A Simple One-Pot Synthesis of Novel [1,2,4]Triazolo[3,4-*f*]purines

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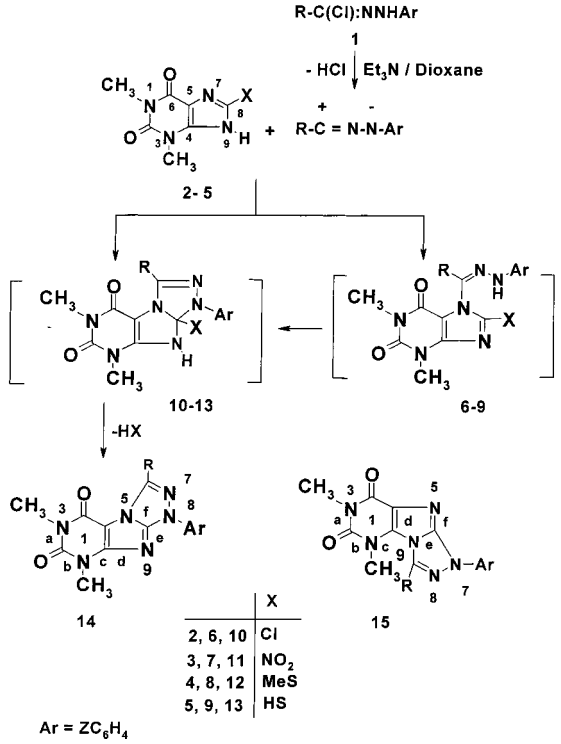
Our longstanding involvement in the use of hydrazonoyl halides **1** as starting materials to prepare new heterocyclic systems[1] led us to investigate their reactions with some natural purine derivatives in an attempt to develop a new synthetic approach for their respective fused annelated derivatives. Here, we wish to report the results of our study of the reaction of such halides with 8-chloro-, 8-nitro-, 8-methylthio-, and 8-mercaptotheophylline derivatives **2**−**5**, respectively. As outlined below, the studied reactions proved useful for synthesis of functionalized derivatives of the previously reported ring system namely [1,2,4]triazolo[3,4-*f*]purines[2] **14** (Scheme 1). The only hitherto known [*f*]-fused purines include pyrrolo[2,1-*f*]-,[3] oxazolo[2,3-*f*]-,[4,5] imidazo[2,1-*f*]-,[6−8] pyrido[2,1-*f*]-,[3] pyrimido[2,1-*f*]-,[3,9] oxazino[2,3-*f*]-,[10] pyrazino-[2,1-*f*]-,[3] [1,2,4]triazino[3,2-*f*]-,[11] and [1,2,4]triazepino [3,2-*f*]-[11] purines. Also, [1,2,4]triazolo[3,4-*i*]- and [1,2,4]triazolo[5,1-*i*]purines were also reported.[12,13] The interest in synthesis of derivatives of the title ring system results from the fact that certain fused xanthines, with theophylline as the prototype, were reported to inhibit many of the pharmacological and physiological effects of adenosine, by acting as competitive antagonists at A_1- and A_2-adenosine receptor subtypes.[14] For this reason, considerable efforts have been devoted in recent years to synthesize functionalized xanthine congeners, as selective antagonists for one or the other type of adenosine receptors.[3,15,16]

Scheme 1[a]



[a] R/Z: a, Ph/H; b, Ph/4-NO_2; c, CH_3/4-NO_2; d, PhCH=CH/H; e, CH_3CO/H; f, PhCO/H; g, PhCO/4-Me; h, PhCO/4-NO_2 i, 1-naphthoyl/H; j, 1-naphthoyl/4-Cl; k, 2-thenoyl/H; l, PhNHCO/H; m, PhNHCO/4-Me; n, PhNHCO/4-Cl; o, EtOCO/H.

