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Viehe's salt in a novel one pot synthesis of pyrimidines

Alexander S. Kiselyov*

Small Molecule Drug Discovery, Chemical Diversity, 11558 Sorrento Valley Rd., San Diego, CA 92121, USA

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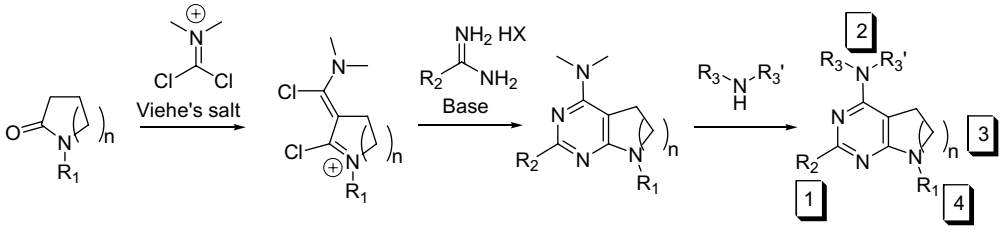
Abstract—A series of pyrimidine derivatives are synthesized from *N*-substituted lactams, and Viehe's salt. A short reaction sequence, good yields of the targeted heterocyclic compounds (44–67%), as well as their convenient isolation and purification are the distinct advantages of the reported protocol.

Synthesis of polysubstituted pyrimidines received substantial attention due to the pronounced activity as anti-inflammatory and analgetic agents.[1] Several reports in the literature describe the application of these substrates for the treatment of hypoxemia,[2] neuronosis,[3] and neuropathy.[4] In our medicinal chemistry program, we required a robust approach to a diverse set of the title heterocycles. Retrosynthetic analysis of the targeted molecules suggested that these may be accessed from the corresponding lactams by treatment with Viehe's salt followed by the reaction of the resultant iminium dichlorides with amidines in the presence of base (Scheme 1). A variety of heterocyclic ring systems have been constructed using Viehe's salt. These include the derivatives of 4-pyrone,[5] 2-pyrone,[6] pyrimidine,[7] 1,3-oxadiazin-6-one,[8] thiazole,[9] pyrazole,[10] various fused heterocycles,[11] and nonaromatic species.[12] The proposed reaction sequence allows for the introduction of four elements of diversity into the resultant molecules, including: (1) R_2 substituent originating from the amidine input; (2) amino functionality resulting from the nucleophilic aromatic substitution of the NMe_2 group;[13] (3) and (4) both the size of the fused aliphatic ring, as well as the R_1 substituent resulting from the lactam.

In the initial study, we synthesized a set of pyrimidines with varying R_1, and R_2 substituents. Three commercially available *N*-substituted 2-pyrrolidinones **1a–c** (R_1 = Me, cyclohexyl, and Ph) were selected for the preparation of **2** followed by their reaction with a set of seven amidinium salts. The results of these experiments are summarized below (Table 1).

Addition of dry DMF to the reaction mixture proved to be highly beneficial in increasing the yields of the targeted heterocycles. This may be attributed to the improved solubility of amidines in the toluene/DMF (2:1) solvent mixture. Larger ratios of toluene/DMF did not affect the outcome of the cyclization. Similar reactions conducted in toluene/dioxane, toluene/THF,



Scheme 1.

Keywords: Pyrimidines; Iminium salts; Amidines; Condensations.
* Tel.: +1 858 794 4860; fax: +1 858 794 4931; e-mail: ask@chemdiv.com

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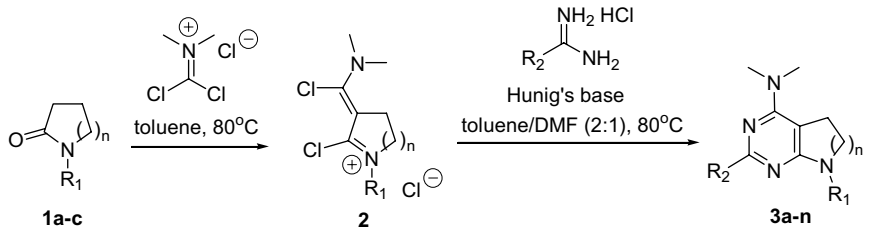
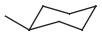
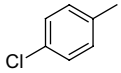
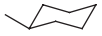
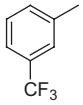
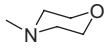
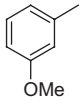
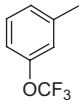
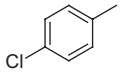
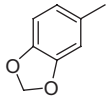
Table 1. Yields of pyrimidines **3a–n**[14]

