CYCLIZATION OF GUANIDINES WITH α,β-UNSATURATED KETONES: IMPROVED SYNTHESIS OF 2-AMINODIHYDROPYRIMIDINE DERIVATIVES CONTAINING GUANIDINE MOIETY

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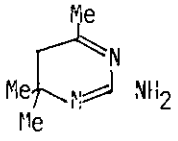
Abstract - 3,4-Dihydro-2-amino pyrimidine derivatives 4a, 4b, 4c, 4d, 4e and 4f containing guanidine moiety were successfully synthesized by cyclization of free N-monosubstitued guanidines with α,β-unsaturated ketones in tertiary butanol at 25°C. These products are the first examples to be isolated as pure compounds which are unstable in protic solvents such as water, methanol and ethanol. However they are stable in solid states or in aprotic solvents such as dimethyl sulfoxide, dimethyl formamide, pyridine and chloroform.

With the aim of obtaining 2-aminohydropyrimidine derivatives containing guanidine moiety, cyclization of guanidines with α,β-unsaturated ketones were examined. Both potent neurotoxin of tetrodotoxin[1] and saxitoxin[2] containing guanidine moiety have been known to be biologically active. Simple ring compounds containing guanidine moiety[3] have been also demonstrated to be biologically active like that of tetrodotoxin. Earlier, Traube and Schwarz[4] reported that 1 was obtained by cyclization of guanidine with mesityl oxide under refluxing in tertiary butanol. Later, Wendelin and Harler[5] have revealed that the reaction of guanidine and mesityl oxide affords a mixture of 2, 3 or 4 and its dimer instead of 1. They carried out the reactions at reflux temperature in tertiary butanol. It is likely that a major factor responsible for such



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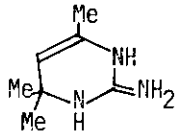

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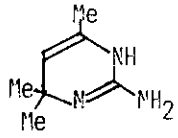

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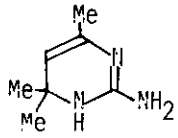

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formation of a mixture of isomers and dimers is due to a thermal isomerization and dimerization of the unstable products. This should be especially critical at the elevated temperature utilized in both reaction procedure and purification by recrystallization with protic solvents. Accordingly we carried out the cyclization at room temperature and have found that the reactions of guanidines with mesityl oxide, dypnone or benzalacetophenone at ca. 25°C afforded highly pure products of 3,4-dihydro-2-amino pyrimidine derivatives (4a-4e)[6] in good yields.

4n

		yield (%)
$R_1=R_2=R_3=CH_3$, $R_4=H$, CH_3, CH_2CH_3	4a: $R_1=R_2=R_3=CH_3$, $R_4=H$	80
$R_1=R_2=Ph$, $R=CH_3$	4b: $R_1=R_2=Ph$, $R_3=CH_3$, $R_4=CH_3$	81
$R_1=R_2=Ph$, $R_3=H$	4c: $R_1=R_2=R_3=R_4=CH_3$	80
	4d: $R_1=R_2=R_3=CH_3$, $R_4=CH_2CH_3$	84
	4e: $R_1=R_2=Ph$, $R_3=H$, $R_4=H$	72
	4f: 4a acetate salt	

A typical procedure is as follows. Guanidine thiocyanate (5.9g, 0.05M) was suspended in tert-BuOH-tert-BuOK (K: 1.95g, 0.05M, tert-BuOH:80ml) under anhydrous nitrogen. After the mixture was refluxed for 1h with good stirring, precipitate of KSCN (ca. 4.3g) was removed by filtration. Mesityl oxide (4.9g, 0.05M) was slowly added to the free guanidine solution. The mixture was kept at ca. 25°C for ca. 3h with stirring under anhydrous nitrogen. Removal of tert-BuOH at 25°C under vacuum gave a red color solid (6.80g). The residue was twice washed with acetonitrile (10ml) to remove impure side products and solvent, and then dried to give a pale yellow needle crystal (5.52g, 80%), whose nmr, uv, ir spectra and elemental analysis meet 4a. Elemental analyses of 4b-4f meet their corresponding formulas.

4a: mp 161-63°C, ^1H nmr (DMSOd_6) δ 1.01 (6H, s, CMe_2), 1.51 (3H, s, =CMe), 4.26 (1H, s, =CH) 5.55 (3H, s, NH). uv $\lambda_{max}^{CHCl_3}$ nm (ε), 250 (3.04×10^3), ir cm^{-1} 3420, 3300, 3090, 2975, 2950, 2920, 1700, 1520, 1450, 1380, 1370, 1330, 1240, 1160, 1150 and 970.

4b: mp 184-85°C, ^{1}H nmr (DMSOd_6) δ 1.47 (3H, s, CMe), 2.35 (3H, s, NMe), 5.27 (2H, s, NH_2), 7.0-7.73 (10H, m, 2Ph), uv λ_{max}^{MeOH} nm (ε), 222 (2.52 x 10^4), 268 (6.16 x 10^3).

