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Mechanism of Oxidative Amidation of Nitroalkanes with Oxygen and Amine Nucleophiles by Using Electrophilic Iodine

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Abstract: Recently, we developed a direct method to oxidatively convert primary nitroalkanes into amides that entailed mixing an iodonium source with an amine, base, and oxygen. Herein, we systematically investigated the mechanism and likely intermediates of such methods. We conclude that an amine–iodonium complex first forms through N–halogen bonding. This complex reacts with *aci*-nitronates to give both α-iodo- and α,α-diiodonitroalkanes, which can act as alternative sources of electrophilic iodine and also generate an extra equimolar amount of I^+ under O_2. In particular, evidence supports α,α-diiodonitroalkane intermediates reacting with molecular oxygen to form a peroxy adduct; alternatively, these tetrahedral intermediates rearrange anaerobically to form a cleavable nitrite ester. In either case, activated esters are proposed to form that eventually reacts with nucleophilic amines in a traditional fashion.

The structural and functional importance of the amide bond to natural products and bioactive small molecules is clear.[1] Yet, the efficient synthesis of amides and peptides with simple reagents is still a challenge.[2] Several alternative oxidative and decarboxylative methods to form amides and peptides have been developed over the last decade.[3] Related interest has also been in the use of iodine-based reagents to promote or catalyze C–N amine bond formations.[4] In 2010, a major advancement in oxidative amidation was disclosed by the Johnston group with the use of *N*-iodosuccinimide (NIS) and is termed umpolung amide synthesis (UmAS).[5] The method centers on α-bromo-substituted nitroalkanes **1**′ reacting with electrophilic *N*-iodoamines **2**′ (in situ generated with NIS) to form reactive tetrahedral α-amino-α-bromonitroalkanes **3**′ (Figure 1).

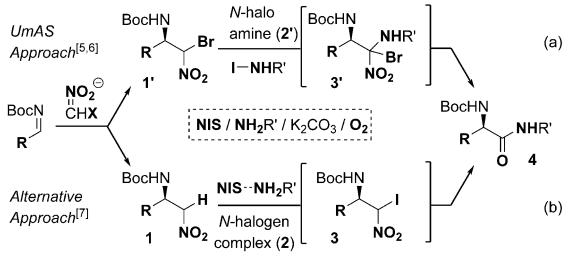

Figure 1. Oxidative approaches to umpolung amide synthesis (UmAS).[5–7]

Later mechanistic studies supported such tetrahedral intermediates **3**′ coupling with molecular oxygen in a homogenic manner to eventually form the amide products **4** (Figure 1 a).[6] Through a systematic study of our recently developed oxidative amidation procedure on unsubstituted nitroalkanes **1**,[7] we now provide evidence that the tetrahedral intermediates are more likely α,α-dihalogenated nitroalkanes derived from α-halonitroalkanes like **1**′ or **3** (Figure 1 b). Under our reaction conditions, we propose that there is no umpolung of reactivity in the amine component and an extra equivalent of iodonium source is generated in the process.

Thus, having discovered[8] and developed[9] a Nef conversion of nitroalkenes and nitroalkanes into their carbonyl counterparts under base and oxygen, we recently extended our mechanistic understanding of such oxidative conversions into an atom-economical and direct amidation of primary nitroalkanes **1** by mixing in I_2 or NIS with amines (Figure 1 b).[7] During these amidation studies, we could not confirm the intermediacy of *N*-iodoamines **2**′ or early-stage α-aminonitroalkanes **3**′ derived from **1** as anticipated from UmAS rationales (Figure 1 a).[5a,b,6] Instead, we isolated a halogen bonded amine–NIS complex **2**, which was shown to form the α-iodonitroalkane **3** (Figure 1 b) through its anion, and realized data that put the mechanistic basis of UmAS into question (vide infra). We thus began to discern each step and intermediate of these clearly interrelated schemes in a systematic and precise fashion (Scheme 1).

