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Solid-phase synthesis of phenols and pyridinones via arylboronation/oxidation protocol using aryl bromides

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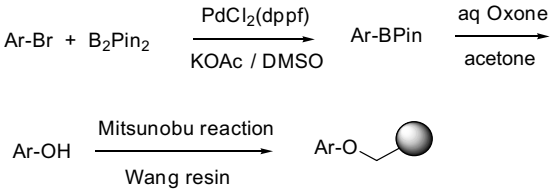
Abstract—A sequence of two known reactions, palladium catalyzed arylboronation of arybromide and subsequent oxidation of arylboronate with oxone, has been carried out to prepare functionalized phenols and pyridin-2(1*H*)-one which were later loaded on to resin for solid-phase synthesis. Using these resin-bound templates, a number of solid-phase methods were developed to generate libraries of substituted phenols and pyridin-2(1*H*)-one.

Substituted phenols are prevalent in many compounds that are of biological interest, and also serve as synthetic building blocks in organic synthesis.[1] Synthetic methods developed for the formation of phenols include classical aromatic substitution,[2] metal-catalyzed coupling reactions,[3] *ortho*-metalation, and functionalization reactions.[4] In recognition of their importance, many innovative approaches to phenols have been reported.[5]

Recently, a variety of phenols were prepared by an iridium-catalyzed C–H activation/borylation/oxidation protocol.[5a] By slight modification of the literature method,[6] phenols were obtained in one-pot by oxidation of arylboronic esters with oxone. This novel approach can efficiently provide meta-substituted phenols bearing *ortho*-/*para*-directing group. The regiochemistry of arylboronate and phenols prepared in this manner is determined by iridium-catalyzed borylation of arenes.

We were interested in obtaining a diverse set of highly functionalized phenols which would be used as core templates to build small molecule libraries for pharmaceutical evaluation. Since it is known that arylboronate can be synthesized by palladium-catalyzed arylboronation of arylhalides (ArBr or ArI),[7] we envisioned that a unified Miyaura arylboronation/oxidation protocol



Scheme 1.

(Scheme 1) would be a very practical synthetic route to phenols. Although this unified route has a potential to provide phenols which are not readily accessed by other synthetic methods, there is no literature precedent addressing this merit. Here, we report the synthesis of phenols and pyridine-2-one by an arylboronation/oxidation strategy and discuss solid-phase methodologies which are designed for further diversification of phenols and pyridin-2-one.

The reaction conditions for arylboronation of arylbromides (**1**–**4**)[7] and oxidation of the resulting arylboronates[5a] were adapted from literature procedures. The crude arylboronate intermediates, without further purification except simple extraction during workup, were subjected to subsequent oxidation with oxone to provide phenols (**5**–**7**) and pyridin-2-one **8**. The dibromopyridine analog **4** gave rise to pyridin-2-one **8** which is believed to be the more stable tautomeric form of 2-hydroxypyridine. For solid-phase synthesis, loading of the phenols and pyridin-2-one to Wang resin (**9**–**12**) were carried out under Mitsunobu conditions. As summarized in Table 1, the desired ArOH (**5**–**8**) were obtained in

Keywords: Solid-phase synthesis; Arylboronation; Oxidation; Phenol; Pyridinone.
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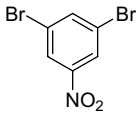
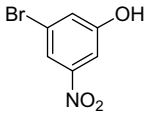
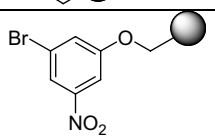
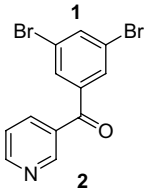
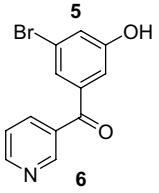
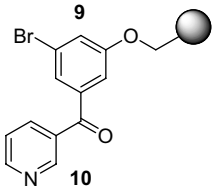
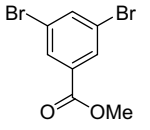
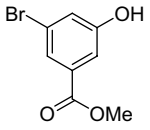
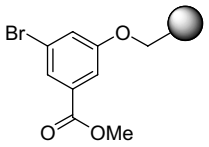
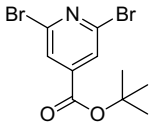
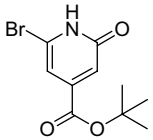
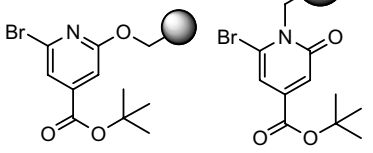
Table 1. Phenols and pyridine-2-one via arylboronation/oxidation and loading to Wang resin[a]

