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Formal Olefination and Acylaziridination of Imidazolones†

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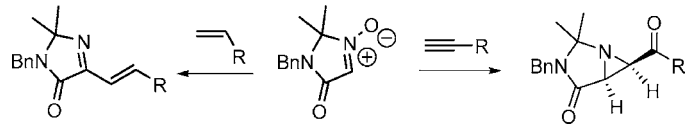
ABSTRACT



The first formal olefination and acylaziridination of imidazolones were obtained by cycloaddition of cyclic nitrones with alkenes and alkynes, respectively.

The imidazolone and imidazolidinone skeletons are key structural motifs that appear in the core structures of natural products and drug candidates. For example, alkaloids Kottamides A−C (**1**), isolated from the endemic ascidian *Pycnoclavella kottae*, have exhibited anti-inflammatory and antimetabolic activity as well as cytotoxicity toward tumor cell lines (Figure 1).[1] For recent pharmaceutical candidates, the spiro-condensed imidazolone (**2**) is an example of a glycine transporter inhibitor, a potential therapeutic agent for Schizophrenia,[2] while the 2,3,5-substituted imidazolidin-4-one (**3**) is a β-secretase (BACE-1) inhibitor, which has potential for treating Alzheimer's disease.[3] Despite the importance of these molecules, very few methods have been developed to functionalize these heterocycles,[4] especially for 1*H*-imidazol-5(2*H*)-ones. In this paper, we describe the preparation of two novel imidazolone derivatives **5** and **6**

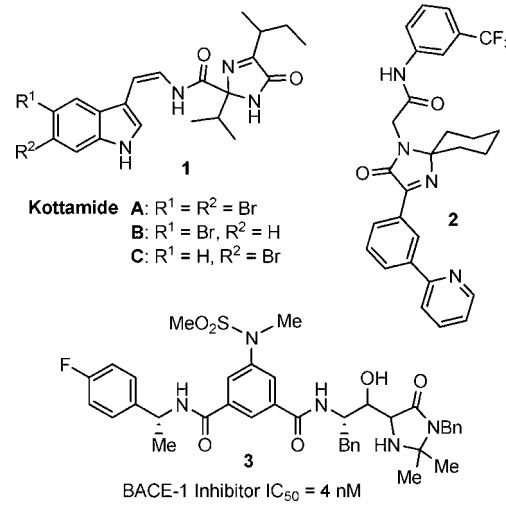


Figure 1. Biologically active compounds.

that are made from the cycloaddition of heterocyclic nitrone **4** with alkenes and alkynes, respectively (Figure 2).

The 1,3-dipolar cycloaddition reaction of nitrones has attracted considerable attention as one of the most important methodologies for the construction of N-containing heterocycles.[5] For instance, the [3+2] cycloaddition of nitrones with alkenes is a classic reaction for the synthesis of

† This paper is dedicated to Professor Huw M. L. Davies on the occasion of his 54th birthday.

(1) Appleton, D. R.; Page, M. J.; Lambert, G.; Berridge, M. V.; Copp, B. R. *J. Org. Chem.* **2002**, *67*, 5402.

(2) (a) Blunt, R.; Cooper, D. G.; Porter, R. A.; Wyman, P. A. WO 2009034061, 2009. (b) Ahmad, N. M.; Lai, J. Y. Q.; Andreotti, D.; Marshall, H. R.; Nash, D. J.; Porter, R. A. WO 2008092876, 2008. (c) Coulton, S.; Porter, R. A. WO 2008092872, 2008.

(3) Barrow, J. C.; Rittle, K. E.; Ngo, P. L.; Selnick, H. G.; Graham, S. L.; Pitzenberger, S. M.; McGaughey, G. B.; Colussi, D.; Lai, M.-T.; Huang, Q.; Tugusheva, K.; Espeseth, A. S.; Simon, A. J.; Munshi, S. K.; Vacca Jo, P. *ChemMedChem* **2007**, *2*, 995.

