Preparation and Reactions of Isocyano-1,3,5-triazines

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The title compounds **3** were prepared in low yields from the carbylamine reaction of amino-1,3,5-triazines **1** under phase-transfer conditions. Isocyanotriazine **3a** readily reacted with amines in the presence of copper salts to afford triazinylformamidines **4**, and also with active methylene compounds in the presence of base to afford addition products **5** and **6**, indicating the high electrophilicity of **3**. The reactions of isocyanotriazine with electrophiles such as carbonyl compounds and bromine are also described.

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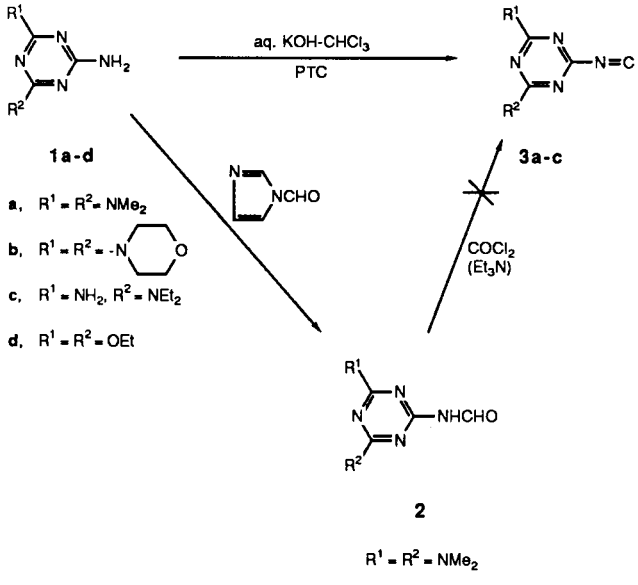
Although numerous isocyanides have been known, relatively little has appeared on the heteroaryl isocyanides. Wentrup *et al.* [1] have prepared an hitherto unknown class of isocyanides including indole and pyrazole systems from the thermolysis of 4-iminoisoxazolones. Furthermore, Christian *et al.* [2] have reported that triisocyano-1,3,5-triazine can be isolated as a pentacarbonylchromium complex from the reaction of cyanuric chloride with pentacarbonylcyano chromate. As part of a work on the functionalized 1,3,5-triazines, we were interested in preparing isocyanotriazine and their properties.

Preparation of Isocyanotriazine.

Starting with readily available amino-1,3,5-triazine **1**, general methods were examined for the synthesis of isocyanotriazine (Scheme 1). *N*-Monosubstituted formamide is well established as a precursor for the formation of isocyanide, *e.g.*, phosgene in the presence of a tertiary amine is the most commonly employed dehydrating agent [3]. The triazinylformamide **2** required for this work was successfully obtained by reacting aminotriazine **1a** with *N*-formylimidazole in 55% yield [4]. However, attempted dehydration of **2** with phosgene in the presence of triethylamine resulted in a complicated mixture of compounds which were difficult to separate.

Scheme 1



Next, we employed the well-known Hofmann carbylamine reaction under phase-transfer conditions according to the literature method [5]. For example, treatment of aminotriazine **1a** with 50% aqueous potassium hydroxide-chloroform in the presence of benzyltriethylammonium chloride as a catalyst at room temperature afforded the multi-component mixture, from which isocyano-1,3,5-triazine **3a** was easily isolated as the first eluent by column chromatography in poor yield (15%). Other products included starting **1a** (25%) and triazinylformamide **2** (8%), probably formed by the hydrolysis of isocyanotriazine **3a**. In an effort to improve the yield, we also examined the reaction conditions including phase transfer catalysts (Table 1). As Table 1 shows, elongation of reaction time resulted in lower yields due to extensive side product formation (entry 4), and significant improvement was observed only when a low reaction temperature was employed (entry 5). Similar treatment of aminotriazine **1b** at room

Table 1

Preparation of 2,4-Bis(dimethylamino)-6-isocyano-1,3,5-triazine (**3a**) [a]

Entry	PTC	Conditions		Conversion (%)	Yield (%) of **3a** [b]
		Time (h)	Temp (°C)		
1	BTEAC [c]	0.5	40	53	8(15)
2	BTEAC	1.0	40	75	10(13)
3	BTEAC	3.0	40	94	13(14)
4	BTEAC	6.0	40	99	9(9)
5	BTEAC	20	0	82	30(37)
6 [d]	BTEAC	6.0	40	85	13(15)
7	18-Crown-6	6.0	40	97	12(12)

