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A Simple Modification to Prevent Side Reactions in Swern-Type Oxidations Using Py·SO_3

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Abstract:

Additional pyridine was used to convert pyridine sulfuric acid 1:1 salt in commercial pyridine sulfur trioxide to the inactive 2:1 salt and prevent side reactions in the Swern oxidation.

Pyridine sulfur trioxide is a widely used reagent in Swern-type oxidation[1] on large scale. The commercial material very often contains large amounts of pyridine sulfuric acid 1:1 and 2:1 salts despite >95% purity most vendors claim (eq 1).[2] During process development for **2**, a key intermediate

$$\mathrm{Py{\cdot}SO_3 + H_2O \rightarrow Py{\cdot}H_2SO_4 + Py_2{\cdot}H_2SO_4} \qquad (1)$$

in a human rhinovirus (HRV) protease inhibitor,[3] significant amounts of a series of impurities were formed (Scheme 1). A systematic investigation was conducted. Significant increase of the impurity formation was observed when the reaction was spiked with pyridine sulfuric acid 1:1 salt, but not with the less acidic 2:1 salt. As a method for purification of commercial Py·SO_3, it was initially found effective to slurry pyridine sulfur trioxide commercial material in refluxing acetone, but the process also reduced active sulfur trioxide (eq 2). A simple and more effective modification

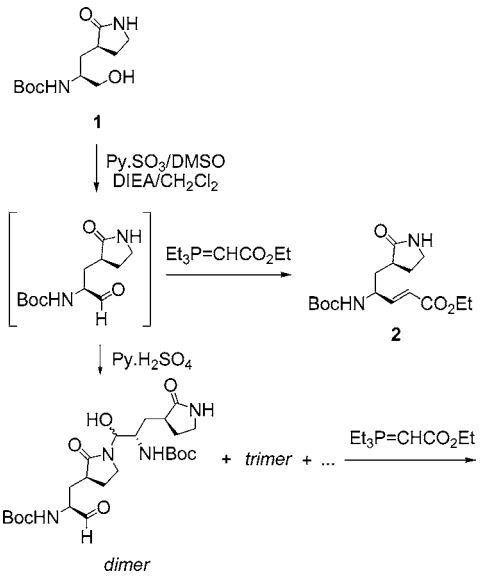
$$\mathrm{Py{\cdot}SO_3 + Py{\cdot}H_2SO_4 \xrightarrow{heat} Py_2{\cdot}H_2SO_4 + SO_3\uparrow} \qquad (2)$$

was developed by adding additional pyridine to convert the 1:1 salt to the inactive 2:1 salt. With this simple modification, polymerization impurities were reduced to undetectable level.

Experimental Section

1 (2.00 kg, 7.74 mol) was dissolved in DMSO (2.75 L, 38.7 mol) and methylene chloride (10 L). Diisopropylethylamine (4.73 L, 27.1 mol) was added at −5 °C. In another reactor, pyridine sulfur trioxide complex (2.46 kg, 15.5 mol) was mixed with pyridine (1.25 L, 15.5 mol) and DMSO (2.75 L, 38.7 mol) at room temperature and stirred

Scheme 1



for 10 min. The resulting suspension was added to the previously formed **1**/DMSO mixture at −5 °C. The reaction mixture was stirred for 1 h at −5 °C. A preformed Wittig salt solution from triethylphosphine (1 M in THF, 11.6 L, 11.6 mol) and ethyl bromoacetate (1.28 L, 11.6 mol) in methylene chloride (8 L) was added at −5 °C. Additional diisopropylethylamine (1.35 L, 7.74 mol) was added.[4] The reaction mixture was stirred for 1 h at −5 °C, allowed to warm to room temperature, and then stirred for 15 h. The mixture was concentrated under house vacuum at 25 °C, and the residue was dissolved in ethyl acetate (12 L). The solution was washed twice with 20% citric acid solution (20 L, 10 L), saturated sodium bicarbonate (10 L), and brine (10 L) and was dried over Na_2SO_4. The solution was concentrated to about 5 L, and hexanes (6 L) was added at 55 °C. The clear solution was gradually cooled to 35 °C in 2 h, and additional hexanes (6 L) was added. The resulting mixture was cooled to 0 °C in 1 h and stirred for 2 h. The slurry was filtered, and the wet cake was washed with 1:8 mixture of ethyl acetate−hexanes (5 L) and dried under vacuum at 40 °C to give **2** as a white solid (2.17 kg, yield 86%) with chemical and chiral purity of 97.1% and 98.6% by HPLC, respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (dd, J = 15.6, 5.0 Hz, 1H), 6.56 (s, 1H), 5.95 (dd, J = 15.6, 1.7 Hz,

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(1) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(2) The NMR spectrum clearly shows two sets of pyridine proton signals, although chemical shifts change from time to time, depending on salt ratio.

(3) Tian, Q.; Nayyar, N. K.; Babu, S.; Chen, L.; Tao, J.; Lee, S.; Tibbetts, A.; Moran, T.; Liou, J.; Guo, M.; Kennedy, T. P. *Tetrahedron Lett.* **2001**, *42*, 6807.

(4) Depending on the impurity level in Py·SO_3, the amount may vary. If racemization is not a concern, the second portion of the base could be added with the first one.

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1H), 5.34 (d, J = 8.1 Hz, 1H), 4.43−4.26 (br, s, 1H), 4.19 (q, J = 7.0 Hz, 1H), 3.41−3.27 (m, 2H), 2.56−2.36 (m, 2H), 2.08−1.92 (m, 1H), 1.90−1.72 (m, 1H), 1.66−1.52 (m, 1H), 1.44 (s, 9H), 1.28 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0, 166.2, 155.5, 148.1, 120.8, 79.6, 60.4, 50.1, 40.3, 38.2, 35.8, 28.3, 28.2; HRMS (CI) m/z 327.1933 (327.1920 calcd for $C_{16}H_{27}N_2O_5$, MH^+).

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