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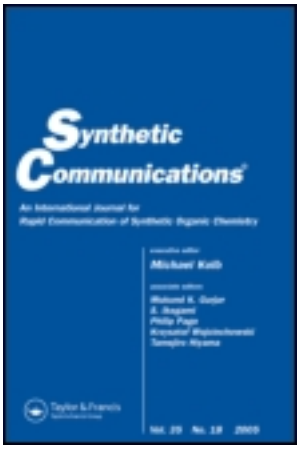

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Efficient One-Pot Synthesis of Substituted Pyrido[2,3-d]pyrimidines from Vinamidinium and Chloropropeniminium Salts

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EFFICIENT ONE-POT SYNTHESIS OF SUBSTITUTED PYRIDO[2,3-d]PYRIMIDINES FROM VINAMIDINIUM AND CHLOROPROPENIMINIUM SALTS

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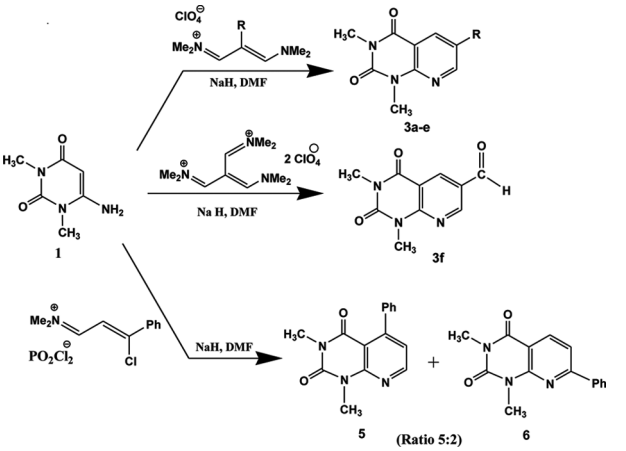
GRAPHICAL ABSTRACT



Abstract *A novel and efficient one-pot preparation of 6-substituted pyrido-[2,3-d]pyrimidines by cyclocondensation of 6-amino-1,3-dimethyluracil with symmetrical vinamidinium salts under basic conditions has been developed. Regioselectivity was observed with an unsymmetrical chloropropeniminium salt.*

Keywords 6-Amino-uracil; chloropropeniminium salts; cyclocondensation; trisubstituted pyrido[2,3-d]pyrimidines; vinamidinium salts

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INTRODUCTION

The importance of uracil and its annulated derivatives is well recognized by synthetic[1] and biological[2] chemists. 6-Amino-uracil derivatives represent a very important class of functionalized uracils. Moreover, 6-amino-uracils have wide applications as starting materials for the synthesis of a number of fused uracils of biological significance, such as pyrano-, pyrido-, pyrazolo-, pyrimido-, and pyridazinopyrimidines.[3,4]

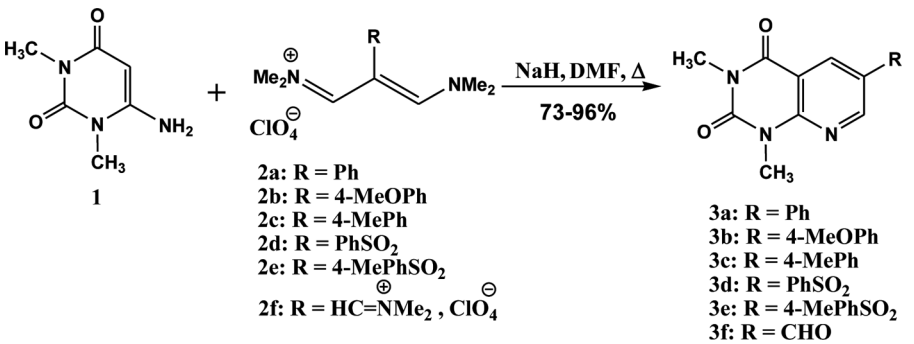
Pyrido[2,3-d]pyrimidines constitute a broad class of annelated uracils that received considerable attention in past years because of their wide range of biological activities as antibacterial,[5] antitumor,[6] cardiotonic,[7] hepatoprotective, [8] and vasodilator activities.[9] Additionally, some compounds of this class exhibit antialergic,[10] antimalarial,[11] and anticonvulsive[12] activities. Therefore, much effort has been directed toward the synthetic manipulation of uracil to prepare these complex molecules. However, there still remain many challenges in the synthesis of these naturally occurring complex molecules.[13–16]