[a] Conditions: unless otherwise noted, 50% aqueous potassium hydroxide (12 ml); substrate **1a**, 2.00 g (11 mmoles); chloroform (100 ml); phase transfer catalyst, 5.0 mole% based on substrate. [b] Isolated yields; yields in parentheses based on the substrate consumed. [c] Benzyltriethylammonium chloride. [d] 33% Aqueous potassium hydroxide was employed.

temperature afforded the corresponding isocyanotriazine **2b** (18% yield), while diamino-1,3,5-triazine **1c** afforded only monoisocyano-1,3,5-triazine **3c** (8% yield) as the isolated isocyanide. The reaction with 2-amino-4,6-diethoxy-1,3,5-triazine (**1d**), however, was unsuccessful owing to its limited solubility in the solvent system.

Isocyanotriazine **3** isolated were stable during storage, but they decomposed slowly in concentrated solution.

Reaction of Isocyanotriazine.

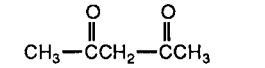
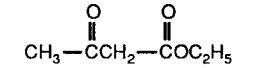
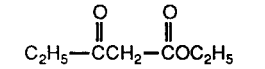
Although isocyanide undergo a wide variety of reactions including nucleophilic and electrophilic reactions [6], isocyanotriazines are expected to act as stronger electrophile owing to an electron-attracting triazinyl group.

In order to test the utility of isocyanotriazine and also to gain some insight into its reactivity as an electrophile, we examined the reactions of isocyanotriazine **3a** with amines and active methylene compounds (Scheme 2 and Table 2).

In the absence of catalyst, no reactions were observed between **3a** and primary or secondary amines, while the addition of small amounts of copper(I) or silver(I) salt as a catalyst [7] provided triazinylformamidines **4** in excellent

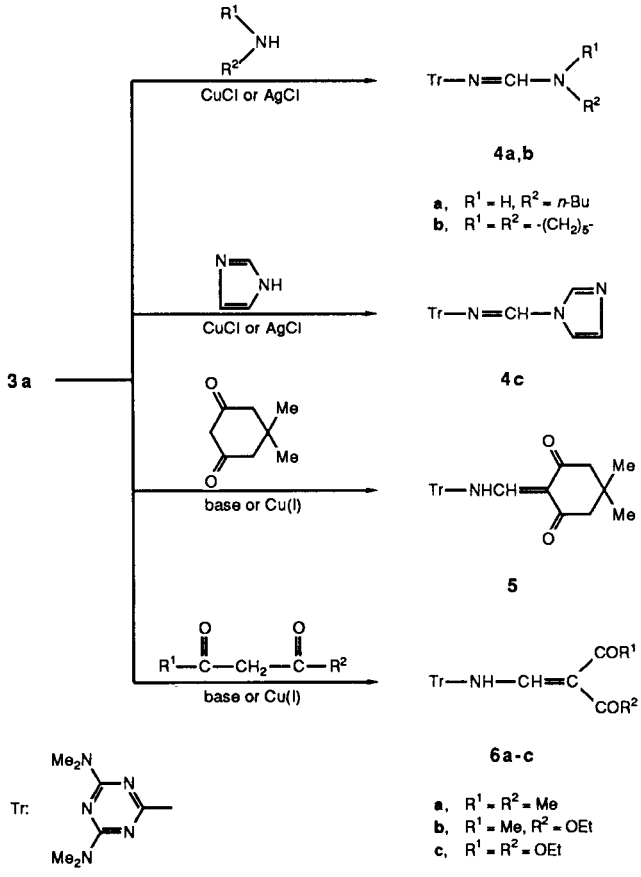
TABLE 2

Reaction of 2,4-Bis(dimethylamino)-6-isocyano-1,3,5-triazine (**3a**) with Amines and Active Methylene Compounds in Refluxing Benzene

