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Observation of differential reactivity of cyclic amines in S_N2 and S_NAr displacement reactions in the course of synthesizing C-6, C-7 substituted quinolinecarbonitrile MEK1 kinase inhibitors

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Abstract—We have previously reported on a series of 4-anilino-6,7-dialkoxy-3-quinolinecarbonitriles as potent inhibitors of MEK1 kinase. Herein, we describe our synthetic efforts toward a series of 4-anilino-6-alkoxy-7-amino-3-quinolinecarbonitriles. In the course of this work, we were able to rapidly construct a library of 4-anilino-6-alkoxy-7-amino-3-quinolinecarbonitriles by simultaneous or sequential S_N2 (displacement) reactions on the C-6 chloroalkoxy moiety and S_NAr (addition/elimination) reactions at C-7 with nucleophilic amines.

We have previously described 4-anilino-3-quinolinecarbonitriles as potent MEK1 kinase inhibitors.[1a–c] MEK1 kinase is a component of the Ras-MAPK signaling pathway, which is of central importance to cell growth and proliferation.[2] Aberrant signaling within this pathway has been associated with various human cancers and inflammatory diseases.[3] Thus, it has been proposed that MEK1 kinase inhibitors could serve as useful pharmaceutical agents in the treatment of these diseases.[4] As part of our effort to optimize 4-anilino-3-quinolinecarbonitriles **I** as potential drug candidates, our goal was to synthesize novel analogs containing basic amine water solubilizing groups attached through an alkoxy chain at C-6 and an additional amino heterocycle at C-7 via simultaneous or sequential reactions (Fig. 1). Target compounds **I** possessing the same cyclic amine at the C-6 alkoxy linker and at C-7 were synthetically accessible by heating intermediate **II** with an excess of amine under appropriate reaction conditions. However, to attach two different amines at these positions, it would be necessary to discriminate between a nucleophilic substitution reaction S_N2 (displacement) on the C-6 chloroalkoxy moiety and the S_NAr (addition/elimination) at C-7.

The key 4-anilino-3-cyanoquinoline intermediates **5** and **6** were synthesized as outlined in Scheme 1. Thus 4-chloroquinoline-3-carbonitrile **1**[5] was reacted with aniline **2**[1c] in the presence of pyridine hydrochloride to give the 6-methoxy, 7-fluoro intermediate **3**,[1c] which was subsequently demethylated using LiI in 2,4,6-collidine to give **4**. The reaction of **4** with chloroethyl or chloropropyl tosylate provided intermediates **5** and **6**[6], respectively.

Compounds **7**, **8**, **10–12** (Table 1), which possess the same cyclic amines on the C-6 alkoxy chain and at

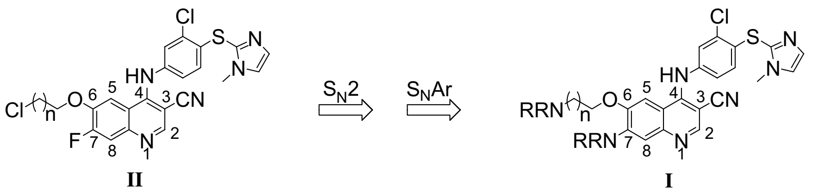

Figure 1.

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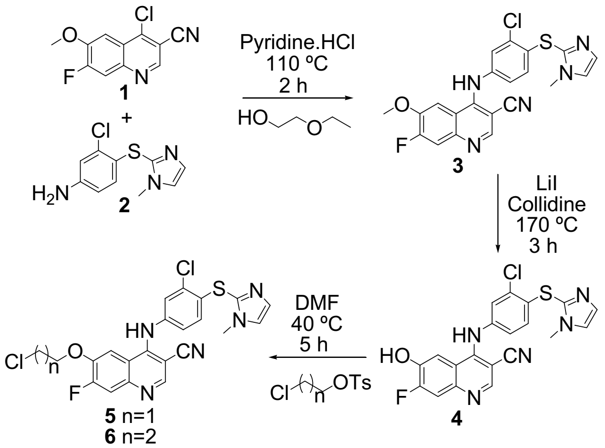
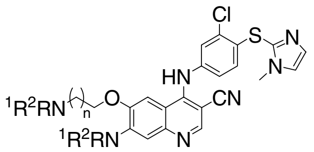


Scheme 1.

Table 1.



