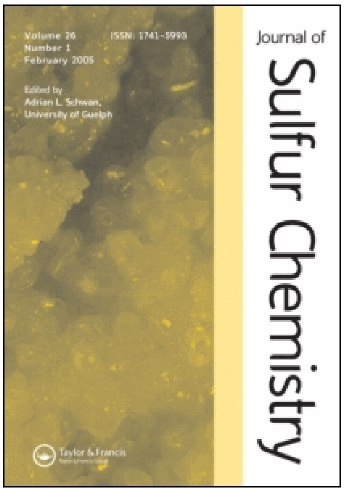

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RESEARCH ARTICLE

Addition of alkyllithiums to 3*H*-quinazoline-4-thione and various substituted quinazoline derivatives; application in synthesis

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Reaction of 3*H*-quinazoline-4-thione (**1**) with two mole equivalents of an alkyllithium (*t*-BuLi, *n*-BuLi or MeLi) at −78 °C in dry THF gave the corresponding 2-alkyl-1,2-dihydro-3*H*-quinazoline-4-thione (**4**, **5** or **6**) in high yield. Similarly, reactions of 4-(methylthio)quinazoline (**7**), 4-(ethylthio)quinazoline (**8**) and 4-methoxyquinazoline (**9**) with alkyllithiums (one mole equivalent) gave the corresponding 4-substitued 2-alkyl-1,2-dihydroquinazolines **11–18**. On the other hand, blocking position 2 with a phenyl group in 4-(methylthio)-2-phenylquinazoline (**20**) and 4-methoxy-2-phenylquinazoline (**21**) resulted in reaction with two mole equivalents of alkyllithiums to give 4,4-dialkyl-2-phenyl-3,4-dihydroquinazolines **22–24**.

Keywords: 3*H*-Quinazoline-4-thione; 4-(Alkylthio)quinazoline; Synthesis; Alkyllithiums; Nucleophilic addition

1. Introduction

Quinazoline derivatives exhibit a wide variety of pharmacological activities [1–8]. Therefore methods for the synthesis and/or modification of this ring system are always of interest. Reactions of organic compounds with organolithium reagents offer useful opportunities for the production of modified derivatives [9–13]. However, the literature reveals that there are only a few reports of syntheses of substituted quinazoline derivatives *via* such reactions [14–22]. As part of our interest in the use of organolithium reagents in organic synthesis [23–28], we have investigated the ring and side-chain lithiation of various 3*H*-quinazolin-4-ones for the production of derivatives substituted and/or modified at the 2-position, which might be difficult to prepare by other means [29–36]. However, while many of these reactions were successful, 2,3-unsubstituted 3*H*-quinazolin-4-one was recovered unchanged after treatment with either an alkyllithium or lithium diisopropylamide (LDA) followed by treatment with an

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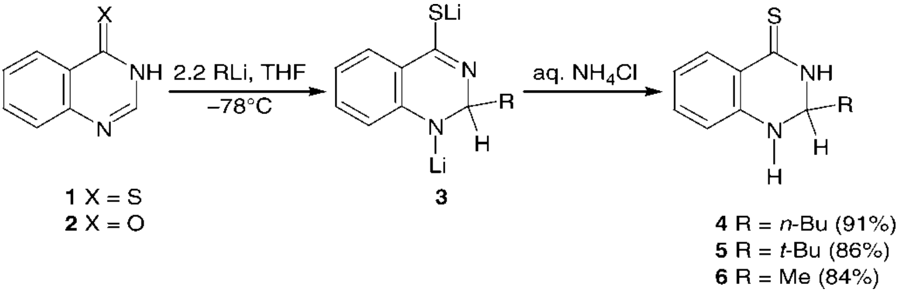
electrophile. It was of interest to carry out analogous reactions with 3*H*-quinazoline-4-thione and its derivatives in order to investigate whether the presence of sulfur instead of oxygen would have any significant influence.

In the present work we report the reaction of alkyllithiums with 3*H*-quinazoline-4-thione, resulting in addition at the 2-position. We also report reactions of alkyllithiums with 4-alkylthio- and 4-methyoxyquinazolines, which also result in addition to the 2-position. By contrast, we report that 4-(methylthio)-2-phenyl- and 4-methoxy-2-phenylquinazolines undergo addition and substitution at the 4-position to give 4,4-dialkyl-2-phenyl-3,4-dihydroquinazolines.

2. Results and discussion

3*H*-Quinazoline-4-thione (**1**) was prepared from 3*H*-quinazolin-4-one (**2**) according to the literature procedure [37]. It was found that reaction of **1** with two mole equivalents of an alkyllithium (*tert*-butyllithium, *n*-butyllithium or methyllithium) occurred smoothly at −78 °C in dry THF, and resulted in the production of the corresponding 2-alkyl-1,2-dihydro-3*H*-quinazoline-4-thione **4**, **5** or **6** in high yield (Scheme 1). This contrasts sharply with the situation for 3*H*-quinazolin-4-one (**2**), which resulted in recovery of unchanged **2** under such conditions, and indicates the important role played by sulfur in this reaction. Although we have not yet investigated the reasons for this difference, it is possible that the thiolate anion in **3** is less effective at donating negative charge to the ring than its oxygen counterpart. The acquisition of negative charge by the ring would be expected to deactivate the ring towards nucleophilic attack by organolithium reagents.

