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Tetrahedron Letters 46 (2005) 4997–4999
Tetrahedron Letters

Synthesis of phenoxyquinolin-4(1*H*)-one through copper(II)-mediated cross-coupling of phenylboronic acid and hydroxyquinolin-4(1*H*)-one

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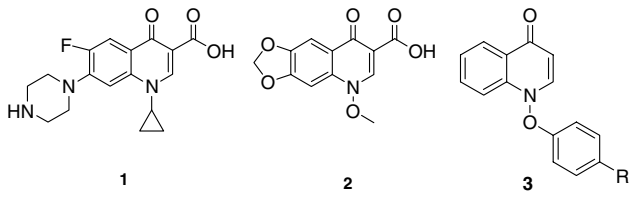
Received 29 January 2005; revised 19 May 2005; accepted 20 May 2005
Available online 9 June 2005

Abstract—A synthetic method to prepare novel phenoxyquinolin-4(1*H*)-one compounds via cross-coupling of hydroxyquinolin-4(1*H*)-one with a variety of phenylboronic acids is reported. The reaction is mediated by copper(II) acetate at room temperature in air and is tolerant of several functional groups on the phenylboronic acids.

Quinolone antibiotics constitute an important class of pharmaceuticals such as the drugs Ciprofloxacin (**1**) and Miloxacin (**2**) (Fig. 1).[1] The quinolin-4-(1*H*)-one is the core structural feature that is commonly found in these antibiotics and other biologically active compounds. Most of the previously synthesized analogs of quinolone compounds, for example, Ciprofloxacin (**1**), have an alkyl group at the nitrogen atom and the alkyl group was found to play an important role in enhancing the antibacterial activity.[2] In an ongoing effort for our fragment-based *in silico* drug discovery, we identified phenoxyquinolin-4(1*H*)-one (**3**) as a key structural feature that appeared in several protein target focused libraries. Surprisingly, no synthetic method has been published for the preparation of the phenoxyquinolin-4(1*H*)-one.



1 2 3

Figure 1. Ciprofloxacin (**1**), Miloxacin (**2**), and phenoxyquinolin-4(1*H*)-one (**3**).

Copper promoted cross-coupling with arylboronic acids is emerging as a powerful synthetic method of preparation of aryl ethers, arylamines, and arylate heterocycles due to its mild conditions.[3] Evans et al.[4] and Chan et al.[5] have initially reported the Cu(II)-mediated cross-coupling of arylboronic acids with phenols at room temperature to produce diaryl ethers. One recent report of coupling of phenylboronic acid with *N*-hydroxyphthalimide via Cu(I) assisted coupling prompted us to test its feasibility for the coupling of phenylboronic acids and hydroxyquinolin-4(1*H*)-one.[6] Based on these reports, we sought to develop a procedure for O-arylation of hydroxyquinolin-4(1*H*)-one with phenylboronic acid using a copper salt. To the best of our knowledge, the direct coupling of phenylboronic acid with hydroxyquinoline-4(1*H*)-one has not been reported. Herein, we report the synthesis of a novel class of phenoxyquinolin-4(1*H*)-one compounds by O-arylation of 1-hydroxyquinoline with a variety of substituted phenylboronic acids under mild conditions.

The initial conditions explored were those reported by Petrassi et al.[6] for the CuCl-mediated cross-coupling of *N*-hydroxyphthalimide with arylboronic acid. 1-Hydroxyquinolin-4(1*H*)-one (**4**) was chosen as the phenol part because it is readily obtained in a one step reaction from a commercially available starting material (4-nitroquinoline *N*-oxide) by treatment with sulfuric acid.[7] One equivalent of **4**, 2 equiv of phenylbornic acid, 1.1 equiv of pyridine, and 1 equiv of CuCl were allowed to react at room temperature in air for 24–48 h in

Keyword: Cross-coupling.
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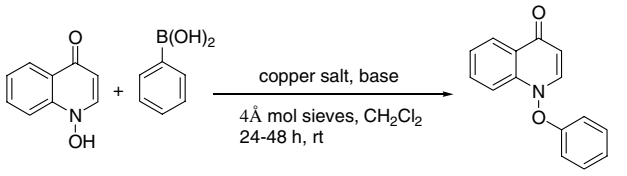
doi:10.1016/j.tetlet.2005.05.090

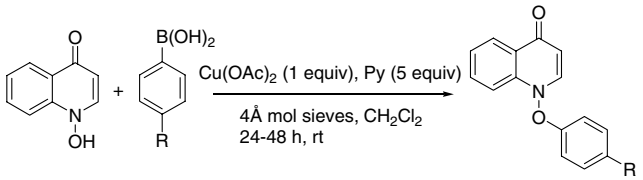
Table 1. Effect of the copper salt and base on the cross-coupling reaction product **6a**



4 **6a**

Entry	Copper salt	Base	Yield (%)
1	CuCl	Pyridine	0
2	CuCl	Et_3N	0
3	CuI	Pyridine	0
4	CuI	Et_3N	0
5	$Cu(OAc)_2$	Pyridine	60
6	$Cu(OAc)_2$	Et_3N	43