	Ar–Br	Ar–OH	Yield[b] (%)	Ar-O [c]
1	 **1**	 **5**	41	 **9**
2	 **2**	 **6**	46	 **10**
3	 **3**	 **7**	47	 **11**
4	 **4**	 **8**	77	 **12**

[a] Typical conditions: Ar–Br, bis(pinacolato)diboron (B_2Pin_2), $PdCl_2$(dppf), KOAc, DMSO, 80 °C, 6–12 h; then extraction, aqueous oxone, 25 °C, 10 min.

[b] After silica gel column chromatography.

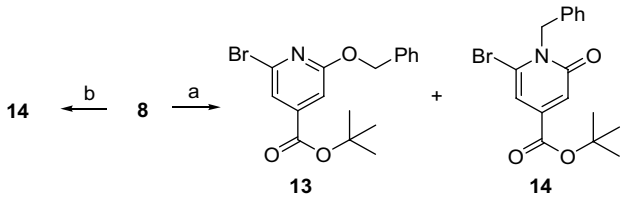
[c] Typical conditions for loading to resin: Ar–OH, Wang resin (0.9 mmol/g), PPh_3, DIAD, THF, 1–2 days (loading level of resins: **9** 0.78 mmol/g; **10** 0.55 mmol/g; **11** 0.74 mmol/g; **12** 0.62 mmol/g).

reasonable yields (41–77%) from the arylboronation/oxidation protocol. Only mono-arylboronates have been apparently obtained from the palladium-catalyzed arylboronation of dibromoaryls as other side products, such as substituted resorcinols, were not detected by LC/MS analysis of the products.

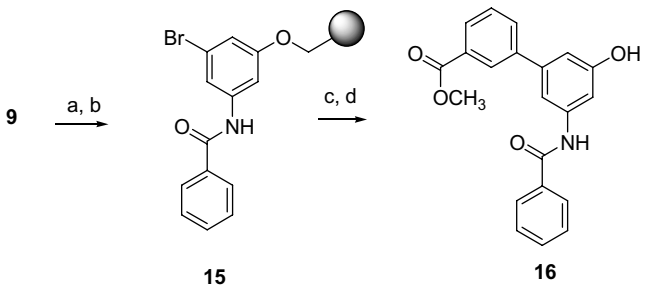
The pyridine-2-one **8**, with an electron withdrawing group at the α-carbon to the nitrogen, possesses a N–H which is capable of competition with oxygen under Mitsunobu conditions. Therefore, it was not clear if the compound **8** was attached to the polymeric resin via a covalent bond with the oxygen or nitrogen atom.

As a model study to understand how **8** was connected to the resin under Mitsunobu conditions, Wang linker was mimicked in solution using benzyl alcohol as shown in Scheme 2. Under typical Mitsunobu conditions at 60 °C, **8** was consumed to give a mixture of *O*-benzyl **13** and *N*-benzyl isomer **14** in a ratio of 2.5–1. On the other hand, only *N*-benzyl isomer was isolated as a single product from the alkylation reaction of **8** with benzyl bromide in the presence of K_2CO_3. Analysis of the chemical shifts of ^{13}C NMR for the benzylic carbon was used as a tool to assign **13** (69.1 ppm) as an *O*-benzyl isomer and **14** (52.4 ppm) as a *N*-benzyl isomer, respectively. On the basis of this solution-phase model reaction, we expect that both *O*-benzyl and *N*-benzyl isomers exist on the resin-bound template **12** derived from **8**.