In this article, we present an unprecedented synthetic approach for the preparation of pyrido[2,3-d]pyrimidines using vinamidinium salts. In the past years, one of the primary interests of our research group has been to investigate the preparation and the application of vinamidinium salts[17–20] in organic synthetic chemistry. These substances are very important synthons that have the potential to serve as three carbon building blocks for the synthesis of carbocyclic and heterocyclic compounds.[21] Some fused heterocyclic systems such as carbazoles, benzodiazepines, and triazolo[1,5-a]pyrimidines were also successfully obtained via cyclocondensation of vinamidinium salts with appropriate nucleophiles.[22–24] However, this methodology was not yet investigated in pyrido-pyrimidines synthesis.

RESULTS AND DISCUSSION

Herein, we report the one-pot, two-component condensation of 6-amino-1,3-dimethyluracil **1** and vinamidinium salts **2**, leading to the desired 6-substituted pyrido[2,3-d]pyrimidines **3** with good yields (Scheme 1).

The cyclocondensation of 6-amino-uracil **1** with symmetrical vinamidinium perchlorates **2a–f** has provided the desired 6-substituted pyrido[2,3-d]pyrimidines



Scheme 1. Synthesis of 6-substituted pyrido[2,3-d]pyrimidines **3a–f**.

Table 1. Synthesis of 6-substituted pyrido[2,3-d]pyrimidines **3a–f**

Compound	R	Yield[a] (%)
3a	Ph	92
3b	4-MeOPh	96
3c	4-MePh	90
3d	$PhSO_2$	73
3e	$4\text{-}MePhSO_2$	78
3f	CHO	89

[a]Isolated yield.

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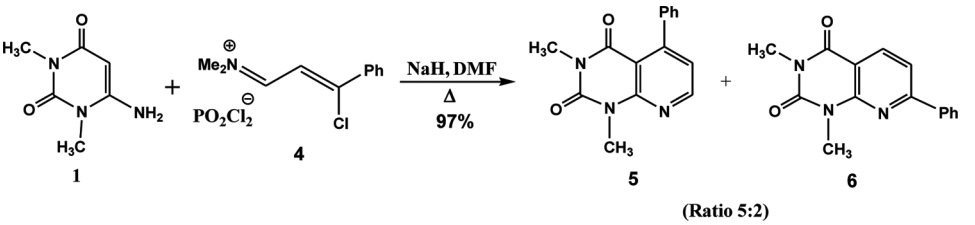
3a–f in good to excellent yields (Table 1). The reactions were conducted by heating the reagents in dimethylformamide (DMF) at 100 °C for 12 h in the presence of sodium hydride.

Additionally, as shown in Table 1, the phenylsulfonyl and 4-methylphenylsulfonyl at the C_6-substituent (**3d** and **3e**) affected the cyclocondensation reaction. This may be the result of the ''push–pull'' relationship between the strong electron-withdrawing sulfonyl group at the C_2 position and the enamine group, in the corresponding vinamidinium salts (**2d** and **2e**), allowing the imino group to behave like an isolated moiety. This behavior has been also observed in a previous work.[20]

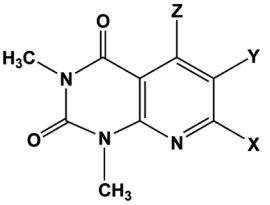
It has already been mentioned that chloropropeniminium salts, which are precursors to unsymmetrical vinamidinium salts, function also as useful three-carbon synthons for the preparation of heterocyclic compounds.[25] Because there could be two possible substituted pyrido[2,3-d]pyrimidine products, the question of regiochemistry needed to be addressed. The reaction of uracil **1** and chloropropeniminium salt **4** was performed under similar conditions to those reported previously. Both regioisomers were obtained in good yield, but the 5-substituted pyrido[2,3-d]pyrimidine isomer **5** was preferred in a ratio of 5:2 (Scheme 2).

