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Facile Synthesis of 9*H*-*s*-triazolo-[3,4-*i*]purin-5(6*H*)-ones.

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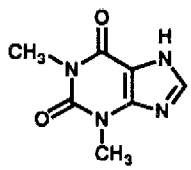
Abstract: New tricyclic heterocycles, 9*H*-*s*-triazolo[3,4-*i*]purin-5(6*H*)-ones(**2**, **3**), were prepared from 6-methylthio-7*H*-purin-2(3*H*)-ones (**5a**, **5d**)

Theophylline (**1**) is currently recognized as a drug of choice for the maintenance therapy of asthma.[1] However, theophylline has a narrow optimum therapeutic range due to its side effects such as central nervous system stimulation, cardiotonic activity and emesis.[2] As a part of our ongoing efforts to screen for superior analogs of theophylline, we have studied the synthesis and pharmacological activity of new tricyclic heterocycles such as 9*H*-*s*-triazolo[3,4-*i*]purin-5(6*H*)-ones. Among them, compounds **2** and **3** were recently found to exhibit 5- to 100-fold more potent bronchodilatory activity than theophylline.[3] This discovery prompted us to devise facile and general synthesis of such heterocycles. Entry to those molecular systems and their derivatives are of interest, not only in terms of their potent bronchodilatory activities, but also structurally defined probes for multi-biological reactions of theophylline. This communication reports a synthesis of this unique ring system starting from 6-methylthio-7*H*-purin-2(3*H*)-ones (**5a**, **5d**), which are readily available from 6-thioxanthines.



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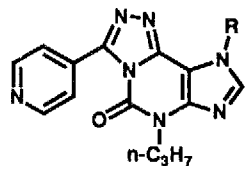
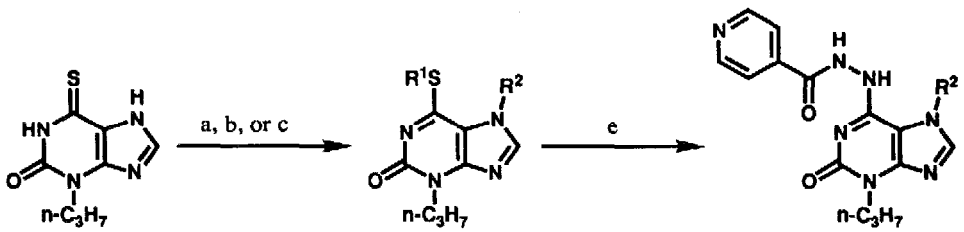


R= CH_3, **2**
H, **3**

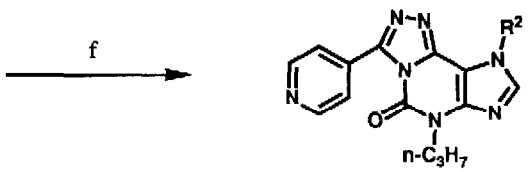
3-Propyl-6-thioxanthine (**4**)[4] was methylated with 2 equiv of methyl iodide and 2 equiv of sodium hydride in DMF both at sulfur and nitrogen to yield 7-methyl-6-methylthio-7*H*-purin-2(3*H*)-one (**5a**). The methylthio derivative (**5a**) was easily transformed[5] by equimolar isonicotinic hydrazide in DMSO at 150 °C to 3,7-dihydro-6-(*N*'-isonicotinoylhydrazino)-7*H*-purin-2(3*H*)-one (**6a**).[6]

Although the synthesis of fused *s*-triazole system has been documented in several ring system,[7,8] there is little known about cyclization of the hydrazinoimidate derivatives (**8**) deactivated by the carbonyl group such as **6**. When the hydrazide (**6a**) was heated with a catalytic amount of p-toluene sulfonic acid in toluene/1,1,2,2-tetrachloroethane at reflux temperature, **6a** surprisingly underwent easy cyclodehydration to the desired 9*H*-*s*-triazolo[3,4-*i*]purin-5(6*H*)-one (**2**) in 76% yield.[9] In contrast to thermal instability of *s*-triazolo[3,4-*i*]purines (**9**) which are biologically inactive,[7a] **2** was proven to be stable under the above acidic reaction condition presumably



4 **5a**: $R^1 = R^2 = CH_3$- **5b**: $R^1 = CH_3$-, $R^2 = H$ **5c**: $R^1 = R^2 = C_6H_5CH_2$- **5d**: $R^1 = CH_3$-, $R^2 = C_6H_5CH_2OCH_2$- **6a ~ 6d**

