Heterocycle Synthesis

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# Synthesis of 3,4,5-Trisubstituted Isoxazoles from Morita–Baylis–Hillman Acetates by an $NaNO_2/I_2$-Mediated Domino Reaction

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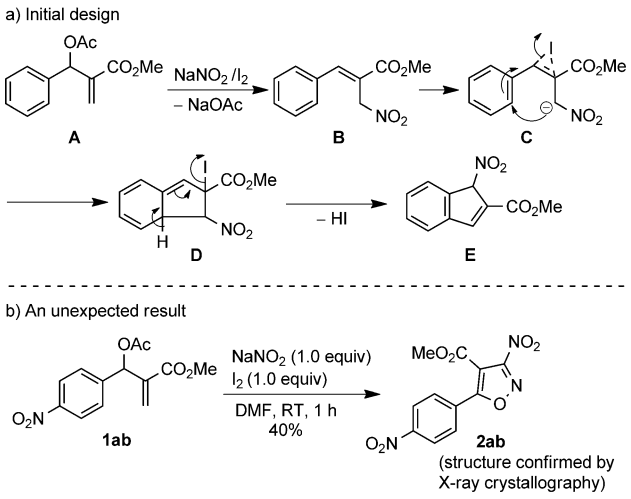
***Abstract:*** *An efficient $NaNO_2/I_2$-mediated one-pot transformation of Morita–Baylis–Hillman (MBH) acetates into alkyl 3-nitro-5-(aryl/alkyl)isoxazole-4-carboxylates is described. In a cascade event, initial Michael addition of $NaNO_2$ to the MBH acetate furnishes the allylnitro intermediate which undergoes $I_2$-catalyzed oxidative α-C−H nitration of the nitromethyl subunit followed by [3+2] cycloaddition to afford the title compounds. Structural elaborations of these highly substituted isoxazoles by $S_NAr$ reactions and hydrogenolysis allows access to useful products.*

Isoxazoles, a privileged class of five-member nitrogen heterocycles, occupy an important place in organic chemistry because of their wide applications in pharmaceuticals, biologically active molecules, advanced organic materials, and as intermediates in organic synthesis.[1–5] Owing to this ubiquity, their preparation has received remarkable attention and there are already scores of elegant methods which are general, regioselective, and high yielding.[6] As summarized by Carreira et al.,[6m] the classical routes to isoxazole derivatives involve condensations with hydroxylamine, cyclization of ketoxime dianions, and propargylic oximes, as well as 1,3-dipolar cycloaddition reactions. Unfortunately, these methods were inefficient for the synthesis of 3-nitroisoxazoles, which are potent antimicrobials.[7] As a consequence, a new route to 3-nitroisoxazoles by reacting tetranitromethane with electrophilic alkenes was developed.[8] But later, based on the X-ray analysis, these products turned out to be 5-nitroisoxazoles.[9] Therefore a general approach to substituted 3-nitroisoxazoles utilizing readily available starting materials is desired. Herein, we report a versatile route to new alkyl 3-nitro-5-(aryl/alkyl)isoxazole-4-carboxylates from a reaction between Morita-Baylis–Hillman (MBH) acetates and $NaNO_2$ in the presence of $I_2$/DMSO at room reaction time. The process not only represents a novel cascade transformation but provides preparative access to useful 3,4,5-trisubstituted isoxazoles. Furthermore, these products are exemplified to be apposite precursors to a range of novel isoxazoles by nucleophilic aromatic substitution ($S_NAr$) reactions and new 3,3-diamino-2-benzoylacrylates through hydrogenolysis.

The MBH adducts are advanced synthetic intermediates for several complexity generating reactions and this is manifested by their use in the construction of a plethora of heterocycles, natural products, and drug molecules.[10] In one of our research programs focused on realizing the synthetic potential of MBH chemistry, we developed synthesis of quinolines, pyrazolo[4,3-*b*]pyridines, and thieno[3,2-*b*]pyridines by $I_2$-mediated intramolecular electrophilic aromatic cyclization of primary allylamines.[11] Later, Yu et al. accomplished the synthesis of quinolones from allyl azides by cyclization of iminyl radicals generated by *N*-bromosuccinimide in light.[12] These results inspired us to examine the reaction of the MBH acetate **A** with $NaNO_2$ and $I_2$ since we anticipated that a Michael reaction with **A** would afford the allyl nitro derivative **B**, which would undergo intramolecular cyclization to offer the alkyl 1-nitro-3*a*,7*a*-dihydro-1*H*-indene-2-carboxylate **E** (Scheme 1). To test the hypothesis, the MBH acetate **1ab** was treated with $NaNO_2$ (1.0 equiv) and iodine (1.0 equiv) at room temperature in DMF. The reaction was complete in 1 hour, thus affording a solid product in 40% yield. Unexpectedly, the structure of the product was established as methyl 3-nitro-5-(4-nitrophenyl)-