Reactant	Additive [a]	Time (hours)	Product	Yield (%)
n-$BuNH_2$	CuCl	0.5	**4a**	80
	AgCl	0.2	**4a**	87
Piperidine	-	6.0	-	-
	CuCl	0.5	**4b**	69
	AgCl	0.2	**4b**	75
Imidazole	-	5.0	-	-
	CuCl	1.0	**4c**	63
Dimedone	Et_3N	10	**5**	49
		10	**5**	30
	$Cu(C_5H_7O_2)_2$	4.0	**5**	76
		10	**6a**	35
	$Cu(C_5H_7O_2)_2$	3.0	**6a**	73 [b]
		10	**6b**	30
	CuCl	4.0	**6c**	83

[a] Transition metal catalyst, 2 mole% based on **3a**; amine, equimolar amounts based on **3a**; $Cu(C_5H_7O_2)_2$, bis(acetylacetonate)copper (II).
[b] The reaction was conducted in refluxing chloroform.

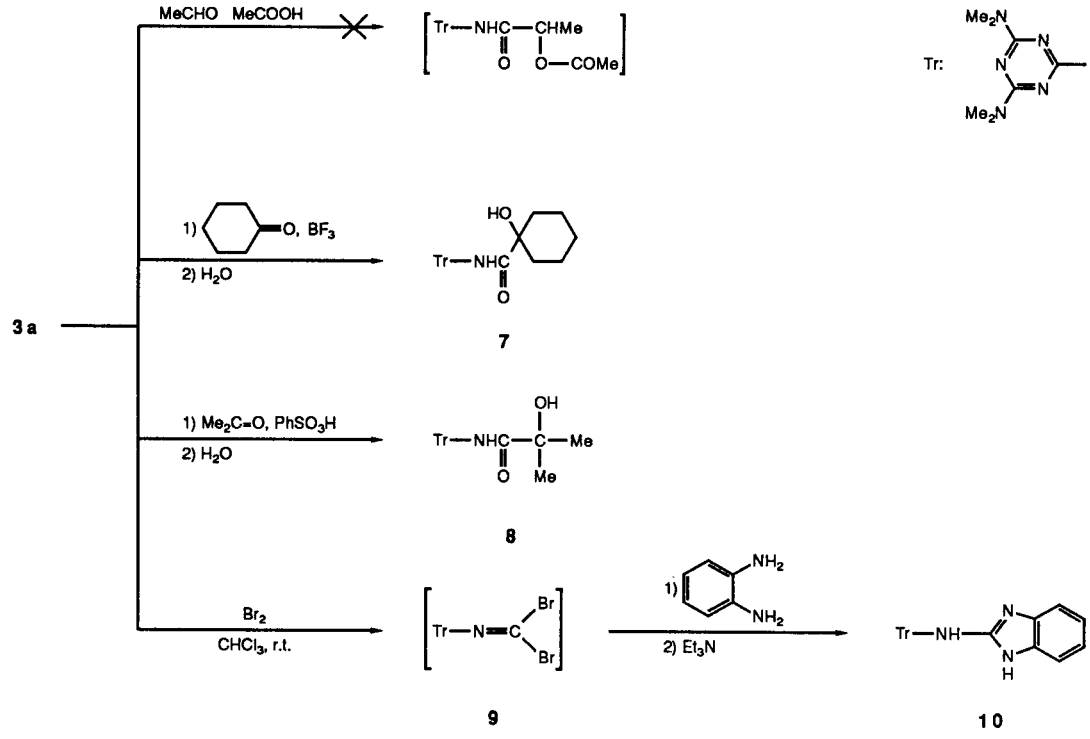
Scheme 2



yields. A similar addition reaction also took place for active methylene compounds in the presence of copper salts or organic bases such as triethylamine as a proton acceptor from the methylene group. It is of interest to note that even dimedone (5,5-dimethyl-1,3-cyclohexanedione) anion of low nucleophilicity [8] can add to the isocyanide moiety. These observations clearly show the higher electrophilic reactivity of **3a** than simple alkyl isocyanides, which react only with strong carbon nucleophile such as Grignard reagent and alkyllithium [9].