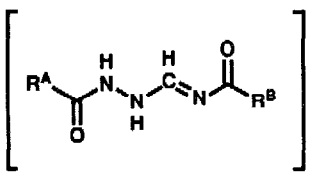
d



2: $R^2 = CH_3$- **3**: $R^2 = H$ **7c**: $R^2 = C_6H_5CH_2$- **7d**: $R^2 = C_6H_5CH_2OCH_2$-

g

Reaction Conditions
a = 2 equiv CH_3I / 2 equiv NaH, DMF, r.t. (81%); b = 2 equiv $PhCH_2Br$ / 2 equiv NaH, DMF, r.t. (89%); c = 1.5 equiv CH_3I / NaOH aq. - EtOH, r.t. (78%); d = $PhCH_2OCH_2Cl$ / NaH, DMF, 0 ℃ ~ r.t. (92%); e = isonicotinic hydrazide, DMSO, 150 ℃; f = 0.2 equiv TsOH, Tol-$Cl_2CHCHCl_2$, reflux; g = BBr_3, Tol, -78 ℃ ~ r.t. (73%)



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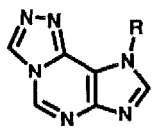

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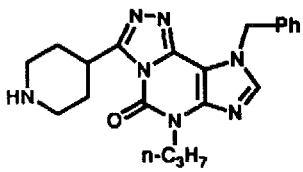

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Scheme I.

due to the electronegative character of the carbonyl group at the 5-position. The desired compound (**2**) was also directly obtained by the prolonged reaction of isonicotinic hydrazide with **5a**, but the yield was very low.

Then the synthesis of compound **3** was examined. When **4** was treated with methyl iodide in an aqueous alkaline solution,[10] selective monomethylation at sulfur occurred to afford 6-methylthio-7*H*-purin-2(3*H*)-one (**5b**) in 78% yield. Excess hydrazide (2 equiv) was needed to obtain the corresponding hydrazide (**6b**) from **5b**. Cyclodehydration of **6b** was failed under several conditions (treatment with p-TsOH, $SOCl_2$ or $POCl_3$). Thus the nitrogen atom of the imidazole ring was protected with the benzyl or benzyloxymethyl group.

7-Benzyl-6-benzylthio-7*H*-purin-2(3*H*)-one (**6c**) readily prepared by the bis-benzylation of 6-thioxanthine(**4**), was similarly converted to the corresponding 9-benzyl-9*H*-*s*-triazolo[3,4-*i*]purin-5(6*H*)-one (**7c**). Bridson et al.[9] reported that the 7-benzyl group in 1,3-disubstituted xanthine derivatives could be removed by catalytic hydrogenolysis but reaction of **7c** under catalytic hydrogenation condition (H_2 (70 psi) / PtO_2, AcOH) gave only piperidine derivative (**10**). Then **7c** was treated with boron tribromide[12] in toluene/1,1,2,2-tetrachloroethane at reflux temperature for 8 hr, but **7c** was mainly recovered together with many side-products. Thus an another protecting group was introduced.

7-Benzyloxymethyl-6-methylthio-7*H*-purin-2(3*H*)-one (**5d**) easily prepared from **5b** was treated with isonicotinic hydrazide followed by cyclodehydration reaction (p-TsOH, Tol / $Cl_2CHCHCl_2$, reflux, 30 min) to afford 9-benzyloxymethyl-9*H*-*s*-triazolo[3,4-*i*]purin-5(6*H*)-one (**7d**; 90% yield) accompanied by the deprotected desired compound (**3**; 9% yield). The deprotection of the benzyloxymethyl group was accomplished by the treatment with boron tribromide in toluene[13] in 73% yield. Thus the benzyloxymethyl group is a suitable protecting group for the imidazole nitrogen.

We have demonstrated that the readily available key intermediate (**5a** or **5d**) can be conveniently elaborated to 3-(4-pyridyl)-9*H*-*s*-triazolo[3,4-*i*]purin-5(6*H*)-one derivatives, which are potent bronchodilators. The application of the present synthetic method for the other condensed purine derivatives will be reported in due course.

