

Lithiation and Side-Chain Substitution of 3-Alkyl-1*H*-quinoxalin-2-ones

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Abstract: 3-Methyl-1*H*-quinoxalin-2-one has been doubly lithiated with *n*-butyllithium at –78 °C in THF. The dilithio reagent thus obtained reacts with various electrophiles (iodomethane, iodoethane, D₂O, benzaldehyde, benzophenone, cyclohexanone) to give modified 3-substituted 1*H*-quinoxalin-2-ones in good yields. In the reaction of the dilithio reagent with phenyl isothiocyanate the product was a tautomer of the simple substitution product. Reaction of the dilithio reagent with iodine gives an oxidatively dimerised product instead of the 3-iodomethyl derivative. Lithiations of 3-ethyl- and 3-propyl-1*H*-quinoxalin-2-ones, followed by reactions with representative electrophiles (benzaldehyde, benzophenone, cyclohexanone), behaved in a similar manner to give the corresponding modified 3-substituted derivatives in good yields.

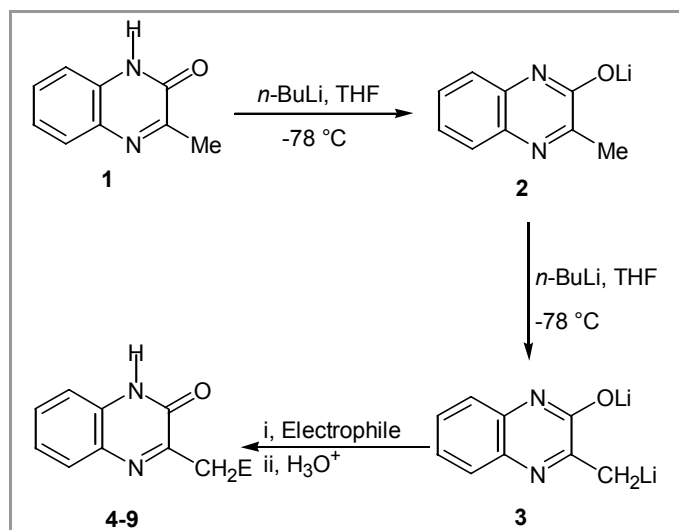
Key words: double lithiation, 1*H*-quinoxalin-2-ones, electrophiles, tautomerisation, oxidative dimerisation

Lithiation of aromatic compounds has provided an important synthetic alternative to electrophilic substitution reactions.² Various heterocycles have been lithiated by the use of lithium reagents at low temperatures. The organolithiums thus obtained in such reactions are very useful intermediates for the synthesis of more complex substituted heterocycles.³ The high reactivity of diazines towards nucleophilic reagents makes the lithiation of such derivatives more difficult than that of most heterocyclic compounds due to nucleophilic addition of the lithium reagent to the C=N bond. However, successful lithiation of diazines has been achieved by the use of less nucleophilic lithium reagents such as LDA or LTMP.⁴ We have previously reported many examples of the synthetic application of organolithium compounds,⁵ and in particular on the syntheses of more complex 2-substituted 3*H*-quinazolin-4-ones *via* directed lithiation.⁶

Lithiation of quinoxalines containing substituents that direct *ortho*-lithiation provides a method of producing substituted derivatives in moderate to good yields.⁷ In the course of the development of new synthetic methods for the synthesis of pharmaceutical intermediates, we became interested in α -lithiation of 3-alkyl-1*H*-quinoxalin-2-ones as a possible method for the synthesis of more complex modified substituted 1*H*-quinoxalin-2-one derivatives. Compounds possessing the quinoxaline ring system have important agricultural and pharmaceutical applications.⁸ We now report on the successful synthesis of 3-substituted 1*H*-quinoxalin-2-ones *via* lithiation of 3-alkyl-1*H*-quinoxalin-2-ones.

3-Methyl-1*H*-quinoxalin-2-one (**1**) was prepared according to the literature procedure.⁹ Double lithiation of **1** occurred smoothly and rapidly with *n*-butyllithium (2.2 equivalents) at –78 °C in THF. Initial addition of *n*-BuLi provided the monolithio reagent **2** as a yellow solution until approximately one equivalent had been added, then gave the dilithio reagent **3** as an orange solution as the remaining *n*-BuLi was added. Reactions of the dilithio reagent **3** with a variety of electrophiles (iodomethane, iodoethane, D₂O, benzaldehyde, benzophenone, cyclohexanone) gave the modified 3-substituted

1*H*-quinoxalin-2-ones (**4-9**) (Scheme 1) in good yields (Table 1).



