ACS Combinatorial Science

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Isoxazolodihydropyridinones: 1,3-Dipolar Cycloaddition of Nitrile Oxides onto 2,4-Dioxopiperidines

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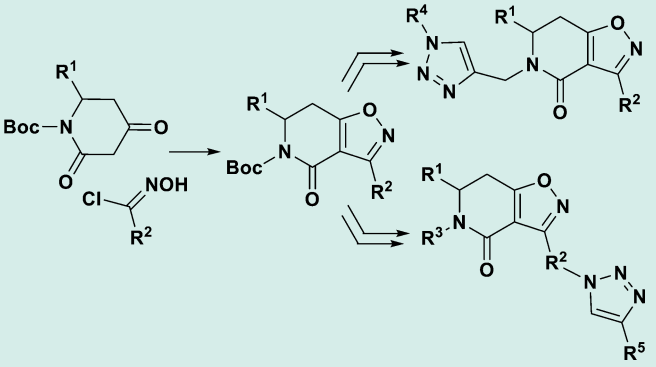
Supporting Information

ABSTRACT: Practical and efficient methods have been developed for the diversity-oriented synthesis of isoxazolodihydropyridinones via the 1,3-dipolar cycloaddition of nitrile oxides onto 2,4-dioxopiperidines. A select few of these isoxazolodihydropyridinones were further elaborated with triazoles by copper-catalyzed azide−alkyne cycloaddition reactions. A total of 70 compounds and intermediates were synthesized and analyzed for drug likeness. Sixty-four of these novel compounds were submitted to the NIH Molecular Libraries Small Molecule Repository for high-throughput biological screening.



KEYWORDS: *isoxazole, triazole, heterocycle, 1,3-dipolar cycloaddition, Cu(I)-catalyzed azide−alkyne cycloaddition*

INTRODUCTION

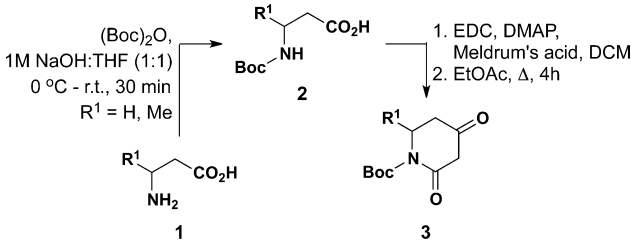
Isoxazoles are an important class of nitrogen containing heterocycles found in many natural products and biologically active compounds.[1] While many methods have been developed for isoxazole formation, the cycloaddition of nitrile oxides to alkynes is the most effective.[2] Emphasis has been placed on the synthesis of highly substituted isoxazoles by Larock,[3] Miyata,[4] and others.[5] While the reactions of nitrile oxides with cyclic 1,3-diketones[6] and β-ketoesters[7] have been studied, the cycloaddition of nitrile oxides onto heterocyclic 1,3-dicarbonyl compounds has, to our knowledge, not been reported. Although other routes have been reported for the preparation of isoxazolo[4,5-c]pyridinones,[8] our method provides convergent access to a variety of diversity points around the core scaffold.

We recently reported the hydrolytic opening of the amide of an isoxazolodihydropyridinone substrate as a route to orthogonally protected heterocyclic diamino acids.[9] As a continuation of this line of research, we report here the synthesis of a library of isoxazolodihydropyridinones via the 1,3-dipolar cycloaddition of nitrile oxides onto 2,4-dioxopiperidine to yield eleven novel 6,7-dihydroisoxazolo[4,5-*c*]2yridine-4(5*H*)-ones. Noting the many recent synthetic applications of copper catalyzed azide−alkyne cycloaddition (CuAAC) reactions for the rapid diversification of library collections (→ triazole diversification),[10] we also report exploiting the CuAAC reaction to diversify a subset of these isoxazolodihydropyridinones leading to an additional 42 triazole-functionalized isoxazolodihydropyridinones. The resulting collection has been added to the NIH Molecular Libraries Small Molecule Repository for high-throughput biological screening.

RESULTS AND DISCUSSION

As a starting point, Boc-protected 2,4-dioxopiperidines were synthesized from substituted β-amino acids by a three-step process that commenced with Boc protection of β-alanines (**1**) following a modified literature procedure (90−95% yield).[11] These *N*-protected amino acids (**2**) were then coupled to Meldrum's acid using standard EDC and DMAP coupling conditions.[9] The resulting conjugates were immediately dissolved in EtOAc and refluxed for four hours to yield Boc-protected dioxopiperidines **3** in 85−90% yield over 2 steps (via the presumed intermediacy of a Meldrum's acid-derived acylketene, which subsequently underwent intramolecular cyclization with the Boc-protected amine moiety; Scheme 1).

