New [*f*]-Fused Theophyllines: A Simple One-Step Synthesis of the Pyrimido[2,1-*f*]purine System via 8-Azidopurines

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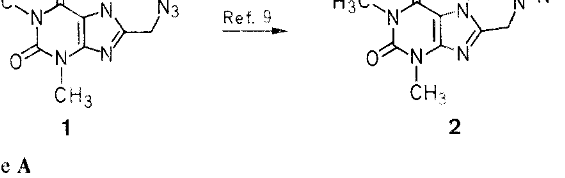
An approach to novel tetrahydro- and hexahydropyrimido[2,1-*f*] purines starting from 7-(2-alkenyl)- or 7-(2-alkynyl)-8-azidotheophyllines is described.

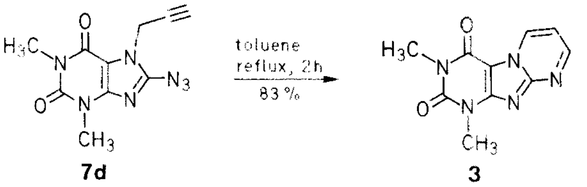
Intramolecular 1,3-dipolar cycloaddition reactions constitute a useful methology for the preparation of fused heterocyclic rings. Otherwise inaccessible heterocyclic skeletons can thus be built up, provided that the appropriate starting materials having the required reactive moieties in the required positions are available. The cycloaddition can be accomplished both thermally and photochemically. Of special interest as starting materials are *ortho*-substituted aromatic or heterocyclic azides, which readily undergo intramolecular cyclization with or without prior elimination of nitrogen. The outcome of such reactions is usually ring closure,[1,2] ring enlargement,[3,4] ring contraction,[5] or ring opening.[6,7]

In continuation of previous studies on the synthesis of theophylline derivatives fused at the "*e*" or "*f*" bond of the purine moiety,[8] we now report a synthetic approach starting from azidotheophyllines. As we have found,[9] 7-(2-alkenyl)- or 7-(2-propynyl)-8-azidomethyltheophyllines **1** (Scheme **A**) upon heating are converted in good yields into tetracyclic theophylline derivatives having the 1,2,3-triazolo[1′,5′:1,2]pyrazino-[5,4-*f*]purine structure.



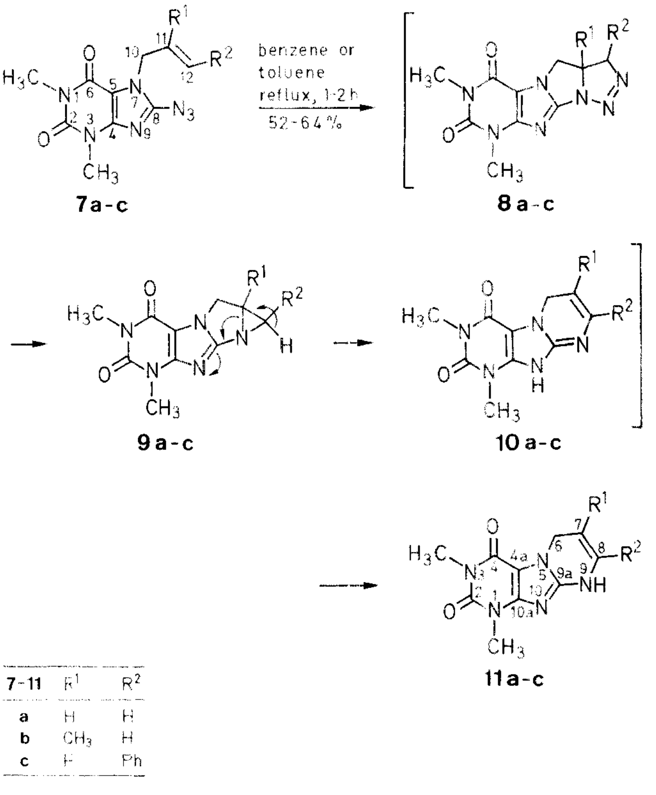
Scheme **A**

Contrary to our expectations, 8-azido-7-(2-propynyl)theophylline (**7d**) under similar conditions was converted into 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[2,1-*f*]purine (**3**) in 83% yield (Scheme **B**) but not into the tetracyclic product of dipolar cycloaddition.



Scheme **B**

Similarly, 7-(2-alkenyl)-8-azidotheophyllines **7** on heating in dioxane or aromatic hydrocarbons (benzene, toluene) were converted into derivatives of 1,3-dimethyl-2,4-dioxo-1,2,3,4,6,9-hexahydropyrimido[2,1-*f*]purine **11** in 52–64% yields. A tentative reaction mechanism proposed by us (Scheme **C**) involves 1,3-dipolar cycloaddition of the azido group to the C=C double bond of the side chain of **7a–c** in the first step. The tetracyclic intermediate **8** thus formed loses nitrogen to give, after a rearrangement, the isolable product **11**.



