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Facile preparation of 3-acetoxycyclobutanone

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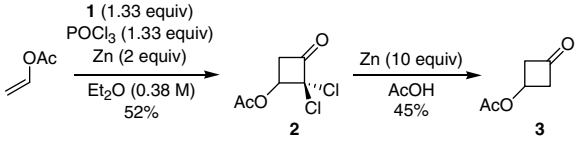
ABSTRACT

3-Acetoxycyclobutanone is a versatile intermediate to access cyclobutanes with a variety of substitution patterns. Established procedures require a two step process that includes multiple distillations. We report a one-pot procedure that renders this compound readily available. Additionally, it was determined that copper plays a key role in the reaction sequence.

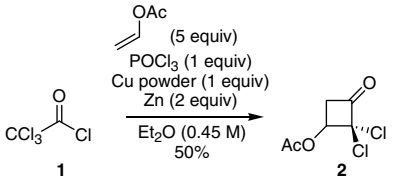
The importance of substituted cyclobutanes is evident in organic synthesis,[1] pharmaceutical intermediates,[2] and natural products.[3] In many instances, 3-acetoxy cyclobutanone (**3**, Scheme 1) could be used to access a desired cyclobutane with a specific substitution pattern.[4] Because of its synthetic versatility, we became interested in a direct and reliable route to **3** from inexpensive starting materials. The existing procedure, shown in Scheme 1, for generating this compound relies on a $\pi 2_s + \pi 2_a$ cycloaddition of vinyl acetate and dichloroketene (generated in situ from **1**).[5] Unfortunately, for our purposes this procedure has four problems from a practical point of view: (1) The procedure requires distillations of phosphorus oxychloride, vinyl acetate, **1**, **2**, and **3** to obtain the literature yield, otherwise a 2–5% overall yield results. (2) Activation of the zinc using $CuSO_4$ requires a separate step.[6] (3) A super-stoichiometric amount of phosphorus oxychloride complicates the workup and is a handling concern. (4) The ethereal solvent is a flammability hazard on scale up. Herein, we report the development of a one-pot procedure for the preparation of **3** which addresses these issues and provides material in the same overall yield.

We began by exploring methods to sidestep the separate zinc activation step that used $CuSO_4$.[6] Initially, more traditional in situ activation methods were tested including HCl in Et_2O, trifluoroacetic acid, trimethylsilyl chloride, and 1,2-dibromoethane. These methods, however, provided a zinc species that, when used in the $\pi 2_s + \pi 2_a$ cycloaddition, afforded only polymeric products associated with **1**. Based on the lack of success with the in situ activation procedures that did not include copper salts, we hypothesized that copper could play a crucial role in the reaction. Based on this idea, we added one equivalent of copper powder to a reaction using unactivated zinc and unpurified materials (Scheme 2). This additive gave a reaction with complete conversion and a 50% yield of **2** after distillation. As a control experiment, we ran the same reaction without zinc dust and with three equivalents of copper powder. This only afforded a complex mixture; desired product **2** was not present based on GSMS data, indicating the importance of *zinc and copper* for this transformation.



Scheme 1. Literature procedure.[5]

Next, we attempted to increase the yield and experimental ease of the process. It was eventually determined that 0.1 equiv of



Scheme 2.

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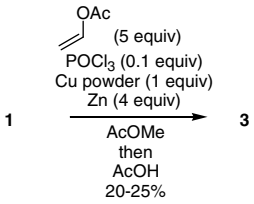

Scheme 3. Optimized procedure.

phosphorus oxychloride could be successfully used in the reaction without affecting the yield or the purity profile.[7] Additionally, 5 equiv of vinyl acetate were used[8] and methyl acetate was identified as the best solvent for the conversion of **1**–**2**. This solvent switch allowed a one-pot sequence from the two reactions (**1**–**2** and **2**–**3**) simply by adding acetic acid and two additional equivalents of zinc (Scheme 3).