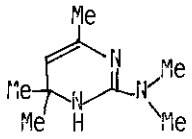
4c: mp 192°C (dec), ^{1}H nmr (DMSOd_6) δ 1.03 (6H, s, CMe_2), 1.57 (3H, s, =CMe), 2.57 (3H, s, NMe), 4.23 (1H, =CH), 5.27 (2H, s, NH_2), uv $\lambda_{max}^{iso\text{-}PrOH}$ nm (ε), 266 (3.12 x 10^3).

4d: mp 142-45°C, ^{1}H nmr (DMSOd_6) δ 1.03 (6H, s, CMe_2), 1.53 (3H, s, CMe), 0.98 (3H, t, Me, J= 7 Hz), 3.02 (2H, q, N-CH_2, J=7 Hz), 4.18 (1H, s, =CH), uv $\lambda_{max}^{CHCl_3}$ nm (ε), 254 (3.18 x 10^3).

4e: mp 103-05°C, ^{1}H nmr (DMSOd_6) δ 5.26 (1H, d, =CH), 5.13 (1H, d, CH), 7.13-7.76 (10H, m, 2Ph), uv $\lambda_{max}^{tert\text{-}BuOH}$ nm (ε), 217 (2.45 x 10^4), 270 (6.05 x 10^3).

4f: mp 172-74°C (prism), ^{1}H nmr (DMSOd_6) δ 1.10 (6H, s, CMe_2), 1.57 (3H, s, CO_2Me), 1.66 (3H, s, =CMe), 4.45 (1H, s, =CH), 8.95 (4H, s, NH).

The double bond of 4 can be readily confirmed by the vinyl proton (δ 4.26 in DMSOd_6, =CH)[7] at C-5 position and the conjugated system of two double bonds observed by comparison of uv spectra of 4a-4e with that of 5.



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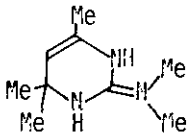

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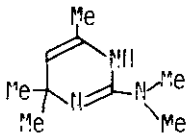

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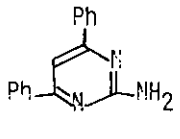

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The λ_{max} (269 nm in ios-PrOH) and ε (3.41 x 10^3) values of 5[8] are close to those of 4a, 4c and 4d. The double bond of the imine in 5' can not be formed because of N-disubstituted amine by two methyl groups. Since the two double bonds of 5' and 5" are not in conjugative system, uv spectrum of 5' and 5" should be different from that of 5 or 4a-4e. All the compounds, 4a-4e and 5 have never been isolated as pure materials. For instance, 4e has been postulated to be an intermediate to lead the corresponding stable compound of 2-amino-4,5-diphenyl pyrimidine 6 by Wendelin and Harler[9]. High reaction temperature (ca. 78°C) in protic solvent of ethanol must be critical for the formation of 6. In fact, 4a, 4c, 4d, and 4e were observed to be unstable in protic solvents such as water and methanol at room temperature[10]. While, pure products, 4a-4f are stable in solid state or in aprotic solvents such as dimethyl sulfoxide, dimethyl foramide, pyridine and chloroform. Thus, best way to obtain these compounds is to keep low reaction temperature (lower than 25°C) and to avoid using protic solvents for crystallization.

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6) The purities of products 4 were decided by ^{1}H nmr spectra: No proton peak of impurity were observed within standard error, TLC showed only one spot in MeOH:acetone(1:2) or in $CHCl_3$: MeOH:AcOH(18:6:1).

7) When 4 was treated with hot water or with methanol, new peak (δ 1.8, s, 2H in $DMSOd_6$) appeared along with disappearance of vinyl proton (δ 4.26, in DMSOd) and methyl proton (=C-CH_3): probably 4 was isomerized to 1 or dimerized.

8) The compound 5 was prepared by the same procedure. But it was purified by quick recrystallization from ethyl acetate in cold room (ca. 4°C) because of its unstability even in ethyl acetate at room temperature. mp. 88-90°C, red color needless, ^{1}H nmr ($CDCl_3$) δ 1.1 (6H, s), 1.8 (3H, s), 2.94 (6H, s, N-Me_2) 4.2 (1H, =CH). It meets structure 5 and elemental analysis met formula $C_9H_{17}N_3$.

9) W. Wendelin and A. Harler, Monatsh Chem., 1976, 107, 133.

10) Their unstabilities were observed by UV spectra (at 25°C) in various solvents: 4n, solvent (% of ε value decrease at λ_{max} after 15 min), 4a; MeOH(56), EtOH(14), iso-PrOH(1.5), tert-BuOH (0, no change) 4c; H_2O(61), MeOH(48), EtOH(24), iso-PrOH(2.5), tert-BuOH(0), 4d; H_2O(53), MeOH(48), EtOH(27), iso-PrOH(3), tert-BuOH(0).

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