SYNTHESES AND TRANSFORMATIONS OF 4-AMINO-2-METHYLTHIO- AND 4-AMINO-2-METHOXYPYRIMIDINE-5-CARBOXAMIDE OXIMES

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Abstract - 4-Amino-5-cyano-2-methylthio- (1) and 4-amino-5-cyano-2-methoxypyrimidine (13) were transformed with hydroxylamine into the corresponding pyrimidine-5-carboxamide oximes (2 and 14). Acylation and carbethoxylation under mild conditions produced O-substituted carboxamide oximes (3, 7, 9, 15, 18, and 19), while under more vigorous conditions cyclization occurred producing 5-(1,2,4-oxadiazolyl)-pyrimidines (4, 6, 8, and 16).

N-Heteroarylformamidines and N-heteroarylformamide oximes have been our research interest for several years,[1] since they are valuable intermediates in heterocyclic chemistry, especially in those cases in which there is hydroxy, cyano, mercapto or any other reactive group attached at ortho position.[2-10]

Recently, we described some new approaches to the synthesis of pyrimido[4,5-d] pyrimidines starting from substituted 4-amino-5-cyanopyrimidines.[11,12] A common feature of all of these transformations is the reaction of amino group with N,N-dimethylformamide dimethyl acetal (DMFDMA), followed either by cyclization with hydrazine or transformation with hydroxylamine into N-hydroxyiminomethyleneamino derivatives and subsequent thermal cyclization.

In this communication we report on transformations of the cyano group in substituted 4-amino-5-cyanopyrimidines with hydroxylamine into the corresponding carboxamide oximes, and futher acylations, carbethoxylation,and cyclizations into 1,2,4-oxadiazolyl substituted pyrimidines.

4-Amino-5-cyano-2-methylthiopyrimidine (1) was transformed with hydroxylamine into 4-amino-2-methylthiopyrimidine-5-carboxamide oxime (2). This was further converted with acetic anhydride at room temperature into 4-amino-2-methylthiopyrimidine-5-

