NOTE

A Facile Synthesis of 4,6-Dimethoxy-2-methylsulfonylpyrimidine

DEFENG XU*, ZHILING ZHU, HUI XU and ZIQIAO WANG

School of Pharmaceutical and Life Sciences, Changzhou University, Changzhou, Jiangsu 213164, P.R. China

*Corresponding author: Fax: +86 519 86334598; Tel: +86 519 86334597; E-mail: markxu@cczu.edu.cn

Received: 22 July 2013;

Accepted: 21 August 2013;

Published online: 26 December 2013;

AJC-14531

A facile and efficient synthesis of 4,6-dimethoxy-2-methylthiopyrimidine can be achieved by nucleophilic substitution of 2-chloro-4,6-dimethoxypyrimidine with sodium methyl mercaptide for a 95.6 % yield. 4,6-Dimethoxy-2-methylsulfonylpyrimidine can be produced via oxidation using hydrogen peroxide in the presence of sodium tungstate dihydrate in a 95 % yield.

Keywords: Nucleophilic substitution, Oxidation, 4,6-Dimethoxy-2-methyl sulfonylpyrimidine, 2-Chloro-4,6-dimethoxypyrimidine.

4,6-Dimethoxy-2-methylsulfonyl pyrimidine (**5**) was a key intermediate of the preparation of some pyrimidinylbenzoic acid herbicides, such as bispyribac sodium (**1**) and pyribenzoxim (**2**)^{1,2}. These herbicides, which belonged to the group of acetolactate synthase (ALS) inhibiting herbicides, acted against a broad spectrum of weeds associated with the rice crop³. It is used for large-scale or whole water body control of submerged, emergent and floating-leaf vegetation. Nezu *et al.*⁴ reported the preparation of bispyribac sodium and its key intermediate 4,6-dimethoxy-2-methylthiopyrimidine (**4**). Several syntheses of 4,6-dimethoxy-2-methylthiopyrimidine (**4**) had also been reported in the literature^{5,6}. Most of methods used high-toxic reagents such as dimethyl sulphate and phosphorus oxychloride. A large quantity of water pollution was produced in the process^{7,8}. A clean and environmentally friendly hydrogenation technique needs to be used. This paper reports a facile and efficient synthesis of 4,6-dimethoxy-2-methylthiopyrimidine (**4**) utilizing 2-chloro-4,6-dimethoxy pyrimidine (**3**) via nucleophilic substitution and oxidation in good yield.

Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on a XT34 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. ¹H NMR spectra were recorded on Mercuryplus 400 (300 MHz) spectrometer, chemical shifts (δ) were reported in ppm relative to TMS. Chemical shifts were reported in parts per million relative to the solvent resonance as the internal standard (CDCl₃, δ = 7.16 ppm). Analytical TLC and column chromatography were performed on silica gel GF₂₅₄.

4,6-Dimethoxy-2-methylthiopyrimidine (4): A mixture of 2-chloro-4,6-dimethoxy pyrimidine (17.5 g, 100 mmol), tetrabutylammonium bromide (1.6 g, 5 mmol), 25 % sodium methyl mercaptide (30.1 g, 107 mmol) and methanol (80 mmol) was heated to 45 °C and maintained at 45-50 °C for 2 h. An off-white precipitate formed which was collected by vacuum filtration and washed by cool water, the solid was recrystallized with isopropanol:water (2:1) to yield **4** as colourless crystals (17.8 g, 95.6 % in yield), m.p. 52.5-53.8 °C. (Lit⁹. m.p. 50-52 °C). ¹H NMR: (400 Hz, CDCl₃), δ (ppm), 3.51 (s, 3H, SCH₃), 3.84 (s, 6H, OCH₃), 6.15 (s, 1H, CH). ¹³C NMR: (400 Hz, CDCl₃), δ (ppm), 171.30, 171.06, 85.53, 53.40, 14.14.

