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A microwave-assisted nucleophilic substitution reaction on a quinoline system: the synthesis of amino analogues of nitroxoline

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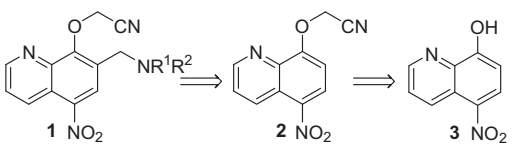
ABSTRACT

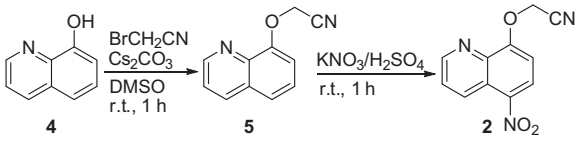
A reliable protocol for the synthesis of a series of 8-amino analogues of pharmacologically interesting nitroxoline (5-nitro-8-hydroxyquinoline) is described. The unprecedented displacement of the cyanomethoxy group of an O-cyanomethylated quinoline derivative by various primary and secondary amines selectively affords 5-nitroquinolin-8-ylamines in moderate-to-high yields. The reactions were accelerated significantly under microwave conditions in comparison with conventional heating.

The quinoline scaffold is prevalent in several natural and synthetic compounds that display a broad range of biological activities.[1] For example, 8-aminoquinolines exhibit antimalarial[2a] and antimicrobial[2b] behavior, whereas compounds containing the hydroxyquinoline pharmacophore proved to be anti-tumor,[3a,c] anti-fungal[3b], and herbicidal[3b] agents. Furthermore, it was discovered that the well-established anti-microbial agent, nitroxoline[4] (5-nitro-8-hydroxyquinoline, **3**) is a potent inhibitor of cathepsin B, which is a promising therapeutic target as it participates in the degradation of extracellular matrix proteins in tumor tissues.[5] Moreover, nitroxoline has already shown promise as a potential anti-angiogenic[6a] and anti-cancer agent,[6b] and 7-aminomethylated derivatives (Mannich bases) of nitroxoline were examined for their growth-inhibitory effect.[7] Nitriles, on the other hand, are attractive because of their biological robustness.[8] A series of potent peptidomimetic cysteine cathepsin inhibitors containing C-terminal nitriles have been developed.[9]

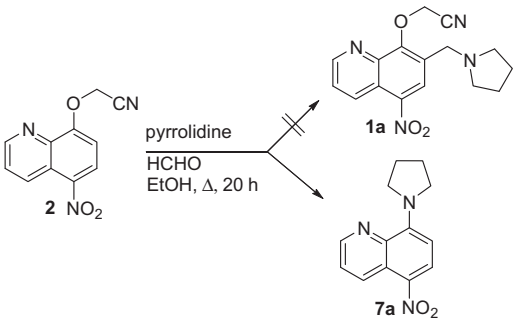


Scheme 1. Retrosynthetic pathway to nitroxoline-derived compounds **1**.

These facts have prompted us to design nitroxoline-derived compounds. Initially, we planned to synthesize 8-cyanomethoxy-7-aminomethylquinolines **1** starting from nitroxoline (**3**), as



Scheme 2. Synthesis of O-cyanomethylated quinoline **2**.



Scheme 3. Reaction of **2** with pyrrolidine under Mannich-reaction conditions.

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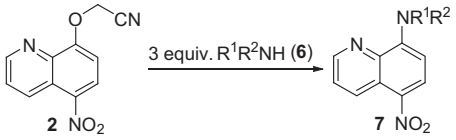
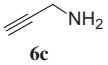
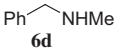
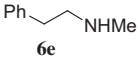
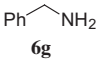
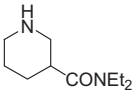
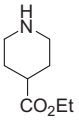
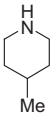
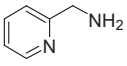
depicted in Scheme 1, since this synthetic strategy would allow us to incorporate a nitrile function into potentially active Mannich bases of nitroxoline.

Unfortunately, the first step, the reaction of nitroxoline (**3**) with bromoacetonitrile was not successful under the applied conditions, probably due to the combined electronic effects of the nitro group and the fused pyridine ring. Next, we found that 8-hydroxyquinoline (**4**) reacted easily in the presence of Cs_2CO_3 with one equivalent of bromoacetonitrile via its portion-wise addition to the reaction mixture, giving the 8-cyanomethoxy product **5** in an excellent yield of 91%. Standard nitration (HNO_3/H_2SO_4) of **5** led to the 5-nitro product **2** in a poor isolated yield (35%), mostly at the expense of the hydrolyzed by-product. Therefore we applied an efficient nitration procedure using a KNO_3/H_2SO_4 mixture that afforded the desired product **2** in an 85% yield (Scheme 2). To obtain selectively the 5-nitro product **2** it was crucial that a minimum amount of sulfuric acid was used and that the reaction was quenched after a short time by the rapid introduction of cold K_2CO_3 solution.