Scheme 1. Synthesis of 2,4-Dioxopiperidines 3 (R^1 = H and Me)



These dioxopiperidines were then treated with NaH in THF followed by the slow addition of various *N*-hydroxybenzimidoyl

Received: November 24, 2011
Revised: January 26, 2012
Published: February 21, 2012

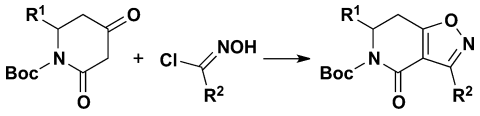
dx.doi.org/10.1021/co200200u | *ACS Comb. Sci.* 2012, 14, 280−284

chlorides 4{*1*−*8*} to give isoxazolodihydropyridinones 5{*1*−*11*} in 43−76% yield (Table 1). The requisite *N*-hydroxybenzimidoyl chlorides 4{*1*−*8*} were prepared from the corresponding benzaldehydes in 2 steps following well-established literature procedures.[12]

A detailed NMR study of 5{*3*} was undertaken to verify its structure and completely assign all carbons and protons within the molecule. While many of the assignments could be made from the ^{1}H and ^{13}C NMR spectra, we were unable to assign carbons C3, C4, C5 and C6 (see Figure 1) from these spectra alone. Therefore, several additional NMR experiments were undertaken, including INADEQUATE,[13] HSQC,[14] HMBC,[15] and COSY.[16] From the two-dimensional INADEQUATE experiment on 5{*3*} (Figure 1), we could assign all of its carbons, including C3, C4, C5, and C6. By analogy, the insights gained through this INADEQUATE proved useful in making complete carbon assignments in all of the isoxazolodihydropyridinones reported here; for example, we were able to completely assign carbons for alkyne derivative 6{*1*} (Figure 2). All of the spectra obtained for 5{*3*} are available in the Supporting Information.

Three of the isoxazolodihydropyridinones delineated in Table 1 (5{*1*−*3*}) were selected for diversification through CuAAC reactions by first installing an alkyne moiety on the dihydropyridinone nitrogen. As outlined in Scheme 2, this chemistry commenced by first removing the Boc group with TFA in $CHCl_3$ (30 min) to yield the secondary amide in quantitative yield. Each amide was then deprotonated with NaH in dry THF and *N*-propargylated with propargyl bromide to yield the alkyne- containing scaffold 6{*1*−*3*} in 50−55% yield. Subsequent copper-mediated 1,3-dipolar cycloaddition to these substrates with eight azides (7{*1*−*8*}) delivered triazole products 8{*1*−*3*,*1*−*8*} in good to excellent yields (Table 2). The azides employed in these CuACC reactions were generated in situ from the corresponding amines following one of

Table 1. 1,3-Dipolar Cycloaddition of Nitrile Oxides onto 2,4-Dioxopiperidines



3 4{*1-8*} 5{*1-12*}

entry	compound	R^1	R^2	yield
1	5{*1*}	H	2-$MeOC_6H_4$	52
2	5{*2*}	H	4-BrC_6H_4	64
3	5{*3*}	H	2-FC_6H_4	58
4	5{*4*}	H	4-$NO_2C_6H_4$	54
5	5{*5*}	H	3-$NO_2C_6H_4$	50
6	5{*6*}	H	2-$NO_2C_6H_4$	68
7	5{*7*}	H	2-NO_2,5-ClC_6H_3	50
8	5{*8*}	H	4-ClC_6H_4	55
9	5{*9*}	Me	2-$MeOC_6H_4$	76
10	5{*10*}	Me	2-NO_2,5-ClC_6H_3	43
11	5{*11*}	Me	4-ClC_6H_4	64

