A Facile "One Pot" Synthesis of 2,9-Disubstituted 8-Azapurin-6-ones (3,5-Disubstituted 7-Hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines)

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A series of title compounds have been synthesized by utilising benzylazide, cyanoacetamide, ethyl or methyl esters of aliphatic or aromatic carboxylic acids and sodium ethoxide as catalyst.

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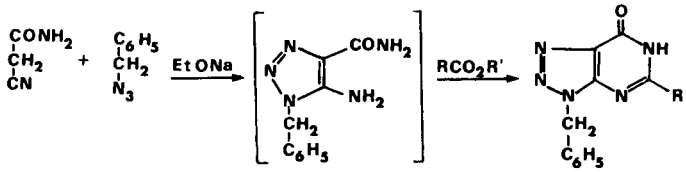
The continuing medical interest in 8-azapurin-6-one and its derivatives arises from their anti-cancer [1] and anti-allergic [2] properties. Moreover 8-azapurin-6-ones may also be interesting as inhibitors of enzymes related to the purine catabolism [1,3].

To date some title compounds were prepared by heating a 4-amino-1,2,3-triazole-5-carboxamide with carboxylic acid amides [4] (poor yields) and with amidines [5] (better results). Another route starts from 4,5-diamino-6-pyrimidones substituted in the 2-position, which could be submitted to ring closure by action of nitrous acid [6]. However, these synthetic routes show a lack of generality.

We are now able to communicate our first findings about a simple synthetic method to achieve these compounds bearing two substituents in the 2,9-positions. This procedure, which is indicated in the Scheme 1, consists in the addition of benzylazide to an ethanolic suspension of the sodium salt of cyanoacetamide according to Hoover and Day [7] to obtain 4-amino-3-benzyltriazole-5-carboxamide. Subsequently, an excess of ethyl or methyl ester of the appropriate carboxylic acid is added and the solution is then heated under gentle reflux for some hours (Table 1).

Scheme 1



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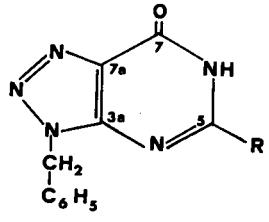
In such a way it is unnecessary to isolate the triazole intermediate. The target compounds (8-azapurin-6-ones) are easily isolated in moderately good to good yields by evaporating the reaction mixture and pouring the residue in cold dilute acetic acid.

Elemental analysis and spectral characteristics of all the described compounds are consistent with the proposed structures (Table 2). Further, the mild reaction temperature and the stabilizing effect of the benzyl group [8] should assure the absence of Dimroth isomers, which were never isolated.

Owing to literature ^{13}C nmr data regarding 8-azapurines have been scarcely reported, we have tentatively assigned chemical shifts (Scheme 2 and Table 3) on the basis of spectra registered for a model compound [9] and described for similar compounds [10].

Scheme 2



A previously reported analogous of the second step of this method is the ring closure of 5-amino-4-imidazolecarboxamide to obtain hypoxanthine, 2-alkylhypoxanthine and xanthine [11]. More recently, Wong and Meyer [12] described many examples of this reaction whereas Kato and coworkers [13] accomplished a similar heteroannulation which started from β-aminocrotonamide and allowed the synthesis of 2-substituted 6-methylpyrimidin-4(3*H*)-ones.

At present we are also taking an interest in the generalization of the described method in the aim of verifying its preparative limits.

EXPERIMENTAL

All melting points are taken on a Kofler apparatus and are uncorrected. The ir spectra were determined in nujol mulls with a Perkin-Elmer 197 spectrometer. The nmr spectra were obtained with a Varian CFT 20