The hydrazonoyl halides **1a**−**i**[17] and 8-substituted theophylline derivatives **2**−**5**,[18] prepared as reported in the literature, were the key starting reagents for the synthesis of the title compounds (Scheme 1). Reaction of 8-chlorotheophylline **2** with **1a**−**i** in refluxing dioxane in the presence of triethylamine as a base catalyst gave in each case a single product as evidenced by TLC analysis of the crude products. Likewise, refluxing of either **1a** with 8-nitrotheophylline **3** in dioxane in the presence of triethylamine or with 8-methylthiotheophylline **4** or 8-mercaptotheophylline **5** in pyridine yielded in each case one and the same product that proved identical in all respects with that one obtained above from similar reaction of **1a** with **2**.

Both the mass spectral and elemental analysis data of the isolated products are consistent with either [1,2,4]-triazolo[3,4-*f*]theophylline or [1,2,4]triazolo[4,3-*e*]theo-

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phylline derivatives **14** or **15**, respecively (Scheme 1). The latter structure was discarded, however, due to the steric hindrance caused by the proximity of the N1−CH_3 and R groups as shown by molecular models. Assignment of the structure **14** to the products isolated from the studied reactions rather than the possible alternative structure **15** is also based on similar results in the literature reports documenting that N-7 of the theophylline ring system is the site of preference for nucleophilic additions[5] as well as nucleophilic substitutions.[3,19,20] In addition, the structures of **14a**−**o** were further evidenced by their ^{1}H NMR data. For example, the ^{1}H NMR spectra of the isolated products revealed the signal of the N1−CH_3 protons at δ 3.50−3.70. This value is very close to that of N3-CH_3 of theophylline (δ 3.59). This similarity of δ values is consistent with structure **14**. This is because had the products structure **15**, it would be expected that the N1−CH_3 group will be shielded by the neighboring group R, and thus its δ value will be less than 3.50 and it will vary with the degree of shielding exerted by the R group.

To account for the formation of the products **14** from reactions of **1** with each of **2**−**4**, the tentative mechanism outlined in Scheme 1 is proposed. According to this mechanism, it is suggested that the reaction of **1** with each of **2**−**4** starts with 1,3-dipolar addition of N7−H of **2** to the nitrilium imide, generated in situ by the action of triethylamine on **1**, to give the respective amidrazone intermediates **6**−**9**, respectively. The latter then undergo intramolecular addition to give the cycloadducts **10**−**13**, respectively. Alternatively, the latter cycloadducts **10**−**13** can result directly via cycloaddition of the nitrilium imide to the C═N bond in theophylline derivatives. The resulting cycloadducts **10**−**13** in turn eliminate an HX molecule to give **14** as the end products (Scheme 1). In our hands, all attempts to isolate the amidrazone intermediates **6**−**9** or the cycloadducts **10**−**13** failed.

With respect to reaction of **1** with **5** leading to **14**, it can be suggested that the reaction in this case can start with the formation of the thiohydrazonate ester which undergoes in situ Smiles type rearrangement to give the respective thiohydrazide which in turn cyclizes intramolecularly to give **14** as end product via elimination of hydrogen sulfide. Similar rearrangements of the thiohydrazonate esters followed by elimination of hydrogen sulfide have been reported previously.[21] However, it is not unreasonable to conclude, on the basis of our finding that reactions of **1** with either **4** or **5** gave the same product **14**, that both reactions proceed via similar intermediates, namely **12** and **13**, respectively, as outlined in Scheme 1.

Compounds **14a**−**o** represent important extensions in the chemistry ring-fused purines. The availability of various functional groups for further reactions offers the potential for novel biologically active materials. Further studies to shed light on the affinity of the compounds prepared above for A_1- and A_2-adenosine receptors and their inhibitory effects on phosphodiesterase are still in progress.

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Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR specra were recorded at 200 MHz in $CDCl_3$ or DMSO-d_6 and referenced to TMS (^{1}H). IR spectra were recorded in KBr. Mass spectra were measured at 70 eV using a GC-MS. Elemental analyses were provided by the Microanalytical Laboratory at Cairo University, Giza, Egypt. The starting hydrazonoyl halides **1a**−**o**[17] and 8-substituted theophyllines **2**−**5**[18] were prepared as previously described.

