Sterically Demanding Oxidative Amidation of α-Substituted Malononitriles with Amines Using O₂

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Abstract: An efficient amidation method between readily available 1,1-dicyanoalkanes and either chiral or nonchiral amines was realized simply with molecular oxygen and a carbonate base. This oxidative protocol can be applied to both sterically and electronically challenging substrates in a highly chemoselective, practical, and rapid manner. The use of cyclopropyl and thioether substrates support the radical formation of α-peroxy malononitrile species, which can cyclize to dioxiranes that can monooxygenate malononitrile α-carbonions to afford activated acyl cyanides capable of reacting with amine nucleophiles.

Adding to such challenges is a drive to develop new ways to make amide bonds by activating nontraditional substrates oxideratively, as represented by the methods from the groups of Milstein, Rovis, Johnston, Bode, Lei, and Garg, as well as ours.[4,5] Stemming from recent mechanistic insights[6c,d] into the umpolung amide synthesis (UmAS) method of Johnston and co-workers,[4c] we now present our oxidative advancement of the masked acyl cyanide (MAC) method to make amides, which was introduced by Yamamoto and co-workers[3c] in 1990 and elegantly exploited in 2013 by the group of Rawal.[5c] Specifically, we disclose the direct, oxygen-based conversion of 1,1-dicyanoalkanes to make hindered amides and peptides in high yield and stereochemical integrity. This mild, yet powerful method simply entails stirring α-substituted malononitriles with chiral or nonchiral amines in acetonitrile under O₂ with a carbonate base.

The stimulus for this work began during our discovery and development of the base-promoted Nef oxidation of nitroalkenes or nitroalkanes to form their ketones with oxygen (Figure 1a). In this case, the efficiency and rapid formation of amides and peptides falls into such a challenge. A key feature of the amide bond plays a pivotal role in organic, biological, and materials chemistry,[1] it still presents a great synthetic challenge when confronted with sterically or electronically demanding substrates.[2] Seminal synthetic methods to making such challenging or complex amides have been reported by the groups of Bode, Rawal, Danishefsky, and Schafmeister.[3] These substituents can thus not only stabilize transient radicals and anions, but also act as one- or two-electron leaving groups.

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First, we explored NO$_2$[7] CN,[8] SO$_2$R,[9] and PO(OR)$_2$[10] as suitable X/Y groups for the proposed oxidative amidation sequence (Figure 1c). These studies are summarized in Table 1. Under our recently established oxidative conditions,[5b] reactions of either α-sulfonyl- or α-chloro-substituted nitroalkanes 1 with allylamine (2) did not produce the amide product 3 at all (entries 1 and 2). Suspecting the need for alternative electron-exchanging groups to facilitate single-electron transfer (SET) mechanisms with O$_2$[5b] we prepared and explored various α-substituted nitrile derivatives (1, X = CN). To our delight, when the 1,1-dicyanide 1 (X, Y = CN) was exposed to the amine 2 in the presence of K$_2$CO$_3$ under O$_2$ the desired amide was generated in 96% chemical yield within 3.5 hours at room temperature (entry 3). Further studies revealed the cooperative nature of CN and SO$_2$Ph groups in 1, which gave a 70% yield of 3, albeit over three days (entry 4). Otherwise, only trace amounts of the amide 3 were observed (entries 5–7).

With appropriate functionality and initial reaction conditions in place for the 1,1-dicyanide 1 (X, Y = CN), the scope of the oxidative amidation method was first investigated by changing the amine component (Scheme 1). Common functional groups, such as allyl, propargyl and benzyl amines, displayed high reactivity to amide formation (3, 4a–b). The unprotected hydroxy amine generated the corresponding amide 4c chemoselectively in 87% yield and the electron-deficient 2-aminoacetonitrile gave the desired amide in 96% yield (4d). Amines with increasing steric hindrance, including tert-butylamine, cyclohexylamine, pyrrolidine, N-methylbenzylamide, diethylamide, and morpholine, all gave the desired amides in greater than 80% yield (4e–j). The reaction conditions were also found suitable for the Weinreb amide formation (4k). Notably, coupling of 1 with amino-acid methyl esters or an amine-free dipeptide generated the corresponding amides and peptides in 70–84% yields upon isolation (4l–p) without epimerization. Also, 2-propylmalononitrile reacts with allylamine to give the desired amide 4q in 90% yield.

Next, our aim was to apply this oxidative method to more challenging amides (see Table S2 in Supporting Information for optimization studies). In short, we studied the α-tert-butyl malononitrile 5 (R’ = Bu) and N-methylbenzylamine for optimization to the sterically hindered amide 6a, whereby Cs$_2$CO$_3$ was demonstrated to be superior, at elevated temperatures, to bases like K$_2$CO$_3$, KOAc, and K$_2$PO$_4$, as well as to stronger bases like KOBu and CsOH (Scheme 2; Conditions A or B). To prevent carboxylic acid formation, presumably derived by 5 reacting with residual water, strictly anhydrous conditions were adopted and predried 4 Å molecular sieves and Cs$_2$CO$_3$ with two equivalents of amine gave the amide 6a reliably in 71% yield. We thus explored the scope of these simple oxidative conditions for making other challenging amide and peptide systems (Scheme 2). Besides the notable formation of the congested aromatic amide 7e with allylamine, the formation of the amides 6–10 proceeded in good yield at 50°C, despite both sides of the amide bond being fully substituted (Conditions A). Furthermore, chiral amino-acid methyl esters and amides could be coupled with sterically hindered malononitriles in acceptable yields and reaction times at 70°C (Conditions B) with complete stereochemical integrity in the amine component (see the Supporting Information).