In particular, we noted the anaerobic reaction of monoiodide **3** with allylamine and K_2CO_3 not only produced the amide **4** (18%), but also a significant amount (40%) of the deiodinated nitroalkane **1** (Scheme 1 a).[7] Without the amine under O_2, carboxylic acid **5** was generated from **3** (Scheme 1 b). These results led to the idea that the monoiodide **3** could act as a source of electrophilic iodine for α-carbanions, as opposed to reacting with amines to generate *N*-haloamines (**2**′).[6] This would logically produce a hitherto unobserved diiodide inter-

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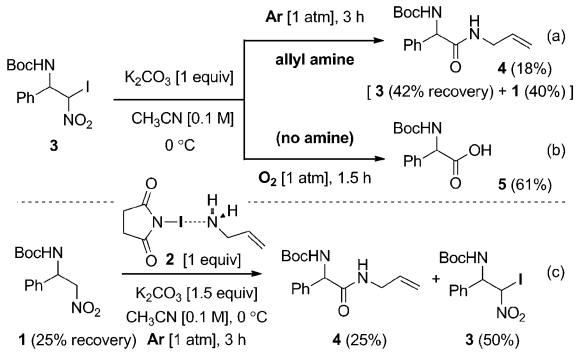
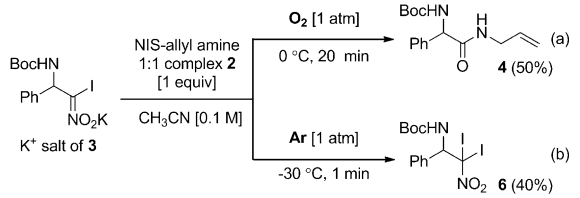


Scheme 1. Control amidation study of protonated nitroalkanes **1** and **3**.

mediate (vide infra) and the isolated deiodinated compound **1**. We thus decided to react the starting nitroalkane **1** directly with the NIS–amine complex **2** under Ar (Scheme 1c). Notably, about 25% of the starting nitroalkane **1**, 50% of the α-iodonitroalkane **3**, and 25% of the amide product **4** were produced under Ar with one equivalent of the 1:1 NIS–amine complex **2**. This means that a 25% yield of amide **4** required 50% of the iodinating reagent **2** under anaerobic conditions (cf. Schemes 1a and 1c).

Suspecting the need for iodine transfer by **3**, we studied the reactivity of the pure anion of **3** with one equivalent of the NIS–amine complex **2** under O_2 and under Ar (Scheme 2). The

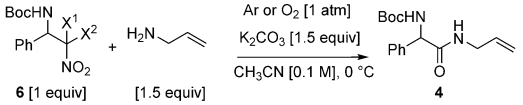


Scheme 2. Control amidation study of the pure anion of **3**.

aerobic conditions produced the amide **4** in moderate yields in 20 min when conducted at 0 °C (Scheme 2a). Markedly, the potassium salt of **3** rapidly produced the diiodide **6** at −30 °C with the NIS–amine complex **2** when the reaction was stopped within 1 min (Scheme 2b). Longer reaction times or higher temperatures produced the expected amide **4**, and diiodide **6** was not observed. Although the anion of **3** transformed into amide **4** with NIS–amine complex **2** under O_2 (Scheme 2a), **3** readily oxidized with O_2 to carboxylic acid **5** in the absence of amine and iodonium sources (cf. Scheme 1b). In such cases, we observed I_2 being generated and, among other possibilities, these control experiments (cf. Schemes 1 and 2) reinforced the idea that the amide **4** and carboxylic acid **5** can be derived from the corresponding α,α-diiodonitroalkane **6**, which is generated by sequential bis-iodination of **1** via intermediate **3**.

Considering such types of dihalogenated species **6** as reactive tetrahedral intermediates to the amide **4**, as alternatives to α-amino-α-bromonitroalkanes **3**′,[6] we prepared and compared the reactivity of dihalonitroalkanes **6** (X^1, X^2 = Cl, Br, and/or I)

Table 1. Direct amidation of dihalogenated nitroalkanes **6**.[a]

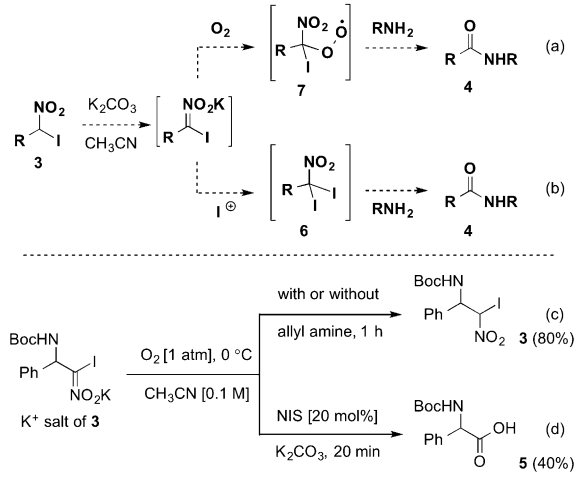


Entry	X^1	X^2	Yield under Ar [%][b]	Yield under O_2 [%][c]
1	Cl	Cl	trace	<5
2	Cl	Br	35	20
3	Cl	I	48	72
4[d]	Br	Br	10	31
5	Br	I	55	70
6[e]	I	I	50	60

