A Facile Method for the Preparation of 2-Substituted Pyrimidin-4(3*H*)-ones by a Retro-Diels-Alder Reaction[1]

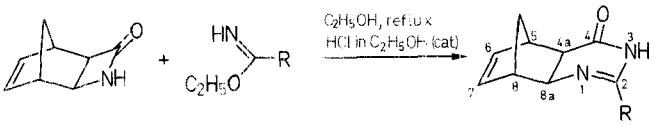
Géza Stájer,[a] Angela E. Szabó,[a] Gábor Bernáth,*[a] Pál Sohár[b]

[a] Institute of Pharmaceutical Chemistry, University Medical School, H-6720 Szeged, Eötvös u. 6, Hungary
[b] EGIS Pharmaceuticals, H-1475 Budapest, POB 100, Hungary

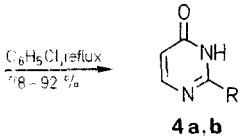
diexo-3-Aza-4-oxotricyclo[4.2.1.$0^{2,5}$]non-7-ene (**1**) reacted with carboximidic esters by ring expansion to yield tricyclic 5,6-dihydropyrimidin-4(3*H*)-ones **3**; when the latter were refluxed in chlorobenzene solution, cyclopentadiene split off to give 2-alkyl, 2-aralkyl-, 2-cycloalkyl and 2-arylpyrimidin-4(3*H*)-ones **4a–h**. This method, which is conveniently carried out in a "one-pot" reaction from **1**, provides a good alternative pathway for the preparation of compounds **4**.

With *diendo*- and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids as starting compounds, a new method based on the retro-Diels-Alder reaction has recently been worked out for the preparation of the 6*H*-1,3-oxazin-6-ones, which are difficult to obtain by other means.[2] These experiments prompted us to follow this work with a new preparation of 2-substituted pyrimidin-4(3*H*)-ones.

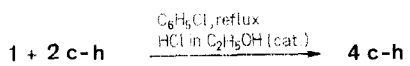
By the addition of chlorosulphonyl isocyanate to bicyclo[2.2.1]hepta-2,5-diene[3,4] and subsequent reduction of the adduct,[5] *diexo*-3-aza-4-oxotricyclo[4.2.1.$0^{2,5}$]non-7-ene (**1**) was obtained. When this 2-azetidinone was boiled in chlorobenzene with the carboximidic esters **2a–h**, it furnished 2-alkyl, aralkyl-, cycloalkyl- and arylpyrimidin-4(3*H*)-ones (**4a–h**), in yields of 78–90% (Table 1). Reaction of compound **1** with the carboximidic esters first gave 2-substituted 5,8-methano-*r*-4a,*c*-



1 **2a,b** **3**



4a,b



1 + **2c–h** → **4c–h**

2/4	R	2/4	R
a	CH_3	**e**	C_6H_5
b	C_2H_5	**f**	*p*-ClC_6H_4
c	*c*-C_6H_{11}	**g**	*m*-ClC_6H_4
d	*p*-$ClC_6H_4CH_2$	**h**	*p*-$CH_3C_6H_4$

Table 1. Tricyclic Pyrimidinone **3a** and 2-Substituted Pyrimidin-4(3*H*)-ones **4a–h** Prepared

Product	Yield (%)	Reaction Time (h)	m.p. (°C)	Molecular Formula[a] or Lit. m.p. (°C)
3a[c]	91	8	170–171	$C_{10}H_{12}N_2O$ (176.2)
4a[b]	82	8	212–214	213–214[7], 212.5–213[10] 214[13]
4b[b]	78	9	112–114	118.5–120.5[11], 116[12]
4c	92	12	214–216	$C_{10}H_{14}N_2O$ (178.2)
4d	80	11	223–225	$C_{11}H_9N_2ClO$ (220.7)
4e	88	13	204–205	207–208[6], 200–202[9], 207–208[12], 212[14]
4f	85	8	245–246	244–245[8]
4g	83	11	212–214	$C_{10}H_7N_2ClO$ (206.6)
4h	90	12	212–213	212–213[14]

[a] Compounds **3a** and **4a–h** gave satisfactory microanalyses: C, H, N ± 0.2.
[b] The reaction mixture was first refluxed in abs. ethanol for 8 h.
[c] Compound **3a** was prepared by reflux in abs. ethanol, followed by evaporation and recrystallization from ethanol.

