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Synthesis of a 1-Benzylpiperazin-2-one Nitrone and Its Reaction With Alkynes and Alkenes

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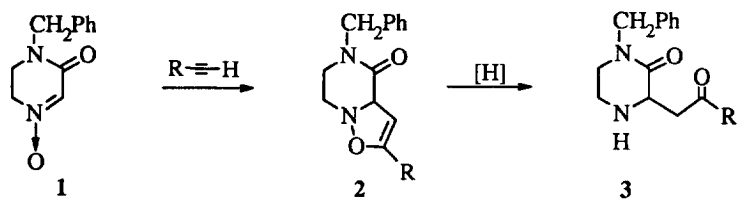
Abstract: A novel 1-benzylpiperazin-2-one nitrone has been synthesized. It readily undergoes [3+2] cycloadditions with alkynes and alkenes to give Δ^4-isoxazolines and isoxazolidines, respectively, which can be reductively opened to 3-substituted piperazin-2-ones and 1,3-amino alcohols.

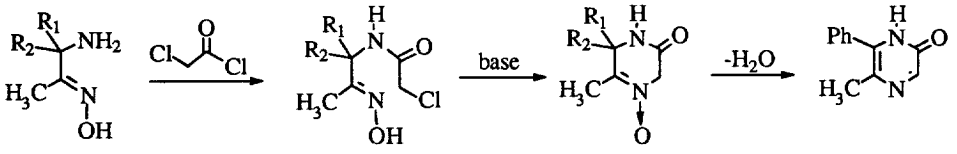
As part of a project targeting neuroactive compounds, we required a method for synthesizing 3-substituted piperazin-2-ones **3**. These compounds can be viewed as peptide units constrained by an ethylene bridge and they have been incorporated into peptides to make enkephlinase inhibitors.[1] Past syntheses of 3-substituted piperazin-2-ones have relied on the addition of various ethylene diamines to α-haloesters[2] and unsaturated esters.[3] Alternately, the dianion of a protected piperazin-2-one has been alkylated with reactive electrophiles.[4] However, for our purposes, a more versatile approach was required. The method we have developed begins with the cycloaddition of nitrone **1** with an alkyne to produce Δ^4-isoxazolines **2**, which can be opened to 3-substituted piperazin-2-ones (Equation 1). We describe in this report the synthesis of nitrone **1**, its reactions with alkynes and alkenes, and the reduction of the cycloadducts to give piperazin-2-ones **3**.



1 **2** **3** (1)

A consideration of our synthetic requirements and an awareness of several potential pitfalls guided us in our choice of nitrone **1**. For the ultimate targets of this investigation, a nitrone without any carbon substitutents was needed. The potential for aromatization problems in such a system was clear from work of Gnichtel.[5] Gnichtel was able to synthesize gem-dialkyl nitrone **6a** from **4a**; however, attempts to convert analogous **4b** into **6b**, in which a hydrogen has replaced one of the carbon substituents, gave only dehydration product **7** (Equation 2). To minimize pyrazinone formation with our nitrone, the amide nitrogen was

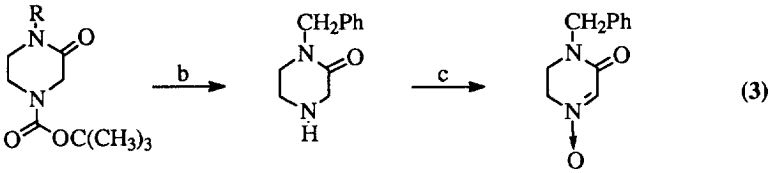
protected with a benzyl group to give a tertiary amide. In addition, the nitrone carbon was placed adjacent to the amide carbonyl since the extended conjugation might help stabilize the molecule. Synthetically, oxidative generation of the nitrone from an amine should give the desired regioisomer selectively, based on the propensity for nitrone generation alpha to a carbonyl.[6]



(2)

4a $R_1, R_2 = CH_3$ **5a,b** **6a,b** **7**
b R_1 = Ph, R_2 = H

The synthesis of nitrone **1** started with the known[4] 4-(*t*-butyloxycarbonyl)piperazin-2-one (**8**) (Equation 3). Alkylation with benzyl bromide afforded **9** which was deprotected with neat trifluoroacetic acid to give amine **10**. Oxidation of **10** was accomplished using 30% aqueous hydrogen peroxide in ethanol with catalytic sodium tungstate.[7] Nitrone **1** was isolated as a low melting, crystalline solid[8] and is stable for at least several months at room temperature. A sample heated at reflux in d_8-tetrahydrofuran for 24 hours showed no evidence of decomposition by ^1H or ^{13}C NMR.



