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Autoinductive Conversion of $\alpha, \alpha$-Diiodonitroalkanes to Amides and Esters Catalysed by Iodine Byproducts under O$_2$

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Studies to convert nitroalkanes into amides and esters using I$_2$ and O$_2$ revealed in situ-generated iodine species facilitate the homolytic C–I bond cleavage of $\alpha, \alpha$-diiodonitroalkanes, arguably in an autoinductive or autocatalytic manner. Consequently, we devised a rapid and economical I$_2$/O$_2$-based method to synthesise sterically hindered esters directly from primary nitroalkanes.

It is not trivial to decipher the most meaningful and productive pathway within a multistep reaction process. 1 A case in point comes from our studies to transform primary nitroalkanes 1 directly into amides 4 in the presence of I$_2$, O$_2$, bases, and nucleophilic amines (Figure 1a; HNu = HNR'R''). From these studies, we found the doubly $\alpha$-iodinated derivative 2 of the nitroalkane 1 to be key to the oxidative process. 2b In contrast to mechanisms involving the $\alpha$-amination of $\alpha$-bromonitroalkanes with electrophilic N-iodinated amines, 5 we have proposed the amide product 4 is generated by nucleophilic amine attack on the acyl derivative 3, as derived by addition of O$_2$ onto 2 through the homolytic cleavage of C–I bonds. 2b

Clearly the acyl derivative 3 can also react with other nucleophiles, such as residual water to form carboxylic acids and alcohols to form esters. Indeed, we have previously isolated carboxylic acids 4 (HNu = HOH) as side-products. 2 If made synthetically useful under mild conditions with less nucleophilic amines or alcohols, we could expand the one-pot transformation of nitroalkanes into other useful functionalities. 5 Herein, we detail our mechanistic development of oxidatively converting primary nitroalkanes 1, via $\alpha, \alpha$-diiodonitroalkanes 2 under O$_2$, into sterically congested esters 4 (HNu = HOR'). This method was achieved by realising that the rate-limiting step during the conversion of 2 to 3 is autoinduced by the iodine byproducts derived from 2 itself (Fig. 1(b)). 7

Most strikingly, the reactions from 2a to 6 (Eq. (1)) with relatively weak nucleophiles (CH$_3$OH, CF$_3$CH$_2$NH$_2$) displayed clear sigmoidal kinetic profiles at room temperature on the NMR timescale (Fig. 2, red and black curves). In contrast, the initial reaction between 2a and benzylamine proceeded exponentially with no slow induction period at room temperature, whereas an uncommon sigmoidal profile was observed at $-10^\circ$C (Fig. 2, cyan and blue curves). Several mechanistic reasons can be attributed to causing such sigmoidal kinetic profiles: For instance, the final product, an intermediate-product, a byproduct or a side-product of the reaction could be accelerating a rate-determining step in a chain-like, cross-catalytic, autoinductive or autocatalytic fashion. 7 We thus decided to study the oxidative conversion of the $\alpha, \alpha$-diiodonitroalkane 2a to the carboxylic derivatives 7/8 systematically and quantify the kinetic effects of adding each identifiable reaction product at 20 mol% by $^1$H NMR analysis (Eq. (2), Figure 3).

In the first instance, without any additives, the methyl ester 7 and carboxylic acid 8 were isolated in 75% and 25% yield, respectively, and characterized by $^1$H NMR (Eq. (2)). This reaction under standard conditions also produced nitrite salts (KNO$_3$)$_2$ b and I$_2$ crystals as byproducts, as detected by ion chromatography and observed after solvent removal. Next, we
monitored the effect of adding each reaction product at the start of the reaction, including the ester 7, carboxylate 8, nitrite and hydrogen carbonate salts (Fig. 3(a)). All these cases displayed sigmoidal kinetic profiles similar to the reaction with no additives, although small variations in initial induction times were observed.

Eventually, I$_2$ was selected as an additive to the reaction (Eq. (2); Fig. 3(b)). This gave a dramatic improvement in the initial reaction rate, similar to conventional pseudo-first-order kinetic profiles (Fig. 3(a), red curve). Here the addition of I$_2$ gave a sustained purple-red colour throughout the course of the reaction. In comparison, without pre-adding I$_2$, the reaction turned from yellow to a similar purple-red colour after 30 minutes, at which time the rapid formation of the ester product 7 was clearly observed (Fig. 3(a), black curve). The effect of I$_2$ was therefore studied in more detail by monitoring the in situ consumption of the α,α-diiodonitroalkane 2a and the in situ formation of ester 7 by React-IR (Fig. 3(b)). Again, we followed the standard reaction without any additives (Eq. (2)) and, although the IR-data were consistent with our initial $^{1}$H NMR analysis, the 0–40 min induction periods were better resolved (cf. Fig. 3(a), black curve; Fig. 3(b), blue curve). Addition of I$_2$ also gave a similar conventional kinetic profile to our $^{1}$H NMR analysis, which produced the desired ester 7 within 80 min (cf. Fig. 3(a) and Fig. 3(b), red curves).