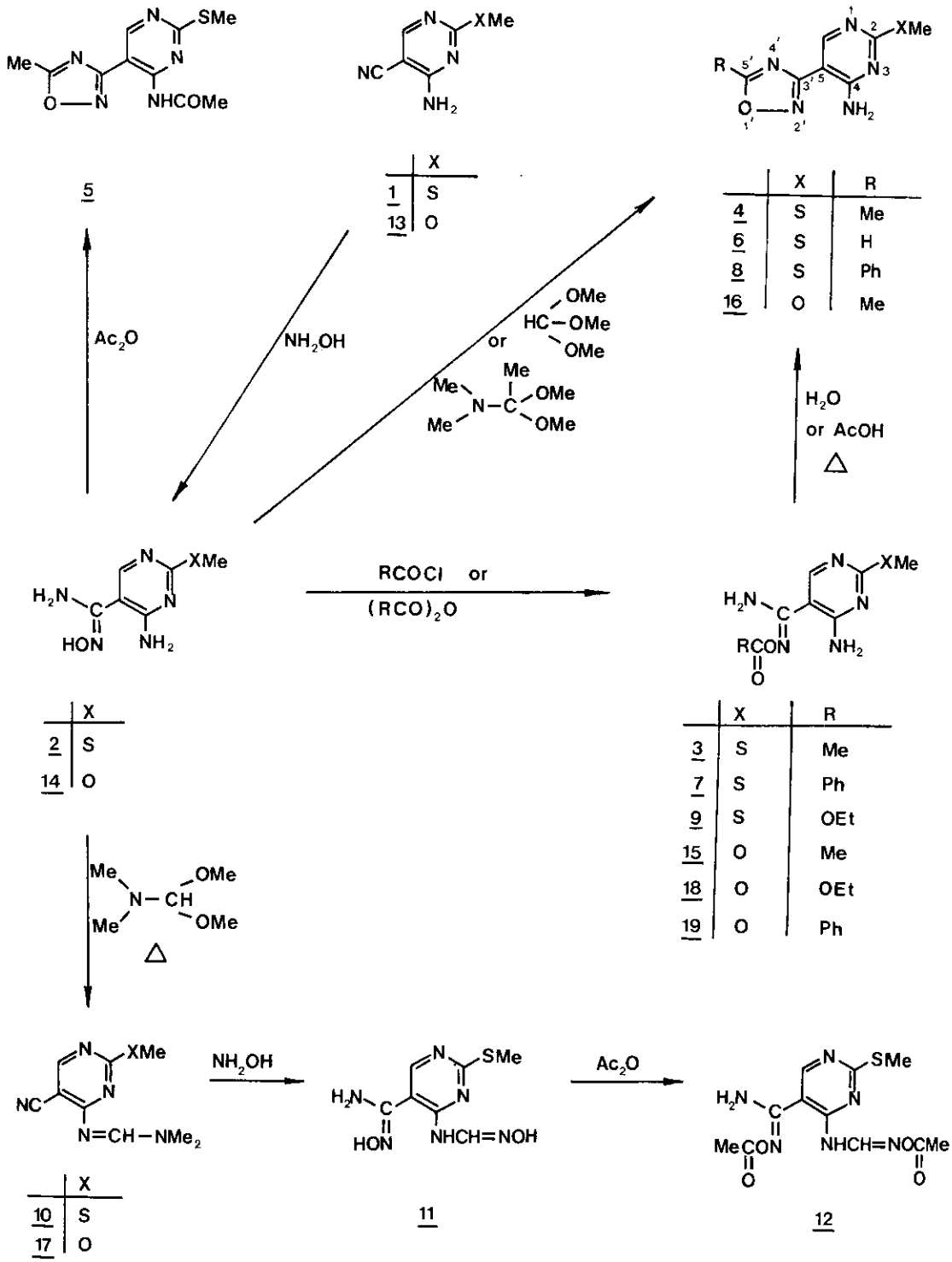
carboxamide O-acetyl oxime (3) which was cyclized by heating in water or in acetic acid into 4-amino-2-methylthio-5-(5-methyl-1,2,4-oxadiazolyl-3)-pyrimidine (4). The same compound could also be obtained in the reaction of 4-amino-2-methylthiopyrimidine-5-carboxamide oxime (2) with N,N-dimethylacetamide dimethyl acetal (DMADMA) at room temperature. On the other hand, when the compound 2 was heated in acetic anhydride, acetylation of the amino group was also taking place to give 4-acetylamino-2-methylthio-5-(5-methyl-1,2,4-oxadiazolyl-3)-pyrimidine (5).

In the reaction of 4-amino-2-methylthiopyrimidine-5-carboxamide oxime (2) with triethyl orthoformate 4-amino-2-methylthio-5-(1,2,4-oxadiazolyl-3)-pyrimidine (6) was formed as the only product. The formation of pyrimido[4,5-d]pyrimidine N-oxide derivative, as an alternative structure, is excluded on the basis of a negative color test for N-oxides.[13]

This reaction is in contrast with the reaction of the corresponding derivatives in pyridine series, in which a mixture of the (1,2,4-oxadiazolyl-3)-pyridine and pyrido|2,3-d|pyrimidine 3-oxide derivatives have been formed.[14]

When 4-amino-2-methylthiopyrimidine-5-carboxamide oxime (2) reacted with benzoyl chloride in the presence of triethylamine 4-amino-2-methylthiopyrimidine-5-carboxamide O-benzoyl oxime (7) was formed, which could be cyclized in glacial acetic acid into 4-amino-2-methylthio-5-(5-phenyl-1,2,4-oxadiazolyl-3)pyrimidine (8), while with ethyl chloroformate the compound 2 was converted into 4-amino-2-methylthiopyrimidine-5-carboxamide O-ethoxycarbonyl oxime (9) which was isolated in the form of its hydrochloride salt.