The reactions of **3a** with some electrophiles were also studied (Scheme 3). The Passerini reaction [6], which involve α-addition of an hydrogen-bonded adduct of the carboxylic acid and carbonyl compounds to the isocyanide carbon, was unsuccessful and starting **3a** was recovered unchanged. The result suggests the low reactivity of isocyanotriazine toward an electrophile. However, **3a** reacted sluggishly with ketones, *i.e.*, cyclohexanone and acetone, activated by Lewis acid or strong protonic acid, to afford the corresponding 2-hydroxy amides **7** (30% yield) and **8** (35% yield), respectively. Furthermore, **3a** was found to have a sufficient nucleophilicity to react with bromine. One equivalent of bromine was added into a chloroform solution of **3a**, and the mixture was allowed to stand until **3a** disappeared (checked by tlc). Evaporation of solvent

Scheme 3



gave a hygroscopic residue, whose mass spectrum showed a molecular ion peak [m/z (relative intensity) 350 (1), 352 (2), 354 (1)] corresponding isocyanide dibromide **9**. Although isolation of the dibromide by recrystallization was unsuccessful owing to its instability to moisture, it was traped by the reaction with *o*-phenylenediamine to provide 2-triazinylaminobenzimidazole **10** in 40% yield.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H nmr spectra were recorded in deuteriochloroform, unless otherwise noted, with TMS as the internal standard on a Hitachi EM-360 instrument. Mass spectra were taken on a Shimazu QP-1000 spectrometer operated at 70 ev. Amino-1,3,5-triazine **1** were prepared by a method described in the literature [10]. *N*-Formylimidazole was obtained by the reaction of *N,N'*-carbonyldiimidazole with formic acid [11]. Column chromatography was carried out on a silica gel.

2,4-Bis(dimethylamino)-6-formylamino-1,3,5-triazine (**2**).

A solution of amino-1,3,5-triazine **1a** (2.60 g, 15 mmoles) and *N*-formylimidazole (1.44 g, 15 mmoles) in THF was stirred for 30 hours at room temperature. The solvent was evaporated and the residue was recrystallized from benzene-hexane to give **2** (1.73 g), mp 172-173°; ^{1}H nmr: δ 3.10 (s, 12H, NMe_2), 8.10 (s, 1H, CHO), 9.50 (s, 1H, NH); ms: m/z 210 (M^+).

Anal. Calcd. for $C_8H_{14}N_6O$: C, 45.70; H, 6.71; N, 39.97. Found: C, 45.91; H, 6.56; N, 39.75.

General Procedure for Preparing Isocyanotriazine **3**.

Aminotriazine **1** (0.10 mole) and benzyltriethylammonium chloride (4.4 mmoles) were introduced into a stirred chloroform (500 ml), into which 50% aqueous potassium hydroxide solution (50 ml) was added. Then, the mixture was further stirred vigorously for 30 minutes at room temperature, diluted with water (500 ml), and neutralized with hydrochloric acid to *ca. p*H 7. After the organic layer was separated, the aqueous layer was extracted twice with 30 ml portions of chloroform. After the combined extracts was dried (magnesium sulfate), the solvent was evaporated and the residue was extracted with benzene. Recrystallization of the insoluble residue from ethanol gave starting material **1**. After the combined benzene extracts was concentrated, the residue was chromatographed (eluent benzene) to give isocyanotriazine **3**.

2,4-Bis(dimethylamino)-6-isocyano-1,3,5-triazine (**3a**).

Pure **3a** was obtained by recrystallization from benzene-hexane, mp 113-114° dec; ir (potassium bromide): 2120 cm^{-1} (-N=C); ^{1}H nmr: δ 3.17 (NMe_2); ms: m/z 192 (M^+).

Anal. Calcd. for $C_8H_{12}N_6$: C, 49.99; H, 6.29; N, 43.72. Found: C, 50.14; H, 6.21; N, 43.65.

2,4-Dimorpholino-6-isocyano-1,3,5-triazine (**3b**).

Pure **3b** was obtained by recrystallization from hexane, mp 172-174° dec; ir (potassium bromide): 2110 cm^{-1} (-N=C); ms: m/z 276 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_6O_2$: C, 52.17; H, 5.84; N, 30.42. Found: C, 52.19; H, 5.85; N, 30.18.

2-Amino-4-diethylamino-6-isocyano-1,3,5-triazine (**3c**).

Pure **3c** was obtained by recrystallization from hexane, mp 88-90° dec; ir (potassium bromide): 2120 cm^{-1} (-N=C); ^{1}H nmr: δ 1.20 (t, 6H, CH_3), 3.20 (q, 4H, NCH_2), 5.8 (broad, 2H, NH_2); ms:

m/z 192 (M^+).

