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Synthesis of 7-aryl-1,8-naphthyridines via addition of aryl boronic acids to 1,8-naphthyridine *N*-oxides

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ABSTRACT

Simply combining aryl boronic acids with 1,8-naphthyridine *N*-oxides and heating at 110 °C in toluene or dimethylformamide affords the corresponding 7-aryl-1,8-naphthyridines. The reaction is not sensitive to air or moisture and the process can be extended to other electron-deficient heteroaromatic *N*-oxides.

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1,8-Naphthyridine derivatives show an exceptionally broad range of biological activities.[1] Consequently, new methods that allow the rapid and late-stage derivatisation of this class of molecule are highly attractive in research and optimisation of new pharmaceuticals and agrochemicals. Due to our own interest in 1,8-naphthyridines as novel herbicides,[2] we sought to prepare a range of 7-aryl substituted analogues (Fig. 1).

Whilst classic cross-coupling chemistry can be envisaged to instal the 7-aryl substituents, synthesis of the desired 7-chloronaphthyridine coupling partners suffered from a tedious chlorination step affording undesirable mixtures of the 5- and 7-chloronaphthyridines which were difficult to separate by chromatography (Scheme 1).[3] However, the preceding oxidation to the naphthyridine *N*-oxide occurs in good yield for a range of 6-halo-substituents as well as the 6-H parent compound (Scheme 1).[4,5] Consequently, our efforts turned toward introducing the aryl substituents directly from *N*-oxide.

Recently, Fagnou and co-workers reported the direct arylation of a range of heteroaromatic *N*-oxides.[6] However, the requirement for an excess of the *N*-oxide (1.5–4 equiv) coupling partner in this methodology was undesirable to us as the naphthyridine *N*-oxides were advanced intermediates. The arylation of pyridine *N*-oxides via the two-step Grignard addition, dehydration sequence reported by Almqvist and Olsson offers an alternative approach.[7] Inspired by this methodology and the Petasis reaction,[8] we reasoned that addition of aryl boronic acids to the naphthyridine *N*-oxides, followed by dehydration could also offer a plausible route towards the 7-arylated naphthyridines. As many aryl boronic acids are air and moisture stable, in addition to being commercially available with a vast range of aromatic substituents, this approach seemed attractive.[9] We report herein this novel chemistry towards 7-aryl-1,8-naphthyridines.

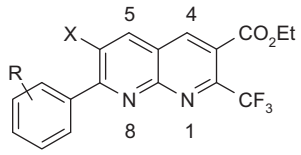

Figure 1.

Simply combining the naphthyridine *N*-oxide with the appropriate aryl boronic acid in toluene or DMF and heating the mixture to 110 °C for 16 h afforded the desired 7-aryl-1,8-naphthyridines (Table 1). In all cases, the aryl addition was completely selective for the 7-position of the 1,8-naphthyridines. The reactions were performed open to the air, with solvents used as purchased, making this process convenient for the synthesis of chemical libraries.

In general, electron-rich aryl boronic acids afforded the desired products in good yields (Table 1, entries 1–7). Aryl boronic acids which contained weak inductively withdrawing groups afforded the products in low to moderate yields (entries 8–11). Interestingly, the presence of a phenolic OH group caused no detrimental effect to the reaction (entry 3). Sterically hindered boronic acids could also be successfully employed in the reaction (entries 2 and 5), although a longer reaction time was needed for the mesityl analogue (entry 5). Whilst 3-furyl and 3-thienyl boronic acids gave