4-Amino-2-methylthiopyrimidine-5-carboxamide oxime (2) was heated with N,N-dimethylformamide dimethyl acetal (DMFDMA) and the corresponding 5-cyano-4-(N,N-dimethylaminomethyleneamino)-2-methylthiopyrimidine (10) was obtained, identical with the compound prepared from 4-amino-5-cyano-2-methylthiopyrimidine (1) and DMFDMA. The compound 10 was converted with hydroxylamine into 4-hydroxyiminomethylamino-2-methylthiopyrimidine-5-carboxamide oxime (11) and subsequently acetylated with acetic anhydride into 4-acetoxyiminomethylaminopyrimidine-5-carboxamide O-acetyl oxime (12).


5
1 S
13 O
4 S Me
6 S H
8 S Ph
16 O Me
Ac2O
NH2OH
or
H2O
or AcOH
RCOCl or
(RCO)2O
2 S
14 O
3 S Me
7 S Ph
9 S OEt
15 O Me
18 O OEt
19 O Ph
10 S
17 O
NH2OH
Ac2O
11
12

SCHEME

The fact, that the compound 2 gives two different types of products 4 and 10 with DMADMA and DMFDMA, respectively, is not surprising. The explanation for this is that DMFDMA contrary to DMADMA reacts as a strong dehydrating agent. In this respect, dehydration of N-heteroarylformamide oximes with DMFDMA to give the corresponding cyanoamino derivatives, has been reported.[8]

In an analogoues manner, 4-amino-5-cyano-2-methoxypyrimidine (13) gave 4-amino-2-methoxypyrimidine-5-carboxamide oxime (14) with hydroxylamine. This was converted with acetic anhydride in anhydrous pyridine into 4-amino-2-methoxypyrimidine-5-carboxamide O-acetyl oxime (15), which cyclized either by heating in water or in glacial acetic acid into 4-amino-2-methoxy-5-(5-methyl-1,2,4-oxadiazolyl-3)pyrimidine (16). Heating of the compound 14 in DMFDMA afforded 5-cyano-4-(N,N-dimethylaminomethyleneamino)-pyrimidine (17), with ethyl chloroformate in the presence of triethylamine 4-amino-2-methoxypyrimidine-5-carboxamide O-ethoxycarbonyl oxime (18), and with benzoyl chloride in the presence of triethylamine 4-amino-2-methoxypyrimidine-5-carboxamide O-benzoyl oxime (19) were produced.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^{1}H nmr spectra were obtained on a JEOL JNM C60-HL spectrometer with TMS as internal standard, ir spectra on a PERKIN-ELMER instrument 727B, mass spectra on a HITACHI-PERKIN-ELMER mass spectrometer RMU-6L, and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 240C.

4-Amino-2-methylthiopyrimidine-5-carboxamide oxime (2).- To a solution of 4-amino-5-cyano-2-methylthiopyrimidine (1)[15] (500 mg) in EtOH (10 ml), H_2NOH (250 mg) was added and the mixture stirred at room temperature (12 h). The precipitate was filtered and recrystallized from water to give 2 in 74 % yield, mp 227-229°C, nmr (DMSO-d_6/TMS) δ : 2.4 (s, SMe), 5.9 (br s, NH_2), 7.8 (br s, NH_2), 8.35 (s, H_6), 9.85 (s, OH).

Anal. Calcd. for $C_6H_9N_5OS$: C, 36.17; H, 4.65; N, 35.15. Found: C, 36.38; H, 4.73; N, 34.87.

4-Amino-2-methylthiopyrimidine-5-carboxamide O-acetyl oxime (3). - A mixture of 2 (100 mg), Ac_2O (3 ml) and anhydrous pyridine (1 ml) was stirred at room temperature (12 h). The precipitate was filtered and recrystallized from a mixture of DMF and water to give 3 in 33 % yield, mp 175-177°C, m/e 241 (M^+), nmr (DMSO-d_6/TMS) δ : 2.15 (s, COMe), 2.45 (s, SMe), 6.85 (br s, NH_2), 7.85 (br s, NH_2), 8.39 (s, H_6).

This compound was converted without further purification into 4-amino-2-methylthio-5-(5-methyl-1,2,4-oxadiazolyl-3)pyrimidine (4).