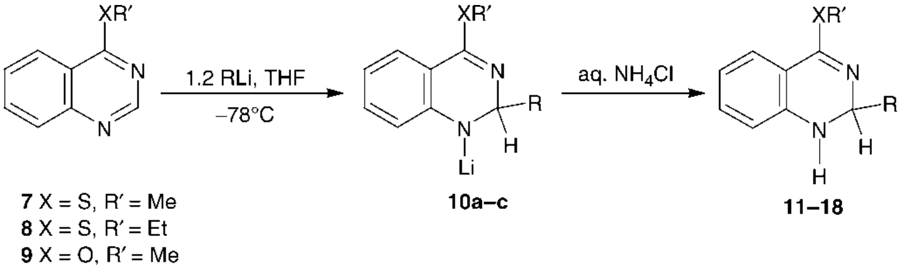


SCHEME 1

The structures of compounds **4–6** were confirmed by ^{1}H NMR and ^{13}C NMR spectoscopy, and both low and high resolution mass spectral data (see experimental section for details). The ^{1}H NMR spectra showed a characteristic H2 signal in the δ 4.75–4.32 ppm range while the ^{13}C NMR spectra showed that C2 appeared as a doublet in the δ 72–61 ppm region.

Although it was interesting to note that compound **1** was far more reactive towards organlithium reagents than was compound **2**, the nature of the products of the reaction (*i.e.* addition products) was not very useful. Therefore, an attempt was made to bring about lithiation with a less nucleophilic base, LDA. In order to determine whether lithiation had occurred, benzophenone was added as electrophile prior to work up. Unfortunately only starting material was recovered, indicating that no lithiation took place at position 2 under the conditions tried.

Our attention was therefore turned next to the reactions of alkyllithiums with compounds having alkylthio or alkoxy groups at position 4, in order to see what effect the sulfur atom would have on the reactivity of such compounds. 4-(Methylthio)quinazoline (**7**), 4-(ethylthio)quinazoline (**8**) and 4-methoxyquinazoline (**9**) were all prepared according to literature procedures [37–40]. It was found that reactions of compounds **7–9** with alkyllithiums (*t*-BuLi, *n*-BuLi, MeLi) occurred smoothly and rapidly at −78 °C in dry THF. The lithium reagents **10a–c** were presumably obtained as intermediates and after quenching with aqueous NH_4Cl solution gave the corresponding 4-substituted 2-alkyl-1,2-dihydroquinazolines **11–18** (Scheme 2) in high yields (table 1). LDA did not react with **7–9** under similar conditions.



SCHEME 2

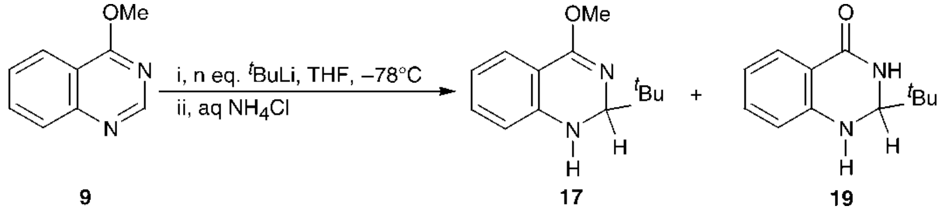
As indicated in table 1, the yields of compounds **11–18** are extremely good in all cases. The structures of compounds **11–18** were confirmed by ^1H NMR, ^{13}C NMR, and both low and high resolution mass spectral data (see experimental section for details). The ^1H NMR spectra showed a characteristic H2 signal in the $\delta = 4.99–4.37$ ppm range while the ^{13}C NMR spectra showed that C2 appears as a doublet in the $\delta = 79–66$ ppm region.

The above results showed few major differences between compounds **7** and **9**. However, the reaction of excess *t*-BuLi with 4-methoxyquinazoline (**9**) was different than that with 4-(methylthio)quinazoline (**7**). The reaction of *t*-BuLi with **9** gave a mixture of 2-*tert*-butyl-4-methoxy-1,2-dihydroquinazoline (**17**) and 2-*tert*-butyl-1,2-dihydro-3*H*-quinazolin-4-one (**19**) (Scheme 3), in proportions that depended on the amount of *t*-BuLi used (table 2). Compound **19** was the very product that might have been expected from the reaction of 3*H*-quinazolin-4-one (**2**) with *tert*-butylithium, but, of course, this direct reaction of **2** with *t*-BuLi did not occur.

Table 1. Synthesis of 4-substituted 2-alkyl-1,2-dihydroquinazolines **11–18** according to Scheme 2.

