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One-pot syntheses of 6-mercaptopurines (6MP) from 4,5-diamino-6-chloro-pyrimidines ☆

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Abstract—A one-pot synthesis of 6-mercaptopurines from 4,5-diamino-6-chloro-pyrimidine, an aldehyde and elemental sulfur is presented. The key advantage of this procedure is that it utilizes the in situ generated H_2S to convert the chloro to a mercapto group.
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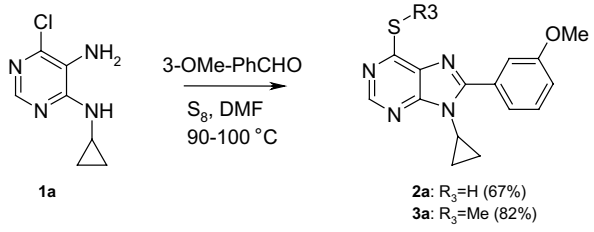
In the past two decades, 6-mercaptopurine (6MP) and its analogues have been a synthetic target for SAR programs in therapeutic areas of cancer,[1] viral infections,[2] and in CNS as ligands for benzodiazepine receptors.[3] In one instance, there has been a report of it being clinically used in the treatment of leukemia.[1] In these reports, thiopurines are obtained by treating chloropurines with thiourea,[1,3,4] NaSH/EtOH,[2] and in some cases with H_2S/base.[5] These methods can be undertaken for small scale synthesis (milligram to gram quantities). However, they may not be very attractive in larger scales due to the associated problems with stench in laboratories and surroundings.

We have discovered a simple, one-pot conversion of 4,5-diamino-6-chloropyrimidines such as **1a** to 6-mercaptopurines such as **2a** (Scheme 1).[6,7] The reaction consists of heating a mixture of pyrimidine **1a**, 3-methoxybenzaldehyde, and an equimolar amount of sulfur in DMF to 90–100 °C for 17 h. Work-up involves addition of water, and product isolation by filtration and drying. In this



Scheme 1.

one-pot conversion, the first step could either be the formation of dihydro derivatives of imidazopyrimidine[8] or a thioamide[9] before leading to the chloropurine and onwards to thiopurine via an S_NAr displacement of the chlorine by the in situ generated H_2S.[10]

Mercaptopurines were characterized by chemical and analytical methods. Mercaptopurine **2a** was methylated under standard conditions to afford the thiomethylpurine **3a** in 82% yield. The LCMS of the mercaptopurine **2a** showed a very characteristic MH^+ corresponding to the ^{34}S isotope with the expected intensity to that of the MH^+ of natural ^{32}S.

The generality of the one-pot conversion of 4,5-diamino-6-chloropyrimidines to thiopurines was

Keywords: Thiopurines; H_2S; One-pot synthesis; 4,5-Diamino-6-chloro-pyrimidines.
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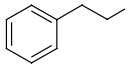
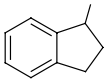
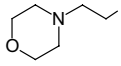
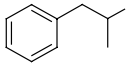
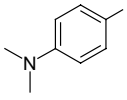
Table 1. Yields of thiopurines

Entry	R_1	R_2	Yield (%)[a]
1	C_6H_{13}	Ph	82
2		Ph	70
3		Ph	65
4		Ph	81
5		Ph	89
6	H	Ph	89
7			70
8			93
9			45
10	H		18

[a] Crude yields after isolation.

demonstrated by synthesizing thiopurines from a variety of chloropyrimidines and aldehydes, respectively, as shown in Table 1. From the table, it is clear that the yields in the synthesis depend only on the type of aldehyde independent of whether N-9 was substituted or not, as in entry 6 ($R_1 = H$) versus entries 1–5 ($R_1 =$ alkyl). Thiopurines derived from aliphatic aldehydes (entries 9 and 10) were obtained in low yields possibly due to the inherent inefficiency of imidazole formations from aliphatic aldehydes.

