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SYNTHESIS OF SUBSTITUTED QUINAZOLIN-4(3*H*)-ONES AND QUINAZOLINES *VIA* DIRECTED LITHIATION

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Abstract - Various quinazolin-4(3*H*)-ones and quinazolines were successfully lithiated using different lithiating reagents at low temperatures. Reactions of lithio reagents thus obtained with a variety of electrophiles afforded the corresponding substituted derivatives in very good yields.

CONTENTS

1. INTRODUCTION

Compounds possessing quinazolin-4(3*H*)-one ring system show a variety of biological activities,[1] which provides additional impetus for the development of new synthetic approaches to substituted quinazolin-4(3*H*)-one derivatives. The use of directing groups to facilitate lithiation followed by reaction of the organolithium reagents thus obtained with various electrophiles had found wide application in a variety of synthetic transformations.[2-4] In particular, the pivaloylamino group is useful for directed *oath*-lithiation of aromatic compounds and had been applied to pyridine derivatives.[5,6] However there are relatively few examples of the use of such groups for directed lithiation of more complicated heterocycles.[7] Lithiation reactions can be applied to diaza heterocycles to produce various derivatives.[8] The rapid expansion of the list of functionalities capable of directing lithiation[9] had made this reaction a very important strategy for the synthesis of regiospecifically substituted benzenes and pyrimidines.[10-20]

The addition of organolithium compounds to the C=N bond of pyridine and related nitrogen heterocycles is a well-established reaction.[21-24] In particular, organolithium reagents undergo 1,2-addition to pyridine and quinoline.[25] In some cases addition is followed by electrophilic addition at position 5 of pyridine to give 2,5-disubstituted 2,5-dihydropyridines,[26,27] which are known to be unstable. Such attack on pyridine or quinoline compounds sometimes causes ring-opening,[28] giving substituted butadienes,[29] which can cyclise again.[30] Butyllithium also undergoes exclusive addition to some fluoroquinolines, but in the case of 2-fluoro- and 7-fluoroquinolines competitive lithiation takes place at positions 3 and 8, respectively.[31] However, these reactions become completely chemoselective for lithiation by use of lithium diisopropylamide (LDA) at low temperature. The high reactivity of diazines towards nucleophiles makes the lithiation of these compounds even more difficult than that of most heterocylic compounds. However, successful lithiation of diazines in recent years had been achieved by the use of less nucleophilic lithium dialkylamides such as LDA or LTMP (lithium 2,2,6,6-tetramethylpiperidide).[32,33]

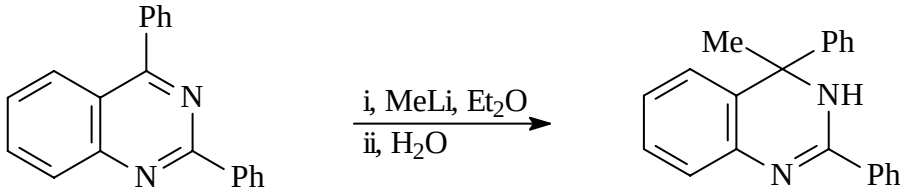
As part of our containing interest in quinazolin-4(3*H*)-ones chemistry[34-39] and in lithiation chemistry,[40-43] we have shown that quinazolin-4(3*H*)-ones undergo double lithiation by use of *n*-BuLi or LDA in THF at –78 °C.[44-47] The organolithiums thus obtained in such lithiation reactions are very useful intermediates for the synthesis of more complex substituted quinazolin-4(3*H*)-ones.[44-47] In the last few years lithiation of quinazolin-4(3*H*)-ones becomes the topic for some researchers which provide a simple and efficient

method for the production of substituted derivatives which might have high pharmacological activities and difficult to be prepared by other means. This review will concentrate on the work published in this area, particularly on directed lithiation of various quinazoline derivatives, quinazolin-4(3*H*)-ones, 3-aryl-quinazolin-4(3*H*)-ones, 3-acylaminoquinazolin-4(3*H*)-ones, 2-alkylquinazolin-4(3*H*)-ones, 3-substituted 2-methylquinazolin-4(3*H*)-ones, 2-alkyl-3-aminoquinazolin-4(3*H*)-ones, 2-alkyl-3-methylaminoquinazo-lin-4(3*H*)-ones as well as directed lithiation of 3-acylamino-2-alkylquinazolin-4(3*H*)-ones.

2. DIRECTED LITHIATION OF RING CARBON ON QUINAZOLINES

2.1. LITHIATION OF SUBSTITUTED QUINAZOLINES

Reaction of 1,3-diphenylquinazoline (**1**) with methyllithium in ether afforded the corresponding addition product (**2**) (Scheme 1) in 55% yield in which methyllithium was added to the imine bond.[48]

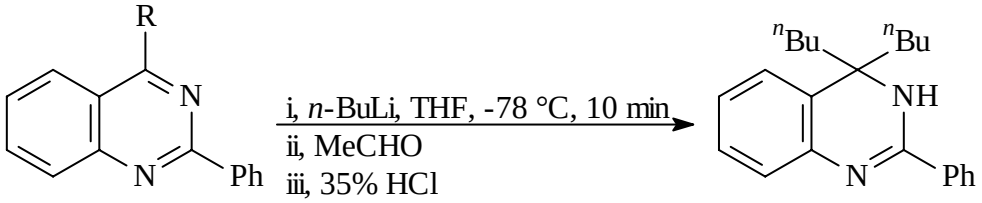


1 **2** (55%)

Scheme 1

Similarly reaction of 4-methoxy-2-phenylquinazoline (**3**) with *n*-BuLi (1.1 equivalents) in THF at –78 °C for 10 min, followed by reaction with acetaldehyde gave the addition product (**5**) in 50% yield (Scheme 2).[49] The author assumed that a nucleophilic attack by *n*-BuLi occurred first at C-4, followed by elimination reaction led to 4-butyl-2-phenylquinazoline. This compound underwent a nucleophilic addition to give **5**.[49] When an excess of *n*-BuLi (4 equivalents) was used, compound (**5)** was obtained in even better yield (86%).[49] The site of lithiation did not influenced when the methoxy group was replaced by a more complexing group as the methoxyethoxy group.[49] It was found that reaction of 4-(2-methoxyethoxy)-2-phenylquinazoline (**4**) with *n*-BuLi (2.2 equivalents) under the same reaction condition used for **3** led to the addition product (**5**) in 50% yield (Scheme 2).[49] It was noticed that the

methoxy group did not induce the regioselective lithiation as it was for 1-methoxynaphthalene[50] but rather by the ring nitrogen atom. Lithiation *peri* to the nitrogen have been reported in lithiation of 4-pivaloylaminoquinoline[51] and 4-chlorocinnoline.[52]

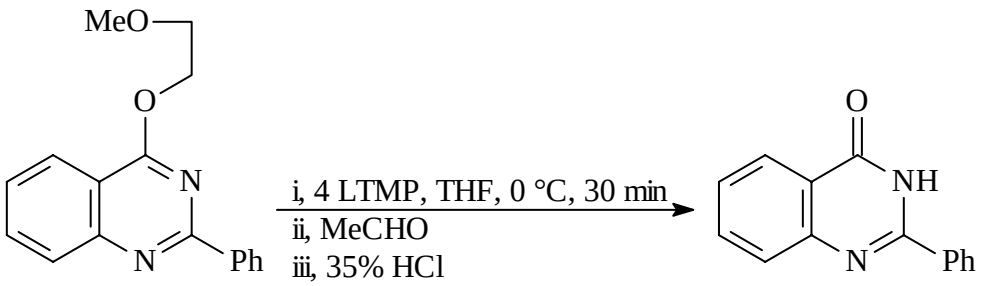


3, R = OMe
4, R = $O(CH_2)_2OMe$

5

Scheme 2

Lithiation of **4** was not successful when LTMP was used as a lithiating reagent in which 2-phenyl-quinazolin-4(3*H*)-one (**6**) (Scheme 3) was obtained in 67% yield with recovery of the starting material (23%).[49]

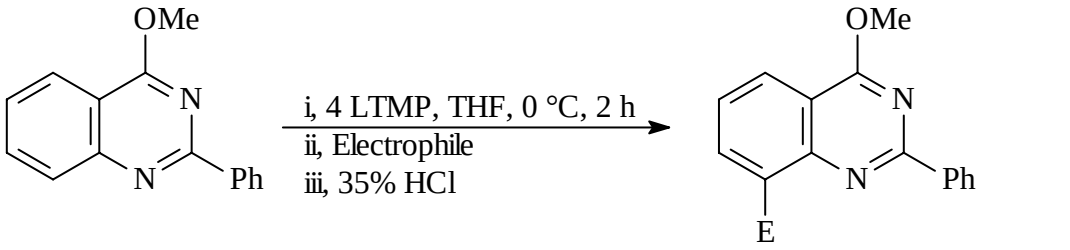


4

6 (67%)

Scheme 3

However, successful lithiation of **3** was achieved by use of less nucleophilic lithiating reagent (LTMP).[49] Lithiation of **3** took place at C-4 by use of excess LTMP (4 equivalents) in THF at 0 °C for 30 min.[49] Reaction of lithio reagent thus obtained with acetaldehyde and trimethylsilyl chloride afforded the corresponding 8-substituted derivatives (**7**) and (**8**) in 56 and 94% yields, respectively (Scheme 4).[49]

