A New Synthesis of Bipyrimidones by Reaction of Hydrazine Derivatives with Ethyl Carbonochloridate

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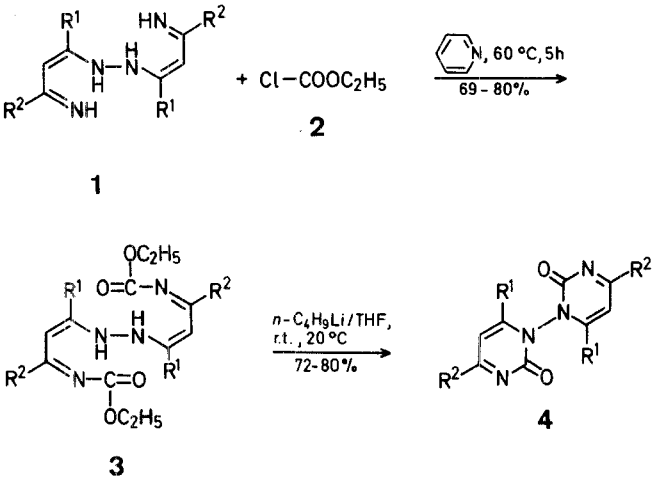
Hydrazine derivatives react with ethyl carbonochloridate through a double condensation process. The new compounds obtained afford 2,2′-dioxo-1,1′2,2′-tetrahydro-1,1′-bipyrimidines when treated with an alkyllithium reagent.

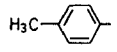
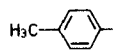
The addition of saturated nitriles to ketazines yields hydrazone derivatives[1]. These compounds can be transformed into pyrimidones by reaction with ethyl carbonochloridate. On the other hand, hydrazine derivatives **1** are obtained by addition of ketazines at the C-α hydrogen atom to saturated nitriles[2]. Compounds **1** are converted to 3*H*-pyrazolo[1,5*a*]-pyrimidines by treatment with mineral acids.

The pyrimidine ring is found in a great number of biologically active compounds[3], so we thought that it would be of interest to use hydrazines **1** as starting materials for synthesis of new pyrimidine derivatives. However, when hydrazine derivatives **1** react with ethyl carbonochloridate (**2**) in pyridine as solvent, at 60°C, only di-condensation products **3** are isolated and no traces of **4** are detected.

Compounds **3** were characterised on the basis of their microanalytical and spectral data. All compounds **3** display in their I.R. spectra a clear absorption at $\nu = \sim 1750\ cm^{-1}$ (C=O): The ^{1}H-N.M.R. spectra display a singlet at $\delta = 5.0-5.3$ ppm corresponding to a =CH grouping. This carbon appears in the ^{13}C-N.M.R. spectra at $\delta = \sim 105$ ppm. (doublet in off-resonance). These data are only consistent with the symmetrical structure of compounds **3**. On treatment of **3** with mineral acids *N*-aminopyrimidones and dicarbonyl compounds are obtained. The structure of these *N*-aminopyrimidones was corroborated by an alternative synthesis[1].

The cyclization of **3** to afford the corresponding heterocycles **4** takes place by treatment of **3** with an alkyllithium reagent in tetrahydrofuran. Thus, when 1 mol of **3** is allowed to react with 4 mol of *n*-butyllithium in tetrahydrofuran at room temperature, bipyrimidones **4** are isolated in high yields (Table).



1,3,4	R¹	R²
a	CH_3	
b	CH_3	
c	CH_3	
d	C_2H_5	
e	C_2H_5	
f	C_2H_5	

Heterocycles **4** were characterised on the basis of their microanalytical and spectral data. These compounds show in their ^{1}H-N.M.R. spectra a singlet centered at $\delta = \sim 6.5$ ppm. corresponding to the =CH ring proton. The ^{13}C-N.M.R. spectra show a single signal (doublet in off-resonance experiments), centered at $\delta = 110$ ppm, which is in agreement with the symmetrical structure **4**.

