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Fused Pyrazolo Heterocycles: Intramolecular [3+2]-Nitrile Oxide Cycloadditions Applied to Syntheses of Pyrazolo[3,4-g][2,1]dihydrobenzoisoxazol(in)es

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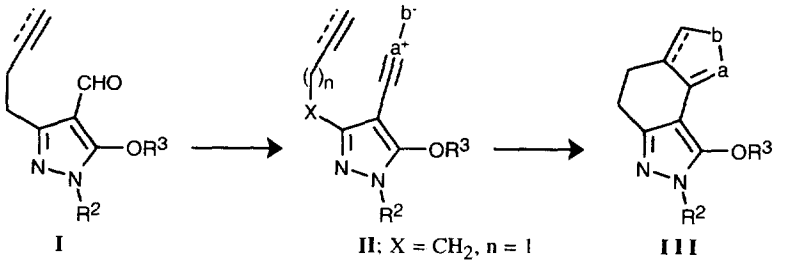
Abstract: *A general method is described to prepare pyrazolo[3,4-g]-[2,1]dihydrobenzoisoxazol(in)es utilizing intramolecular nitrile oxide cycloaddition (INOC) as the key step.*

The intramolecular 1,3-dipolar cycloaddition reaction is a powerful tool in the preparation of heterocycles.[1] There are numerous examples of intramolecular [3+2] cycloadditions in aryl rings ortho substituted with dipolarophile and 1,3-dipole functional groups.[2] The potent antibiotic and antineoplastic biological activity[3] of ring-fused pyrazole heterocycles has stimulated the development of various methods for their synthesis.[4] As part of a synthetic program directed toward the synthesis of pyrazoloisoxazol(in)e-based heterocycles with biological and/or metal chelating potential,[5] we have explored the development of a general protocol for the preparation of these novel heterocycles from ethyl acetoacetate. In this paper, we report our initial studies on the construction of pyrazoloisoxazol(in)e-based heterocycle **III** utilizing the intramolecular cycloaddition[6] of 1,3-dipole **II**, in turn generated from dipolarophile "tethered" pyrazolo aldehyde **I** (**Scheme 1**).

Scheme 1:



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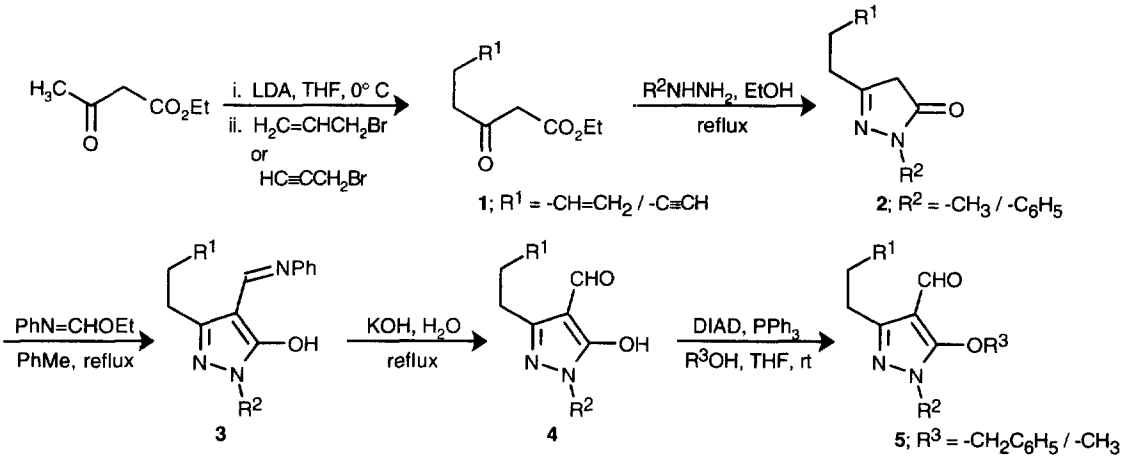
Our synthesis of the targeted heterocycles (**III**) begins as depicted in **Scheme 2**. Formation of the dianion of ethyl acetoacetate[7] with 2 eq. of LDA at 0° C in THF followed by alkylation (propargyl or allyl bromide) provided β-keto ester **1** (R^1 = -C≡CH or -CH=CH_2) in 62% and 75% yield, respectively. Condensation of **1** with phenyl or methyl hydrazine in refluxing anhydrous ethanol gave the corresponding pyrazolone **2** (R^1 = -C≡CH or -CH=CH_2; R^2 = -C_6H_5 or -CH_3). Attempts to install a formyl group at C-4 using classic Vilsmeir conditions (DMF, $POCl_3$, 0° to 100° C, 2h) were not successful. Thus, introduction of the formyl group at C-4 was accomplished using a two step procedure involving formation of Schiff base **3** by condensing ethyl N-phenylformimidate with **2** in refluxing toluene. Subsequent hydrolysis of **3** with aqueous potassium hydroxide and neutralization with concentrated HCl provided 4-formyl derivative **4**. The presence of a C-5 hydroxyl tautomer in **4** was indicated by a broad O–H band at 2835 cm^{-1} in the infrared spectrum, a broad singlet at 10.12 ppm in the ^1H NMR spectrum, and ^{13}C NMR resonances at 104.9 and 158.4 ppm for C-4 and C-5, respectively. Model experiments revealed that it was necessary to mask the C-5 hydroxyl moiety prior to intramolecular nitrile oxide cycloaddition. Accordingly, **4** was alkylated under Mitsunobu conditions[8] with methyl or benzyl alcohol to give pyrazole **5** (R^1 = -C≡CH or -CH=CH_2; R^2 = -C_6H_5 or -CH_3; R^3 = -CH_3 or -$CH_2C_6H_5$; in 32-40% yield from **4**).