Table 2. Cross-coupling of **4** with substituted phenylboronic acid (**5**) to give O-arylation products **6b–i**



4 **5** **6b-i**

Entry	R-group	Product	Yield (%)
1	CH_3	**6b**	53
2	F	**6c**	45
3	Cl	**6d**	37
4	Br	**6e**	35
5	CF_3	**6f**	36
6	CN	**6g**	32
7	$COCH_3$	**6h**	32
8	OCH_3	**6i**	40

1,2-dichloroethane with 4 Å molecular sieves but gave no desired products (Table 1, entry 1). We then used $Cu(OAc)_2$ and employed the conditions reported by Evans for the coupling of phenol and arylboronic acid. Under these conditions, 1 equiv of **4**, 2 equiv of phenylbornic acid, 5 equiv of pyridine, and 1 equiv of $Cu(OAc)_2$ were allowed to react at room temperature in air for 24–48 h in methylene chloride with 4 Å molecular sieves to give the desired product (**6a**) in 60% yield (Table 1, entry 5).[8] The regiospecificity of the reaction was assigned on the basis of the ^{13}C NMR analysis of **6a**. The chemical shift at 176.5 ppm indicated that the carbonyl group is kept intact during the coupling process.

To establish the reaction conditions further, the effects of copper salt, base, and solvent were evaluated. The results of this initial screening are summarized in Table 1. $Cu(OAc)_2$ instead of Cu(I) salt is very effective for the cross-coupling reaction and pyridine is a better base than triethylamine under this condition (Table 1, entries 5 and 6). A limited examination of the solvents revealed that methylene chloride is optimal compared to acetonitrile and 1,2-dichloroethane. It was also found in our case that exposure of the reaction to air and the use of freshly activated 4 Å molecular sieves powder increased the yield of the reaction, which is in accord with others' observations.[9] A rationale for the enhancement of the yield of the reaction by O_2 and molecular sieves has been proposed by Evans et al.[4] and Lam et al.,[10] respectively. Under these generalized conditions,[8] we were able to couple **4** with **5** to prepare a series of 1-phenoxyquinoline-4(1*H*)-one (**6b–i**) in moderate yields (Table 2). Analysis of the reaction mixtures by HPLC/MS and NMR revealed the formation of phenol and diphenyl ether as the by-products, which were also generated under the Evans's conditions for diaryl ether formation.[4]

A number of structurally and electronically diverse arylboronic acids were then evaluated (Table 2). The functional group tolerance is good (entries 3, 4, and 7). For example, bromo- and chloro substituents (entries 4 and 3) were well tolerated on the phenylboronic acid and could be used for further functionalizations on the phenyl ring. The reaction also appeared to work well with both electron-withdrawing and electron-donating groups at the phenylboronic acid (entries 2, 6, 7, and 8).

In summary, we have developed a method to synthesize a series of novel phenoxyquinolin-4-(1*H*)-one compounds. The mild reaction conditions and functional group tolerance make this approach applicable to the rapid preparation of phenoxyquinoline-4-(1*H*)-one analogs that were unavailable previously. Further assessment of the scope of this chemistry is currently underway.

Acknowledgments

We would like to thank Dr. Dennis G. Sprous for helpful discussions.

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8. Procedure for **6a**. An oven dried disposable culture tube (5 mL) was charged with **4** (50 mg, 0.30 mmol, 1.0 equiv), $Cu(OAc)_2$ (56 mg, 0.30 mmol, 1.0 equiv), phenylboronic acid (**5**) (73 mg, 0.60 mmol, 2.0 equiv), and freshly activated powdered 4 Å molecular sieves (~300 mg). The reaction mixture was diluted with CH_2Cl_2 (3.0 mL), and

the pyridine (121 μL, 1.5 mmol, 5.0 equiv) was added. The tube was then put on a Bohdan Miniblock synthesizer and shook for 24 h at room temperature under ambient atmosphere. The reaction mixture was diluted with CH_2Cl_2 (1.0 mL) and the TLC was taken before silica gel (~300 mg) was added to the reaction mixture. The solvent was evaporated using a Thermo SpeedVac system. Solid loading of the reaction mixture to the Isco Combi-Flash system was performed. The reaction mixture was then purified by RediSep™ silica gel column (4 g of silica gel) eluting with a linear gradient of methylene chloride and methanol. Detector wavelength was set to 254 nm and the UV active fractions were collected and the solvent was removed by Thermo SpeedVac system to generate **6a** as a white solid (42 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (dd, J = 8.0, 1.2 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.55–7.68 (m, 6H), 7.38–7.42 (m, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.17 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.5, 144.0, 140.9, 132.1, 130.3, 129.4, 127.7, 126.0, 125.6, 123.7, 117.4, 109.2. MS (ESI) *m*/*z*: 238 $(M+H)^+$.

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