Addition of α-Lithiated Nitriles to Azaheterocycles

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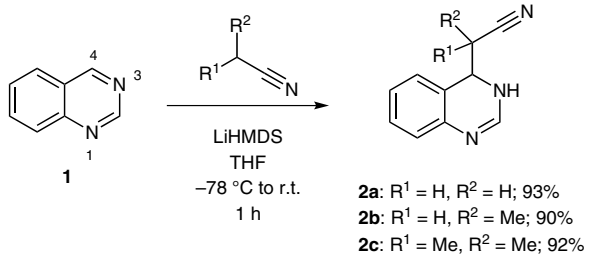
Abstract: The addition of α-deprotonated nitriles to azaheterocycles followed by rearomatization is described. A simple two-step, one-pot procedure for the sequence is also presented.

Key words: quinazoline, oxidation, nitrile, dehydrogenation, pyrimidine

During the course of a medicinal chemistry program, we observed that α-lithiated nitriles readily added across the N3=C4 bond in the quinazoline (**1**) ring system (Scheme 1). Inspired by this observation, we felt that this reaction could be useful for the introduction of fragments that readily increases the fraction sp^3 character[1] of a molecule and provides a handle for additional manipulation.



Scheme 1 Preparation of dihydroquinazolines

The addition of organolithium and Grignard reagents across the N1=C6 position of a pyrimidine ring, followed by oxidation, is a well-established route to substituted alkyl and aryl pyrimidines.[2] Addition of a *tert*-butyl radical[3] and enolates (such as malonate) to the N3=C4 bond of quinazoline (**1**) have been briefly described, but were limited to very reactive carbanions and further oxidation was not thoroughly investigated.[4] Alternatively, direct displacement of 4-chloroquinazoline or 4-methoxyquinazoline with the sodium enolates has also been used to synthesize similar compounds,[5] but this introduces the need to prepare the activated quinazoline ring.

We felt that addition of α-deprotonated nitriles to the N3=C4 bond in the quinazoline system, followed by rearomatization, was an underutilized synthetic sequence worth exploring. Our aim was to develop reaction conditions that allowed the introduction of a wide variety of nitrile inputs onto the quinazoline core followed by dehydrogenation to the parent heterocycle. We were also interested in evaluating if this sequence could be extended to other heterocyclic systems and enolates.

Initially, the addition of α-lithiated nitriles[6] to quinazoline (**1**) was evaluated; acetonitrile, propiononitrile, and isobutyronitrile all added to quinazoline smoothly yielding the desired dihydroquinazaolines **2a**–**c** in excellent yields (Scheme 1).

It is worth noting that these intermediates were stable and readily isolated by column chromatography. With these building blocks in hand, dehydrogenation conditions to convert the newly substituted dihydroquinazoline into its corresponding quinazoline were explored (Table 1).

Oxidation conditions based around bleach (NaClO),[7] $NaClO_2$,[8] DDQ,[2] oxone,[9] or iron[10] failed to provide any dehydrogenation of the functionalized quinazoline (data not shown). Iodine,[11] hypervalent iodine reagents,[12] and CAN showed promise,[13] but in some cases also caused the cleavage of the nitrile back to the starting quinazoline (Table 1, entries 1–5). Oxidation conditions using catalytic copper chloride with *tert*-butyl hydrogen peroxide (TBHP) gave an excellent conversion into product (Table 1, entry 6).[14] Increasing the amount of the $CuCl_2$ and TBHP shortened the reaction time and improved the yield (Table 1, entry 7). Manganese dioxide under microwave conditions[15] provided a fast conversion into **3**, but did not translate to a favorable isolated yield due to oxygenated side products (Table 1, entry 8). Aqueous potassium permanganate in the presence of acetic acid gave an incomplete conversion into product (Table 1, entry 9) and caused the undesired formation of quinazoline (**1**). However, stirring **2c** with $KMnO_4$ in acetonitrile at room temperature provided rapid and clean conversion into **3** in a good isolated yield (Table 1, entry 10).

Having established oxidation protocols, we wanted to simplify the procedure by developing a one-pot addition–oxidation sequence. In these reactions, the oxidant was added directly to the reaction mixture after the intermediate dihydroquinazoline was formed. Slightly altered conditions were evaluated to account for the lack of purification between steps. In all cases (Table 2) the desired product was formed, with the addition of two equivalents of $KMnO_4$ and acetonitrile as a cosolvent providing results identical to the two-step sequence.