Since I$_2$ can act as a dual source of cationic iodonium species (I$^+$) and anionic iodide species (I$^{-}$) in solution, we performed separate reactions either by adding 20 mol% of NIS as an I$^+$ source or by adding 20 mol% of NEt$_4$I as an I$^{-}$ source. While NIS demonstrated a slight retardation on the initial reaction rate (cf. Fig. 3(b), purple and blue curves), NEt$_4$I dramatically accelerated the overall reaction rate and gave no observable induction period (Fig. 3(b), blue curve).

Furthermore, a similar iodide-mediated acceleration effect was observed in the case of CF$_3$CH$_2$NH$_2$ reacting with 2a to form the amide 6 (X$^r$ = NHCH$_2$CF$_3$; see ES1†). Collectively, these data support iodide byproducts (I$^{-}$) as the principal species which catalyse the oxidative conversion of the diiodide 2a to the ester 7 under O$_2$.

The mechanistic implications of these findings are thought provoking, especially when we take related studies into account. Several mechanistic observations are worth noting:

1. From previously reported radical clock experiments, the
radical 10 is an evidenced key intermediate in this process.\textsuperscript{2b} (2) The direct reaction of O$_2$ to generate the radical 10 from an α-iodo, α-nitro, α-carbanion 9, which can conceivably be formed by ionic attack of an iodo anion or another nucleophile onto an α,α-diodonitroalkane 2, can be ruled out from our previous experiments.\textsuperscript{2b} (3) The reaction remains unaffected by light exposure, which indicates that the homolytic cleavage of the carbon-iodine bond of 2 via photo-activation can be ruled out. (4) Experiments with the addition of relatively non-nucleophilic radical initiators (e.g., (PhCO)$_2$O$_2$ or AlIB at 50 °C) or radical inhibitors (e.g. TEMPO at 25 °C) were found to not alter the induction periods under our reaction conditions and substrates. Such additive effects would be expected to be significant for radical chain reactions, but not for iodoine-atom transfer reactions (see ESI\textsuperscript{†}).\textsuperscript{7d}

Based on these results, our autoinductive interpretation between the α,α-diodonitroalkane 2 and iodoine-byproucts (Fig. 1(b)) is presented in Scheme 1. As iodoine anions (I$_n^-$) are known to be good electron donors and can afford alkyl radicals from alkyl iodoines,\textsuperscript{9-12} it is reasonable to expect iodoine-atom transfer from the more highly electron deficient α,α-diodonitroalkane 2 to I$. This process would give a putative diiodide radical anion (I$_2^•$) and the previously evidenced carbon radical 10 (Scheme 1). The subsequent reaction of carbon radical 10 with oxygen would be similar to the mechanism we established during the oxidative NF reaction of nitroalkanes with molecular oxygen.\textsuperscript{2b} That is, the radical 10 reacts with O$_2$ to generate the peroxy-adduct 11,\textsuperscript{12} which would provide the dioxirane 5.\textsuperscript{2,3b,4} The I$_2$•$^+$ byproduct can then couple homogeneously with mono-iodine (I$_1^-$) to generate I$_2^•$ as a known source of I$_2$ and I$_1^-$\textsuperscript{8}. Latterly, in addition to our previous proposal,\textsuperscript{2a} dioxiranes 5 can also conceivably transform to the acyl derivative 3 through the action of I$.\textsuperscript{13}

Under this mechanistic framework, the observed autoinduction profiles of Fig. 2 and Fig. 3 would be explained as follows: As diiodine (I$_2$) is also a source of electrophilic mono-iodine (I$_1^-$) and an extra equivalent of anionic mono-iodide (I$^-$),\textsuperscript{8} the iodoine byproducts of 2 can increase up to two-equivalents during every turn of this cycle, making the reaction autoinductive (cf. Fig. 1(b) and Scheme 1).\textsuperscript{7-13} The initial absence of I$_n^-$ species thus accounts for the observed 30-40 minute induction periods (cf. Fig. 2 and Fig. 3). Iodoine can be generated, however, through alternative reaction pathways, for example, through a slow C-$\text{N}_2$O$_2$→C-ONO homogenous rearrangement, C-O homolytic bond cleavage, or by nucleophilic attack on the gem-diiodide 2.\textsuperscript{2,5}