The convenience of all the reagents, their ease of handling, and the simplicity of the procedure for the isolation of the products make this synthesis convenient for the preparation of 2,2′-dioxo-1,1′,2,2′-tetrahydro-1,1′-bipyrimidines **4**.

Table. Compounds **3** and **4** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ[ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS) δ[ppm][b]
3a[c]	70	161–163°	$C_{26}H_{30}N_4O_4$ (462.6)	1610, 1720	1.2 (t, CH_3, J = 6.3 Hz); 2.3 (s, CH_3); 4.1 (q, CH_2, J = 6.3 Hz); 5.3 (s, =CH); 7.1–7.6 (m, $5H_{arom}$); 11.2 (m, NH)	164.24 (s); 153.40 (s); 147.27 (s); 136.89–127.34 (aromatic); 108.73 (d); 61.14 (t); 20.27 (q); 14.14 (q)
3b	75	181–183°	$C_{28}H_{34}N_4O_4$ (490.6)	1630, 1740	1.2 (t, CH_3, J = 6.3 Hz); 2.3 (s, CH_3); 2.4 (s, CH_3); 4.1 (q, CH_2, J = 6.3 Hz); 5.3 (s, =CH); 7.0–7.5 (m, $4H_{arom}$); 11.1 (m, NH)	164.08 (s); 153.39 (s); 147.31 (s); 138.60–127.24 (aromatic); 108.29 (d); 61.01 (t); 21.17 (q); 20.18 (q); 14.12 (q)
3c	74	164–166°	$C_{26}H_{42}N_4O_4$ (474.6)	1630, 1740	1.2 (t, CH_3, J = 6.3 Hz); 1.4–2.1 [m, 10H, $(CH_2)_5$]; 2.2 (s, CH_3); 3.4 (m, 1H, Cy); 4.2 (q, CH_2, J = 6.3 Hz); 5.0 (s, =CH); 10.8 (m, NH)	164.02 (s); 155.18 (s); 153.04 (s); 101.00 (d); 60.58 (t); 38.70 (d); 32.62 (t); 26.50 (t); 26.30 (t); 20.36 (q); 14.19 (q)
3d	69	181–183°	$C_{28}H_{34}N_4O_4$ (490.6)	1630, 1750	1.0–1.5 (m, $2CH_3$); 2.7 (q, CH_2, J = 6.3 Hz); 4.1 (q, CH_2, J = 6.3 Hz); 5.3 (s, =CH); 7.1–7.5 (m, $5H_{arom}$); 11.3 (m, NH)	169.08 (s); 153.31 (s); 147.47 (s); 137.03–127.24 (aromatic); 107.24 (d); 61.06 (t); 26.67 (t); 14.14 (q); 11.60 (q)
3e	78	182–184°	$C_{30}H_{38}N_4O_4$ (518.6)	1620, 1750	1.2 (m, $2CH_3$); 2.4 (s, CH_3); 2.7 (q, CH_2, J = 6.3 Hz); 4.1 (q, CH_2, J = 6.3 Hz); 5.3 (s, =CH); 7.0–7.5 (m, $4H_{arom}$); 11.3 (m, NH)	168.95 (s); 153.40 (s); 147.27 (s); 138.60–127.27 (aromatic); 106.99 (d); 61.10 (t); 26.70 (t); 21.21 (q); 14.24 (q); 11.65 (q)
3f	80	218–220°	$C_{28}H_{46}N_4O_4$ (502.7)	1640, 1740	1.0–2.1 (m, 16H); 2.5 (q, CH_2, J = 6.3 Hz); 3.3–3.6 (m, 1H); 4.1 (q, CH_2, J = 6.3 Hz); 5.0 (s, =CH); 8.6 (m, NH)	168.63 (s); 155.13 (s); 152.65 (s); 99.08 (d); 60.28 (t); 38.57 (d); 32.44 (t); 26.52 (t); 26.28 (t); 14.07 (q); 11.51 (q)
4a	78	308–310° (dec.)	$C_{22}H_{18}N_4O_2$ (370.4)	1610, 1690	2.3 (s, CH_3); 6.8 (s, =CH); 7.3–8.3 (m, $5H_{arom}$)	172.22 (s); 157.64 (s); 153.24 (s); 135.28–128.24 (aromatic); 102.65 (d); 18.57 (q)