Product	X	R′	R	Yield (%)[a]
11	S	Me	*n*-Bu	90
12	S	Me	*t*-Bu	88
13	S	Me	Me	89
14	S	Et	*n*-Bu	91
15	S	Et	*t*-Bu	89
16	O	Me	*n*-Bu	89
17	O	Me	*t*-Bu	89
18	O	Me	Me	94

[a] Yield of isolated, purified product.



SCHEME 3

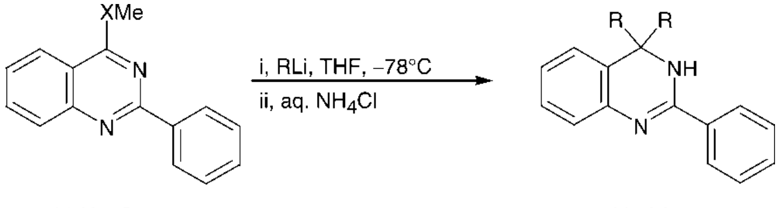
Table 2. Yields of **17** and **19** from reaction of 4-methoxyquinazoline (**9**) with *t*-BuLi according to Scheme 3.

t-BuLi (mole equiv.)	Yield (%)[a]	
	17	**19**
1.2	89	–
1.4	76	6
2.0	66	15
2.4	50	27
3.0	37	42

[a]Yield of isolated, purified product.

The NMR and mass spectra confirmed the structure of compound **19**. The ^{1}H NMR spectrum showed the presence of two exchangeable singlets which resonated at $\delta = 7.11$ and 5.75 ppm due to two NH protons, while the singlet due to the OMe group had disappeared. The ^{13}C NMR spectrum showed that C4 appeared as a singlet at $\delta = 164.9$ ppm and also showed all the other appropriate carbon resonances. The CI mass spectrum showed an intense pseudo molecular ion peak (MH$^+$) at $m/z = 205$, and there was also a molecular ion peak at $m/z = 204$ in the EI mass spectrum. The accurate mass of the pseudo molecular ion confirms the formula as $C_{12}H_{17}N_2O$ (MH$^+$).

In all the reactions so far, the only significant process observed was addition of organolithium reagent at position 2. In an attempt to divert reaction to other sites, attention was next turned to the reactions of alkyllithiums with 4-(methylthio)-2-phenylquinazoline (**20**) [39] and 4-methoxy-2-phenylquinazoline (**21**) [39], in which position 2 was blocked with a phenyl group. Interestingly, when a 1:1 molar mixture of **20** and an alkyllithium (*n*-BuLi or MeLi) was allowed to react for one hour at −78°C in dry THF (Scheme 4; X = S), 4,4-dialkyl-2-phenyl-3,4-dihydroquinazoline (**22** or **23**) was obtained in moderate yield (table 3), along with a significant amount of the starting material **20**, which was recovered unreacted. Use of 2.2 mole equivalents of the alkyllithiums gave **22** and **23** in high yields, presumably *via* initial addition of alkyllithium, then elimination of methanethiolate anion and further addition



20 X = S
21 X = O

22–24

SCHEME 4

Table 3. Synthesis of 4,4-dialkyl-2-phenyl-3,4-dihydroquinazolines **22–24** from **20** according to Scheme 4 (X =S).

Product	RLi (mole equiv.)	R	Yield (%)[a]
22	1.1	*n*-Bu	47
22	2.2	*n*-Bu	96
23	1.1	Me	40
23	2.2	Me	81
24	2.2	*t*-Bu	49[b]

[a]Yield of isolated, purified product.

[b]TLC indicated the presence of other products which were difficult to separate.

of alkyllithium. Even with this reactant ratio, however, *t*-BuLi gave only a modest yield of product **24** (table 3) due to the formation of other by-products.

Reaction of 4-methoxy-2-phenylquinazoline (**21**) with *n*-BuLi (4 equivalents) has been reported previously [19] to give 4,4-dibutyl-2-phenyl-3,4-dihydroquinazoline **22**. We investigated the reactions of **21** with other alkyllithiums under conditions similar to those used for compound **20** in order to have a comparison between the effect of methylthio and methoxy groups on the reactivity of the quinazoline ring system. It was found that compound **21** behaved similarly to compound **20** in its reactions with alkyllithiums. Again it was found that reaction of **21** with *n*-BuLi (1.1 equivalent) resulted in the production of 4,4-dibutyl-2-phenyl-3,4-dihydroquinazoline **22**, but in modest yield. However, using two equivalents of alkyllithiums gave **22** and **23** (Scheme 4; X = O) in good yields (table 4). Again the yield of **24** was lower due to the formation of other by-products.

The NMR and mass spectra confirmed the structures of compounds **22–24** (see experimental section for details). The ^{1}H NMR spectra showed the presence of an exchangeable singlet which resonated at $\delta = 5.60$–4.65 ppm due to the NH proton, while the ^{13}C NMR spectra showed that C4 appeared as a singlet at $\delta = 68$–53 ppm and also showed all the other appropriate carbon resonances.

