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4-Bromo-2,3-dihydroisoxazoles: synthesis and application in halogen-lithium exchange reactions

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ABSTRACT

The synthesis of novel types of 4-bromo-2,3-dihydroisoxazoles using pyridinium tribromide in the presence of base is described. Reactivity of the initial substrates and the yields depend on the substituent at C3. To demonstrate a practical scope of the 4-bromo-substituted 2,3-dihydroisoxazoles, representative 2-benzyl-4-bromo-3,5-diphenyl-2,3-dihydroisoxazole is subjected to halogen-lithium exchange reaction. The corresponding (2,3-dihydroisoxazol-4-yl)lithium reacts with three selected electrophiles to afford 4-substituted 2,3-dihydroisoxazoles in moderate yields.

1. Introduction

Small metalated heterocycles represent attractive substrates in organic synthesis due to their wide applicability in forming new carbon–carbon bonds.[1] Specifically, five-membered aromatic (isoxazol-4-yl)lithium species **1** (Fig. 1) are powerful building blocks in medicinal chemistry and play an important role as promising substrates in the processes of screening for potent pharmacological candidates.[2] For instance, Valdecoxib (nonsteroidal antiinflammatory drug) and Oxacillin (β-lactamase-resistant antibiotic) have been recently synthesized from 4-bromo-5-methylisoxazole **2** using bromine-lithium exchange reaction at the 4-position also.[2a] On the other hand, a method for the successful preparation of nonaromatic lithiated isoxazolines **3** has not been described to date.

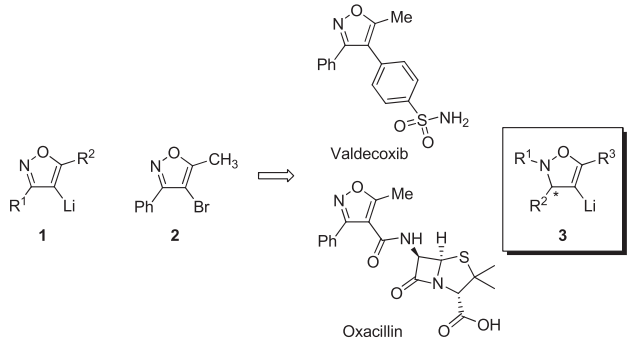
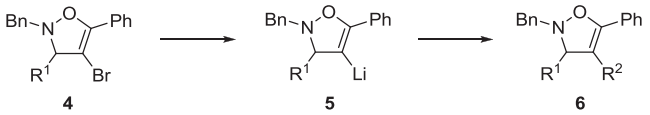


Fig. 1. (Isoxazol-4-yl)lithium species as suitable substrates for biologically active molecules.

Based on our interest in the field of 2,3-dihydroisoxazoles,[3] we investigated the synthesis of such novel lithiated heterocycles. In this paper, we report on the preparation of *N*-benzyl-4-bromo-2,3-dihydroisoxazoles **4** by means of bromination reactions of 4-unsubstituted 2,3-dihydroisoxazoles, and on their utilization in bromine-lithium exchange reactions to afford (2,3-dihydroisoxazol-4-yl)lithium compounds **5** as suitable substrates for carbon–carbon bond formation at C4 (Scheme 1). The presented synthetic route provides the possibility for 4-substituted 2,3-dihydroisoxazoles **6** that could be hard to prepare by other methods.



Scheme 1. General synthetic route to 4-substituted 2,3-dihydroisoxazoles via bromine-lithium exchange.

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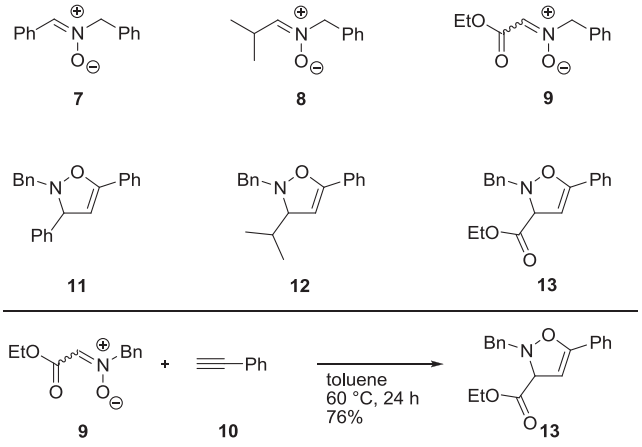
2. Results and discussion

2.1. Synthesis of 2,3-dihydroisoxazoles

In accordance with the literature, the starting *N*-benzyl-2,3-dihydroizoxazoles **11** and **12** were readily available from the corresponding nitrones (Scheme 2).[4] The reactions of nitrones **7**[4b] and **8**[5] with phenylacetylene (**10**) in the presence of $Zn(OTf)_2$ afforded propargylic *N*-hydroxylamines,[4b] which upon zinc iodide catalyzed cyclization gave 2,3-dihydroizoxazoles **11** and **12** in very good yields (89% and 92%) nearly consistent with published results.[4c] 2,3-Dihydroizoxazole **13** was prepared via direct 1,3-dipolar cycloaddition of nitrone **9**[6] with phenylacetylene (**10**) in satisfactory 76% yield (Scheme 2). Contrary to previously published procedures for **13**,[7] the presented reaction was performed in toluene at 60 °C in 24 h without catalyst.

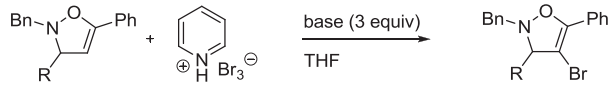


Scheme 2. Starting *N*-benzyl-2,3-dihydroisoxazoles prepared from the corresponding nitrones.

