Synthesis of spiro 3-bromo-4,5-dihydroisoxazoles via [1,3]dipolar cycloaddition reactions

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Synthesis of spiro 3-bromo-4,5-dihydroisoxazoles via [1,3]dipolar cycloaddition reactions

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Abstract: A group of novel 4-bromo-7,9-dimethyl-1-aryl-2-oxa-3,7,9-triaza-spiro[4.5]dec-3-ene-6,8,10-trione derivatives is prepared through 1,3-dipolar cycloadditions between benzylidenes and bromonitrile oxide. This reaction is shown to have high atom economy.

Keywords: 1,3-dipolar cycloaddition, bromonitrile, 4,5-dihydroisoxazoles, dibromoformaldoxime.

The synthetic utility of the 1,3-dipolar cycloaddition reaction is evident from the number and scope of targets that can be prepared by this chemistry.[1-4] As one of the most thoroughly investigated 1,3-dipoles, nitrile oxides are arguably the most useful due to their ability to generate nitrogen- and oxygen-based functionalities from the cycloadducts, as well as the potential to install multiple stereogenic centers through high degrees of regio- and stereoselectively.[5-9]

Several simple and convenient methods for the preparation of nitrile oxides have been developed over the years. One of the important procedures for the easy access and preparative use of nitrile oxides is the in situ technique with hydroximoyl halides.[10-12]

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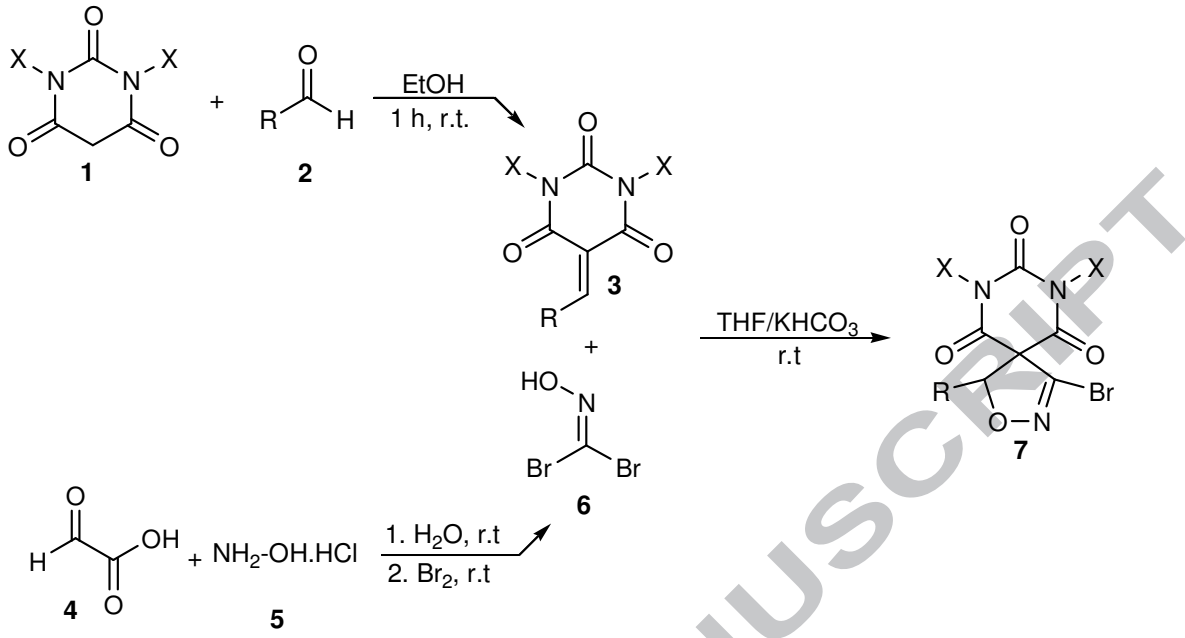
The 3-isoxazolidone nucleus constitutes the basic skeleton of natural compounds such as the antibiotic, D-cycloserine,[13] the L-canavanine catabolite,[14] and a series of compounds that have been designed in medicinal chemistry as ligands for different receptors of the central nervous system.[15] The construction of isoxazoline and isoxazole rings by the 1,3-dipolar cycloaddition (13DC) of a nitrile oxide to an alkene or alkyne has proven to be extremely useful.[5-9, 16]