3. Conclusions

We have demonstrated a convenient procedure that allows regiospecific nucleophilic addition of alkyllithiums to 3*H*-quinazoline-4-thione and various quinazoline derivatives containing an alkylthio or a methoxy group at position 4 and a hydrogen or a phenyl group at position 2.

Table 4. Synthesis of 4,4-dialkyl-2-phenyl-3,4-dihydroquinazolines **22–24** from **21** according to Scheme 4 (X = O).

Product	RLi (mole equiv.)	R	Yield (%)[a]
22	1.1	*n*-Bu	46
22	2.2	*n*-Bu	88
23	2.2	Me	83
24	2.2	*t*-Bu	49[b]

[a]Yield of isolated, purified product.

[b]TLC indicated the presence of other products which were difficult to separate.

The procedure provides efficient syntheses of 2-alkyl-1,2-dhiydroquinazolines, *via* 1,2-addition of alkyllithiums, and 4,4-dialkyl-3,4-dihydro-2-phenylquinazolines *via* 3,4-additon followed by displacement of the substituent (SMe or OMe) at position 4. This should be beneficial for the synthesis of analogues with potentially useful pharmacological properties.

4. Experimental

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. Chemical shifts are reported relative to TMS. Assignments of signals are based on coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra were recorded on a Quattro II spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) at 50 eV by the use of NH_3 as ionization gas. Accurate mass data were obtained on a MAT900 instrument. Column chromatography was carried out using Fischer Scientific silica 60A (35–70 micron). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham [41]. Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures [42, 43].

4.1 *2-Alkyl-1,2-dihydro-3H-quinazoline-4-thiones (4–6); general procedure*

A solution of alkyllithium (2.2 mmol) was added to a cold (−78 °C), stirred solution of 3*H*-quinazoline-4-thione, **1** (0.16 g, 1 mmol), in anhydrous THF (50 mL) under N_2. The yellow solution obtained was stirred at −78 °C for 1 h. The reaction mixture was removed from the cooling bath and allowed to warm to r.t., diluted with Et_2O (10 mL) then quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The solid obtained was treated with Et_2O (10 mL), filtered then dried to give the pure product **4**, **5** or **6**.

4.1.1 2-Butyl-1,2-dihydro-3*H*-quinazoline-4-thione (4). Mp: 119–120 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 10.13 (s, exch., 1H, NH), 8.04 (dd, $J = 8, 1$ Hz, 1H, H5), 7.25 (app. dt, $J = 1, 8$ Hz, 1H, H7), 6.92 (s, exch., 1H, NH), 6.73 (br d, $J = 8$ Hz, 1H, H8), 6.66 (app. dt, $J = 1, 8$ Hz, 1H, H6), 4.63 (t, $J = 6$ Hz, 1 H, H2), 1.69–1.64 (m, 2H, CH_2), 1.42–1.25 (m, 4H, 2CH_2), 0.88 (t, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm): 189.8 (s, C4), 144.7 (s, C8a), 134.1 (d, C7), 131.9 (d, C5), 120.0 (s, C4a), 117.5 (d, C6), 115.1 (d, C8), 64.8 (d, C2), 33.8 (t, CH_2), 25.8 (t, CH_2), 22.3 (t, CH_2), 14.3 (q, CH_3); EI-MS: m/z (%) = 220 (M^+, 21), 176 (13), 163 (100), 145 (9), 136 (10), 129 (12), 41 (84); CI-MS: m/z (%) = 221 (MH^+, 100), 187 (18), 163 (7); HRMS: m/z calcd for $C_{12}H_{17}N_2S$ (MH^+), 221.1107; found, 221.1105.

4.1.2 2-*tert*-Butyl-1,2-dihydro-3*H*-quinazoline-4-thione (5). Mp: 166–167 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 9.97 (br s, exch., 1 H, NH), 8.01 (dd, $J = 8, 1$ Hz, 1H, H5), 7.22 (app. dt, $J = 1, 8$ Hz, 1H, H7), 7.05 (br s, exch., 1H, NH), 6.74 (d, $J = 8$ Hz, 1H, H8), 6.55 (app. t, $J = 8$ Hz, 1H, H6), 4.32 (app. t, $J = 4$ Hz, 1H, H2), 0.88 [s, 9 H, $C(CH_3)_3$]; ^{13}C

NMR (DMSO-d_6) δ (ppm): 189.6 (s, C4), 144.4 (s, C8a), 134.4 (d, C7), 131.7 (d, C5), 119.0 (s, C4a), 116.4 (d, C6), 114.1 (d, C8), 72.1 (d, C2), 39.6 [s, *C*(CH$_3$)$_3$], 24.7 [q, C(*C*H$_3$)$_3$]; EI-MS: m/z (%) = 220 (M$^+$, 17), 203 (15), 171 (19), 163 (100), 129 (23), 91 (24), 77 (20), 41 (47); CI-MS: m/z (%) = 221 (MH$^+$, 100), 189 (33), 187 (24), 163 (21), 131 (25); HRMS: m/z calcd for $C_{12}H_{17}N_2S$ (MH$^+$), 221.1107; found, 221.1110.