The generally applicable method presented here provides good yields of 2-substituted pyrimidin-4(3*H*)-ones, and offers an attractive alternative to earlier preparations, which employ ethyl 3-oxopropionate and amidines.[6–14] In contrast with other retrodiene reactions, which usually need more rigorous conditions and occasionally special equipment,[18] our method simply requires refluxing in chlorobenzene for 8–13 h. So far only a few procedures are known for the preparation of heterocycles by a retro-Diels-Alder reaction under such mild conditions.[19] A further favorable aspect is that synthetic intermediate **1** could be used without the preparation of the amino acid, as is the case in the synthesis of the 6*H*-1,3-oxazin-6-ones.[2] Physical data on the compounds prepared are listed in Table 1.

2-Substituted-pyrimidin-4(3*H*)-ones (4a–h)

diexo-3-Aza-4-oxotricyclo[4.2.1.$0^{2,5}$]non-7-ene[3–5] (**1**; 1.35 g, 0.01 mol), carboximidic ester (**2c**: 1.55 g; **2d**: 2.0 g; **2e**: 1.5 g; **2f**: 1.8 g; **2g**: 1.8 g; **2h**: 1.6 g; 0.01 mol) and 1 drop of hydrogen chloride-saturated ethanol are refluxed in dry chlorobenzene (20 ml) for the time given in Table 1. The mixture is evaporated, and the residue is recrystallized from ethanol.

Table 2. Spectral Data for Compounds **3a** and **4a–h**[a]

Compound	IR (KBr) (cm^{-1})		^{1}H-NMR and ^{13}C-NMR ($CDCl_3$ or DMSO-d_6[c]/TMS) δ (ppm)						
	ν_{NH} (broad)	$\nu_{NC=O}$	H-5[b]	H-6[b]	C-2	C-4	C-5	C-6	^{1}H- and/or ^{13}C-NMR signals of the substituent *R*
3a[j]	3300–2700	1709	2.27	3.70	147.8	172.2			CH_3: 2.06[d], 21.6[e]
4a	3250–2500	1680	7.80	6.14	161.5	164.0	114.3	155.6	CH_3: 2.27[d], 22.9[e]
4b	3250–2500	1690	8.01	6.35	163.7	164.7	112.4	155.4	CH_3: 1.36[f], 10.8[e]; CH_2: 2.75[f], 28.1[e]
4c	3300–2500	1682	7.98	6.32	164.7	166.5	113.0	155.7	CH: 44.2; CH_2: 25.7[e], 25.8[e], 30.7[e]
4d[g]	3200–2700	1678	7.83	6.18	162.8	164.0	114.8	155.7	CH_2: 44.1; C_{Ar}: 136.9, 132.5, 130.1, 133.4
4e	3300–2900	1670	8.14	6.46	160.6	165.2	114.2	155.9	C_{Ar}: 134.6, 130.2, 129.4, 133.2
4f	3200–2600	1680	~8.15[i]	6.39	159.5	165.6	113.7	156.2	C_{Ar}: 138.1, 130.3, 131.2, 133.8
4g	3250–2600	1690	~8.10[i]	6.42	159.3	113.8	113.8	156.3	C_{Ar}: 137.2, 128.0, 132.8, 132.1, 135.2, 129.2
4h	3300–2800	1666	8.12	6.42	159.8	165.1	114.0	155.9	CH_3: 2.44[d], 22.6[e]; C_{Ar}: 131.7, 130.8, 129.3, 143.3

[a] Recorded on a Bruker FT-spectrometer, with an ASPECT 2000 computer, of type IFS-113v (IR), WM-250 (^{1}H-NMR, 250 MHz) or WP-80 SY (^{13}C-NMR, 20 MHz).
[b] Doublet, $J(5,6) = 6.4–6.7$ Hz.
[c] For **4a,d,g,f** (^{1}H- and ^{13}C-NMR spectra) and **4e** (^{13}C-NMR spectrum).
[d] Singlet in ^{1}H-NMR spectrum.
[e] Carbon lines.
[f] Triplet, $J = 7.6$ Hz.
[g] Assignments of the carbon lines were proved in a DEPT experiment.[20,21]
[h] Quartet.
[i] Overlapping with the AA'BB' multiplet of the aromatic protons.
[j] Further ^{1}H-NMR data: CH_2: 1.38 and 1.44, AB spectrum (J = ~ 10 Hz); H-4a: 2.27, d (J = 8.6 Hz); H-5: 3.14, ~ s; H-6: 6.31, dd (J = 5.5 and 2.9 Hz); H-7: 6.21, dd; H-8: 3.30, ~ s; H-8a: 3.70 d. ^{13}C-NMR data: C-4a: 52.1; C-5: 44.0; C-6,7: 136.1 and 138.5; C-8: 48.5; C-8a: 60.7; CH_2: 40.9.