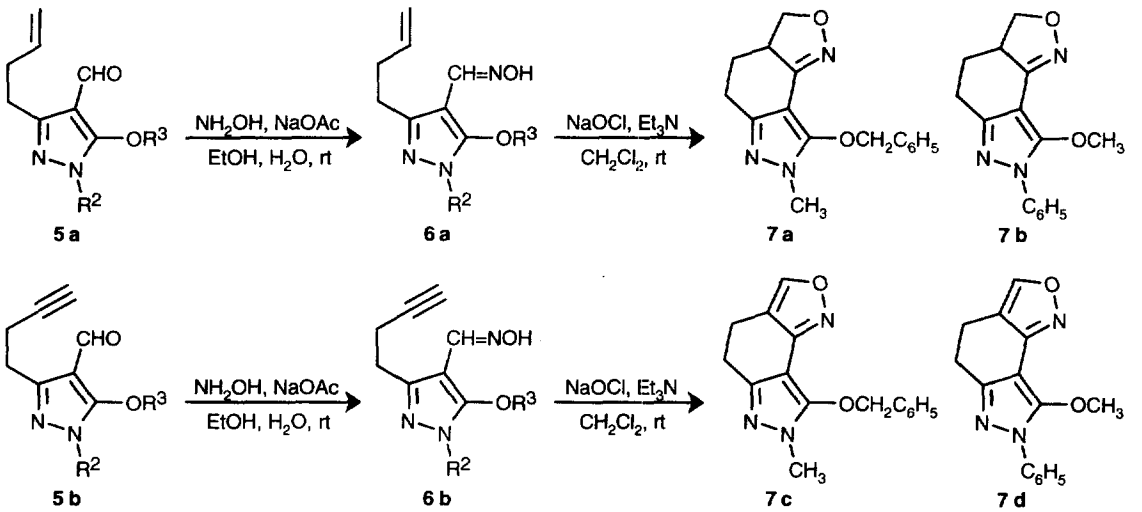
Scheme 2:



With sufficient quantities of alkene (R^1 = -CH=CH_2) and alkyne (R^1 = -C≡CH) intermediates **5** in hand, we were in a position to prepare pyrazolo[3,4-g][2,1]-dihydrobenzoisoxazolines **7a/b** and pyrazolo[3,4-g][2,1]dihydrobenzoisoxazoles **7c/d** (**Scheme 3**). The requisite nitrile oxide intermediates were prepared in two steps

by the Huisgen method. First, room temperature condensation of aldehyde **5** with hydroxylamine hydrochloride in 95% EtOH containing NaOAc (2.5 eq.) gave oxime **6**. Subsequent dropwise addition of aqueous sodium hypochlorite[9] (5.25%) to a solution of this oxime and triethylamine in CH_2Cl_2 at 0° C generated the nitrile oxide intermediate which underwent concomitant cycloaddition to **7a-d** in 65-80% yield.[10]

Scheme 3:



It is interesting to note that **7d** exhibited a four proton singlet at 2.85 ppm (methylene protons) in its $CDCl_3$ ^1H NMR spectrum. However, in benzene-d_6, these two methylenes were shifted to lower field and were rendered magnetically non-equivalent; appearing as two triplets centered at 2.02 and 2.33 ppm (J = 7.0 Hz). The isoxazole methine was also shifted upfield by nearly one ppm (from 8.11 ppm in $CDCl_3$ to 7.14 ppm in benzene-d_6). Compound **7c** behaves similarly in $CDCl_3$ and benzene-d_6.

In summary, we have demonstrated that intramolecular nitrile oxide cycloaddition provides an efficient means for the preparation of novel fused pyrazolo[3,4-g][2,1]dihydrobenzoisoxazol(in)e heterocycles **7**. Extension of this methodology to systems employing additional dipolarophile "tethers" (**II**; X=O, n=1,2) and 1,3-dipoles (azomethine ylide, nitrile imide, etc.) is currently under study and the results will be reported in due course.

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