4.1.3 2-Methyl-1,2-dihydro-3*H*-quinazoline-4-thione (6). Mp: 149–151 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 10.15 (s, exch., 1H, NH), 8.05 (d, $J = 8$ Hz, 1H, H5), 7.27 (app. t, $J = 8$ Hz, 1H, H7), 6.93 (s, exch., 1H, NH), 6.70–6.67 (m, 2H, H6 and H8), 4.75 (q, $J = 6$ Hz, 1H, H2), 1.38 (d, $J = 6$ Hz, 3H, CH$_3$); ^{13}C NMR (DMSO-d_6) δ (ppm): 190.2 (s, C4), 145.2 (s, C8a), 134.1 (d, C7), 131.9 (d, C5), 120.3 (s, C4a), 117.8 (d, C6), 115.0 (d, C8), 61.4 (d, C2), 20.5 (q, CH$_3$); EI-MS: m/z (%) = 178 (M$^+$, 90), 163 (100), 145 (64), 143 (53), 136 (22), 129 (27), 104 (33), 91 (29), 77 (36), 42 (54); CI-MS: m/z (%) = 179 (MH$^+$, 69), 162 (13), 147 (100), 145 (81); HRMS: m/z calcd for $C_9H_{11}N_2S$ (MH$^+$), 179.0637; found, 179.0635.

4.2 *4-Substituted 2-alkyl-1,2-dihydroquinazolines (11–18); general procedure*

A solution of alkyllithium (2.4 mmol) was added to a cold (−78 °C), stirred solution of **7**, **8** or **9** (2.0 mmol) in anhydrous THF (10 mL) under N_2. The reaction mixture was stirred at −78 °C for 1 h then removed from the cooling bath and allowed to warm to r.t. The reaction mixture was diluted with Et_2O (10 mL) then quenched with aq sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; Et_2O-hexane, 1:4) to give the pure product.

4.2.1 2-Butyl-4-(methylthio)-1,2-dihydroquinazoline (11). Mp: 32–33 °C; ^{1}H NMR (CDCl$_3$) δ (ppm): 7.34 (dd, $J = 8$, 1 Hz, 1H, H5), 7.07 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.60 (app. dt, $J = 1$, 8 Hz, 1H, H6), 6.45 (br d, $J = 8$ Hz, 1H, H8), 4.75 (t, $J = 6$ Hz, 1H, H2), 3.91 (br s, exch., 1H, NH), 2.33 (s, 3H, SCH$_3$), 1.78–1.61 (m, 2H, CH$_2$), 1.48–1.25 (m, 4H, 2CH$_2$), 0.84 (t, $J = 6$ Hz, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$) δ (ppm): 161.3 (s, C4), 143.8 (s, C8a), 132.3 (d, C7), 124.2 (d, C5), 117.0 (s, C4a), 116.9 (d, C6), 113.0 (d, C8), 69.4 (d, C2), 35.5 (t, CH$_2$), 26.0 (t, CH$_2$), 21.6 (t, CH$_2$), 13.1 (q, CH$_3$), 11.2 (q, SCH$_3$); EI-MS: m/z (%) = 234 (M$^+$, 3), 190 (12), 177 (100), 147 (22), 129 (12), 118 (11), 102 (12), 77 (8), 41 (18); CI-MS: m/z (%) = 235 (MH$^+$, 100), 205 (69), 203 (39), 189 (25), 187 (41); HRMS: m/z calcd for $C_{13}H_{19}N_2S$ (MH$^+$), 235.1263; found, 235.1263.

4.2.2 2-*tert*-Butyl-4-(methythio)-1,2-dihydroquinazoline (12). Mp: 31–32 °C; ^{1}H NMR (CDCl$_3$) δ (ppm): 7.30 (dd, $J = 8$, 1 Hz, 1H, H5), 7.08 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.58 (app. dt, $J = 1$, 8 Hz 1H, H6), 6.44 (dd, $J = 8$, 1 Hz, 1H, H8), 4.45 (s, 1H, H2), 3.88 (br s, exch., 1H, NH), 2.33 (s, 3H, CH$_3$), 0.97 [s, 9H, C(CH$_3$)$_3$]; ^{13}C NMR (CDCl$_3$) δ (ppm): 160.6 (s, C4), 144.5 (s, C8a), 131.3 (d, C7), 123.9 (d, C5), 116.6 (d, C6), 116.2 (s, C4a), 112.5 (d, C8), 77.2 (d, C2), 35.2 [s, *C*(CH$_3$)$_3$], 24.3 [q, C(*C*H$_3$)$_3$], 11.1 (q, SCH$_3$); EI-MS: m/z (%) = 234 (M$^+$, 4), 190 (14), 177 (100), 161 (20), 144 (21), 129 (12), 118 (16), 102 (17), 77 (8), 41 (20); CI-MS: m/z (%) = 235 (MH$^+$, 100), 189 (25), 187 (41), 177 (18), 147 (11), 131 (18); HRMS: m/z calcd for $C_{13}H_{19}N_2S$ (MH$^+$), 235.1263; found, 235.1262.

