capillary columns of 10 or 25 m in length, 0.53 mm in inner diameter, 2.56 or 1.33 micrometer in film thickness were used. Aluminum-backed cut sheets of Merck Kieselgel 60 PF_{254} were used for TLC, and Merck Kieselgel 60 (70-230 mesh ASTM) was used for column chromatographic separation and purification of products.

Bromination of toluene with TMSBr-$NaBrO_3$. Toluene (184 mg, 2 mmol) was dissolved in 6 mL of CCl_4. Sodium bromate (302 mg, 2 mmol) and benzyltriethylammonium chloride (22 mg, 0.1 mmol) were added. To the stirring reaction mixture bromotrimethylsilane (615 mg, 4 mmol) dissolved in 2 mL of CCl_4 was added. The resulting mixture was stirred at ambient temperature for a designated period of time or until the TLC showed a complete consumption of toluene. Insoluble salts were filtered off, and the low boiling components were evaporated. The crude product was analyzed by GC or NMR. The product distributions from other reactions are listed in Table 2.

Preparative procedure. A substrate (0.1 mol) was dissolved in 40 mL of CCl_4. Sodium bromate (15 g, 0.1 mol) and benzyltriethylammonium chloride (150 mg) were added. To the stirring reaction mixture bromotrimethylsilane (30 g, 0.2 mol) dissolved in 10 mL of CCl_4 was added from a dropping funnel over a period 5-10 min. The resulting mixture was stirred at ambient temperature for a designated period of time or until the TLC showed a complete consumption of the substrate. The reaction mixture was poured into 300 mL of ice-cold water. The products were extracted with 15 mL of CCl_4 twice and the combined extracts were washed with water, dried over anhydrous $MgSO_4$. The filtrate was concentrated and the residue was either distilled or recrystallized. 1-Bromo-1-phenylethane was obtained in 90% yield after distillation. The isolated yields of the products were slightly lower than those by chromatography.

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Synthesis of Symmetric 3,6-Disubstituted-1,2,4,5-Tetrazines using an Activated Catalyst Prepared by the Reaction of Copper Nitrate with Excess Zinc in the Presence of Hydrazine Monohydrate

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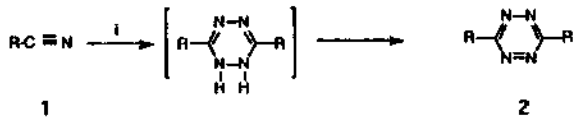
Since the first symmetric 3,6-disubstituted-1,2,4,5-tetrazine derivatives **2**[1] were prepared by the dimerization of ethyl diazoacetate, several different routes to symmetric and unsymmetric 3,6-disubstituted-1,2,4,5-tetrazines have been described including the treatment of hydrazine with iminoethers,[2] iminoesters,[3] thioamides,[4] selenoesters,[5] selenoamides,[5] imidates,[6] amidines,[7] dichloroazines,[8] hydrazonoyl chlorides,[9] fluoroolefines,[10] and chloroformylhydrazone.[11]

Even though direct synthesis of 1,2,4,5-tetrazines from a cyano group could be the best method, only a few examples have been previously reported in the literature.[12] For example, Abdel-Rahman[12c] reported direct synthesis of tetrazine by the action of hydazine monohydrate-sulphur mixture on various nitriles. However, we and others[7a] found that treatment of benzyl cyanide with sulphur-hydrazine hydrate gave 4-amino-3,5-dibenzyl-1,2,4-triazole,[13] not 3,6-diphenyl-dihydro-1,2,4,5-tetrazine. In the case of benzonitrile, we isolated the corresponding dihydrotetrazine which is readily oxidized in air to the red-colored 3,6-diphenyl-1,2,4,5-tetrazine. Similarly with acetonitrile, the product was not 3,6-dimethly-dihydro-1,2,4,5-tetrazine but 4-amino-3,5-dimethyl-1,2,4-triazole.[13]

Zajac *et al.*[12d] also reported a direct sythesis of 3,6-disubstituted-1,2,4,5-tetrazines from cyano compounds with Raney nickel-hydrazine monohydrate under reflux with ethanol. However, only 2-cyanopyridine and 4-cyanopyridine were illustrated.