To provide evidence of possible nucleophilic attack on 2 releasing iodide, the differing kinetic profiles of benzylamine at room temperature and −10 °C were studied in more detail (see Fig. 2). Firstly, the addition of 20 mol% of NEt$_4$I for the reaction at −10 °C (cf. Eq. (1)) exhibited a conventional kinetic profile with no induction period—see ESI\textsuperscript{†} for comparative reaction profiles of benzylamine in CD$_2$CN by $^1$H NMR analysis. Secondly, without iodoine additives at room temperature, $^1$H NMR experiments showed that benzylamine forms an amine halogen bonded complex with 2a and a mono α-iodinated derivative 9, as well as benzyldihydro after work up (see ESI\textsuperscript{†}). Thirdly, the same amine complex of 2a was also observed at −10 °C, but deiodinated 2a and benzyldihydro were not detected. Collectively, this evidence indicates that 2a can transfer an iodoine to the amino group of benzylamine at room temperature, which likely results in amine formation and the release of iodoine catalyst. In further support of the need to release iodoine, we also observed the accelerating effect of adding strong nucleophiles such as PPh$_3$ and SMe$_2$ (see ESI\textsuperscript{†}). Indeed, under unfavorable conditions with weak nucleophiles, the α,α-diodonitroalkane 2a is suggested to produce iodoine byproducts relatively slowly.\textsuperscript{2b} Reactions with methanol at room temperature or benzylamine at −10 °C thus necessitate the gradual generation of iodoine anions in sufficient concentrations to catalyse the formation of the radical 10 from 2a, as reflected in their kinetic profiles (cf. Scheme 1, Fig. 2 and Fig. 3).

On the mechanistic basis of iodoine-mediated autoinduction, we thus decided to explore the direct oxidative esterification between primary nitroalkanes and primary alcohols with a slight excess of I$_2$ (1.2 equiv.) under a variety of basic conditions (see Scheme 2 and ESI\textsuperscript{†} for optimization studies). Compared to conventional methods, which first convert primary nitroalkanes to carboxylic acids before ester formation,\textsuperscript{14} our aim was to develop a one-pot method to directly make sterically challenging esters via \textit{in situ} α,α-diodonitroalkanes 2 from readily prepared, but hindered primary nitroalkanes 12 (Scheme 2).\textsuperscript{6} Here, 1.2 equivalents of I$_2$ were considered to be sufficient because I$^-$ would oxidise to I$_1^-$ under O$_2$, as reported previously.\textsuperscript{2b} Thus I$_2$ was chosen to act as a source of iodonium cations to not only form 2, but also to form iodoine byproducts to facilitate the homolytic cleavage of 2 to the O$_2$-reactive carbon-radical 10 (cf. Scheme 1).\textsuperscript{5} Experimentally, the α-amino, α-hydroxy, α-alkyl or α-phenyl functionalized α,α-trisubstituted methyl esters 13a-f all formed in good yields in a direct and rapid manner (Scheme 2). Although an increase in the bulkiness of the β-position of the starting nitroalkane gave slightly longer reaction times, the yields remained good (cf. 13d-f). Conveniently, the α-chiral trisubstituted esters 13g-h and γ-lactone 15 can be prepared in high enantioslectivity from chiral nitroalkanes via the asymmetric organocatalysed Michael reaction of nitromethane with β,β-disubstituted α,β-enals.\textsuperscript{15}
In summary, the direct aerobic conversion of α,α,α-tridiodonitroalkanes 2 to amides or esters with relatively weak nucleophiles was found to display unusual sigmoidal reaction profiles, as evidenced by quantitative $^1$H NMR and React-IR studies (Fig. 3). Systematic addition of sub-stoichiometric amounts of potential products derived from 2 (Eq. (2)) clearly identified mono-iodide anions to accelerate the reaction. Due to the increasing generation of up to two-equivalents of iodine byproducts after each catalytic cycle, 8 we herein propose a new case of autoinduction,7 whereby the iodide-mediated formation of O$_2$-reactive carbon radicals 10 from 2 is reasoned to occur through an iodine-atom transfer event (Scheme 1). Under this mechanistic framework, we developed a convenient one-pot oxidative transformation of readily prepared α,α,α-trisubstituted nitroalkanes 15 into sterically encumbered α,α,α-trisubstituted esters, which are difficult to access directly by conventional methods. Application of these fundamental understandings 7–13 to useful metal-free and iodine-based oxidative transformations are ongoing.2–6

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Conflicts of interest

There are no conflicts to declare.

Notes and references