4.2.3 2-Methyl-4-(methylthio)-1,2-dihydroquinazoline (13). Mp: 70–71 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.37 (dd, $J = 8$, 1 Hz, 1H, H5), 7.11 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.63 (app. dt, $J = 1$, 8 Hz, 1H, H6), 6.48 (br d, $J = 8$ Hz, 1H, H8), 4.90 (q, $J = 6$ Hz, 1H, H2), 3.91 (br s, exch., 1H, NH), 2.34 (s, 3H, SCH_3), 1.42 (d, $J = 6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 163.2 (s, C4), 145.3 (s, C8a), 132.9 (d, C7), 125.7 (d, C5), 118.6 (d, C6), 118.4 (s, C4a), 114.5 (d, C8), 67.0 (d, C2), 23.7 (q, CH_3), 12.7 (q, SCH_3); EI-MS: m/z (%) = 192 (M^+, 12), 190 (10), 177 (100), 145 (22), 118 (14), 102 (21), 76 (15); CI-MS: m/z (%) = 193 (MH^+, 100), 177 (17), 147 (30), 145 (41); HRMS: m/z calcd for $C_{10}N_{13}N_2S$ (MH^+), 193.0794; found, 193.0794.

4.2.4 2-Butyl-4-(ethylthio)-1,2-dihydroquinazoline (14). Mp: 136–38 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32 (dd, $J = 8$, 1 Hz, 1H, H5), 7.05 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.57 (app. dt, $J = 1$, 8 Hz, 1H, H6), 6.42 (dd, $J = 8$, 1 Hz, 1H, H8), 4.72 (t, $J = 6$ Hz, 1H, H2), 3.92 (br s, exch., 1H, NH), 2.95 (q, $J = 7$ Hz, 2H, SCH_2), 1.73–1.60 (m, 2H, CH_2), 1.45–1.26 (m, 4H, $2CH_2$), 1.24 (t, $J = 7$ Hz, 3H, SCH_2CH_3), 0.83 (t, $J = 6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 162.1 (s, C4), 145.4 (s, C8a), 132.8 (d, C7), 125.7 (d, C5), 118.5 (s, C4a), 118.3 (d, C6), 114.4 (d, C8), 70.8 (d, C2), 37.0 (t, CH_2), 27.5 (t, CH_2), 23.9 (t, CH_2), 23.1 (t, SCH_2), 14.7 (q, CH_3), 14.5 (q, CH_3); EI-MS: m/z (%) = 248 (M^+, 2), 217 (29), 204 (40), 191 (100), 163 (79), 161 (41), 147 (80), 129 (38), 102 (35), 92 (24), 77 (21), 65 (20), 41 (53); CI-MS: m/z (%) = 249 (MH^+, 100), 247 (30), 222 (12), 219 (22), 205 (31), 189 (22); HRMS: m/z calcd for $C_{14}H_{21}N_2S$ (MH^+), 249.1420; found, 249.1421.

4.2.5 2-*tert*-Butyl-4-(ethylthio)-1,2-dihydroquinazoline (15). 175–177 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.27 (dd, $J = 8$, 1 Hz, 1H, H5), 7.02 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.53 (app. dt, $J = 1$, 8 Hz 1H, H6), 6.39 (dd, $J = 8$, 1 Hz, 1H, H8), 4.37 (s, 1H, H2), 3.87 (br s, exch., 1H, NH), 3.00–2.85 (m, 2H, CH_2), 1.24 (t, $J = 7$ Hz, 3H, CH_3), 0.94 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ (ppm): 161.6 (s, C4), 146.1 (s, C8a), 132.7 (d, C7), 125.4 (d, C5), 118.1 (d, C6), 117.8 (s, C4a), 114.1 (d, C8), 78.6 (d, C2), 36.5 [s, $C(CH_3)_3$], 25.8 [q, $C(CH_3)_3$], 23.8 (t, CH_2), 15.1 (q, CH_3); EI-MS: m/z (%) = 248 (M^+, 2), 217 (9), 191 (95), 163 (64), 147 (73), 129 (40), 118 (29), 103 (21), 92 (22), 77 (25), 65 (37), 57 (83), 41 (100); CI-MS: m/z (%) = 249 (MH^+, 100), 247 (54), 205 (50), 191 (20), 189 (18); HRMS: m/z calcd for $C_{14}H_{21}N_2S$ (MH^+), 249.1420; found, 249.1419.

