HETEROCYCLES, Vol. 85, No. 7, 2012, pp. 1721 - 1726. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 27th April, 2012, Accepted, 23rd May, 2012, Published online, 1st June, 2012
DOI: 10.3987/COM-12-12499

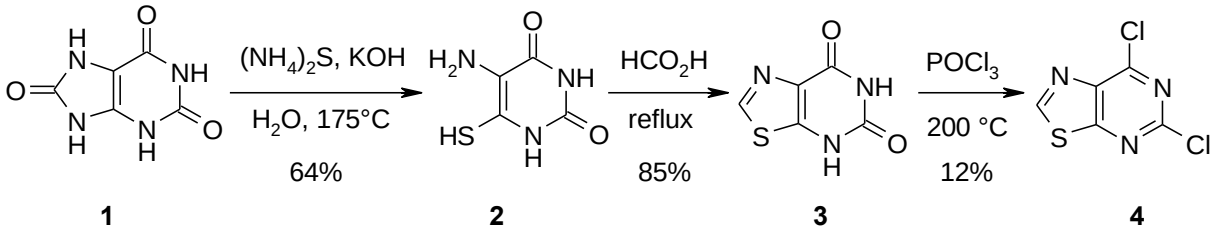
CONVENIENT SYNTHESIS OF 5,7-DICHLOROTHIAZOLO[5,4-*d*]PYRIMIDINE

Lianhe Shu,* Lady Mae Alabanza, and Chen Gu

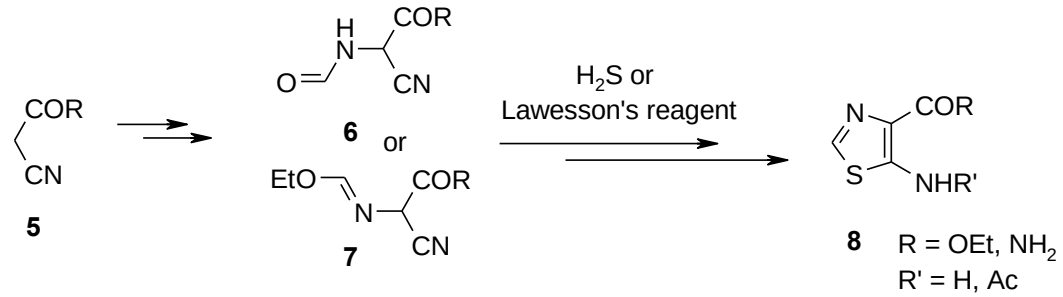
Process Research and Synthesis, Pharma Research and Early Development (pRED), Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA; E-mail: lianhe.shu@roche.com

Abstract – A convenient synthesis of 5,7-dichlorothiazolo[5,4-*d*]pyrimidine is reported. The condensation of ethyl isocyanoacetate and ethoxycarbonyl isothiocyanate selectively gave the key 5-aminothiazole intermediate in high yield under mild conditions. This intermediate was then converted to the target product in three steps.

Heterocyclic compounds have been widely used in the pharmaceutical industry. Recently, a drug discovery program at Roche required a heterocyclic building block, 5,7-dichlorothiazolo[5,4-*d*]pyrimidine (**4**). While this compound is available from multiple vendors around the world, it is very expensive and the limited stocks could not fulfill our immediate needs. An in-house campaign of this compound was thus pursued. Though the synthesis of **4** is known in the literature (Scheme 1),[1-3] and uric acid (**1**) is readily available, the conversion of **1** to **2** requires quite harsh conditions.[1] In addition, the use of ammonium sulfide is clearly undesirable for large scale preparations. Alternatively, the 5-aminothiazole precursor **8** can be prepared in several steps from **5** according to the literature (Scheme 2);[4-7] however, these routes are also not suitable for scale-up due to the use of hydrogen sulfide or Lawesson's reagent, and low overall yield. Herein, we describe a convenient, 4-step synthesis of **4** from readily available starting materials.