We recently reported that activated metal powders prepared from the reaction of copper(II) sulfate or nickel chloride with excess zinc and hydrazine monohydrate in dry ethanol under reflux easily reduces nitroarenes to the corresponding amino compounds in high yields.[14~15] We also reported that



1 2

R=C_6H_5, *m*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$, 2-Pyridyl, 4-pyridyl, $C_6H_5CH_2$

Scheme 1. Reagents and conditions; i, $Cu(NO_3)_2 \cdot 3H_2O$-Zn*, $NH_2NH_2 \cdot H_2O$, C_2H_5OH, reflux.

Table 1. Yields of Symmetric 3,6-Disubstituted-1,2,4,5-Tetrazine[a]

R	Reaction time (h)	2[b]	Isolated Yields, %
1a: C_6H_5	5	**2a**: C_6H_5	85
1b: *o*-$CH_3C_6H_4$	10	**2b**: *o*-$CH_3C_6H_4$	0
1c: *m*-$CH_3C_6H_4$	10	**2c**: *m*-$CH_3C_6H_4$	87
1d: *p*-$CH_3C_6H_4$	10	**2d**: *p*-$CH_3C_6H_4$	90
1e: *o*-BrC_6H_4	5	**2a**: C_6H_5	85
1f: *p*-BrC_6H_4	5	**2f**: *p*-BrC_6H_5	82
1g: *o*-ClC_6H_4	5	**2a**: C_6H_5	90
1h: *p*-ClC_6H_4	5	**2h**: *p*-ClC_6H_4	85
1i: *o*-$CH_3OC_6H_4$	10	**2i**: *o*-$OCH_3C_6H_4$	0
1j: *p*-$CH_3OC_6H_4$	10	**2j**: *p*-$OCH_3C_6H_4$	20
1k: 2-pyridyl	10	**2k**: 2-pyridyl	80
1l: 4-pyridyl	12	**2l**: 4-pyridyl	87
1m: $C_6H_5CH_2$	10	**2m**: $C_6H_5CH_2$	80
1n: CH_3	10	**2n**: CH_3	<1[d]
1o: $CH_3CH_2CH_2$	10	**2o**: $CH_3CH_2CH_2$	<1[d]

[a]The reaction was carried out by adding 10 mmol of cyano compounds and 2.0 mL (40 mmol) of hydrazine monohydrate to activated catalyst prepared from 2.46 g (10 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$ and 1.3 g (20 mmol) of Zn in 10ml of dry ethanol and heated under nitrogen at reflux for 5-12 h. [b]Satisfactory spectroscopic and analytical data were obtained for all compounds. [c]4-Amino-3,5-di(2-pyridyl)-1,2,4-triazole was also formed in 10% yields in this case. [d]Corresponding tetrazines were detected only by GC-Mass and were unable to isolate due to to low yields.

activated metal powders prepared from nickel nitrate with excess zinc reduces nitroarenes to azoxy compounds exclusively.[15]

In continuation of our work, we decided to study the reactivity of activated Cu-Zn catalyst towards cyano groups in the presence of hydrazine monohydrate.

We found that the activated catalyst prepared by the reaction of copper nitrate trihydrate with excess zinc in dry ethanol showed exceptional catalytic activity for the reaction of benzonitrile with hydrazine monohydrate to give the corresponding 3,6-diphenyl-1,2,4,5-tetrazine via dihydro-1,2,4,5-tetrazine, in high yields.

Results of some symmetric 3,6-disubstituted-1,2,4,5-tetrazines prepared by this method are presented in Table 1.

One step direct prepration of **2** in high yields under mild conditions is the obvious advantages although the reactions are not optimized.

The preparation of the highly reactive activated catalyst was readily carried out by stirring a mixture of copper nitrate trihydrate with excess zinc in dry ethanol for 0.5 h at room temperature. The blue color had almost disappeared after subsiding the exothermic reaction, and a finely divided dark-gray powder had formed[believed to be a mixture of $Cu\text{-}Zn\text{-}Zn(NO_3)_2$].[16] This catalyst was used for this reaction without further treatment. The cyano compound and hydrazine monohydrate were added to this solution and refluxed under nitrogen for 5-12 h. The resulting solution was then allowed to cool to room temperature and filtered to remove the catalyst through a pad of silica gel or filter paper using ethanol or methylene chloride as an eluent. Removal of the solvent under reduced pressure and crystallization of the residue in ethanol gave the corresponding red-colored 3,6-disubstitued-1,2,4,5-tetrazine.