In continuation of our interest in the synthesis of heterocyclic compounds based on multicomponent reactions (MCRs),[17] we describe the synthesis of spiro 3-bromo-4,5-dihydroisoxazoles **7** in high yields via the two-component condensation reaction of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **3** and dibromoformaldoxime (**6**) in THF using $KHCO_3$ at room temperature (Scheme 1). It should be noted that 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **3** were synthesized by the condensation between barbituric acids **1** and benzaldehydes **2** in ethanol over 1 hour at room temperature.[18] Dibromoformaldoxime (**6**) was synthesized by the reaction of glyoxylic acid (**4**) with hydroxylamine hydrochloride (**5**) followed by bromination according to the literature.[19]



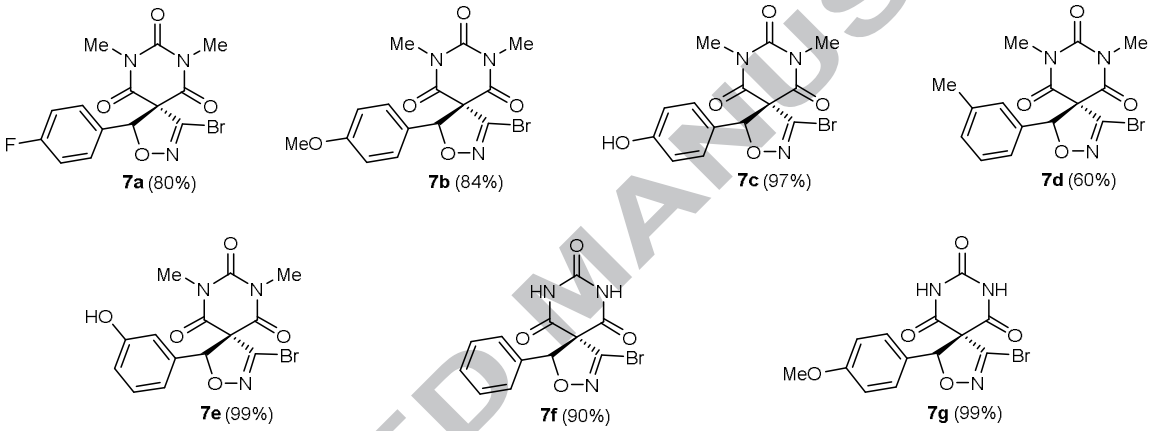
Scheme 1.

We chose the reaction of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1a**, X = Me) with dibromoformaldoxime (**6**) as a model system for an optimization study. We first investigated the reaction rate in different solvents by measuring the isolated yield of the product, using identical amounts of reactants in the presence of 1.5 equivalents of $KHCO_3$ for a fixed reaction time of 24 hours at room temperature. The desired product was obtained in solvents such as THF, ethyl acetate, and toluene, but THF gave the product in the highest yield. Next, different basic catalysts including Na_2CO_3, K_2CO_3, Et_3N, NaOH, $KHCO_3$ and $NaHCO_3$ were examined in the reaction. The results indicated that although K_2CO_3 and Na_2CO_3 were found to be effective, the best result was obtained when $KHCO_3$ (1.5 equiv) was utilized as the base.

With optimized conditions established, we next extended the process to two different barbituric acids, barbituric acid and 1,3-dimethylbarbituric acid, and various aldehydes including benzaldehyde, 4-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-

fluorobenzaldehyde, 4-methoxybenzaldehyde and 3-methylbenzaldehyde. The results in Figure 1 show that all the reactions proceeded smoothly to afford the expected 3-bromo-4,5-dihydroisoxazole derivatives in good to excellent yields. The structures of the products were deduced from their IR, mass, ^{1}H NMR and ^{13}C NMR spectra (see the Supporting Data).