5,*c*-8,*c*-8a-tetrahydroquinazolin-4(3*H*)-ones (**3**) by ring expansion; these were decomposed by cyclopentadiene splitting under the applied mild reaction conditions and gave the known[6–14] pyrimidin-4(3*H*)-ones. Since the boiling points of the carboximidic esters **2a, b** were lower than that of chlorobenzene (**2a**: 90 °C,[15] **2b**: 90–92 °C), the preparation of **4a, b** was carried out in two steps. The reaction partners were refluxed first in ethanol and then, after removal of the solvent, in chlorobenzene.

The carboximidic ester reaction of the azetidinone derivative **1** occurred analogously to an earlier ring expansion in various laboratories.[16,17] The transformation of the *cis*-trimethyleneazetidinone with carboximidic esters to *cis*-5,6-trimethylene-5,6-dihydropyrimidin-4(3*H*)-ones was achieved previously.[17] To prove the presumed reaction path, however, we recently also isolated 5,8-methano-2-methyl-*r*-4a,*c*-5,*c*-8,*c*-8a-tetrahydroquinazolin-4(3*H*)-one (**3a**) (Table 1) and confirmed the structure by IR and NMR spectroscopy (Table 2).

For the preparation of **4a, b**, **1** and the carboximidic ester (**2a**: 0.9 g; **2b**: 1.0 g; 0.01 mol) are refluxed first in abs. ethanol (20 ml) for 8 h, and the residue of the evaporated mixture is then refluxed for 8–13 h in chlorobenzene (20 ml).

Received: 4 November 1985

(1) This paper is regarded as Part 97 of the series *Saturated Heterocycles*. Part 96: Tamás, J., Mák, M., Csukonyi, K., Lázár, J., Bernáth, G. *Org. Mass Spectrom.* **1986**, *21*, 91.
(2) Stájer, G., Szabó, A.E., Fülöp, F., Bernáth, G. *Synthesis* **1984**, 345.
(3) Moriconi, E.J., Crawford, W.C. *J. Org. Chem.* **1968**, *33*, 370.
(4) Stájer, G., Mód, L., Szabó, A.E., Fülöp, F., Bernáth, G., Sohár, P. *Tetrahedron* **1984**, *40*, 2385.
(5) Durst, T., Sullivan, M.J. *J. Org. Chem.* **1970**, *35*, 2043.
(6) Ruhemann, S., Hemmy, A.S. *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1491.
(7) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 3638.
(8) Moffatt, J.S. *J. Chem. Soc.* **1950**, 1603, 1605.

(9) Vanderhaeghe, H., Claesen, M. *Bull. Soc. Chim. Belg.* **1957**, *66* 276.
(10) Hertog, H.J., van der Plas, H.C., Pieterse, M.J., Streef, J.W. *Recl. Trav. Chim. Pays-Bas.* **1965**, *84*, 1569.
(11) Jonak, J.P., Hopkins, G.C., Minnemeyer, H.J., Tieckelmann, H. *J. Org. Chem.* **1970**, *35*, 2512.
(12) van der Plas, H.C., Haase, B., Zuurdeeg, B., Vollering, M.C. *Recl. Trav. Chim. Pays-Bas.* **1966**, *85*, 1101.
(13) Takamizawa, A. *J. Pharm. Soc. Jpn.* **1954**, *74*, 756; *C.A.* **1955**, *49*, 11663.
(14) Mitter, P.C., Bardhan, J.C. *J. Chem. Soc.* **1923**, 2183.
(15) Sandler, S.R., Karo, W. *Organic Functional Group Preparations in Organic Chemistry*, Vol. 12-III, Academic Press, New York, 1972, p. 284, 289.
(16) Bormann, D. *Chem. Ber.* **1974**, *107*, 270.
(17) Bernáth, G. et al., to be published.
(18) Ripoll, J.L. *Bull. Soc. Chim. Fr.* **1974**, 2567.
(19) Huisgen, R., Seidel, M., Wallbillich, G., Knupfer, H. *Tetrahedron* **1962**, *17*, 3.
(20) Burum, D.P., Ernst, R.R. *J. Magn. Reson.* **1980**, 163.
(21) Doddrell, D.M., Pegg, D.T. *J. Am. Chem. Soc.* **1980**, *102*, 6388.