Scheme 1

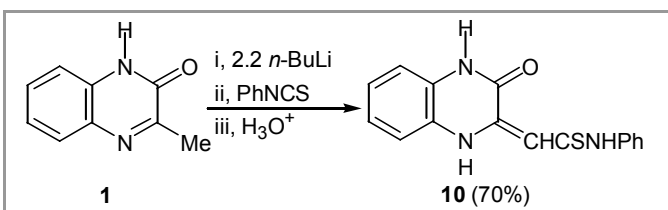
Table 1 Yields of products **4-9** according to Scheme 1

Product	Electrophile	E	Yield (%) ^a
4	MeI	Me	77
5	EtI	Et	72
6	D ₂ O	D	78
7	PhCHO	PhCH(OH)	71
8	Ph ₂ CO	Ph ₂ C(OH)	80
9			72

^a Yield of isolated, purified products.

As indicated in Table 1, the yields of isolated, purified products were good. No *N*-substitution was observed when an excess of iodomethane or iodoethane was used as electrophile.

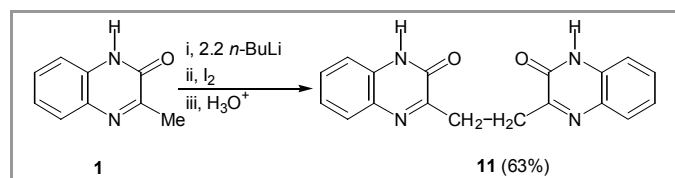
Reaction of the dilithio reagent of compound **1** with phenyl isothiocyanate proceeded in an interesting manner to give compound **10** in 70% isolated yield (Scheme 2). Compound **10** is a tautomer of the simple substitution product (as would be obtained according to Scheme 1, where E is PhNHCS).



Scheme 2

The structure of compound **10** was confirmed by its NMR and mass spectra. The EI mass spectrum showed a molecular ion peak at *m/z* 258, and the CI mass spectrum showed a pseudo molecular ion peak at *m/z* 259, while the high resolution mass of the pseudo molecular ion confirmed the formula as C₁₅H₁₉N₂O₂ (MH⁺). The ¹H NMR spectrum showed the presence of three exchangeable singlets due to three NH protons, resonating at 14.25, 11.76 and 11.21 ppm. The ¹³C NMR spectrum showed six quaternary and eight CH carbons, whereas the simple substitution product would have shown six quaternary, seven CH and one CH₂ carbons.

Reaction of the dilithio reagent of compound **1** with iodine as electrophile resulted in oxidative dimerisation to give compound **11** in 70% crude yield (Scheme 3). Compound **11** is highly insoluble in most solvents. After extraction of impurities with hot methanol, the yield was reduced to 63%.

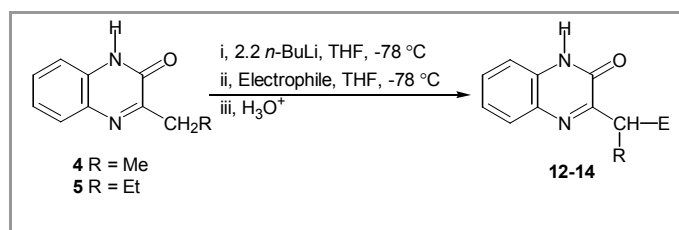


Scheme 3

The structure of compound **11** was confirmed by its ¹H NMR and mass spectra. The EI mass spectrum showed

a molecular ion peak at m/z 346, while the high resolution mass of the molecular ion confirmed the formula as $C_{18}H_{14}N_4O_2$. The 1H NMR spectrum was consistent with the structure **11**, but the material was too insoluble to give a good ^{13}C NMR spectrum.