4b[d]	75	318–320° (dec.)	$C_{24}H_{22}N_4O_2$ (398.5)	1610, 1680	2.3 (s, CH_3); 2.4 (s, CH_3); 6.8 (s, =CH); 7.1–8.3 (m, $4H_{arom}$)	172.01 (s); 157.24 (s); 143.52 (s); 132.64–128.04 (aromatic); 102.37 (d); 21.55 (q); 18.62 (q)
4c	77	240–242° (dec.)	$C_{22}H_{30}N_4O_2$ (382.5)	1620, 1700	1.0–2.9 (m, 14H); 6.3 (s, =CH)	184.54 (s); 156.67 (s); 153.11 (s); 104.27 (d); 47.17 (d); 30.87 (t); 30.74 (t); 25.75 (t); 18.04 (q)
4d	72	225–227° (dec.)	$C_{24}H_{22}O_2$ (398.5)	1610, 1730	1.1 (t, CH_3, J = 6.3 Hz); 2.4 (q, CH_2, J = 6.3 Hz); 7.0 (s, =CH); 7.1–8.2 (m, $5H_{arom}$)	171.37 (s); 164.98 (s); 163.81 (s); 132.67–128.27 (aromatic); 100.36 (d); 23.91 (q); 10.38 (q)
4e[e]	80	236–238° (dec.)	$C_{26}H_{26}N_4O_2$ (426.5)	1600, 1710	1.2 (t, CH_3, J = 6.3 Hz); 2.2–2.3 (m, 5H); 6.7 (s, =CH), 7.0–8.0 (m, $4H_{arom}$)	182.04 (s); 162.10 (s); 143.44 (s); 132.67–128.33 (aromatic); 99.93 (d); 24.10 (t); 21.53 (q); 10.30 (q)
4f	77	172–174° (dec.)	$C_{24}H_{34}N_4O_2$ (410.6)	1590, 1690	0.5–2.8 (m, 16H); 6.1 (s, =CH)	182.60 (s); 159.74 (s); 151.37 (s); 100.02 (d); 29.13 (d); 28.94 (t); 24.83 (t); 24.74 (t); 24.48 (t); 23.89 (q)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.24, H ±0.09, N ±0.16.
[b] Chemical shifts (δ) downfield from TMS.
[c] M.S.: m/e = 462 (M^+).
[d] M.S.: m/e = 398 (M^+).
[e] M.S.: m/e = 426 (M^+).

Hydrazine Derivatives 3; General Procedure:
Ethyl carbonochloridate (**2**; 50 mmol) is added to a solution of the hydrazine derivative **1** (10 mmol) in pyridine (100 ml); the solution is cooled at 0°C during the addition. After being stirred at 60°C for 5 h, the mixture is poured into ice-cooled 2 normal sulfuric acid (350 ml) and extracted with ether (200 ml). The organic layer is dried with sodium sulfate, evaporated, and the residue recrystallised from hot hexane/chloroform.

2,2'-Dioxo-1,1',2,2'-tetrahydro-1,1'-bipyrimidines 4; General Procedure:
To a solution of **3** (10 mmol) in dry tetrahydrofuran (60 ml), *n*-butyllithium (40 mmol) is added with cooling during the addition. The mixture is stirred at room temperature for 20 h after which it was poured into ice/water (200 ml). The organic layer is extracted with ether (150 ml), the extract is dried with sodium sulfate, filtered, and evaporated. The residue is purified by recrystallisation from ethanol.

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