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Catalyst-Free Formation of Nitrile Oxides and Their Further Transformations to Diverse Heterocycles

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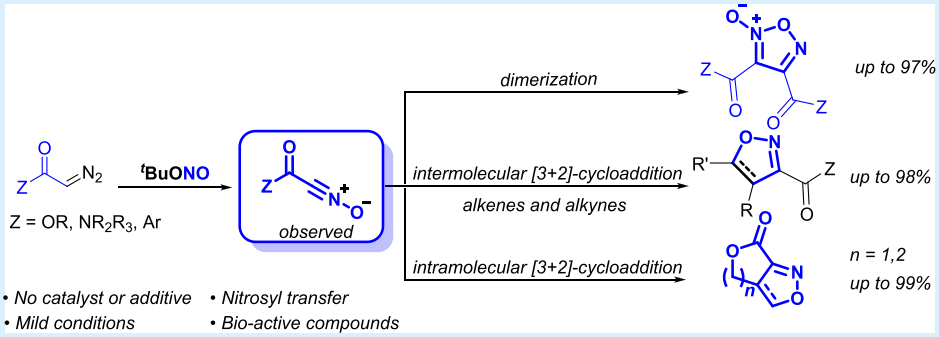
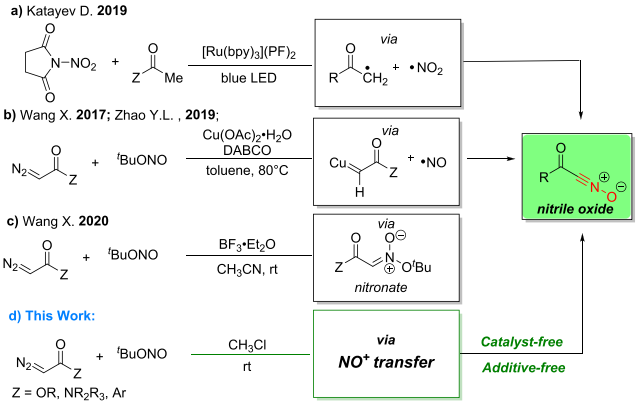


ABSTRACT: The formation of nitrile oxides with diazocarbonyl compounds by nitrosyl transfer from *tert*-butyl nitrite under mild conditions and without the use of a catalyst or an additive is reported. This transformation is broadly applicable to the synthesis of furoxans by dimerization and isoxazoles and isoxazolines by cycloaddition. This methodology is also applied for the millimole-scale synthesis of two biologically active compounds. The formation of the nitrile oxide from a diazoacetamide is stable and confirmed experimentally.

Nitrile oxides are highly reactive synthetic dipoles that undergo [3 + 2] cycloaddition with alkenes and alkynes to generate isoxazoles and isoxazolines, respectively, or dimerize to form furoxans.[1] They have wide applications in drug discovery, functionalization of materials, and organic synthesis.[2−6] Because of their instability, nitrile oxides are formed in situ. Conventional processes include dehydrohalogenation of hydroximoyl chlorides,[7] dehydration of primary nitroalkanes, and oxidation of aldoximes.[8,9] However, these methods suffer from harsh conditions,[10] low yields for the preparation of precursors,[11] or the use of stoichiometric amounts of metal oxidants.[12,13] Recently the photoinduced formation of nitrile oxides from nitrogen dioxide and ketones using a bench-stable succinimidyl nitrating agent (Scheme 1a) has been reported.[14] Similarly, *tert*-butyl nitrite (TBN) has been found to be effective for nitrile oxide production with terminal diazo compounds when treated with a copper catalyst and a base (Scheme 1b)[15,16] or with sulfoxonium ylides with copper(II) triflate and/or sodium acetate.[17] These methodologies have used a catalyst and are most often interpreted as involving either nitrogen dioxide or nitric oxide and associated free radical intermediates as well as metal carbene intermediates in reactions with diazo compounds. Very recently, acyclic nitronates have been proposed as intermediates in boron trifluoride-catalyzed reactions of TBN with terminal diazo compounds (Scheme 1c); these reactions were performed in acetonitrile, and computational analyses were consistent with the involvement of nitronates.[18] However, we