In order to obtain the 7-aminomethylated nitroxoline-derived compounds of type **1** we investigated the Mannich reaction of the O-cyanomethylated compound **2** with pyrrolidine in the presence of formaldehyde, as has been reported for the aminomethylation of nitroxoline.[7] Surprisingly, instead of **1a** we isolated only the

Table 1
Reactions of **2** with amines **6**



Entry	R^1R^2NH	Solvent	Reaction conditions	Time	Product (yield;%)[a]
1	 **6a**	EtOH MeCN	Reflux, standard heating[b] 100 °C (μW, 150 W)	20 h 1 h	**7a** (88) **7a** (89)
2	 **6b**	EtOH MeCN	Reflux, standard heating[b] 100 °C (μW, 150 W)	20 h 1 h	**7b** (85)[c] **7b** (76)[c]
3	 **6c**	EtOH EtOH	Reflux, standard heating[b] 100 °C (μW, 80 W)[d]	20 h 15 min	— **7c** (54)[c]
4	 **6d**	MeCN	100 °C (μW, 150 W)	1 h	**7d** (87)[c]
5	 **6e**	MeCN	100 °C (μW, 150 W)	1 h	**7e** (81)[c]
6	$Me_2NH{\cdot}HCl$ **6f**	MeCN	100 °C (μW, 150 W)[e]	2 h	**7f** (85)[c]
7	 **6g**	MeCN	100 °C (μW, 150 W)	2 h	**7g** (55)[c]
8	 **6h**	MeCN	100 °C (μW, 150 W)	1.5 h	**7h** (58)[c]
9	 **6i**	MeCN	100 °C (μW, 150 W)	2 h	**7i** (62)[c]
10	 **6j**	MeCN	100 °C (μW, 150 W)	2 h	**7j** (87)[c]
11	 **6k**	MeCN	100 °C (μW, 150 W)	2 h	**7k** (32)[c]

[a] Yields of isolated products.
[b] 10 equiv of amine **6**.
[c] Product isolated by radial chromatography.
[d] 5 equiv of amine **6c**.
[e] 2 equiv of $NaHCO_3$ was added.

8-aminoquinoline product **7a** resulting from the nucleophilic displacement of the cyanomethoxy group by pyrrolidine (Scheme 3). It is worth mentioning that a reverse approach, the reaction of 7-aminomethylated nitroxoline with bromoacetonitrile, was not successful.

Quinolines bearing good leaving groups, such as halo-, methoxy- or sulfonyloxy- are known to undergo aromatic nucleophilic substitution with sulfur,[10] oxygen,[10c] and nitrogen[10c,11] nucleophiles. Due to the very common presence of arylamine moieties in pharmaceutically relevant compounds,[2] methods for the amination of (hetero)aromatics are of significant utility. It was reported that the 8-dimethylamino group in highly activated 5,7-bis(trifluoroacetyl)quinoline could be replaced by various amines to afford the desired 8-quinolylamines.[12] Quinolylmethylamines were also prepared by the oxidative methylamination of nitroquinolines, but the method was rather unselective.[13] On the other hand, the Pd-catalyzed cross-coupling of 5- and 8-quinolyl halides and different amines (Buchwald–Hartwig reaction) provided efficiently the corresponding 5- and 8-quinolylamines.[14] To the best of our knowledge, there are no examples of the cyanomethoxy group acting as a leaving group in aromatic nucleophilic substitutions.

Thus, we focused our attention on the synthesis of 8-amino-5-nitroquinoline derivatives **7**, which actually represents the amino analogues of nitroxoline, in order to take advantage of the displacement of the cyanomethoxy group of quinoline **2** by nitrogen nucleophiles. After optimization, the reaction of **2** with a large excess (10 equiv) of pyrrolidine or morpholine in refluxing ethanol for 20 h afforded the products **7a** and **7b** in 88% and 85% yields, respectively (Table 1, entries 1 and 2). While the reaction of **2** with prop-2-yn-1-amine (**6c**) failed to provide the desired product **7c** under conventional heating for 20 h, substitution of the cyanomethoxy group occurred with the use of microwave (μW) conditions. Thus, a fifteen-minute irradiation (power level 80 W) of an ethanolic solution of quinoline **2** and five equivalents of amine **6c** provided *N*-(prop-2-ynyl)quinolin-8-amine **7c** in a 54% isolated yield (Table 1, entry 3). While the application of microwaves has received much attention in organic synthesis,[15] only a few examples of nucleophilic substitution in quinoline systems using microwave irradiation have been described.[10c,16] This encouraging result prompted us to investigate the microwave-promoted nucleophilic substitution reaction further.

