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CHLORINATION AND SUBSEQUENT CYCLIZATION TO 1,3,4-OXADIAZOLES OF N^1-ACYL-N^3-CYANOGUANIDINES AND RERATED COMPOUNDS

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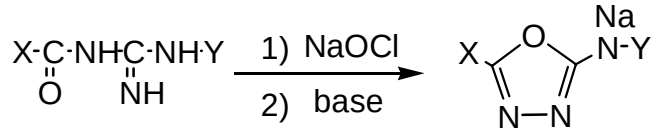
Abstract- N^1-Acyl-, N^1-alkoxycarbonyl-, and N^1-(*N*,*N*-dialkylcarbamoyl)guanidines bearing electron-withdrawing cyano or sulfonyl group at the N^3-position were found to provide corresponding rearranged products, 1,3,4-oxadiazoles, when these guanidines were chlorinated by sodium hypochlorite followed by treating with base. Assignments of obtained compounds were accomplished by means of some reactions such as acid hydrolysis, alkoholysis, and catalytic hydrogenations, and of MS spectra.

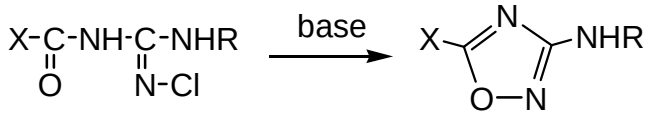
We previously reported that N^1-acyl-N^3-cyanoguanidines reacted with hydroxylamine hydrochloride to afford various type of 1,2,4-oxadiazoles.[1] In this connection, we subsequently investigated the chlorination and cyclization of N^1-benzoyl-N^3-cyanoguanidine in order to obtain 3-cyanoamino-5-phenyl-1,2,4-oxadiazole. However, the product thus obtained was found to be 2-cyanoamino-5-phenyl-1,3,4-oxadiazole. It was also clarified that N^1-acylguanidines, N^1-alkoxycarbonylguanidines (*N*-amidinocarbamates), and N^1-(*N*,*N*-dimethylcarbamoyl)guanidine (1-amidino-3,3-dimethylurea) bearing electron-withdrawing cyano or sulfonyl group at the N^3-position gave corresponding rearranged 1,3,4-oxadiazoles.



X : Ph, Me, MeO, EtO, Me_2N Y : C≡N , SO_2Ar

Scheme 1

Fuchigami and Odo first reported in 1974 that treatment of *N*-benzoyl-*N'*-chlorobenzamidine with base gave 3,5-diphenyl-1,2,4-oxadiazole.[2] This reaction has been proved to be applicable to *N*-chloro derivatives of benzoylguanidines **(1),**[3] alkoxycarbonylguanidines **(2),**[3] and carbamoylguanidines **(3)**[4] providing 3-amino-1,2,4- oxadiazoles **(4)**.

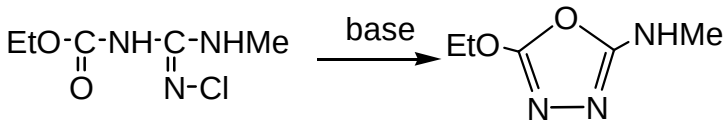


! : X=Ph
2 : X=MeO,R=Ar
3 : $X=NH_2$

4

Scheme 2

On the other hand, L'abbe *et al.* found that the structure of the reaction product of N^2-chloro-N^1-ethoxycarbonyl-N^3-methylguanidine **(2d)** with base was 2- ethoxy-5-methylamino-1,3,4-oxadiazole **(5d)** on the bases of X-Ray diffraction analysis.[5]

