Supplementary Method for

Copper(I)/TEMPO Catalyzed Aerobic Oxidation of Primary Alcohols to Aldehydes with Ambient Air

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Supplementary Method. Detailed procedure for 10 mmol scale oxidation reaction.

Equipment that is different from that required for the standard (1 mmol) procedure is indicated with italics.

MATERIALS

REAGENTS

- alcohol substrate
- copper(I) tetrakis(acetonitrile) trifluoromethanesulfonate ($[Cu^{I}(MeCN)_4](OTf)$, Aldrich 685038)
- 2,2'-bipyridine (bpy, Aldrich D216305)
- 2,2,4,4-tetramethylpiperidine 1-oxyl (TEMPO, Aldrich 214000)
- *N*-methylimidazole (NMI, Aldrich M50834)
- anhydrous acetonitrile (MeCN, anhydrous solvent was employed, but has been shown to not be necessary)
- ethyl acetate (EtOAc, Aldrich 319902), hexanes (Hex, Aldrich 178918), pentane (Aldrich 148941), diethyl ether (Aldrich 673811). These are used for reaction workup and need not be anhydrous.

EQUIPMENT

- weighing balance (Mettler Toledo)
- 13 x 100 mm test tubes (VWR 47729-572)
- spatula (VWR 82027-490)
- magnetic stirplate (Corning)
- Teflon coated stir bar, 1/2" x 1/8" (VWR 58948-091)
- *250 mL roundbottom flask (Chemglass 1506-17)*
- *50 mL graduated cylinder*
- TLC plates (EMD 5715-7)
- TLC spotters (Chemglass 1182-01)
- polypropylene funnel
- *1 L round bottom flask (Chemglass 1506-23)*
- rotary evaporator (Heidolph WB eco)
- ice

For reaction conditions B:
- silicon oil (Aldrich 378380)
- crystallizing dish (VWR)

For reaction conditions C:
- water condenser, Liebig (Chemglass 128-A-20)
- rubber septum (SubaSeal 13 mm Aldrich Z124567)
- latex balloon (Aldrich Z154989)
- 3 mL plastic syringe (Becton Dickinson-309604)
- disposable needle (Becton Dickinson 20 g 1½ VWR BD-305175)
- electrical tape

For reaction workup Method A:
- *separatory funnel with Teflon stopcock, 1 L (Chemglass 1742-06)*
- polypropylene funnel (Fisher 10-347G)
- *3 x 500 mL Erlenmeyer flasks (Chemglass 8496-500)*
- filter paper, 18.5 mm diameter (Whatman)

For reaction workup Method B:
- *150 mL M porosity fritted Büchner funnel (Chemglass 8590-150M)*
- *1 L filter flask (Chemglass 8514-1L)*
- vacuum filtration adapter (VWR 24035)
- silica gel (Silicycle Ultrapure)

For reaction workup Method C:
- *glass flash chromatography column with a 250 mL reservoir, 4 in id x 12 EL with a Teflon stopcock*
- silica gel (Silicycle Ultrapure)
- test tubes for collecting column fractions (16 x 150 mm VWR 47729-580)

PROCEDURE

1 Weigh the alcohol (10 mmol) into a 250 mL round bottom flask add a stir bar and 20 mL of MeCN.
MeCN obtained from a drying column was typically employed, however untreated MeCN was shown to give similar yields and reactions times.

2 Weigh $[Cu(MeCN)_4](OTf)$ (188 mg, 0.05 equiv, 0.5 mmol), bpy (78 mg, 0.05 equiv, 0.5 mmol) and TEMPO (78 mg, 0.05 equiv, 0.5 mmol) into separate small test tubes.

3 Add sequentially the $[Cu(MeCN)_4](OTf)$, bpy, and TEMPO as solids to the reaction vessel, following each addition with a 10 mL rinse of MeCN (for a total of 50 mL solvent volume).

4 Add NMI (80 uL, 0.1 equiv, 0.1 mmol). The reaction mixture is typically dark red/brown at this point (Figure 2a).

5 Setup the remaining apparatus according to the desired reaction conditions below:
(A) Standard conditions

For most reactions the reaction mixture can be stirred open to air at room temperature in the round bottom flask.

(B) Reactions requiring higher temperatures
Fit the round bottom flask with a water condenser and a septum. Insert a balloon of house air or O_2 attached to a needle through the septum in order to maintain a closed system and prevent evaporation of the solvent. Then submerge the bottom portion of the reaction vessel in a preheated 50 °C oil bath.

(C) For the synthesis of volatile aldehydes
Fit the round bottom flask with a water condenser and a septum. Insert a balloon of house air or O_2 attached to a needle through the septum in order to maintain a closed system and prevent evaporation of the product.

6 Stir the reaction rapidly and monitor by TLC until no starting material remains. TLC conditions using 2:1 Hex/EtOAc and a $KMnO_4$ stain works for most alcohols. Completion of the reaction often occurs with a color change from dark red/brown to green/blue.

7 Purify the aldehyde according to one of the workup methods below, either by aqueous extraction (see option A), silica plug (see option B), or silica column chromatography (see option C).
Options A and B are both reliable methods to obtain product that is pure by analytical techniques in step 8. These methods leave trace residual TEMPO which can be removed by silica column chromatography (Option C).

(A) Purification by Aqueous Extraction

i Transfer the reaction mixture to a 1 L separatory funnel with water (250 mL) and pentanes (250 mL).

ii Extract the aldehyde into the organic solvent with vigorous shaking. The aqueous layer should be blue at this point (Figure 3a).

iii Remove the aqueous layer and extract it with pentanes (2 x 250 mL).

iv Combine the organic layers and wash with saturated NaCl solution (~250 mL).

v Dry the combined organic layers over $NaSO_4$.

vi Remove the $NaSO_4$ by filtration through filter paper into a weighed round bottom flask.

vii Remove the solvent by rotary evaporation.

CRITICAL STEP. For volatile aldehydes solvent removal should be done with the flask in an ice bath at ~0°C (Figure 3c).

(B) Purification by Silica Plug

i Prepare the setup for vacuum filtration by placing a 150 mL medium porosity fritted funnel containing ~100g of silica gel in a filter flask attached to a vacuum source.

ii Dilute the reaction mixture with 1:1 pentanes/ether (100 mL).

iii Filter the diluted reaction mixture through the silica plug and rinse with 1:1 pentanes/ether (3 x 100 mL). The top of the silica should turn blue from Cu, leaving a slightly pink colored filtrate (Figure 3b).

iv Transfer the filtrate to a weighed round bottom flask and remove the solvent by rotary evaporation.

CRITICAL STEP. For volatile aldehydes solvent removal should be done with the flask in an ice bath at ~0°C (Figure 3c).

(C) Purification by Silica Column Chromatography

i Transfer the crude reaction mixture to a round bottom flask and concentrate by rotary evaporation.

ii Purify the crude product by flash chromatography on silica gel using a mixture of hexanes and ethyl acetate.

iii Collect the fractions that contain the pure product (determined by TLC) into a round bottom flask and remove the solvent using a rotary evaporator.

CRITICAL STEP. For volatile aldehydes solvent removal should be done with the flask in an ice bath at ~0°C (Figure 3c).

8 Confirm the structure and purity of the product using ^{1}H and ^{13}C NMR spectroscopy.