Anal. Calcd. for $C_8H_{12}N_6$: C, 49.99; H, 6.29; N, 43.72. Found: C, 50.20; H, 6.41; N, 43.47.

General Procedure for Preparing Triazinylformamidine **4**.

A stirred mixture of **3a** (5.0 mmoles), amine (5.3 mmoles), and metal chloride (0.10 mmole) in benzene (10 ml) was refluxed under the conditions described in Table 2. After evaporation of the solvent, the residue was purified by recrystallization.

N^1-Butyl-N^2-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]formamidine (**4a**).

Pure **4a** was obtained by recrystallization from benzene-hexane, mp 154-155°; ^{1}H nmr: δ 0.90 (t, 3H, CH_3), 1.5 (m, 4H, $(CH_2)_2$), 3.10 (s, 12H, NMe_2), 3.40 (m, 2H, NCH_2), 8.70 (s, 1H, =CH); ms: m/z 265 (M^+).

Anal. Calcd. for $C_{12}H_{23}N_7$: C, 54.32; H, 8.74; N, 36.95. Found: C, 54.06; H, 8.31; N, 36.71.

N^1-(1-Piperidinyl)-N^2-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-formamidine (**4b**).

Pure **4b** was obtained by recrystallization from benzene-hexane, mp 161-163°; ^{1}H nmr: δ 1.65 (m, 6H, $(CH_2)_3$), 3.20 (s, 12H, NMe_2), 3.60 (t, 4H, NCH_2), 8.80 (s, 1H, = CH); ms: m/z 277 (M^+).

Anal. Calcd. for $C_{13}H_{23}N_7$: C, 56.29; H, 8.36; N, 35.25. Found: C, 56.15; H, 8.33; N, 35.62.

N^1-(1-Imidazolyl)-N^2-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-formamidine (**4c**).

Pure **4c** was obtained by recrystallization from benzene, mp 186-187°; ^{1}H nmr: δ 3.15 (s, 12H, NMe_2), 7.20 (m, 1H, ArH), 7.80 (m, 1H, ArH), 8.15 (m, 1H, ArH), 9.20 (s, 1H, =CH); ms: m/z 260 (M^+).

Anal. Calcd. for $C_{11}H_{16}N_8$: C, 50.77; H, 6.20; N, 43.04. Found: C, 50.62; H, 6.13; N, 42.95.

General Procedure for Preparing Compounds **5** and **6**.

A solution of **3a** (5.2 mmoles), active methylene compound (6.0 mmoles), and amine (6.7 mmoles) in benzene (50 ml) was refluxed under the conditions described in Table 2. After removal of the solvent, the residue was chromatographed (eluent benzene) to give products **5** and **6**.

2,4-Bis(dimethylamino)-6-[(4,4-dimethyl-2,6-dioxocyclohexylidene)methylamino]-1,3,5-triazine (**5**).

Pure **5** was obtained by recrystallization from hexane, mp 207-208° dec; ^{1}H nmr: δ 1.10 (s, 6H, Me), 2.45 (s, 4H, $(CH_2)_4$), 3.15 (s, 12H, NMe_2), 9.15 (d, 1H, -CH=), 11.85 (d, 1H, NH); ms: m/z 332 (M^+).

Anal. Calcd. for $C_{16}H_{24}N_6O_2$: C, 57.81; H, 7.28; N, 25.28. Found: C, 58.05; H, 7.26; N, 24.88.

2,4-Bis(dimethylamino)-6-(3-oxo-2-acetyl-1-butenylamino)-1,3,5-triazine (**6a**).

Pure **6a** was obtained by recrystallization from hexane, mp 145-146°; ^{1}H nmr: δ 2.40 (s, 3H, Me), 2.55 (s, 3H, Me), 3.15 (s, 12H, NMe_2), 8.95 (d, 1H, -CH=), 11.60 (d, 1H, NH); ms: m/z 292 (M^+).

Anal. Calcd. for $C_{13}H_{20}N_6O_2$: C, 53.41; H, 6.90; N, 28.75. Found: C, 53.41; H, 6.80; N, 28.99.

2,4-Bis(dimethylamino)-6-(3-oxo-2-ethoxycarbonyl-1-butenylamino)-1,3,5-triazine (**6b**).