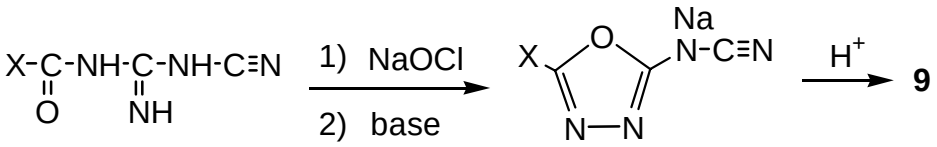


2d **5d**

Scheme 3

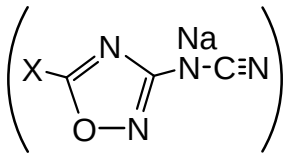
Shortly later, Tilley *et al.*[4] reinvestigated that N^2-chloro-N^1-methoxycarbonyl-N^3-phenylguanidine **(2a)** gave corresponding 1,2,4-oxadiazole as reported by Goetz *et al.*[3] and they suggested that N^1-alkoxycarbonyl-N^2-chloro-N^3-substituted guanidines in which the N^3-alkyl derivative underwent rearrangement, whereas the corresponding N^3-aryl derivative cyclized with essentially no rearrangement. They also suggested that electron-withdrawing groups on the aromatic ring of the N^3-aryl-N^1-carbamoylguanidines **(3)** seemed to favor 1,2,4-oxadiazole formation. Contrary to above description, it was interested that the N^1-acylguanidines bearing strong electron-withdrawing groups at N^3-position were found to give exclusively corresponding rearranged 1,3,4-oxadiazoles in present work.

To begin with, N^1-benzoyl-N^3-cyanoguanidine **(6a)** was chlorinated with sodium hypochlorite and treated with base. Chlorination was performed in a few minutes at room temperature. Thin layer chromatography of the reaction mixture at this point revealed one spot which developed orange color by treatment with o-tolidine showing to be *N*-chloro compound. Subsequent cyclization proceeded by treating the *N*-chloro compound with sodium carbonate at rt. However, the best cyclization condition was proved to carry out with sodium hydroxide at elevated temperature(Table 1, Runs 1-3).
Similarly, N^1-acetyl-N^3-cyanoguanidine (**6b**), N^1-alkoxycarbonyl-N^3-cyanoguanidines **(7c,d)**, and N^3-cyano-N^1-(*N*,*N*-dimethyl)- guanidine **(8e)** were chlorinated and treated with sodium hydroxide. It was clarified that all of these compounds obtained here were the rearranged products, 2-cyanoamino-1,3,4-oxadiazoles **(9)**, instead of the expected 1,2,4-oxadiazoles **(10)**, whose structures were confirmed by some reactions shown below and spectral analysis.



6a : X=Ph
6b : X=Me
7c : X=MeO
7d : X=EtO
8e : X=Me_2N

sodium salt of **9**

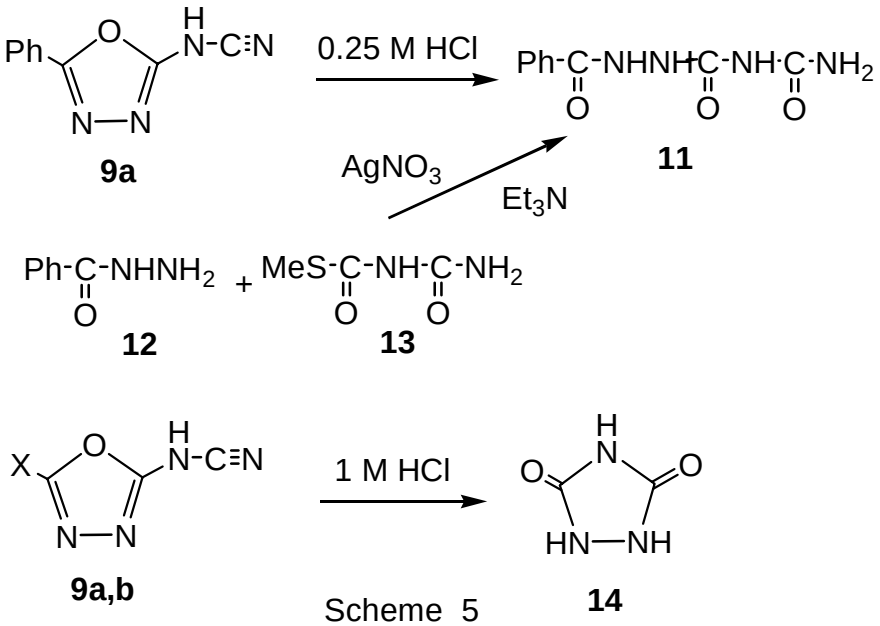


10

Scheme 4

Hydrolysis of **9a** (X = Ph) in 0.25 M (0.25 mol dm^{-3}) hydrochloric acid gave 1-benzoyl-4-carbamoylsemicarbazide **(11)**. The characterization of **11** could be accomplished by spectral analysis and by an independent synthesis. A molecular ion could not be observed in MS spectrum of **11**, but the fragment peak at m/z 136 was thought to be $PhCONHNH_2^{+\cdot}$. Compound **(11)** could be obtained by the reaction of benzohydrazide **(12)** with *S*-methyl *N*-carbamoylcarbamothioate **(13)** in the presence of

silver nitrate and triethylamine. In the absence of these reagent, compound **(12)** did not react with **13** even at elevated temperatures. Further hydrolysis of **9a** or **9b** (X = Me) gave 1,2,4-triazolidine-3,5-dione **(14)**.