Scheme 1. Generation of Nitrile Oxides



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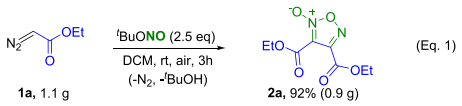
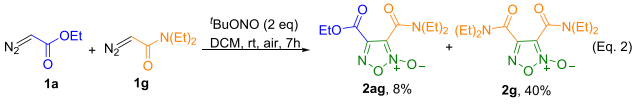
have long recognized TBN as a potent electrophilic nitrosyl transfer reagent[19] and consequently have believed that TBN alone, at room temperature without the use of a catalyst or an additive, could undergo nitrosyl transfer to diazo compounds, resulting in the formation of nitrile oxides (Scheme 1d).

To test this hypothesis, commercially available ethyl diazoacetate (EDA, **1a**) was treated with excess TBN (90% TBN in ^{t}BuOH, 2.5 equiv) all at once. As result, without solvent, the reaction was immediate and exothermic, and the reaction mixture changed in color from orange, the typical color of **1a**, to light-green, forming furoxan dimer **2a**, which after removal of ^{t}BuOH and excess TBN was isolated in 85% yield. The exothermic reaction was moderated by performing the addition of TBN to EDA in a solvent, and as a consequence, the reaction time increased but with no loss in product yield (see Table S1). The reaction rate correlated with the number of equivalents of TBN, and 2.5 equiv was judged to be optimal for a reaction time of 2−3 h. DCM was found to be the most suitable solvent. Notably, no reduction in yield was observed in a gram-scale reaction (eq 1).



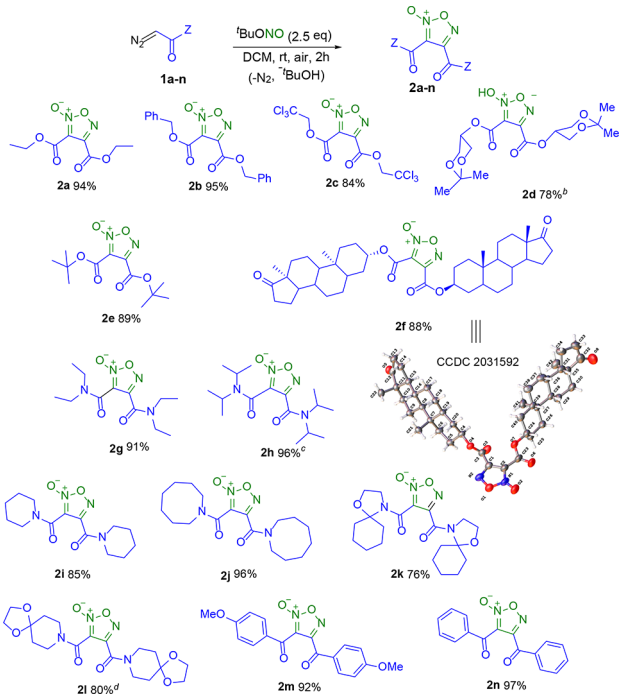
Considering the balance between the number of TBN equivalents and the reaction time, representative terminal diazocarbonyl compounds, including diazoacetates, diazoacetamides, and diazoketones, were treated under the optimum reaction conditions. Good to excellent yields of their corresponding furoxan compounds **2** were found, suggesting the broad scope of this direct uncatalyzed nitrile oxide generation (Scheme 2). α-Diazocarbonyl compounds **1a−n** bearing alkoxy, amide, and aryl groups reacted with TBN at room temperature in an air atmosphere within a reaction time of 2 h. These reactions occurred without interference from ether, ester, halide, ketal, or ketone functional groups, and the dimer furoxan structure was further confirmed by X-ray crystallography of the product from the reaction of androsterone diazoacetate with TBN (**2f**).

Although diazoacetamides are ordinarily much less reactive toward electrophiles than diazoacetates or diazoketones,[20] diazoacetamide **1g** was more reactive toward TBN than diazoester **1a**. The competitive reaction with equivalent amounts of **1a** and **1g** gave a 40% yield of **2g** and an 8% yield of **2ag**, and **2a** was not observed (eq 2).