4.2.6 2-Butyl-4-methoxy-1,2-dihydroquinazoline (16). Oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.34 (dd, $J = 8$, 1 Hz, 1H, H5), 7.04 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.53 (app. dt, $J = 1$, 8 Hz, 1 H, H6), 6.37 (dd, $J = 8$, 1 Hz, 1H, H8), 4.83 (t, $J = 6$ Hz, 1H, H2), 3.92 (br s, exch., 1H, NH), 3.69 (s, 3H, OCH_3), 1.64–1.59 (m, 2H, CH_2), 1.33–1.21 (m, 4H, 2 CH_2), 0.81 (t, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 159.4 (s, C4), 147.6 (s, C8a), 132.9 (d, C7), 125.5 (d, C5), 118.0 (d, C6), 113.8 (d, C8), 113.2 (s, C4a), 69.6 (d, C2), 52.9 (q, OCH_3), 38.0 (t, CH_2), 27.4 (t, CH_2), 23.1 (t, CH_2), 14.5 (q, CH_3); EI-MS: m/z (%) = 218 (M^+, 14), 187 (20), 174 (41), 162 (52), 161 (100), 147 (81), 130 (24), 120 (57), 103 (25), 92 (64), 65 (23), 41 (55); ESI-MS: m/z (%) = 219 (MH^+, 100), 217 (49), 205 (9), 161 (18); HRMS: m/z calcd for $C_{13}H_{19}N_2O$ (MH^+), 219.1492; found, 219.1490.

4.2.7 2-*tert*-Butyl-4-methoxy-1,2-dihydroquinazoline (17). Oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32 (dd, $J = 8$, 1 Hz, 1H, H5), 7.03 (app. dt, $J = 1$, 8 Hz, 1H, H7), 6.52 (app. dt, $J = 1$, 8 Hz, 1H, H6), 6.38 (br d, $J = 8$ Hz, 1H, H8), 4.60 (s, 1H, H2), 3.89 (br s, exch., 1H, NH), 3.71 (s, 3H, OCH_3), 0.90 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ (ppm): 158.7 (s, C4), 148.2 (s, C8a), 132.9 (d, C7), 125.2 (d, C5), 117.5 (d, C6), 113.2 (d, C8), 112.4 (s, C4a), 77.5 (d, C2), 52.8 (q, OCH_3), 37.2 [s, $\mathit{C}(CH_3)_3$], 25.5 [q, $C(\mathit{C}H_3)_3$]; EI-MS: m/z (%) = 218 (M^+, 2), 201 (10), 161 (100), 120 (18), 92 (16), 40 (23); ESI-MS: m/z (%) = 219 (MH^+, 100), 217 (29), 161 (39); HRMS: m/z calcd for $C_{13}H_{19}N_2O$ (MH^+), 219.1492; found, 219.1491.

4.2.8 4-Methoxy-2-methyl-1,2-dihydroquinazoline (18). Oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.36 (dd, J = 8, 1 Hz, 1H, H5), 7.06 (app. dt, J = 1, 8 Hz, 1H, H7), 6.57 (app. dt, J = 1, 8 Hz, 1H, H6), 6.41 (dd, J = 8, 1 Hz, 1H, H8), 4.99 (q, J = 6 Hz, 1H, H2), 3.99 (br s, exch., 1H, NH), 3.71 (s, 3H, OCH_3), 1.35 (d, J = 6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 159.8 (s, C4), 147.7 (s, C8a), 133.0 (d, C7), 125.6 (d, C5), 118.2 (d, C6), 113.9 (d, C8), 113.2 (s, C4a), 65.8 (d, C2), 53.1 (q, OCH_3), 15.9 (q, CH_3); EI-MS: m/z (%) = 176 (M^+, 64), 174 (33), 162 (60), 161 (100), 145 (31), 130 (41), 120 (88), 103 (55), 92 (86), 76 (39), 65 (52), 56 (54), 42 (52); CI-MS: m/z (%) = 177 (MH^+, 100), 175 (52), 161 (6), 145 (7); HRMS: m/z calcd for $C_{10}H_{13}N_2O$ (MH^+), 177.1022; found, 177.1021.

4.2.9 2-*tert*-Butyl-1,2-dihydro-3*H*-quinazolin-4-one (19). Mp 203–204 °C; ^{1}H NMR (DMSO-d$_6$) δ (ppm): 7.63 (dd, J = 8, 1 Hz, 1H, H5), 7.13 (app. dt, J = 1, 8 Hz, 1H, H7), 7.11 (d, J = 2 Hz, exch., 1H, NH), 6.70 (br d, J = 8 Hz, 1H, H8), 6.57 (app. dt, J = 1, 8 Hz, 1H, H6), 5.75 (br s, exch., 1H, NH), 4.41 (d, J = 2 Hz, 1H, H2), 0.91 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR (DMSO-d_6) δ (ppm): 164.9 (s, C4), 148.3 (s, C8a), 133.4 (d, C7), 127.5 (d, C5), 116.9 (d, C6), 114.2 (s, C4a), 114.0 (d, C8), 73.0 (d, C2), 36.8 [s, $\mathit{C}(CH_3)_3$], 24.5 [q, $C(\mathit{C}H_3)_3$]; EI-MS: m/z (%) = 204 (M^+, 1), 147 (34), 92 (14), 57 (78), 41 (100); CI-MS: m/z (%) = 205 (MH^+, 100), 203 (48), 164 (9), 147 (22); HRMS: m/z calcd for $C_{12}H_{17}N_2O$ (MH^+), 205.1335; found, 205.1335.