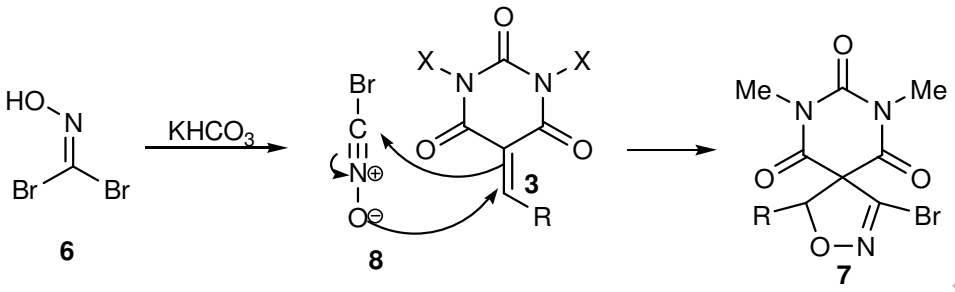
Figure 1. Structures of the prepared spiro 3-bromo-4,5-dihydroisoxazole derivatives.[a,b]



[a]Reaction conditions: benzylidene **3** (1 mmol), dibromoformaldoxime (**6**) (1 mmol), $KHCO_3$ (1.5 mmol), THF (4 mL), r.t., 24 h. [b]Isolated yields.

To explore the scope and limitations of this process, we further examined the reactions of various aliphatic aldehydes with 1,3-dimethylbarbituric acid in ethanol at room temperature. However, in all these cases, the desired products **3** were not formed.

Mechanistically, it is conceivable that the reaction involves the initial formation of the bromonitrile oxide **8** via the reaction of dibromoformaldoxime (**6**) with $KHCO_3$. Next, this bromonitrile oxide undergoes a 1,3-dipolar cycloaddition with benzylidenes **3** to afford the 3-bromo-4,5-dihydroisoxazole derivatives **7** (Scheme 2).



Scheme 2. Proposed mechanism for the reaction

It is important to note that two isomers (A and B) are expected for the product (Figure 2). However the ^{1}H NMR and ^{13}C NMR spectra of the crude reaction mixtures were consistent with one isomer. Therefore, the reaction proceeded with high regioselectively. This might be due to the fact that there would be repulsion between the R and Br groups in the isomer B. Therefore we expected compound A as the major product.

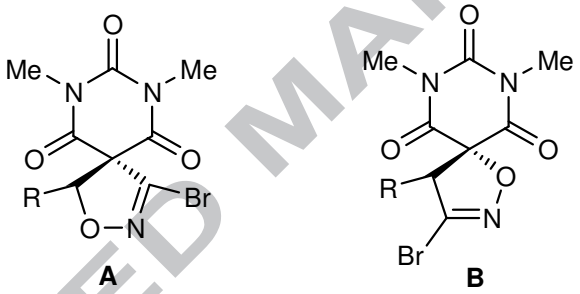


Figure 2. Structures of the two regioisomers.

In conclusion, the efficient synthesis of spiro 3-bromo-4,5-dihydroisoxazole derivatives in THF, in the presence of $KHCO_3$ as the base has been described. A two-component reaction involving 5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **3** and dibromoformaldoxime (**6**) afforded the desired spiro products in good to excellent yields. A range of aromatic aldehydes was used, including examples bearing electron-donating or electron-withdrawing substituents. We hope that this approach may be of value to

others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

Synthesis of benzylidene derivatives 3

A solution of a benzaldehyde **2** (1 mmol) and a barbituric acid **1** (1 mmol) in EtOH (5 mL) was stirred for 1 h at room temperature. After completion of the reaction, as indicated by TLC, the solid residue was removed by filtration and washed with H_2O (3×5 mL) to afford the pure products as colorless crystals.

Synthesis of dibromoformaldoxime (6)

To a stirred solution of glyoxylic acid (**4**) (10 mmol) in H_2O (50 ml) was added hydroxylamine hydrochloride (**5**) (10 mmol) and the solution was stirred for 24 h at room temperature. Next, $NaHCO_3$ (20 mmol) was added carefully followed by CH_2Cl_2 (60 ml). To the two-phase, well-stirred mixture at 6 ˚C was added Br_2 (1 ml) dropwise over 20 min. Upon completion of the addition of Br_2, the solution was stirred for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined organic extract was dried ($MgSO_4$), filtered and evaporated. The residue was crystallized from *n*-hexane (50 mL). Yield 1.60 g (81%), m.p. 65-66 °C (Lit.[19] m.p. 63-65 °C), white crystals.