Nitrile oxides undergo [3 + 2] cycloaddition with alkenes and alkynes, and these reactions occur in competition with nitrile oxide dimerization. To determine whether cycloaddition was competitive, **1a** and TBN as precursors of the nitrile oxide dipole and ethyl propiolate (**3a**) as a representative dipolarophile were chosen. In order to avoid the formation of dimer **2a**, TBN was introduced over a period of 1 h using a syringe pump. The reaction of **1a** (0.2 mmol), TBN (1.5 equiv), and **3a** (1.2 equiv) furnished isoxazole **5a** in 84% yield after 4 h at room temperature. Optimal conditions were found to be chloroform as the solvent for reactions at room

Scheme 2. Direct TBN Reactions with Diazoacetates, Diazoacetamides, and Terminal Diazoketones: Synthesis of Furoxan Dimers[a]



[a]Reaction conditions: TBN (2.5 equiv) was added all at once to **1** (0.4 mmol) in 3.0 mL of DCM, and the reaction was terminated at 2 h. [b]10% of **1d** was recovered. [c]6 h. [d]18 h.

temperature using 2.5 equiv of TBN, which gave isoxazole **5a** in 94% yield in just 2 h (Table S2). When non-halogenated solvents were used, the reaction proceeded at a lower rate. The substrate scope for the synthesis of isoxazole and isoxazoline compounds was investigated under the optimized conditions using three representative diazo compounds; acetate **1a**, amide **1g**, and ketone **1n** (Scheme 3). Heterocycles **5** and **6** were obtained via [3 + 2] cycloaddition at room temperature in about 2 h in moderate to excellent yields, and the slow addition of TBN prevented formation of the furoxan dimer **2** with only the exception of alkyne **3d**. This method delivered isoxazoles and isoxazolines from a variety of alkenes and alkynes (**5a−c**, **5g−l**, **6a−c**, and **6g−l**). Notably, unprotected alcohols did not undergo competitive nitrosyl exchange with TBN[19] and provided the corresponding heterocycle-carbinol products in good to excellent yields without a decrease in reaction efficiency (**5d−f** and **6d−f**). As expected from the electrophilic nitrosyl exchange, the [3 + 2] cycloaddition with secondary amine **3e** and TBN furnished *N*-nitroso isoxazole **5m**.

To further demonstrate the synthetic applications of the generation of nitrile oxide with **1a** and TBN, we turned our attention to the gram-scale synthesis of biologically active isoxazole **8**, which was shown to have antituberculosis activities,[21] and the precursor of **SS-208**, which is an effective antitumor agent (Scheme 4).[22] Cycloaddition of alkyne **7** with EDA/TBN afforded **8** in 78% isolated yield with a total amount of 2.2 equiv of **1a** (1.2 equiv at the beginning and another 1.0 equiv after 12 h) and TBN at room temperature (Scheme 4a). Isoxazole **10**, the precursor of the biologically

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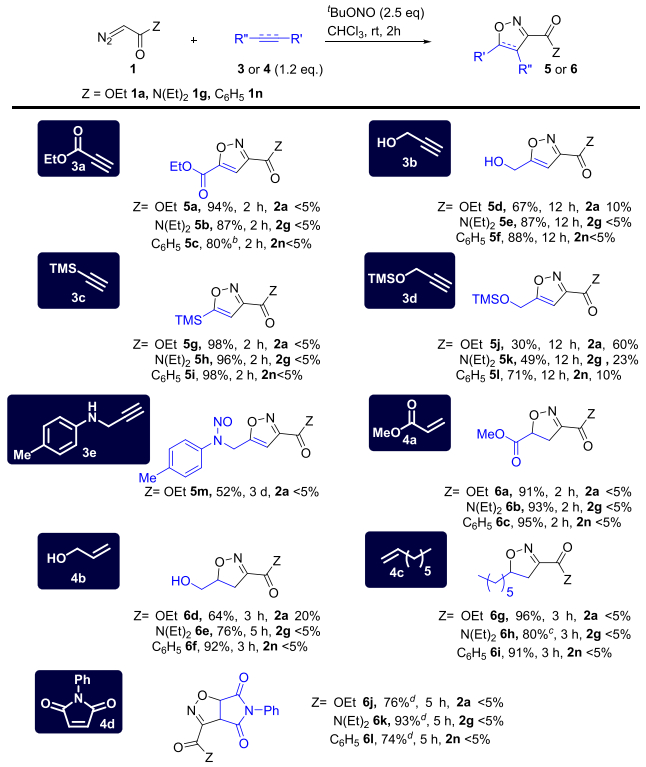
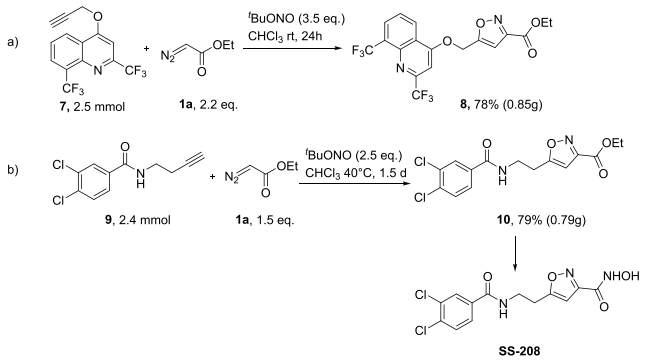
Scheme 3. TBN Reactions of Alkynes and Alkenes with Diazoacetates, Diazoacetamides, and Terminal Diazoketones[a]