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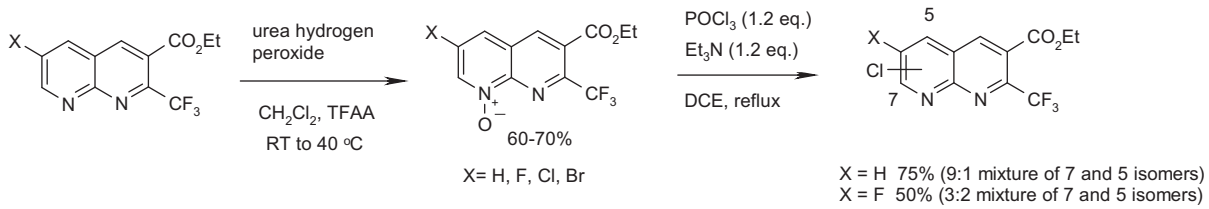
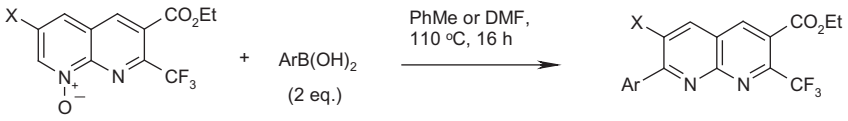


Scheme 1.

Table 1
Aryl boronic acid additions to naphthyridine *N*-oxides



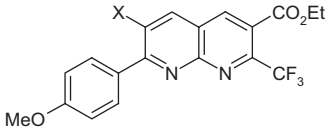
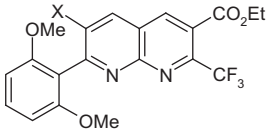
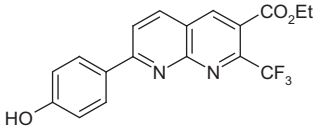
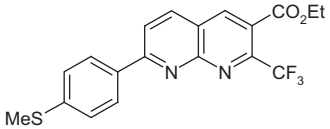
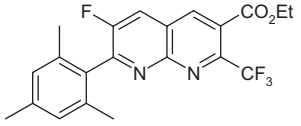
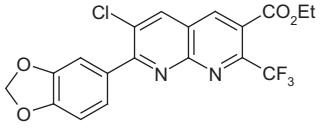
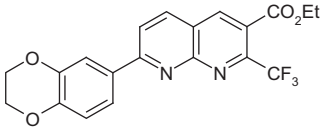
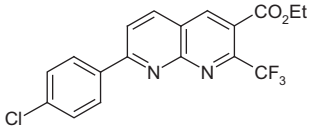
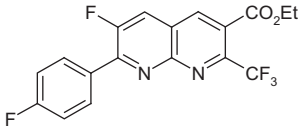
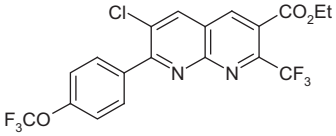
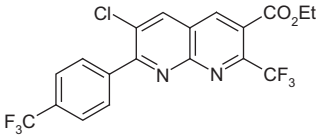
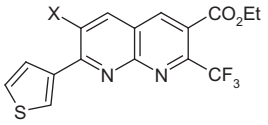
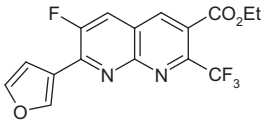
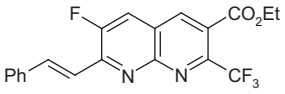
Entry	Product	Solvent	Yield (%)[a]
1		DMF PhMe DMF	**1a**:63 (X = H) **1b**:60 (X = F) **1c**:55 (X = Br)
2		DMF DMF	**2a**:63 (X = H) **2b**:60 (X = Cl)
3		DMF	**3**:72
4		PhMe	**4**:60
5[b]		PhMe	**5**:43
6		DMF	**6**:72
7		PhMe	**7**:71
8		DMF	**8**:30
9		PhMe	**9**:50

Table 1 (*continued*)

Entry	Product	Solvent	Yield (%)[a]
10		PhMe	**10**:35
11		PhMe	**11**:26
12		PhMe DMF	**12a**:57 (X = F) **12b**:52 (X = Br)
13		PhMe	**13**:34
14		PhMe	**14**:55