Compound	*n*	NR^1R^2	Yield[a] (%)	Temperature (°C)
7	1	Pyrrolidine	40	90
8	1	Piperidine	29	90
9	2	Pyrrolidine	41	40
10	2	Piperidine	52	70
11	2	Morpholine	55	110
12	2	Thiomorpholine	57	110

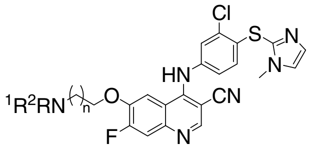
[a] Isolated yields.

C-7, were synthesized by reacting the amines with intermediate **5** or **6** at 70–110 °C in NMP, with catalytic NaI added (Scheme 2, Step A).[7] Notably, pyrrolidine was sufficiently nucleophilic to provide target compound **9** from intermediate **6** when reacted at 40 °C. It was anticipated that amines could first be attached to the C-6 alkoxy chains by performing the S_N2 reaction at lower temperatures (Scheme 2, Step B), followed by the installation of a second amine at C-7 via a S_NAr reaction (Scheme 2, Step D) at elevated temperatures. Thus, the chloride displacement step was carried out with morpholine, thiomorpholine, and *N*-methylpiperazine (β-heteroatom containing cyclic amines) at 70 °C to provide **13**–**18** in 37–78% yield (Table 2), with no detectable fluoride displacement at C-7 (Scheme 2, Step B). From these intermediates, different amines were subsequently added at C-7 (Scheme 2, Step D) to provide **23**–**33** (Table 3).

When alkyl cyclic amines pyrrolidine and piperidine were reacted with intermediates **5** and **6**, selective S_N2 displacement of the C-6 alkyl chlorides did not occur even at lower temperatures. As already noted, pyrrolidine displaced both the alkoxy chloride and the C-7 aryl fluoride simultaneously when reacted with **5** or **6** even at 40 °C. A similar result was observed with piperidine at 70 °C. An LC–MS analysis of the partially completed reactions (data not shown) revealed that both S_N2 and S_NAr reaction products were proceeding at similar rates. Thus, while all of the amines readily displaced the alkyl chloride at 40–70 °C, a clear difference in reactivity was observed in the C-7 aryl fluoride displacement between the β-heteroatom containing cyclic amines and the alkyl cyclic amines.

Previous studies have demonstrated that cyclic amines undergo S_N2 displacement reactions at relatively similar rates. Thus, for example, Bunting et al.[8] showed that pyrrolidine and piperidine had reaction rate constants

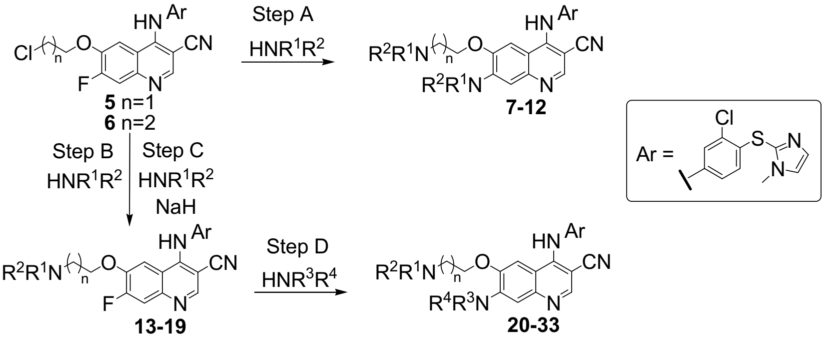
Table 2.



Compound	*n*	NR^1R^2	Yield[a] (%)	Temperature (°C)
13	1	Morpholine	54	70
14	1	Thiomorpholine	54	70
15	1	*N*-Methylpiperazine	37	70
16	2	Morpholine	78	70
17	2	*N*-Methylpiperazine	65	70
18	2	*N*-Ethylpiperazine	44	70
19	2	Pyrrolidine[b]	29	40

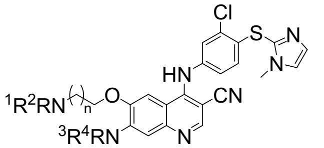
[a] Isolated yields.

[b] Typical reaction conditions,[7] with 2 equiv NaH added.



Scheme 2.

Table 3.



