Activated Lactams: New Syntheses of Azacycloalka[2,3-*d*]pyrimidine and -[2,3-*c*]pyrazole Derivatives

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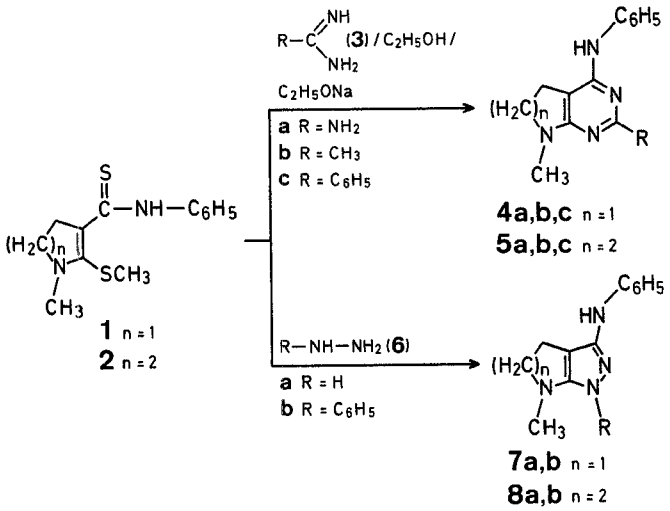
The most commonly used method for the synthesis of pyrimidines and pyrazoles involves the condensation of 1,3-carbo

nyl compounds with amidines or guanidines and hydrazines, respectively[1,2]. In a preceding paper[3] we reported a simple and facile synthesis of cyclic β-aminothiocarbonyl-α-methylthioenamines **(1, 2)** by the reaction of semicyclic ketene *S,N*-acetals with phenyl isothiocyanate. These enamines **(1, 2)** appear to be an attractive new synthetic equivalent of 1,3-dicarbonyl compounds. The present paper describes the use of the new 1,3-bis-electrophilic reagent **1** and **2** for the syntheses of azacycloalka[2,3-*d*]pyrimidines and -[2,3-*c*]pyrazoles.

The reaction of 1-methyl-5-methylthio-2,3-dihydropyrrole-4-(*N*-phenylcarbothioamide) **(1)** with guanidine **(3a)**, acetamidine **(3b)**, and benzamidine **(3c)** in the presence of sodium ethoxide in boiling ethanol gave 2-substituted 4-anilino-7-methyl-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidines **(4a, b, c)** and the similar treatment of 1-methyl-2-methylthio-1,4,5,6-tetrahydropyridine-3-(*N*-phenylcarbothioamide) **(2)** with compounds **3a, b, c** afforded 2-substituted 4-anilino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines **(5a, b, c)**. The cyclocondensation of compounds **1** or **2** with hydrazines **(6a, b)** in ethanol furnished 3-anilino-6-methyl-4,5-dihydro-6*H*-pyrrolo[2,3-*c*]pyrazoles **(7a, b)** or 3-anilino-7-methyl-4,5,6,7-tetrahydropyrido[2,3-*c*]pyrazoles **(8a, b)**, respectively. The products thus obtained are of biological interest.



2-Substituted 4-Anilino-*N*-methylazacycloalka[2,3-*d*]pyrimidines (4, 5); General Procedure:

To a mixture of sodium ethoxide [prepared by dissolving sodium (92 mg, 4 mg-atom) in ethanol (10 ml)] and guanidine nitrate **(3a)**, acetamidine hydrochloride **(3b)**, or benzamidine hydrochloride **(3c)** (2 mmol) is added compound **1** or **2** (2 mmol) and the reaction mixture is refluxed with stirring for the period of time indicated in Table 1. The

Table 1. 2-Substituted 4-Anilino-7-methyl-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidines **(4)** and 2-Substituted 4-Anilino-8-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines **(5)**

Product	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (Nujol)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
4a	4	67	178–180° (CH_2Cl_2/diisopropyl ether)	$C_{13}H_{15}N_5$ (241.3)	3480, 3320, 1620, 1600, 1560	2.90 (s, 3H, N—CH$_3$); 4.90 (s, 2H, NH$_2$); 6.47 (s, 1H, NH)
4b	4	61	Viscous liquid	$C_{14}H_{16}N_4$[c] (240.3)	3450, 3360, 3160, 1610, 1570	2.42 (s, 3H, CH$_3$); 2.92 (s, 3H, N—CH$_3$); 6.67 (s, 1H, NH)
4c	4	71	193–195° (ethanol)	$C_{19}H_{18}N_4$ (302.4)	3400, 1620, 1590, 1550	3.03 (s, 3H, N—CH$_3$); 6.17 (s, 1H, NH)
5a	8	58	153–155° (CH_2Cl_2/diisopropyl ether)	$C_{14}H_{17}N_5$ (255.3)	3500, 3360, 1620, 1580, 1550	2.83 (s, 3H, N—CH$_3$); 4.33 (s, 2H, NH$_2$); 5.77 (s, 1H, NH)
5b	8	53	Viscous liquid	$C_{15}H_{18}N_4$[d] (254.2)	3480, 3380, 3160, 1610, 1570	2.43 (s, 3H, CH$_3$); 3.13 (s, 3H, N—CH$_3$); 6.03 (s, 1H, NH)
5c	8	61	134–136° (ethanol)	$C_{20}H_{20}N_4$ (316.4)	3260, 1615, 1560	3.20 (s, 3H, N—CH$_3$); 6.10 (s, 1H, NH)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.20; N, ±0.43; except if noted otherwise.