In order to choose an appropriate solvent, the microwave-assisted reaction of quinoline **2** and *N*-benzylmethylamine (**6d**) was examined using CD_3OD, DMSO-d_6, and CD_3CN as solvents, respectively, at 100 °C (150 W) for 20 min. The crude product mixtures were investigated by ^1H NMR spectroscopy, which revealed that the reaction in deuterated acetonitrile resulted in the formation of the product **7d** solely, whereas in methanol-d_4 an unidentified by-product was formed. In DMSO-d_6, however, the quinoline **2** was not totally consumed. Therefore, acetonitrile was chosen as the solvent for this reaction.

The microwave-assisted nucleophilic substitution reaction of 8-cyanomethoxy-5-nitroquinoline (**2**) was carried out with a number of primary and secondary aliphatic as well as alicyclic amines **6** giving the corresponding 8-aminoquinoline derivatives **7** in reasonable yields (Table 1).

In a typical procedure,[17] a mixture of quinoline substrate **2** and three equivalents of an appropriate amine was subjected to microwave irradiation (150 W) at 100 °C in acetonitrile for the indicated time. When the syntheses of **7a** and **7b** were performed under microwave conditions, not only was the reaction accelerated (1 vs 20 h), but also, a smaller excess of amine was required (3 vs 10 equiv) compared to standard heating. The isolated yields, however, were comparable (Table 1, entries 1 and 2). While the yields of the products **7d–f** derived from secondary aliphatic amines **6d–f** were high (81–87%), the primary amine benzylamine (**6g**) gave a significantly lower isolated yield of product **7g** (55%) (Table 1, entries 4–7). Piperidines **6h** and **6i** containing either amide or ester functional groups afforded the 8-aminoquinolines **7h** and **7i** in modest yields; 4-methylpiperidine, on the other hand, gave a much higher yield of the amino product **7j** (Table 1, entries 8–10). Surprisingly, the reaction of **2** with pyridin-2-ylmethanamine (**6k**) led to the product **7k** in a disappointing isolated yield of 32% after chromatographic purification (Table 1, entry 11). Although the cyanomethoxy group could depart as formaldehyde and cyanide ion, following the reaction by NMR spectroscopy we were not able to detect such species [CAUTION!].[18]

In conclusion, we have demonstrated for the first time that a cyanomethoxy group can serve as a good leaving group in nucleophilic aromatic substitution in a quinoline system. The microwave-assisted displacement of the cyanomethoxy group of 8-cyanomethoxy-5-nitroquinoline (**2**) by various primary and secondary amines provided selectively the corresponding 8-quinolylamines in moderate-to-high yields. Our methodology provides rapid access to various 8-amino analogues of pharmacologically interesting nitroxoline.

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures, spectroscopic and analytical data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.017.

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17. Typical procedure for the microwave-assisted synthesis of 5-nitro-8-qunolinylamines **7**: a mixture of 8-cyanomethoxy-5-nitroquinoline (**2**) (115 mg, 0.502 mmol), morpholine (131 mg, 1.5 mmol), and acetonitrile (2 mL) was irradiated in a focused μW reactor (Discover by CEM Corporation, Matthews, NC) at 100 °C (150 W) for 1 h. The volatiles were evaporated and the residue purified by radial chromatography (eluent: CH_2Cl_2/MeOH, 50:1) to give 99 mg (76%) of product **7b**. Pale yellow crystals; mp 123.5–127 °C. IR (KBr, cm^{-1}) 3468, 3418, 2947, 2862, 2823, 1591, 1561, 1508, 1487, 1392, 1314, 1291, 1239, 1144, 1117, 1026, 980, 895, 829, 791, 741. 1H NMR (500 MHz, CDCl3) δ 3.68 (m, 4H), 4.03 (m, 4H), 7.03 (d, J = 9.0 Hz, 1H), 7.63 (dd, J = 9.0, 4.0 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 8.91 (dd, J = 4.0, 1.5 Hz, 1H), 9.26 (dd, J = 9.0, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 148.0, 140.8, 137.6, 133.0, 127.4, 123.9, 123.6, 112.1, 66.9, 52.0. HRMS (EI$^+$): calcd for $C_{13}H_{14}N_3O_3$ [M+H]$^+$: 260.103, found: 260.102. Anal calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 59.74; H, 5.00; N, 15.97.
18. CAUTION: the reaction may produce HCN.