4,6-Dimethoxy-2-methylsulfonyl pyrimidine (5): A mixture of 2-methylthio-4,6-dimethoxypyrimidine (18.6 g, 100 mmol), sodium tungstate dihydrate (1.5 g, 4.5 mmol), tetrabutylammonium bromide (1.6 g, 5 mol) and acetic acid (25 mL) was stirred at room temperature. To the vigorously stirred solution, hydrogen peroxide (19.5 g, 200 mmol) as a 35 % aqueous solution was added slowly at 45 °C. Stirring was continued at 55 °C for an additional 4 h. The excess hydrogen peroxide was destroyed by the addition of an aqueous solution of sodium sulfite, the solid filtered and recrystallized from ethanol to give **5** as colourless crystals (21.6 g, 99.0 % in yield). m.p. 126.3-127.7 °C. (Lit⁹. m.p. 126-127.5 °C). ¹H NMR: (400 Hz, CDCl₃), δ (ppm), 3.34 (s, 3H, SCH₃), 4.06 (s, 6H, OCH₃), 6.20 (s, 1H, CH), ¹³C NMR: (400 Hz, CDCl₃), δ (ppm), 171.90, 164.42, 93.11, 55.11, 39.81.

Recently studies using the pyrimidinyloxybenzoic acid herbicides and a key intermediate 4,6-dimethoxy-2-methylsulfonyl pyrimidine (**5**), showed that the facile synthesis of 4,6-dimethoxy-2-methylthiopyrimidine (**4**) using 2-chloro-4,6-dimethoxy pyrimidine with sodium methyl mercaptide under the phasetransfer catalyst in very high yields. Meantime, the optimization of the synthetic conditions for the oxidation of 4,6-dimethoxy-2-methylthiopyrimidine (**4**) was conducted.

In several literatures, 4,6-dimethoxy-2-methylsulfonyl pyrimidine (**5**) can be prepared by methylation of dimethyl sulphate in the presence of phase translation catalytic and chlorination of 2-methylthiobarbiturate in neat phosphorus oxychloride or with phosgene. It is very difficult to treat polluted industrial waste waters in this process. This synthesis method for 4,6-dimethoxy-2-methylthiopyrimidine (**4**) is a friend-environment process. The process is more suitable for a large-scale preparation for 4,6-dimethoxy-2-methyl sulfonyl pyrimidine (**5**) for some pyrimidinyloxybenzoic acid herbicides development.

Scheme-I

ACKNOWLEDGEMENTS

This project is supported by the introduction talent fund of Changzhou University.

REFERENCES

1. S.J. Koo, S.C. Ahn, J.S. Lim, S.H. Chae, J.S. Kim, J.H. Lee and J.H. Cho, *Pesticide Sci.*, **51**, 109 (1997).
2. K.T. Kim, B.B. Lee, G.H. Joe *et al.*, Process for Preparing 2,6-Di(4,6-dimethoxy pyrimidin-2-yl)oxybenzoic Acid Oxime Ester Derivatives as Herbicides, Can. Pat. Appl., 2194080 (1997).
3. B. Kanrar and A. Bhattacharyya, *J. Environ. Sci. Health B*, **44**, 788 (2009).
4. Y. Nezu, M. Miyazaki, K. Sugiyama, N. Wada, I. Kajiwarra and T. Miyazawa, *Pestic. Sci.*, **47**, 115 (1996).
5. C.U. Hur, J.H. Cho, S.M. Hong, H.W. Kim, Y.H. Lim, J.S. Rim, J.S. Kim and S.H. Chae, Pyrimidine Derivatives, Process for their Preparation and their Use as Herbicides, EP 658549 A1 (1995).
6. C. Luthy, H. Zondler, T. Rapold, G. Seifert, B. Urwyler, T. Heinis, H.C. Steinracken and J. Allen, *Pest Manage. Sci.*, **57**, 205 (2001).
7. Z.G. Tian, A.C. Liu, S. Yao and H.-Y. Chen, *Modern Agrichem.*, **10**, 27 (2011).
8. S. Ravi, K.M. Mathew, D. Padmanabhan, V.K.P. Unny and N. Sivaprasad, *J. Labelled Comp. Radiopharm.*, **49**, 339 (2006).
9. K.D. Barnes, J.A. Dixon and N. Murugesan, Herbicidal Substituted Benzoylsulfonamides, US5149357 A (1990).