4-Amino-2-methylthio-5-(5-methyl-1,2,4-oxadiazolyl-3)-pyrimidine (4). - a) A solution of 3 (93 mg) in glacial AcOH (2 ml) was heated under reflux (3 h). The volatile components were evaporated *in vacuo* and the dry residue was recrystallized from MeOH to give 4 in 75 % yield, mp 196-199°C, nmr (DMSO-d_6/TMS) δ : 3.48 (s, SMe), 2.65 (s, 5'-Me), 5.25 (br s, NH_2), 8.66 (s, H_6).

Anal. Calcd. for $C_8H_9N_5OS$: C, 43.04; H, 4.06; N, 31.37. Found: C, 43.01; H, 4.15; N, 31.42.

b) A suspension of 2 (50 mg) in DMADMA (1 ml) was stirred at room temperature (5 days). The precipitate was filtered and recrystallized from MeOH to give 4 in 15 % yield. The ir spectrum of the compound was identical with that of the compound described under a).

4-Acetylamino-2-methylthio-5-(5-methyl-1,2,4-oxadiazolyl-3)-pyrimidine (5). - A solution of 2 (90 mg) in Ac_2O (3 ml) was heated under reflux (3 h). Ether (5 ml) was added to the oily residue from evaporation of volatile components *in vacuo* and the solid filtered to give 5 in 45 % yield, mp 113-116°C, m/e 265 (M^+), nmr (DMSO-d_6/TMS) δ : 2.60 (s), 2.65 (s), 2.70 (s) (SMe, 5'-Me, COMe), 9.1 (s, H_6), 10.8 (br s, NH_2).

Anal. Calcd. for $C_{10}H_{11}N_5O_2S$: C, 45.27; H, 4.18; N, 26.40. Found: C, 44.86; H, 4.29; N, 26.06.

4-Amino-2-methylthio-5-(1,2,4-oxadiazolyl-3)-pyrimidine (6). - A suspension of 2 (100 mg) in $HC(OEt)_3$ (3 ml) was heated under reflux (3 h). The volatile components were evaporated *in vacuo*, MeOH (3 ml) was added to the oily residue and the solid filtered to give 6 in 28 % yield, mp 198-205°C, m/e 209 (M^+), nmr (DMSO-d_6/TMS) δ : 2.45 (s, SMe), 8.70 (s, H_6), 9.75 (s, H_5,).

Anal. Calcd. for $C_7H_7N_5OS$: C, 40.18; H, 3.37; N, 33.47. Found: C, 40.35; H, 3.41; N, 33.22.

4-Amino-2-methylthiopyrimidine-5-carboxamide O-benzoyl oxime (7). - To a suspension of 2 (100 mg) in $CHCl_3$ (2 ml), PhCOCl (71 mg) and NEt_3 (98 %, 50 mg) were added. The mixture was stirred at room temperature (12 h). Water (2 ml) was added to the dry residue from evaporation of volatile components in vacuo. The solid was filtered and recrystallized from EtOH to give 7 in 83 % yield, mp 203-205°C, nmr (DMSO-d_6/TMS) δ : 2.43 (s, SMe), 6.95 (br s, NH_2), 7.40-7.65 (m, Ph; overlapped by br s, NH_2), 8.0-8.3 (m, Ph), 8.40 (s, H_6).
Anal. Calcd. for $C_{13}H_{13}N_5O_2S$: C, 51.47; H, 4.32; N, 23.09. Found: C, 51.68; H, 4.43; N, 22.67.

4-Amino-2-methylthio-5-(5-phenyl-1,2,4-oxadiazolyl-3)-pyrimidine (8). - A mixture of 7 (100 mg) and glacial AcOH (3 ml) was heated under reflux (5 h). Methanol (3 ml) was added to the dry residue from evaporation of volatile components in vacuo. The solid was filtered and recrystallized from MeOH to give 8 in 59 % yield, mp 210-212°C, nmr (DMSO-d_6/TMS, 100°C) δ : 2.47 (s, SMe), 7.35 (br s, NH_2),7.45-7.70 (m, Ph), 8.0-8.2 (m, Ph), 8.73 (s, H_6).
Anal. Calcd. for $C_{13}H_{11}N_5OS$: C, 54.72; H, 3.89; N, 24.54. Found: C, 54.45; H, 4.01; N, 24.36.