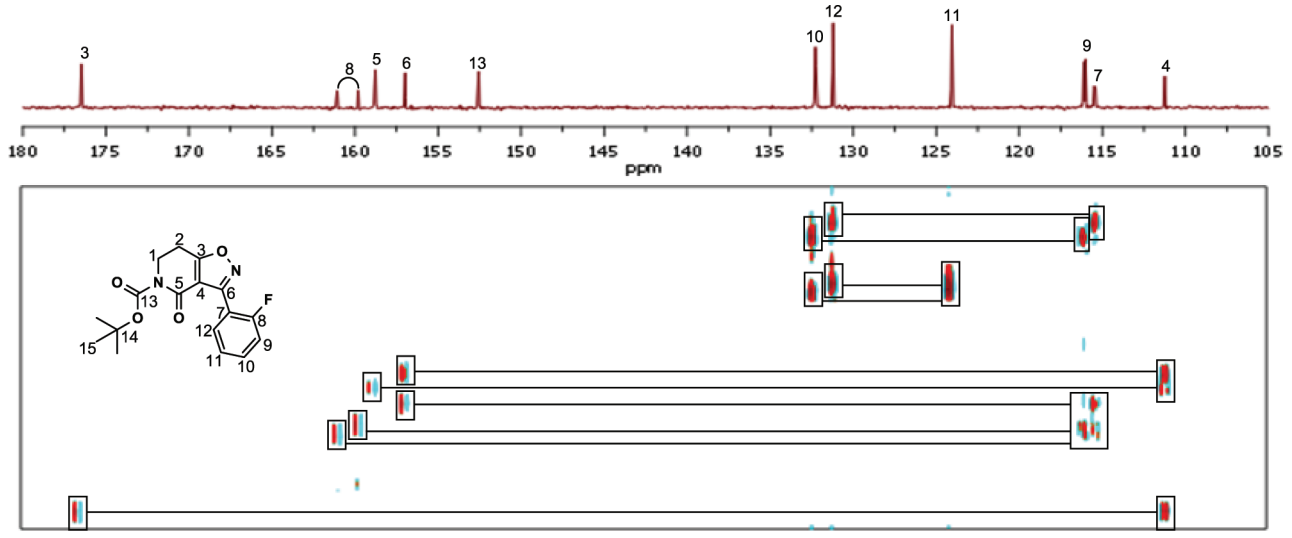


Figure 1. INADEQUATE-based assignments of C3, C4, C5, and C6 in 5{*3*}.

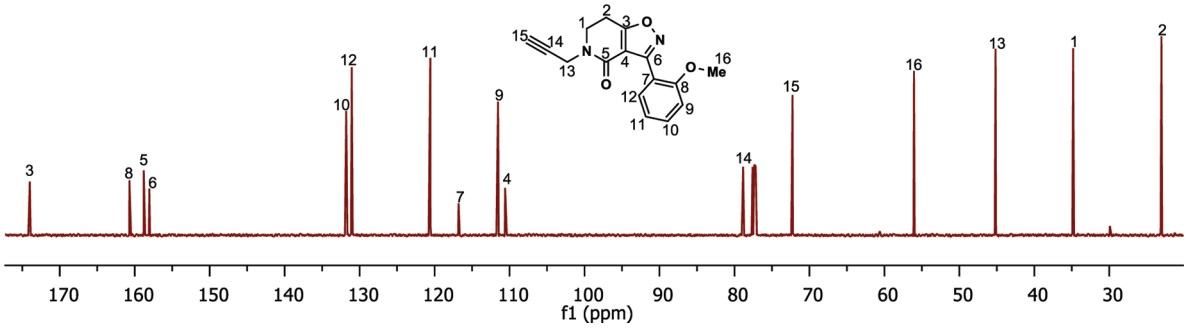


Figure 2. Assignments for 6{*1*} based on the INADEQUATE data from 5{*3*}.

dx.doi.org/10.1021/co200200u | *ACS Comb. Sci.* 2012, 14, 280−284

Scheme 2. CuAAC of the Isoxazolodihydropyridinones

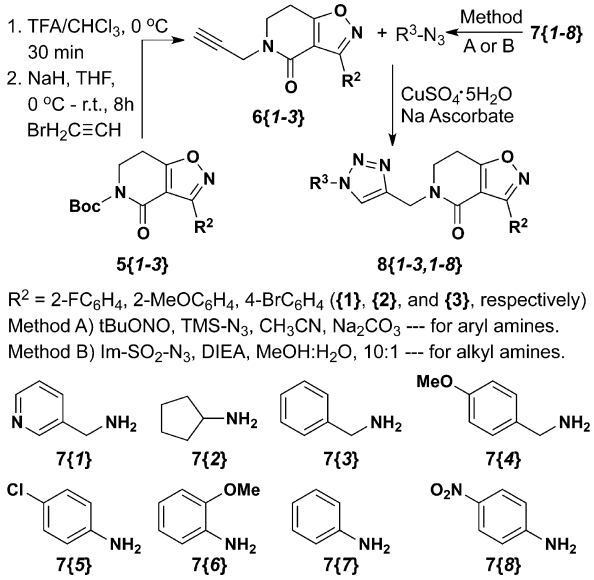
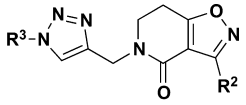