On the basis of our previous mechanistic studies into making ketones[9] and amides[9,4d] from nitroalkanes, one plausible pathway for the oxidative amidation of malononi-
triles with amines is proposed in Figure 2. Thus, the \( \alpha \)-substituted malononitrile first deprotonates to generate the anion 11, which is then capable of SET and addition with molecular oxygen, either directly or indirectly. If a radical pair is produced, they would couple to form the peroxide adduct 13. In either case, 13 can cyclize and expel cyanide anion to form the reactive dioxirane intermediate 14 (see the Supporting Information for an alternative \( O_2 \) addition pathway to eliminate cyanate anions via a four-membered adduct through 12 or 13). In turn, electrophilic mono-oxygen transfer from 14 to another 1,1-dicyano carbanion (11) produces a bis(tetrahedral) adduct 15 which can fragment into two acylating species (16) capable of being intercepted by the amine nucleophile. It is conceivable that the initial steps between the intermediates 11/12 can be considered to be reversible. A selection of control reactions were carried out to evaluate this mechanistic proposal (also see the Supporting Information).

The role of \( O_2 \) was considered first [Eq. (1)]. When 1 \((X,Y=CN)\) was mixed with allyl amine in the presence of \( K_2 CO_3 \) under argon, the amide 3 was not formed and 1 was recovered completely. This outcome is in stark contrast to when the reaction was conducted under \( O_2 \) (Scheme 1; 96% yield of 3). Next, the reaction of molecular oxygen with 11 was considered. Based on our Nef study to make ketones from secondary nitroalkanes,[5b] and related reports for ketone formation from monocyanide compounds using \( O_2 \),[11] processes involving SET were deemed feasible (Figure 2). Thus to determine the existence of a radical species like 12, we prepared the \( \alpha \)-cyclopropyl malononitrile cis-18 as its pure cis isomer for suitable radical clock experiments.[12] Exposure of the preformed potassium salt of cis-18 to \( O_2 \) for 10 minutes gave a 1:3 cis-18/trans-18 mixture in 90% yield [Eq. (2)]. Control experiments with added TEMPO (1.0 equiv) and under strictly \( O_2 \)-free atmosphere gave near complete recovery of cis-18 (around 90%). Moreover, when cis-18 was exposed to the allylamine in the presence of \( K_2 CO_3 \) under \( O_2 \), the cyclopropyl amide was isolated as a 1:3.5 cis-19/trans-19 mixture in 90% yield after 4 hours [Eq. (3)]. Further experiments demonstrated a mixture of cis-18 and cis-19 to be isomerically stable to the reaction conditions under argon (see the Supporting Information). Collectively, these results support the anion 11 reacting reversibly with \( O_2 \) via SET to form the radical 12, which can conceivably couple with superoxide to form the peroxide adduct 13 as shown in Figure 2.

![Scheme 2. Oxidative amidation of sterically hindered \( \alpha \)-alkylated malononitriles and steric N-capping of amino-acid esters/peptides. M.S. = molecular sieves.](image)

![Figure 2. Proposed mechanism of amide formation via the acyl cyanide 16.](image)
The fate of the cyan group was also considered. Thus, the quantities of cyanide and cyanate anions were determined by ion chromatography as produced from the reaction given in the generation of 3 in Scheme 1. With respect to a total theoretical yield of 2 equivalents, cyanide ions were detected in low yield (7.6%), whereas cyanide ions were formed in high yield (84.8%; see the Supporting Information). On the basis of these results, we further suggest that 13 cyclizes to form the dioxirane intermediate 14, thus releasing the first equivalent of cyanide, after which the second equivalent of cyanide would be generated after amine addition to the proposed acyl cyanide 16 to give the amide product 17 (Figure 2).

Next, to support the electrophilic dioxirane intermediate 14, intramolecular thioether-trapping experiments were performed in O₂-saturated CH₂CN, such that the reaction of the anion 11 with molecular O₂ would be independent of the concentration of 11 [Eq. (4)]. In the event, the 5%-ethylnyl β-benzyl malononitrile 20 was prepared and reacted under dilute conditions at −20°C. This reaction gave the oxidized sulfynil amide 22 reliably in 5% yield. The direct oxidation of 20 or the sulfide product 21 by O₂ was excluded by additional control experiments at room temperature for over 48 hours (see the Supporting Information).

In summary, we have presented a new powerful way to construct challenging amide bonds between α-substituted malononitriles and amines under O₂. The oxidative amidation proceeds under mild reaction conditions, is highly practical, and simply employs cheap inorganic carbonate bases. Mechanistic studies support an initial SET pathway between the anion 11 of the α-substituted malononitrile and O₂ (via radical 12) to form the α-oxo adduct 13 as a precursor to the dioxirane 14, which generates acyl cyanide (16) via the formation and fragmentation of bis(tetrahedral) adducts 15 (Figure 2). Notably, our method does not require the formation of either congested pre-oxidized hydroxycarbonyl malononitriles as masked acyl cyanides (MACs)⁵ or congested halogenated nitroalkanes as precursors to activated esters⁶ which therefore offers good substrate scope for sterically hindered systems. It is thus reasoned that the SET induction addition of O₂ to 11 proceeds in a relatively unencumbered way to generate the acyl cyanide 16, which is known to react readily with amines (or alcohols) in a mild manner.¹³ This process compares favorably to either making and reacting acid chlorides with metal cyanides or by activating carboxylic acids with traditional reagents (e.g., with phosphorocyanidates).²¹,²² Lastly, we anticipate this method to find wide synthetic use in difficult N-terminal capping amidations and throughout the chemical sciences.²¹,²²

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### Keywords

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