Solid-phase synthesis on resin-bound template **9** is illustrated in Scheme 3. The nitro group was reduced and the



Scheme 2. Solution-phase model reactions of **8**. Reagent and conditions: (a) Benzyl alcohol, PPh_3, DIAD, THF, 60 °C, 3 h. (b) Benzyl bromide, K_2CO_3, acetone/THF, rt, 7 h.

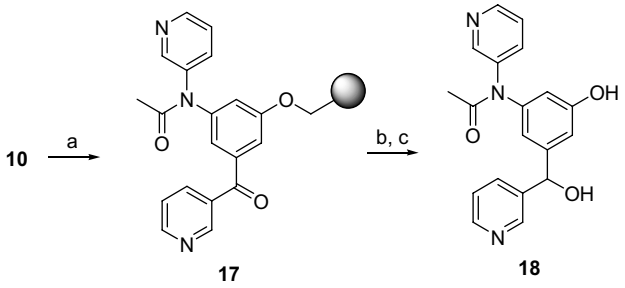


Scheme 3. Solid-phase synthesis using **9**. Reagent and conditions: (a) $SnCl_2$ $2H_2O$, DMF, 16 h. (b) Benzoyl chloride, DIEA, DCM, 6 h. (c) 3-(Methoxycarbonyl)-phenylboronic acid, KF, Pd(II),[8] THF, 65 °C, 16 h. (d) 50% TFA/DCM, 3 min.

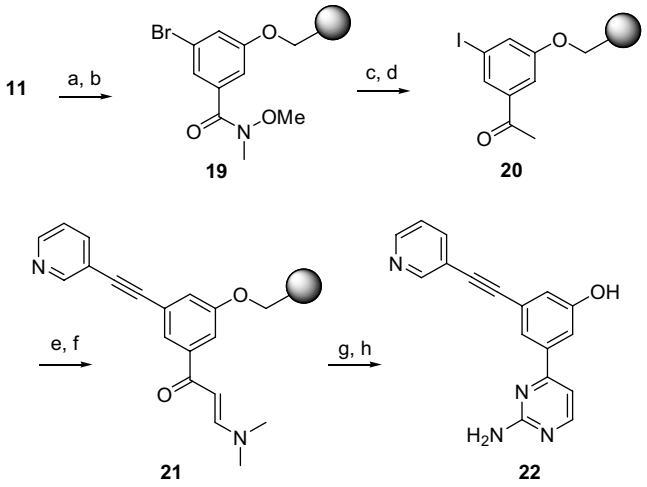
resulting amine was benzoylated in the presence of base to afford **15**. The substitution of bromide **15** by a Pd[8]-catalyzed Suzuki coupling with boronic acid and subsequent cleavage reaction under acidic conditions (50% TFA in DCM) gave **16** in 48% yield.

Copper-catalyzed amidation of arylhalides has been recently reported by Buchwald's group.[9] A number of amides including lactams and formamides were successfully demonstrated to undergo amidation. As shown in Scheme 4, translation of this carbon–nitrogen bond forming process to solid-phase cleanly converted resin-bound bromide **10** to a (pyridin-3-yl)acetamide derivative **17** by copper-catalyzed reaction in the presence of a diamine ligand. Subsequent reduction of ketone to an alcohol and cleavage from the resin provided **18** in 37% yield.

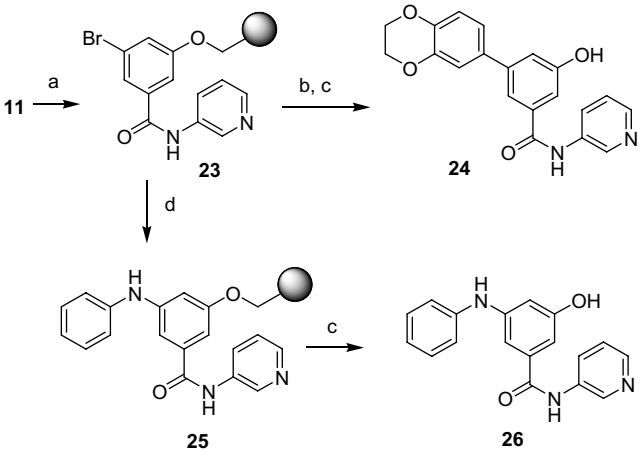
In Schemes 5 and 6, a number of solid-phase synthetic approaches were described to diversify both the bromide