The structure of each isomer was determined by comparison of their proton–proton coupling constants with pyridine system and known samples. As an example, the 7-substituted isomer **6** is known[26] and has a coupling constant of 8 Hz, which is consistent with the minor isomer having a coupling constant of 8.1 Hz. This is also in accordance with the coupling constant for pyridine hydrogens at the 3 and 4 positions ranging from 7.2 to 8.5 Hz. Moreover, the coupling constant of the major isomer **5** is 4.8 Hz, which is consistent with pyridine hydrogens at 2 and 3 positions. The proton–proton coupling constants of compounds **3a–f, 5** and **6** are listed in Table 2.



Scheme 2. Regioselective condensation of 6-amino-1,3-dimethyluracil with chloropropeniminium salt **4**.

Table 2. Proton–proton coupling constants of products **3a–f**, **5**, and **6**



Compound	X	Y	Z	Solvent	J_{ab} (Hz)	J_{bc} (Hz)	J_{ac} (Hz)
3a	Ha	Ph	Hc	$CDCl_3$	—	—	2.3
3b	Ha	4-MeOPh	Hc	$CDCl_3$	—	—	2.4
3c	Ha	4-MePh	Hc	$CDCl_3$	—	—	2.0
3d	Ha	$PhSO_2$	Hc	$CDCl_3$	—	—	2.2
3e	Ha	4-$MePhSO_2$	Hc	$CDCl_3$	—	—	2.3
3f	Ha	CHO	Hc	$CDCl_3$	—	—	2.4
5	Ha	Hb	Ph	$CDCl_3$	4.8	—	—
6	Ph	Hb	Hc	$CDCl_3$	—	8.1	—

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CONCLUSION

In conclusion, we have described a novel, efficient, simple, and regioselective method for the preparation of pyrido[2,3-d]pyrimidine derivatives in reasonably good yield, via cyclocondensation reaction of 6-amino-1,3-dimethyluracil with symmetrical vinamidinium salts and an unsymmetrical chloropropeniminium salt.

EXPERIMENTAL

Pyrido[2,3-d]pyrimidines 3a–e

General procedure. A mixture of 6-amino-1,3-dimethyluracil (1 mmol), vinamidinum salt (1 mmol), and sodium hydride (2.2 mmol) in DMF (5 mL) was stirred at 100 °C for 12 h (the progress of reaction was monitored by thin-layer chromatography, TLC). After cooling to room temperature, the reaction mixture was quenched by saturated NH_4Cl solution and extracted three times with $CHCl_3$. The combined organic layers were washed two times with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by column chromatography on silica gel (hexane/EtOAc 8:2).

1,3-Dimethyl-6-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 3a. White solid: mp 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.56 (s, 3H), 3.75 (s, 3H), 6.90 (m, 3H), 7.43 (d, 2H, $J = 8.4$ Hz), 8.50 (d, 1H, $J = 2.3$ Hz), 8.81 (d, 1H, $J = 2.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.4, 29.2, 118.4, 127.1, 128.6, 129.8, 131.3, 135.7, 142.3, 151.0, 152.5, 154.8, 162.6. Anal. calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72%. Found: C, 67.36; H, 4.87; N, 15.68%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$267.

1,3-Dimethyl-6-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 3b. White solid: mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$)

δ: 3.45 (s, 3H), 3.69 (s, 3H), 3.80 (s, 3H), 6.96 (d, 2H, $J = 8.7$ Hz), 7.49 (d, 2H, $J = 8.7$ Hz), 8.53 (d, 1H, $J = 2.4$ Hz), 8.79 (d, 1H, $J = 2.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9, 30.1, 55.8, 110.9, 115.2, 128.4, 128.9, 132.4, 135.1, 152.0, 152.4, 154.3, 160.4, 162.0. Anal. calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13%. Found: C, 64.59; H, 5.06; N, 14.10%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$297.

1,3-Dimethyl-6-(*p*-tolyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 3c. White solid: mp 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 7.11 (d, 2H, $J = 8.6$ Hz), 7.56 (d, 2H, $J = 8.6$ Hz), 8.44 (d, 1H, $J = 2.0$ Hz), 8.75 (d, 1H, $J = 2.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1, 27.8, 28.6, 120.5, 128.4, 129.2, 133.7, 135.4, 137.6, 140.9, 148.5, 153.3, 154.0, 164.6. Anal. calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94%. Found: C, 68.26; H, 5.35; N, 14.90%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$281.