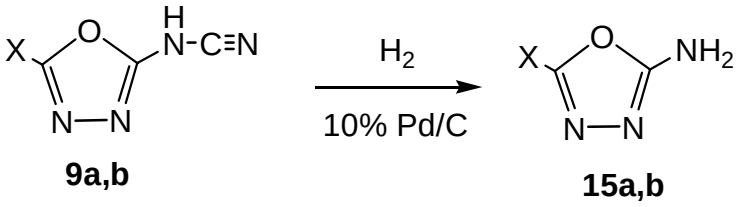


9a

9a,b

Scheme 5

The 1,2,4-oxadiazole is known to be readily hydrogenated and to open the ring,[6] whereas catalytic hydrogenation of **9a,b** occurred merely at cyano groups to afford corresponding known compounds, 2-amino-1,3,4-oxadiazoles **(15a,b)**, at room temperature under atmospheric pressure, confirming the assignment of **9a,b** as rearranged products.

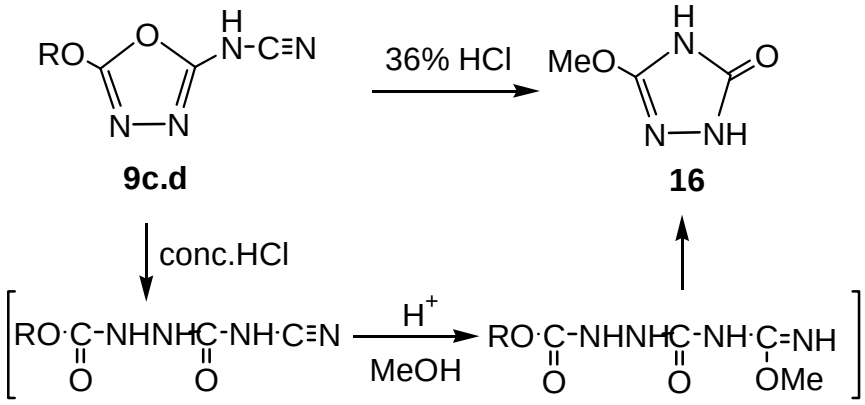


9a,b

15a,b

Scheme 6

The structural assignment of alkoxy derivatives **(9c,d)** was confirmed on treatment with concentrated hydrochloric acid in methanol to give 5-methoxy-1,2,4-triazol-3(2*H*)-one **(16)**. The formation of **16** could be thought to proceed as shown in Scheme **7** ; ring opening occurred in the first step and addition of methanol to the cyano group followed by reclosure could finally give **16**. Formation of **16** showed that compounds **(9c,d)** possess, at least, N-N bond.



9c.d

Scheme 7

Table 1. Chlorination and Cyclization of N^1-Acyl-N^3-substituted Guanidines

Run	Compd.	X	Temp.[b]	Time/h	Product	Yield/%
1	**6a**	Ph	RT	19	**9a**	56
2[a]			Reflux	2	**9a**	63
3			Reflux	2	**9a**	80
4	**6b**	Me	Reflux	3	**9b**	68
5	**7c**	MeO	RT	3	**9c**	55
6	**7d**	EtO	RT	4	**9d**	67
7	**8e**	Me_2N	RT	12	**9e**	64
8	**17a**	Ph	Reflux	0.5	**19a**	86
9	**17a'**	Ph	Reflux	0.5	**19a'**	94
10	**18d**	EtO	RT	10	**19d**	63

a) Sodium carbonate was used as base instead of sodium hydroxide.
b) in aqueous methanol

MS spectra show characteristic features which aid in structure identification of 1,3,4-oxadiazoles. Thus, the base peak in the spectrum of phenyl derivatives **(9a)** was at m/z 118. This fragment was proven to be $C_7H_6N_2$(m/z 118.0545; calcd 118.0531) by high-resolution MS spectrum which was thought to be **Ⅰ** (X=Ph) shown in Figure 1. It was reported[7] that 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one lost CO_2 to form fragment ion m/z 119, probably C_6H_5-C=N=$NH^{+\cdot}$, which was further rearranged into C_6H_5-N=C=$NH^{+\cdot}$. Other compounds **(9b,c,e)**, and (**15)** also exhibited similar fragments (**Ⅰ**). In the case of **9d**, initial loss of ethylene from the parent ion resulted in fragment (**Ⅱ**) whose composition was also established by high-resolution MS spectrum.