Using this optimized one-pot procedure,[16] the scope of secondary nitriles was evaluated in the reaction sequence (Table 3). Simple nitriles performed best in this reaction (Table 3, entries 1–3). Alkyl amines and free amino groups were tolerated but the latter at the cost of a lower

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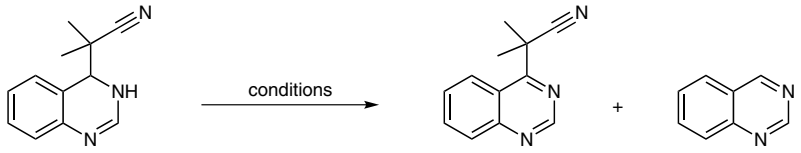
Table 1 Evaluation of Oxidation Conditions

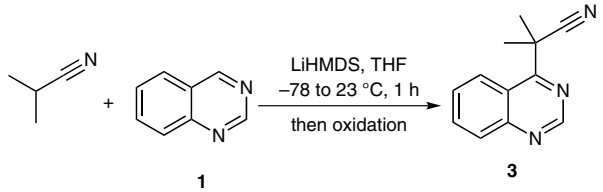


2c **3** **1**

Entry	Reaction conditions	Ratio **2c**/**3**/**1**[a]	Yield (%)[b]
1	I_2 (2 equiv), MeCN, 50 °C	37:10:53	–
2	IBD (2.2 equiv), CH_2Cl_2, r.t., 24 h	7:31:62	–
3	IBX (1.1 equiv), CH_2Cl_2, r.t. to 80 °C, 24 h	0:88:12	–
4	DMP (2.2 equiv), MeCN, r.t., 3 h	86:14:0	–
5	CAN (3 equiv), acetone, 50 °C, 24 h	38:62:0	–
6	$CuCl_2$ (0.01 equiv), TBHP (2 equiv), K_2CO_3 (0.1 equiv), CH_2Cl_2, 35 °C, 24 h	4:92:4	54
7	$CuCl_2$ (0.1 equiv); TBHP (4 equiv), K_2CO_3 (0.3 equiv), CH_2Cl_2, 35 °C, 3 h	2:96:2	63
8	MnO_2 (10 equiv), CH_2Cl_2, 100 °C, microwave	0:94:6	38
9	$KMnO_4$ (1 equiv), H_2O–AcOH (8:1), 60 °C, 24 h	35:48:17	–
10	$KMnO_4$ (1 equiv), MeCN, r.t., 3 h	0:99:1	74

[a] Conversion as analyzed by LC–MS at 220.
[b] Isolated yield of **3**.

Table 2 One-Pot Addition then Oxidation



1 **3**

Entry	Conditions	Yield (%)[a]
1	IBD (1.1 equiv), 23 °C, 8 h	43
2	$CuCl_2$ (0.01 equiv), TBHP (2 equiv), 50 °C, 8 h	31
3	MnO_2 (10 equiv), 50 °C, 7 h	66
4	$KMnO_4$ (2 equiv), MeCN, r.t., 4 h	75

[a] Isolated yield.

yield (Table 3, entries 4 and 5). Common amine protecting groups such as Boc, Bn, and Cbz were unaffected in the synthetic sequence (Table 3, entries 6–8).

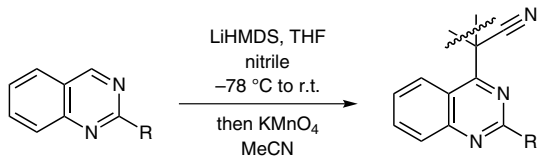
In addition, both the 2-chloroquinazoline (Table 3, entry 10) and ethyl quinazoline-2-carboxylate (Table 3, entry 11) reacted likewise, but in reduced yield. In the case of the ester, the lower yield was due to a competing side reaction of the deprotonated nitrile with the ester to produce a ketone; this could be minimized by not allowing the reaction mixture to go above 0 °C during the addition of the lithiated nitrile to quinazoline. The use of secondary benzylic nitriles (Table 3, entry 9) was limited by its poor addition to quinazoline (ca. 10% conversion by LC–MS analysis) and attempted oxidation gave a mixture of over-oxidized products.