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REFERENCES and NOTES

1. Rall, T. W.: Drugs Used in the Treatment of Asthma. In *The Pharmacological Basis of Therapeutics. 8th Ed;* Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P. Eds.; Pergamon Press, Inc.: New York, 1990; pp. 618-637.
2. Svedmyr, N.: Xanthines. In *Asthma: Basic Mechanisms and Clinical Management;* Barnes, P. J.; Rodger, I. W.; Thomson, N. C. Eds.; Academic Press Ltd.: London, 1988; pp. 607-625.
3. Suzuki, F.; Shimada, J.; Ohmori, K.; Manabe, H.; Kubo, K.; Karasawa, A.; Ohno, T.; Shiozaki, S.; Ishii, A.; Shuto, K. Eur. Patent, 417 790, 1990.
4. Hofer, P. Eur. Patent, 191 313, 1986; *Chem. Abst.* **1986**, *105*, 226214w.
5. (a) Yamazaki, A.; Kumashiro, I.; Takenishi, T.; Ikehara, M. *Chem. Pharm. Bull.* **1968**, *16*, 2172-2181. (b) Kazimierczuk, Z.; Shugar, D. *Acta Biochem. Pol.* **1974**, *21*, 455-463; *Chem. Abst.* **1975**, *82*, 125358x. (c) Hori, M.; Kataoka, T.; Shimizu, H.; Imai, E.; Yokomoto, M.; Ando, Y. *Synthesis* **1987**, 278-280.
6. A mixture of **5a** (4.00 g, 16.8 mmol) and isonicotinic hydrazide (2.77 g, 20.2 mmol) in 15 mL of DMSO was heated at 150 ℃ for 30 min. After cooling, water (500 mL) was added and the mixture was extracted with $CHCl_3$ (100 mL) three times. The organic extracts were washed with brine, dried and concentrated. Silicagel column chromatography gave 2.95 g (54%) of **6a** as a yellow powder.
7. (a) Temple, Jr., C; Kussner, C. L.; Montgomery, J. A. *J. Org. Chem.* **1965**, *30*, 3601-3603. (b) Thompson, R. D.; Castle R. N. *J. Heterocyclic Chem.* **1981**, *18*, 1523-1527. (c) Brown, D. J.; Shinozuka, K. *Aust. J. Chem.* **1982**, *35*, 1263-1267. (d) Champaigne, E.; McLaughlin, A. R. *J.*

Heterocyclic Chem. **1983**, *20*, 781-782. (e) Tarzia, G.; Occelli, E.; Toja, E.; Barone, D.; Corsico, N.; Gallico, L.; Luzzani, F. *J. Med. Chem.* **1988**, *31*, 1115-1123.

8. Grandolini, G.; Rossi, C.; Tiralti, M. C.; Orzalesi, G.; De Regis, M. *Il Farmaco Ed. Sci.* **1985**, *40*, 221 -236.
9. A solution of **6a** (1.70 g, 5.20 mmol) in 20 mL of Tol / $Cl_2CHCHCl_2$ (1:1) was heated under reflux in the presence of p-TsOH (198 mg, 1.04 mmol) for 2 hr. After cooling, the reaction mixture was poured into an aqueous saturated $NaHCO_3$ solution (100 mL) and extracted with $CHCl_3$ three times. Usual workup followed by recrystallization from EtOH gave 1.22 g (76%) of **2** as pale yellow needles.
10. Lichtenberg, D.; Bergmann, F.; Neiman, Z. *J. Chem. Soc. Perkin II* **1972**, 1676-1681.
11. Bridson, P. K.; Richmond, G.; Yeh, F. *Syn. Commun.* **1990**, *20*, 2459-2467.
12. Hosmane, R. S.; Lim, B. B.; Burnett, F. N. *J. Org. Chem.* **1988**, *53*, 382-386.
13. Kundu, N. G.; Hertzberg, R. P.; Hannon, S. J. *Tetrahedron Lett.* **1980**, *21*, 1109-1112.
14. The spectral and physical data for **5a**, **5b**, **5d**, **6a**, **6b**, **2**, **3** and **7d** are:

5a: mp 225-226 ℃ (MeCN); IR (KBr) 1630, 1596, 1557, 1393 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ (ppm): 7.53 (1H, s), 4.16 (2H, t, *J*=7.5 Hz), 4.01 (3H, s), 2.71 (3H, s), 1.95-1.77 (2H, m), 0.98 (3H, t, *J*=7.5 Hz); ^{13}C NMR (270MHz, $CDCl_3$) δ (ppm): 160.9, 154.7, 151.6, 143.3, 114.3, 45.0, 34.7, 21.2, 12.2, 11.2; Anal. Calcd. for $C_{10}H_{14}N_4OS$: C 50.40, H 5.92, N 23.51, Found: C 50.30, H 5.95, N 23.35.