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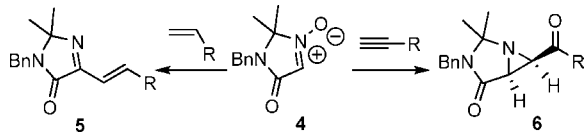


Figure 2. Novel products from imidazolone nitrones.

isoxazolidines **7**, which have been utilized to access β-amino alcohols, and both pyrrolizidine and indolizidine alkaloids (Figure 3). On the other hand, isoxazolines **8** that are cycloaddition products from nitrones and alkynes tend to undergo rearrangement due to their thermal instability.[6]

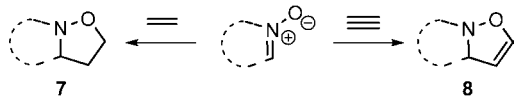
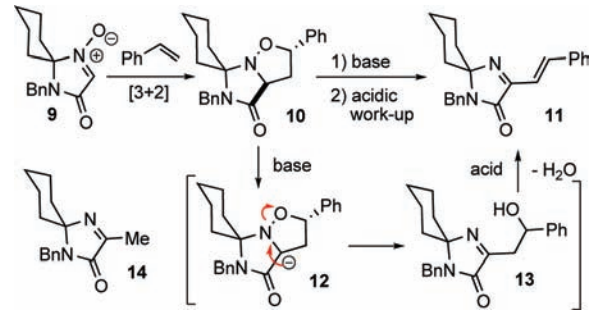


Figure 3. Classic [3+2] cycloaddition of nitrones.

We have been interested in the synthesis of imidazolone derivatives that could impact our current project targeting type-II diabetes. One of our model studies was to test a 1,3-dipolar reaction on spiro-imidazolone **9** (Scheme 1).[7] When the [3+2] adduct **10**[8] was treated with base, trans-olefinated product **11** was isolated after acidic workup in 80% yield, along with a minor side product **14** (<5%).[9] Presumably, the proton adjacent to the carbonyl group is removed by the base to form the anion **12**, in which the N−O bond is subsequently cleaved to afford the alcohol **13**. Dehydration of **13** under acidic conditions would generate the product **11**.

Scheme 1. Formation of **11**



To the best of our knowledge, this is the first example of a formal olefination reaction via a [3+2] cycloaddition of a nitrone with an alkene. More interestingly, only the (*E*)-isomer of the olefin product was formed. This result prompted us to optimize the reaction conditions and study its scope. As shown in Scheme 1, there are actually three stages from the starting nitrone **9** to the final product (**11**). However, a one-pot and practical procedure would be ideal. Toward this goal, we determined that a mixture of nitrone **4** (1 equiv) and olefins **15** (5 equiv) in ethanol at 80 °C provided the desired [3+2] adducts. The reaction mixture was cooled to room temperature and then successively treated with 1 N aqueous sodium hydroxide (2 equiv) and 1 N aqueous hydrochloric acid (3 equiv) at 0 °C to generate the desired products **5** (Table 1).[10]

Under the optimal reaction conditions, a range of terminal olefins were screened (Table 1). The reaction of **4** with styrene (**15a**) afforded the olefinated imidazolone **5a** in 90% yield (Table 1, entry 1). For styrene derivatives, a variety of synthetically common functional groups, including electron-withdrawing and electron-donating groups, such as ether (**15b**), ester (**15c**), and halogen (**15d**,**f**) are tolerated (Table 1, entries 2−7). Ethyl acrylate (**15h**) showed comparable reactivity to styrene (Table 1, entry 8). Reactions of aliphatic olefins (**15i**,**j**) also produced the desired product, although the rate of [3+2] cycloaddition is much slower than that observed for styrenes (Table 1, entries 9 and 10). Interestingly, the reaction of ethyl vinyl ether (**15k**) with nitrone **4** generated predominantly imidazolidinone **5k** under conditions without acidic workup. Presumably, the ethoxy moiety, a good leaving group, played a major role in the formation of this different product.[11]

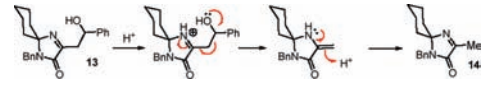
(5) For reviews on nitrones and their cycloaddition reactions, see: (a) Jones, R. C. F.; Martin, J. N. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, *The Chemistry of Heterocyclic Compounds*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; Vol. 59, pp 1−81; (b) Feuer, H. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2008. (c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (e) Cardona, F.; Goti, A. *Angew. Chem.* **2005**, *117*, 8042. Cardona, F.; Goti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7832. (f) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (g) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285. (h) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, *15*, 2349. (i) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 7808.

(6) For a review, see: (a) Freeman, J. P *Chem. Rev.* **1983**, *83*, 241. Also see recent examples: (b) Heaney, F.; Fenlon, J.; O'Mahony, C.; McArdle, P.; Cunningham, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3382. (c) Friebolin, W.; Eberbach, W. *Tetraheron* **2001**, *57*, 4349.