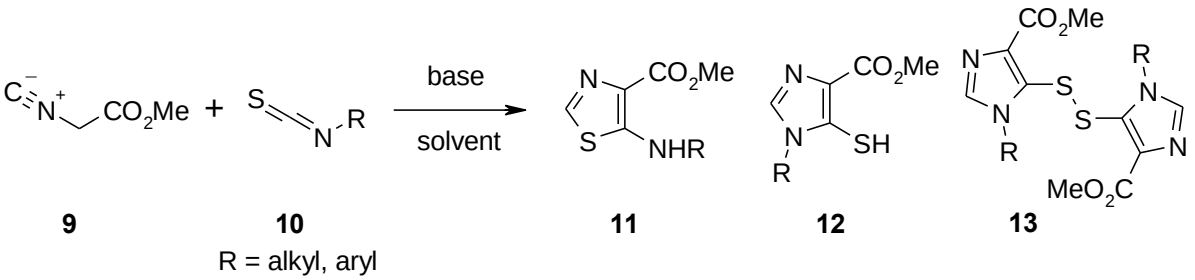


Scheme 1



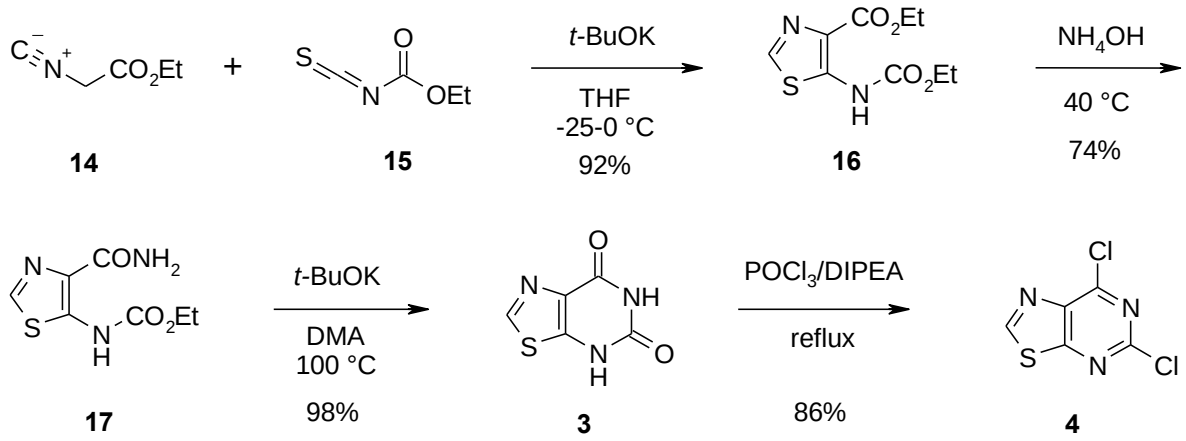
Scheme 2

The reaction of isocyanoacetate with isothiocyanate (Scheme 3) is of particular interest to us, as it provides an easy access to the key precursor **11**. However, reactions of **9** with **10** (R = alkyl or aryl) were reported to give **11** in only moderate yield.[8,9] A detailed study on the effect of temperature, solvent, base, and mode of addition by Solomon *et al.* revealed a significant competing pathway leading to the formation of imidazole **12** along with its dimerization product **13**.[9] This is consistent with our initial observation that the reaction of *t*-butyl isothiocyanate (**10**, R = *t*-Bu) at room temperature in the presence of potassium *t*-butoxide in THF gave essentially a 1 : 1 mixture of **11** : **12**, together with minor dimeric impurities. When benzyl isothiocyanate (**10**, R = Bn) was used, **11** became the major product. However, the product isolated was contaminated with unidentified impurities. Subsequently, the selectivity towards the desired thiazole was significantly improved by using a more electron deficient substrate, ethoxycarbonyl isothiocyanate (**15**). When the temperature was maintained between -25 and 0 °C, the reaction of **14** with **15** gave exclusively **16**, with no other isomers detected by LCMS analysis (Scheme 4).[10]



Scheme 3

Thus, **14** was added dropwise to a solution of potassium *t*-butoxide in THF maintained below -25 °C. The resulting enolate solution was stirred at this temperature for additional 10 min, then compound **15** was added dropwise while keeping the temperature below -20 °C. The reaction mixture was allowed to warm to 0 °C and quenched with acetic acid. After extractive work up with isopropyl acetate, concentration gave **16** in 92% yield as a light brown solid, which was directly used in the next step.



Scheme 4

Ethyl ester **16** can be directly converted to the corresponding amide **17** by aminolysis with ammonium hydroxide. Compound **16** was dissolved in aqueous ethanol at 40 °C. Then, ammonium hydroxide was added and the resulting suspension was stirred at 40 °C overnight to achieve complete conversion. When run at room temperature, the reaction took 4 days to complete. The resulting suspension was diluted with water and **17** was isolated by filtration as a white solid in 74% yield.

