ORGANIC LETTERS

2010
Vol. 12, No. 8
1876−1879

Highly Substituted 2,3-Dihydroisoxazoles by Et_3N-Catalyzed Tandem Reaction of Electron-Deficient 1,3-Conjugated Enynes with Hydroxylamines

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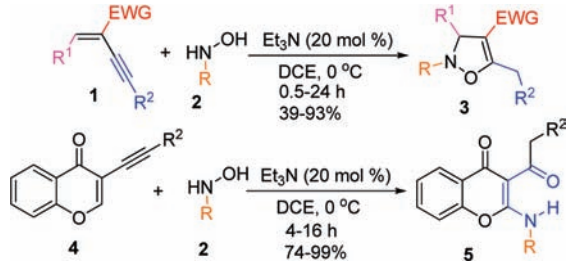
Received February 26, 2010

ABSTRACT



An Et_3N-catalyzed tandem reaction of electron-deficient 1,3-conjugated enynes with hydroxylamines was developed which provided rapid, metal-free, and regioselective access to highly substituted multifunctionalized 2,3-dihydroisoxazoles under mild conditions. The reactions of 3-(2-arylethynyl)-4*H*-chromen-4-ones with hydroxylamines afford *β*-amino enones under the same reaction conditions.

2,3-Dihydroisoxazoles represent a class of heterocycles that may be employed as useful building blocks for organic synthesis[1] since the N−O bond can be easily cleaved under mild reducing conditions leading to 1,3-amino alcohols[2,3] or 1,3-amino ketones.[2,4] They are also found in many

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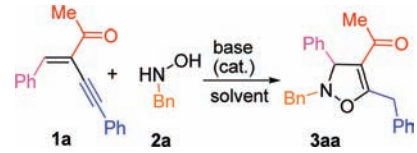
10.1021/ol100490y
Published on Web 03/24/2010

bioactive molecules and pharmaceuticals.[5] Among many methods developed in past years, 1,3-dipolar cycloaddition reactions between nitrones and alkynes or metal acetylides under the catalysis of transition metals or Lewis acids are the most common synthetic methods for the construction of 2,3-dihydroisoxazoles.[6] However, metal-catalyzed 1,3-dipolar cycloadditions often furnish regioisomeric mixtures of adducts, proceed in low yield,[6g−i] or have functional group tolerance.[6a−c] Herein, we report a base-catalyzed tandem reaction[7] of electron-deficient 1,3-conjugated enynes with substituted hydroxylamines, providing a metal-free, efficient, and regioselective approach to highly substituted 2,3-dihydroisoxazoles.

Recently, our group[8] and others[9] have demonstrated that electron-deficient 1,3-conjugated enynes are readily available and attractive precursors for the construction of various acyclic and cyclic compounds. During these studies, we envisaged that 2,3-dihydroisoxazoles might be prepared from the corresponding electron-deficient 1,3-enynes and hydroxylamines by tandem inter- and intramolecular nucleophilic addition.

To test this hypothesis, enyne **1a** and *N*-benzylhydroxylamine **2a** were subjected to DMF at 40 °C in the presence of Et_3N (20 mol %). Gratifyingly, the desired product **3aa** was obtained in 77% isolated yield after 4 h (Table 1, entry 1). Interestingly, the reaction gives 44% yield of **3aa** without any additional base, indicating that hydroxylamine itself can play the role of a base (Table 1, entry 2). Other organic and inorganic bases such as DBU, DABCO, DMAP, $PhCO_2Na$, and $NaHCO_3$ were next tested. In contrast with the previous result,[8c] DBU here failed to give the desired product (Table 1, entry 3), while DABCO (entry 9) or DMAP (entry 10) catalyzed this reaction at ambient temperature, providing **3aa** in 80% and 66% yield, respectively. Both $NaHCO_3$ (entry 4) and $PhCO_2Na$ (entry 5) are less effective. Furthermore, the reaction temperature and catalyst loading were also examined (Table 1, entries 6−8, 14). There is little solvent effect on this tandem reaction (Table 1, entries 11−14). Finally, we were pleased to find that **3aa** could be isolated in 91% yield after stirring at 0 °C in DCE for 1.5 h with 20 mol % of Et_3N as catalyst (Table 1, entry 14, standard conditions).

Table 1. Screening Conditions for Tandem Reaction of **1a** with **2a**



entry[a]	base (20 mol %)	solvent	temp (°C)	yield of **3aa**[f] (%)
1	Et_3N	DMF	40	77
2		DMF	40	44
3[b]	DBU	DMF	40	<5
4	$NaHCO_3$	DMF	40	19
5	$PhCO_2Na$	DMF	40	32
6[c]	Et_3N	DMF	40	72
7	Et_3N	DMF	60	64
8	Et_3N	DMF	rt	83
9[d]	DABCO	DMF	rt	80
10[e]	DMAP	DMF	rt	66
11	Et_3N	DMF	0	87
12	Et_3N	CH_3CN	0	86
13	Et_3N	DCM	0	88
14	Et_3N	DCE	0	91

[a] All reactions were carried out using **1a** (0.3 mmol) and **2a** (0.45 mmol) in the presence of base under N_2 atmosphere in solvent (2.5 mL) for 1−12 h. [b] DBU = 1,8-diazabicyclo[5.4.0]undecen-7-ene. [c] 10 mol % of Et_3N. [d] DABCO = 1,4-diazabicyclo[2.2.2]octane. [e] DMAP = 4-dimethylaminopyridine. [f] Isolated yield.

