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LETTERS

Mild and Convenient Oxidation of Aromatic Heterocyclic Primary Alcohols by 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium Perchlorate

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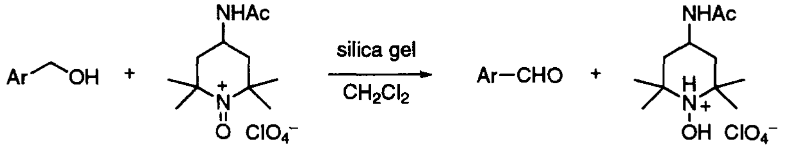
Abstract: Hydroxymethyl substituted aromatic heterocycles, including pyridines, furans, and thiophenes, are oxidized to the corresponding aldehydes in excellent yields by 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate (**1**) with minimal workup.

During our investigation of new chiral ligands for asymmetric catalysis,[1] it became necessary to obtain certain aromatic heterocyclic aldehydes that are not commercially available or are prohibitively expensive. An attractive and viable route to many of these consists of oxidizing the corresponding alcohol. For this purpose we sought an oxidation method that would not be hindered by the presence of strong σ-donor heteroatoms and could be carried out on a large scale without significant disposal problems. Oxidation of furan, thiophene, and pyridine methanols with reagents based on chromium,[2] manganese,[3] other transition metals,[4] selenium,[5] iodine,[6] and sulfur[7] have been reported with varying degrees of success and convenience. Although chromium reagents are typically quite successful, disposal problems and complications with strongly σ-donating substrates limits their utility.



(1)

1

Ar = aromatic heterocycle

Oxidations with recently reported oxoammonium reagent **1**,[8] first reported as the active species in nitroxide mediated oxidations,[8b] are generally carried out in under mild conditions, proceed in high yield, and require minimal workup (eq 1). In addition, **1** can be regenerated after trivial isolation of the hydroxylamine byproduct and subsequent treatment with bleach.[8a] An initial trial oxidation with **1** led us to the conclusion that this may be a general method for the oxidation of primary heterocyclic aromatic alcohols to the corresponding aldehydes.[9]

Our results of using **1** to oxidize a variety of furan, thiophene, and pyridine methanols are shown in Table 1. Stirring substrate alcohol in a methylene chloride slurry of **1** and silica gel, which has been found to

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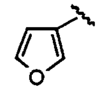
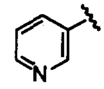
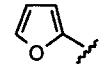
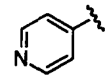
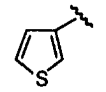
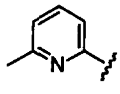
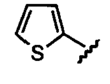
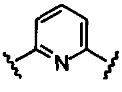
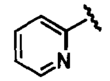
Table 1. Oxidation of heterocyclic aromatic primary alcohols to aldehydes ($RCH_2OH \rightarrow RCHO$) with **1**.

entry	R[a]	% Yield[b]	% Purity[c]	entry	R[a]	% Yield[b]	% Purity[c]
1		89	100	6		88	98
2		96	92	7		90	100
3		96	98	8		96	97
4		92	96	9		86	100
5		85	100				

[a] All products gave rise to ^1H NMR which were identical with those reported in the literature. [b]Isolated yields. [c]GLC.

accelerate the reaction,[8a] resulted in a clean conversion to product aldehyde which was isolated in excellent yield and purity by simple filtration and concentration.[10] Further purification, only necessary in the case of pyridyl alcohols (entries 5-9), merely consisted of passing the filtrate through a pad of silica gel before concentration. Proximity of the heteroatom in the aromatic ring to the site of oxidation appeared to have little effect on the course of the reaction (compare entries 1 and 2, 3 and 4, 5-7).

In conclusion, oxoammonium salt **1** has proven to be an effective reagent for the oxidation of aromatic heterocyclic primary alcohols to the corresponding aldehydes in high yields. The further utility of this reagent is currently under investigation.

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(9) For a nitroxide mediated process see H.E. Fried, US Patent 5,336,811, 1994.

(10) Typical procedure: To a slurry of alcohol (10.3 mmol) and silica gel (1 g) in CH_2Cl_2 (ca. 60 mL) was added **1** (11 mmol (1.07 equiv) per —CH_2OH), and the resulting mixture was allowed to stir at room temperature for 2-12 hrs. After TLC (SiO_2, EtOAc-hexanes) indicated consumption of starting alcohol, the reaction mixture was filtered and concentrated under reduced pressure to provide the desired aldehyde. In the case of pyridyl alcohols the residue was purified by passing through a plug of SiO_2 (CH_2Cl_2 eluent).