Scheme 4. Solid-phase synthesis using **10**. Reagent and conditions: (a) *N*-(Pyridin-3-yl)acetamide, CuI, *N*,*N*′-dimethylethylenediamine, Cs_2CO_3, dioxane, 110 °C, 16 h. (b) $NaBH_4$, THF/EtOH (1:1), rt, 16 h. (c) 50% TFA/DCM, 3 min.



Scheme 5. Solid-phase synthesis using **11**. Reagent and conditions: (a) LiOH, dioxane/H_2O (4:1), 16 h. (b) *N*,*O*-Dimethylhydroxylamine hydrochloride, HOBt, EDCI, DIEA, DCM/DMF, 16 h. (c) CH_3MgBr, THF, 2 h. (d) NaI, CuI, *N*,*N*′-dimethylethylenediamine, Na_2CO_3, dioxane, 110 °C, 5 h. (e) 3-Ethynylpyridine, Cu(phen)-(PPh_3)Br, K_2CO_3, toluene, 110 °C, 16 h. (f) *N*,*N*′-Dimethylformamide diethylacetal, 120 °C, 3 h. (g) Guanidine hydrochloride, MeONa, EtOH, 90 °C, 16 h. (h) 50% TFA/DCM, 3 min.

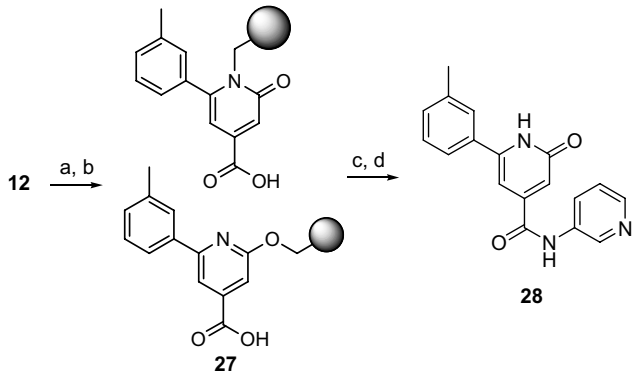


Scheme 6. Solid-phase synthesis using **11**. Reagent and conditions: (a) 3-Aminopyridine, $LiN(TMS)_2$, 60 °C, 3 h. (b) 1,4-Benzodioxane-6-boronic acid, KF, Pd(II), THF, 65 °C, 16 h. (c) 50% TFA/DCM, 3 min. (d) Aniline, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 60 °C, 16 h.

and carboxylic ester function of **11**.[10] Hydrolysis of the ester and subsequent reaction with *N*,*O*-dimethylhydroxylamine resulted in Weinreb amide on resin **19**. Addition of Grignard reagent (CH_3MgBr) to **19** in THF followed by copper-catalyzed conversion of bromide to iodide[11] gave the desired intermediate **20**. Sonogashira coupling of 3-ethynylpyridine with iodide **20** was mediated by the well defined copper complex, Cu(phen)-(PPh_3)Br,[12] in the absence of palladium catalyst. Heating of the resulting intermediate in *N*,*N*′-dimethylformamide diethylacetal to 120 °C afforded an enaminone **21**. Cyclization of **21** with guanidine at elevated temperature formed an aminopyrimidine system.[13] Cleavage from the resin produced **22** in 36% yield with a purity higher than 90% in 8-step solid-phase synthetic process from **11**. To the best of our knowledge, this represents the first successful translation of solution phase procedure for 2-aminopyrimidine to the corresponding solid-phase reactions.

Alternatively, ester **11** was directly converted to an amide **23** by amidation with 3-aminopyridine in the presence of $LiN(TMS)_2$ at 60 °C (Scheme 6). Under the same reaction conditions as described in Scheme 3, Suzuki coupling of the bromide **23** with boronic acid followed by cleavage gave rise to **24**. Arylamine intermediate **25** was obtained by Buchwald–Hartwig cross coupling[14] of **23** with aniline under mild conditions to ultimately provide **26** in 24% yield after cleavage reaction from the resin.