4-Amino-2-methylthiopyrimidine-5-carboxamide O-ethoxycarbonyl oxime (9). - To a suspension of 2 (200 mg) in $CHCl_3$ (4 ml), ClCOOEt (120 mg) and NEt_3 (98 %, 100 mg) were added, and the mixture was stirred at room temperature (12 h). Water (3 ml) was added to the dry residue from evaporation of volatile components in vacuo. The solid was filtered and recrystallized from EtOH to afford 9 in 71 % yield, mp 174-177°C, nmr (DMSO-d_6/TMS) δ : 1.27 (t, $CH_2\underline{Me}$, J = 6.5 Hz), 2.45 (s, SMe), 4.22 (q, $\underline{CH_2}Me$, J = 6.5 Hz), 6.85 (br s, NH_2), 7.75 (br s, NH_2), 8.38 (s, H_6).
Anal. Calcd. for $C_9H_{13}N_5O_3S$: C, 39.85; H, 4.83; N, 25.81. Found: C, 39.94; H, 4.96; N, 25.86.

5-Cyano-4-(N,N-dimethylaminomethyleneamino)-2-methylthiopyrimidine (10). - A mixture of 2 (100 mg) and DMFDMA (300 mg) was heated under reflux (4 h). The solid was,

after cooling, filtered and recrystallized from a mixture of $CHCl_3$ and petroleum ether to give 10 in 14 % yield. The ir spectrum was identical with that of the compound described in lit.[12], mp 104-105°C, nmr ($CHCl_3$/TMS) δ : 2.50 (s, SMe), 3.20 (s, NMe_2), 8.37 (s, H_6), 8.75 (s, N=CH).

4-Hydroxyiminomethyleneamino-2-methylthiopyrimidine-5-carboxamide oxime (11). - A mixture of 10 (120 mg) and H_2NOH (100 mg) in EtOH (3 ml) was stirred at room temperature (5 h). The precipitate was filtered and recrystallized from a mixture of DMF and water to afford 11 in 84 % yield, mp 230-231°C, nmr (DMSO-d_6/TMS) δ : 2.50 (s, SMe), 6.15 (br s, NH_2) , 8.0 (d, NHCH, J = 9.6 Hz), 8.63 (s, H_6), 10.16 (s, OH), 10.68 (s, OH), 11.3 (d, NHCH, J = 9.6 Hz).
Anal. Calcd. for $C_7H_{10}N_6O_2S$: C, 34.71; H, 4.16; N, 34.69. Found: C, 34.50; H, 4.22; N, 34.68.

4-Acetoxyiminomethyleneamino-2-methylthiopyrimidine-5-carboxamide O-acetyl oxime (12). A mixture of 11 (100 mg), Ac_2O (2 ml), and anhydrous pyridine (1 ml) was stirred at room temperature (12 h). The solid was filtered and recrystallized from EtOH to give 12 in 39 % yield, mp 181-184°C, nmr (DMSO-d_6/TMS) δ : 2.15 (s) and 2.20 (s) (2 COMe), 2.55 (s, SMe), 7.2 (br s, NH_2), 8.5 (d, NHCH, J = 9.5 Hz), 8.8 (s, H_6), 11.3 (d, NHCH, J = 9.5 Hz).
Anal. Calcd. for $C_{11}H_{14}N_6O_4S$: C, 40.49; H, 4.32; N, 25.75. Found: C, 40.30; H, 4.32; N, 25.37.

4-Amino-2-methoxypyrimidine-5-carboxamide oxime (14). - To a suspension of 13[15] (100 mg) in EtOH (4 ml) H_2NOH (50 mg) was added and the mixture was stirred (8 h) at room temperature. The precipitate was filtered and recrystallized from EtOH to give 14 in 47 % yield, mp 228-231°C, nmr (DMSO-d_6/TMS) δ : 3.75 (s, OMe), 5.8 (br s, NH_2), 7.75 (br s, NH_2), 8.25 (s, H_6), 9.65 (s, OH).
Anal. Calcd. for $C_6H_9N_5O_2$: C, 39.34; H, 4.95; N, 38.23. Found: C, 39.65; H, 4.81; N, 37.83.