(7) See recent example of 1,3-dipolar cycloaddition of imidazolone nitrones: (a) Cheng, S.; Wu, H.; Hu, X. *Synth. Commun.* **2007**, *37*, 297. (b) Aouadi, K.; Jeanneau, E.; Msaddek, M.; Praly, J.-P. *Tetrahedron: Asymmetry* **2008**, *19*, 1145. (c) Aouadi, K.; Jeanneau, E.; Msaddek, M.; Praly, J.-P. *Synthesis* **2007**, *21*, 3399. (d) Aouadi, K.; Vidal, S.; Msaddek, M.; Praly, J.-P. *Synlett* **2006**, *19*, 3299. (e) Pernet-Poil-Chevrier, A.; Cantagrel, F.; Le Jeune, K.; Philouze, C.; Chavant, P. Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1969. (f) Cantagrel, F.; Pinet, S.; Gimbert, Y.; Chavant, P. Y. *Eur. J. Org. Chem.* **2005**, *70*, 2694. (g) Pernet-Poil-Chevrier, A.; Cantagrel, F.; Jeune, K. L.; Philouze, C.; Chavant, P. Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1969. (h) Westermann, B.; Walter, A.; Florke, U.; Altenbach, H.-J. *Org. Lett.* **2001**, *3*, 1375. (i) Baldwin, S. W.; Long, A. *Org. Lett.* **2004**, *6*, 1653.

(8) The sterochemistry of **10** was confirmed by NOESY. Also see ref 7a.

(9) Possible mechanism to form **14**



(10) Other solvents (such as toluene, 1,2-dichloroethane, acetonitrile, etc.), bases (such as NaH, KO^{t}Bu, etc.), and acids (CF_3COOH, CH_3COOH, etc.) also work in these reactions. However, these combinations have not been optimized.

(11) Possible mechanism to **5K**:

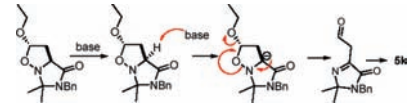
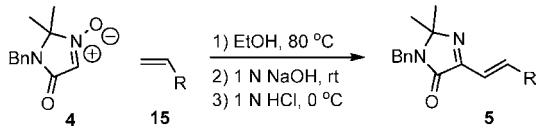


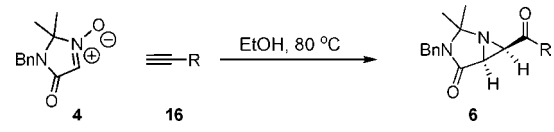
Table 1. One-Pot Formal Olefination of Imidazolone[a]



entry	substrate	product	isolated yield/%
1	**15a**	**5a**	90
2	**15b** OMe	**5b** OMe	84
3	**15c** CO_2Et	**5c** CO_2Et	78
4	**15d** Br	**5d** Br	71
5	**15e** ^tBu	**5e** ^tBu	83
6	**15f** Cl	**5f** Cl	89
7	**15g** CF_3	**5g** CF_3	72
8	**15h** OEt	**5h** OEt	60
9[b]	**15i**	**5i**	41
10[b]	**15j**	**5j**	68
11[c]	**15k**	**5k**	96

[a] Reactions were performed with 5 equiv of alkene in ethanol at 80 °C for 18 h. [b] The reaction was performed with 10 equiv of alkene and heated for 3 days. [c] The reaction was run without acidic workup.

Table 2. Formal Acylaziridination of Imidazolone[a]



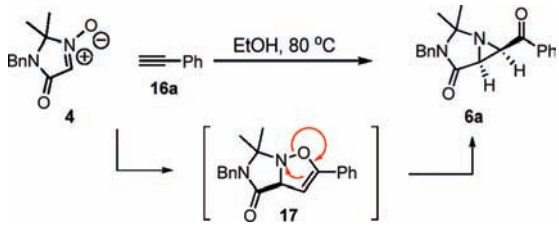
entry	substrate	product	isolated yield/%
1	**16a**	**6a**	92
2	**16b** Me	**6b** Me	93
3	**16c** F_3C	**6c** CF_3	72
4	**16d** Br	**6d** Br	75
5	**16e** Br	**6e** Br	89
6	**16f** CF_3	**6f** CF_3	85
7	**16g** N	**6g** N	49
8[b]	**16h**	**6h**	62
9[b]	**16i**	**6i**	63
10[b]	**16j**	**6j**	88
11[b]	**16k**	**6k**	87
12[b]	**16l** Si	**6l** $SiEt_3$	61

[a] Reactions were performed with 5 equiv of alkyne in ethanol at 80 °C for 18 h. [b] The reaction was performed with 5 equiv of alkyne and heated for 2 days.