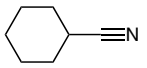
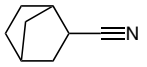
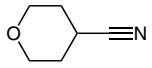
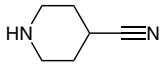
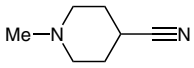
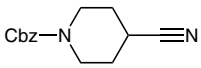
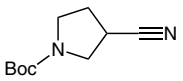
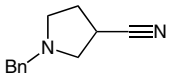
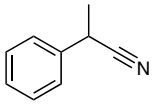
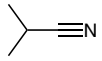
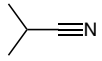
Heterocycles other than quinazoline were evaluated under the one-pot reaction conditions (Table 4). Pyrimidines with an ester or halogen gave the desired products, but in reduced yield. LC–MS analysis of the reaction mixture showed that the nitrile did add to the pyrimides in >80% conversion, but oxidation generated undesired side products and may have caused some of the intermediate to revert back to the starting heterocycle thus reducing the yields.

The electronics of the ring system played an important part in facilitating reactivity. Pyrimidines with multiple electron-donating groups (Table 4, entry 6), did not react to provide the dihydropyrimidine intermediate (via LC–MS analysis). Conversely, heterocycles with strong electron-withdrawing groups (Table 4, entry 7) reacted readily with the deprotonated nitrile to provide the dihydro intermediate followed by dehydrogenation to the desired product. Nitrile- and CF_3-substituted pyridines were also evaluated, but failed to undergo reaction with the α-lithiated nitrile.

In addition to secondary nitriles, we were interested in being able to introduce both primary nitriles and acetonitrile to the heterocyclic core. Compounds **2a** and **2b** were subject to $KMnO_4$ dehydrogenation, but the major product in

Table 3 Nitrile Inputs



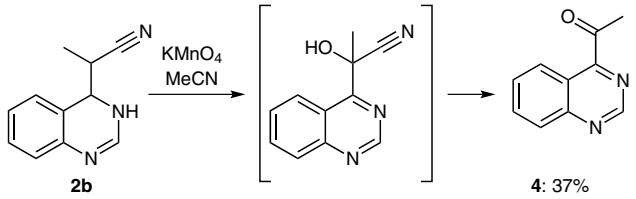
Entry	Nitrile	R	Yield (%)[a]
1		H	94
2		H	92
3		H	76
4		H	51
5		H	82
6		H	84
7		H	82
8		H	84
9		H	0[b]
10		Cl	46
11		CO_2Et	42

[a] Isolated yield.
[b] See text.

both cases was rearomatization followed by further oxidation of the benzylic center. Reducing the equivalents of $KMnO_4$ did not stop the overoxidation. In the case of the secondary nitrile **2b**, aromatization was followed by benzylic hydroxylation. A retro-Strecker-type process eliminates cyanide to give the methyl ketone derivative in 37% yield (Scheme 2).[17] Although, not the desired outcome, this represents a novel way to produce 4-keto-quinazolines.

Other nucleophiles were evaluated to expand the inputs available to us. Deprotonated sulfones participated in the sequence to give both quinazoline and pyrimidine derivatives (Table 5).

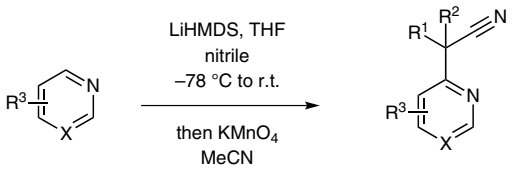
The lithium enolate of ethyl isopropylester readily added to give a dihydroquinazoline intermediate (as observed by LC–MS analysis), but instead of dehydrogenation, the intermediate converted back into quinazoline after the addition of $KMnO_4$ (Table 5, entry 5).[18] Isolation of the intermediate dihydroquinazoline was also unsuccessful.

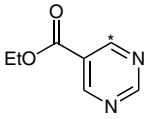
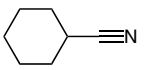
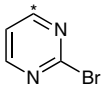
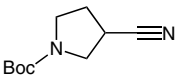
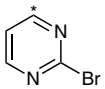
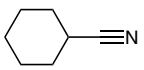
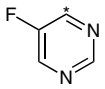
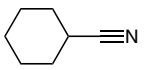
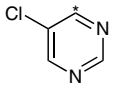
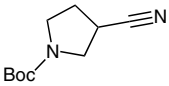
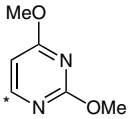
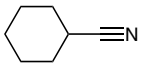
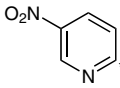
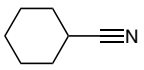