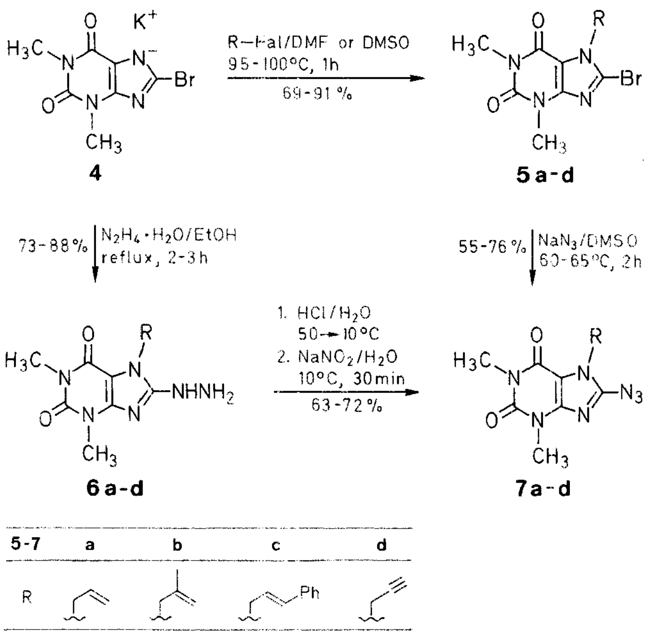
7-11	R^1	R^2
a	H	H
b	CH_3	H
c	H	Ph

Scheme **C**

In summary, a novel purine derivative [*f*]-fused with a tetrahydropyrimidine ring is formed. Our attempts to isolate one of the tentative intermediates **8–10** failed; we therefore have no evidence as to how the nitrogen is lost (the loss of nitrogen from the azide with intermediate formation of a nitrene would be an alternative). From the synthetic point of view, this question is of little importance.

The intermediacy of aziridine derivatives in similar reactions has been corroborated[10] by the investigation of the thermal decomposition of 2-azido-1-(2-alkenyl)benzenes which leads to 2-alkylindoles.

The requisite 8-azidotheophyllines **7** were prepared (Scheme **D**) by a two- or three-step synthesis from 8-bromotheophylline which was first converted to its potassium salt **4** by heating with aqueous potassium hydroxide; alkylation of **4** with alkenyl or alkynyl halides afforded the corresponding 7-(2-alkenyl)- and 7-(2-alkynyl)-8-bromotheophyllines **5** in 69–91% yields. Similar methods for the preparation of compounds **5a**, **d** by the alkylation of 8-bromotheophylline in protic solvents have been described.[11,12] However, we found that this method also gives



Scheme **D**

the corresponding 9-alkenyl (9-alkynyl) derivatives along with products **5**. The formation of the side products could be suppressed by using polar aprotic solvents such as dimethylformamide or dimethyl sulfoxide in which alkylation took place exclusively at N-7. Introduction of the azido group into position 8 can be achieved by nucleophilic displacement of bromine by the azido group (sodium azide in dimethyl sulfoxide at 60–65°C, 55–76% yields), or in two steps, via the corresponding hydrazine derivative (80% hydrazine hydrate, 73–88% yields) and its reaction with sodium nitrite (63–72% yields).

Although the direct substitution of the Br-atom by the azido group gives higher yields and would appear to be the method of choice, the thermal instability of the resultant azide represents a limitation to both methods as the high yield can in both cases be achieved only at the expence of product purity.

All reagents were of commercial quality and were taken from freshly opened containers. 8-Bromotheophylline, 3-bromo-1-propyne, 3-chloro-2-methyl-1-propene, and 3-bromo-1-phenyl-1-propene were purchased from Fluka Chemical Co. 3-Bromo-1-propene, sodium azide, hydrazine hydrate, sodium nitrite, and silica gel were purchased from Lachema (Czechoslovakia) and TLC plates (SILUFOL®) from