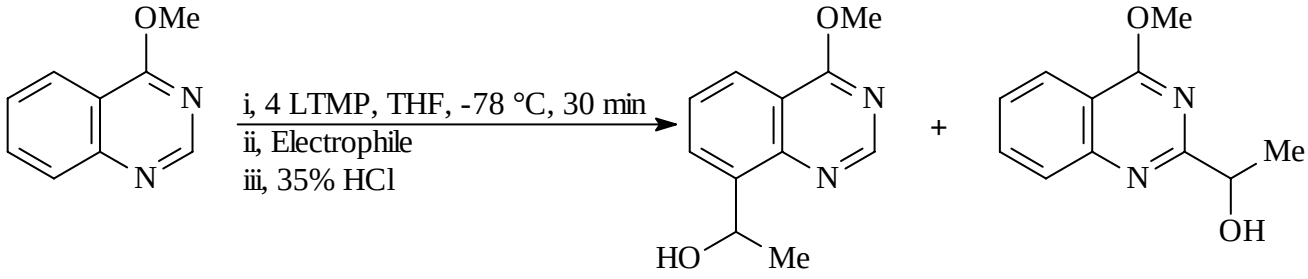


3

7, E = MeCH(OH) (56%)
8, E = $SiMe_3$ (94%)

Scheme 4

Lithiation of 4-methoxyquinazoline (**9**) with LTMP in THF at –78 °C for 30 min, followed by reaction of the lithio reagent thus obtained with acetaldehyde afforded a mixture of the corresponding secondary alcohols (**10**) and (**11**) in 34 and 66% yields, respectively (Scheme 5).[49] Lithiation took place at C-8 to produce compound (**10**) and at C-2 to produce compound (**11**).[49]



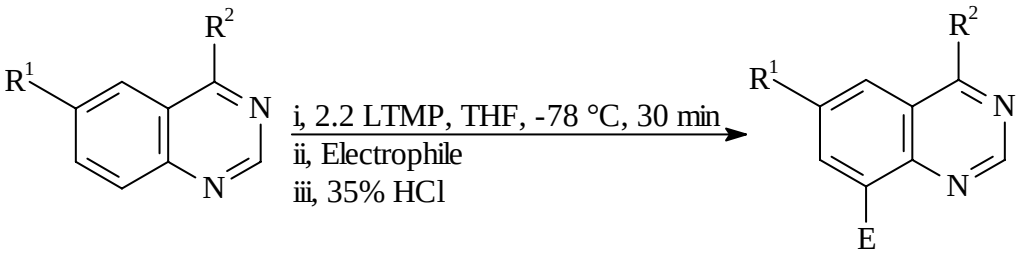
9

10 (34%)

11 (66%)

Scheme 5

Lithiation of 4,6-disbstituted quinazolines (**12-15**) by LTMP (2.2 equivalents) in THF at –78 °C for 30 min, followed by reaction of the lithio reagents thus obtained with some electrophiles (acetaldehyde, benzaldehyde, iodine, trimethylsilane) afforded the corresponding 8-substituted quinazolines (**16-23**) (Scheme 6) in moderate yields (Table 1).[49]



12-15

16-23

Scheme 6

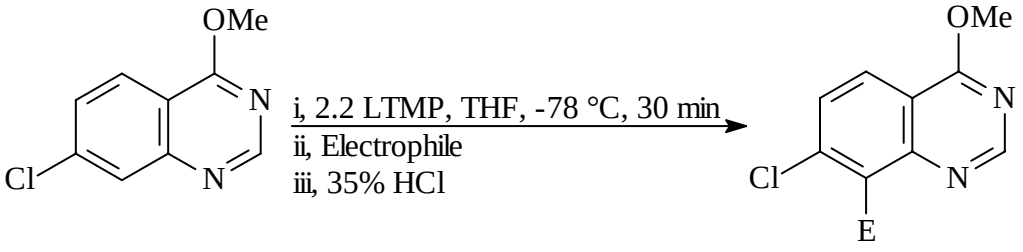
Table 1: Synthesis of 8-substituted quinazolines (**16-23**) from reactions of the lithio reagents of compounds (**12-15**) with electrophiles[49]

Product	R^1	R^2	Electrophile	E	Yields (%)
16	OMe	OMe	MeCHO	MeCH(OH)	54[a]
17	Cl	OMe	MeCHO	MeCH(OH)	50
18	Cl	$O(CH_2)_2OMe$	MeCHO	MeCH(OH)	29
19	Cl	NEt_2	MeCHO	MeCH(OH)	55[b]
20	Cl	OMe	MeCHO	MeCH(OH)	50
21	Cl	OMe	PhCHO	PhCH(OH)	19
22	Cl	OMe	I_2	I	25
23	Cl	OMe	Me_3SiCl	Me_3Si	35[c]

[a] 7-Carbinol was obtained in 39% yield. [b] A 15% of starting material was recovered.
[c] Obtained with the *in situ* trapping technique.

In the case of 4,6-dimethoxyquinazoline (**12**), lithiation took place at C-8, *peri* to the ring N-1 nitrogen atom to give the corresponding lithio reagent which, on reaction with acetaldehyde afforded 8-substituted derivative (**16**) in 54% yield and at C-7, *ortho* to the methoxy group to give 7-substituted quinazoline derivative in 39% yield.[49] Regioselective lithiation of 6-chloro-4-substituted quinazolines (**13-15**) occurred at C-8.[49]

Lithiation of 7-chloro-4-methoxyquinazoline (**24**) with 2.2 LTMP in THF at –78 °C for 30 min had taken place at C-8.[49] Reaction of lithio reagent thus obtained with various electrophiles (acetaldehyde, benzaldehyde, iodomethane, iodine, trimethylsilyl chloride) afforded the corresponding 8-substituted quinazolines (**25-29**) (Scheme 7) in better yields than for **15** (Table 2).[49] When iodomethane was used as electrophile, 7-chloro-8-ethyl-4-methoxyquinazoline was obtained in 8% yield as a result of a further lithiation on methyl group of the product (**27**).[49]



24 **25-29**

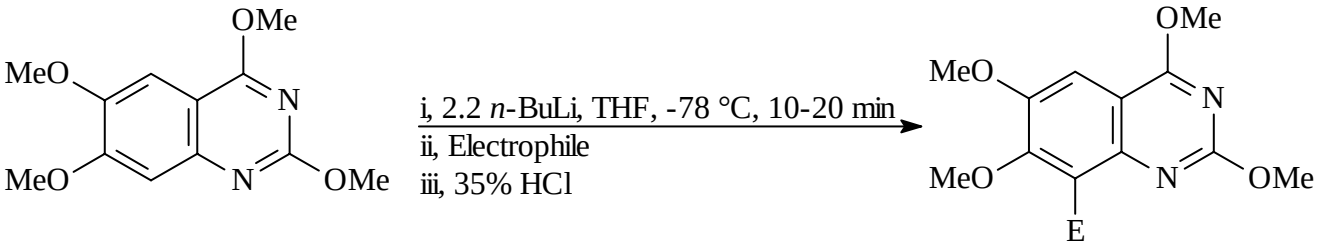
Scheme 7

Table 2: Synthesis of 8-substituted quinazolines (**25-29**) from reactions of the lithio reagent of compound (**24**) with electrophiles[49]

Product	Electrophile	E	Yields (%)
25	MeCHO	MeCH(OH)	85
26	PhCHO	PhCH(OH)	73
27	MeI	Me	40[a]
28	I_2	I	32[a,b]
29	Me_3SiCl	Me_3Si	40[a,c]

[a] Starting material was recovered. [b] Carried out by use of 1.2 LTMP. [c] Obtained with the *in situ* trapping technique.

Lithiation of 2,4,6,7-tetramethoxyquinazoline (**30**) with LTMP as lithiating reagent in THF at –78 °C, followed by reaction with acetaldehyde afforded the corresponding 8-substituted product (**31**) in 85% yield.[49] However, it was found that compound (**30**) is less sensitive to nucleophilic addition by lithiating reagent.[49] Lithiation of **30** with *n*-BuLi (2.2 equivalents) in THF at –78 °C occurred rapidly and smoothly at C-8 (Scheme 8).[49] Reaction of the lithio reagent thus obtained with a variety of electrophiles (acetaldehyde, EtOD/DCl, benzaldehyde, iodomethane, iodine, hexachloroethane) afforded the corresponding 8-substituted quinazolines (**31-36**) (Scheme 8) in good yields (Table 3).[49]



30 **31-36**

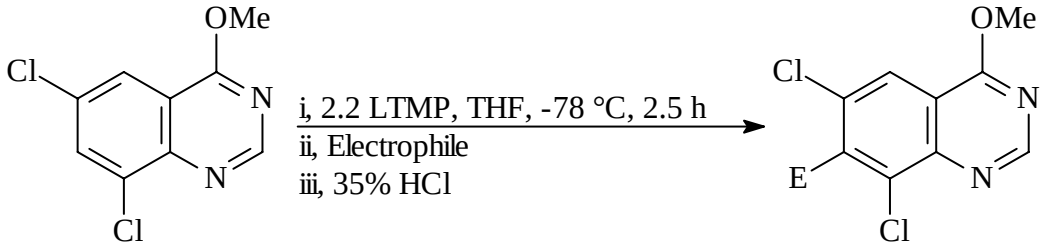
Scheme 8

Table 3: Synthesis of 8-substituted quinazolines (**31-36**) from reactions of the lithio reagent of compound (**30**) with electrophiles[49]

Product	Electrophile	E	Yields (%)
31	MeCHO	MeCH(OH)	97
32	EtOD/DCl	D	96
33	PhCHO	PhCH(OH)	99
34	MeI	Me	51[a]
35	I_2	I	89[a]
36	C_2Cl_6	Cl	90[a]

[a] Starting material was recovered.

