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Application of Organolithium in Organic Synthesis: A Simple and Convenient Procedure for the Synthesis of More Complex 6-Substituted 3*H*-Quinazolin-4-ones

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Summary. 6-Methyl-3*H*-quinazolin-4-one reacted with alkyllithium reagents at −78°C in *THF* to give 2-alkyl-1,2-dihydro-6-methyl-3*H*-quinazolin-4-ones in high yields. However, no reaction took place when *LDA* was used as the lithium reagent. 6-Bromo-3*H*-quinazolin-4-one reacted with excessive butyllithium to give 2-butyl-1,2-dihydro-3*H*-quinazolin-4-ones in very good yields. However, the lithiation of 6-bromo-3*H*-quinazolin-4-one was achieved by the use of a combination of methyllithium (1.1 equivalents) and *tert*-butyllithium (2.2 equivalents) at −78°C in *THF*. The dilithio reagent thus obtained reacted with a variety of electrophiles (H_2O, iodoethane, benzaldehyde, anisaldehyde, cyclohexanone, 2-hexanone, benzophenone, phenyl isothiocyanate, *TITD*) to give the corresponding 6-substituted 3*H*-quinazolin-4-ones in excellent yields. Reaction of the dilithio reagent with 1,3-dibromopropane gave 6,6′-(propanediyl)bis(3*H*-quinazolin-4-one).

Keywords. 3*H*-Quinazolin-4-one; Nucleophilic addition; Bromine-lithium exchange; Dilithio reagent; Electrophiles.

Introduction

Recently, it was observed that lithiation of various heterocyclic compounds using lithium reagents at low temperature followed by reactions with electrophiles resulted in the production of substituted heterocycles in good yields [1]. Literature reveals that current attention is focused on the preparation of substituted quinazoline derivatives *via* directed lithiation in order to improve their biological activities

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[2–5]. More recent work involved successful lithiation of 3-*tert*-butoxycarbonyl-3*H*-quinazolin-4-one using lithium diisopropylamide (*LDA*) [6]. The reactions of the dilithio reagent thus formed with electrophiles followed by removal of the *tert*-butoxycarbonyl group afforded the corresponding 2-substituted derivatives [6].

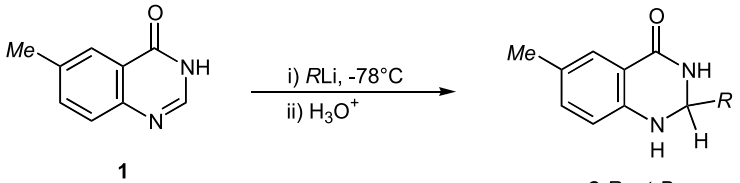
As a part of our own interest in heterocyclic chemistry [7], particularly in the use of directed lithiation in organic synthesis [8], we have shown that lithiation of various 3*H*-quinazolin-4-ones produced a wide range of more complex 2-substituted 3*H*-quinazolin-4-one derivatives in very good yields [9, 10]. Synthesis of the 3*H*-quinazolin-4-one ring system, which provides the backbone for compounds having numerous pharmacological activities [11], is an interesting challenge. We now report on the successful synthesis of 6-substituted 3*H*-quinazolin-4-ones *via* bromine–lithium exchange of 6-bromo-3*H*-quinazolin-4-one.

Results and Discussion

6-Methyl-3*H*-quinazolin-4-one (**1**) was prepared according to Ref. [12]. It was hoped that lithiation of **1** would take place as for 2-methyl-3*H*-quinazolin-4-one [11], so that substitution of the hydrogen of the methyl group at position 6 by lithium could be achieved, followed by reactions with electrophiles to give the corresponding 6-substituted derivatives. However, it was found that lithiation of **1** did not take place with alkyllithiums. Instead, nucleophilic attack by alkyllithiums occurred at the imine bond to give 1,2-addition products. The reactions of **1** with one equivalent of alkyllithiums (*tert*-butyllithium, *n*-butyllithium, methyllithium) at −78°C in *THF* took place within 15 minutes to give 2-alkyl-1,2-dihydro-6-methyl-3*H*-quinazolin-4-ones (**2**–**4**) (Scheme 1) in high yields (85–90%).

The compounds **2**–**4** are fluorescent. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR, mass spectra, and high resolution mass spectral data. Their ^{1}H NMR spectra showed a characteristic H-2 signal in the $\delta = 4.31$–4.77 ppm region, and their ^{13}C NMR spectra showed that C-2 appears in the $\delta = 61$–72 ppm region (see Experimental for details).

It was found that lithiation of **1** with a less nucleophilic lithium reagent, such as lithium diisopropylamide (*LDA*) did not take place and only starting material was recovered, indicating that no reaction took place under the conditions tried. No further attempts were made to try to find conditions under which lithiation of **1** could be effected.



1

2 *R* = *t-Bu*
3 *R* = *n-Bu*
4 *R* = *Me*

Scheme 1