[a]Reaction conditions: TBN (2.5 equiv) in 1.0 mL of $CHCl_3$ was added to diazo compound **1** (0.2 mmol) and dipolarophile **3** or **4** (0.24 mmol, 1.2 equiv) in 1.0 mL of $CHCl_3$ (2.0 mL) over 1 h at rt, and the reaction was terminated at the determined time. [b]10% of **1n** was recovered. [c]10% of **1g** was recovered. [d]*cis*:*trans* = 20:1. The *cis*:*trans* ratio was determined by ^{1}H NMR spectroscopy.

Scheme 4. Synthesis of Biologically Active Compounds

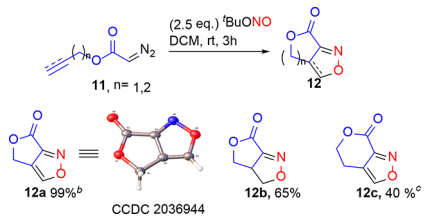


active hydroxylamide **SS-208**, was prepared in 79% yield from alkyne **9**, EDA, and TBN under mild conditions (Scheme 4b).

Intramolecular [3 + 2] cycloaddition of diazo compounds with TBN also occurs under mild conditions to generate lactone-fused rings (Scheme 5). Under the reaction conditions, γ- and δ-lactone-fused isoxazoles and isoxazolines were prepared in good to excellent yields, suggesting the universality of this process. The exact structure of the fused bicyclic isoxazole **12a** was further confirmed by X-ray crystallography.

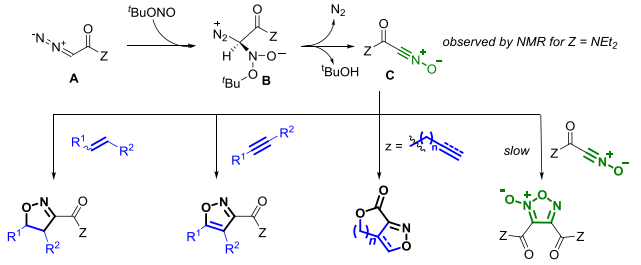
A probable mechanism is proposed in Scheme 6. The terminal diazo compound **A**, which is recognized as a

Scheme 5. Intramolecular Cycloaddition Reactions[a]



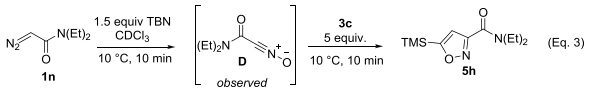
[a]Reaction conditions: TBN (2.5 equiv) in 1.0 mL of DCM was added to diazo compound **11** (0.2 mmol) in 10.0 mL of DCM over 1 h at rt, and the reaction was terminated at 3 h. [b]24 h. [c]3 days at 40 °C.

Scheme 6. Plausible Mechanism for the Formation of Nitrile Oxide



nucleophile,[23] undergoes nitrosyl addition with the electrophilic TBN to generate diazonium ion intermediate **B**, which loses dinitrogen and ^{t}BuOH in a stepwise or concerted fashion to form nitrile oxide **C**. Finally, **C** either dimerizes to generate a furoxan or is trapped by an alkyne or alkene to furnish the isoxazole or isoxazoline compound, respectively.