Table 1

Reaction Conditions and Analytical Data

Starting ester	Reaction product A	Reaction time (hours)	Yields (%)	Mp °C [X]	Molecular formula	Analyses % Calcd./Found C	H	N
$HCO_2C_2H_5$	**1**, R = H	8	95	246-248 [4]	—	—	—	—
$CH_3CO_2C_2H_5$	**2**, R = CH_3	6	85	191-193 [5]	—	—	—	—
$CH_3CH_2CO_2C_2H_5$	**3**, R = CH_2CH_3	8	81	181-183 [a]	$C_{13}H_{13}N_5O$	61.16 60.97	5.13 4.97	27.44 27.21
$CH_3CH_2CH_2CO_2C_2H_5$	**4**, R = $CH_2CH_2CH_3$	8	81	161-163 [b]	$C_{14}H_{15}N_5O$	62.44 62.19	5.61 5.67	26.01 26.18
$ClCH_2CO_2CH_3$	**5**, R = $CH_2OCH_2CH_3$	7	71	192-194 [a]	$C_{14}H_{15}N_5O_2$	58.93 59.12	5.30 5.45	24.55 24.71
$(CH_3CH_2O)_2CHCO_2C_2H_5$	**6**, R = $CH(OCH_2CH_3)_2$	8	92	190-192 [a]/[c]	$C_{16}H_{19}N_5O_3$	58.35 58.21	5.82 5.95	21.27 21.22
$(CH_2CO_2C_2H_5)_2$	**7**, R = $CH_2CH_2CO_2H$	8	61	211-213 [b]	$C_{14}H_{13}N_5O_3$	56.18 56.15	4.30 4.12	23.40 23.48
$(CO_2C_2H_5)_2$	**8**, R = $CO_2C_2H_5$	20	75	188-189 [b]	$C_{14}H_{13}N_5O_3$	56.18 56.07	4.30 4.39	23.40 23.48
$C_6H_5CO_2C_2H_5$	**9**, R = C_6H_5	8	43	271-273 [d]/H_2O	$C_{17}H_{13}N_5O$	67.31 67.46	4.32 4.46	23.09 23.13
$C_6H_5CH_2CO_2C_2H_5$	**10**, R = $CH_2C_6H_5$	8	70	215-217 [a]	$C_{18}H_{15}N_5O$	68.12 67.98	4.76 4.78	22.07 21.99
$C_6H_5CONHCH_2CO_2CH_3$	**11**, R = $CH_2NHCOC_6H_5$	8	75	262-264 [c]	$C_{19}H_{16}N_6O_2$	63.32 63.40	4.48 4.63	23.32 23.39

[X] = Crystallization solvent: [a] = methanol, [b] = ethanol, [c] = acetone, [d] = *N,N*-dimethylformamide.

Table 2

IR [a] ν (cm^{-1}) and PMR δ (ppm) Data

1 ir, 1705 (CO); pmr [b], 6.12 (s, NCH_2, 2H), 7.37 (s, aromatic, 5H), 8.27 (s, C-5-H, 1H), [c]

2 ir, 1695 (CO); pmr [d], 2.63 (s, CH_3, 3H), 5.73 (s, N-CH_2, 2H), 7.4 (s, aromatic, 5H), [c]

3 ir, 1720 (CO); pmr, 1.24 (t, CH_3, 3H, J = 7.5 Hz), 2.70 (q, CH_2, 2H), 5.71 (s, N-CH_2, 2H), 7.34 (s, aromatic, 5H), 8.74 (br s, NH, 1 exchangeable H).

4 ir, 1715 (CO); pmr, 0.92 (t, CH_3, 3H), 1.75 (m, CH_2, 2H), 2.67 (t, C-5-CH_2, 2H), 5.71 (s, N-CH_2, 2H), 7.34 (s, aromatic, 5H), 8.77 (br s, NH, 1 exchangeable H)

5 ir, 1693 (CO); pmr, 1.16 (t, CH_3, 3H, J = 7.0 Hz), 3.58 (q, CH_2, 2H), 4.44 (s, C-5-CH_2, 2H), 5.74 (s, N-CH_2, 2H), 7.34 (s, aromatic, 5H), 8.74 (br s, NH, 1 exchangeable H).

6 ir, 1699 (CO); pmr, 1.18 (t, CH_3, 6H, J = 7.0 Hz), 3.66 (q, CH_2, 2H), 3.69 (q, CH_2, 2H) [e], 5.73 (s, C-5-CH, 1H), 5.75 (s, N-CH_2, 2H), 7.34 (s, aromatic, 5H), 8.73 (br s, NH, 1 exchangeable H).

7 ir, 1705 (CO); pmr, 2.87 (m, CH_2-CH_2, 4H), 5.68 (s, N-CH_2, 2H), 7.36 (s, aromatic, 5H), 8.75 (br s, NH or COOH, 1 exchangeable H), [c]

8 ir, 1692, 1750 (CO); pmr, 1.35 (t, CH_3, 3H, J = 7.0 Hz), 4.40 (q, CH_2, 2H), 5.79 (s, N-CH_2, 2H), 7.33 (s, aromatic, 5H), [c]

9 ir, 1693 (CO); pmr, 5.80 (s, N-CH_2, 2H), 7.37 (s, aromatic, 5H), 7.43-7.71 (m, aromatic, 3H), 8.06-8.26 (m, aromatic, 2H), 8.44 (br s, NH, 1 exchangeable H).