Attention was next turned to the lithiation of 3-ethyl-1*H*-quinoxalin-2-one (**4**) and 3-propyl-1*H*-quinoxalin-2-one (**5**), which had been obtained by alkylation of the dilithio reagent **3** according to Scheme 1. If successful, this would suggest that the lithiation process was tolerant of a variety of primary alkyl groups at position 3. It was found that successful lithiation of **4** and **5** was achieved using *n*-BuLi (2.2 equivalents) in THF at -78 °C under nitrogen for 1 h. The dilithio reagents thus obtained reacted with representative electrophiles (benzaldehyde, benzophenone, cyclohexanone) (Scheme 4) to give the corresponding modified derivatives **12–14** in good yields (Table 2).



Scheme 4

Table 2 Yields of products **12–14** according to Scheme 4

Product	R	Electrophile	E	Yield (%) ^a
12	Me	PhCHO	PhCH(OH)	77
13	Me	Ph ₂ CO	Ph ₂ C(OH)	71
14	Et			70

^a Yields of isolated purified products.

The spectral characteristics of compounds **12–14** were consistent with the assigned structures. The NMR spectra of compound **12** showed the expected presence of two racemic diastereoisomers in unequal proportions.

In conclusion, this work describes a simple and convenient method for the high yield synthesis of more complex 3-substituted 1*H*-quinoxalin-2-ones, which might have pharmacological activities and are difficult to prepare by other means.

Melting points were determined on an electrothermal digital melting point apparatus and are reported uncorrected. 1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz for 1H and 100 MHz for ^{13}C measurement. Chemical shifts are reported in parts per million relative to tetramethylsilane. Low-resolution mass spectra were recorded on a VG 12-253 spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) by use of ammonia as ionizing gas. Accurate mass data were obtained on a VG ZAB-E instrument. *n*-Butyllithium was obtained from Aldrich Chemical Company and was estimated prior to use by the method of Watson and Eastham.¹⁰ THF was distilled from sodium benzophenone ketyl. Other chemicals were obtained from Aldrich Chemical Company and used without further purification.

General procedure for the synthesis of modified 3-substituted 1*H*-quinoxalin-2-ones (**4–14**)

A solution of *n*-BuLi (1.76 mL, 2.5 M, 4.4 mmol) was added in a dropwise manner to a stirred solution of 3-alkyl-1*H*-quinoxalin-2-one (2.0 mmol) in dry THF (60 mL in the case of **1** and 20 mL in the cases of **4** and **5**) maintained at -78 °C under N_2 . Formation of the dilithio reagent was observed as an orange solution. The mixture was stirred at -78 °C under N_2 for an additional 1 h, after which an electrophile (2.2 mmol), in dry THF (10 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C under N_2 , then removed from the cooling bath and allowed to warm to room temperature, diluted with ethyl acetate (20 mL) and quenched with aqueous ammonium chloride solution (20 mL). The organic layer was washed with water (2 x 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The products were recrystallised, subjected to column chromatography or washed with hot methanol to give the appropriate pure products **4–14**.

3-Ethyl-1*H*-quinoxalin-2-one (**4**)

Recrystallised from aq. MeOH; mp 190 – 191 °C (lit.¹¹ 191 °C).

3-Propyl-1*H*-quinoxalin-2-one (5)

Recrystallised from aq. MeOH; mp 184–185 °C (lit.¹¹ 185 °C).

3-Deuteriomethyl-1*H*-quinoxalin-2-one (6)

Recrystallised from MeOH; mp 245–247 °C.

¹H NMR (DMSO-*d*₆): δ = 12.33 (s, exch., 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.45 (apparent t, *J* = 8 Hz, 1 H), 7.27–7.22 (m, 2 H), 2.37 (1:1:1 t, *J* = 2 Hz, 2 H).

¹³C NMR (DMSO-*d*₆): δ = 159.5 (s), 155.2 (s), 132.2 (s), 132.0 (s), 129.6 (d), 128.2 (d), 123.3 (d), 115.5 (d), 20.8, 20.6, 20.4 (1:1:1 t).

EI-MS: *m/z* (%) = 162 (*M*⁺ + 1, 9), 161 (*M*⁺, 83), 131 (96), 132 (100), 105 (15), 90 (42), 63 (38).

CI-MS: *m/z* (%) = 179 (*M*⁺ + NH₄, 6), 162 (MH⁺, 100), 146 (47), 133 (9), 94 (8).

