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Synthesis of novel aryl-1,2-oxazoles from *ortho*-hydroxyaryloximes

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ABSTRACT

The reaction of *ortho*-hydroxyaryloximes with *p*-toluenesulfonyl chloride in the presence of an amine base efficiently generates the corresponding aryl-1,2-oxazole. Investigations revealed that solvent polarity greatly affected the rate of the reaction with faster rates observed in more polar solvents. The reaction proceeds to completion in only a few minutes in acetonitrile at room temperature, and the synthesis of four novel aryl-1,2-oxazoles is presented.

Aryl-1,2-oxazole-containing compounds have displayed some promising biological activity[1], and a number of useful synthetic methods for the conversion of *ortho*-hydroxyaryloximes to the corresponding aryloxazoles have been employed.[2] An elegant method employing triphenylphosphine and DDQ was reported recently by Iranpoor et al. to produce the desired heterocycles in high yields.[3] As a supplement to these works, we describe here simple yet rapid cyclization conditions for the efficient synthesis of novel aryl-1,2-oxazoles.

During the course of an investigation into oxime reactivity, a surprisingly mild and efficient synthesis of 1,2-aryloxazoles was encountered. Starting from *ortho*-hydroxyaryloximes, reaction with *p*-toluenesulfonyl chloride (TsCl) in organic solvents in the presence of a tertiary amine base (iPr$_2$NEt or Et$_3$N) efficiently generated the corresponding aryloxazole. This appears to occur via a cyclization reaction at the sp^2 nitrogen of the oxime by the phenolic oxygen (Scheme 1).

Initially we investigated the conversion using the simple substrate 2-hydroxy-naphthalene-1-carbaldehyde oxime, **2** (Scheme 2). To this end, commercially available 2-hydroxy-1-naphthaldehyde **1** was converted to the desired *ortho*-hydroxyaryloxime **2** by heating in the presence of hydroxylamine hydrochloride. Cyclization to naphtho[1,2-*d*]oxazole **3** proceeded quickly at room temperature upon the addition of both the amine base and TsCl.

The cyclization reaction was easily monitored by a change in absorbance since the long wavelength λ_{max} of aryloxazole **3** was greatly blue-shifted from the initial oxime **2** (Fig. 1). The reaction proceeded cleanly through an isosbestic point indicating that the initial tosylation reaction was the rate-limiting step in the 2-step reaction scheme. Additional evidence for this was obtained upon further analysis: the reaction rate was found to be dependent upon the concentration of TsCl present and the reaction rate was retarded when weaker electrophiles (e.g., *p*-toluenesulfonyl fluoride or diethylchlorophosphate) were employed.

Additional investigations revealed that the rate of naphthoxazole **3** formation was highly solvent dependent and the reaction proceeded at a greater rate as the polarity of the solvent was increased.[4] The slowest rate was measured in THF while the fastest rate was measured in acetonitrile (Table 1).

After completing these initial studies, the synthesis of additional aryloxazoles was attempted using the developed conditions. The aryloxazole of pyridoxal, **6**, was synthesized as shown in Scheme 3. Commercially available pyridoxal hydrochloride **4** was converted to the *ortho*-hydroxyloxime **5** with hydroxylamine hydrochloride in ethanol at room temperature. As anticipated, cyclization to the corresponding aryloxazole **6** occurred rapidly in acetonitrile with TsCl and iPr$_2$NEt. The reaction yielded the desired aryloxazole quantitatively in only a few minutes.

To expand the reaction to a more general starting material, the goal was to construct aryloxazoles from phenol compounds with a vacant *ortho* site. Aromatic formylation of the open site followed by oxime formation and cyclization produces the desired aryloxazole. Two novel fluorescent analogues were subsequently constructed using this methodology: coumarinoxazole **9** and pyreneoxazole **14**.

Coumarinoxazole **9** was synthesized as shown in Scheme 4. Compound **7**,[6] synthesized according to a literature procedure from 7-hydroxycoumarin and employing a Duff reaction,[7] was converted to aryloxime **8** with hydroxylamine hydrochloride in EtOH. Application of the cyclization reaction conditions produced the desired 1,2-oxazole **9** in 90% yield in less than 5 min.

Pyreneoxazole **14** was synthesized as shown in Scheme 5. Commercially available 1-hydroxypyrene was protected as the methoxymethyl (MOM) ether with chloromethyl methyl ether (MOMCl) in DMF. Ether **11** was selectively lithiated with *n*-butyllithium using the *ortho*-directing MOM group[8] and quenched with DMF to install the formyl group and afford 1-methoxymethoxy-2-pyrene carboxaldehyde **12**. Conversion of the aldehyde to aryloxime **13** was accomplished by heating in the presence of

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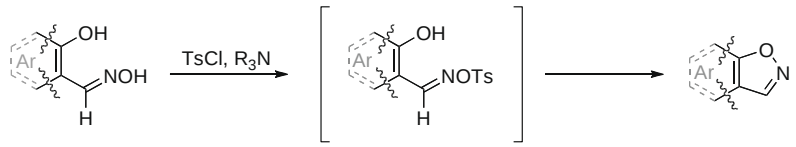
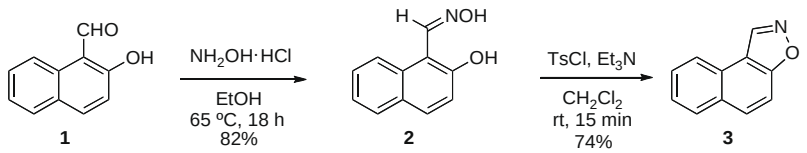


Scheme 1. Reaction of an *ortho*-hydroxyaryloxime with TsCl in the presence of an amine base generates the corresponding aryloxazole.



