Activated Lactams: A One-Step Synthesis of Azacycloalka[2,3-*d*]pyrimidine Derivatives using Ketene-*S,N*-acetals

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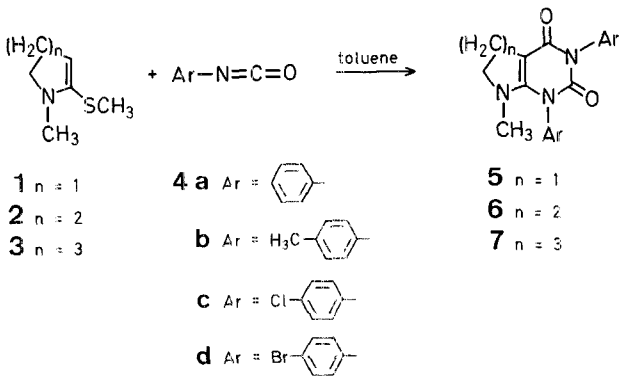
As a continuation of our study on reactions with activated lactams[1], we now report a one-step synthesis of some 1,3-diaryl-2,4-dioxo-*N*-methylazacycloalka[2,3-*d*]pyrimidines **(5a–d, 6a–d, 7a–d)** by the reaction of ketene-*S,N*-acetals **(1, 2, 3)**[2] derived from *N*-methyl-thiolactams with aryl isocyanates **(4a–d)**. The addition of two equivalents of **4a–d** to **1, 2, 3** in boiling toluene gave 1,3-diaryl-2,4-dioxo-7-methyl-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidines **(5a–d)**, 1,3-diaryl-2,4-dioxo-8-methyl-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines **(6a–d)**, and 1,3-diaryl-2,4-dioxo-9-methyl-1,2,3,4,5,6,7,8-octahydro-9*H*-pyrimido[4,5-*b*]azepines **(7a–d)**, respectively. Compounds **5, 6,** and **7** are of biological interest.



The structures assigned to compounds **5, 6,** and **7** were unambiguously confirmed by the mass-, I.R.-, U.V.-, and ^{1}H-N.M.R.-spectral data.

1,3-Diaryl-2,4-dioxo-*N*-methylazacycloalka[2,3-*d*]pyrimidines (5, 6, 7); General Procedure:

To a solution of the aryl isocyanate **4** (4 mmol) in toluene (20 ml) is added the semicyclic ketene *S,N*-acetal **1, 2,** or **3** (2 mmol) and the mixture is refluxed for 15 h with stirring. The solvent is evaporated and the resultant oil is crystallized from diisopropyl ether to afford a solid. Recrystallization of the solid from dichloromethane/diisopropyl ether gives **5, 6,** or **7,** respectively.

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Table. 1,3-Diaryl-2,4-dioxo-7-methyl-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidines **(5)**, 1,3-Diaryl-2,4-dioxo-8-methyl-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines **(6)**, and 1,3-Diaryl-2,4-dioxo-9-methyl-1,2,3,4,5,6,7,8-octahydro-9*H*-pyrimido[4,5-*b*]azepines **(7)**

Product	Yield [%]	m.p. [°C]	Molecular[a,b] formula	I.R. (nujol) ν [cm^{-1}]	U.V. (ethanol) λ_{max} [nm] (logε)	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm] N—CH_3	Ar—CH_3
5a	43	234–235°[c]	$C_{19}H_{17}N_3O_2$ (319.4)	1690, 1650, 1590	301 (9.44)	2.17 (s, 3H)	
5b	46	218–220°	$C_{21}H_{21}N_3O_2$ (347.4)	1700, 1660, 1600	300 (10.1)	2.13 (s, 3H)	2.33 (s, 3H); 2.40 (s, 3H)
5c	36	220–221°	$C_{19}H_{15}Cl_2N_3O_2$[c] (388.2)	1700, 1660, 1580	302 (9.81) 221 (9.98)	2.17 (s, 3H)	
5d	32	229–231°	$C_{19}H_{15}Br_2N_3O_2$[d] (477.2)	1700, 1660, 1590	303 (9.80) 226 (10.0)	2.20 (s, 3H)	
6a	67	215–218°	$C_{20}H_{19}N_3O_2$ (333.4)	1700, 1640, 1605	298 (9.66)	2.32 (s, 3H)	
6b	67	211–213°	$C_{22}H_{23}N_3O_2$ (361.4)	1705, 1645, 1610	298 (9.74)	2.27 (s, 3H)	2.35 (s, 6H)
6c	62	200–203°	$C_{20}H_{17}Cl_2N_3O_2$ (402.3)	1705, 1640, 1605	298 (9.58) 223 (9.92)	2.33 (s, 3H)	
6d	78	214–216°	$C_{20}H_{17}Br_2N_3O_2$ (491.2)	1700, 1640, 1600	298 (9.70) 227 (10.0)	2.30 (s, 3H)	
7a	62	273–276°	$C_{21}H_{21}N_3O_2$ (347.4)	1700, 1650, 1610	306 (9.25)	2.27 (s, 3H)	
7b	71	222–223°	$C_{23}H_{25}N_3O_2$ (373.5)	1705, 1650, 1620	304 (9.69)	2.23 (s, 3H)	2.40 (s, 6H)
7c	70	227–229°	$C_{21}H_{19}Cl_2N_3O_2$ (416.3)	1700, 1650, 1610	305 (9.53) 224 (9.90)	2.30 (s, 3H)	
7d	54	206–209°	$C_{21}H_{19}Br_2N_3O_2$ (505.2)	1700, 1640, 1605	306 (9.58) 227 (10.0)	2.23 (s, 3H)	

[a] The microanalyses were in good agreement with the calculated values: C, ±0.28; H, ±0.11; N, ±0.50, except if noted otherwise.

[b] The mass spectra of all products showed *m/e:* M^+, $(M-ArN-CO)^+$.

[c] The high-resolution mass spectrum of **5c** proved the assigned structure. Exact mass calculated for $C_{19}H_{15}Cl_2N_3O_2$: 387.0540, 389.0513, 391.0481; found: 387.0494, 389.0561, 391.0547.

[d] The high mass spectrum of **5d** proved the assigned structure. Exact mass calculated for $C_{19}H_{15}Br_2N_3O_2$: 474.9530, 476.9513, 478.9492; found: 474.9504, 476.9545, 478.9579.

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[2] R. Gompper, W. Elser, *Justus Liebigs Ann. Chem.* **725**, 64 (1969).

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