***Scheme 1.*** Initial design and unexpected results.

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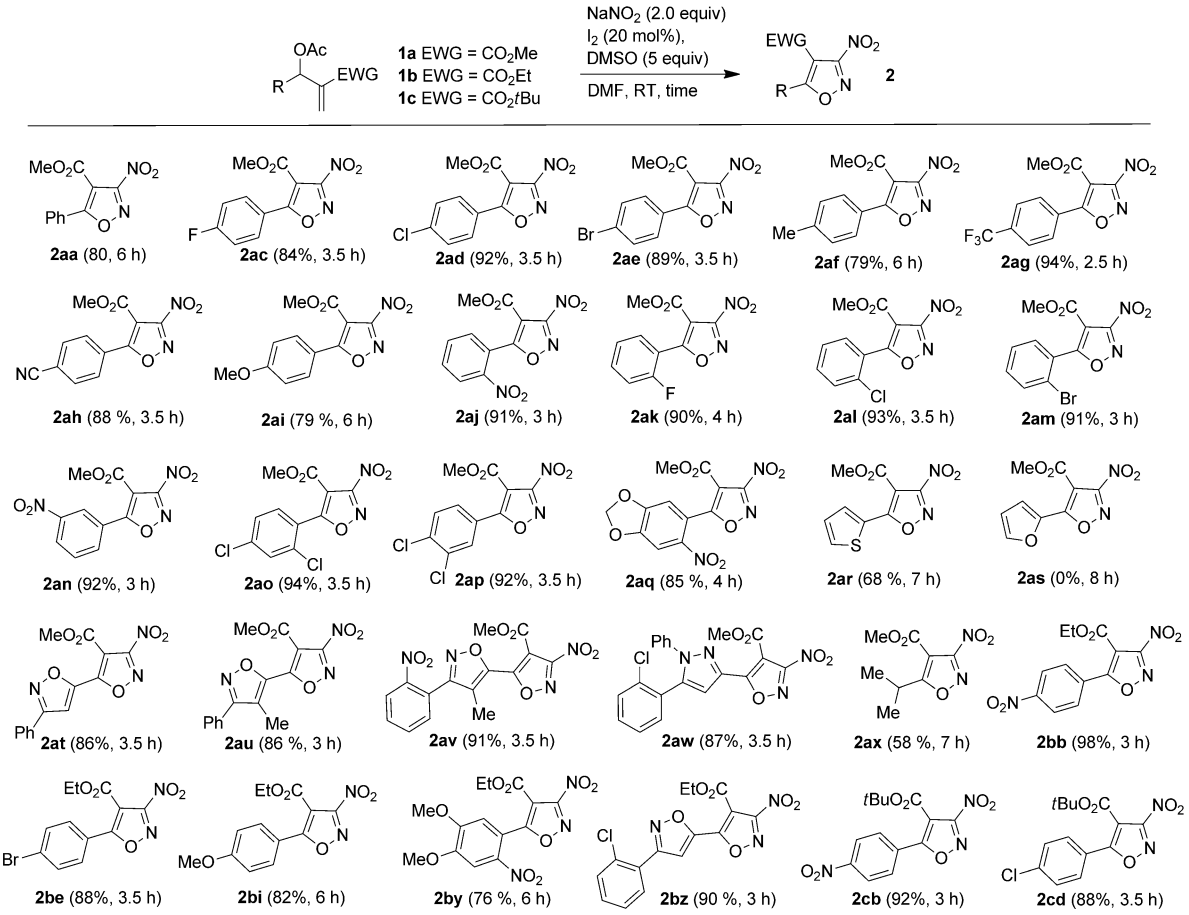
isoxazole-4-carboxylate (**2ab**). The formation of **2ab** can be explained on the basis of initial Michael addition of $NaNO_2$ and subsequent $I_2$-catalyzed oxidative α-C–H activation, nucleophilic addition of second nitrite ion, and [3+2] cycloaddition. Notably, nucleophilic additions by oxidative α-C–H activation in ketones, for formation of C–N and C–O bonds, is widely reported,[13] but analogous nucleophilic addition on the C–H bond α to the nitro group is unprecedented.