1,3-Dimethyl-2,4-dioxo-6,8-disubstituted-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purines 14. **General Method**. To a mixture of the appropriate hydrazonoyl halide **1** (0.01 mol) and 8-chlorotheophylline **2** (0.01 mol) in dioxane (30 mL) was added triethylamine (1.5 mL, 0.01 mol). The mixture was then refluxed for 5.0−10.0 h according to the halide used. Then the excess solvent was distilled under reduced pressure. The crude product that precipitated upon cooling was collected by filtration, washed with ethanol, dried, and finally crystallized from the appropriate solvent to give the corresponding **14**.

When the above procedure was repeated using 8-nitrotheophylline **3** in place of **2**, it yielded the respective **14** identical in all respects with that one obtained above from **1** and **2**.

Furthermore, when an equimolar mixture (0.01 mol each) of **1** and 8-methylthiotheophylline **4** (or 8-mercaptotheophylline **5**) in pyridine (20 mL) was refluxed till methanethiol (or hydrogen sulfide) ceased to evolve (4.0−5.0 h), the respective **14** was also obatined after workup.

The physical constants of the products **14a**−**o** are given below.

1,3-Dimethyl-2,4-dioxo-6,8-diphenyl-1,2,3,4-tetrahydro-[1,2,4]triazolo[3,4-*f*]purine (**14a**): yield 82%, mp 286−288 °C (dioxane); IR(KBr) 1712, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 3H, N3-Me), 3.70 (s, 3H, N1-Me), 7.50−8.26 (m, 10H, ArH); MS *m*/*z* 372(M^+, 100%), 373(M^+ +1, 92%). Anal. Calcd for $C_{20}H_{16}N_6O_2$: C, 64.51; H, 4.33; N, 22.57. Found: C, 64.4; H, 4.5; N, 22.3.

1,3-Dimethyl-2,4-dioxo-6-phenyl-8-(*p*-nitrophenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (**14b**): yield 80%, mp > 340 °C (DMF), IR(KBr) 1716, 1682 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.26 (s, 3H, N3-Me), 3.59 (s, 3H, N1-Me), 7.60−8.60 (m, 9H, ArH); MS *m*/*z* 417(M^+, 100%), 418(M^+ +1, 30%). Anal. Calcd for $C_{20}H_{15}N_7O_4$: C, 57.55; H, 3.62; N, 23.49. Found: C,57.5; H, 3.7; N, 23.7.

1,3-Dimethyl-2,4-dioxo-6-methyl-8-(*p*-nitrophenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (**14c**): yield 80%, mp 278−280 °C (dioxane /EtOH), IR(KBr) 1711, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 3H, CH_3), 3.46 (s, 3H, N3-Me), 3.59 (s, 3H, N1-Me), 7.80−8.70 (m, 4H, ArH); MS *m*/*z* 355 (M^+, 26%), 356-(M^+ +1, 17%). Anal. Calcd for $C_{15}H_{13}N_7O_4$: C, 50.71; H, 3.69; N, 27.59. Found: C,50.4; H, 3.4; N, 27.3.

1,3-Dimethyl-2,4-dioxo-6-(2-phenylethenyl)-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (**14d**): yield 78%, mp 296−298 °C (dioxane), IR(KBr) 1707, 1665 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 3.31 (s, 3H, N3-Me), 3.51 (s, 3H, N1-Me), 7.10−8.15 (m, 12H, ArH, CH═CH); MS *m*/*z* 398 (M^+, 78%), 399-(M^+ +1, 77.8%). Anal. Calcd for $C_{22}H_{18}N_6O_2$: C, 66.32; H, 4.55; N, 21.09. Found: C,66.6; H, 4.3; N, 21.3.