Scheme 2 $KMnO_4$ oxidation of **2b**

In conclusion, we have shown that the lithium salts of nitriles efficiently add to quinazolines yielding dihydroquinazolines. The products from the addition of secondary nitriles undergo dehydrogenation to the desired quinazoline derivative with several oxidizing reagents, $KMnO_4$ proving to be the most efficient. Pyrimidines, as well as other enolates, also have the potential to undergo this type

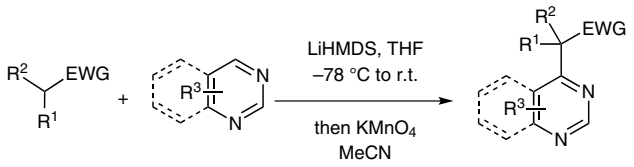
Table 4 Heterocyclic Inputs

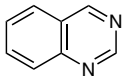
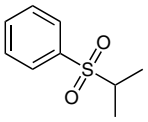
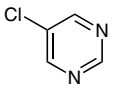
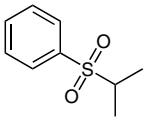
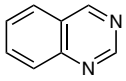
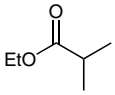


Entry	Heterocycle[a]	Nitrile	Yield (%)[b]
1			19
2			26
3			19
4			20
5			43
6			0[c]
7			21[d]

[a] * Denotes the position of substitution.
[b] Isolated yield.
[c] See text.
[d] Addition was only observed at the 6 position of the pyridine.

Table 5 Other α-Lithiated Electrophiles



Entry	Heterocycle	$R^1R^2CH_2EWG$	Yield (%)[a]
1			38
2			45
5			0[b]

[a] Isolated yield.
[b] See text.

of chemistry, but in lower yields. Future work will be directed to expanding the scope of heterocycles that can participate in this reaction along with enabling the use of other enolates.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) **General Procedure: 1-(Quinazolin-4-yl)-cyclohexanecarbonitrile (Table 3 Entry 1)**
To a solution of cyclohexanecarbonitrile (146 μL, 1.2 mmol, 1.2 equiv) in THF (5 mL) at –78 °C was added LiHMDS (1.2 mL of 1 M in THF, 1.2 mmol, 1.2 equiv) dropwise and stirred at –78 °C for 5 min. Quinazoline (130 mg, 1.0 mmol, 1.0 equiv) was added, the cooling bath was removed, and the reaction mixture was stirred for 1 h. Solid $KMnO_4$ (316 mg, 2 mmol, 2 equiv) and MeCN (1 mL) were added, and the reaction mixture was stirred at r.t. until the reaction was complete (as judged by LC–MS analysis, in this case 4.5 h). The reaction mixture was poured into sat. aq $NaHCO_3$ and extracted with EtOAc (3×). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The crude residue was purified by silica gel flash chromatography (12 g silica, 0–40% EtOAc in hexanes) to yield 1-(quinazolin-4-yl)cyclohexane-carbonitrile as a white solid (222 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1 H), 8.70 (d, *J* = 8.6 Hz, 1 H), 8.13 (d, *J* = 8.2 Hz, 1 H), 7.94 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1 H), 7.72 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1 H), 2.52 (d, *J* = 12.3 Hz, 2 H), 2.17–2.08 (m, 2 H), 2.02–1.95 (m, 4 H), 1.93–1.87 (m, 1 H), 1.40–1.28 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.61, 153.75, 151.05, 133.79, 130.02, 127.89, 124.73, 122.31, 121.92, 44.40, 35.58, 25.06, 22.97 ppm.
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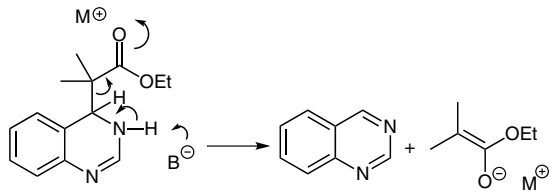
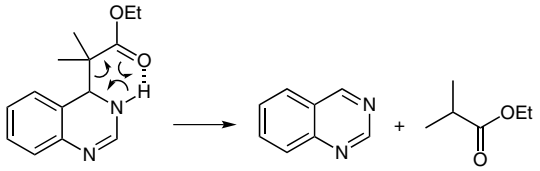
(18) We speculate that the ease of enolate formation may be why dehydrogenation was not observed under these conditions (Scheme 3). Alternatively, as pointed out by a reviewer, the ester intermediate can adopt a six-membered transition state that could facilitate the reverse process (Scheme 4).



Scheme 3



Scheme 4