Lithiation of 6,8-dichloro-4-methoxyquinazoline (**37**) with LTMP (2.2 equivalents) in THF at –78 °C, followed by reaction with a range of elctrophiles (EtOD/DCl, acetaldehyde, benzaldehyde, iodomethane, iodine, hexachloroethane) afforded the corresponding 7-substituted quinazoline derivatives (**38-43**) (Scheme 9) in very good yields (Table 4).[49]



37 **38-43**

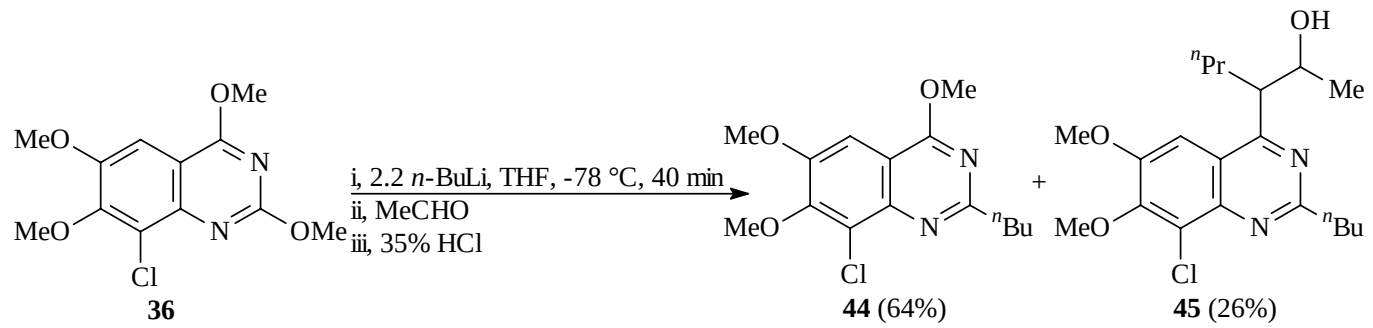
Scheme 9

Table 4: Synthesis of 7-substituted quinazolines (**38-43**) from reactions of the lithio reagent of compound (**37**) with electrophiles[49]

Product	Electrophile	E	Yields (%)
38	EtOD/DCl	D	88[a]
39	MeCHO	MeCH(OH)	99[a]
40	PhCHO	PhCH(OH)	92[a]
41	MeI	Me	93
42	I_2	I	90
43	C_2Cl_6	Cl	88[b]

[a] Starting material was recovered. [b] Obtained with the *in situ* trapping technique.

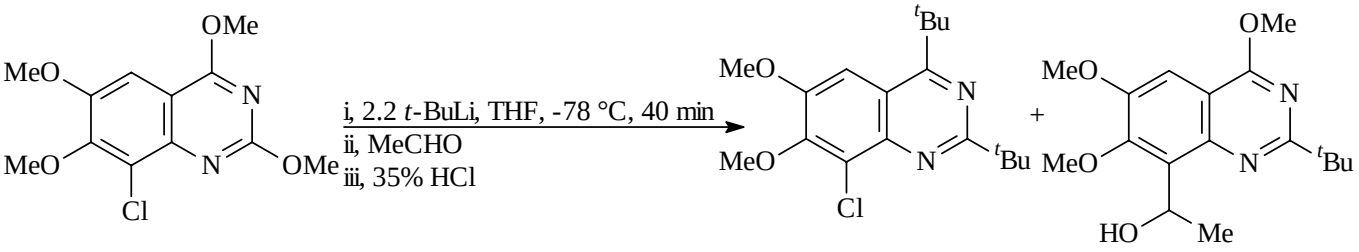
Lithiation of 8-chloro-2,4,6,7-tetramethoxyquinazoline (**36**) with LTMP was not successful under different reaction coditions.[49] However, successful lithiation of **36** was achieved by use of 2 equivalents of *n*-BuLi in THF at –78 °C. Reaction of lithio reagent thus obtained with acetaldehyde gave a mixture of **44** and **45** in overall 90% yield (Scheme 10).[49] Compound (**44**) was obtained in 64% yield in which one of the methoxy group of pyrimidine moiety was substituted by a butyl group from *n*-BuLi.[49] Compound (**45**) was obtained in 26% yield in which the two methoxy groups of pyrimidine moiety were substituted by butyl groups from *n*-BuLi then one of them was lithiated at α-carbon.[49] Reaction of the lithio reagent thus obtained with acetaldehyde afforded compound (**45**) (Scheme 10).[49]



36 **44** (64%) **45** (26%)

Scheme 10

However, lithiation of **36** with 2 equivalents of *t*-BuLi in THF at –78 °C for 40 min followed by reaction with acetaldehyde gave a mixture of **46** and **47** (Scheme 11).[49] Compound (**46**) was obtained in 32% yield in which two methoxy groups of pyrimidine moiety was replaced by *t*-butyl groups.[49] Compound (**47**) was obtained in 39% yield in which one of the methoxy group of pyrimidine moiety was replaced by a *t*-butyl group and unexpected chlorine-lithium exchange took place to give lithio derivative that react with acetaldehyde to give rise to compound (**47**) (Scheme 11).[49]



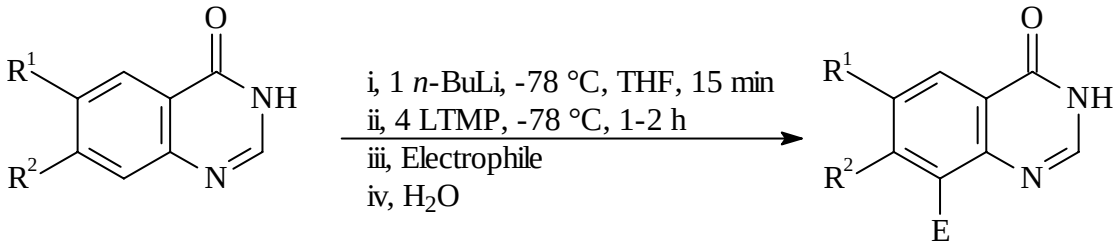
36 **46** (32%) **47** (39%)

Scheme 11

2.2. LITHIATION OF SUBSTITUTED QUINAZOLIN-4(3*H*)-ONES

Various attempts were made to lithiate 6,8-dichloroquinazolin-4(3*H*)-one.[53] However, none of these conditions was successful, in which a starting material or degraded product was obtained.[53] On the other hand, lithiation of 7-chloroquinazolin-4(3*H*)-one (**48**) and 6,7-dimethoxyquinazolin-4(3*H*)-one (**49**) took place at C-8 by means of *n*-BuLi (1 equivalent) followed by addition of excess LTMP (4 equivalents) for 1 h at –78 °C (Scheme 12).[53] Reactions of lithio reagents thus obtained with acetaldehyde and

benzaldehyde afforded the corresponding alcohols (**50-53**) along with a small amount of starting material (Table 5).[53]



48, R^1 = H, R^2 = Cl
49, R^1 = R^2 = OMe

50-53

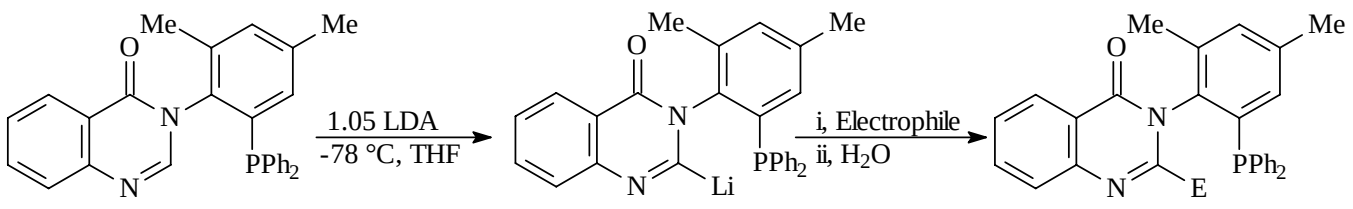
Scheme 12

Table 5: Synthesis of 8-substituted quinazolin-4(3*H*)-ones (**50-53**) from reactions of the lithio reagents of compounds (**48**) and (**49)** with electrophiles[53]

Product	R^1	R^2	Electrophile	E	Yields (%)
50	H	Cl	MeCHO	MeCH(OH)	73
51	H	Cl	PhCHO	PhCH(OH)	95
52	OMe	OMe	MeCHO	MeCH(OH)	50
53	OMe	OMe	PhCHO	PhCH(OH)	50

2.3. LITHIATION OF 3-ARYLQUINAZOLIN-4(3*H*)-ONES

Lithiation of 3-arylquinazolin-4(3*H*)-ones (**54**) took place rapidly by LDA in THF at –78 °C to give the corresponding 2-lithio reagent (**55**) (Scheme 13).[54] Reactions of **55** with representative electrophiles (chlorodiphenylphosphine, S_8, dimethyl disulfide) for 1 h at –78 °C afforded the corresponding 2-substituted derivatives (**56-58**) in good yields (Table 6).[54]



54 **55** **56-58**

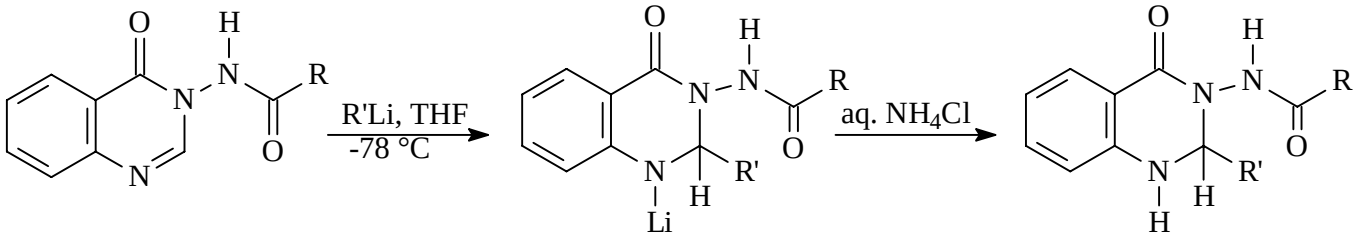
Scheme 13

Table 6: Synthesis of 2-substituted 3-arylquinazolin-4(3*H*)-ones (**56-58**) from reactions of the lithio reagent (**55**) with electrophiles[54]

Product	Electrophile	E	Yields (%)
56	PPh_2Cl	PPh_2	88
57	S_8	SH	84
58	$(MeS)_2$	SMe	88