Table. Compounds **5**–**7** Prepared

Product	Method	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c] or Lit. mp (°C)	MS (70 eV) m/z (M^+)	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	A B	86 74	144–145	140–141[11]	298, 300	3.28 (s, 3H, 1-CH_3); 3.47 (s, 3H, 3-CH_3); 4.97 (d, 2H, J = 4, H-10); 5.06 (d, 1H, J = 17, H-12a); 5.28 (d, 1H, J = 10.5, H-12b); 6.02 (m, 1H, J = 4, H-11)
5b	A B	84 72	126–128	$C_{11}H_{13}BrN_4O_2$ (313.1)	312, 314	1.80 (s, 3H, 11-CH_3); 3.39 (s, 3H, 1-CH_3); 3.57 (s, 3H, 3-CH_3); 4.53 (m, 1H, H-12a); 4.90 (s, 2H, H-10); 4.96 (m, 1H, H-12b)
5c	A B	88 69	151–151.5	$C_{16}H_{15}BrN_4O_2$ (375.2)	374, 376	3.21 (s, 3H, 1-CH_3); 3.40 (s, 3H, 3-CH_3); 5.06 (d, 2H, J = 4, H-10); 6.38 (d, 1H, J = 4, H-11); 6.43 (s, 1H, H-12); 7.33–7.42 (m, 5H, H_{arom})
5d	A B	91 78	195–195.5	189–191[12]	296, 298	3.28 (s, 3H, 1-CH_3); 3.45 (s, 3H, 3-CH_3); 3.51 (d, 1H, J = 3, H-12); 5.21 (d, 2H, J = 3, H-10)
6a		88	245–248	245–247[13]	250	3.26 (s, 3H, 1-CH_3); 3.47 (s, 3H, 3-CH_3); 4.76 (d, 2H, J = 2.5, H-10); 5.07 (d, 1H, J = 9, H-12a); 5.17 (d, 1H, J = 5.1, H-12b); 5.93 (m, 1H, H-11); 8.12 (br s, 3H, $NHNH_2$)
6b		85	194–196	$C_{11}H_{16}N_6O_2$ (264.3)	264	1.64 (s, 3H, 11-CH_3); 3.33 (s, 3H, 1-CH_3); 3.38 (s, 3H, 3-CH_3); 4.38 (s, 1H, H-12a); 4.59 (s, 2H, H-10); 4.76 (s, 1H, H-12b); 8.08 (br s, 3H, $NHNH_2$)
6c		73	231–234	$C_{16}H_{18}N_6O_2$ (326.3)	326	3.17 (s, 3H, 1-CH_3); 3.38 (s, 3H, 3-CH_3); 4.85 (d, 2H, J = 4, H-10); 6.36 (d, 1H, J = 4, H-11); 6.39 (s, 1H, H-12); 7.30–7.37 (m, 5H, H_{arom}); 8.03 (br s, 3H, $NHNH_2$)
6d		82	243–245	$C_{10}H_{12}N_6O_2$ (248.3)	248	3.26 (s, 3H, 1-CH_3); 3.46 (s, 3H, 3-CH_3); 4.48 (br s, 1H, H-12); 5.03 (d, 2H, J = 2.3, H-10); 8.06 (br s, 3H, $NHNH_2$)
7a	C D	55 72	135–137	$C_{10}H_{11}N_7O_2$[d] (261.2)	261	3.31 (s, 3H, 1-CH_3); 3.54 (s, 3H, 3-CH_3); 4.64 (d, 2H, J = 4.6, H-10); 4.92 (d, 1H, J = 8, H-12a); 5.27 (d, 1H, J = 6, H-12b); 5.92 (m, 1H, H-11)
7b	C D	66 63	114–114.5	$C_{11}H_{13}N_7O_2$[d] (275.2)	275	1.76 (s, 3H, 11-CH_3); 3.37 (s, 3H, 1-CH_3); 3.55 (s, 3H, 3-CH_3); 4.62 (s, 1H, H-12a); 4.65 (s, 2H, H-10); 4.91 (s, 1H, H-12b)
7c	C D	68 67	143–145	$C_{16}H_{15}N_7O_2$[d] (337.3)	337	3.21 (s, 3H, 1-CH_3); 3.39 (s, 3H, 3-CH_3); 4.82 (d, 2H, J = 4, H-10); 6.42 (d, 1H, J = 4, H-11); 6.46 (s, 1H, H-12); 7.26–7.37 (m, 5H, H_{arom})
7d	C D	76 70	159–160.5	$C_{10}H_9N_7O_2$[d] (259.1)	259	3.21 (s, 3H, 1-CH_3); 3.39 (s, 3H, 3-CH_3); 3.47 (d, 1H, J = 2.5, H-12); 4.91 (d, 2H, J = 2.5, H-10)

[a] Yield of pure isolated product.

[b] From ethanol.

[c] Satisfactory microanalyses: C ±0.30, H ±0.07, N ±0.30, Br ±0.21.