The mixture of isomers **12** was used in the solid-phase reaction sequence as depicted in Scheme 7. Suzuki coupling with *m*-tolylboronic acid was performed to form a C–C bond, and the *tert*-butyl ester group was hydrolyzed to yield an acid **27**. Amide formation with 3-aminopyridine in the presence of HBTU and cleavage from resin afforded **28** in 46% yield. Synthesis of various pyridine-2-ones is known.[15] However, facile introduction of various substituents to functionalized pyridine-2-ones such as **8** is scarce in the literature.[16]



Scheme 7. Solid-phase synthesis using **12**. Reagent and conditions: (a) *m*-Tolylboronic acid, KF, Pd(II), THF, 65 °C, 16 h. (b) LiOH, dioxane/H_2O (4:1), 110 °C, 3 h. (c) 3-Aminopyridine, HBTU, DIEA, DCM, rt, 16 h. (d) 50% TFA/DCM, 3 min.

In summary, we have demonstrated the synthesis of phenols or pyridine-2-ones by oxidation of arylboronates which were prepared from arylbromides.[17] Since a variety of arylbromides is readily available, this unified arylboronation/oxidation protocol provides an access to substituted phenols or pyridine-2-ones which may not be easily prepared by other methods. We also have developed a number of solid-phase methodologies suitable for rapid parallel synthesis of substituted phenols and pyridine-2-one. The bromides of the resin-bound templates (**9**–**12**) have been efficiently replaced with various building blocks, such as boronic acids, amides, amines, and acetylenes by well known palladium- or copper-catalyzed coupling. When combined with other on-resin functional group manipulations demonstrated in this report, a very unique set of small molecule libraries can be generated. Focused libraries prepared using solid-phase methods described here will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.034.

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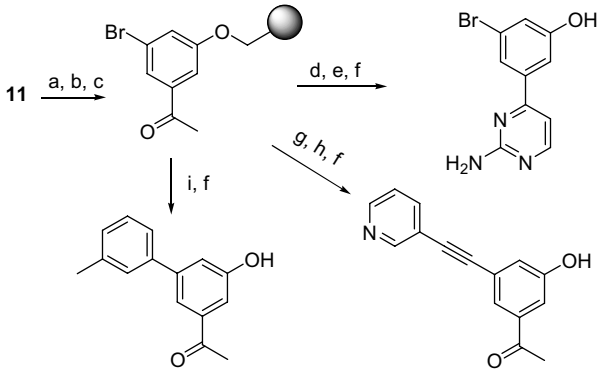

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17. Synthetic procedure and characterization data of selected compound **5**: To a solution of 1,3-dibromo-5-nitrobenzene (**1**, 2.8 g, 10 mmol) in DMSO (30 mL) were added bis(pinacolato)diboron (2.5 g, 10 mmol), potassium acetate (2.9 g, 30 mmol) and $PdCl_2$(dppf) complex (300 mg), and the solution was flushed with nitrogen, then the reactor was sealed. After heating for 6 h at 80 °C, the mixture was diluted with ethyl acetate (100 mL) and extracted with brine (2×50 mL), followed by saturated sodium bicarbonate (50 mL), and the organic layer was dried and concentrated. To the crude mixture in acetone (20 mL) was added an aqueous solution of oxone (12.3 g in 50 mL of water), and the reaction mixture was stirred vigorously for 10 min at rt. The reaction was quenched with aqueous sodium hydrogensulfite. The brown solution was extracted with ethyl acetate, and the organic layer was extracted with brine followed by water. After drying of the organic layer, the resulting crude residue was purified by silica gel column chromatography using a gradient of methanol in DCM (0–40%) to obtain **5** (890 mg, 41%). ^{1}H NMR (400 MHz, acetone-d_6) δ 9.68 (s, 1H, OH), 7.81 (s, 1H), 7.64 (s, 1H), 7.42 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6) δ 159.1, 149.9, 124.8, 122.6, 117.5, 109.8.