Table 2. CuAAC Diversification of Isoxazolodihydropyridinones



8{1-3,1-8}

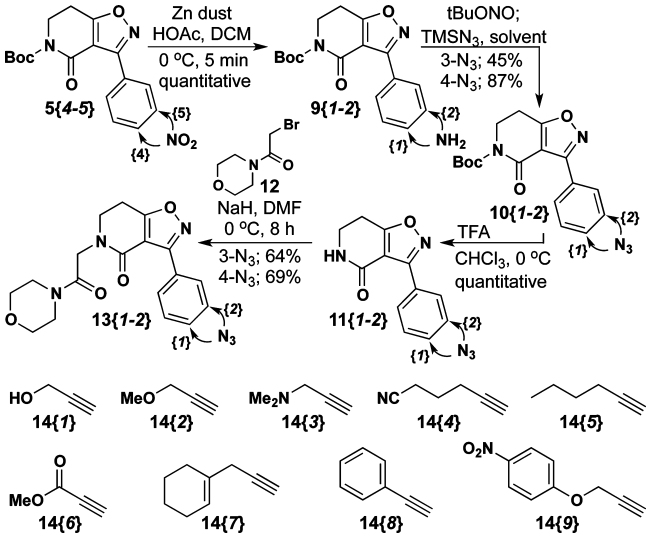
entry	azide	8{1,1−8} % yield	8{2,1−8} % yield	8{3,1−8} % yield
1	{1}	28	85	89
2	{2}	57[a]	95	92
3	{3}	52	76	79
4	{4}	46	92	88
5	{5}	76	74	76
6	{6}	78	74	94
7	{7}	84	79	77
8	{8}	70	89	92

[a]Decomposed upon isolation.

two protocols: (i) alkyl 1°-amines were treated with the diazo-transfer reagent imidazole-SO_2N_3 to yield the azide as reported by Stick[17] and (ii) aryl 1°-amines were treated with ^{t}BuONO and subsequent $ArN_2^+ \rightarrow ArN_3$ conversion was effected with TMS-N_3 as reported by Moses.[18] These in situ prepared azides, the alkynes (**6**{*1*−*3*}), $CuSO_4$, and sodium ascorbate were combined and the ensuing 1,3-dipolar cycloaddition reactions yielded triazole-substituted products **8**{*1*−*3*,*1*−*8*} (Table 2).

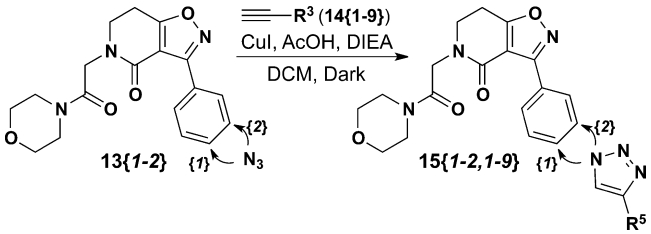
Two additional isoxazolodihydropyridinones delineated in Table 1 (**5**{*4*−*5*}) were selected for diversification through CuAAC reactions by taking advantage of the nitro group for azide entry. Isoxolopyridinones **5**{*4*−*5*} were treated with Zn/AcOH to deliver the *m*- and *p*-anilines **9**{*1*−*2*} in quantitative yields (Scheme 3). These anilines were then treated with ^{t}BuONO and the targeted azides were obtained by displacement of the diazonium salt with TMS-N_3 to yield **10**{*1*−*2*} in 45% and 87% yield (meta and para), respectively. The Boc group in **10**{*1*−*2*} was then removed by TFA treatment in $CHCl_3$ to give **11**{*1*−*2*} in quantitative yield. At this juncture, *N*-alkylation of the 2°-amide in **11**{*1*−*2*} proceeded smoothly by deprotonation with NaH in dry THF and subsequent treatment with 2-bromo-1-morpholinoethanone (**12**) to give

Scheme 3. Azide Synthesis for CuAAC



13{*1*−*2*} in 64% and 69% yield, respectively. 2-Bromo-1- morpholinoethanone **12** was prepared by dropwise addition of morpholine to a solution of bromoacetyl bromide in dry DCM under nitrogen (clear oil; 82% yield).[19] Nine alkynes (Scheme 3) were then used to diversify this azide set to give 16 additional triazole products (**15**{*1*−*2*,*1*−*9*}; Table 3).