It is apparent from the tentative mechanism that the reaction essentially requires 2.0 equivalents of $NaNO_2$ and less than a stoichiometric amount of $I_2$ should work. Hence we screened the reaction under different reaction conditions (see the Supporting Information). Enhancing $NaNO_2$ to 2.0 equivalents and reducing $I_2$ to 0.5 equivalents prolonged the reaction time to 6 hours but **2ab** was isolated in 92% yield. NIS (1.0 equiv), as a $I_2$ source was found to be effective too, thus affording **2ab** in 90% yield. Often the $I_2$-catalyzed oxidative α-C–H activation in ketones is supported by the use of terminal oxidants. Therefore we probed the reaction in the presence of 0.2 equivalents of $I_2$ and external oxidants including TBHP, $H_2O_2$, and DMSO, and it was pleasing to note that in each case the reaction was expedited and the yields of **2ab** were excellent though, DMSO proved to be superior (96%). The $CuBr_2$-catalyzed nucleophilic addition to α-C–H groups of ketones by oxidative α-C–H activation has been reported by MacMillan et al.[13d] Likewise we too examined the reaction in the presence of $CuBr_2$ in DMSO and found that **2ab** was isolated in 94% yield. Even $Cu(OAc)_2$ was successful under identical reaction conditions, thus affording **2ab** in 86% yield. Nevertheless, the best reaction conditions for the transformation was reacting the MBH acetate (1.0 equiv) with $NaNO_2$ (2.0 equiv), $I_2$ (20 mol%), and DMSO (5.0 equiv) in DMF as a medium at room temperature for 3 hours.

Having optimized the reaction conditions, we turned our attention to test the scope of the protocol with various MBH acetates derived from aromatic, heteroaromatic, and aliphatic aldehydes, and the results are presented in Scheme 2. It is evident that the protocol was compatible to all MBH acetates (**1aa–aq**), generated from MBH adducts of substituted benzaldehydes and methyl acrylate, to afford the products **2aa–aq** in excellent yields. The reaction with acetates derived from heteroaldehydes revealed that thiophene, isoxazole, and pyrazole-based substrates (**1ar**,**1at–aw**) produced the corresponding products (**2ar**,**2at–aw**) in good yields but furan-based acetate **1as** only furnished methyl 3-(furan-2-yl)-2-(nitromethyl)acrylate (**3as**). Perhaps the electron-withdrawing nature of the nitro group in **3as** may lead to dearomatization of the furan ring because of its low resonance energy (see the Supporting Information). This dearomatization would

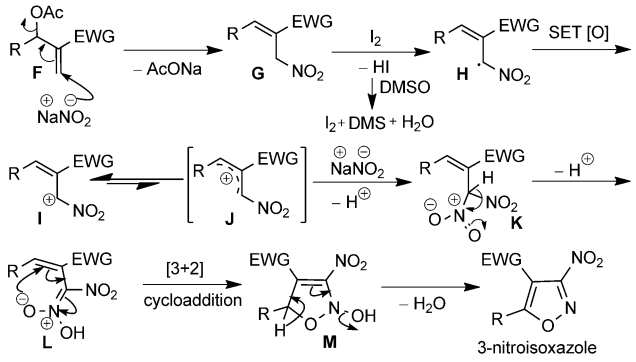



***Scheme 2.*** Scope of the transformation of MBH acetates (**1a–c**) into isoxazoles **2**. The yield is that of the isolated product and the time to completion is provided. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

have inhibited the α-C–H activation and concomitant attack of the nitrite ion. It may be noted that bis(isoxazole)s analogous to **2at**–**av** are useful in materials chemistry.[4a] The acetate **1ax**, prepared from MBH adducts of isobutyraldehyde, also produced the isoxazole **2ax**, albeit in moderate yield. Finally varying the alkyl ester from methyl to ethyl (**1b**) or *tert*-butyl (**1c**) in the starting substrates also produced the respective 3-nitroisoxazoles (**2bb**, **2be**, **2bi**, **2by**, **2bz,** and **2cb**, **2cd**) in excellent yields.