2.4. LITHIATION OF 3-ACYLAMINOQUINAZOLIN-4(3*H*)-ONES

Attempted lithiation of 3-pivaloylaminoquinazolin-4(3*H*)-one (**59**) and 3-acetylaminoquinazolin-4(3*H*)-one (**60**) with alkyllithiums in THF at various reaction conditions was not successful. Instead of lithio derivatives being formed, a nucleophilic attack occurred at the imine bond of quinazolin-4(3*H*)-ones to give 1,2-addition products. The reactions of **59** and **60** with one equivalent of alkyllithium (*n*-BuLi, *t*-BuLi, MeLi) in THF at –78 °C were very fast and completed within 5 min to give 2-alkyl-1,2-dihydro-3-acylaminoquinazolin-4(3*H*)-ones (**62-67**) (Scheme 14) in good yields (Table 7).[44]



59, R = *t*-Bu
60, R = Me

R' = *n*-Bu, *t*-Bu, Me

61

62-67

Scheme 14

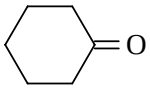
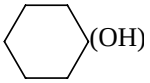
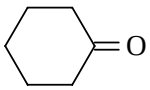
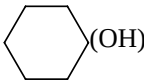
Table 7: Synthesis of 2-alkyl-1,2-dihydroquinazolin-4(3*H*)-ones (**62-67**)[44]

Product	R	R′	Yield (%)[a]
62	*t*-Bu	*n*-Bu	96
63	*t*-Bu	*t*-Bu	98
64	*t*-Bu	Me	90
65	Me	*n*-Bu	82
66	Me	*t*-Bu	84
67	Me	Me	70

[a] Yields reported are for purified materials.

However, chemoselective lithiation of 3-acylaminoquinazolin-4(3*H*)-ones (**59**) and (**60**) was achieved by use of LDA in THF at –78 °C and the reaction was regioselective at position 2. Two mole equivalents of LDA are necessary to be use, the first mole removed the NH proton and the second mole removed the hydrogen from position 2 to produce the dilithio derivatives (**68**) (Scheme 15). It is interesting that there is no lithiation occurred at the acetylamino methyl group in the case of compound (**60**) (R = Me), in view of the acidic character of the α-protons.[55] Such side reactions take place with simple acetanilides and account for the preferred use of the pivaloylamino group in directed lithiation reactions.[9] Reactions of the dilithio reagents (**68**) with a variety of electrophiles (benzophenone, iodomethane, D_2O, cyclohexanone, acetophenone, phenyl isocyanate) afforded the corresponding 2-substituted quinazolin-4(3*H*)-one derivatives (**69**-**84**) (Scheme 15) in good yields (Table 8).[44]

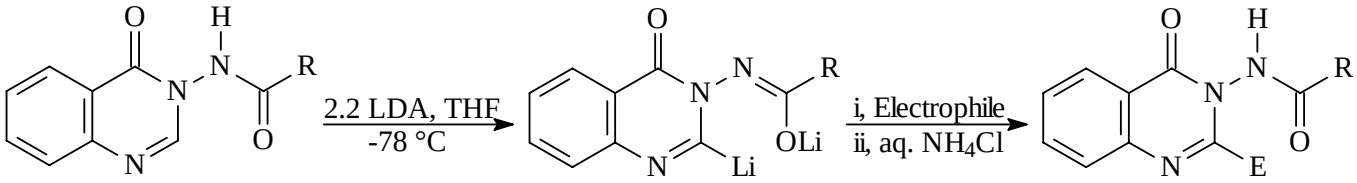
Table 8: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**69**-**84**) from reaction of dilithio reagents (**68**) with electrophiles[44]

Products	R	Electrophile	E	Yield (%)[a]
69	*t*-Bu	$(C_6H_5)_2CO$	$(C_6H_5)_2C(OH)$	85
70,71,72	*t*-Bu	MeI	Me, Et, *i*-Pr	89[b,c]
73	*t*-Bu	D_2O	D	88
74	*t*-Bu			87
75	*t*-Bu	C_6H_5COMe	$C_6H_5C(OH)(Me)$	85
76	*t*-Bu	C_6H_5NCO	C_6H_5NHCO	76
77	Me	$(C_6H_5)_2CO$	$(C_6H_5)_2C(OH)$	80
78,79,80	Me	MeI	Me, Et, *i*-Pr	92[b,d]
81	Me	D_2O	D	79
82	Me			81
83	Me	C_6H_5COMe	$C_6H_5C(OH)(Me)$	80
84	Me	C_6H_5NCO	C_6H_5NHCO	80

[a] Yields reported are for purified materials. [b] Overall yield obtained with MeI. [c] **70** (67%), **71** (16%), **72** (6%). [d] **78** (59%), **79** (28%), **80** (5%).

The reactions with excess iodomethane (4 equivalents) resulted in almost quantitative yields of alkylated products, but as mixtures of 2-methyl-, 2-ethyl- and 2-(1-methylethyl)quinazolin-4(3*H*)-one derivatives.[44] It appears, therefore, that the 2-methylquinazolin-4(3*H*)-ones initially produced undergo lithiation by the

excess LDA present in the reaction mixture, and then methylate by iodomethane to give the 2-ethylquinazolin-4(3*H*)-ones. These in turn react further to give the 2-(1-methylethyl) derivatives.[44]



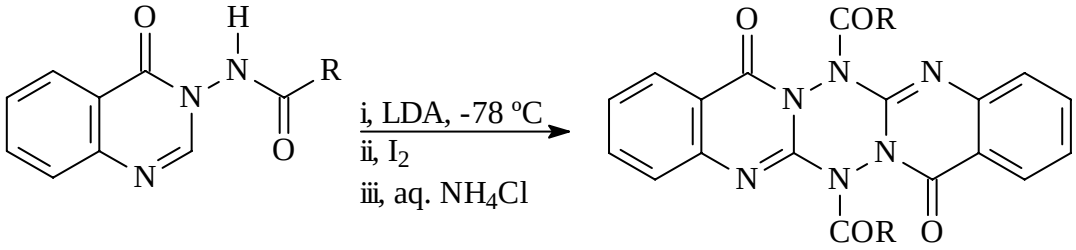
59, R = *t*-Bu
60, R = Me

68

69-84

Scheme 15

Reactions of the dilithio reagents of compounds (**59**) and (**60**) with iodine had taken place in different manner. Instead of 2-iodoquinazolin-4(3*H*)-one derivatives being formed, oxidative dimerization took place to give 6,13-dipivaloyl-1,2,4,5-tetrazino[3,2-*b*:6,5-*b'*]bisquinazolin-7,14(6*aH*,13*aH*)-dione (**85**) and 6,13-diacetyl-1,2,4,5-tetrazino[3,2-*b*:6,5-*b'*]bisquinazolin-7,14(6*aH*,13*aH*)-dione (**86**) in 67 and 66% yields, respectively (Scheme 16).[44]



59, R = *t*-Bu
60, R = Me

85, R = *t*-Bu (67%)
86, R = Me (66%)

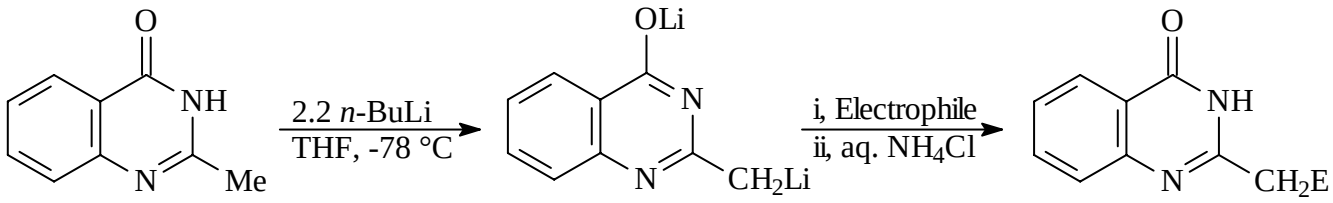
Scheme 16

3. LITHIATION OF ALKYL GROUPS ON QUINAZOLIN-4(3*H*)-ONES

3.1. LITHIATION OF 2-ALKYLQUINAZOLIN-4(3*H*)-ONES

It was found that double lithiation of 2-methylquinazolin-4(3*H*)-one (**87**) with 2.2 equivalents of *n*-BuLi at -78 °C in THF occurred smoothly and rapidly with no nucleophilic attack of *n*-BuLi at either the carbonyl or the imine group of the quinazolin-4(3*H*)-one ring.[45,56] Initial addition of *n*-BuLi gave

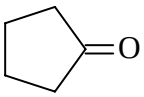
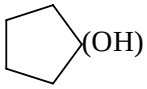
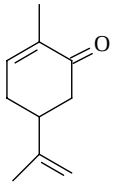
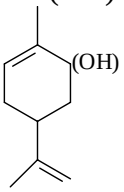
monolithio reagent as a reddish solution until approximately one equivalent had been added, then monolithio reagent converted to the dilithio reagent (**88**) as a very deep red solution when the remaining *n*-BuLi was added (Scheme 17).[45,56] The formation of the dilithio reagent (**88**) was confirmed by it reaction with a range of electrophiles (iodomethane, D_2O, phenyl isocyanate, benzaldehyde, benzophenone, cyclopentanone, 2-butanone, *R*-(-)-carvone, benzyl chloride, ethyl bromide, acetophenone) to afford the corresponding 2-substituted quinazolin-4(3*H*)-one derivatives (**89-99**) (Scheme 17).[45,56]



87 **88** **89-99**

Scheme 17

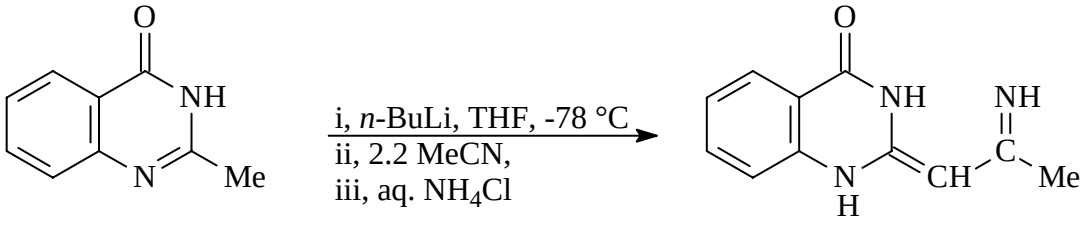
Table 9: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**89-99**) from the reactions of the dilithio reagent (**88)** with electrophiles[45,56]

Product	Electrophile	E	Yield (%)[a]
89	MeI	Me	89
90	D_2O	D	90
91	PhNCO	PhNHCO	80
92	PhCHO	PhCH(OH)	77
93	Ph_2CO	$Ph_2C(OH)$	79
94			81
95	EtCOMe	EtC(OH)Me	80
96			82[b]
97	$PhCH_2Cl$	$PhCH_2$	58
98	EtBr	Et	57
99	PhCOMe	PhC(OH)(Me)	63

[a] Yields reported are for purified materials. [b] ^{1}H- and ^{13}C-NMR spectra indicate a mixture of two diastereoisomers in a ratio 1:4.

