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A convenient synthesis of phenols

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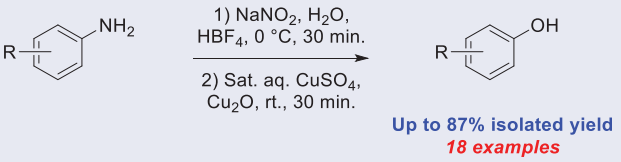
ABSTRACT

Anilines are rapidly, often within 60 minutes, converted into the corresponding phenols in up to 87% isolated yield. The presented experimentally simple protocol display broad compatibility with a variety of functional groups, and in particular, well suited for the preparation of methyl-substituted phenols. Such phenols are not easily available by other synthetic approaches. The formation of phenolic radical coupling products was not observed even for activated anilines using this open flask method.

GRAPHICAL ABSTRACT



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Anilines; copper sulfate; diazotization; 3-iodo catechol; phenols

Introduction

Phenols and hydroxylated heteroarenes are important structural elements in pharmaceuticals and natural products.[1] These aromatic compounds and derivatives are often utilized as starting materials or intermediates in synthesis. Hence, this field of synthetic organic chemistry continues to remain an area of active investigation.[2,3]

Substituted phenols have traditionally been synthesized by nucleophilic aromatic substitution[4] or hydrolysis of arenediazonium salts.[5] These reactions are often hampered by several drawbacks, such as limited substrate scope and harsh reaction conditions for the formation of potential explosive arenediazonium salts. The use of boronic acids[6] or silanes[7] in oxidative protocols, but also transition metal catalyzed C–H activation/oxidation methodology,[8] has emerged recently. Moreover, aryl or heteroaryl halides under Cu-catalysis have also been utilized for making phenols and hydroxylated heteroarenes.[9] These methods often require multi-step protocols for making the desired starting materials. Moreover, the cost of the transition metals and phosphine ligands, as well as their sensitivity to air and moisture, limit their large-scale applications. Alternatively, Friedel–Crafts chemistry may also be used for the synthesis of alkyl substituted phenols.

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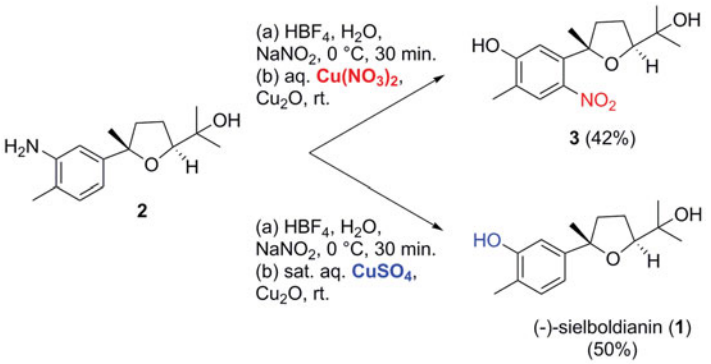


Scheme 1. The last step in the synthesis of (–)-sielboldianin A.

However, problems with regioselectivity, polyalkylation, or rearrangements of intermediates are often observed.[10] Therefore, the development of benign, regioselective, and experimentally simple synthetic protocols are of interest.

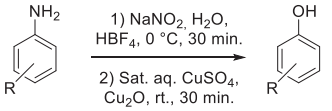
Two mechanistically different transformations exist for converting an aniline to the corresponding phenol through its diazonium salt. Thermal hydrolysis of the acidic aqueous solution leads to the formation of an aryl cation intermediate that is converted into the corresponding phenol.[1] A milder alternative is a Sandmeyer type redox reaction, reported by Cohen et al.,[11] in which an aryl radical is formed from the diazonium ion by Cu_2O, and oxidized to the phenol by hydrated cupric ions. During our efforts towards the total synthesis of the sesquiterpenoid (–)-sielboldianin (**1**) A, the conversion of aniline **2** to **1** was needed, see Scheme 1.[12]

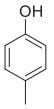
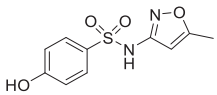
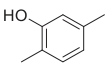
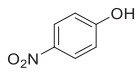
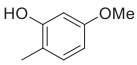
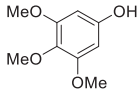
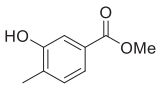
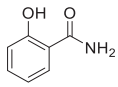
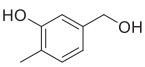
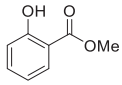
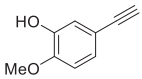
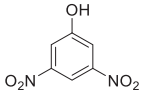
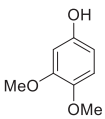
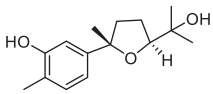
When the classical conditions for the Sandmeyer type reaction were applied to compound **2,**[11] product **3** was formed in 42% isolated yield. As expected, the aniline functionality in **2** was converted to the phenol. However, nitration of the activated *para*-position of the formed phenol functionality was also observed. Accordingly, replacing $Cu(NO_3)_2$ with $CuSO_4$ yielded (–)-sielboldianin A (**1**) after chromatographic purification (Scheme 1). There are a few reported examples of these reaction conditions in the literature.[13] In order to further investigate the generality and applicability of this method, we set out to broaden its substrate scope. Herein, we reveal the results from our studies extending this cheap, practical, and convenient experimental protocol.

Results and discussion

The substrate scope using commercially available functionalized anilines was evaluated. In most cases, the products were obtained in moderate to good yields (Table 1). Accordingly, methyl-substituted phenols not easily obtained by the Friedel–Crafts protocol were obtained in good yields (Table 1, entries 1–5). For the four examples with yields below 40% (Table 1, entries 6–9), this straightforward method using cheap and commercially available reagents is still a convenient alternative for the preparation of these types of compounds. For instance, the alkyne substituted phenol product in entry 7 is a precursor in the synthesis of combretastatin A-4 and analogs.[14] Some of the

Table 1. Synthesis of substituted phenols.



Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1		40	10		66
2		53	11		69
3		61	12		87
4		67	13		76
5		86	14		44
6		30	15		50
7		30	16		65
8		36	17		39
9		18	18		50[b]

[a]The yields are the average of two experiments of isolated and purified material.
[b]See reference.[11]

anilines were also subjected to the original protocol using $Cu(NO_3)_2$ for comparison of the methods. Performing the reaction in the presence of $Cu(NO_3)_2$ with 3-methoxyaniline yielded the nitrated phenol product, whereas employing 2-aminophenol and 3,4-dimethoxyaniline, neither the desired phenol nor the nitrated phenol was obtained (determined by NMR and MS). However, when subjecting these anilines to the modified method using $CuSO_4$ (Table 1, entries 8–10), the desired phenol products were obtained in 36, 18, and 66% yields, respectively. Several different functional groups were tolerated, such as hydroxyl, methoxy, ester, nitro, isoxazole, tetrahydrofuran, sulfonamide, halogens, and amide substituents (Table 1, entries 10–18). Regarding electronics, anilines containing either electron donating, -withdrawing, and/or -neutral substituents

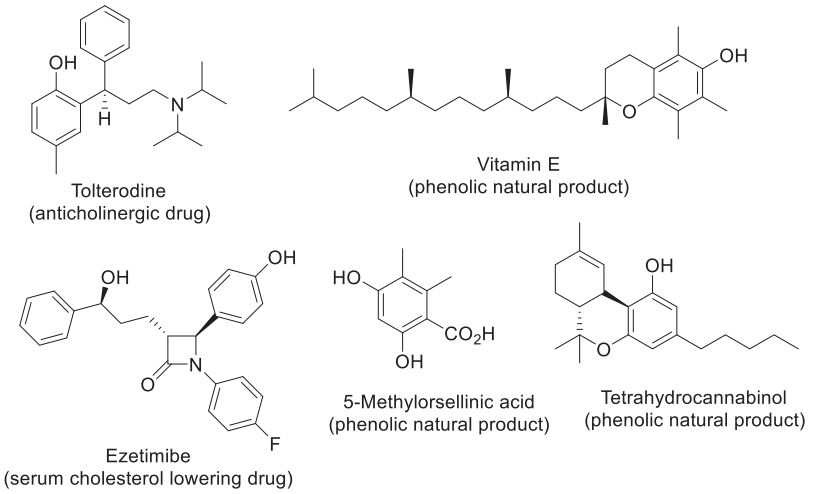


Figure 1. Examples of pharmaceuticals and phenolic natural products.

gave the desired products. Of great synthetic interest, 3-iodocatechol was formed in a reasonable yield of 40%, which compares well with earlier reported enzymatic[15] and synthetic\cenveospan{ }[16] protocols. Of note, aniline **2** (Scheme 1, Table 1, entry 18) was cleanly converted to the phenol using this method, even with several acid sensitive functionalities present in the molecule. Other sources of Cu(II) have been reported to induce phenolic radical coupling reactions.[5,12] Hence, for the preparation of activated and methyl substituted phenols, the presented protocol is attractive.

Conclusions

The results of the modified protocol have been demonstrated for the preparation of substituted phenols and catechols. The reaction takes place at ambient temperature resulting in good yields of the products. In particular, methyl substituted phenols are readily available using this practical and simple protocol. Of note, the formation of phenolic radical coupling products was not observed using this open flask procedure. The diazonium salts are prepared *in situ* making this protocol rather safe. Nevertheless, care should always be taken when handling diazonium compounds.[17]

Experimental

Typical experimental procedure for the synthesis of phenols: Water (4 mL) and HBF_4 (~48–50% aq. sol., 4 mL) was added to the aniline (0.50 mmol, 1.0 equiv.) and stirred for a couple of minutes at room temperature in an open reaction flask. $NaNO_2$ (0.038 g, 1.1 equiv.) in water (2.8 mL) was added dropwise at 0 °C and stirred for 30 minutes. To the cold solution of the resulting diazonium salt was added sat. aq. copper(II)sulfate (50 mL), followed by copper(I)oxide (1.0 equiv., 0.072 g), and stirred at room temperature for 30 minutes. The reaction mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated *in vacuo*. The crude products were purified by silica gel chromatography. *Potential hazard note:* Diazonium compounds can be explosive, however, the risk

is greatly reduced by following several rules for precaution.[17] Additional points that render the experimental procedure reported herein safer is that the diazonium salt is prepared *in situ* under dilute conditions and is not isolated, the reaction is performed open to air, the reaction temperature is 0° C to ambient, HBF_4^- is used as the counter-ion in this procedure, and arene diazonium *tetra*-fluoroborates, in contrast to the chloride salts, are renowned in general for their enhanced thermal stability and shock-insensitivity. Nevertheless, care should always be taken when handling diazonium compounds.

5 -Methoxy-2-methylphenol

Prepared according to the general procedure. Yield: 46 mg (67%).[1] H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, $J = 8.2$ Hz, 1H), 6.43 (dd, $J = 8.2$, 2.5 Hz, 1H), 6.40 (d, $J = 2.5$ Hz, 1H), 5.00 (s, 1H), 3.76 (s, 3H), 2.18 (s, 3H); [13] C NMR (101 MHz, $CDCl_3$) δ 158.9, 154.5, 131.2, 115.8, 105.9, 101.4, 55.3, 14.7.

Disclosure statement

No potential conflict of interest was reported by the authors.{AQ8}

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