Based on our experimental findings, the final optimized procedure is as follows: Over 4 h, add (via a dropping funnel) a solution of trichloroacetyl chloride (Aldrich, 12.3 mL, 20.0 g, 110 mmol) and phosphorus oxychloride (Aldrich, 1.0 mL, 1.69 g, 11 mmol, 0.1 equiv) in anhydrous methyl acetate (100 mL) to a suspension of zinc dust (Aldrich, 14.2 g, 220 mmol, 2 equiv), copper powder (Aldrich, 7.0 g, 110 mmol, 1 equiv) and vinyl acetate (Aldrich, 50 mL, 47.4 g, 550 mmol, 5 equiv) in anhydrous methyl acetate (Aldrich, 100 mL) at 18–23 °C. The mixture was stirred for 12 h after addition was completed. Zinc dust (14.2 g, 220 mmol, 2 equiv) was then added and the mixture was cooled to 0–5 °C. Acetic acid (Aldrich, 45 mL) was added dropwise at a rate to keep the internal temperature <10 °C. After addition was complete, the mixture was stirred for 3 h at 18–23 °C, concentrated to remove ca. 90% of the methyl acetate, and stirred for 12 h at 18–23 °C. The mixture was then diluted with heptane (40 mL) and methyl acetate (40 mL), and filtered to remove the solids. The solids were washed with methyl acetate (2×20 mL) and the yellow/brown filtrate was concentrated to remove ca. 90% of the methyl acetate. The resulting residue was purified by fractional distillation (bath 20 → 125 °C, 15 Torr, collected 85–90 °C) to afford 2.8 g (20% yield, typically 20–25% yield depending on scale, >97% pure) of 3-acetoxycyclobutanone as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.30–5.22 (1H, m) 3.53–3.41 (2H, m) 3.28–3.12 (2H, m) 2.13 (3H, s).[5] The ^{1}H NMR data for the intermediate 2, 2-dichloro-3-acetoxycyclobutanone are as follows: (300 MHz, $CDCl_3$, ppm) δ 5.45 (1H, dd, J = 6.0, 9.0 Hz) 3.47 (2H, ABdd, J = 6.0, 9.0, 18 Hz) 2.23 (3H, s).[5]

Three other olefins were subjected to the optimized reaction conditions: ethoxyacetylene, 2-acetoxypropene, and ethyl vinyl ether. Ethoxyacetylene gave no discernable product by GCMS and 2-acetoxypropene gave only trace amounts of the dichlorocyclobutanone intermediate. Ethyl vinyl ether, however, cleanly afforded the desired 3-ethoxycyclobutanone before distillation. As this material was heated for distillation, however, decomposition occurred. As a means of isolating pure material, the following alternate procedure was used after filtration: The yellow/brown methyl acetate filtrate was washed with a 5% $NaHCO_3$ solution until the aqueous layer was no longer acidic. The methyl acetate solution was then dried (brine wash then Na_2SO_4), concentrated to a thick oil, diluted with a minimal amount of CH_2Cl_2, and subjected to flash column chromatography on silica gel eluting with CH_2Cl_2. This produced 4.9 g (38% yield) of 3-ethoxycyclobutanone as a clear light-yellow oil.[9]

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7. Reactions were run with either 0.1 or 1.0 equiv $POCl_3$ and either 2 or 5 equiv of vinyl acetate (four reactions total) and analyzed by GCMS for conversion and purity profile. The reactions using 5 equiv of vinyl acetate were superior to those using 2 equiv regardless of the amount of $POCl_3$ used.
8. We feel that the additional vinyl acetate increases the rate of dichloroketene interception prior to dichloroketene polymerization rather than compensating for a background reaction of vinyl acetate that forms polymer or associated byproducts. This is based on examination of crude extracts by ^{1}H NMR which do not show vinyl acetate-type impurities.
9. The ^{1}H NMR matched the literature data: Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2194.