HRMS: *m/z* calcd for C₉H₈N₂OD (MH⁺), 162.0777; found, 162.0778.

3-(2-Hydroxy-2-phenylethyl)-1*H*-quinoxalin-2-one (7)

Recrystallised from MeOH; mp 183–185 °C.

¹H NMR (DMSO-*d*₆): δ = 12.36 (s, exch., 1 H), 7.75 (dd, *J* = 8, 1 Hz, 1 H), 7.48 (apparent dt *J* = 8, 1 Hz, 1 H), 7.41 (d, *J* = 7 Hz, 2 H), 7.32–7.20 (m, 5 H), 5.36 (br s, exch., 1 H), 5.28 (t, *J* = 6.7 Hz, 1 H), 3.12 (d, *J* = 6.7 Hz, 2 H).

¹³C NMR (DMSO-*d*₆): δ = 159.8 (s), 155.3 (s), 146.0 (s), 132.1 (s), 132.0 (s), 129.9 (d), 128.5 (d), 128.4 (d), 127.2 (d), 126.1 (d), 123.4 (d), 115.5 (d), 70.6 (d), 44.0 (t).

CI-MS: *m/z* (%) = 267 (MH⁺, 52), 249 (21), 161 (100), 147 (19), 138 (12), 119 (14), 105 (15), 94 (13).

HRMS: *m/z* calcd for C₁₆H₁₅N₂O₂ (MH⁺), 267.1133; found, 267.1136.

3-(2-Hydroxy-2,2-diphenylethyl)-1*H*-quinoxalin-2-one (8)

Recrystallised from MeOH; mp 200–201 °C.

¹H NMR (DMSO-*d*₆): δ = 12.56 (s, exch., 1 H), 7.65 (dd, *J* = 8, 1 Hz, 1 H), 7.55–7.44 (m, 5 H), 7.28–7.24 (m, 6 H), 7.14 (t, *J* = 7 Hz, 2 H), 6.83 (s, exch., 1 H), 3.84 (s, 2 H).

¹³C NMR (DMSO-*d*₆): δ = 160.1 (s), 155.6 (s), 147.8 (s), 131.5 (s), 131.2 (s), 130.5 (d), 128.3 (d), 128.2 (d), 126.8 (d), 126.1 (d), 123.9 (d), 115.8 (d), 78.0 (s), 42.7 (t).

CI-MS: *m/z* (%) = 343 (MH⁺, 4), 325 (11), 200 (34), 183 (100), 161 (14), 145 (23), 105 (34), 94 (44), 78 (25).

HRMS: *m/z* calcd for C₂₂H₁₉N₂O₂ (MH⁺), 343.1446; found 343.1449.

3-[(1-Hydroxycyclohexyl)methyl]-1*H*-quinoxalin-2-one (9)

Recrystallised from MeOH; mp 174–175 °C.

¹H NMR (DMSO-*d*₆): δ = 12.42 (s, exch., 1 H), 7.73 (dd, *J* = 8, 1 Hz, 1 H), 7.48 (apparent dt, *J* = 8, 1 Hz, 1 H), 7.30–7.25 (m, 2 H), 4.66 (s, exch., 1 H), 2.97 (s, 2 H), 1.60–1.51 (m, 4 H), 1.43–1.12 (m, 6 H).

¹³C NMR (DMSO-*d*₆): δ = 160.2 (s), 156.1 (s), 132.0 (s), 131.9 (s), 130.0 (d), 128.5 (d), 123.5 (d), 115.6 (d), 71.5 (s), 45.1 (t), 37.8 (t), 25.7 (t), 20.0 (t).

EI-MS: *m/z* (%) = 258 (*M*⁺, 5), 240 (10), 160 (93), 132 (90), 131 (100), 121 (41), 107 (54), 93 (73), 91 (89), 81 (70), 79 (78), 67 (91).

CI-MS: *m/z* (%) = 259 (MH⁺, 33), 241 (13), 178 (7), 161 (100), 147 (12), 132 (8), 116 (49), 98 (12).

HRMS: *m/z* calcd for C₁₅H₁₉N₂O₂ (MH⁺), 259.1446; found, 259.1446.