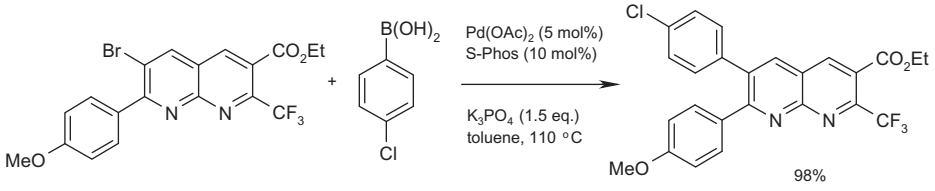
[a] Isolated yield.
[b] Reaction time of 40 h.

the expected products (entries 13 and 12), 2-thienyl boronic acid failed under the current reaction conditions. Styryl boronic acid was also found to couple well (entry 14).

The tolerance of chloro- and bromo-substituents under the reaction conditions is attractive as further elaboration of the scaffold can be carried out through cross-coupling chemistry. An example of this is shown in Scheme 2. After isolating the product from the boronic acid addition to the *N*-oxide, a Suzuki–Miyaura coupling afforded a 7,8-biaryl substituted 1,8-naphthyridine.[10]

Analysis of these reactions by LC–MS suggests the formation of the hydroxylamine intermediate **15** (Fig. 2) or its respective boric acid ester. This presumably eliminates water to afford the desired product.[11] It is possible that boronic acid aids this dehydration, forming boric acid in the process, although we have no evidence of this. Furthermore, selective 7-arylation may be a result of intramolecular transfer of the aryl group from boronate **16**. The only by-product isolated was the corresponding naphthyridine **17**. Notably, whilst these reactions tended to occur faster in dimethylformamide than toluene, larger amounts of by-product **17** resulted in dimethylformamide.[12] A limited solvent screen showed that dimethylformamide, toluene and 1,4-dioxane afforded comparable isolated yields. Performing the reaction in acetonitrile, at reflux, led to good conversion into intermediate **15**, however, dehydration to the naphthyridine was much slower in this solvent. The reaction failed completely when *N*-methyl-2-pyrrolidone or *n*-butanol was employed as the solvent. Furthermore, for the sterically hindered mesityl group, (Table 1, entry 5), formation of **15** seemed to be complete after 16 h, however, the dehydration step was found to be very slow for this analogue.

In an attempt to broaden the scope of this methodology, a small screen of other heterocyclic *N*-oxides was undertaken. Whilst the *N*-oxides of pyridine and quinoline resulted in no product or poor yield (Table 2, entries 1 and 2), the more electron-deficient pyridopyrazine and 1,7-naphthyridine *N*-oxides afforded the desired products in moderate yields (Table 2, entries 3 and 4).



Scheme 2.

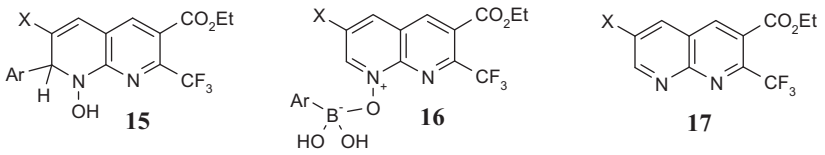
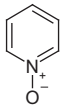
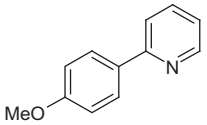
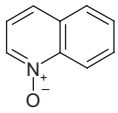
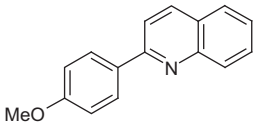
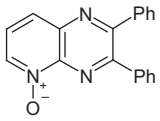
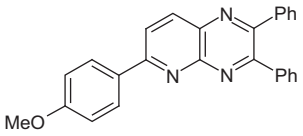
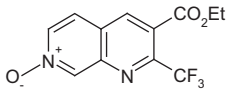
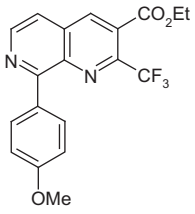


Figure 2.