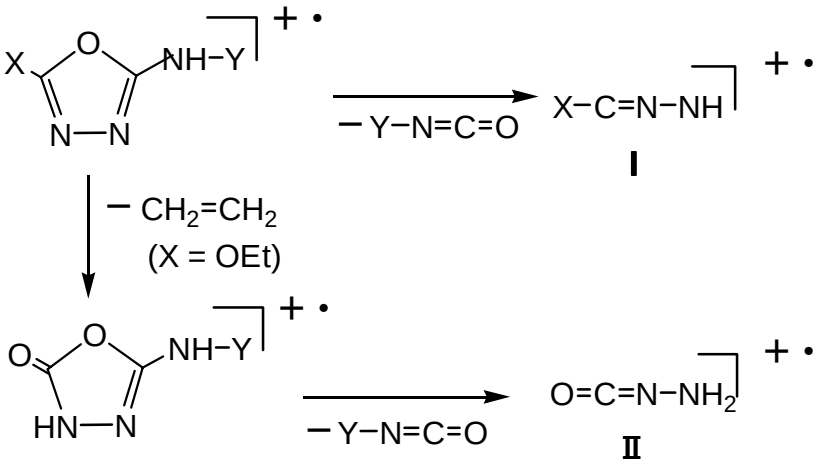
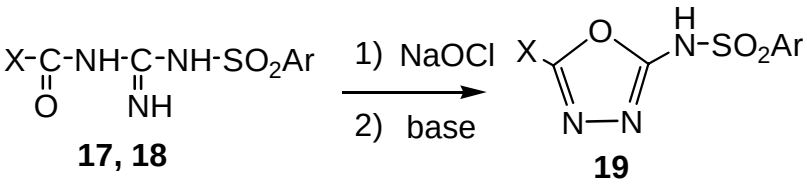


Figure 1 MS Fragmentation of 1,3,4-Oxadiazoles

In order to know whether the acylguanidines bearing strong electron-withdrawing group would generally provide

corresponding rearranged products, N^1-benzoyl-N^3-phenylsulfonylguanidine **(17a)**, N^1-benzoyl-N^3-(*p*-nitrophenylsulfonyl)-guanidine **(17a')**, and N^1-ethoxycarbonyl-N^3-phenylsulfonylguanidine **(18d)** were subjected to the cyclization conditions described in case of N^1-cyano compounds. And the resulting products were confirmed as predicted 1,3,4-oxadiazoles **(19)** by MS spectra. It is recognized that increasing electron-withdrawing property tends to increase yield (Table 1, Runs 8,9). 5-Phenyl-2-phenylsulfonylamino-1,3,4-oxadiazole**(19a)** was identified by direct comparison with the sample synthesized independently by the reaction of 2-amino-5-phenyl-1,3,4-oxadiazole**(15)** with benzenesulfonyl chloride. All of the products couldn't be hydrogenated.



17, 18 **19**

17a,19a: X=PH, Ar=Ph **18d,19d** : X=EtO, Ar=Ph

17a', 19a' : X=Ph, Ar=4-NO_2-Ph

Scheme 8

Conventional chlorination and cyclization were performed either by successive treatment of free acylguanidines with *t*-butyl hypochlorite and potassium *t*-butoxide or treatment of the crude chloroguanidines obtained by the reaction of the guanidine hydrochloride(or the mixture of equimolar amount of the guanidine and hydrochloric acid in aqueous methanol) with sodium hydroxide or sodium carbonate. Whereas, in the present work, the acylguanidines bearing electron-withdrawing group behave as weak acid and could be successfully chlorinated with sodium hypochlorite in the absence of acid to form probably sodium salt of chlorinated acylguanidines. In one experiment using **7d**, the crude sodium salt was obtained by freeze-drying of reaction mixture. IR spectrum of this product showed at 1690 and 1600cm^{-1}, but none in the region (*ca.* 1750-1800 cm^{-1}) where C=N functions of diaziridinimines are known to absorb.[8] This salt gave original guanidines **(7d)** on treatment with dilute acetic acid, and corresponding 1,3,4-oxadiazole **(9d)** on treatment with sodium hydroxide. These results reveal that **7d** couldn't be chlorinated with hypochloric acid, and rearrangement would eventually occur after treating sodium salt of chlorinated acylguanidines with sodium hydroxide.