4-Amino-2-methoxypyrimidine-5-carboxamide O-acetyl oxyme (15).- A mixture of 14 (100 mg) Ac_2O (3 ml) and anhydrous pyridine (1 ml) was stirred (5 h) at room temperature. The solid was filtered and washed with MeOH to give 15 in 57 % yield, mp 200-202°C, nmr (DMSO-d_6/TMS) δ : 2.10 (s, COMe), 3.77 (s, OMe), 6.75 (br s, NH_2), 7.75 (br s, NH_2), 8.35 (s, H_6).

Anal. Calcd.for $C_8H_{11}N_5O_3$: C, 42.67; H, 4.92; N, 31.10. Found C, 42.89; H, 4.78; N, 30.97.

4-Amino-2-methoxy-5-(5-methyl-1,2,4-oxadiazolyl-3)-pyrimidine (16). - A solution of 15 (280 mg) in glacial AcOH was heated under reflux (4 h). The solvent was evaporated in vacuo and the dry residue recrystallized from DMF to give 16 in 44 % yield, mp 236-241°C, nmr (DMSO-d_6/TMS, 110°C) δ : 2.57 (s, 5'-Me), 3.82 (s, OMe), 5.4 (br s, NH_2), 8.60 (s, H_6).
Anal. Calcd. for $C_8H_9N_5O_2$: C, 46.38; H, 4.38; N, 33.80. Found: C, 46.15; H, 4.52; N, 33.68.

5-Cyano-2-methoxy-4-(N,N-dimethylaminomethyleneamino)-pyrimidine (17). - A mixture of 14 (100 mg) and DMFDMA (300 mg) was heated under reflux (4 h). The crystals were, after cooling, filtered and washed with MeOH to give the compound 17 in 21 % yield. Its ir spectrum was identical with that of the compound described in lit.[12], mp 135-137°C, nmr (DMSO-d_6/TMS) δ : 3.77 (s, OMe), 5.0 (br s, NH_2), 5.67 (br s, NH_2), 8.35 (s, H_6).

4-Amino-2-methoxypyrimidine-5-carboxamide O-ethoxycarbonyl oxime (18).- To a suspension of 14 (80 mg) in $CHCl_3$ (3 ml), ClCOOEt (332 mg) and NEt_3 (98 %, 310 mg) were added and the mixture was heated under reflux (18 h). The volatile components were evaporated in vacuo. Water was added to the dry residue, the precipitate was filtered and washed with MeOH to give 18 in 21 % yield, mp 167-168°C, nmr (DMSO-d_6/TMS) δ : 1.25 (t, $CH_2\underline{Me}$, J_{CH_2Me} = 6.5 Hz), 3.72 (s, OMe), 4.14 (q, $\underline{CH_2}Me$, J_{CH_2Me} = 6.5 Hz), 6.7 (br s, NH_2), 7.6 (br s, NH_2), 8.25 (s, H_6).
Anal. Calcd. for $C_9H_{13}N_5O_4$: C, 42.35; H, 5.13; N, 27.44. Found: C, 42.57; H, 5.19; N, 27.49.

4-Amino-2-methoxypyrimidine-5-carboxamide O-benzoyl oxime (19). - To a suspension of 14 (100 mg) in $CHCl_3$ (3 ml), PhCOCl (100 mg) and NEt_3 (98 %, 80 mg) were added. The mixture was stirred (12 h) at room temperature. To the dry residue, water (2 ml) was added and the precipitate filtered and recrystallized from EtOH to give 19 in 75 % yield, mp 195-198°C, m/e 287 (M^+), nmr (DMSO-d_6/TMS) δ : 3.80 (s, OMe), 6.9 (br s, NH_2), 7.4-7.7 (m) and 8.0-8.3 (m) (Ph), 7.9 (br s, NH_2), 8.44 (s, H_6).

Anal. Calcd. for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found C, 54.49; H, 4.75; N, 24.24.

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