, the yield of aldehyde **2a** was the highest in case of both lithium nitrate and nitron as additives (25% after 4 h), as opposed to all the other reactions (15–17% after 4 h); the observation remains unexplained at present.

All of the above results are consistent with a radical rather than ionic pathway for the reaction. Nitric acid (3 equiv) is known to generate NO_2^\bullet and NO_3^\bullet radicals.^{7,11}



To evaluate whether NO_2^\bullet alone can trigger the nitrodecarboxylation reaction, we used the recently discovered reagent HNO_3 /catalytic *N*-hydroxyphthalimide (PiNOH).¹² We hoped that the latter could in principle promote nitrodecarboxylation by pathways shown in Scheme 2. Surprisingly, PiNOH was

Scheme 2



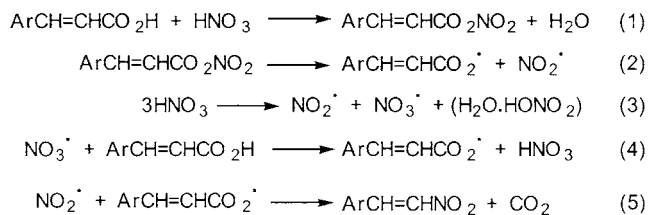
found to retard the nitrodecarboxylation significantly, the yield of **2** being 35, 44, and 50% after 15, 30, and 60 min, respectively. We therefore conclude that the NO_3^\bullet radical has a dominating effect in the initiation step of the reaction.

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Scheme 3



While detailed mechanistic studies are underway in our laboratory, a hypothesis for the present nitrodecarboxylation is presented in Scheme 3. The mechanism is similar to Bachman's original proposal on acylnitrate decomposition pathways and the mechanism proposed by Moodie et al.^{4,6} An acyloxy radical can be generated either by the decomposition of acylnitrate (step 2) or by the reaction of an NO_3^\bullet radical with acid (step 4). From the observed data, we believe that the initiation phase majorly involves steps 3 and 4 rather than 1 and 2. Thereafter, the NO_2^\bullet radical can combine in a bimolecular fashion with the acyloxy radical to promote nitrodecarboxylation (step 5). The nature of this bimolecular

Table 1. Nitrodecarboxylation of Unsaturated Carboxylic Acids to Nitrostyrenes and Nitroarenes Using Nitric Acid (21.35 M) and Catalytic AIBN at 50 °C^a

#	acid	acid no.	time (h)	nitro no.	yield nitro (%)
1		1	4	2	75
2		3	9	4	75
3		5 ^b	29	6	62
4		7 ^c	2	8	80
5		9	24	10	30
6		11	12	12	40
7		13	12	14	58
8		15	21	16	78
9		17 ^b	24	18	40

^a Unless otherwise stated, reactions were carried out with 3 equiv of HNO_3 in MeCN as the solvent. ^b HNO_3 (6 equiv). ^c HNO_3 (1.5 equiv) at 35 °C.

interaction is not yet clear, and we believe that both theoretical studies and kinetic experiment will be helpful in rationalizing the interaction.¹³

Following the preliminary studies as detailed above, we tested the nitrodecarboxylation over a number of substituted α,β -unsaturated carboxylic acids and aromatic acids with nitric acid and catalytic AIBN, and the results are shown in Table 1.¹⁴ Substituted cinnamic acids **3** and **5**, bearing electron-donating groups, provided the corresponding nitrostyrene **4** in 75% and **6** in 62% isolated yields. In the case of the highly activated substrate **7**, reaction proceeds at 35 °C, giving rise to product **8** in 80% yield. An absence of the activating substituent lowered the product yields. Thus, acids **9** and **11** yielded corresponding β -nitrostyrenes **10** and **12** in 30% and 40% yields, respectively. It is interesting to

note that (*E*)- α -phenylcinnamic acid **13**, having two phenyl groups across the double bond, reacted smoothly in 12 h to provide the corresponding (*E*)-nitrostyrene **14** in 58% yield. However, in the case of aromatic carboxylic acids, reaction proceeded only with ring-activated substrates such as **15** and **17** to obtain nitroarenes **16** (78%) and **18** (40%), respectively.

In summary, we have shown that facile nitrodecarboxylation of unsaturated carboxylic acids in general and α,β -unsaturated carboxylic acids in particular can be carried out under the aegis of HNO₃—catalytic AIBN, which could be a meaningful addition to the existing nitration methodologies. Evidence of radical rather than ionic pathways for the present nitrodecarboxylation is reminiscent of Hunsdiecker-type halodecarboxylation reaction. We therefore wish to name it the nitro-Hunsdiecker reaction. Studies are underway to further widen the scope of the reaction.

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Supporting Information Available: General methods, experimental procedures, and tables. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) **Typical Procedure.** Nitric acid (21.35 M, 0.3 mL, 6 mM) was added to a stirred solution of α -phenylcinnamic acid **13** (448 mg, 2 mM) in MeCN (5 mL) at room temperature under an argon atmosphere followed by AIBN (7 mg, 0.042 mM), and the mixture was stirred at 50 °C. Upon completion (GC, TLC monitoring), ice-cold water (5 mL) was added and the product was extracted with diethyl ether (4 \times 10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, concentrated, and subjected to column chromatography (silicagel, eluent 19:1 v/v *n*-hexane/ethyl acetate) to afford (*E*)- α -phenylnitrostyrene **14** (260 mg, 58%).