While the conversion of **17** to **3** could be achieved by a 2-step sequence, hydrolysis of the ethyl carbamate followed by cyclization with phosgene or its derivatives, the direct cyclization of **17** is more desirable in terms of efficiency and atom economy. It has previously been described[4] that **17** decomposes at 245-250 °C to give **3**, though no yield was reported. Such a high temperature step, however, is not considered practical for preparative purposes. The direct cyclization was initially tested in alcoholic solvents with acid additives, such as *p*-toluenesulfonic acid and sulfuric acid. No reaction was observed at reaction temperatures up to 120 °C. Treatment with bases, such as pyridine, *N,N*-diisopropylethylamine, DBU, and potassium hydroxide, at elevated temperature also did not induce any desired reaction. Subsequently, a clean cyclization was achieved within one hour by heating a mixture of **17** with potassium *t*-butoxide at 100 °C in *N,N*-dimethylacetamide (DMA) or *N*-methylpyrrolidinone (NMP). Sodium *t*-butoxide can also be used though the reaction was slower. After neutralization with acetic acid and dilution with water, the resulting solid was collected by filtration and dried under vacuum at 80 °C to give **3** in 98% yield.

For the final step, conversion of **3** to **4**, two conditions have been reported in the literature. In an early example **4** was isolated in 12% yield after heating **3** with phosphoryl chloride at 200 °C for 12 hours.[2] Hancox *et al.* reported the reaction at 80 °C, however, no detailed procedure and yield were provided.[3] Subsequently, we found that in the presence of *N,N*-diisopropylethylamine the reaction proceeded under relatively milder conditions and the yield was significantly improved. Thus, **3** was treated with

phosphoryl chloride in the presence of *N,N*-diisopropylethylamine at 110 °C for 30 hours. The reaction mixture was then concentrated under reduced pressure to remove excess phosphoryl chloride. After aqueous work up, the product was precipitated from isopropyl acetate-heptane, and was isolated as a brown solid in 86% yield and greater than 99% purity.

In summary, we report an efficient synthesis of 5,7-dichlorothiazolo[5,4-*d*]pyrimidine under relatively mild conditions from readily available starting materials. This 4-step synthesis, which has been scaled up to a 100 gram scale, gave this versatile building block in 57% overall yield.

EXPERIMENTAL

Ethyl 5-(ethoxycarbonylamino)thiazole-4-carboxylate (16) A 500 mL round-bottomed flask equipped with a magnetic stirrer, thermocouple probe and N_2 bubbler was charged with 1 M potassium *t*-butoxide in THF (180 mL, 180 mmol). The contents of the flask were cooled with a dry-ice acetone bath to below -25 °C, then **14** (18.0 g, 159 mmol) was added over 5 min while maintaining the internal temperature below -25 °C. After stirring at this temperature for 10 min, **15** (21.0 g, 160 mmol) was added dropwise over 10 min, while maintaining the internal temperature below -20 °C. After the addition was complete, the mixture was stirred for 10 min, then warmed to 0 °C over 30 min. The reaction was then quenched with acetic acid (10.5 mL, 183 mmol), diluted with water (90 mL), and concentrated under reduced pressure to remove THF. The residue was extracted with isopropyl acetate (180 mL). The organic layer was washed with water (2 × 90 mL), and concentrated under reduced pressure to give **16** (35.9 g, 92% yield) as a brown oil, which solidified upon standing at room temperature. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.59 (s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.31 (t, J =7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.72, 152.56, 146.49, 145.08, 126.76, 62.71, 60.80, 14.14, 14.10; HRMS *m/z* calcd. for $C_9H_{12}N_2O_4S$+H 245.0591, found 245.0591.

(4-Carbamoylthiazol-5-yl)carbamic acid ethyl ester (17)[4] A 250 mL round-bottomed flask equipped with a magnetic stirrer, heating mantle and condenser was charged with **16** (18.0 g, 73.7 mmol) and ethanol (18 mL). The suspension was stirred at 40 °C until all the solids had dissolved. The resulting solution was diluted with water (36 mL), then ammonium hydroxide (72 mL, 1.85 mol) was added. The mixture was stirred at 40 °C overnight, then diluted with water (72 mL) and heated under gentle reflux for 30 min. After cooling to room temperature, the resulting solid was collected by filtration, washed with water (2 × 72 mL) and dried at 80 °C under vacuum overnight to give **17** (11.7 g, 74% yield) as a white solid. mp 244.0 °C (decomp);[4] ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.58 (s, 1H), 7.88 (s, 1H), 7.78 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.98, 125.50, 144.22, 142.71, 128.87, 62.41, 14.18; HRMS *m/z* calcd. for $C_7H_9N_3O_3S$+H 216.0440, found 216.0437.