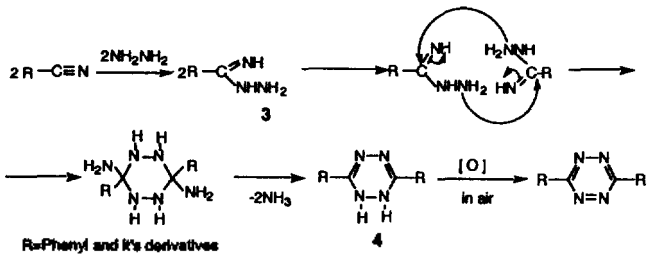
Interestingly, a mixture of commercially available copper powder, zinc powder, and zinc nitrate instead of activated catalyst was inert under our conditions even with a longer reaction time. Activated catalyst prepared from nickel nitrate with excess zinc or nickel chloride with zinc was also inactive for this reaction.

When a mixture of benzonitrile, copper nitrate, hydrazine monohydrate and zinc in dry ethanol was refluxed for 6 h under nitrogen without using the activated catalyst, 3,6-Diphenyl-1,2,4,5-tetrazine was isolated in only 10% yields after usual workup along with unreacted benzonitrile. Several trends in reactivity for the activated catalyst are also apparent. For example, the introduction of a methyl group to different positions on the benzene ring leads to a change in reactivity. While meta and *para* tolunitriles (**1c, 1d**) are converted to the corresponding tetrazine in high yields, the ortho tolunitrile (**1b**) is not converted. Since the electronic contribution of the ring methyl group to the cyano group is essentially equal for ortho and *para*-tolunitriles, this difference in reactivity can be attributed to steric hindrance by the *ortho* substituent. Similarly *para* methoxy benzonitrile (**1j**) is converted to the corresponding tetrazine in 20% yields, while the ortho methoxy benzonitrile (**1i**) is not converted. An unexpected reaction took place in the case of *o*-bromo and *o*-chlorobenzonitrile (**1e, 1g**). The single product isolated in both cases was indeed dehalogenated 3,6-diphenyl-1,2,4,5-tetrazine (**2a**) in high yields. We could not mechanistically interpret the dehalogenation process under the activated catalyst at this stage.

However, *para* bromo and *para* chloro benzonitrile (**1f, 1h**) gave the expected tetrazine in high yield without losing the halogen.

We also undertook the reaction of cyano pyridine isomers with our activated catalyst and found that 2-cyano pyridine and 4-cyano pyridine (**1k, 1l**) gave the corresponding tetrazine in high yields. Benzyl cyanide (**1m**) was also converted to the corresponding 3,6-dibenzyl-1,2,4,5-tetrazine in 80% yields, whereas acetonitrile and butyronitrile (**1n, 1o**) were converted to the corresponding tetrazine in less than 1% yields. A suggested reaction mechanism is given by the Scheme 2.

It is reasonable to postulate the conversion of cyano to amidrazone (**3**) in the first step. Tetrazine can be formed from 3,6-disubstitued-dihydro-1,2,4,5-tetrazine (**4**) which come



Scheme 2.

from amidrazone (3) (Scheme 2). When the workup was carried out carefully under atmospheric nitrogen in the case of benzonitrile, compound, **4** was actually isolated in 20% yields as yellow solid from 3,6-diphenyl-1,2,4,5-tetrazine. These results are consistent with a mechanism also proposed by Lions.[17] Attempts to synthesize the unsymmetric 3,6-disubstituted-1,2,4,5-tetrazines with our activated catalyst were unsucessful. For example, benzonitrile, *p*-chlorobenzonitrile and hydrazine monohydrate were added to activated cataylst in dry ethanol and refluxed for 6h under nitrogen. Copious red solid was isolated after usual workup. However, the major products were the corresponding symmetric disubstituted tetrazines with equal amount. Unsymmetric tetrazine was only detected on careful TLC analyses, but hardly isolated due to the small amount. In conclusion, we have prepared symmetric 3,6-disubstituted-1,2,4,5-tetrazine directly from a cyano group using an activated catalyst prepared by the reaction of copper nitrate with excess zinc in the presence of hydrazine monohydrate. We are trying to explore further synthetic potential use of these catalysts.

Experimental

Reagents and solvents were purchased from common commercial suppliers and were purified and dried prior to use when deemed necessary. Melting points were obtained on an electro thermal (ENG. LTD.S NO F-01265) and were uncorrected.