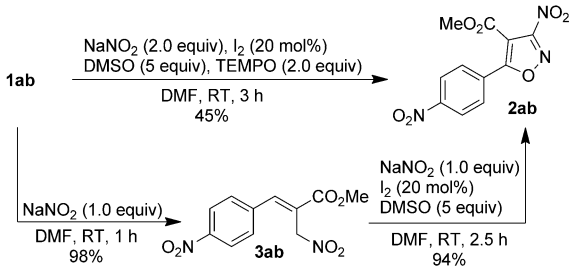
A plausible mechanism for the formation of the isoxazoles is delineated in Scheme 3. The first step is the Michael




***Scheme 3.*** Plausible mechanism for the transformation of MBH acetates into 3,4,5-trisubstituted isoxazoles. SET = single-electron transfer.

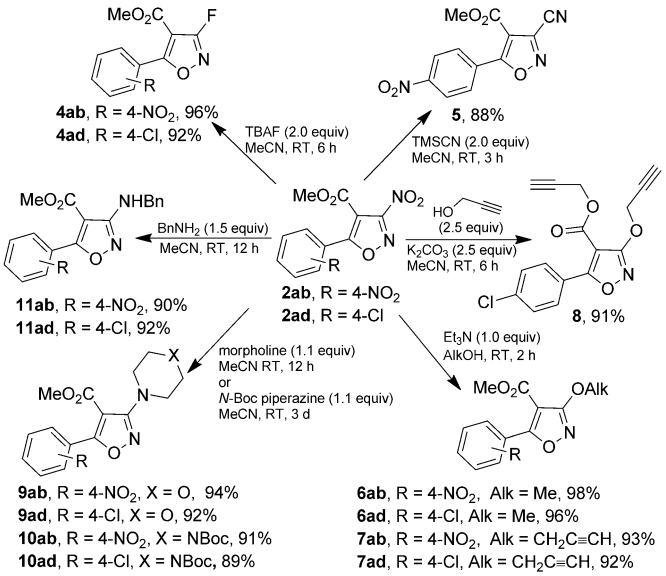
addition of the nitrite ion onto the MBH acetate to furnish the allylnitro derivative **G**. Molecular $I_2$ under the influence of DMSO is decomposed to the $I_2$ radical. The $I_2$ radical abstracts the α-hydrogen atom of **G** to form the carbon radical intermediate **H**, accompanied by liberation of one molecule of HI, which is trapped by DMSO to afford the molecular $I_2$. Through additional single-electron oxidation, **H** is converted into the intermediate cation **I** which may undergo delocalization to afford the intermediate **J**. Attack of the second nitrite ion may occur either at the benzylic or allylic carbon atom, but as the allylic carbon atom is more stabilized because of the extended conjugation and *E* configuration (thermodynamically stable), it regioselectively furnishes the dinitro intermediate **K**. Rearrangement of **K** into **L** followed by a [3+2] cycloaddition reaction gives **M**, which loses water to afford 3,4,5-trisubstituted isoxazole. To gather support for the proposed mechanism during a control experiment in the presence of radical inhibitor TEMPO, we observed that the yield of **2ab** fell to 45% (Scheme 4). When reaction of **2ab** was conducted in the absence of iodine, the allylnitro derivative **3ab** was isolated in 98% yield exclusively. The reaction of **3ab** with $NaNO_2$ (1.0 equiv) and $I_2$/DMSO afforded the isoxazole **2ab** in 94% yield.

To demonstrate the scalability of this protocol, the reactions of **1ab** and **1ad** were conducted on a 10 g scale, and were smoothly transformed into the isoxazole **2ab** (94%) and **2ad** (92%), respectively. Next, to demonstrate the applications of the 3-nitro-4-isoxazolecarboxylates for preparing useful isoxazole derivatives, $S_NAr$ reactions with different nucleophiles were examined. It has been reported




***Scheme 4.*** Control experiments. TEMPO = 2,2,6,6-etramethylpiperidine-*N*-oxyl.

that the fluorinated isoxazoles are important for medicinal chemistry but direct electrophilic fluorination in isoxazole was inefficient.[14] In contrast nucleophilic aromatic fluorination of heteroarenes can be realized with anhydrous TBAF under milder reaction conditions.[15] As a result reaction of **2ab** and **2ad** with TBAF, in a THF solution, in MeCN was performed and smoothly afforded the fluorinated isoxazoles **4ab** and **4ad**, respectively, in excellent yields (Scheme 5).