[d] IR (KBr): ν_{N_3} = 2158 (**7a,c**), 2164 (**7d**), 2160 (**7b**) cm^{-1}.

Kavalier (Czechoslovakia). Reagent-quality solvents were used without further purification. Benzene, toluene, and xylene were freshly distilled from sodium.

Melting points were determined using a Kofler apparatus (MLW, GDR) and are uncorrected. Microanalyses were obtained using a Carlo Erba Model 1106 element analyser. Samples for analysis were crystallized from the appropriate solvents and dried over P_2O_5 at 100°C/0.65 mbar (compounds **7** at room temperature) for 8–10 h. Compounds **7** were purified by column chromatography (silica gel 50:1, 150–350 mesh; $CHCl_3$/acetone, 25:1) prior to crystallization. Mass spectra were obtained using a Varian MS-902S spectrometer with DEI ionization. IR spectra were obtained on a Perkin-Elmer 457 spectrophotometer, ^1H- and ^{13}C-NMR spectra on a Jeol FX-100 (100 MHz and 25.05 MHz, respectively) spectrometer.

7-(2-Alkenyl)- and 7-(2-Alkynyl)-8-bromotheophyllines 5; General Procedures:

Method A: 8-Bromotheophylline (130 g, 500 mmol) is suspended in aqueous KOH (35 g, KOH, 620 mmol; 400 mL) and the mixture is gently refluxed till complete dissolution. To the hot solution, EtOH (400 mL) is added. The crystalline potassium salt **4** is isolated by suction, washed with acetone (200 mL), and dried at 100°C/26 mbar; yield: 128 g (86%); mp above 350°C.

The appropriate haloalkene or haloalkyne (110–140 mmol) is added to a suspension of **4** (29.8 g, 100 mmol) in DMF (70 mL) and the mixture is stirred at 95–100°C for 1 h. The inorganic salts which precipitate on cooling are filtered off and the filtrate is evaporated to dryness. The residue is recrystallized from EtOH.

Method B: A mixture of the haloalkane or haloalkyne (110–140 mmol), the salt **4** (29.8 g, 100 mmol), and DMSO (70 mL) is stirred at 95–100°C for 1 h. After cooling, the mixture is poured into the a two-fold volume of H_2O. The oily layer solidifies after standing for 2 h. The crude product is isolated by suction and recrystallized from EtOH using charcoal.

7-(2-Alkenyl)- and 7-(2-Alkynyl)-8-hydrazinotheophyllines 6; General Procedure:

A mixture of the compound **5** (100 mmol), EtOH (125 mL), and $N_2H_4 \cdot H_2O$ (80%; 40 mL) is refluxed with stirring for 2–3 h (monitored by TLC; CH_2Cl_2/acetone, 6:1). Then, H_2O (100 mL) is added, the precipitated product is isolated by suction, washed thoroughly with H_2O, and dried at 100°C/26 mbar.

7-(2-Alkenyl)- and 7-(2-Alkynyl)-8-azidotheophyllines 7; General Procedures:

Method C: To a solution of the compound **5** (10 mmol) in DMSO (13 mL) is added NaN_3 (1.0 g, 15 mmol) and the mixture is heated at 60–65°C with stirring for about 2 h (monitored by TLC after Ph_3P derivatization of the azido group in **7**: CH_2Cl_2/acetone, 25:1). Then, H_2O (50 mL) is added, the mixture cooled, and the precipitated product isolated by suction, dried, and purified by passing its solution in CCl_4 (220 mL) through silica gel (5 x 2 cm; 150–350 mesh). After evaporation of the solvent, the product is recrystallized from 75% EtOH.

Method D: The hydrazino compound **6** (10 mmol) is dissolved in H_2O (20 mL)/conc. aq. HCl (3 mL) with gentle heating. On cooling to 10°C, the hydrochloride of **6** precipitates. To the vigorously stirred suspension, a solution of $NaNO_2$ (0.83 g, 12 mmol), in H_2O (7 mL) is added dropwise and stirring is continued at 10°C for 30 min. The separated product is isolated by suction, washed with H_2O, and recrystallized from 75% EtOH.

1,3-Dimethyl-2,4-dioxo-1,2,3,4,6,9-hexahydropyrimido[2,1-*f*]purine (11a):

A solution of compound **7a** (2.60 g, 10 mmol) in dry toluene (50 mL) is refluxed for 1 h [evolution of N_2 (10 mmol, volumetrically)]. After cooling, the crude product is isolated by suction and purified by sublimation (200–220°C/1.3 mbar); yield: 1.5 g (64%); mp 292–294°C.