This compound had mp 131-132°; ^{1}H nmr: δ 1.30 (s, 3H, Me), 2.55 (s, 3H, Me), 3.15 (s, 12H, NMe_2), 4.25 (s, 2H, CH_2), 9.10 (d, 1H, -CH=), 11.65 (d, 1H, NH); ms: m/z 322 (M^+).

Anal. Calcd. for $C_{14}H_{22}N_6O_3$: C, 52.16; H, 6.88; N, 26.07. Found: C, 52.09; H, 6.88; N, 25.75.

2,4-Bis(dimethylamino)-6-[2,2-bis(ethoxycarbonyl)ethenylamino]-1,3,5-triazine (**6c**).

This compound had mp 134-135°; ^{1}H nmr: δ 1.25 (t, 3H, Me), 1.30 (t, 3H, Me), 3.15 (s, 12H, NMe_2), 4.20 (q, 2H, CH_2), 4.25 (q, 2H, CH_2), 9.10 (d, 1H, -CH=), 10.15 (d, 1H, NH); ms: m/z 352 (M^+).

Anal. Calcd. for $C_{15}H_{24}N_6O_4$: C, 51.13; H, 6.86; N, 23.85. Found: C, 51.24; H, 6.81; N, 23.43.

2,4-Bis(dimethylamino)-6-(2-hydroxycyclohexylcarbonylamino)-1,3,5-triazine (**7**).

Into a solution of **3a** (5.2 mmoles) in 1,2-dichloroethane-methanol (10:1, 20 ml) was added a solution of boron trifluoride etherate (5.3 mmoles) in ether (5 ml) at −10°. After stirring for 30 minutes, the reaction mixture was washed with 5% aqueous sodium carbonate. The organic layer was separated, dried over magnesium sulfate, and concentrated. The residue was prepurified by column chromatography (eluent benzene-acetone), followed by recrystallization from benzene-hexane to yield the title product, mp 215-216°; ^{1}H nmr: δ 1.70-1.80 (m, 10H, cyclohexyl), 3.20 (s, 12H, NMe_2), 3.35 (broad, 1H, OH), 7.30 (s, 1H, NH); ms: m/z 308 (M^+).

Anal. Calcd. for $C_{14}H_{24}N_6O_2$: C, 54.65; H, 7.69; N, 27.05. Found; 54.53; H, 7.84; N, 27.25.

2,4-Bis(dimethylamino)-6-(2-hydroxy-2-methylpropanoylamino)-1,3,5-triazine (**8**).

A solution of **3a** (5.2 mmoles) and benzenesulfonic acid monohydrate (6.0 mmoles) in acetone-chloroform (2:1, v/v, 15 ml) was stirred for 2 hours at room temperature. After the reaction mixture was washed with 5% aqueous sodium carbonate, the mixture was filtered off and the filtrate was dried over magnesium sulfate. After filtration, the solvent was evaporated off and the resulting residue was prepurified by column chromatography (eluent benzene-acetone), followed by recrystallization from benzene-hexane (1:1) to yield the title product, mp 140-142°; ^{1}H nmr:δ 1.55 (s, 6H, CMe_2), 3.20 (s, 12H, NMe_2), 3.35 (broad, 1H, OH), 7.10 (s, 1H, NH); ms: m/z 268 (M^+).

Anal. Calcd. for $C_{11}H_{20}N_6O_2$: C, 49.24; H, 7.51; N, 31.32. Found: C, 49.12; H, 7.47; N, 31.28.

2-[4,6-Bis(dimethylamino)-1,3,5-triazin-2-ylamino]benzimidazole (**10**).

Bromine (6.0 mmoles) in chloroform (5 ml) was added to a chloroform (20 ml) solution of **3a** (5.2 mmoles) at *ca.* −5°. A solution of *o*-phenylenediamine (5.3 mmoles) in chloroform (20 ml) was then added, and stirred for 30 minutes at room temperature. Triethylamine (2 ml) was added to the solution, and the precipitate formed was collected. Recrystallization from benzene gave the title product, mp 250°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.25 (s, 12H, NMe_2), 5.2 (broad, 2H, NH), 7.3-7.9 (m, 4H, ArH); ms: m/z 298 (M^+).

Anal. Calcd. for $C_{14}H_{18}N_8$: C, 56.36; H, 6.08; 37.56. Found: C, 56.37; H, 6.23; N, 37.29.

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