[b] The I.R. spectra of **4b** and **5b** were measured in chloroform solution.

[c] The high-resolution mass spectrum of **4b** proved the assigned structure. Exact mass calculated for $C_{14}H_{16}N_4$: 240.1374; found: 240.1364.

[d] The high-resolution mass spectrum of **5b** proved the assigned structure. Exact mass calculated for $C_{15}H_{18}N_4$: 254.1531; found: 254.1506.

Table 2. 3-Anilino-6-methyl-4,5-dihydro-6*H*-pyrrolo[2,3-*c*]pyrazoles **(7)** and 3-Anilino-7-methyl-4,5,6,7-tetrahydropyrido[2,3-*c*]pyrazoles **(8)**

Product	Reaction Conditions	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
7a	2 h/20 °C	22	107–109°	$C_{12}H_{14}N_4$ (214.3)	3360, 1630, 1600, 1550	2.73 (s, 3H, N—CH$_3$); 6.33 (s, 2H, NH, NH)
7b	4 h/reflux	73	140–142°	$C_{18}H_{18}N_4$ (290.4)	3300, 1600, 1580, 1560	2.67 (s, 3H, N—CH$_3$); 5.63 (s, 1H, NH)
8a	4 h/reflux	53	110–112°	$C_{13}H_{16}N_4$ (228.3)	3320, 1600, 1550, 1530	2.77 (s, 3H, N—CH$_3$); 6.23 (s, 2H, NH, NH)
8b	8 h/reflux	63	162–164°	$C_{19}H_{20}N_4$ (304.4)	3240, 1605, 1530, 1500	2.97 (s, 3H, N—CH$_3$); 5.27 (s, 1H, NH)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.34; H, ±0.26; N, ±0.35.

solvent is evaporated and water is added to the residue. The mixture is extracted twice with dichloromethane and the extract is evaporated to dryness. The residue is chromatographed on alumina [eluent: **4a, 5a** dichloromethane/methanol (100/1); **4b, 5b** dichloromethane; **4c, 5c** benzene/dichloromethane (1/1)] to yield product **4** or **5**, respectively.

4-Anilino-*N*-methylazacycloalka[2,3-*c*]pyrazoles (7, 8); General Procedure:

A mixture of compound **1** or **2** (2 mmol) and hydrazine hydrate **(6a)** or phenylhydrazine **(6b)** (2 mmol) in ethanol is stirred under reflux except for the reaction of **1** with **6a** (at 20 °C) for the period indicated in Table 2. The solvent is concentrated and chromatographed on alumina [eluent: **7a, 8a** dichloromethane/methanol (100/1); **7b, 8b** benzene/dichloromethane (1/1)] to give **7** or **8**, respectively.

Received: July 20, 1982

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[1] P. J. Brown, *The Pyrimidines*, A. Weissberger, ed., Intersciences Publishers, New York, 1962, p. 31.

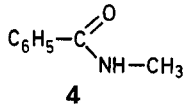
[2] L. A. Paquette, *Principles of Modern Heterocyclic Chemistry*, W. A. Benjamin Inc., New York, 1968, p. 183.

[3] H. Takahata, M. Nakano, T. Yamazaki, *Synthesis* **1983**, 225.

Errata and Addenda 1983

E. Haug, W. Kantlehner, P. Speh, H.-J. Bräuner, *Synthesis* **1983** (1), 35–37:

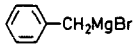
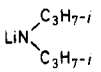
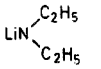
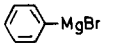
Compound **4** should be *N*-methylbenzamide:



4

A. I. Meyers, K. A. Lutomski, *Synthesis* **1983** (2), 105–107:
The first seven entries in the Table (p. 106) should be as follows:

Table. Addition of Organometallic Reagents to 2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-methoxynaphthalene **(1)** leading to 1-Substituted 2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-naphthalenes **2**