It is known that the [3+2] addition reactions of acetylenes with nitrones usually generate rearranged products instead of the normal product isoxazolines **8**, which are often thermally labile (Figure 3). The key intermediate in these reactions is an acylaziridine.[2a] Having discovered this novel formal olefination reaction of imidazolone, we wondered what would form from the reaction of nitrone **4** with alkynes. Thus, the cycloaddition of phenyl acetylene **16a** with nitrone **4** was performed. The reaction afforded the single diastereomeric cis-fused-acylaziridine **6a**[12] in 92% yield (Table 2, entry 1). The first step of this process involves a concerted cycloaddition to give the corresponding intermediate **17**, which likely immediately rearranges to the acyl-substituted aziridine **6a** (Scheme 2).

(12) For other isolated acylaziridines, please see ref 6a and the references cited therein.

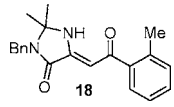
Scheme 2. Cycloaddition of Phenyl Acetylene with Nitrone **4**



The significance of aziridines in organic synthesis has been well recognized.[13] This newly discovered fused-acylaziridine core is unique and thus has the potential to be a very interesting and useful structural element. To study the reaction scope, the cycloadditions of **4** with various terminal alkynes were performed and the results are summarized in Table 2. *Ortho*- (**16b**, **16c**, **16d**), *para*- (**16e**), and *meta*-substituted (**16f**) phenyl acetylenes are all tolerated (Table 2, entries 2−6).[14] It should be pointed out that the *o*-bromo-substituted product **6d** could be easily derivatized to indazole or benzoisoxazole under known conditions.[15] Addition of heteroaromatic acetylene (**16g**) afforded a moderate yield of product (Table 2, entry 7). Primary (**16h**), secondary (**16i**), and cyclic aliphatic acetylenes (**16j**,**k**) also could be efficiently added to nitrone **4** under these conditions to generate the expected products in moderate to good yields (Table 2, entries 8−11). Finally, 1-triethylsilyl acetylene (**16l**) produced the expected acylsilane **6l** (Table 2, entries 12), which is a very useful synthon in many reactions such as the silyl benzoin reaction[16] and sila-Stetter reaction[17] by taking advantage of the Brook rearrangement.

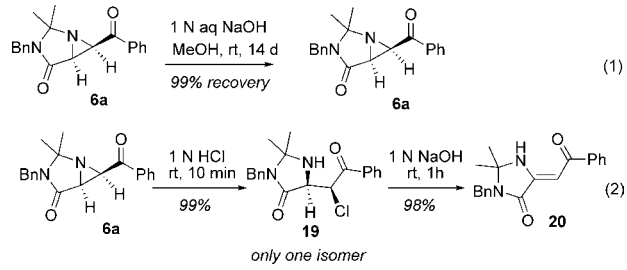
(13) For reviews on reactions of aziridines, see: (a) Mitunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 6, Chapter 1.3. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, Chapter 4.9. (c) Thompson, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, Chapter 4.1. (d) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, Chapter 8.1. (e) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

(14) After silica gel chromatograpgy, there is a minor side product (**18**) isolated (<5%) for entry 2. The *Z*-isomer has been comfirmed by COSY and J-resolved HMBC data. This type of side product has been found from other substrates as well.



(15) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695.

As mentioned above, acylaziridines formed from isoxazolines are usually not stable and rearrange to other products. An obvious concern is the stability of this newly discovered cis-fused-acylaridine core. Thus, **6a** was treated with 20 equiv of NaOH in methanol for 14 days, and it was found that **6a** was recovered in 99% yield without any rearrangement or decomposition (eq 1). In contrast, under acidic conditions, the aziridine was labile and generated the α-chloro ketone **19** as a single isomer in quantitative yield (eq 2). This result indicates that the nucleophilic ring-opening reaction is highly stereospecific and efficient. Subsequently, under basic conditions, a conjugated product **20** was generated from **19** by a simple elimination.



In summary, we report the first formal olefination of an imidazolone via [3+2] cycloaddition of terminal alkenes with an imidazolone *N*-oxide. This transformation provides trans-olefinated imidazolones that would be difficult to prepare by other methods. Through the [3+2] cycloaddition of terminal alkynes with imidazalone *N*-oxide, we have also developed the first formal acylaziridination of imidazolones.

Acknowledgment. We would like to thank Dr. William Greenlee for strong support of this program, Mr. Ibrahim Daaro for mass spectrometry assistance, Drs. Tze-Ming Chan, Mary Senior, and Alexei Buevich for NMR studies, Drs. Guoqing Li and Duane DeMong for helpful discussion, and Dr. Robert Aslanian for insightful suggestions. We also thank Drs. Jaemoon Yang and Jared Cumming for proofreading.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (e) Xin, L.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833, and references cited therein.

(17) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314.