General procedure for the synthesis of spiro 3-bromo-4,5-dihydroisoxazoles 7a-g

To a solution of benzylidene **3** (1 mmol) and dibromoformaldoxime (**6**) (1 mmol) in THF (5 mL) was added $KHCO_3$ (1.5 mmol) and the mixture stirred for 24 h at room temperature. After completion of the reaction, as indicated by TLC, the solvent was removed under vacuum and the solid residue was washed with H_2O (5 mL). The solid

residue was crystallized from CH_2Cl_2/*n*-hexane (1:2) to afford the products as colorless crystals.

4-Bromo-1-(4-fluorophenyl)-7,9-dimethyl-2-oxa-3,7,9-triaza-spiro[4.5]dec-3-ene-6,8,10- trione (7a)

White powder (yield 80%); mp 187-200 °C. IR (KBr) (ν_{max}/cm^{-1}): 3362, 2958, 2920, 1725, 1685, 1600, 1506. MS, *m/z* (%): 384 (M^++2), 382 (M^+), 304, 287, 274, 258, 154, 85, 57. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.75 (3H, s, CH_3), 3.35 (3H, s, CH_3), 4.95 (1H, s, CH), 7.00-7.20 (4H, m, H-Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 24.7 (CH_3), 25.7 (CH_3), 64.7 (*C*C=O), 84.0 (CH), 112.5, 121.0, 127.0, 133.0, 145.3, 159.1, 160.0, 161.2, 162.0 (C-Ar, 3C=O, C=N). Anal. Calcd for $C_{14}H_{11}BrFN_3O_4$: C, 43.77; H, 2.89; N, 10.94. Found: C, 43.73; H, 2.92; N, 10.91.

4-Bromo-1-phenyl-2-oxa-3,7,9-triaza-spiro[4.5]dec-3-ene-6,8,10-trione (7f)

White powder (yield 90%); mp 201-203 °C. IR (KBr) (ν_{max}/cm^{-1}): 3350, 3330, 2980, 2925, 1730, 1675, 1600, 1510. MS, *m/z* (%): 338 (M^++2), 336 (M^+), 278, 259, 258, 216, 128, 120, 121, 58, 43. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 4.90 (1H, s, CH), 7.00-7.35 (5H, m, H-Ar), 8.35-8.70 (2H, br s, 2NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 66.3 (*C*C=O), 84.5 (CH), 117.0, 121.2, 124.3, 131.6 (C-Ar), 144.5, 145.5, 157.6, 160.5 (3C=O, C=N). Anal. Calcd for $C_{12}H_8BrN_3O_4$: C, 42.63; H, 2.38; N, 12.43. Found: C, 42.60; H, 2.36; N, 12.44.

Acknowledgements

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Supplementary data

Experimental procedures and spectral data for all new compounds are available. Supplementary data related to this article can be found at http://

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19. Dibromoformaldoxime is commercially available but can be readily prepared, see: Rohloff, J. C.; Rubinsun, J., III; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113–3116.