5b: mp 241-243 ℃ ; IR (KBr) 3400 (br), 1600, 1588, 1572 cm^{-1}; ^1H NMR (270MHz, DMSO-d_6) δ (ppm): 13.54 (1H, brs), 8.13 (1H, brs), 3.99 (2H, t, *J*=7.5 Hz), 2.57 (3H, s), 1.80-1.62 (2H, m), 0.88 (3H, t, *J*=7.5 Hz); ^{13}C NMR (270MHz, DMSO-d_6) δ (ppm): 160.6 (br), 153.8, 149.4 (br), 141.9 (br), 112.8 (br), 44.4, 20.6, 11.3, 11.0; Anal. Calcd. for $C_9H_{12}N_4OS \cdot H_2O$: C 44.61, H 5.82, N 23.12, Found: C 44.80, H 5.94, N 23.03.

5d: mp 167-168 °C ; IR (KBr) 1623, 1592, 1556 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$) δ (ppm) 7.58 (1H, s), 7.29 (5H, s), 5.61 (2H, s), 4.59 (2H, s), 4.12 (2H, t, *J*=8 Hz), 2.70 (3H, s), 2.00-1.60 (2H, m), 0.99 (3H, t, *J*=8 Hz); Anal. Calcd. for $C_{17}H_{20}N_4O_2S$: C 59.28, H 5.85, N 16.27, Found: C 58.99, H 5.80, N 16.22.

6a: ^1H NMR (270MHz, DMSO-d_6) δ (ppm) 10.68 (1H, brs), 10.61 (1H, brs), 8.73 (2H, d, *J*=6.0 Hz), 7.84 (1H, s), 7.82 (2H, d, *J*=6.0 Hz), 3.92 (3H, s), 3.83 (2H, t, *J*=7.5 Hz), 1.80-1.60 (2H, m), 0.88 (3H, t, *J*=7.5 Hz); Anal. Calcd. for $C_{15}H_{17}N_7O_2 \cdot 0.2$ DMSO: C 53.93, H 5.35, N 28.59, Found: C 54.24, H 5.30, N 28.40.

6b: ^1H NMR (90MHz, DMSO-d_6) δ (ppm) 10.5 (2H, brs), 8.70 (2H, d, *J*=5 Hz), 7.80 (2H, d, *J*=5 Hz), 7.78 (1H, s), 3.83 (2H, t, *J*=7 Hz), 1.80-1.45 (2H, m), 0.88 (3H, t, *J*=8 Hz); MS, *m/e* 313 (M^+), 295, 253, 106, 78.

2: mp 236-238 ℃ (EtOH-MeCN); IR (KBr) 1718, 1650 cm^{-1}; ^1H NMR (270MHz, DMSO-d_6) δ (ppm) 8.72 (2H, d, *J*=4.8 Hz), 8.12 (1H, s), 7.72 (2H, d, *J*=4.8 Hz), 4.10 (3H, s), 4.07 (2H, t, *J*=7.5 Hz), 1.90-1.70 (2H, m), 0.90 (3H, t, *J*=7.5 Hz); Anal. Calcd. for $C_{15}H_{15}N_7O \cdot 0.8$ MeCN: C 58.27, H 5.13, N 31.93, Found: C 58.20, H 4.91, N 32.15.

3: mp > 330 ℃ (dioxane-H_2O); IR (KBr) 1732, 1659, 1603, 1568, 1514 cm^{-1}; ^1H NMR (270MHz, DMSO-d_6) δ (ppm) 14.03 (1H, s), 8.71 (2H, d, *J*=5.5 Hz), 8.14 (1H, s), 7.73 (2H, m), 4.10 (2H, t, *J*=7.5 Hz), 1.85-1.65 (2H, m), 0.91 (3H, t, *J*=7.8 Hz); Anal. Calcd. for $C_{14}H_{13}N_7O$: C 56.94, H 4.44, N 33.20, Found: C 56.59, H 4.35, N 33.42.

7d: mp 272-274 ℃ (EtOH); IR (KBr) 1715, 1628, 1558, 1506 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$) δ (ppm) 8.73 (2H, d, *J*=8.9 Hz), 7.78 (1H, s), 7.69 (2H, d, *J*=8.9 Hz), 7.23 (5H, brs), 5.93, (2H, s), 4.78 (2H, s), 4.20 (2H, t, *J*=7.5 Hz), 2.00-1.65 (2H, m), 1.01 (3H, t, *J*= 7.6 Hz); MS, *m/e* 415 (M^+), 385, 295, 266, 253, 146, 91.

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