The formation of 1,3,4-oxadiazoles **(9)** and **(19)** under these conditions could be explained most likely by a pathway suggested by Tilly for the formation of 1,2,4-oxadiazoles and rearranged by-products, triazolones, on treatment of the hydrochlorides of arylamidinoureas with sodium hypochlorite and base. Chlorination of acylguanidines is expected to occur on unsubstituted basic N^2-atom and should give predominantly **20**(Figure 2). In case of N^3-alkyl or aryl derivatives, these salts could form as intermediates when free N^2-chloro derivatives were treated with base. A factor in determining whether these intermediates will give 1,2,4-oxadiazoles **(4)** or rearranged products **(5**, **9** or **19)** seems to be electron density on carbamoyl group as assumed by Tilly. The corresponding aryl derivatives, especially having electron-withdrawing groups on the N^3-aryl group, cause an intramolecular nucleophilic attack of the anionic carbamoyl O-atom in **20** and cyclize without any rearrangement. Whereas in case of **2d** alkyl substituent could enhance nucleophilicity of carbamoyl N-atom and intramolecular displacement of chloride by the N-atom would lead to the diazirine **(21).** Further reaction with base would cause opening to the carbodiimide **(24)** which could finally close intramolecularly to **5d**.

The rearrangement of the present work could be also explained on the assumption described above. Sodium salts of

N^2-chloro-N^1-acylguanidines **(20)** bearing strong electron-withdrawing group on N^3-position are relatively stable and could eventually reacted after forming dianion **(22)** on treating with sodium hydroxide, where –N^--Y(-N^--CN or –N^--SO_2R) group would act as strong electron-donating group leading to the corresponding 1,3,4-oxadiazoles**(9** and **19)** *via* the diazirine **(23)**.

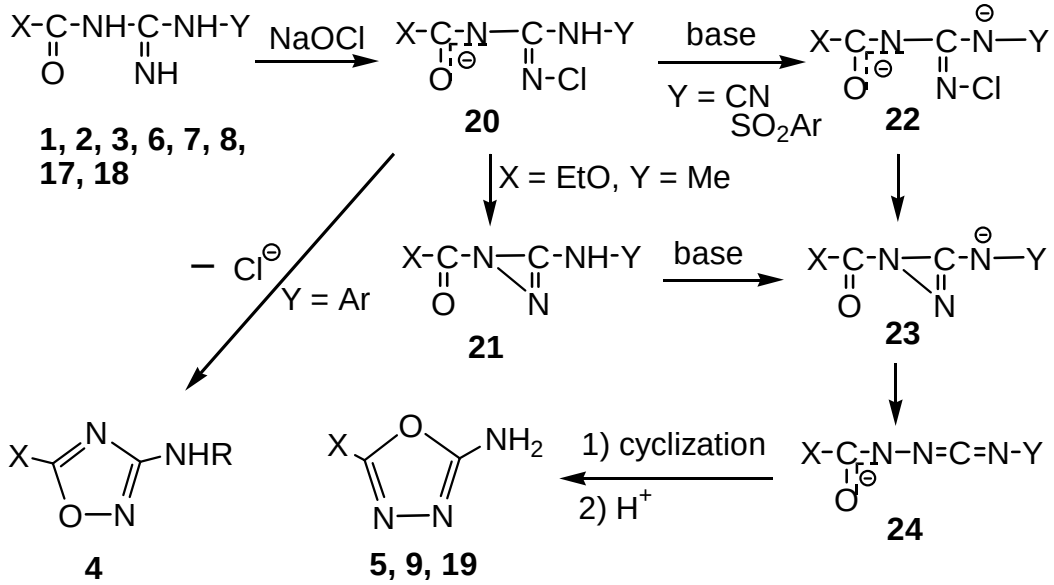


Figure 2 Probable Pathway to 1,2,3- and 1,3,4-Oxadiazole

Taking into consideration that 1,3,4-oxadiazoles have been generally difficult to prepare, the present chlorination and cyclization process may serve the simple and effective method for the preparation of 2-(substituted amino)-1,3,4-oxadiazoles, by selection of acylguanidines and by more detailed investigation for cyclization conditions.