1,3-Dimethyl-2,4-dioxo-6-acetyl-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (**14e**): yield 75%, mp 300−302 °C (dioxane), IR(KBr) 1717, 1697, 1662 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H, CH_3), 3.39 (s, 3H, N3-Me), 3.68 (s, 3H, N1-Me), 7.20−8.20 (m, 5H, ArH); MS *m*/*z* 338 (M^+, 85.9%), 339 (M^+ +1, 78.5%). Anal. Calcd for $C_{16}H_{14}N_6O_3$: C, 56.80; H, 4.17; N, 24.84. Found: C, 56.8; H, 4.0; N, 24.6.

1,3-Dimethyl-2,4-dioxo-6-benzoyl-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (**14f**): yield 80%, mp 298−300 °C (dioxane), IR(KBr) 1712, 1670 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 3.38 (s, 3H, N3-Me), 3.58 (s, 3H, N1-Me), 7.35−8.30 (m, 10H, ArH); MS *m*/*z* 400 (M^+, 66.1%), 401 (M^+ +1, 44.6%). Anal. Calcd for $C_{21}H_{16}N_6O_3$: C, 63.00; H, 4.03; N, 20.99. Found: C, 63.0; H, 4.1; N, 21.1.

1,3-Dimethyl-2,4-dioxo-6-benzoyl-8-(*p*-methylphenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (**14g**): yield 80%, mp 236−238 °C (AcOH/H_2O), IR(KBr) 1713,1666 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 3.46 (s, 3H, N3-CH_3), 3.71 (s, 3H, N1−CH_3), 7.20−8.40 (m, 9H, ArH); MS *m*/*z* 413 (M^+-1, 0.4%), 415 (M^+ + 2, 34%). Anal. Calcd for $C_{22}H_{18}N_6O_3$: C, 63.76; H, 4.38; N, 20.28. Found: C, 64.0; H, 4.1; N, 20.1.

1,3-Dimethyl-2,4-dioxo-6-benzoyl-8-(*p*-nitrophenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14h): yield 78%, mp 280−282 °C (AcOH/H_2O), IR(KBr) 1705, 1659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (s, 3H, N3-CH_3), 3.74 (s, 3H, N1−CH_3), 7.20−8.50 (m, 9H, ArH); MS *m*/*z* 445 (M^+, 25%), 446 ($M^+ + 1$, 27%). Anal. Calcd for $C_{21}H_{15}N_7O_5$: C, 56.63; H, 3.39; N, 22.01. Found: C, 56.3; H, 3.1; N, 22.0.

1,3-Dimethyl-2,4-dioxo-6-(1-naphthoyl)-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14i): yield 83%; mp 288−290 °C (AcOH/H_2O); IR(KBr) 1711, 1672 cm^{-1}; ^1H NMR-(DMSO-d_6) δ 3.47 (s, 3H, N3-CH_3), 3.54 (s, 3H, N1−CH_3), 7.30−8.50 (m, 12H, ArH); MS *m*/*z* 450 (M^+, 58.5%), 451 ($M^+ + 1$, 53.9%). Anal. Calcd for $C_{25}H_{18}N_6O_3$: C, 66.66; H, 4.03; N, 18.66. Found: C, 66.8; H, 4.2; N,18.5.

1,3-Dimethyl-2,4-dioxo-6-(1-naphthoyl)-8-(*p*-chlorophenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14j): yield 82%; mp 296−298 °C (AcOH/H_2O); IR(KBr) 1705, 1659 cm^{-1}; ^1H NMR($CDCl_3$) δ 3.54 (s, 3H, N3-CH_3), 3.68 (s, 3H, N1−CH_3), 7.20−8.90 (m, 11H, ArH); MS *m*/*z* 485 ($M^+ + 1$, 33.6%), 486 ($M^+ + 2$, 9.1%), 487 ($M^+ + 3$, 11.8%). Anal. Calcd for $C_{25}H_{17}ClN_6O_3$: C, 61.93; H, 3.53; N, 17.33. Found: C, 61.7; H, 3.2; N, 17.1.