10 ir, 1705 (CO); pmr, 4.02 (s, C-5-CH_2, 2H), 5.68 (s, N-CH_2, 2H), 7.32 (s, aromatic, 5H), 8.46 (br s, NH, 1 exchangeable H).

11 ir, 1692 (CO); pmr, 4.48 (d, C-5-CH_2, 2H, J = 5 Hz), 5.63 (s, NCH_2, 2H), 7.24 (s, aromatic, 5H), 7.47-7.63 (m, aromatic, 3H), 7.85-8.00 (m, aromatic, 2H), 8.54 (br s, NH, 1 exchangeable H), 9.08 (t, NHCO, 1 exchangeable H, J = 5 Hz)

[a] NH stretching broad signals are not significant and are not reported. [b] Deuteriochloroform + DMSO-d_6 as solvent. [c] One exchangeable H does not show any sharp signal. [d] Deuteriochloroform as solvent. [e] Methylene groups are not equivalent being attached to a prochiral carbon.

spectrometer (pmr: DMSO-d_6 as the solvent, unless otherwise indicated, TMS as internal standard; cmr: DMSO-d_6 as the solvent).

General Procedure for the Preparation of Compounds **A**.

To a stirred hot ethanolic solution of sodium ethoxide obtained from sodium (0.46 g, 2 × 10^{-2} g-atom) and anhydrous ethanol (20 ml), cyanoacetamide (0.84 g, 1 × 10^{-2} mole), benzylazide (1.33 g, 1 × 10^{-2} mole),

Table 3

CMR Data (ppm)

A	C-3a	C-5	C-7	C-7a	Benzylic Carbons CH_2	Benzylic Carbons C quat	Benzylic Carbons Others	R Subtituent Carbons
1	148.5	149.9	155.3	129.6	49.8	135.3	128.7, 128.1, 127.8	
2	149.0	159.9	155.8	[a]	49.4	135.5	128.7, 128.0, 127.6	21.4 (CH_3)
3	149.0	163.9	155.9	[a]	49.5	135.4	128.7, 128.1, 127.9	27.6 (CH_2), 11.1 (CH_3)
4	149.0	162.9	155.9	[a]	49.6	135.4	128.7, 128.1, 127.9	35.9 (CH_2), 20.2 (CH_2), 13.2 (CH_3)
5	148.6	159.4	155.6	[a]	49.7	135.4	128.7, 128.1, 127.8	69.1 (CH_2), 66.2 (CH_2), 14.9 (CH_3)
6	148.2	157.7	155.4	129.1	49.8	135.2	128.7, 128.1, 127.8	98.6 (CH), 62.6 (CH_2), 14.9 (CH_3)
7	148.8	162.0	155.8	[a]	49.8	135.4	128.8, 128.3 [b]	29.8 (CH_2), 28.9 (CH_2), 173.4 (CO)
8	147.9 [c]	147.5 [c]	155.0	129.4	49.9	135.1	128.8, 128.2, 127.8	159.1 (CO), 63.2 (CH_2), 13.8 (CH_3)
9	148.9	157.1	156.1	131.5	49.7	135.4	128.7, 128.1, 128.0 [c]	132.1 (C quat), 128.6 [b], 128.4 [c] (others)
10	148.9	161.3	155.9	[a]	49.8	135.3 [c]	128.7, 128.1 [b] [c]	40.3 (CH_2), 135.7 [c] (C quat), 128.9, 128.4, 127.0 [c] (others)
11	148.7	160.3	155.7	131.5	49.8	135.2	128.6, 128.1 [b], 128.3 [c]	41.9 (CH_2), 166.8 (CO), 133.8 (C quat), 128.1 [b], 127.4 [c] (others)

[a] Overlapped to aromatic signals. [b] Degenerate line. [c] Interchangeable.

and after one hour, the appropriate methyl or ethyl ester (2×10^{-2} mole) were added. Heating was continued for the time indicated in Table 1. Evaporation of the solvent at reduced pressure, dilution with water of the residue and acidification with acetic acid allowed us to obtain the products **A**.

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[9] Unsubstituted 8-azapurin-6-one shows the following cmr data (DMSO-d_6): 155.6 (C-3a), 145.8 (C-5), 156.7 (C-7), 128.5 (C-7a).

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