Our discovered method uses an in situ generated H_2S for the conversion of the chloro to the mercapto group thereby avoiding any offensive odor in the laboratory. In conclusion, we have discovered a simple one-pot conversion of 4,5-diamino-6-chloropyrimidines to 6-mercaptopurines in good to high chemical yields. We are currently exploring further utility of this methodology and the results will be reported in due course.

Supplementary data available Spectral data (^1H, ^{13}C and LCMS-ELSD) for **2a**. The supplementary data is available online with the paper in ScienceDirect.

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References and notes

1. Banerjee, S.; Dutta, S.; Chakraborti, S. K. *J. Indian Chem. Soc.* **1982**, *59*(3), 417–418, and references cited therein.
2. Murakami, K.; Shirasaka, T.; Yoshioka, H.; Kojima, E.; Aoki, S.; Ford, H.; Driscoll, J. S.; Kelley, J. A.; Mitsuya, H. *J. Med. Chem.* **1991**, *34*, 1606–1612.
3. Kelley, J. L.; McLean, E. W.; Ferris, R. M.; Howard, J. L. *J. Med. Chem.* **1990**, *33*, 1910–1914.
4. Holý, A.; Rosenberg, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **1989**, *54*(9), 2470–2501, and references cited therein.
5. Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685–693.
6. Sulfur has been used for the synthesis of 2-arylimidazo[4,5-*b*]- and 2-arylimidazo[4,5-*c*]-pyridines from *o*-/*m*-diaminopyridines and aromatic aldehydes. See: Yutilov, Y. M.; Shcherbina, L. I. *Chem. Heterocycl. Compd.* **1987**, *23*(5), 529–535.
7. All new compounds were characterized by analytical methods such as NMR and LCMS. Typical procedure: A solution of **1a** (923 mg, 5 mmol), 3-methoxybenzaldehyde (681 mg, 5 mmol) and sulfur (177 mg, 5.5 mmol) in DMF (20 mL) was heated at 100 °C for 17 h. The cooled reaction mixture was slowly added to vigorously stirred ice cold water (200 mL). The brown solid that separated was filtered, dried in the vacuum to afford pure **2a** (980 mg, 67%) as a brown solid. An analytically pure sample was obtained as a brown solid by silica gel purification, mp: 98–100 °C. ^1H NMR (DMSO-d_6) δ 13.70 (s, 1H), 8.22 (s, 1H), 7.47–7.55 (m, 3H), 7.22–7.06 (m, 1H), 3.86 (s, 3H), 3.81–3.69 (m, 1H), 1.21–0.93 (m, 2H), 0.92–0.63 (m, 2H): ^{13}C (DMSO-d_6) δ 175.06, 158.94, 152.54, 147.02, 144.59, 134.36, 130.79, 129.46, 121.39, 115.79, 114.20, 55.32, 39.51, 26.14, 8.40. MS (ESI) m/z: 299.2 [$C_{15}H_{14}N_4OS+H^+$].
8. Dubey, P. K.; Ratnam, C. V. *Proc. Indian Acad. Sci.* **1977**, *85A*, 204.
9. When aniline was treated with benzaldehyde and sulfur in hot DMF, *N*-phenylbenzenecarbothioamide was obtained in high yields. For similar published results, see: Pelova, R.; Kozhukharova, A. *Nauchni, Trudove Plovdivski Universitet Paisii Khilendarski* **1982**, *20*(3, Khim), 79–90.
10. No chlorine displacement is observed on performing a 1.0 mmol scale reaction under a constant stream of N_2 to displace the generated H_2S. An additional proof for the in situ produced H_2S is from the observation that when phenylenene diamine, *m*-hydroxybenzaldehyde and 6-chloro-9-cyclopentyl-9H-purine were subjected to the reaction conditions, the expected 3-(1H-benzimidazol-2-yl)phenol and 9-cyclopentyl-9H-purine-6-thiol were obtained. However, no mercapto product was obtained in the absence of the diamine and benzaldehyde.