EXPERIMENTAL

Commercially available reagent-grade solvents were used without further purification. The melting points were uncorrected. The ^{1}H NMR and IR spectra were recorded on JEOL JNM-PMX60SI and Hitachi 260-10 spectrophotometer, respectively. The MS spectra were recorded on Shimadzu GCMS-QP 1000A or Hitachi M-80B.

*Preparation of **8e*** A suspension of 8.41 g(0.1 mol) of N^1-cyanoguanidine and 13.0 g (0.2 mol) of 86% potassium hydroxide in 80 mL of acetone were stirred for 1 h at rt, then 9.4 mL of *N*,*N*-dimethylcarbamyl chloride was added dropwise. After 40 min, 70 mL of water was added and the solution was acidified with acetic acid. A precipitate was collected by filtration and recrystallized from water to give pure **8e**. Yield: 9.26 g (60%). needles. mp 208-209℃. IR (KBr) 3300, 2210, 1690, 1600,1370, and 1180 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=2.92 (6H, s, CH_3), 8.57(2H, br, NH_2), 9.35(1H, br, NH). MS (70 ev) m/z 155(M), 72(Me_2NCO). Anal. Calcd for $C_5H_9N_5O$: C, 38.71; H, 5.85; N, 45.13. Found: C, 38.60; H, 6.02; N, 45.17.

*General procedure for the chlorination and cyclization to prepare **9*** A suspension of 0.05 mol of **6a,b**,[9] **7c,d**,[10] or **8e** in 250-600 mL of methanol was cooled to 0℃(ice/salt bath) and 0.05 mol of aqueous sodium hypochlorite was added dropwise with stirring. After completion of addition, the mixture was stirred for 30 min. Then 0.05 mol of sodium hydroxide was dissolved and the solution was stirred at rt or refluxed. The solvent was removed in vacuo and the residue was extracted with 400-600 mL of hot ethanol. Upon cooling, precipitated sodium salt of **9** was collected and recrystallized from ethanol. The filtrate was dried up and the residue was redissolved in water, and trace amounts of

impurities were filtered off. The filtrate was acidified with 1 M hydrochloric acid to precipitate free acid of **9**. In the case of **9d**, precipitate did not appear and was obtained after concentration of the aqueous solution (Tables 1 and 2). All sodium salts of **9** have water of crystallization after recrystallization from ethanol.

Sodium salt of **9a** (monohydrate): mp 260-261℃. IR (KBr) 3500, 2200, 1600, and 1560 cm^{-1}. ^1H NMR (DMSO-d_6) δ=3.30 (2H, s, H_2O), 7.28-7.81(5H, m, Ph). Anal. Calcd for $C_9H_7N_4O_2Na$: C, 47.74; H, 3.12; N, 24.85. Found : C, 47.89; H, 3.04; N, 24.95.

Sodium salt of **9b** (monohydrate): mp 262-263℃. IR (KBr) 3530, 2180, 1625, and 1560 cm^{-1}. Anal. Calcd for $C_4H_5N_4O_2Na$: C, 29.27; H, 3.07; N, 34.14. Found: C, 28.93; H, 2.93; N, 33.82.