With the optimized conditions in hand, we next examined the scope of this tandem reaction with various substituted electron-deficient 1,3-conjugated enynes **1** and various *N*-substituted hydroxylamines (Scheme 1). Several points are noteworthy: (1) In general, highly substituted 2,3-dihydroisoxazoles can be prepared in moderate to excellent yields under standard conditions from the corresponding electron-deficient conjugated enynes and hydroxylamines. The yield of **3ra** is low because of the unstable substrate **1r**. (2) Various electron-withdrawing groups (EWG) such as ketone (**3ba**−**na**), aldehyde (**3ra**), ester (**3qa** and **3uc**), and amide (**3oa**) can be effectively introduced to the products. (3) The substituent on the alkene moiety (R^1) can be an aryl (**3aa**−**3ad**), alkyl (**3ea**), styryl (**3la**), or ester (**3qa**) group. (4) The substituent (R^2) on the alkyne moiety can also be an aryl or alkyl (**3ea**) group. (5) Besides **2a**, we also tested other substituted or unsubstituted hydroxylamines such as *N*-(naphthalen-1-ylmethyl) hydroxylamine (**2b**), MeNH(OH)•

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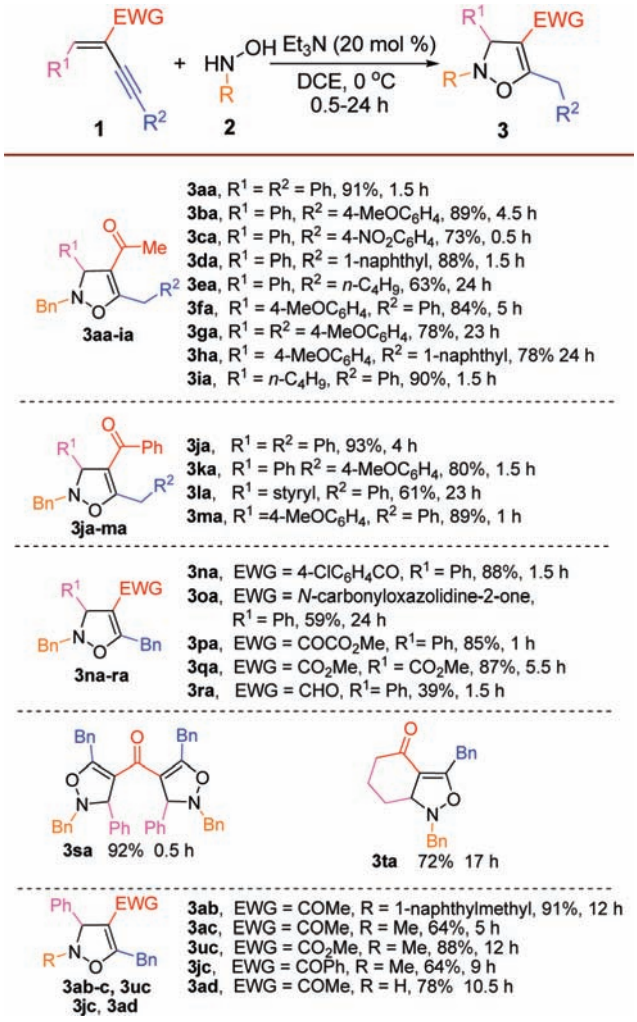
Scheme 1. Synthesis of Multifuncionalized 2,3-Dihydroisoxazoles **3**[a]



[a] MeNH(OH)·HCl or $HONH_2$·HCl and 170 mol % of Et_3N were used for **3ac**, **3uc**, **3jc**, and **3ad**. [b] The designation **3aa** for the product indicates that the reactants used were **1a** and **2a**, respectively.

HCl (**2c**), $HONH_2$·HCl (**2d**), and the *N*-phenylhydroxylamine (**2e**). (6) Due to its weak nucleophilicity, only **2e** cannot react with electron-deficient 1,3-enynes. (7) The structure of the products was confirmed by single-crystal X-ray analysis of representative **3na** (Figure 1).[10]

It is interesting and surprising that in contrast to the 2-(phenylethynyl)cyclohex-2-enone (Scheme 1, **3ta**), the reaction of **4a** with *N*-benzylhydroxylamine (**2a**) under the same conditions produced novel β-amino enone **5aa** rather than the expected product (Scheme 2), the structure of which was aslo established by single-crystal X-ray diffraction analysis of **5ab** (Figure 1).[10] Phenyl-bearing electron-rich and electron-withdrawing groups on the alkyne moiety (R^2) could be introduced and have little effect on the reaction.