2.2. Bromination reactions

Only a few reports on the synthesis of 4-halogen-substituted 2,3-dihydroizoxazoles have appeared to date. In general, such compounds were considered to be unstable and therefore not applicable in subsequent reactions. They were obtained by reductions of the corresponding isoxazolium salts with $LiAlH_4$ and $NaBH_4$,[8a] or by their reactions with organometallic reagents,[8b] and through the iodocyclization of the propargylic *N*-hydroxylamines in the presence of ICl.[8c] As mentioned earlier, our experiences with the chemistry of 2,3-dihydroisoxazoles inspired us to examine a chemical behavior of such compounds in bromination reactions, with the goal to prepare 4-bromo-2,3-dihydroisoxazoles as suitable starting substrates for halogen-lithium exchange reactions.

At the beginning, we focused our attention on searching for a suitable bromination agent. First attempts were carried out with model dihydroisoxazole **11** (0.16 mmol scale) in anhydrous THF in the presence of triethylamine at 0 °C. NBS did not work, and the use of bromine led to a rapid decomposition of **11** without any evidence of the desired product. Fortunately, pyridinium tribromide (**14**) reacted satisfactorily to afford 4-bromo-2,3-dihydroisoxazole **15** (Scheme 3). A dropwise addition of freshly prepared THF solution of **14** was preferred, compared to a solid. Solvents such as NMP, CH_3CN, $CHCl_3$ and CH_2Cl_2 were also tested, however they were found to be unsuitable. The best results in terms of chemical yield and purity were obtained, when the reaction was performed at −40 °C and with 3 equiv of triethylamine. It is worth noting that the elimination also proceeded without any additional base, however the desired product **15** gradually decomposed. Most likely, released hydrobromic acid caused the quarternisation of N2, which resulted in ring-opening reactions. The use of DBU or pyridine did not have a positive effect on the reaction course. Finally, we prepared dihydroisoxazole **15** in satisfactory 60% yield. The reaction performed in less concentrated solution led to higher yield of **15** (60% at 0.05 M, 26% at 0.1 M and 25% at 0.5 M). With optimized reaction conditions in hand, we scaled up the reaction of **11** (1.6 mmol). Surprisingly, the yield dropped dramatically to 13%. Based on our positive experiences with 2-chloropyridine in elimination reactions,[3d] we have replaced triethylamine for this base. Thus, the bromination of **11** with 1.1 equiv of pyridinium tribromide (**14**) and 3 equiv of 2-chloropyridine in anhydrous THF at −40 °C gave 4-bromo-2,3-dihydroisoxazole **15** in 53% yield (Scheme 3). Contrary to bromination of **11**, the reactions of 2,3-dihydroisoxazoles **12** and **13**, bearing isopropyl and ethoxycarbonyl groups at C3, proceeded slower at −40 °C, and therefore needed to be performed at higher temperature, and moreover with a larger amount of pyridinium tribromide (**14**). Interestingly, triethylamine was again a superior base to 2-chloropyridine. Finally, desired 4-bromo-2,3-dihydroisoxazoles **16** and **17** were prepared in 66% and 50% yields, respectively (Scheme 3). The bromination at C4 was confirmed by ^1H and ^{13}C NMR experiments as follows. Signal of the H-4 proton disappeared and the multiplicity of the H-3 proton of **15** was simplified (singlet, δ=4.98 ppm) compared to H-3 and H-4 protons of starting 2,3-dihydroisoxazole **11**. Furthermore, the signals of C-4 and C-5 were shifted to low field (C-4, **11**: δ=95.9 ppm; **15**: δ=88.4 ppm and C-5, **11**: δ=153.0 ppm; **15**: δ=147.8 ppm). The presence of the bromo atom was clearly confirmed by HRMS.



		T [°C]	r. time	base		
11 R = Ph	1.1 equiv	-40	24 h	2-ClPy	**15** R = Ph	53%
12 R = *i*-Pr	2.0 equiv	rt	5 h	Et_3N	**16** R = *i*-Pr	66%
13 R = CO_2Et	2.5 equiv	rt	4 h	Et_3N	**17** R = CO_2Et	50%

Scheme 3. Bromination reactions of 2,3-dihydroisoxazoles into the 4-position.

2.3. Bromine-lithium exchange reactions

To further demonstrate a practical scope of the 4-bromo-substituted 2,3-dihydroisoxazoles, we focused our attention on bromine-lithium exchange reactions. As shown in Scheme 4, representative 2,3-dihydroisoxazole **15** was treated with *n*-BuLi in anhydrous THF at −80 °C. The rate of lithium insertion was monitored by TLC (hexanes/CH_2Cl_2, 70:30) and HPLC-MS. The quenching of an analytical sample with satd aq NH_4Cl solution caused a rapid hydrolysis of lithium species **18**, affording 4-unsubstituted 2,3-dihydroisoxazole **11**. A starting substrate was completely consumed after stirring for one hour. Subsequently, a neat electrophile was added dropwise and the stirring continued for 24 h at −80 °C. Iodomethane, benzoyl chloride and isobutyraldehyde were selected as appropriate electrophiles due to their good reactivity. Three representative 2,3-dihydroisoxazoles **19**, **20** and **21** were successfully prepared in moderate 51%, 61% and 69% yields, respectively (Scheme 4). Moreover, the reaction with isobutyraldehyde exclusively provided single isomer. Despite the complete bromine-lithium exchange, 2,3-dihydroisoxazole **11** was detected in all cases, even though 4 equiv of each electrophile were used and the reaction time was 24 h.[9]