Table 2 Physical and Analytical Data of 1,3,4-Oxadiazoles

Compound	X	mp /℃	IR(KBr) /cm-1	MS(70eV) m/z(%)	cation	NMR(DMSO-d_6) /ppm	Elemental Analysis found (calcd) C %	H %	N %
9a	Ph	242	1680	186(97)	$M^{+\cdot}$	7.38-7.88(5H,m,Ph)	58.25	3.01	30.27
		-243	980	118(100)	I [a]	11.75(1H,br,NH)	(58.06)	(3.25)	(30.09)
9b	Me	158	1675	124(100)	$M^{+\cdot}$	2.19(3H,s,CH_3)	38.96	3.01	45.42
		-159	990	56(97)	I [b]	9.50(1H,br,NH)	(38.72)	(3.25)	(45.15)
9c	MeO	121	1630	140(42)	$M^{+\cdot}$	___ [f]	34.02	2.68	40.18
			980	72(2)	I [c]		(34.29)	(2.88)	(39.99)
9d	EtO	122	1640	154(88)	$M^{+\cdot}$	___ [f]	38.82	3.69	36.40
		-123	975	58(42)	II [d]		(38.96)	(3.93)	(36.35)
9e	Me_2N	154	2210	153(100)	$M^{+\cdot}$	2.92(6H,s,CH_3)	39.39	4.67	45.86
		-155	1620	85(20)	I [e]	8.20(1H,br,NH)	(39.22)	(4.61)	(45.73)
			975			7.38-8.01(5H,m,Ph)			
19a	Ph	220	1640	301(74)	$M^{+\cdot}$	7.48-7.59(6H,m,Ph)	55.80	3.68	13.94
			920	118(14)	I [a]	8.02(2H,d,Ph)	(55.67)	(3.66)	(13.97)
19a'	Ph	273	1645	346(41)	$M^{+\cdot}$	7.53-7.61(3H,m,Ph)	48.55	2.91	16.18
		-274	1155	118(30)	I [a]	7.86(2H,d,Ph)	(48.59)	(2.87)	(16.35)
			920			8.23(2H,d,Ph)			
						8.39(2H,d,Ph)			
19d	EtO	117	1615	58(17)	II [d]	1.41(3H,t,CH_3)	44.60	4.12	15.60
		-118	1160			4.40(2H,q,CH_2)	(44.40)	(4.20)	(15.60)
			910			7.38-8.01(5H,m,Ph)			
						9.70(1H,br,NH)			

High-resolution MS, m/z(calcd value) ; a) 118.0545($C_7H_6N_2$ 118.0531), b) 56.0358($C_2H_4N_2$ 56.0373), c) 72.0289($C_2H_4N_2O$ 72.0322), d) 58.0156(CH_2N_2O 58.0166), e) 85.0633($C_3H_7N_3$ 85.0640)

f) decomposed on dissolving in DMSO.

Sodium salt of **9d** (monohydrate): mp 170-171**℃**. IR (KBr) 3480, 2160, 1665, and 1560 cm^{-1}. Anal. Calcd for $C_5H_7N_4O_3Na$: C, 30.94; H, 3.64; N, 28.86. Found: C, 31.07; H, 3.53; N, 29.08.

*General procedure for catalytic hydrogenation of **9***. A stirred solution of **9** (0.01 mol) in methanol (50 mL) and 1 M hydrochloric acid (10 mL) was hydrogenated over 10% Pd/C (1.20 g) at atmospheric pressure for 20 h. After filtration, the filtrate was neutralized with 2 M ammonia to afford **11a**. Yield: 68%. mp 237-238**℃** (deccomp, lit.,[11] 241-243**℃**).

In the case of **11b**, after neutralization, the solution was evaporated to dryness and residue was extracted with hot acetone. The filtrate was dried up and the residue was recrystallized with acetonitrile to afford pure **11b**. Yield: 58%. mp 183-184**℃** (lit.,[12] 183**℃**).

*Acid Hydrolysis of **9**.* Compound **(9a)** (1.86 g, 0.01 mol) in 0.25 M hydrochloric acid (150 mL) was refluxed for 1.5 h. After cooling, 1.24 g (54%) of **11** was obtained and recrystallized from water. mp 204.5-205**℃**. IR (KBr) 3400, 3225, 1700, 1645, 1610, 1530, 1490, and 710 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=6.82 (2H, s, NH_2) 7.17-8.17(5H, m, Ph), 8.78(1H, s, NH), 8.93(1H, s, NH), 10.2(1H, s, NH). MS (70 ev) m/z136($PhCONHNH_2$). Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.21. Found: C, 48.84; H, 4.56; N, 25.57%.

Compound **(9a)** (1.86 g, 0.01 mol) in 1 M hydrochloric acid (50 mL) was refluxed for 3.5 h. After cooling, 0.90 g (74%) of benzoic acid was collected by filtration. The filtrate was extracted with benzene to obtain an additional benzoic acid (0.13 g,10%). Concentration of the aqueous layer afforded 0.79 g (78%) of **15**, which was identified, after recrystallization from 1-propanol, by comparing its IR spectrum with that of authentic sample. mp 243**℃** (lit.,[13] 244 **℃**).