1,3-Dimethyl-2,4-dioxo-6-(2-thenoyl)-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14k): yield 82%; mp 324−326 °C (dioxane/H_2O); IR(KBr) 1713, 1672 cm^{-1}; ^1H NMR-(DMSO-d_6) δ 3.45 (s, 3H, N3-CH_3), 3.60 (s, 3H, N1-CH_3), 7.40−8.50 (m, 8H, ArH); MS *m*/*z* 406 (M^+, 46.3%), 407 ($M^+ + 1$, 10.6%); Anal. Calcd. for $C_{19}H_{14}N_6O_3S$: C, 56.15; H, 3.47; N, 20.68. Found: C, 56.1; H, 3.2; N, 20.6.

1,3-Dimethyl-2,4-dioxo-6-phenylcarbamoyl-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14l): yield 80%; mp 352−354 °C (dioxane); IR(KBr) 1697, 1651 cm^{-1}; ^1H NMR(DMSO-d_6) δ 3.40 (s, 3H, N3-CH_3), 3.55 (s, 3H, N1−CH_3), 7.40−8.20 (m, 10H, ArH), 12.6 (s,1H, NH); MS *m*/*z* 415(M^+, 100%), 416 ($M^+ + 1$, 28.2%). Anal. Calcd for $C_{21}H_{17}N_7O_3$: C, 60.72; H, 4.12; N, 23.60. Found: C, 60.7; H, 4.4; N, 23.7.

1,3-Dimethyl-2,4-dioxo-6-phenylcarbamoyl-8-(*p*-methylphenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14m): yield 85%; mp 320−322 °C (DMF/EtOH); IR(KBr) 1705, 1666 cm^{-1}; ^1H NMR(DMSO-d_6) δ 2.40 (s, 3H, CH_3), 3.32 (s, 3H, N3-CH_3), 3.60 (s, 3H, N1−CH_3), 7.30−8.20 (m, 9H, ArH), 12.6 (s,1H, NH); MS *m*/*z* 428 (M^+, 4.9%), 430 ($M^+ + 1$, 99.3%), 431 ($M^+ + 2$, 31.1%). Anal. Calcd for $C_{22}H_{19}N_7O_3$: C, 61.53; H, 4.46; N, 22.83. Found: C, 61.2; H, 4.5; N, 22.6.

1,3-Dimethyl-2,4-dioxo-6-phenylcarbamoyl-8-(*p*-chlorophenyl)-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14n): yield 85%; mp 336−338 °C (dioxane/EtOH); IR(KBr) 1705, 1666 cm^{-1}; ^1H NMR(DMSO-d_6) δ 3.34 (s, 3H, N3-CH_3), 3.56 (s, 3H, N1-CH_3), 7.20−8.20 (m, 9H, ArH), 12.5 (s,1H, NH); MS *m*/*z* 450 (M^+, 95.5%), 451 ($M^+ + 1$, 29.0%), 452 ($M^+ + 2$, 31.7%). Anal. Calcd for $C_{21}H_{16}ClN_7O_3$: C, 56.07; H, 3.59; N, 21.79. Found: C, 56.0; H, 3.2; N, 21.7.

1,3-Dimethyl-2,4-dioxo-6-ethoxycarbonyl-8-phenyl-1,2,3,4-tetrahydro[1,2,4]triazolo[3,4-*f*]purine (14o): yield 76%; mp 244−246 °C (AcOH); IR(KBr) 1741, 1705, 1670 cm^{-1}; ^1H NMR-($CDCl_3$) δ 1.50 (t, J = 7 Hz, 3H,CH_3), 3.46 (s, 3H, N3-CH_3), 3.69 (s, 3H, N1−CH_3), 4.60 (q, J = 7 Hz, 2H, CH_2), 7.50−8.24 (m, 5H, ArH); MS *m*/*z* 368 (M^+, 100%), 369 ($M^+ + 1$, 92.7%). Anal. Calcd for $C_{17}H_{16}N_6O_4$: C, 55.43; H, 4.38; N, 22.82. Found: C, 55.4; H, 4.7; N, 22.8.

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