(10) CCDC 763753 (**3na**) 763754 (**5ab**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

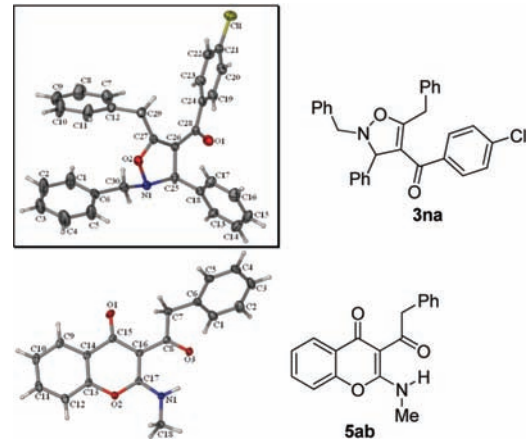
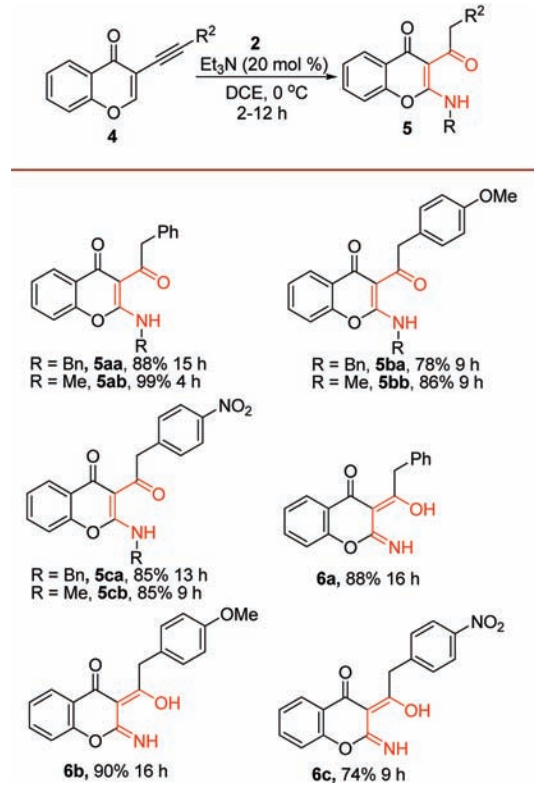


Figure 1. X-ray crystal structures and line drawings of **3na** (top) and **5ab** (bottom).

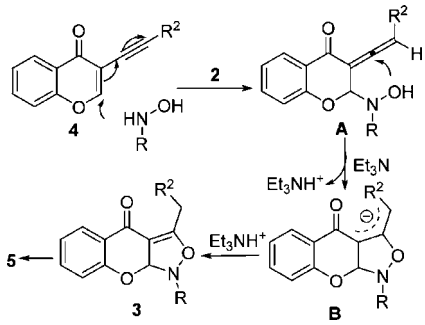
When R is H, imines **6a**−**c** were obtained by further isomerization.

One plausible mechanism that accounts for this Et_3N-catalyzed tandem process is proposed (Scheme 3). The regioselective and chemoselective nucelophilic addition of the hydroxylamine **2** via the *N*-atom[1k] produces 1,2-allenyl ketone intermediate **A**,[8b] which undergoes an intramolecular addition with the *O*-atom to give an allylic carboanion **B** under the catalysis of the base. Subsequent protonation

Scheme 2. Tandem Reactions of Enynes **4** and **2**



Scheme 3. Plausible Mechanism Accounts for this Et_3N-Catalyzed Tandem Process



affords product **3**, which undergoes further rearrangement to give the final product **5**.[6c]

In summary, we have developed an Et_3N-catalyzed tandem intermolecular and intramolecular nucelophilic addition of *N*-hydroxyamines to electron-dificient 1,3-conjugated enynes, which provides a rapid, efficient, and metal-free approach to multifunctionalized, highly substituted 2,3-dihydroisoxazoles. This method is a complementary approach to those metal or Lewis acid catalyzed 1,3-dipolar cycloadditions of nitrones with alkynes. For those 3-(2-arylethynyl)-4*H*-chromen-4-ones, the reaction undergoes further rearrangement to give β-amino enones. Further studies including synthetic applications, the asymmetric catalysis of this reaction, and examination of other binucleophiles are ongoing in this laboratory.

Acknowledgment. Financial support from the National Natural Science Foundation of China (20702015, 20972054) and Shanghai Municipal Committee of Science and Technology (08dj1400101) is greatly appreciated.

Supporting Information Available: Experimental procedures, X-ray data for **3na** and **5ab** (CIF), as well as characterization data of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100490Y