Compound **(9b)** (1.24 g, 0.01 mol) in 2 M hydrochloric acid (30 mL) was also refluxed for 4 h. Solvent was removed in vacuo and 0.90 g (89%) of **15** (mp 236-237**℃**) was obtained after washing residual solid.

*Independent Preparation of **11**.* To a stirred suspension of 1.36 g (0.01 mol) of **12** and 1.34 g (0.01 mol) of **13**[14] together with triethylamine (1.4 mL, 0.01 mol) in acetonitrile (40 mL) was added dropwise a solution of silver nitrate (1.70 g, 0.01 mol) in acetonitrile (15 mL) at rt. The precipitates were collected and extracted with hot water (150 mL × 3). On cooling, the extract deposited **11** (1.45 g, 65.3%), which was identical with the compound obtained from acid hydrolysis of **9b**. mp 203-204**℃**.

*Preparation of **16*** To 0.01 mol of **9c,d** in 100 mL methanol was added 0.01 mol of 36% hydrochloric acid. The mixture was allowed to stand for 3 days at rt and neutralized with 2 M ammonia. The whole was then evaporated and the product extracted with 100 mL of hot acetone. The extract was dried up and recrystallized from acetonitrile providing 31-32% of **16** as granules (mp 213-214**℃**), which was identified by direct comparison with an authentic sample prepared according to the method in literature (mp 219-220**℃**).[15]

*Preparation of **17a, 17a'**,and **18d*** To a solution of 0.01 mol of N^1-acylguanidine in acetone (50 mL) was added 0.82 g (0.02 mol) of sodium hydroxide, then 0.01 mol of benzenesulfonyl chloride (or *p*-nitrobenzenesulfonyl chloride dissolved in acetone) was added dropwise with stirring at 0**℃**. After stirring for 8-15 h, 20mL of water was added to dissolve precipitation. The solution was acidified with acetic acid and a precipitate was collected by filtration and recryatallized from appropriate solvent. In case of ethyl **18d**, the crude product was obtained after the precipitation was extracted with 12 mL of chloroform and dried up.

17a : needles (acetonitrile). mp 219-220**℃** (decomp, depending on heating rate. lit.,[16],233-234**℃**). IR (KBr) 3375, 3250, 1680, 1565, 1270, 1150, and 1090 cm^{-1}. MS (70 ev) m/z 303(M).

17a': yellow needles (acetonitrile). mp 223-224. IR (KBr) 3380,3290, 1680, 1615, 1565, 1285, 1150, and 1085 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_4O_5S$: C, 48.27; H, 3.47; N, 16.08. Found : C, 48.24; H, 3.52; N, 16.22.

18d ; granules (ethanol). mp 141-142. IR (KBr) 3400, 3290, 1720, 1620, 1580, 1280, 1160, and 1090 cm^{-1}. MS (70 ev) m/z 271(M). Anal. Calcd for $C_{10}H_{13}N_3O_4S$: C, 44.40; H, 5.02; N, 14.96. Found : C, 44.27; H, 4.83; N, 15.49.

*General procedure for the chlorination and cyclization to prepare **19*** A suspension of 0.005 mol of **17a,17a'**, or **18d** in 600-800mL of methanol was cooled to 0℃ and 3mL of 1.67 M sodium hypochlorite (0.005 mol) was added dropwise with stirring. After stirring for 30 min, 2.5 mL of 2 M methanolic sodium hydroxide (0.005 mol) was added and the mixture was refluxed (or stirred at rt in case of **18d**) for 30 min. The solvent was removed in vacuo and the residue was dissolved in water and acidified with hydrochloric or acetic acid to precipitate the free acid of **19** (see Tables 1 and 2).

*Independent synthesis of **19a*** To a solution of 0.32 g (2 mmol) of **15** in acetone (50 mL) was added 0.16 g (4 mmol) of sodium hydroxide and 0.26mL (2 mmol) of bennzenesulfonyl chloride was added dropwise with stirring. After stirring for 20 h at rt, the reaction mixture was dissolved by adding 20 mL of water and acidified with 2 M hydrochloric acid to obtain **19a**. Yield: 0.12 g (17.4%). mp : 215-216℃.

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