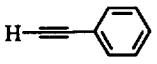
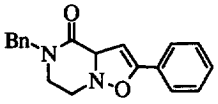
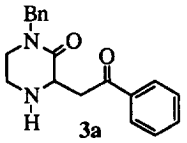
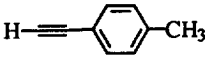
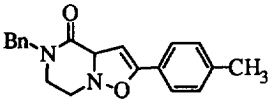
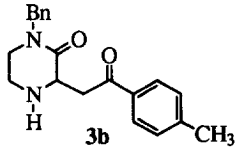
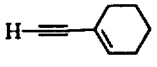
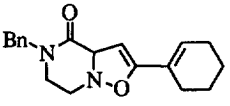
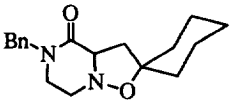
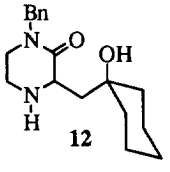
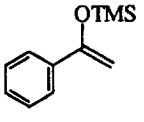
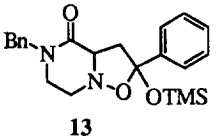
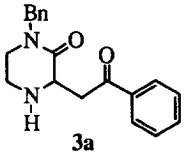
(3)

8 R = H **10** **1**
9 R = CH_2Ph

a) NaH (1.1 eq)/$PhCH_2Br$ (1.1 eq)/DMF/rt/18 h (74%) b) TFA/0 °C/30 min (84%)
c) Na_2WO_4 $2H_2O$ (0.05 eq)/aq. 30% H_2O_2 (2.2 eq)/CH_3CH_2OH/rt/24 h (63%)

Treatment of **1** with monosubstituted alkynes[9] gave Δ^4-isoxazolines **2** in moderate to good yield. Typically, the nitrone was dissolved in tetrahydrofuran (THF) at 0.4 M concentration and treated with three equivalents of a mono-substituted alkyne. After heating at reflux for 3-5 hours under nitrogen, the reaction mixture was simply concentrated *in vacuo* and the crude product was purified by flash chromatography.[10] Δ^4-Isoxazolines are known to be thermally and photochemically unstable[11] and these cycloadducts occasionally required two chromatographies for purification or, in the case of **2c**, a further recrystallization to obtain sufficiently clean compound.[12] In all reactions, only the regioisomer arising from addition of the oxygen to the more substituted end of the alkyne was isolated. The more usual reduction of the Δ^4-isoxazolines with zinc dust in aqueous acetic acid[13] was bypassed in favor of the neutral and milder $Mo(CO)_6$ in refluxing wet acetonitrile[14] which afforded 3-(2-oxoalkyl)-piperazin-2-ones **3** (see Table).

TABLE: [2+3] CYCLOADDITIONS

SUBSTRATE	TIME (H)	CYCLOADDUCT	YIELD (%)	REDUCTION PRODUCT	YIELD (%)
	4	 **2a**	66	 **3a**	54
	5	 **2b**	65	 **3b**	72
	3	 **2c**	38 [a]	Not done [b]	
	24	 **11**	68	 **12**	74
	42	 **13**	70 [c]	 **3a**	60

[a] Yield was 68% after chromatography. [b] Substrate was unstable. [c] Combined yield of diastereomers.

Nitrone **1** also reacts with alkenes[9] to give isoxazolidines. While these cycloadditions required 24-48 hours at reflux, the longer reaction times were not problematic since the isoxazolidines were apparently stable under these conditions. Treatment of methylenecyclohexane with nitrone **1** afforded isoxazolidine **11** which gave 1,3-amino alcohol **12** on reductive opening. Cycloaddition with 1-phenyl-1-(trimethylsilyloxy)ethylene

produced a 3:1 mixture of diastereomers **13** which was readily separable by flash chromatography.[15] The relatively slow reaction rate is likely due to the sterically hindered nature of the silyl enol ether.[16] Reductive opening carried out on the major isomer provided an alternative route to **3a**, demonstrating that either acetylenes or acetophenones (via their enol ethers) can be used as starting materials for compounds **3**.

In conclusion, novel heterocyclic nitrone **1** has been synthesized. It undergoes facile [3+2] cycloaddition reactions with alkynes and alkenes to give Δ^4-isoxazolines and isoxazolidines, respectively. Since these cycloadducts can be readily reduced to 3-(2-oxygenated alkyl)piperazin-2-ones, this approach provides a novel and very versatile route to this class of compounds.

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8. Characterization: Elemental ± 0.4% C, H, N. Mp: 72-73°C. ^{1}H NMR ($CDCl_3$) δ 7.38-7.25 (5H), 7.19 (1H, s), 4.65 (2H, s), 4.01 (2H, t, J = 6.3 Hz), 3.53 (2H, t, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 159.06, 135.51, 128.98, 128.22, 128.16, 58.75, 49.11, 42.00. EIMS: 204 (100%), 132 (85%), 91 (100%).
9. Alkyne and alkene substrates were chosen to avoid the generation of diastereomers upon reduction.
10. Alternatively, the reactions may be run at room temperature though this generally requires 2 or more days to approach completion.
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12. All cycloadducts gave satisfactory elemental (± 0.4% C, H, N) and spectral (^{1}H and ^{13}C NMR, CIMS, and IR) data.
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15. The diastereoselectivity of the cycloadditon is under investigation.
16. Over the course of several hours, NMR samples of both diastereomers of **13** in $CDCl_3$ eliminated trimethylsilyl alcohol to give **2a**. A similar elimination has been observed: Camiletti, C., Dhavale, D. D., Gentilucci, L., Trombini, C. *J. Chem. Soc. Perkin Trans.* **1993**, 3157-3165.

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