As shown in Table 9 the yields of isolated and purified products were extremely good in most cases. There is no *N*-substitution was observed, even when excess iodomethane (3.3 equiv.) was used as electrophile.[45] ^{1}H and ^{13}C-NMR spectra of compound (**96**) showed the presence of a mixture of two diastereoisomers in unequal proportion.[45]

Reaction of the dilithio reagent of compound (**87**) with excess acetonitrile (two equivalents) proceeded in an interesting manner. Instead of 2-substituted derivative being formed, 2-(2-iminopropylidene)-1,2-dihydroquinazolin-4(3*H*)-one (**100**) was obtained in 72% yield (Scheme 18).[45] Presumably the unusual stability of compound (**100**) is a result of intramolecular hydrogen bonding.[45]



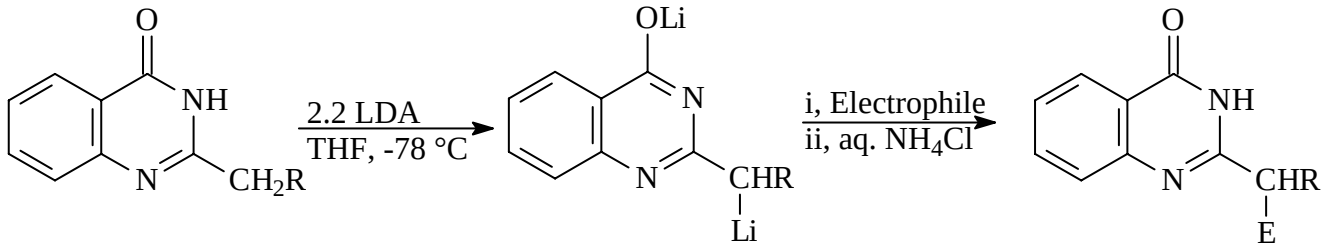
87 **100** (72%)

Scheme 18

It was found that lithiation of 2-ethylquinazolin-4(3*H*)-one (**89**) and 2-propylquinazolin-4(3*H*)-one (**101**) had taken place as lithiation of compound (**87**), which suggest that the process was tolerant for a variety of primary alkyl groups at position 2.[45] Attempted lithiation of **89** and **101** with *n*-BuLi gave only low yields of the products on reaction with a number of electrophiles (D_2O, Ph_2CO and MeI). However, successful lithiation was achieved with 2.2 equivalents of LDA in THF at -78 °C under nitrogen for 2 h.[45] Initial addition of LDA gave monolithio reagents as brownish yellow solutions when approximately one equivalent had been added and then monolithio reagents converted to the dilithio reagent (**102**) or (**103)** as red solutions when the remaining LDA was added (Scheme 19). Reactions of the dilithio reagents (**102**) and (**103**) with a range of electrophiles (iodomethane, D_2O, benzophenone, acetophenone, benzaldehyde, phenyl isocyanate) resulted in the production of the corresponding 2-substituted quinazolin-4(3*H*)-one derivatives (**104-114)** (Scheme 19) in very good yields as shown in Table 10.[45]

The ^{1}H- and ^{13}C-NMR spectra of **111-113** showed the expected presence of two racemic diastereoisomers in unequal proportions.[45] However, ^{1}H- and ^{13}C-NMR spectra of compound (**110**) indicated the presence of only one racemic diastereoisomer, which is clearly not expected when two

asymmetric centers are introduced during lithiation reaction. Similar observations have been made previously for 3-aminoquinazolin-4(3*H*)-one derivatives.[46]



87, R = Me
101, R = Et

102, R = Me
103, R = Et

104-114

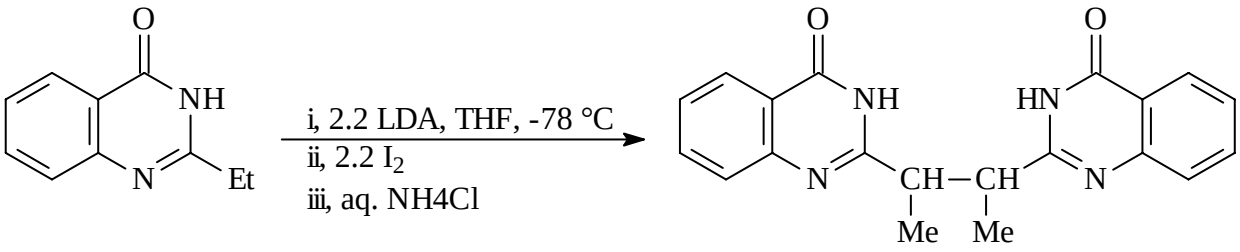
Scheme 19

Table 10: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**104-114**) from the reactions of the dilithio reagents (**102**) and (**103**) with electrophiles[45]

Product	R	Electrophile	E	Yield (%)[a]
104	Me	MeI	Me	82
105	Et	MeI	Me	79
106	Me	D_2O	D	87
107	Et	D_2O	D	77
108	Me	Ph_2CO	$Ph_2C(OH)$	78
109	Et	Ph_2CO	$Ph_2C(OH)$	88
110	Me	PhCOMe	PhC(OH)Me	70
111	Et	PhCOMe	PhC(OH)Me	77[b]
112	Me	PhCHO	PhCH(OH)	73[b]
113	Et	PhCHO	PhCH(OH)	79[b]
114	Me	PhNCO	PhNHCO	62

[a] Yields reported are for purified materials. [b] ^{1}H- and ^{13}C-NMR spectra indicate a mixture of two diastereoisomers

However, reaction of the dilithio reagent of compound (**88**) with iodine had taken place in different manner. Instead of 2-iodoethyl derivative being formed oxidative dimerization took place to give 2,2'-(2,3-butanediyl)bisquinazolin-4(3*H*)-one (**115**) in 71% crude yield (Scheme 20).[45] ^{1}H- and ^{13}C-NMR spectra of **115** suggested that it was a single racemic diastereoisomer.[45]



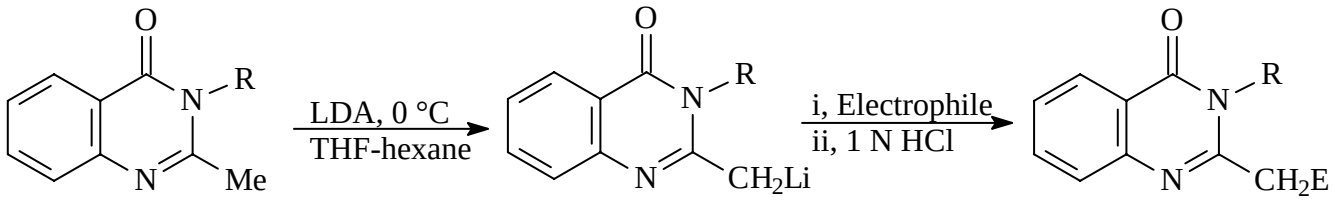
88 **115** (60%)

Scheme 20

Attempted double lithiation of quinazolin-4(3*H*)-one itself was not successful under conditions similar to those used for the successful lithiation of 2-alkylquinazolin-4(3*H*)-ones.[45]

3.2. LITHIATION OF 3-SUBSTITUTED 2-METHYLQUINAZOLIN-4(3*H*)-ONES

2-Methyl-3-(2-tolyl)quinazolin-4(3*H*)-one (**116**) and 2,3-dimethylquinazolin-4(3*H*)-one (**117**) were lithiated on methyl group at position 2 by use of LDA as lithiating reagent in THF-hexane mixture at 0 °C to afford the corresponding 2-lithiomethyl derivatives (**118**) and (**119**), respectively.[57] Reaction of the lithio reagents (**118**) and (**119)** with a range of electrophiles (D_2O, iodomethane, allyl bromide, ethyl iodide, iodobenzene, benzaldehyde, cyclohexanone, diphenyl disulfide, benzophenone and acetone) afforded the corresponding 2,3-disubstituted quinazolin-4(3*H*)-ones (**120-130**) (Scheme 21) in the yields of 22-92% (Table 11).[57]



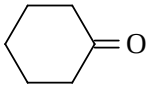
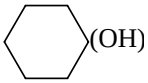
116, R = 2-tolyl
117, R = Me