Graphical abstract

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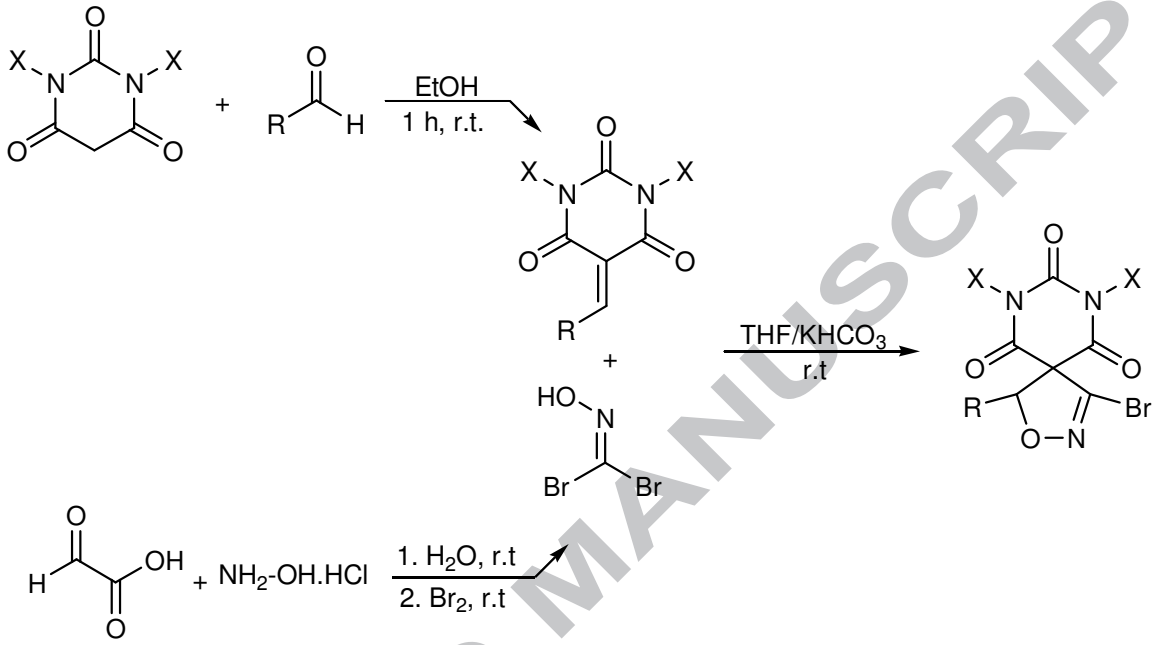

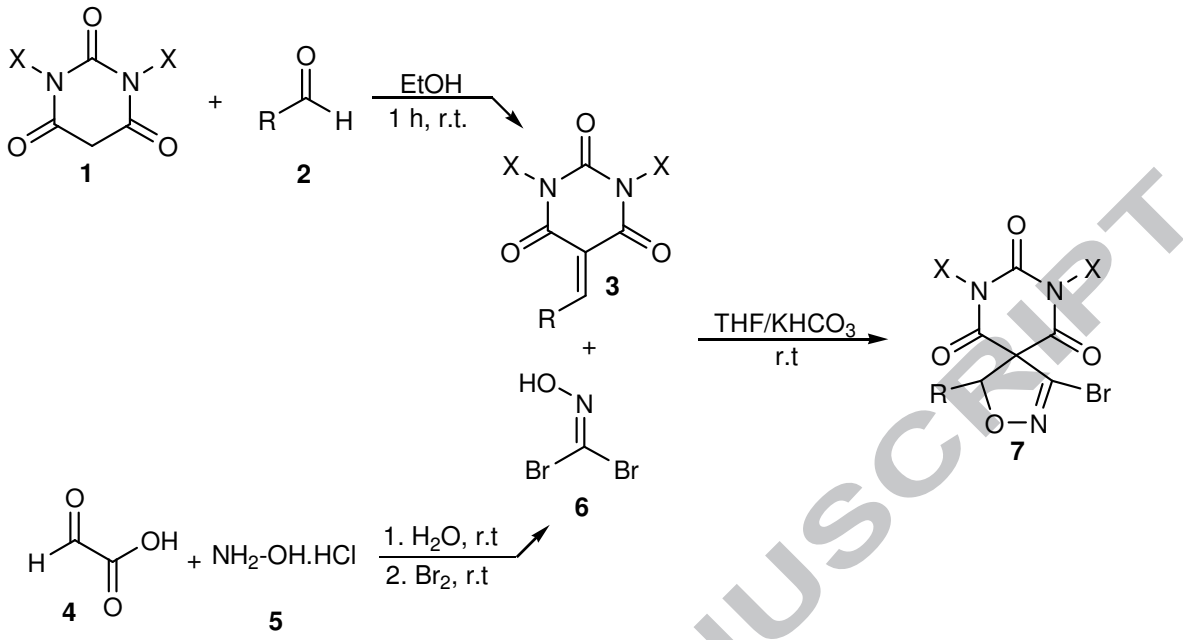

Scheme 1. Synthesis of spiro 3-bromo-4,5-dihydroisoxazoles