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A new synthesis of acetamido phenols promoted by $Ce(SO_4)_2$

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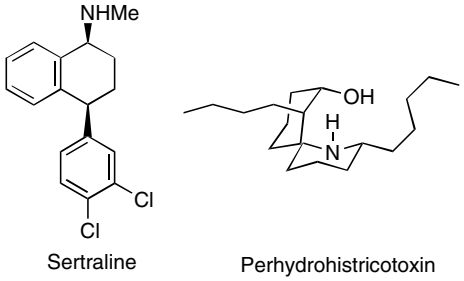
Abstract—A new method for the synthesis of acetamido phenols by a one-pot, three-component Ritter type reaction in moderate to good yields is described. Both electron donating and electron releasing substitution on aromatic rings are tolerated.

Compounds bearing 1,3 amino-oxygenated functional motifs are ubiquitous to a variety of biologically important natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[1] Of particular interest would be a facile method for the construction of 1,3-amido alcohols, as these molecules are versatile precursors for 1,3-amino alcohols and ligands for asymmetric catalysts.[2] It is noteworthy that aminotetraline derivatives manifest a number of important and therapeutically useful biological activities such as antidepressants, immunomodulators and antitumor activities (Fig. 1).[3]

Despite, this broad range of applications, only a few members of this family of compounds have been reported. The development of new methods for their assembly is therefore of considerable synthetic importance.[4]



Sertraline Perhydrohistricotoxin

Figure 1. Examples of a 1,3-amino alcohol and an aminotetralin.

One-pot, multi-component processes have recently gained considerable economic and ecological interest as they address fundamental principles of synthetic efficiency and reaction design.[5] It is evident from the recent literature that there has been considerable interest in the use of Ce(IV) reagents, especially cerium(IV) ammonium nitrate (CAN),[6] in the construction of carbon–carbon and carbon–heteroatom bonds. The use of cerium(IV) sulfate[7] is unprecedented.

During the course of our investigation on the Ce(IV) mediated synthesis of heterocycles,[6d] we carried out exploratory studies on the synthesis of substituted xanthenes[8] from 2-naphthol and an aryl aldehyde in acetonitrile in the presence of anhydrous cerium(IV) sulfate at 85 °C. Interestingly, the ^{1}H NMR spectrum of the resultant product showed the presence of a methyl group and two protons exchangeable with D_2O. The ^{1}H NMR, ^{13}C NMR, 2D NMR studies and single crystal XRD (Fig. 2) confirmed the product to be *N*-[aryl-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide **2e** (as shown in Scheme 1).

This reaction represents a straightforward transformation of an aromatic alcohol to a substituted acetamido phenol.[9]

To explore the generality of the reaction, experiments were conducted with various substituted phenols and the results of these investigations are presented in Table 1. Interestingly, aliphatic aldehydes also gave the expected acetamido phenols in good yield.

Keywords: Acetamidophenols; One-pot three component; Ritter reaction.
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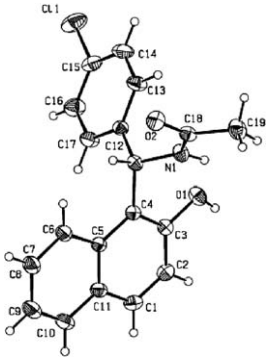
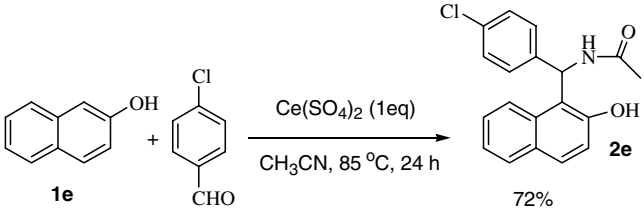
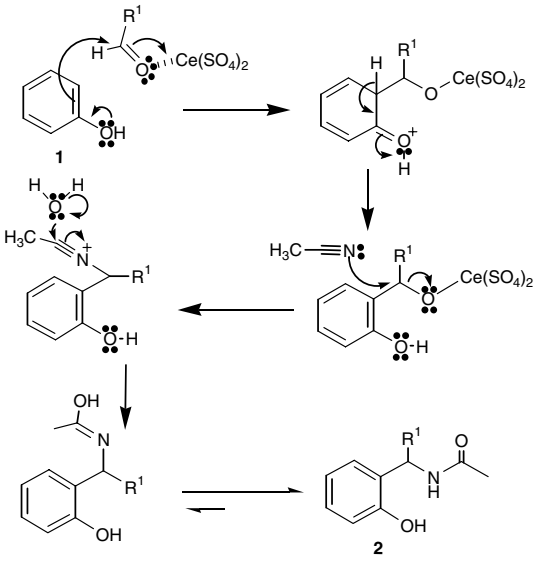


Figure 2. ORTEP diagram of compound **2e**.