118, R = 2-tolyl
119, R = Me

120-130

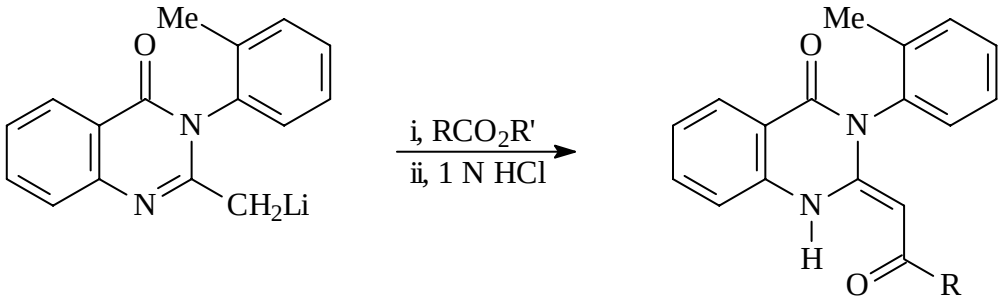
Scheme 21

Table 11: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**120-130**) from the reactions of the lithio reagents (**118)** and (**119)** with electrophiles[57]

Product	R	Electrophile	E	Yield (%)
120	2-tolyl	D_2O	D	92
121	2-tolyl	MeI	Me	53
122	2-tolyl	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	60
123	2-tolyl	EtI	Et	25[a]
124	2-tolyl	PhI	Ph	34[b]
125	2-tolyl	PhCHO	PhCH(OH)	51[c]
126	2-tolyl			22
127	2-tolyl	$(PhS)_2$	PhS	53[d]
128	Me	PhCHO	PhCH(OH)	73
129	Me	Ph_2CO	$Ph_2C(OH)$	69
130	Me	Me_2CO	$Me_2C(OH)$	41

[a] Diethyl derivative was obtained in 5% yield. [b] Diphenylated product was obtained in a small amount. [c] A trace of styryl derivative was obtained. [d] Diphenyl sulfide product was obtained in 17% yield.

Acylation of compound (**116**) had taken place by means of reactions of its lithio reagent (**118**) with a range of ester compounds (ethyl acetate, ethyl trifluoroacetate, methyl benzoate, ethyl 1-adamantyl-carboxylate, ethyl oxalate). The corresponding acylated derivatives (**131-135)** were obtained (Scheme 22) in good yields (Table 12).[57]



118 **131-135**

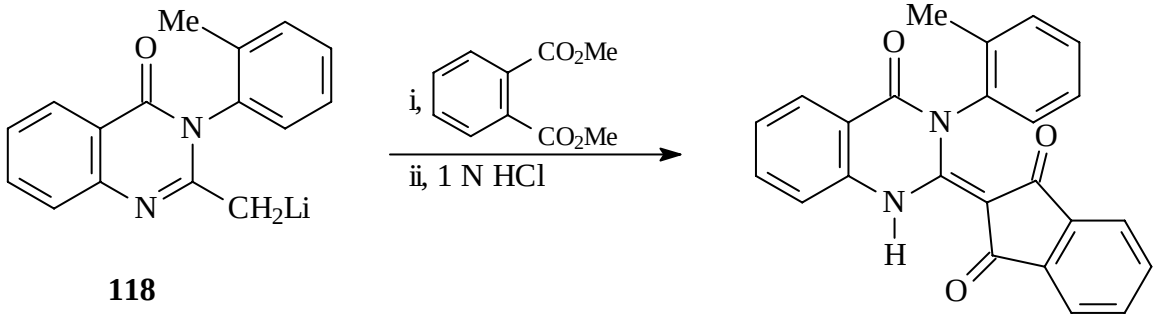
Scheme 22

Table 12: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**131-135**) from the reactions of the lithio reagent (**118**) with esters[57]

Product	RCOOR'	R	Yields (%)
131	$EtCO_2Me$	Me	61
132	$EtCO_2CF_3$	CF_3	87
133	$MeCO_2Ph$	Ph	80
134	Ethyl 1-adamantylcarboxylate	1-adamantyl-	81
135	$(CO_2Et)_2$	CO_2Et	62

The unusual stability of compounds (**131-135**) are presumably due to intramolecular hydrogen bonding.[57]

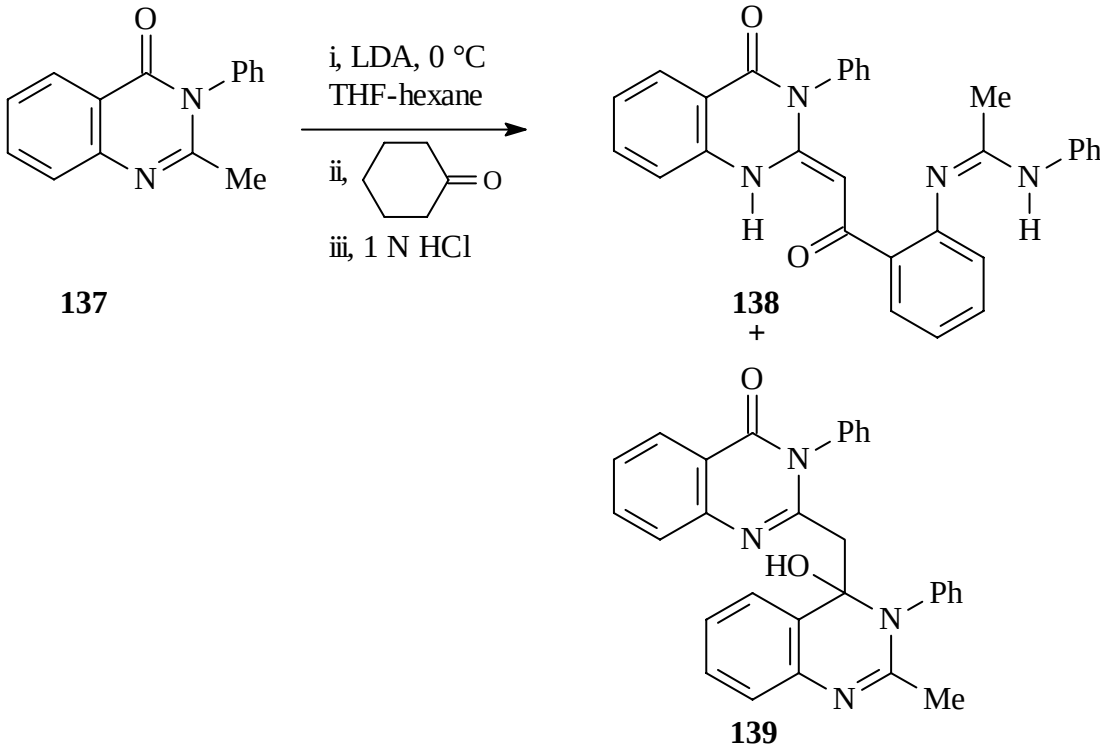
It was found that reaction of lithio reagent (**118**) with dimethyl phthalate afforded 2-(1,3-dioxo-2-indanyl)-3-(2-tolyl)quinazolin-4(3*H*)-one (**136**) in 22% yield (Scheme 23).[57]



118 **136** (22%)

Scheme 23

Similarly lithiation of 2-methyl-3-phenylquinazolin-4(3*H*)-one (**137**) had taken place as for **116** and **117**. LDA in THF-hexane at 0 °C converted **137** to its lithiomethyl derivative which reacted with cyclohexanone to afford a mixture of **138** and **139** in 47% overall yield (Scheme 24).[57] The unusual stability of compounds (**138**) and (**139**) is presumably a result of intramolecular hydrogen bonding.[57]

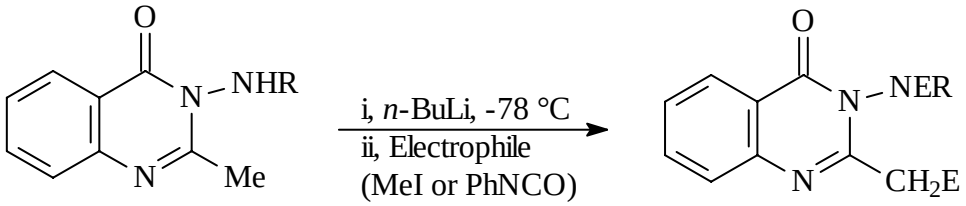


137 **138** + **139**

Scheme 24

3.3. LITHAIATION OF 2-ALKYL-3-AMINO-QUINAZOLIN-4(3*H*)-ONES AND 2-ALKYL-3-METHYLAMINOQUINAZOLIN-4(3*H*)-ONES

Successful lithiation of 3-amino-2-methylquinazolin-4(3*H*)-one (**140**) and 3-methylamino-2-methyl-quinazolin-4(3*H*)-one (**141**) is a very useful to effect lithiation proximate to the amino or methylamino group to produce the 2-substituted derivatives with the advantage that there is no protecting group to be removed in another step. It was found that lithiation of **140** and **141** occurred smoothly and rapidly with 2.2 equivalents of *n*-BuLi at –78 °C in THF.[46] However, this reaction was not successful for simple aromatic amines. Reactions of the dilithio reagents thus formed with 2.2 mole equivalents of iodomethane or phenyl isocyanate afforded the corresponding disubstituted products (**142-144**) (Scheme 25) in good yields (Table 13). However, when phenyl isocyanate (1.1 equivalents) was used a mixture of mono- and disubstituted derivatives was obtained which was not separted.[46]



140, R = H
141, R = Me

142-144

Scheme 25

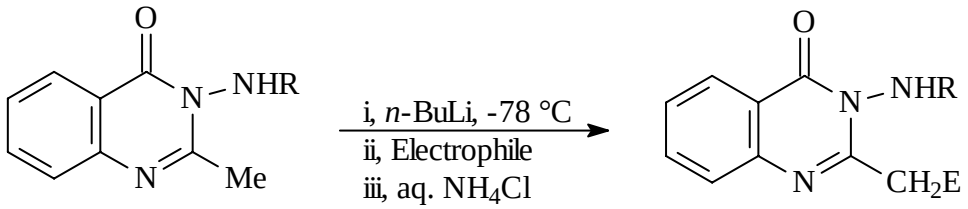
Table 13: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**142-144**) from reaction of dilithio reagents of compounds (**140**) and (**141**) with MeI and PhNCO[46]

Product	R	Electrophile	E	Yield (%)[a]
142	H	MeI	Me	89
143	H	PhNCO	PhNHCO	75
144	Me	PhNCO	PhNHCO	80

[a] Yields reported are purified products.