Evidence from ^{1}H and ^{13}C NMR spectroscopy suggested that nitrile oxide intermediate **D** was formed and is stable up to 10 °C (see Figures S1−S4). In a reaction of TBN with *N*,*N*-diethyldiazoacetamide monitored over time at 0 °C in a dilute solution, a new absorption consistent with the nitrile oxide was detected by ^{13}C NMR spectroscopy at 145.6 ppm (Figure S1) at a reaction time of 4 h; the ^{1}H NMR spectrum of the reaction mixture showed two quartets at 3.51 and 3.40 ppm attributable to the methylene groups of the two ethyl chains of the nitrile oxide *N*,*N*-diethylamide and a distinct singlet at 1.25 ppm attributable to ^{t}BuOH in excess of its amount in TBN (Figure S2). To further substantiate the formation of the nitrile oxide, TMS-acetylene **3c** was added as a trapping agent (eq 3)



immediately after the NMR spectra were obtained at 10 °C. Full conversion of nitrile oxide **D** to **5h** was observed after 10 min, while the dimer **2g** was not formed (Figures S3 and S4).

In summary, a metal- and catalyst-free, mild, and practical method for the in situ formation of nitrile oxides from terminal diazo compounds has been reported. This protocol allows the synthesis of a broad selection of furoxan, isoxazoline, 3,5-di- and 3,4,5-trisubstituted isoxazole derivatives, and lactone-fused rings in high yields. The catalyst-free method was also applied to gram-scale reactions and to the synthesis of two biologically active compounds. The formation of a nitrile oxide from a diazoacetamide, which was observed for the first time, is initiated by nitrosonium ion exchange between TBN and the

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diazo compound, followed by dinitrogen extrusion and elimination of ^{t}BuOH. Because of the relatively high nitrosyl transfer ability of TBN, even the nucleophilic products of nitrile oxide cycloaddition reactions may themselves receive the nitrosyl group from TBN and then serve as somewhat less reactive but still potent nitrosyl transfer agents (see, e.g., Figure S5). Surprisingly, dimer formation from these nitrile oxides can be easily controlled, and cycloaddition reactions with alkynes and alkenes occur at a higher rate than does dimerization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04130.

General experimental procedures and detailed optimization and product analyses, experimental procedures for mechanistic analyses, references, and NMR spectra (PDF)

Accession Codes

CCDC 2031592 and 2036944 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Belen'kii, L. I. Nitrile Oxides. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons: Hoboken, NJ, 2008; pp 1−128.

(2) Agrawal, N.; Mishra, P. The Synthetic and Therapeutic Expedition of Isoxazole and its Analogs. *Med. Chem. Res.* **2018**, *27* (5), 1309−1344.

(3) Zimecki, M.; Bąchor, U.; Mączyński, M. Isoxazole Derivatives as Regulators of Immune Functions. *Molecules* **2018**, *23* (10), 2724.

(4) Lamberth, C. Oxazole and Isoxazole Chemistry in Crop Protection. *J. Heterocycl. Chem.* **2018**, *55* (9), 2035−2045.

(5) Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261−327.

(6) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. Nitric Oxide Donors: Chemical Activities and Biological Applications. *Chem. Rev.* **2002**, *102* (4), 1091−1134.

(7) Hansen, T. V.; Wu, P.; Fokin, V. V. One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles. *J. Org. Chem.* **2005**, *70* (19), 7761−7764.

(8) Roscales, S.; Plumet, J. Metal-Catalyzed 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides. *Org. Biomol. Chem.* **2018**, *16* (44), 8446−8461.

(9) Jäger, V.; Colinas, P. A. Nitrile Oxides. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; pp 363−374.

(10) Crossley, J. A.; Browne, D. L. An Alkynyliodide Cycloaddition Strategy for the Construction of Iodoisoxazoles. *J. Org. Chem.* **2010**, *75* (15), 5414−5416.

(11) Kozikowski, A. P.; Adamcz, M. Methods for the Stereoselective cis-Cyanohydroxylation and -Carboxyhydroxylation of Olefins. *J. Org. Chem.* **1983**, *48* (3), 366−372.