$C_{10}H_{11}N_5O_2$	calc.	C 51.49	H 4.75	N 30.03
(233.2)	found	51.40	4.77	30.22

MS: $m/z = 233$ (M^+).

IR (KBr): $\nu = 1503, 1523, 1635, 1670, 1708, 3000, 3203\ cm^{-1}$.

^1H-NMR (CF_3CO_2D/TMS): $\delta = 3.57$ (s, 3H, 3-CH_3); 3.72 (s, 3H, 1-CH_3); 4.45 (br, 2H, H-6); 5.56, 7.2–7.3 (m, 3H, H-7, H-8, H-9).

^{13}C-NMR (DMSO-d_6/TMS): $\delta = 30.6$ (q, 3-CH_3); 33.6 (q, 1-CH_3); 42.9 (t, C-6); 110.0 (d, C-8); 121.6 (d, C-7); 107.7 (s, C-4a); 140.9 (s, C-9a); 148.1 (s, C-10a); 153.3 (s, C-2); 156.6 (s, C-4).

1,3,7-Trimethyl-2,4-dioxo-1,2,3,4,6,9-hexahydropyrimido[2,1-*f*]purine (11b):

A solution of compound **7b** (2.75 g, 10 mmol) in dry benzene (60 mL) is refluxed for 1.5–2 h. The crude product which precipitates on cooling is isolated by suction washed with EtOH (60 mL), and recrystallized from AcOH/EtOH (1:1); yield: 1.3 g (53%); mp 264–266°C.

$C_{11}H_{13}N_5O_2$	calc.	C 53.43	H 5.29	N 28.32
(247.2)	found	53.01	5.38	28.64

MS: $m/z = 247$ (M^+).

IR (KBr): $\nu = 1420, 1530, 1600–1700, 2980, 3200\ cm^{-1}$.

^1H-NMR (DMSO-d_6/TMS): $\delta = 1.68$ (s, 3H, 7-CH_3); 3.16 (s, 3H, 3-CH_3); 3.31 (s, 3H, 1-CH_3); 4.01 (s, 2H, H-6); 6.81 (br, 1H, H-8); 7.91 (br, 1H, H-9).

1,3-Dimethyl-2,4-dioxo-8-phenyl-1,2,3,4,6,9-hexahydropyrimido[2,1-*f*] purine (11c):

A solution of compound **7c** (3.37 g, 10 mmol) in dry xylene (60 mL) is refluxed for 1 h, then filtered with charcoal (0.15 g), and evaporated to dryness at reduced pressure. The crude product is recrystallized from AcOH and further purified by sublimation at 210°C/0.65 mbar; yield: 1.63 g (52%); mp 282–284°C.

$C_{16}H_{15}N_5O_2$	calc.	C 62.12	H 4.88	N 22.64
(309.3)	found	61.96	4.93	22.91

MS: $m/z = 309$ (M^+).

IR (KBr): $\nu = 1600–1700\ cm^{-1}$.

^1H-NMR (DMSO-d_6/TMS): $\delta = 3.17$ (s, 3H, 3-CH_3); 3.33 (s, 3H, 1-CH_3); 5.39 (br, 2H, H-6); 7.10, 7.36, 8.68 (m, 7H, H-7, 5H_{arom}, H-9).

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[2,1-*f*]purine (3):

A solution of compound **7d** (2.60 g, 10 mmol) in dry toluene (60 mL) is refluxed until N_2 evolution has ceased (2 h). The crude product which precipitates on cooling is purified by sublimation at 210°C/0.13 mbar; yield: 1.9 (83%); mp 255–255.5°C.

$C_{10}H_9N_5O_2$	calc.	C 51.90	H 3.92	N 30.29
(231.2)	found	51.95	3.90	30.23

MS: $m/z = 231$ (M^+).

IR (KBr): $\nu = 1483, 1570, 1598, 1652, 1704, 3095\ cm^{-1}$.

^1H-NMR (DMSO-d_6/TMS): $\delta = 3.27$ (s, 3H, 3-CH_3); 3.52 (s, 3H, 1-CH_3); 7.38 (dd, 1H, $J = 6.6$, 4.4 Hz, H-7); 8.78 (dd, 1H, $J = 4.4$, 2.2 Hz, H-6); 9.25 (dd, 1H, $J = 6.6$, 2.2 Hz, H-8).

^{13}C-NMR (DMSO-d_6/TMS): $\delta = 27.44$ (q, 3-CH_3); 29.9 (q, 1-CH_3); 99.3 (s, C-4a); 111.0 (d, C-7); 135.2 (d, C-6); 149.5, 151.1, 151.3 (3 × s, C_{purine}); 153.9 (d, C-8); 154.2 (s).

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