[a] Unless noted otherwise, all reactions were conducted with dihalogenated nitroalkanes **6** (0.1 mmol), allyl amine (0.15 mmol), and K_2CO_3 (0.15 mmol) at 0 °C in CH_3CN (1 mL) under O_2 or Ar (1 atm); isolated yields are given. [b] Reactions under Ar were conducted over 48 h, except entry 6, which was over 1 h. [c] Reactions under O_2 were conducted over 24 h, except entry 6, which was over 20 min. [d] Reaction conducted at room temperature. [e] Diiodide of **6** was unstable and used immediately after preparation.

under both Ar and O_2 (Table 1; see the Supporting Information for X-ray of bromo/iodo **6**). The experiments clearly showed that the amide **4** formed directly from the dihalide intermediate **6**, whereby higher reactivity and yield resulted with the introduction of at least one iodine substituent. Exceptional reactivity, within 20–60 min, was observed with the unstable diiodide **6** (X^1, X^2 = I), which likely accounted for our difficulty in observing **6** during our initial amidation studies, unlike the dichoride.[7]

In combination with Scheme 2, the results in Table 1 are consistent with the consecutive bis-iodination of the starting nitroalkane **1** and then monoiodide **3** through their respective *aci*-nitronates. However, at this juncture, it was still not clear whether the anion of **3** first reacted with oxygen, for example, either directly or through SET and radical coupling (Scheme 3a) or with an iodonium source, for example, with I_2, NIS or the halogen bonded NIS–complex **2** (Scheme 3b). We thus consid-

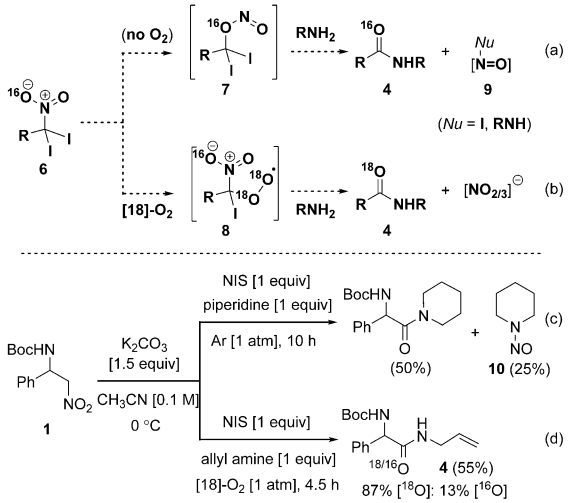


Scheme 3. Pathway selection and reactivity of anion of **3** with O_2 and NIS.

ered two pathways for the formation of amide **4** from monoiodide **3** and performed another set of control experiments with the potassium salt of **3** (Schemes 3c and 3d).

First, with or without amine being present, the experiments clearly demonstrated that, in the absence of an iodonium source, molecular oxygen does not react with the *aci*-nitronate intermediate of **3** at all (Scheme 3c). Thus, SET transfer mechanisms or immediate anionic attack onto O_2 to afford radical[10] or anionic[9] oxygen adducts directly from **3** do not operate. It is more likely the case of molecular oxygen reacting with the diiodinated nitroalkane **6**, as first evidenced during the experiments shown in Scheme 2. Second, in the presence of 20 mol% of NIS and absence of amine, carboxylic acid **5** was isolated in a yield of 40% after aqueous work-up (Scheme 3d). Here, we suggest the diiodide intermediate **6** can regenerate an extra equivalent of the iodonium source (vide infra).