3-(2-Phenylamino-2-thioxoethylidene)-3,4-dihydro-1*H*-quinoxalin-2-one (10)

Recrystallised from MeOH; mp 240–242 °C.

¹H NMR (DMSO-*d*₆): δ = 14.25 (s, exch., 1 H), 11.76 (s, exch., 1 H), 11.21 (s, exch., 1 H), 7.83–7.62 (m, 2 H), 7.39 (apparent t, *J* = 7.6 Hz, 2 H), 7.28–7.18 (m, 2 H), 7.12–7.04 (m, 3 H), 6.58 (s, 1 H).

¹³C NMR (DMSO-*d*₆): δ = 188.2 (s), 157.1 (s), 142.0 (s), 139.7 (s), 128.9 (d), 126.2 (s), 125.8 (d), 125.7 (d), 124.4 (s), 124.0 (d), 123.8 (d), 123.2 (d), 115.6 (d), 115.5 (d).

EI-MS: *m/z* (%) = 295 (*M*⁺, 19), 262 (41), 202 (22), 174 (10), 160 (40), 131 (48), 93 (81), 77 (100), 65 (66), 51 (76).

CI-MS: *m/z* (%) = 296 (MH⁺, 20), 262 (18), 166 (24), 152 (100), 147 (47), 120 (72), 94 (56).

HRMS: *m/z* calcd for C₁₆H₁₄SN₃O (MH⁺), 296.0857; found, 296.0855.

3,3'-(1,2-Ethanediy)bis-1*H*-quinoxalin-2-one (11)

The product was only sparingly soluble in organic solvents. It was washed thoroughly with hot methanol; mp 305–307 °C.

¹H NMR (DMSO-*d*₆): δ = 12.11 (s, exch., 2 H), 7.45 (dd, *J* = 8, 1 Hz, 2 H), 7.24 (apparent dt, *J* = 8, 1 Hz, 2 H), 7.07–7.01 (m, 4 H), 3.04 (s, 4 H).

EI-MS: *m/z* (%) = 319 (*M*⁺ + 1, 5), 318 (*M*⁺, 16), 279 (2), 185 (3), 173 (7), 160 (12), 145 (17), 131 (49), 104 (38), 90 (76), 77 (100), 63 (79).

HRMS: *m/z* calcd for C₁₈H₁₄N₄O₂ (*M*⁺), 318.1117; found, 318.1113.

3-(2-Hydroxy-1-methyl-2-phenylethyl)-1H-quinoxalin-2-one (12)

Purified by column chromatography (silica gel; Et₂O-hexane, 2:1); mp 156–158 °C.

Compound **12** appears in its NMR spectra as a mixture of two isomers, **a** and **b**, in a ratio of 5:2. ¹H NMR (DMSO-*d*₆): **12a**, δ = 12.29 (s, exch., 1 H), 7.75 (d, *J* = 8 Hz, 1 H), 7.47 (apparent t, *J* = 8 Hz, 1 H), 7.40–7.22 (m, 6 H), 7.15 (t, *J* = 7 Hz, 1 H), 5.27 (d, *J* = 5 Hz, exch., 1 H), 5.10 (apparent t, *J* = 5 Hz, 1 H), 3.70 (m, 1 H), 1.19 (d, *J* = 7 Hz, 3 H); **12b**, δ = 12.29 (s, exch., 1 H), 7.75 (d, *J* = 8 Hz, 1 H), 7.47 (apparent t, *J* = 8 Hz, 1 H), 7.40–7.22 (m, 6 H), 7.15 (t, *J* = 7 Hz, 1 H), 5.23 (d, *J* = 4 Hz, exch., 1 H), 4.98 (dd, *J* = 4 & 9 Hz, 1 H), 3.70 (m, 1 H), 0.90 (d, *J* = 7 Hz, 3 H).

¹³C NMR (DMSO-*d*₆): **12a**, δ = 163.6 (s), 154.6 (s), 145.1 (s), 131.9 (s), 131.8 (s), 129.8 (d), 128.6 (d), 128.0 (d), 127.3 (d), 126.5 (d), 123.4 (d), 115.45 (d), 73.7 (d), 43.5 (d), 13.2 (q); **12b**, δ = 164.6 (s), 155.1 (s), 144.7 (s), 132.1 (s), 131.8 (s), 129.8 (d), 128.5 (d), 128.3 (d), 127.5 (d), 126.9 (d), 123.4 (d), 115.49 (d), 76.4 (d), 43.4 (d), 15.7 (q).