1,3-Dimethyl-6-(phenylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 3d. White solid: mp 216–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.65 (s, 3H), 3.72 (s, 3H), 7.48 (m, 1H), 7.75 (m, 4H), 8.54 (d, 1H, $J = 2.2$ Hz), 9.01 (d, 1H, $J = 2.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.6, 28.3, 127.5, 129.8, 131.3, 132.4, 134.1, 142.7, 145.0, 147.2, 150.9, 154.8, 166.5. Anal. calcd. for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68%. Found: C, 54.34; H, 3.91; N, 12.62%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$331.

1,3-Dimethyl-6-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 3e. White solid: mp 242–244 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.49 (s, 3H), 3.68 (s, 3H), 7.43 (d, 2H, J = 8.2 Hz), 7.82 (d, 2H, $J = 8.2$ Hz), 8.51 (d, 1H, $J = 2.3$ Hz), 8.97 (d, 1H, $J = 2.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 28.2, 30.5, 126.2, 129.6, 131.1, 133.5, 142.8, 144.0, 145.3, 148.8, 151.7, 155.3, 165.9. Anal. calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17%. Found: C, 55.60; H, 4.36; N, 12.13%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$345.

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbaldehyde 3f

General procedure. A mixture of 6-amino-1,3-dimethyluracil (1 mmol), vinamidinum salt **2f** (1 mmol), and sodium hydride (2.2 mmol) in DMF (5 mL) was stirred at 100 °C for 12 h. After cooling to room temperature, H_2O (20 mL) and 1 N HCl (2 mL) were added, and the mixture was allowed to stir at room temperature for 2 h, then neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous mixture was extracted with four portions of ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 8:2) to give a white solid (mp 168–170 °C).

Spectroscopic data. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.48 (s, 3H), 3.76 (s, 3H), 8.86 (d, 1H, $J = 2.4$ Hz), 9.11 (d, 1H, $J = 2.4$ Hz), 10.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.8, 30.2, 110.6, 127.3, 139.2, 151.1, 153.9, 155.5, 160.5, 188.7. Anal. calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17%. Found: C, 54.74; H, 4.10; N, 19.15%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$219.

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6-Amino-1,3-dimethyluracil with Chloropropeniminium Salt 4

General procedure. Were added to a solution of 6-amino-1,3-dimethyluracil (1 mmol) in DMF (5 mL), sodium hydride (2.2 mmol) and chloropropeniminium salt **4** (1 mmol). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched by saturated NH_4Cl solution and extracted several times with $CHCl_3$. The combined organic layers were washed two times with water, dried over Na_2SO_4, filtered, and concentrated to give the crude mixture of **5** and **6** in a yield of 97%. The products were isolated by column chromatography on silica gel (CH_2Cl_2).

1,3-Dimethyl-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 5. White solid: mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.38 (s, 3H), 3.78 (s, 3H), 7.02 (d, 1H, $J = 4.8$ Hz), 7.27–7.32 (m, 2H), 7.43–7.46 (m, 3H), 8.61 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9, 30.6, 108.4, 122.4, 128.1, 128.3, 128.6, 139.5, 151.7, 152.3, 152.6, 154.9, 161.0. Anal. calcd. for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72%. Found: C, 67.38; H, 4.85; N, 15.70%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$267.

1,3-Dimethyl-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione 6. White solid: mp 184–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.51 (s, 3H), 3.83 (s, 3H), 7.51–7.54 (m, 3H), 7.67 (d, 1H, $J = 8.1$ Hz), 8.11-8.15 (m, 2H), 8.50 (d, 1H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.5, 29.5, 109.1, 115.2, 127.6, 129.0, 130.7, 137.6, 138.4, 150.8, 151.7, 161.3, 161.4. Anal. calcd. for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72%. Found: C, 67.36; H, 4.87; N, 15.68%. Mass m/z (EI, 30 eV): $\mathbf{M}^+$267.

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