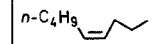
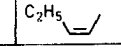
Product	RM	Yield [%]	m.p. [°C]	I.R. (film) $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
2a	H_3CLi	84	oil	1645	(CCl_4): 1.36 (s, 6 H); 2.92 (s, 6 H); 3.97 (s, 2 H); 7.3–8.2 (m, 6 H)
2b	*n*-C_4H_9Li	80	oil	1640	(CCl_4): 0.8–1.85 (m, 13 H); 3.45 (br, t, 2 H); 3.95 (s. 2 H); 7.3–8.2 (m, 6 H)
	n-C_4H_9MgBr	89			
2c		59	oil	1635	(CCl_4): 1.30 (s, 6 H); 3.92 (s, 2 H); 4.97 (s, 2 H); 7.0–8.2 (m, 12 H)
2d		68	oil[a]	1645	($CDCl_3$): 1.00 (d, 6 H); 1.12 (d, 6 H); 1.35 (s, 6 H); 3.45–4.19 (hept, 2 H); 4.0 (s, 2 H); 7.3–7.9 (m, 5 H); 8.65 (m, 1 H)
2e		78	oil[b]	1650	($CDCl_3$): 1.05 (t, 6 H); 1.35 (s, 6 H); 3.30 (d, 4 H); 3.95 (s, 2 H); 7.2–7.8 (m, 5 H); 8.3–8.5 (m, 1 H)
2f		84	oil	1660	(CCl_4): 1.12 (s, 6 H); 3.59 (s, 2 H); 7.2–7.9 (m, 11 H)

S. Takano, K. Seya, E. Goto, M. Hirama, K. Ogasawara, *Synthesis* **1983** (2), 116–117:

The title should read "Synthesis of (*S*)-1-*O*-Benzylglycerol and (*R*)-Benzyl 2,3-Epoxypropyl Ether from (*R*)-1-*O*-Benzylglycerol"; the names of compounds (*R*)-**5**, (*S*)-**5**, and **9** should be (*R*)-1-*O*-benzylglycerol, (*S*)-1-*O*-benzylglycerol, and (*S*)-2,3-Di-*O*-acetyl-1-*O*-benzylglycerol, respectively.

D. Michelot, *Synthesis* **1983** (2), 130–134:

The table under the formula scheme (page 131) should be as follows:

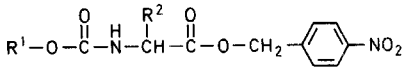
5	m	n	6,7,8,(9)	R
a	4	8	a	*n*-C_4H_9
a	4	8	b	C_2H_5
c		6	c	*n*-C_4H_9 
a	4	8	d	H_2C=CH–
b	6	10	e	C_2H_5 

Compounds **6e**, **7e**, **8c**, and **9e** (p. 133) should be named (*Z*, *Z*)-1-(2-tetrahydropyranyloxy)-11,13-hexadecadiene, (*Z*,*Z*)-11,13-hexadecadienol, (*Z*,*Z*)-7,11-hexadecadien-1-yl acetate, and (*Z*,*Z*)-11,13-hexadecadienal, respectively. Compound **8b** is prepared from **5a** and ethylmagnesium bromide.

M. Künstlinger, E. Breitmaier, *Synthesis* **1983** (2), 161–162:

Compounds **5** and **6** should be named pyrimido[1,2-*a*]benzimidazoles.

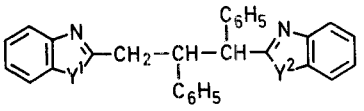
Abstract **6555**, *Synthesis* **1983** (2), 165:

Compound **1** should be: 

1

V. Dryanska, C. Ivanov, *Synthesis* **1983** (2), 143–145:

The formula for compounds **4g, h, 5g, h** (page 144) should be:



4g Y^1 = O, Y^2 = O
4h Y^1 = O, Y^2 = S
5g Y^1 = S, Y^2 = O
5h Y^1 = S, Y^2 = S

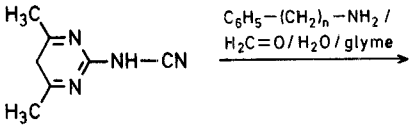
M. A. Brook, T. H. Chan, *Synthesis* **1983** (3), 201–203:

The following addendum should be added:
After publication of our work, our attention was drawn to the fact that the priority for the use of chlorotrimethylsilane for esterification lies with Nakao et al.[24].

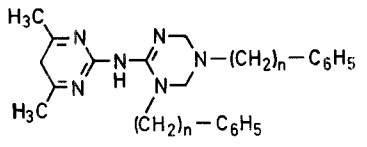
[24] R. Nakao, K. Oka, T. Fukumoto, *Bull. Soc. Chem. Jpn.* **54**, 1267 (1981).

C. W. Thornber, J. M. Farrell, D. S. Clarke, *Synthesis* **1983** (3), 222–223:

The formula scheme **1** ⟶ **10,11** (p. 222) should be:



1



10 n = 1
11 n = 2

H. Takahata, N. Nakajima, Y. Yamazaki, *Synthesis* **1983** (3) 226–228:

Compounds **7** and **8** should be named 3-anilino-6-methyl-1,4,5,6 tetrahydropyrrolo[2,3-*c*]pyrazoles and 3-anilino-7-methyl-4,5,6,7 tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridines, respectively.