Compound	*n*	NR^1R^2	NR^3R^4	Yield[a] (%)	Temp (°C)
20	2	Pyrrolidine	*N*-Methylpiperazine	39	120
21	2	Pyrrolidine	*N*-Ethylpiperazine	54	120
22	2	Pyrrolidine	1-Methyl-1,4-diazepane	58	120
23	1	Morpholine	Pyrrolidine	62	70
24	1	Morpholine	Piperidine	62	70
25	1	Thiomorpholine	Pyrrolidine	94	70
26	1	Thiomorpholine	Piperidine	77	70
27	1	*N*-Methylpiperazine	Pyrrolidine	59	70
28	1	*N*-Methylpiperazine	Piperidine	45	70
29	2	Morpholine	1-Methyl-1,4-diazepane	60	110
30	2	*N*-Methylpiperazine	*N*-Ethylpiperazine	60	115
31	2	*N*-Methylpiperazine	1-Methyl-1,4-diazepane	50	115
32	2	*N*-Ethylpiperazine	Pyrrolidine	55	75
33	2	*N*-Ethylpiperazine	1-Methyl-1,4-diazepane	40	110

[a] Isolated yields.

5.2 and 3.0-fold, respectively, higher than morpholine in the aminolysis of methyl 4-nitrobenzene sulfonate. This is consistent with our finding that the different amines displaced the alkyl chloride under similar conditions. In contrast, the amines with β-heteroatoms were significantly less reactive than piperidine and pyrrolidine in the S_NAr reaction at 70 °C. Consistent with this observation, Caswell and Goldsmith[9] have reported that the uncatalyzed reaction rate constant for morpholine was 106 times less than pyrrolidine and 25 times less than piperidine in an S_NAr reaction with 3-fluoro-*N*-methylphthalimide in acetonitrile. In this work,[9] it was concluded that these rate differences were attributable to molecular size and basicity, with the smaller, strongly basic pyrrolidine providing the fastest reaction rates for the nucleophilic addition and base-catalyzed decomposition of the Meisenheimer adduct. In contrast, the less basic morpholine reacted significantly more slowly in the initial nucleophilic addition step, and apparently did not show evidence of base catalysis in the decomposition step. We believe that the same factors are responsible for the rate differences observed in our fluoro-substituted quinoline ring system, which has allowed us to selectively perform the S_N2 displacement reactions only with the less basic β-heteroatom containing cyclic amines.

To overcome the lack of selectivity of pyrrolidine and piperidine with regard to the S_N2 and S_NAr reactions, it was necessary to implement a new strategy to provide the desired target compounds. We hypothesized that C-7 fluoride displacement could be inhibited by adding sodium hydride to the reaction mixture. The strong base would deprotonate the quinolinecarbonitrile ring system, thereby adding electron density to intermediates **5** and **6**, and inhibiting attack by a nucleophile. This approach proved to be successful using pyrrolidine (Scheme 2, Step C), providing intermediate **19** (Table 2) in acceptable yield. The pyrrolidine-substituted intermediate **19** was further reacted with different amines at C-7 (Scheme 2, Step D) to provide target compounds **20**–**22** (Table 3).

In conclusion, we observed a divergence in reactivity for pyrrolidine and piperidine vs amines that contain β heteroatoms in competing S_N2 and S_NAr reactions on substituted quinoline-3-carbonitrile intermediates **5** and **6**. By utilizing the appropriate reaction conditions, we were able to distinguish between S_N2 and S_NAr reactions and rapidly synthesize a diverse library of 34 target compounds possessing amine groups attached at C-6 and C-7 to explore the structure–activity relationships of this series. Several of these analogs proved to be potent inhibitors of MEK kinase. These results will be published elsewhere in due course.

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7. *Typical procedure* (*example* **11**): A mixture of **2b** (50 mg, 0.1 mmol), morpholine (90 mg, 1.0 mmol), NaI (10 mg) in NMP (1 mL) was stirred at 110 °C for 5 h. The reaction was cooled and diluted with saturated aqueous solution of sodium bicarbonate. The resulting solid was isolated by filtration and washed with water. The crude solid was purified by flash chromatography using a gradient of 97:3 to 92:8 MeOH/CH_2Cl_2 to give a yellow solid (34 mg, 55% yield). ^1H NMR (DMSO-d_6, 400 MHz): 9.53 (s, 1H), 8.48 (s, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.36 (d, 1H, $J = 2.4$ Hz), 7.25 (s, 1H), 7.15 (s, 1H), 7.11 (dd, 1H, $J = 2.4$, 8.4 Hz), 6.57 (d, 1H, $J = 8.4$ Hz), 4.14 (t, 4H, $J = 6$ Hz), 3.78 (m, 4H), 3.59 (m, 6H), 3.19 (m, 4H), 2.37 (m, 4H), 1.91 (m, 2H); MS (M+1) 620.3; mp 224–226 °C.
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