Scheme 2. Synthesis of naphthoxazole **3**.

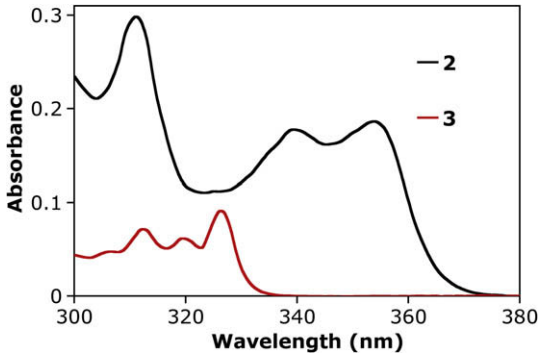


Figure 1. Absorbance spectra for the naphthalene-based oxime **2** and oxazole **3**. Concentration = 3×10^{-5} M in CH_2Cl_2.

hydroxylamine hydrochloride which also served to remove the protecting group ether and afford 1-hydroxy-2-pyrenealdoxime.

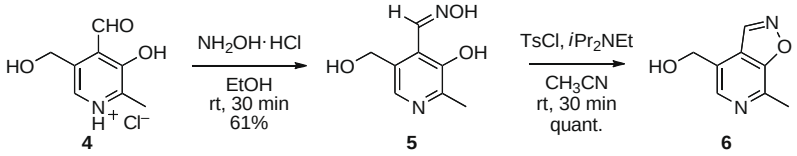
Table 1
Relative rates of naphthoxazole formation in organic solvents of varying polarities

Entry	Solvent	Relative rate	$E_T(30)$[a]
1	Tetrahydrofuran	1.0	37.4
2	Toluene	6.6	33.9
3	Dichloromethane	270	40.7
4	Benzonitrile	810	41.5
5	Acetonitrile	6300	45.6

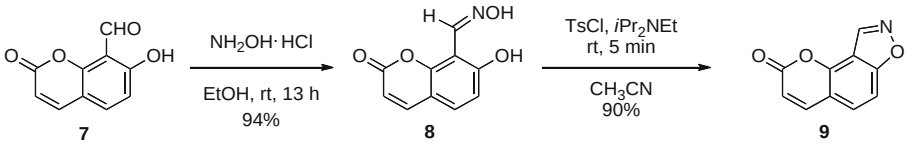
[a] Empirical measure of solvent polarity derived from solvachromic betaine dyes.[5]

The developed reaction conditions again proved effective in generating the desired oxazole **14**, although THF was employed as a solvent in this case for solubility purposes and subsequently the cyclization required additional reaction time (see Table 1).

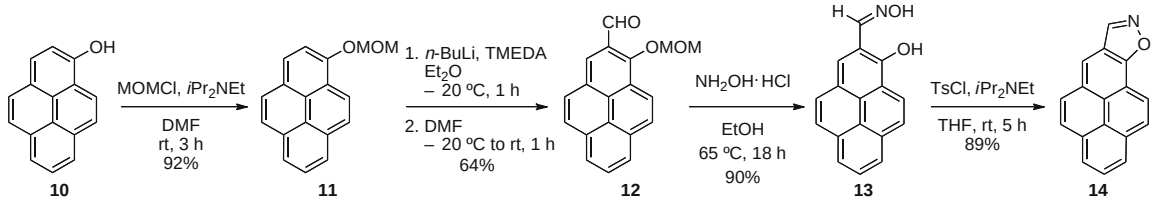
In summary, four novel 1,2-aryloxazoles were synthesized quickly and in high yields from *ortho*-hydroxyaryloximes via an intramolecular cyclization upon reaction with *p*-toluenesulfonyl chloride in the presence of an amine base. Initial tosylation of



Scheme 3. Synthesis of pyridyloxazole **6**.



Scheme 4. Synthesis of coumarinoxazole **9**.



Scheme 5. Synthesis of pyreneoxazole **14**.

the oxime appeared to be the rate-determining step in the two-step reaction scheme and the rate of the overall reaction was highly dependent on the solvent polarity. Employing a highly polar solvent (i.e., acetonitrile) increased the rate greater than 6000-fold relative to the less polar THF. Employing the developed cyclization to previously unsuitable substrates is currently underway. Additionally, the two-step reaction may find application in sensing technology as we have recently demonstrated.[9]

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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.2009.08.086.

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