Various 2-substituted 3-aminoquinazolin-4(3*H*)-ones derivatives (**145-156**) (Scheme 26) were obtained in high yields (Table 14) when the dilithio reagents of compounds (**140**) and (**141**) were reacted with a variety of electrophiles (benzophenone, D_2O, cyclohexanone, cyclopentanone, acetophenone,

benzaldehyde, tetraisopropylthiuram disulfide (TITD), phenyl isocyanate, 2-butanone).[46] In contrast to the situation with the dilithio reagent of compound (**140**), reaction of the dilithio reagent of compound (**141**) with one equivalent of phenyl isocyanate gave only the monosubstituted derivative (**155**), with no disubstituted compound formed.[46]

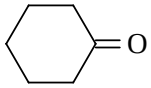
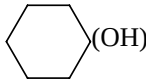
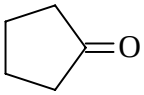
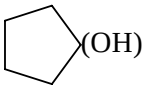


140, R = H
141, R = Me

145-156

Scheme 26

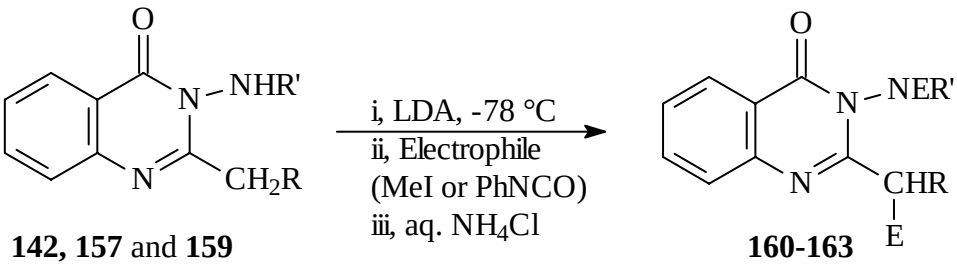
Table 14: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**145-156**) from reaction of dilithio reagents of compounds (**140**) and (**141**) with electrophiles[46]

Product	R	Electrophile	E	Yield (%)[a]
145	H	Ph_2CO	$Ph_2C(OH)$	86
146	H	D_2O	D	88
147	H			84
148	H			89
149	H	PhCOMe	PhC(OH)(Me)	86
150	H	PhCHO	PhCH(OH)	77
151	Me	$[Pr_2^iNC(S)S]_2$	$Pr_2^iNC(S)S$	75
152	Me	Ph_2CO	$Ph_2C(OH)$	83
153	Me	PhCHO	PhCH(OH)	70
154	Me	D_2O	D	90
155	Me	PhNCO	PhNHCO	72
156	Me	EtCOMe	EtC(OH)(Me)	84

[a] Yields reported are for purified materials.

Attempted lithiation of 3-amino-2-ethylquinazolin-4(3*H*)-one (**157**), 3-amino-2-propylquinazolin-4(3*H*)-one (**158**), 2-ethyl-3-methylaminoquinazolin-4(3*H*)-one (**142**) and 3-methylamino-2-propylquinazolin-4(3*H*)-one (**159**) using *n*-BuLi in THF was not very successful, in which a low yields of the desired

products were obtained after reaction with iodomethane as electrophile. However, good lithiation was achieved by use of LDA at –78 °C in THF.[46] Initial addition of LDA provided a yellow solution until approximately one equivalent of LDA had been added, then gave a deep red when the second mole of LDA was added. The dilithio reagents of compounds (**142** and **157-159**) were allowed to stir at –78 °C for 30 min before reaction with electrophiles to ensure complete formation of the corresponding dilithio reagents.[46] Addition of 2.2 mole equivalents of iodomethane to dilithio reagents of (**142**, **157** and **159**) followed by slow warming to 0 °C gave the methylated products (**160-162**) (Scheme 27) in 86, 88 and 79% isolated yields, respectively (Table 15).[46] In contrast, reaction of the dilithio reagent of compound (**157**) with one equivalent of phenyl isocyanate at –78 °C in THF gave a mixture of mono- and disubstituted derivatives which was not separated. However, reaction with 2.2 mole equivalents of phenyl isocyanate gave only the disubstituted derivative (**163**) (Scheme 27) in 70% yield (Table 15).[46]



142, 157 and **159** **160-163**

Scheme 27

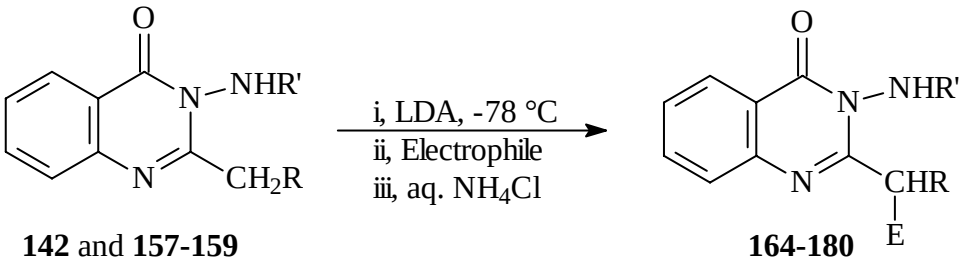
Table 15: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**160-163**) from reaction of dilithio reagents of compounds (**142, 157** and **159**) with MeI or PhNCO[46]

Product	R	R′	Electrophile	E	Yield (%)[a]
160	Me	H	MeI	Me	86
161	Me	Me	MeI	Me	88
162	Et	Me	MeI	Me	79
163	Et	H	PhNCO	PhNHCO	70

[a] Yields reported are for purified materials.

The versatility of the dilithio reagents of compounds (**142** and **157-159)** was tested. They were reacted with a range of electrophiles (cyclohexanone, cyclopentanone, acetophenone, benzaldehyde, 2-hexanone, 3-heptanone, 2-butanone, benzophenone, D_2O, phenyl isocyanate) in THF at 0 °C (Scheme 28). The

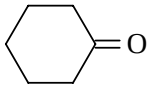
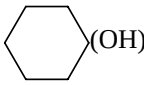
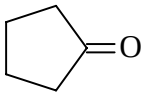
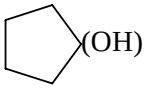
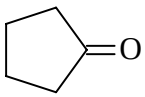
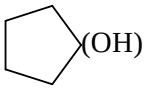
corresponding 2-substituted quinazolin-4(3*H*)-one derivatives (**164-180**) were obtained in good yields (Table 16).[46]



142 and **157-159** **164-180**

Scheme 28

Table 16: Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**164-180**) from reaction of dilithio reagents of compounds (**142** and **157-159**) with electrophiles[46]

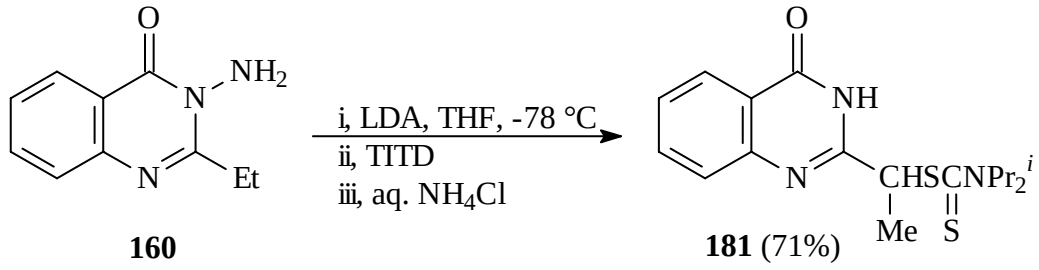
Product	R′	R	Electrophile	E	Yield (%)[a]
164	H	Me			90
165	H	Me			90
166	H	Me	PhCOMe	PhC(OH)(Me)	80
167	H	Me	PhCHO	PhCH(OH)	80
168	H	Me	^{n}BuCOMe	^{n}BuC(OH)(Me)	71
169	H	Me	^{n}BuCOEt	^{n}BuC(OH)(Et)	83
170	H	Me	EtCOMe	EtC(OH)(Me)	88
171	H	Me	Ph_2CO	$Ph_2C(OH)$	84
172	H	Me	D_2O	D	92
173	H	Et	PhCOMe	PhC(OH)(Me)	87
174	H	Et	EtCOMe	EtC(OH)(Me)	92
175	H	Et	Ph_2CO	$Ph_2C(OH)$	90
176	Me	Me	Ph_2CO	$Ph_2C(OH)$	82
177	Me	Me			80
178	Me	Me	D_2O	D	82
179	Me	Me	PhNCO	PhNHCO	66
180	Me	Et	Ph_2CO	$Ph_2C(OH)$	80

[a] Yields reported are for purified materials.