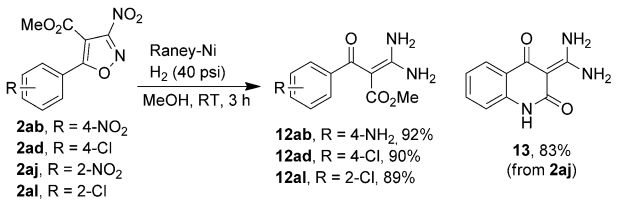



***Scheme 5.*** Utility of 3-nitroisoxazole for preparing novel isoxazole derivatives by $S_NAr$ reactions. Boc = *tert*-butoxycarbonyl, TBAF = tetra-*n*-butylammonium fluoride, TMS = trimethylsilyl.

Likewise reaction of **2ab** with trimethylsilylcyanide in MeCN furnished the 3-cyanoisoxazole **5** in 88% yield. Furthermore nucleophilic reaction of **2ab** and **2ad** with methanol in the presence of triethylamine gave the 3-methoxyisoxazoles **6ab** and **6ad**, respectively, whereas a similar reaction with propargyl alcohol (1.1 equiv) in MeCN furnished **7ab** and **7ad**, respectively. Interestingly performing the reaction of **2ad** in the presence of 2.5 equivalents of propargyl alcohol using $K_2CO_3$ as the base gave **8** in 91% yield. The compounds **7ad** and **8** undergo facile click reaction with sugar azides (see the Supporting Information). The synthesis of 3-aminoisoxazoles was recently reported to be a multistep procedure

which required the formation of 3-bromoisoxazole initially.[16] To demonstrate the utility of the title isoxazoles to access analogous compounds, we performed $S_NAr$ reactions of **2ab** and **2ad** with secondary amines, including morpholine and *N*-Boc piperazine, which smoothly afforded the the 3-aminoisoxazole derivatives **9ab**,**d** and **10ab**,**d**, respectively. Furthermore treating **2ab** and **2ad** with benzylamine gave the methyl 3-(benzylamino)-5-phenylisoxazole-4-carboxylates **11ab** and **11ad**, respectively, in excellent yields. We discovered that **1a** could be transformed into 3-aminoisoxazoles in one pot without attenuating the yield (see the Supporting Information).

Finally, given our interest in hydrogenolysis of isoxazole,[17,5e] we subjected **2ab**, **2ad**, and **2al** to hydrogenation in the presence of Raney-Ni using MeOH as the medium. The reaction was complete in 3 hours and afforded the novel methyl 3,3- diamino-2-benzoylacrylates **12ab**, **12ad**, and **12al**, respectively, in 89–92% yields (Scheme 6). Interestingly, the identical reaction with **2aj** resulted in formation of 3-(diaminomethylene)quinoline-2,4(1*H*,3*H*)-dione (**13**) in 83% yield.




***Scheme 6.*** Hydrogenolysis of 3-nitro-5-arylisoxazole-4-carboxylates.

In summary, we have demonstrated a facile transformation of MBH acetates into alkyl 3-nitro-5-(aryl/alkyl)isoxazole-4-carboxylates catalyzed by $I_2$ in the presence of $NaNO_2$. To the best of our knowledge, it constitutes the first example of nucleophilic addition at the C–H α to the nitro group by oxidative α-C–H activation. The reaction has been delineated to proceed by a radical mechanism. Readily available, cheap starting substrates, an inexpensive catalyst, metal-free mild reaction conditions, a simple experimental procedure, and good yields, even on lareger scale, are some of the attractive attributes of the present protocol. Alternatively, the synthetic protocol is equally effective with copper(II) salts. Furthermore, we have sufficiently demonstrated that 3-nitroisoxazoles are amenable to structural modifications for accessing functionally diverse isoxazoles, 2-aroylacrylates and quinoline-2,4(1*H*,3*H*)-diones. Further work concerning synthetic applications and biological assessment of these isoxazoles is underway and the results shall be reported in due course.

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