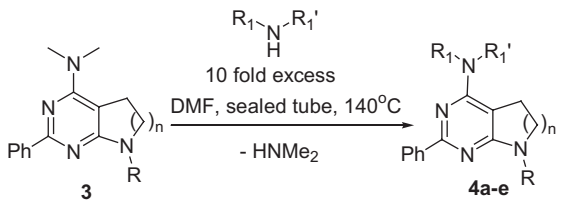


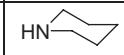
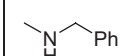
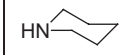
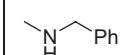
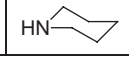
Compound, **3**				
	n	R_1	R_2	Yield, %
a	**1**	Me		48
b	**1**	Me	Ph	62
c	**1**			58
d	**1**			64
e	**1**	Ph		56
f	**1**	Ph		64
g	**1**	Ph		67
h	**2**	Me	Ph	48
i	**2**	Me		55
j	**2**	Ph	Ph	51
k	**2**	Ph		62
l	**2**	Ph		54
m	**2**	Bn		48
n	**2**	Bn	Bn	44

or toluene/MeCN systems furnished lower yields of pyrimidines (15–35%), along with considerable amount of tar products. Guanidines reacted with the intermediate iminium species **2** to afford the corresponding 2-aminopyrimidines (Table 1, entry **e**). A similar reaction sequence performed with the *N*-substituted derivatives of 2-pyrimidinone yielded the corresponding 6,6-fused pyrimidines **3h–n** in good yields (44–62%, Scheme 2).

Pyrimidines **3b**, **3h**, and **3j** react with piperidine and *N*-methylbenzylamine in dry DMF at 140 °C in a sealed tube to furnish products of formal nucleophilic aromatic substitution of the NMe_2 group **4a–e** in 48–61% yields (Scheme 2).[13]

In summary, we have developed a practical procedure for the synthesis of polysubstituted pyrimidines from *N*-substituted lactams, and Viehe's salt. A short reaction sequence, good yields of title compounds (44–67%), as well as their ready isolation, and purification are the distinct advantages of the reported protocol.



Cmpd	R	n	Amine	Yield of 4, %
3b	Me	1		a, 50
3b	Me	1		b, 48
3h	Me	2		c, 54
3h	Me	2		d, 51
3j	Ph	2		e, 61

Scheme 2.

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14. Experimental procedure: 5.5 mmol of Viehe's salt (Aldrich) was added to a vigorously stirred solution of 5 mmol of lactam in dry degassed toluene (70 mL) at room temperature under Ar. The heterogeneous dark yellow mixture was slowly warmed up to 80 °C (30 min), and the resulting mixture was stirred at this temperature for an additional 1.5 h. The dark-red mixture was quickly filtered under argon blanket, and a solution of 7 mmol of amidine hydrochloride in 20 mL of dry DMF followed by 25 mmol of Hunig's base were introduced. The resulting mixture was brought to 80 °C, stirred for 12 h at this temperature, cooled down to room temperature, diluted with 100 mL of EtOAc and washed with 3×50 mL of saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4, concentrated, and the resulting residue was recrystallized twice from EtOH to afford the analytically pure pyrimidines in 48–67% isolated yields. A representative example: **3e**: 56% yield, mp 176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.98 (s, 6H, NMe_2), 3.18 (t, J = 8.0 Hz, 2H, CH_2), 3.54 (m, 4H, morpholino), 3.62 (m, 4H, morpholino), 3.86 (t, J = 8.0 Hz, 2H, CH_2), 6.92 (m, 1H, Ph), 7.23 (m, 2H, Ph), 7.68 (m, 2H, Ph). ESI MS: (M+1) 326, (M−1) 324; HR ESI MS: exact mass calcd for $C_{18}H_{23}N_5O$ 325.1903, found: 325.1907. Elemental analysis, calcd for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.21; H, 7.32; N, 21.47.