Table 3. Diversification of the Alkylated Isoxazolodihydropyridinones



entry	alkyne	*m*-N_3 yield	*p*-N_3 yield
1	{1}	28	79
2	{2}	69	47
3	{3}	51	99
4	{4}	89	99
5	{5}	36	32
6	{6}	57	93
7	{7}	68	99
8	{8}	47	65
9	{9}	85	62

A Lipinski rule-of-five analysis[20] was performed to evaluate the druglikeness of all compounds and intermediates reported (Figure 3). Of the seventy compounds analyzed, fifty-eight were within the parameters set by Lipinski. Of the remaining, nine from chemset **15** had >10 hydrogen bond acceptors and the remaining two compounds (also from chemset **15**) had two violations each (>10 acceptors and a mass >500 Da; both had molecular weights of ∼560 g/mol). The other chemsets combined had only one violation (e.g., **8**{*2*,*8*}), suggesting that this collection of compounds is very appropriate for high-throughput screening to discover drug leads and biological probes.

dx.doi.org/10.1021/co200200u | ACS Comb. Sci. 2012, 14, 280−284

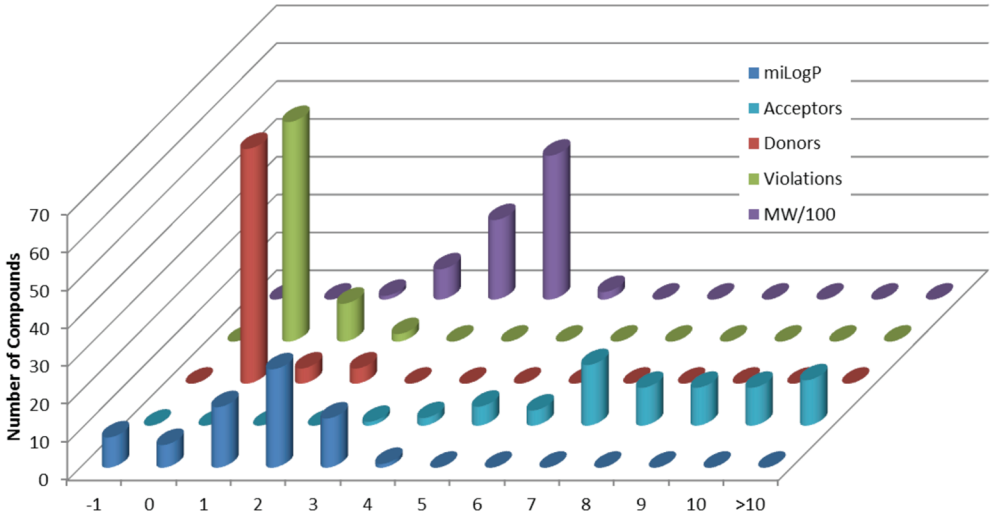


Figure 3. Lipinski rules analysis for 70 compounds and intermediates; calculated using Molinspirations Online Molecular Properties Calculator [http://www.molinspiration.com/cgi-bin/properties?textMode=1].

CONCLUSIONS

A short, reliable, and efficient convergent method has been developed to produce a diverse array of novel isoxazolodihydropyridinones starting from commercially available beta-amino acids and benzaldehydes. Eleven isoxazolopyridinones were synthesized and five of these were diversified further with CuAAC chemistry to give 42 additional isoxazolodihydropyridinone-triazole products. In all, 64 of the 70 compounds and intermediates synthesized were acceptable for submission to the *NIH Molecular Libraries Small Molecule Repository* for high-throughput biological screening; the unsubmitted 6 compounds contained excluded aromatic azides.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all compounds, including COSY, INADEQUATE, HSQC, and HMBC for compound **5**{3}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the National Institutes of Health (GM0891583 and RR1973) and the National Science Foundation [CHE-0910870; and CHE-0443516, CHE-0449845, CHE-9808183, and DBIO 722538 for NMR spectrometers] for their generous support.

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