EI-MS: *m/z* (%) = 281 (M⁺ + 1, 3), 280 (M⁺, 1), 238 (9), 174 (100), 145 (96), 131 (19), 105 (60), 77 (78).

CI-MS: *m/z* (%) = 281 (MH⁺, 20%), 263 (6), 192 (5), 175 (100), 147 (9), 105 (4).

HRMS: *m/z* calcd for C₁₇H₁₇N₂O₂ (MH⁺), 281.1290; found, 281.1288.

3-(2-Hydroxy-1-methyl-2,2-diphenylethyl)-1H-quinoxalin-2-one (13)

Recrystallised from EtOAc-Et₂O (1:1); mp 177–178 °C.

¹H NMR (DMSO-*d*₆): δ = 12.72 (s, exch., 1 H), 7.75–7.65 (m, 5 H), 7.53 (apparent dt, *J* = 8, 1 Hz, 1 H), 7.45–7.32 (m, 4 H), 7.24 (apparent t, *J* = 8 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 2 H), 7.03 (apparent t, *J* = 8, 1 H), 6.07 (s, exch., 1 H), 4.96 (q, *J* = 7 Hz, 1 H), 1.32 (d, *J* = 7 Hz, 3 H).

¹³C NMR (DMSO-*d*₆): δ = 165.8 (s), 156.6 (s), 148.9 (s), 146.4 (s), 132.1 (s), 130.9 (d), 128.6 (d), 128.5 (d), 126.8 (d), 126.1 (d), 125.0 (d), 116.3 (d), 80.8 (s), 41.0 (d), 15.4 (q).

EI-MS: *m/z* (%) = 357 (M⁺ + 1, 12), 356 (M⁺, 32), 339 (10), 238 (19), 223 (100).

CI-MS: *m/z* (%): 357 (MH⁺, 80), 339 (100).

HRMS: *m/z* calcd for C₂₃H₂₁N₂O₂ (MH⁺), 357.1603; found, 357.1608.

3-[1-(1-Hydroxycyclohexyl)propyl]-1H-quinoxalin-2-one (14)

Recrystallised from EtOAc-Et₂O (1:1); mp 156–157 °C.

¹H NMR (DMSO-*d*₆) δ 12.41 (s, exch., 1 H), 7.76 (dd, *J* = 8, 1 Hz, 1 H), 7.49 (apparent dt, *J* = 8, 1 Hz, 1 H), 7.31–7.24 (m, 2 H), 4.43 (s, exch., 1 H), 3.47 (br, 1 H), 1.90–0.95 (m, 12 H), 0.67 (t, *J* = 7 Hz, 3 H).

¹³C NMR (DMSO-*d*₆): δ = 164.1 (s), 156.1 (s), 131.9 (s), 131.6 (s), 130.1 (d), 128.7 (d), 123.6 (d), 115.6 (d), 73.0 (s), 41.7 (d), 35.5 (t), 25.3 (t), 21.7 (t), 21.6 (t), 13.1 (q).

EI-MS: *m/z* (%) = 386 (M⁺, 11), 188 (100), 173 (44), 160 (16), 81 (19), 65 (33).

CI-MS: *m/z* (%) = 287 (MH⁺, 91), 269 (35), 247 (43), 189 (100), 116 (24).

HRMS: *m/z* calcd for C₁₇H₂₃N₂O₂ (MH⁺), 287.1759; found, 287.1755.

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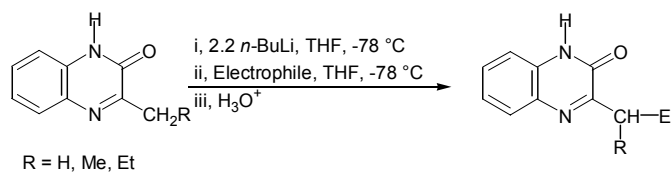
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Lithiation and Side-Chain Substitution of 3-Alkyl-1*H*-quinoxalin-2-ones

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