The ^{1}H- and ^{13}C-NMR spectra of compounds (**167**, **174** and **175**) showed the expected presence of two diastereoisomers.[46] However, NMR spectra for compounds (**166**) and (**168-170**) indicated only one diastereoisomer in each case, which is clearly not expected when two asymmetric centers are introduced

during the lithiation reaction. The ambient temperature NMR spectra of compounds (**173-175**) and (**180**) showed diastereotopism for the two hydrogens of the CH_2 group adjacent to the newly created asymmetric center. This is an indication for a significant barrier to rotation around the N-N bond even at room temperature.[46] The ^{1}H-NMR spectrum of compound (**176**) showed broad NH and CH signals at room temperature, two simple quartets at 60 °C and the appearance of two diastereoisomers in the ratio of 2:11 at –20 °C.[46]

Reaction of the dilithio reagent of compound (**160**) with TITD had taken place in different manner in which deamination had taken place from position 3 to afford 2-[1-(disopropyldithiocarbamoyl)-ethyl]quinazolin-4(3*H*)-one (**181**) in 71% yield (Scheme 29). It is not clear yet why dilithio reagent of **160** behaves differently to dilithio reagent of **140** in this reaction.[46]



160 **181** (71%)

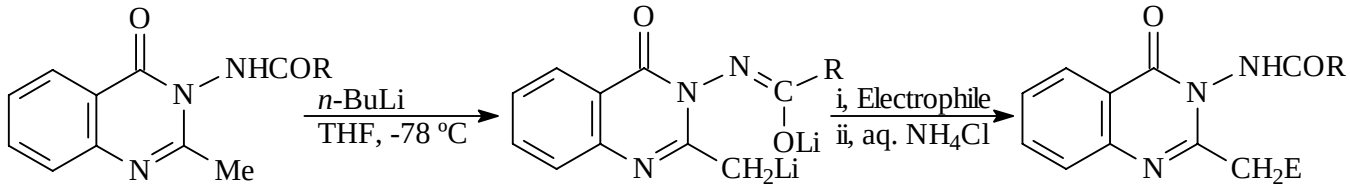
Scheme 29

Attempted lithiation of 3-dimethylamino-2-ethylquinazolin-4(3*H*)-one (**161**) and 3-aminoquinazolin-4(3*H*)-one using various lithiating reagents under different reactions conditions was not successfuel.[46]

3.4. LITHIATION OF 3-ACYLAMINO-2-ALKYLQUINAZOLIN-4(3*H*)-ONES

Attempted lithiation of 3-pivaloylamino-2-methylquinazolin-4(3*H*)-one (**70**) and 3-acetylamino-2-methylquinazolin-4(3*H*)-one (**78**) with two equivalents of *n*-BuLi at –78 °C in THF occurred smoothly and rapidly, with no nucleophilic attack of *n*-BuLi at either the carbonyl group of the acylamino unit or that of the quinazolinone ring.[44] There was also no lithiation at the acetylamino methyl group in the case of compound (**78**) (R = Me). Reaction with the first mole of *n*-BuLi produced monolithio derivatives in which lithiation took place at NH. The monolithio reagent was converted into dilithio derivatives (**182**) when the second mole of *n*-BuLi reacted in which the additional lithiation had occurred at the 2-methyl

group (Scheme 30).[47] Reactions of the dilithio reagents (**182**) with a variety of electrophiles (iodomethane, benzophenone, D_2O, cyclohexanone, acetophenone, phenyl isocyanate) gave the corresponding 2-substituted 3-acylaminoquinazolin-4(3*H*)-ones (**71, 79** and **183-192**) (Scheme 30) in good yields (Table 17).[47]



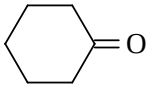
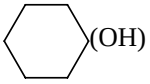
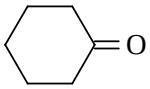
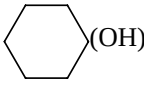
70, R = *t*-Bu
78, R = Me

182

71, 79 and **183-192**

Scheme 30

Table 17: Synthesis of 2-substituted 3-acylaminoquinazolin-4(3*H*)-ones (**71, 79** and **183-192**) from reaction of dilithio reagents (**182**) with electrophiles[47]

product	R	Electrophile	E	Yield (%)[a]
71	*t*-Bu	MeI	Me	89
183	*t*-Bu	Ph_2CO	$Ph_2C(OH)$	83
184	*t*-Bu	D_2O	D	88
185	*t*-Bu			80
186	*t*-Bu	PhCOMe	PhC(OH)Me	81
187	*t*-Bu	PhNCO	PhNHCO	84
79	Me	MeI	Me	75
188	Me	Ph_2CO	$Ph_2C(OH)$	80
189	Me	D_2O	D	74
190	Me			79
191	Me	PhCOMe	PhC(OH)Me	84
192	Me	PhNCO	PhNHCO	83

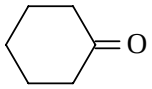
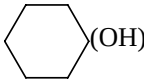
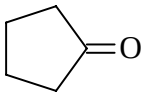
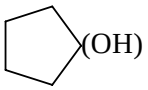
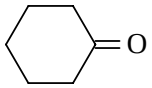
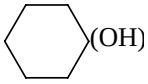
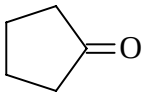
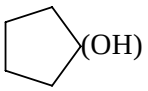
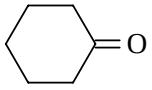
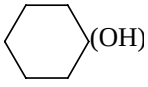
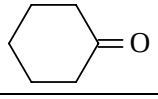
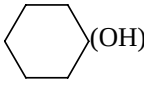
[a] Yields reported are for purified materials.

The ^{1}H- and ^{13}C-NMR spectra of most of the compounds obtained showed diasterotopism for the CH_2 group at position 2 due to hindered to rotation about N-N bond. Barriers to rotation have been reported for di- and tetraacylhydrazines, where both nitrogen atoms are of amide type,[58] and hydrazines,[59] triazines[60] and tetrazines.[61] Recently hindered to rotation about N-N bond in 3-acylaminoquinazolin-

4(3*H*)-ones and 3-diacylaminoquinazolin-4(3*H*)-ones was reported and was found to be high as for hydrazine derivatives (14.7~20.6 Kcal mol^{-1}).[62]

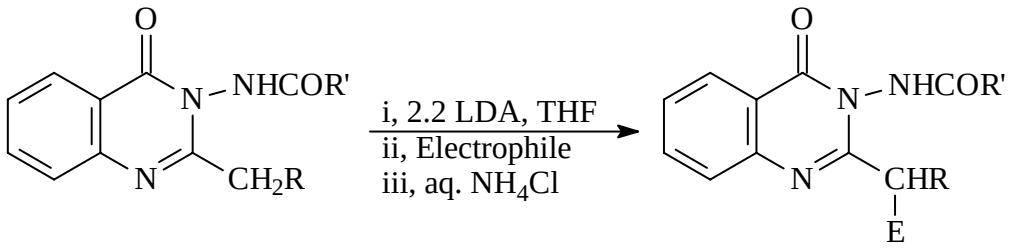
Attempted lithiation of 2-ethyl-3-pivaloylaminoquinazolin-4(3*H*)-one (**71**), 2-propyl-3-pivaloyl-aminoquinazolin-4(3*H*)-one (**193**), 3-acetylamino-2-ethylquinazolin-4(3*H*)-one (**79**) and 3-acetylamino-2-propylquinazolin-4(3*H*)-one (**194**) with *n*-butyllithium in THF at various reaction conditions was not very successful.[44] However, successful lithiation was achieved with 2.2 mole equivalents of LDA in THF at –78 °C (Scheme 31).[44]

Table 18: Synthesis of 2-substituted 3-acylaminoquinazolin-4(3*H*)-ones (**72, 80** and **195-212**) from reaction of dilithio reagents of compounds (**71, 79, 193** and **194**) with electrophiles[44]

Product	R′	R	Electrophile	E	Yield (%)[a]
72	*t*-Bu	Me	MeI	Me	92
195	*t*-Bu	Me	Ph_2CO	$Ph_2C(OH)$	90
196	*t*-Bu	Me	D_2O	D	88
197	*t*-Bu	Me			82
198	*t*-Bu	Me			84
199	*t*-Bu	Me	PhCOMe	PhC(OH)Me	81
200	*t*-Bu	Me	I_2	I	70
80	Me	Me	MeI	Me	84
201	Me	Me	Ph_2CO	$Ph_2C(OH)$	80
202	Me	Me	D_2O	D	81
203	Me	Me			82
204	Me	Me			80
205	Me	Me	PhCOMe	PhC(OH)Me	77
206	Me	Me	I_2	I	70
207	*t*-Bu	Et	MeI	Me	90
208	*t*-Bu	Et	Ph_2CO	$Ph_2C(OH)$	92
209	*t*-Bu	Et			88
210	Me	Et	MeI	Me	86
211	Me	Et	Ph_2CO	$Ph_2C(OH)$	87
212	Me	Et			85

[a] Yields reported are for purified products.

Reactions of the dilithio reagents thus obtained with a variety of electrophiles (iodomethane, benzophenone, D_2O, cyclohexanone, cyclopentanoe, acetophenone, iodine) afforded the corresponding 2-substituted derivatives (**72, 80** and **195-212**) (Scheme 31) in good yields (Table 18).[44]



71, 79, 193 and **194** **72, 80** and **195-212**

Scheme 31

Lithiation of 3-pivaloylamino-2-(1-methylethyl)quinazolin-4(3*H*)-one (**207**) and 3-acetylamino-2-(1-methylethyl)quinazolin-4(3*H*)-one (**210**) with LDA in THF under various reaction conditions were attempted.[44] However, after attempted trapping with methyl iodide, starting materials were recovered unchanged indicating that no lithiation had taken place under the conditions tried.[44] Similarly, attempted lithiation of 2-alkyl-3-diacetylaminoquinazolin-4(3*H*)-ones and 3-diacetylaminoquinazolin-4(3*H*)-one was not successful.[44]

4. CONCLUSIONS

Regiospecific electrophilic substitutions of 3-acylaminoquinazolin-4(3*H*)-ones are a facile, practical and regiospecific process providing access to various 2-substituted quinazolin-4(3*H*)-one derivatives. Lithiation process for 3-amino-2-alkylquinazolin-4(3*H*)-ones is particularly useful in that there is no protecting group to be removed in another step from the amino function. Lithiation of 2-alkylquinazolin-4(3*H*)-ones and various substituted quinazolines followed by electrophilic reactions afforded a complex substituted derivatives. These simple procedures can provide substituted derivatives previously unavailable and difficult to be prepared by other routes.

ACKNOWLEDGEMENTS

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