(12) Itoh, K.-i.; Horiuchi, C. A. Formation of Isoxazole Derivatives via Nitrile Oxide Using Ammonium Cerium Nitrate (CAN): a Novel one-pot Synthesis of 3-Acetyl- and 3-Benzoylisoxazole Derivatives. *Tetrahedron* **2004**, *60* (7), 1671−1681.

(13) Itoh, K.-i.; Sakamaki, H.; Nakazato, N.; Horiuchi, A.; Horn, E.; Horiuchi, C. A. A Convenient and Efficient One-Pot Synthesis of 3-Acylisoxazoles Using Iron(III) Salts. *Synthesis* **2005**, *2005*, 3541−3548.

(14) Zhang, K.; Jelier, B.; Passera, A.; Jeschke, G.; Katayev, D. Synthetic Diversity from a Versatile and Radical Nitrating Reagent. *Chem. - Eur. J.* **2019**, *25* (56), 12929−12939.

(15) Wang, X.-D.; Zhu, L.-H.; Liu, P.; Wang, X.-Y.; Yuan, H.-Y.; Zhao, Y.-L. Copper-Catalyzed Cascade Cyclization Reactions of Diazo Compounds with *tert*-Butyl Nitrite and Alkynes: One-Pot Synthesis of Isoxazoles. *J. Org. Chem.* **2019**, *84* (24), 16214−16221.

(16) Chen, R.; Zhao, Y.; Fang, S.; Long, W.; Sun, H.; Wan, X. Coupling Reaction of Cu-Based Carbene and Nitroso Radical: a Tandem Reaction To Construct Isoxazolines. *Org. Lett.* **2017**, *19* (21), 5896−5899.

(17) Tang, Z.; Zhou, Y.; Song, Q. Synthesis of Furoxans and Isoxazoles via Divergent [2 + 1 + 1 + 1] Annulations of Sulfoxonium Ylides and ^{t}BuONO. *Org. Lett.* **2019**, *21* (13), 5273−5276.

(18) Ma, L.; Kou, L.; Jin, F.; Cheng, X.; Tao, S.; Jiang, G.; Bao, X.; Wan, X. Acyclic Nitronate Olefin Cycloaddition (ANOC): Regio- and Stereospecific Synthesis of Isoxazolines. *Chem. Sci.* **2021**, DOI: 10.1039/D0SC05607C.

(19) Doyle, M. P.; Terpstra, J. W.; Pickering, R. A.; LePoire, D. M. Hydrolysis, Nitrosyl Exchange, and Synthesis of Alkyl Nitrites. *J. Org. Chem.* **1983**, *48*, 3379−3382.

(20) Cleary, S. E.; Li, X.; Yang, L.-C.; Houk, K. N.; Hong, X.; Brewer, M. Reactivity Profiles of Diazo Amides, Esters, and Ketones in Transition-Metal-Free C−H Insertion Reactions. *J. Am. Chem. Soc.* **2019**, *141* (8), 3558−3565.

(21) Mao, J.; Yuan, H.; Wang, Y.; Wan, B.; Pieroni, M.; Huang, Q.; van Breemen, R. B.; Kozikowski, A. P.; Franzblau, S. G. From Serendipity to Rational Antituberculosis Drug Discovery of Mefloquine-Isoxazole Carboxylic Acid Esters. *J. Med. Chem.* **2009**, *52* (22), 6966−6978.
(22) Shen, S.; Hadley, M.; Ustinova, K.; Pavlicek, J.; Knox, T.; Noonepalle, S.; Tavares, M. T.; Zimprich, C. A.; Zhang, G.; Robers, M. B.; Bařinka, C.; Kozikowski, A. P.; Villagra, A. Discovery of a New Isoxazole-3-Hydroxamate-Based Histone Deacetylase 6 Inhibitor SS-208 with Antitumor Activity in Syngeneic Melanoma Mouse Models. *J. Med. Chem.* **2019**, *62* (18), 8557−8577.
(23) Zhang, Y.; Wang, J. Recent Development of Reactions with α-Diazocarbonyl Compounds as Nucleophiles. *Chem. Commun.* **2009**, *36*, 5350−5361.

https://dx.doi.org/10.1021/acs.orglett.0c04130
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