4*H*-Thiazolo[5,4-*d*]pyrimidine-5,7-dione (3)[4] A 500 mL round-bottomed flask equipped with a magnetic stirrer, heating mantle and N_2 bubbler was charged with potassium *t*-butoxide (14.7 g, 131 mmol) and *N,N*-dimethylacetamide (176 mL). Then, **17** (11.0 g, 51.1 mmol) was added. After stirring at 100 °C for 1 h, the reaction mixture was diluted with water (176 mL) and acidified with acetic acid (8.80 mL, 154 mmol). The resulting mixture was stirred at 100 °C for an additional 1 h, cooled to room temperature and filtered. The collected solids were washed with water (66 mL) and dried by suction, then at 80 °C under vacuum overnight to give **3** (8.50 g, 98% yield) as a white solid. mp > 360 °C;[2] ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (brs, 1H), 11.31 (s, 1H), 8.72 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.69, 150.33, 149.90, 146.08, 130.16; HRMS *m/z* calcd. for $C_5H_3N_3O_2S$+H 170.0021, found 170.0019.

5,7-Dichlorothiazolo[5,4-*d*]pyrimidine (4)[2] A 250 mL round-bottomed flask equipped with a magnetic stirrer, heating mantle, condenser and N_2 bubbler was charged with **3** (11.0 g, 65.0 mmol), *N,N*-diisopropylethylamine (33.0 mL, 189 mmol) and phosphoryl chloride (77.0 mL). The stirred mixture was heated to reflux for 30 h, then concentrated under reduced pressure to remove excess phosphoryl chloride. The oily residue was diluted with isopropyl acetate (110 mL) and ice-water (70 mL). After stirring for 10 min, the organic phase was separated, and the aqueous layer was extracted with isopropyl acetate (110 mL). The organic layers were combined, washed with water (2 × 70 mL) and filtered through a pad of Celite® to remove insolubles. The resulting solution was concentrated to *ca.* 50 mL, then diluted with *n*-heptane (132 mL). The suspension was further concentrated to *ca.* 50 mL and cooled to room temperature. The resulting solid was collected by filtration and washed with *n*-heptane (30 mL) to give **4** (11.5 g, 86% yield) as a brown solid. mp 145.0-146.5 °C;[2] ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.81, 156.49, 155.77, 155.36, 140.95; HRMS *m/z* calcd. for $C_5HCl_2N_3S$+H 205.9343, found 205.9341.

ACKNOWLEDGEMENTS

We would like to thank Ms. Amy Hilderbrand of the Formulation Research Department for HRMS analysis.

REFERENCES AND NOTES

1. G. P. Hager and C Kaiser, *J. Am. Pharm. Assoc.*, 1995, **44**, 193.
2. S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, 1951, **73**, 3862.
3. T. C. Hancox, N. A. Pegg, M. C. Beswick, T. J. Blench, E. A. Dechaux, J. J. Kulagowski, A. J. Nadin, and S. Price, *PCT Int. Appl.,* 2008152390, 18 Dec 2008.
4. M. Sekiya and Y. Osaki, *Chem. Pharm. Bull.*, 1965, **13**, 1319.

5. Y. Tamura, T. Miyamoto, K. Shimooka, and T. Masui, *Chem. Pharm. Bull.*, 1971, **19**, 119.
6. A. K. Sen and G. Chattopadhyay, *Indian J. Chem.*, 1979, **17B**, 222.
7. B. Golankiewicz, P. Januszczyk, M. Gdaniec, and Z. Kosturkiewicz, *Tetrahedron*, 1985, **41**, 5989.
8. M. Suzuki, T. Moriya, K. Matsumoto, and M. Miyoshi, *Synthesis*, 1982, 874.
9. D. M. Solomon, R. K. Rizvi, and J. J. Kaminski, *Heterocycles*, 1987, **26**, 651.
10. While the high selectivity may partially be attributed to the lower reaction temperature, we believe the ethoxycarbonyl group is crucial as it helps to localize the negative charge on sulfur atom thus favors the thiazole formation.