Scheme 1. One-pot, three-component synthesis of acetamido phenols. (Reaction performed with 5 mmol of 2-naphthol, 5 mmol of *p*-chlorobenzaldehyde, 5 mmol of anhydrous cerium(IV) sulfate in 50 mL of acetonitrile, under argon at 85 °C.)

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2. The formation of **2** can be explained by the Ritter reaction[10] of the intermediate generated from an aldehyde and phenol.

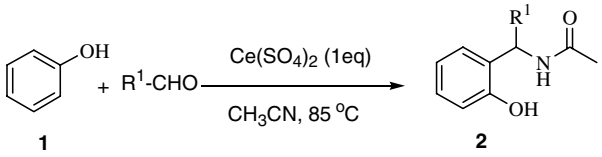


Scheme 2. Proposed mechanism for the formation of acetamido phenols.

Encouraged by these results, we attempted to synthesize acetamido anilines by the reaction of aniline, benzaldehyde and 2-naphthol, which led to the exclusive formation of the Schiff base.

We next attempted the reaction with substituted benzenes (anisole and xylene) under the optimized reaction conditions. Unexpectedly, bis-amides **3** were obtained as exclusive products. Increasing the electrophilicity of the benzene ring also afforded the same bis-amides **3**. The results are summarized in Table 2. Hence, we sus-

Table 1. The synthesis of acetamido phenols from the one-pot Ritter type reaction of phenols with aldehydes[a]

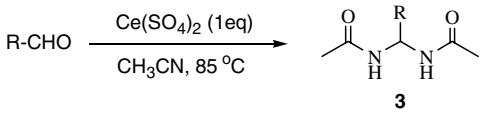


Entry	**1**	R^1	**2** (Yield, %)[b]	Time (h)
1	C_6H_5OH (**1a**)	3-$NO_2C_6H_4$	**2a** (48)	36
2	4-$MeOC_6H_4OH$ (**1b**)	3-$NO_2C_6H_4$	**2b** (45)	24
3	4-ClC_6H_4OH (**1c**)	3-$NO_2C_6H_4$	**2c** (44)	26
4	4-HOC_6H_4OH (**1d**)	3-$NO_2C_6H_4$	**2d** (40)	24
5	2-Naphthol (**1e**)	4-ClC_6H_4	**2e** (72)	24
6	2-Naphthol (**1e**)	2,4-$Cl_2C_6H_3$	**2f** (56)	36
7	2-Naphthol (**1e**)	4-$MeOC_6H_4$	**2g** (68)	24
8	2-Naphthol (**1e**)	4-FC_6H_4	**2h** (60)	36
9	2-Naphthol (**1e**)	1-Naphthyl	**2i** (44)	48
10	2-Naphthol (**1e**)	2-$NO_2C_6H_4$	**2j** (68)	16
11	2-Naphthol (**1e**)	3-$NO_2C_6H_4$	**2k** (65)	16
12	2-Naphthol (**1e**)	Et	**2l** (66)	24
13	2-Naphthol (**1e**)	3,4-$(MeO)_2C_6H_3$	**2m** (74)	24
14	2-Naphthol (**1e**)	4-$N(Me)_2C_6H_4$	**2n** (42)	48
15	2-Naphthol (**1e**)	C_6H_5	**2o** (72)	36

[a] Reaction performed with 5 mmol of phenol, 5 mmol of aldehyde, 5 mmol of anhydrous cerium(IV) sulfate in 50 mL of acetonitrile, under argon at 85 °C.

[b] Isolated yield.

Table 2. Synthesis of bis-amides from the one-pot reaction of aryl aldehydes and substituted benzenes in acetonitrile[a]



3

Entry	R	**3** (Yield, %)[b]	Time (h)
1	4-Cl C_6H_4	**3a** (48)	24
2	3-NO_2 C_6H_4	**3b** (51)	24

[a] Reaction performed with 5 mmol of aryl aldehyde, 5 mmol of substituted benzene (anisole and xylene), 5 mmol of anhydrous cerium(IV) sulfate in 50 mL of acetonitrile, under argon at 85 °C.
[b] Isolated yield.

pect that the phenolic OH in the reactant, might assist the amidation leading to acetamido phenols.

In summary, a novel methodology for the synthesis of acetamido phenols by a one-pot, three-component Ritter reaction is presented. We are currently investigating the mechanism of the reaction and the scope of cerium(IV) sulfate on other bond forming reactions.

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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.2006.08.038.

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