Such suggestions have clear experimental precedence in a recent UmAS study.[6] The difference herein is that we propose tetrahedral α-iodo-α-halonitroalkane **6** instead of α-amino-α-halonitroalkane **3′** as the key intermediate that reacts with oxygen. Further evidence presented in the UmAS-labeling study[6] also showed that the residual $H_2{}^{18}O$ and $N^{18}O_2$-labeled α-halonitroalkanes **3** do not result in significantly ^{18}O-enriched amides **4** under $^{16}O_2$. Thus, having the dioxygen directly reacting with the anion of **3**, two UmAS-like pathways to form the amide **4** were reasoned to occur by the tetrahedral α,α-diiodonitroalkane **6**, and not by its α-amino-α-bromo counterpart **3′**[6] (Scheme 4). Both radical and ionic modes were considered

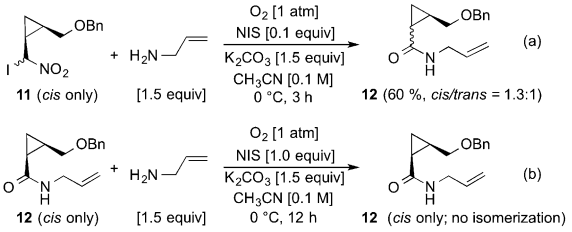


Scheme 4. Nitroso-trapping and $^{18}O_2$-labelling studies of **1**.

feasible, and the generation of *N*-nitrosoamines **9** (Nu = amine)[11] was also deemed possible as products from previously related[5b] diiodo nitrites **7**, the rearranged adducts of **6** (Scheme 4a). The fate of the nitro group was thus uncertain under anaerobic and aerobic conditions, for example, to form either nitrate or nitrite salts from the congested peroxynitroalkane **8** (Scheme 4b), and a further set of control experiments were performed to discern such fates (Schemes 4c and 4d). Specifically, we measured the resultant concentration of nitrate/nitrite salts and the level of ^{18}O incorporation by converting **1** into **4** under $^{18}O_2$.[9]

In the event, piperidine was chosen as a less volatile amine reactant than allylamine, which allowed for the anticipated and known *N*-nitrosoamine **10**[11] to be isolated reliably (Scheme 4c). Under Ar, **10** was isolated in 25% yield. Under O_2, **10** was isolated in 11% yield. The formed nitrosyl iodide **9** (Nu = I) would be expected to also convert to I_2 and NO gas.[12] The fact that *N*-nitrosoamines were isolated supports the existence of nitrite intermediates **7** under the UmAS reaction conditions. Next, isotope labelling experiments with allylamine as the nucleophile revealed an 87% of ^{18}O incorporation in the amide product **4**, which was isolated in a chemical yield of 55% under $^{18}O_2$ (Scheme 4d). The resultant nitro-derived salt ratios were calculated to be 36% nitrite (NO_2^-) and 4–6% nitrate (NO_3^-) under O_2, whereas 3% NO_2^- and 1–2% NO_3^- were detected under anaerobic conditions (see the Supporting Information). Although the data supports the nitro–nitrite rearrangement (**6** to **7**; Scheme 4a) as the predominant fate of the nitro functionality of **1** under anaerobic conditions, it also suggests that both pathways can occur concomitantly under aerobic conditions. Presumably, the proximity and local concentration of solvated O_2 gas to diiodide **6** will be a factor in pathway selection, and $NO_{2/3}$ salt counts were found to be low due to *N*-nitrosoamine formation and loss of NO gas (and I_2) through species like I–N=O.[12]

Next, we performed radical clock experiments (Scheme 5).[9,13] Thus, the pure *cis*-cyclopropanes **11** and **12** were prepared and reacted with the allylamine under our oxidative conditions. Starting from *cis*-**11**, a 1.3:1 *cis*/*trans* ratio of



Scheme 5. Radical clock control experiments of pure *cis*-**11** and *cis*-**12**.

12 was generated in 60% yield (Scheme 5a). In order to exclude epimerization occurring after amide formation, the purified *cis*-cyclopropyl amide **12** was similarly treated with NIS, K_2CO_3 and O_2. This gave complete recovery of the *cis*-cyclopropyl amide, even after 12 h (Scheme 5b). These results support the existence of a cyclopropylcarbinyl radical being generated and undergoing ring opening/closure.

