SILVER-MEDIATED MILD OXIDATION OF NITROGEN-CONTAINING HETEROARYL-2-METHANOLS TO ESTERS

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GRAPHICAL ABSTRACT

Abstract Oxidation of nitrogen-containing heteroaryl-2-methanols to esters with Ag₂O and isopropyl iodide is reported. This methodology is very mild and can tolerate many functional groups.

Keywords Esters; nitrogen-containing heteroaryl-2-methanols; oxidation; silver(I) oxide

INTRODUCTION

The conversion of primary alcohols to esters is an important reaction in organic synthesis.[1] Although many oxidants[2] are known for this conversion, and some of these reagents have been widely used, they still have several disadvantages: they generally require stoichiometric amounts of toxic and hazardous reagents such as sodium dichromate and/or peroxides.[3] Thus, the development of a single-step direct oxidative esterification of alcohols under mild conditions is highly desirable from both economic and environmental points of view.

RESULTS AND DISCUSSION

Silver salts are well known for their ability to oxidize many functional groups.[4] In pursuit of direct mild oxidation of nitrogen-containing heteroaryl-2-methanols to esters, we have studied the effect of silver(I) oxide and isopropyl iodide in dioxane on pyridine-2-methanol (1) and obtained the desired picolinate
ester (2) in good yield. During the course of this reaction, we have also observed simultaneous formation of O-alkylated compound as by-product under these conditions (Scheme 1).

To understand the mechanism of the reaction, we have applied the same reaction conditions to pyridine-2-carboxylic acid and 2-(isopropoxymethyl)pyridine and found that the reaction failed on these substrates where as the oxidation did not take place in the absence of isopropyl iodide on pyridine-2-methanol, suggesting that the oxidation and formation of ester are taking place simultaneously.

With the successful result of this reaction, we have studied the oxidation of pyridine-2-methanol in various solvents and observed better yield with original conditions (Ag₂O, 2-iodopropane, dioxane, room temperature, 24 h) (Table 1).

Further, the influence of various groups on pyridine-2-methanol was studied for general applicability of this reaction condition, leading to substituted picolinic esters (entries 1–7, Table 2). Because of the importance of this methodology for the synthesis of esters we tried to extend this strategy to pyridine-3 and 4-methanols also. However, the results were not encouraging on these substrates (entries 8 and 9, Table 2). With these findings, we propose that the Nsp2 lone pair might be forming a complex with silver oxide during the reaction, which facilitates the oxidation and concomitant esterification reaction with isopropyl iodide.

We have then extended the application of this methodology to other nitrogen-containing heteroaryl-2-methanols under this condition and obtained the esters in moderate to good yields (entries 1–10, Table 3), which enhances the applicability of this methodology.

![Scheme 1. Reagents and conditions: Ag₂O, 2-iodopropane, dioxane, room temperature, 24 h, 65% yield.](image)
Table 2. Oxidation of pyridine methanols to esters (2a–2i)

| Entry | Substrate 1 | Product 2 | Isolated yield (%)$^a$ |
|-------|-------------|-----------|------------------------|
| 1     | ![1a](image1) | ![2a](image2) | 76                     |
| 2     | ![1b](image3) | ![2b](image4) | 66                     |
| 3     | ![1c](image5) | ![2c](image6) | 74                     |
| 4     | ![1d](image7) | ![2d](image8) | 47                     |
| 5     | ![1e](image9) | ![2e](image10) | 61$^b$                 |
| 6     | ![1f](image11) | ![2f](image12) | 46                     |
| 7     | ![1g](image13) | ![2g](image14) | 63                     |
| 8     | ![1h](image15) | ![2h](image16) | —                      |

(Continued)
Table 2. Continued

| Entry | Substrate 1 | Product 2 | Isolated yield (%)$^a$ |
|-------|-------------|-----------|------------------------|
| 9     | ![Image](image1.png) | ![Image](image2.png) | 5$^c$ |

$^a$Isolated yields obtained using 1.00 mmol of substrate, 2.20 mmol of Ag$_2$O, and 2.20 mmol of 2-iodopropane in dioxane at room temperature for 24 h.
$^b$Reference 7.
$^c$Reference 8.

Table 3. Oxidation of heteroaryl methanols to esters (2j–2s)

| Entry | Substrate 1 | Product 2 | Isolated yield (%)$^a$ |
|-------|-------------|-----------|------------------------|
| 1     | ![Image](image1.png) | ![Image](image2.png) | 40$^b$ |
| 2     | ![Image](image3.png) | ![Image](image4.png) | 45 |
| 3     | ![Image](image5.png) | ![Image](image6.png) | 46$^c$ |
| 4     | ![Image](image7.png) | ![Image](image8.png) | 40 |
| 5     | ![Image](image9.png) | ![Image](image10.png) | 48$^{cd}$ |

(Continued)
CONCLUSION

In summary, we have developed a very mild method for the conversion of nitrogen-containing heteroaryl-2-methanols to esters using silver(I) oxide.

EXPERIMENTAL

Analytical thin-layer chromatography (TLC) was carried out on silica precoated glass plates (silica gel 60 F254, 0.25 mm thickness) and visualized with ultraviolet light at 254 nm. Purification of all the compounds was carried out on Redisep 4g silica flash column (catalog no. 69-2203-304) using Biotage Isolera Flash Purification System. $^1$H and $^{13}$C NMR spectra were recorded on Bruker 400-MHz
Ultrashield Advance II 400 model. Chemical shifts (δ) are reported in parts per million (ppm) and with reference to tetramethylsilane (TMS) as internal standard. Liquid chromatography/mass spectrometry (LC/MS) data were obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS instrument are the following: electrospray (+) ionization, mass range of 100–1000 Da, 20-V cone voltage, Acquity BEH C-18 column (2.1 × 100 mm, 1.7 μm), gradient mobile phase consisting of 5 mM ammonium acetate in water and acetonitrile, and a flow rate of 0.3 mL/min.

**General Procedure: Isopropyl Picolinate (2)**[5]

Freshly prepared Ag₂O (2.20 mmol) was added at room temperature to a solution of pyridin-2-ylmethanol (1.00 mmol) and 2-iodopropane (2.20 mmol) in 1,4-dioxane (10 mL) and stirred for 24 h. The reaction mixture was filtered through a Celite bed and washed with ethyl acetate. Filtrate was concentrated under vacuum. The resulting material was purified by flash chromatography on a Biotage instrument using 4-g flash cartridge and eluted with 12–15% ethyl acetate in hexane to give isopropyl picolinate (2) (65% yield).

\[ \text{1H NMR (400 MHz, CDCl₃): } \delta \text{ 8.76 (d, 1H, } J = 4.00 \text{ Hz), 8.11 (d, 1H, } J = 7.60 \text{ Hz), 7.82 (m, 1H), 7.45 (m, 1H), 5.34 (sep, 1H, } J = 6.40 \text{ Hz), 1.42 (d, 6H, } J = 6.40 \text{ Hz) ppm; 13C NMR (100 MHz, CDCl₃): } \delta \text{ 164.78, 149.90, 148.66, 136.91, 126.67, 125.06, 69.56, 21.86 ppm; LC-MS purity: 99.88%. HRMS calcd.: 165.0790; found: 165.0788.} \]

**FUNDING**

We are thankful to Jubilant Chemsys management for providing financial support and analytical facilities for the execution of this research work.

**SUPPORTING INFORMATION**

Supplementary data of compounds synthesized, including full characterization data, 1H and 13C NMR spectra, and LCMS traces can be accessed on the publisher’s website.

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