4.3 *4,4-Dialkyl-2-phenyl-3,4-dihydroquinazolines (22–24); general procedure*

A solution of alkyllithium (4.4 mmol) was added to a cold (−78 °C), stirred solution of **20** or **21** (2.0 mmol) in anhydrous THF (10 mL) under N_2. The reaction mixture was stirred at −78 °C for 1 h then removed from the cooling bath and allowed to warm to r.t., diluted with Et_2O (10 mL), then quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; Et_2O-hexane, 1:4) to give the pure product **22**, **23** or **24**.

4.3.1 4,4-Dibutyl-2-phenyl-3,4-dihydroquinazoline (22). Mp: 161 °C (lit. 154–155 °C [19]); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.87–7.85 (m, 2H, ArH), 7.51–7.45 (m, 3H, ArH), 7.29–7.21 (m, 2H, ArH), 7.08–7.06 (m, 2H, ArH), 4.94 (br s, exch., 1H, NH), 1.95 [app. dt, J = 4, 13 Hz, 2H, $(CH_aH_b)_2$], 1.63 [m, 2H, $(CH_aH_b)_2$], 1.41 [m, 2H, $(CH_cH_d)_2$], 1.33–1.18 [m, 6H, $(CH_cH_d)_2 + 2CH_2$], 0.85 (t, J = 7 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 154.0 (s, C2), 142.1 (s, C8a), 136.2 (s, C1 of Ph), 130.9 (d, C4 of Ph), 129.1 (d, C3 of Ph), 128.1 (d, C5), 126.9 (d, C7), 126.8 (d, C2 of Ph), 124.9 (d, C6), 124.9 (d, C8), 124.3 (s, C4a), 59.9 (s, C4), 45.4 (t, CH_2), 26.6 (t, CH_2), 23.4 (t, CH_2), 14.4 (q, CH_3); EI-MS: m/z (%) = 320 (M^+, 2), 263 (100), 220 (18), 117 (8); CI-MS: m/z (%) = 321 (MH^+, 100), 263 (46); HRMS: m/z calcd for $C_{22}H_{29}N_2$ (MH^+), 321.2325; found, 321.2330.

4.3.2 4,4-Dimethyl-2-phenyl-3,4-dihydroquinazoline (23). Mp: 100–101 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74–7.42 (m, 2H, ArH), 7.38–7.32 (m, 3H, ArH), 7.17–7.12 (m, 2H, ArH), 7.09–6.98 (m, 2H, ArH), 4.65 (br s, exch., 1H, NH), 1.51 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 154.1 (s, C2), 141.9 (s, C8a), 136.1 (s, C1 of Ph), 131.0 (d, C4 of Ph), 130.8 (s, C4a), 129.0 (d, C3 of Ph), 128.3 (d, C5), 127.1 (d, C2 of Ph), 125.2 (d, C7), 124.4 (d, C6), 123.5 (d, C8), 53.3 (s, C4), 32.2 (q, CH_3); CI-MS: m/z (%) $=$ 237 (MH^+, 100), 221 (13); HRMS: m/z calcd for $C_{16}H_{17}N_2$ (MH^+), 237.1386; found, 237.1385.

4.3.3 4,4-Di-*tert*-butyl-2-phenyl-3,4-dihydroquinazoline (24). Oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.81–7.79 (m, 2H, ArH), 7.45–7.39 (m, 4H, ArH), 7.18–6.90 (m, 3H, ArH), 5.60 (br s, exch., 1H, NH), 1.12 [s, 18H, $2C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ (ppm): 154.0 (s, C2), 144.5 (s, C8a), 136.1 (s, C1 of Ph), 131.0 (d, C4 of Ph), 129.0 (d, C3 of Ph), 128.6 (d, C5), 126.9 (d, C7), 126.5 (d, C2 of Ph), 125.9 (d, C6), 125.7 (d, C8), 122.9 (s, C4a), 67.6 (s, C4), 45.3 [s, $\mathit{C}(CH_3)_3$], 30.1 [q, $C(\mathit{C}H_3)_3$]; EI-MS: m/z (%) $=$ 320 (M^+, 1), 263 (71), 247 (22), 233 (18), 220 (15), 205 (13), 180 (10), 160 (12), 104 (15), 77 (32), 57 (100), 41 (88); CI-MS: m/z (%) $=$ 321 (MH^+, 100), 263 (43); HRMS: m/z calcd for $C_{22}H_{29}N_2$ (MH^+), 321.2325; found, 321.2325.

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