Lastly, the regeneration and intermediacy of putative iodonium sources need to be considered under our reaction conditions (Figure 2). In other words, presuming that diiodide **6** is the key intermediate, the oxidative amidation of the mono-iodonitroalkane **3** (in the absence of additional NIS or I_2) is expected to occur by an initial iodine transfer to its anion to afford the diiodide **6** and eventually regenerate an equivalent

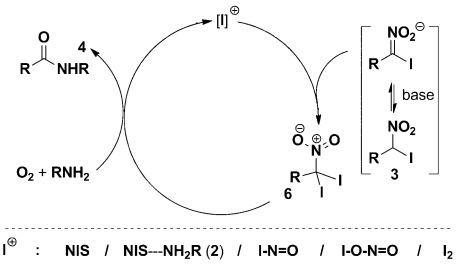


Figure 2. Generic process to regenerate an iodonium source.

amount of the iodinating agent. Furthermore, despite observing the iodo precursor **3** being oxidized to carboxylic acid **5** with oxygen under basic conditions (cf. Scheme 1 b), oxygen does not react with the anion of **3** first (cf. Scheme 3 c), but more likely O_2 reacts with the diiodide **6** after it forms through iodine transfer of **3** to its nitronate anion (cf. Scheme 2 b and Table 1). Moreover, the oxidative amidation of the nitroalkane starting material **1** only requires one equivalent of NIS in the presence of O_2.[7] In accordance with the latest UmAS report,[6] we similarly suggest an extra equivalent of I_2, I–N=O[12] and/or I–ONO species is generated under the reaction conditions (Figure 2). These iodonium species can thus react under either radical or ionic reaction modes and allow the amide oxidation state of **4** to be achieved from monoiodide **3**.

Collectively, our findings are consistent with the mechanism illustrated in Figure 3. We thus propose the primary nitroalkane **1** first becomes α-iodinated with NIS from the halogen-bonded amine complex **2** to afford the monoiodide **3** (Figure 3 a). After further deprotonation, the α-iodo *aci*-nitronate

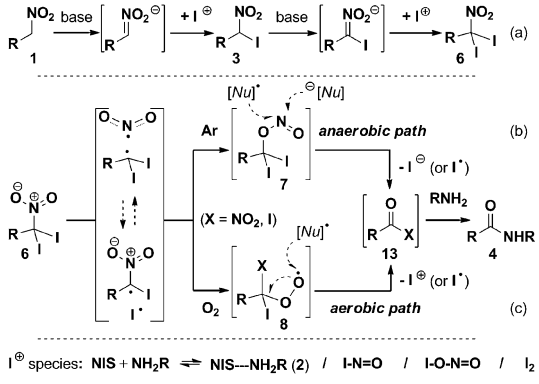


Figure 3. Proposed oxidative amidation of **1** by α-iodide **3** and diiodide **6**.

becomes α-iodinated with another iodonium species (I^+) to afford the diiodide **6**. We propose it is this congested, tetrahedral diiodinated nitroalkane **6** that can either rearrange in a homogenic, anaerobic manner to form the nitrite ester **7** (Figure 3 b) or react with the molecular oxygen to afford peroxy radical adduct **8** (Figure 3 c). From these intermediates onwards, several additive–eliminative pathways, under either radical or ionic reaction modes, can be proposed to afford the amide product **4**.[9–11] On the basis of prior studies, one suggestion for such latter stage is that the peroxy radical **8** cyclizes and expels either a mono-iodine or nitrite radical to form a reactive dioxirane intermediate, which can react with the anion of **3** (Figure 3).[9] The peroxy radical **8** could also couple with a nearby radical derived from **6** to form homo- or heterodimers.[14] In either case, the dioxygenated intermediates would fragment to the acylating species **13**. Besides other possibilities,[10] the exact mechanistic details of such latter amine addition stages (through **7**/**8** and **13**) remains to be supported by further studies. However, we do provide indirect evidence for the anaerobic formation of the nitrite ester **7** by isolation of the *N*-nitrosoamine **10**.

In conclusion, our mechanistic rationales, as depicted in Figure 2 and Figure 3, are consistent with all of the reported data and observations that have been obtained during previously published umpolung amide synthesis (UmAS) studies[5,6] and our recent work.[7] Critically, the key differences in our conclusions include: 1) the intermediacy of a reactive tetrahedral dihalogenated species like **6**, and not α-amino halonitroalkane **3′**; 2) the halogen bonding of NIS with amines to form iodonium complexes like **2**, and not electrophilic *N*-iodoamine **2′**; and 3) the late-stage nucleophilic addition of amines to oxygenated intermediates like **7** or **8**, or a subsequently derived traditional acyl precursor **13**, to give the amide products **4**.

Keywords: amides · iodine · peroxides · radicals · umpolung

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