Asian Journal of Chemistry Vol. 22, No. 1 (2010), 826-828

NOTE

Synthesis of 3-(2,2,2-Trifluoroethoxy)-2-pyridinesulfonamide

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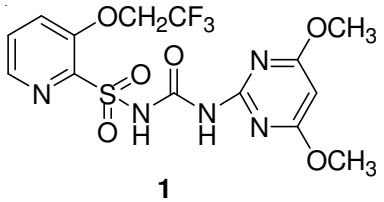
2-Chloro-3-(2,2,2-trifluoroethoxy)pyridine was prepared from 3-amino-2-chloropyridine with *n*-butyl nitrite in presence of the organic acid and 2,2,2-trifluoroethanol. 3-(2,2,2-Trifluoroethoxy)-2-mercaptopyridine was synthesized by mercaptylation with thiourea. The chlorination with chlorine and the amination with NH_3 afforded 3-(2,2,2-trifluoroethoxy)-2-pyridinesulfonamide. The route had several advantages in comparison with the reported synthesis, including less steps, mild condition and higher yields.

Key Words: 3-(2,2,2-Trifluoroethoxy)-2-pyridinesulfonamide, Trifloxysulfuron.

Trifloxysulfuron **1**, {N-[(4,6-dimethoxy-2-pyrimidinyl)carbamoyl]-3-(2,2,2-trifluoroethoy)-pyridin-2-sulfonamide sodium salt} is a sulfonylurea herbicide from Syngenta that developed for postemergence weed control in cotton (*Gossypium hirsutum* L.), sugarcane (*Saccharum officinarium* L.) and turfgrass. In cotton, trifloxysulfuron-sodium can be applied as a broadcast or directed spray, as a single or split application in conventional and glyphosate tolerant cotton[1,2]. 3-(2,2,2-Trifluoroethoxy)-2-pyridinesulfonamide **5** is a key intermediate of trifloxysulfuron, several syntheses of **5** are reported in the literature[3-5]. Most of methods are of low-yield, therefore, not practical. In this paper, a convenient and efficient synthesis of **5** by utilizing 3-amino-2-chloropyridine **2** as starting material is reported.



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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. ^{1}H NMR spectra were recorded on Mercuryplus 400 (300 MHz) spectrometer, chemical shifts (δ) were reported in ppm relative to TMS. Chemical shifts (δ) were reported

in ppm relative to the solvent resonance as the internal standard ($CDCl_3$, $\delta = 7.16$ ppm). Analytical TLC and column chromatography were performed on silica gel GF254 and silica gel H60, respectively.

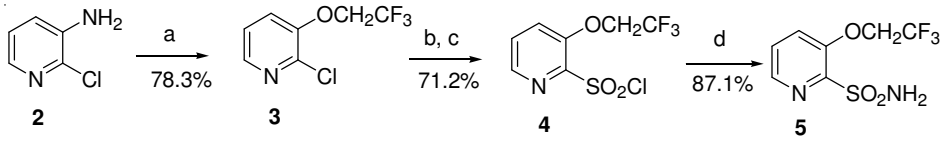
2-Chloro-3-(2,2,2-trifluoroethoxy)pyridine (3): A mixture of 3-amino-2-chloropyridine (10.0 g, 77.8 mmol), 2,2,2-trifluoroethanol (50.0 g, 550 mmol), methane sulfonic acid (3.84 g, 40.0 mmol) and acetic acid (2.40 g, 40.0 mmol) was stirred and cooled to -7 to -2 °C in an ice bath and then *n*-butyl nitrite (9.25 g, 89.6 mmol) was added drop-wise at -7 to -2 °C for 0.5 h. After stirring for 1 h, the solution was added drop-wise to 2,2,2-trifluoroethanol (10.0 g, 110 mmol) at 65-70 °C for 0.5 h. After cooling the solution was treated with the saturated aqueous solution of sodium carbonate (25 mL) and then extracted with ethyl acetate (70 mL × 3). The organic phase was dried by anhydrous magnesium sulfate and condensed to give a crude oil **3** (12.9 g, 78.3 %). ^{1}H NMR ($CDCl_3$): δ = 8.54-8.56 (m, 1H), 7.82-7.84 (m, 1H), 7.65-7.67 (m, 1H), 4.49 (m, 2H).

3-(2,2,2-Trifluoroethoxy)-2-pyridinesulfonyl chloride (4): A mixture of 2-chloro-3-(2,2,2-trifluoroethoxy)pyridine (**3**) (12.0 g, 56.7 mmol), ethanol (85 mL) and thiourea (4.75 g, 62.5 mmol) was refluxed for 5 h. The solution was cooled and added the saturated aqueous solution of sodium carbonate (20 mL) and then was refluxed for 1 h. After cooling, the solution was extracted with dichloromethane (35 mL × 3). The aqueous phase was adjusted to neutral by acetic acid. The reaction mixture was added in dichloromethane (90 mL) and cooled 0 °C, chlorine gas was introduced in system. After confirming disappearance of **3**, introduction chlorine gas was stopped to form 3-(2,2,2-trifluoroethoxy)-2-pyridinesulfonyl chloride (**4**). After the mixture was stirred for an additional 0.5 h at 0 °C, the reaction solution was poured into water and extracted with dichloromethane (50 mL × 3). The collected organic phase was washed with brine, dried over anhydrous magnesium sulfate and to be filtered to give **4**, the yield of two steps is 71.2 %.

3-(2,2,2-Trifluoroethoxy)-2-pyridinesulfonamide (5): The above reaction product was allowed to cool down to room temperature and introduced excess anhydrous ammonia. The anhydrous ammonia addition require more than 0.5 h during which time the temperature was kept below 5 °C. The reaction mixture was stirred for 2 h at room temperature. The product was collected by filtration, washed with cold water and dried. This gave white solid (9.0 g, 87.1 %), m.p. 137-139 °C, (lit.[6] m.p.136-138 °C). ^{1}H NMR ($CDCl_3$): δ = 4.56 (2H, m), 5.17 (2H, s), 7.51(1H, J = 8 Hz, d), 7.56 (1H, J = 8 Hz, d), 8.39 (1H, J = 6 Hz, d).

The synthesis of sulfonylurea herbicide has been studied and found that the efficient synthesis of 3-(2,2,2-trifluoroethoxy)-2-pyridinesulfonamide (**5**) from 3-amino-2-chloropyridine (**2**). Anhydrous diazotization was carried out with *n*-butyl nitrite in presence of the mixture of methanesulfonic acid and acetic acid. The synthetic condition of **3** on a large-scale was optimized according to the reported procedure[7]. The mercaptylation with thiourea, the chlorination with chlorine and the amination with ammonia were dealt with to afford product **5** in very high yield.

In the mean time, this method had several advantages in comparison with the reported synthesis including fewer steps, mild condition and high yields. The overall yield was 48.5 % based on **2**.



2 **3** **4** **5**

Scheme1 Reagents a, CF_3CH_2OH,AcOH, $MeSO_2OH$,n-C_4H_9ONO; b, NH_2CSNH_2,CH_3CH_2OH,CH_3CH_2ONa c, CH_2Cl_2, Cl_2; d NH_3,CH_2Cl_2

ACKNOWLEDGEMENTS

This project is supported by Shanghai Jiaotong University and Shanghai Minhang Government Research and Development Foundation.

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(*Received*: 4 May 2009; *Accepted*: 16 September 2009) AJC-7910