Table 2
4-Methoxyphenyl boronic acid additions to heteroaryl *N*-oxides

Entry	*N*-oxide	Product	Yield (%)[a]
1			0
2			10
3			51
4[b]			32

[a] Isolated yield.
[b] Reaction time of 60 h.

In summary, a novel and user-friendly process for the arylation of 1,8-naphthyridine *N*-oxides is reported that can be extended to other electron-deficient heterocycles.[13] The application of this methodology to the discovery of novel agrochemicals is ongoing within our laboratories.

Acknowledgement

We thank Andrew Blackaby (Syngenta) for mass spectrometry assistance.

References and notes

1. Litvinov, V. P. *Adv. Heterocycl. Chem.* **2006**, *91*, 189–300.
2. (a) Mitchell, G.; Salmon, R; Bacon, D. P.; Aspinall, I. H.; Briggs, E.; Avery, A. J.; Morris, J. A.; Russell, C. J. W.O. Patent 2009115788; *Chem. Abstr.* **2009**, *151*, 403283; (b) Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *9*, 2373–2375.
3. For the effect of base on the regioselectivity of pyridine *N*-oxide chlorination, see: Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* **2001**, *31*, 2507–2511.
4. For the synthesis of the 6-halo-substituted naphthyridines, see: Ref. 2a.
5. Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299–2302.
6. (a) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021; (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781–7786.
7. (a) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335–1337; (b) Andersson, H.; Banchelin, T. S.-L.; Das, S.; Olsson, R.; Almqvist, F. *Chem. Commun.* **2010**, 3384–3386.
8. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.
9. For a silver-catalysed direct arylation of electron-deficient heterocycles with boronic acids, see: Seiple, I. B.; Su, S.; Rodriguez, R. A.; Giantassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196.
10. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.
11. Chung, J. Y. L.; Cvetovich, R. J.; McLaughlin, M.; Amato, J.; Tsay, F.-R.; Jensen, M.; Weissman, S.; Zewge, D. *J. Org. Chem.* **2006**, *71*, 8602–8609.
12. A control experiment showed that heating the naphthyridine *N*-oxide from Scheme 1 (X = H) in DMF for 16 h led to complete deoxygenation to the respective naphthyridine.
13. Typical experimental procedure (Table 1, entry 2): A round bottom flask was charged with the naphthyridine *N*-oxide (286 mg, 1 mmol), 2,6-dimethoxyphenyl boronic acid (364 mg, 2 mmol), DMF (6 mL) and a stir bar. A reflux condenser was fitted and the reaction heated to 110 °C for 16 h. After cooling, the solvent was removed under high vacuum and the residue was purified by flash chromatography (hexane/EtOAc, 8:2) to afford the desired product, 7-(2,6-dimethoxyphenyl)-2-trifluoromethyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester (**2a**), as a pale yellow solid (252 mg, 63%), mp: 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.75 (1H, s), 8.31 (1H, d, J = 8.4 Hz), 7.71 (1H, d, J = 8.4 Hz), 7.38 (1H, t, J = 8.4 Hz) 6.67 (2H, d, J = 8.4 Hz), 4.49 (2H, q, J = 7.2 Hz), 3.72 (6H, s), 1.45 (3H, t, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.2, 162.8, 160.0, 154.6, 147.3 (q, J = 35.7 Hz), 141.0, 136.0, 130.7, 128.5, 124.8, 121.3, 120.8 (q, J = 270 Hz), 117.9, 115.0, 62.6, 55.8, 13.9. MS (ES) m/z 407 $[M+H]^+$. HRMS (ES^+) calcd For $C_{20}H_{18}N_2O_4F_3$ $[M+H]^+$ 406.1140, found 406.1120.