1H-NMR spectra were recorded on a Bruker AC 80 or Bruker AM 300 spectrometer with tetramethylsilane as an internal reference.

Chemical shift and coupling constants were obtained from first-order analysis of the spectra. Analytical TLC performed on precoated aluminum plates with Merk silica gel 60 F-254 as the adsorbent (layer thickness 0.2 mm). The developed plates were air dried and irradiated with UV light. All short column chromatography was carried out on Merk silica gel 60 (70-230 mesh).

Mass spectra (70 eV electron impact) were taken on a Finnigan 4510 instrument equipped with Finnigan-incos data system. GC-mass analysis was porformed on a Hewlett-Packard MSD 5890 series equipped with a capillary column (HP 1, 25 m). The C, H, N elemental analysis was performed on a Perkin-Elmer Model 240C. Yields are not optimized.

Preparation of Activated Catalyst. In a typical experiment, copper nitrate trihydrate (2.46 g, 0.01 mol), zinc (1.3 g, 0.02 mol) and dry ethanol (10 mL). were placed in two necked, 100 mL, round-bottomed flask equipped with septum inlet, magnetic stirring and condenser under nitrogen. The mixture was stirred at room temperature. The blue color had almost faded within 30 min after subsiding the exothermic reaction and a finely divided dark-gray powder had formed. This slurry is ready for this investigation without further treatment.

Typical Procedure for the Preparation of Tetrazine. Cyano compound (0.01 mol) and hydrazine monohydrate (2.3 mL, 0.05 mol) were added to this slurry (as described above) at room temperature. After refluxing under nitrogen for 3-12 h, the reaction mixture was allowed to attain room temperature and filtered to remove the catalyst through a pad of silica gel (2.5 dia×3 cm short column) or filter paper using ethanol or methylene chloride. Removal of solvent under reduced pressure gave the corresponding red solid, and recrystallization of the red solid in ethanol gave the corresponding 3,6-disubstituted-1,2,4,5-tetrazine (**2a-n**).

Preparation and Isolation of 3,6-Diphenyl-1,2-dihydro-1,2,4,5-tetrazine (4). Benzonitrile (1.03 g, 0.01 mol) and hydrazine monohydrate (2.3 mL, 0.05 mol) were added to this slurry (as described above) at room temperature. After refluxing under nitrogen for 3 h, the reaction mixture was allowed to attain room temperature and solid was filtered off under nitrogen. Removal of solvent under reduced pressure and crystallization from dry chloroform-absolute ethanol under nitrogen afforded 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine as yellowish needle shaped crystal (0.24 g, 20% yields). mp 192 ℃ (lit[12c], mp. 192-193 ℃): NMR (DMSO-d_6) δ 9.1 (d, 2H), 8.05-7.60 (m, 4H), 7.70-7.45 (m, 6H). Some physical properties of the products are recorded below.

3,6-Diphenyl-1,2,4,5-tetrazine (2a). **2a** was obtained from **1a**, **1e**, and **1g**. mp 196 ℃ (lit[18], mp 196-198 ℃): ^{1}H NMR ($CDCl_3$) δ 8.71-8.59 (m, 4H), 7.61 (m, 6H); Mass m/z 234 (M^+, 5), 103 (100), 77 (6), 76 (26); Anal. Calcd for $C_{14}H_{10}N_4$ from **1a**: C, 71.80; H, 4.27; N, 23.93. Found: C, 71.91; H, 4.23; N, 23.86. Anal. Calcd for $C_{14}H_{10}N_4$ from **1e**: C, 71.80; H, 4.27; N, 23.93. Found: C, 72.11; H, 4.30; N, 23.59. Anal. Calcd for $C_{14}H_{10}N_4$ from **1g**: C, 71.80; H, 4.27; N, 23.93. Found: C, 72.05; H, 4.33; N, 23.62.

3,6-Bis(3-methylphenyl)-1,2,4,5-tetrazine (2c). mp 151 ℃ (lit[19] mp 151 ℃): ^{1}H NMR ($CDCl_3$) δ 8.55-8.43 (m, 4H), 7.55-7.45 (m, 4H), 2.51 (s, 6H); Mass m/z 262 (M^+, 14), 117 (100), 92 (25), 90 (35); Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.28; H, 5.34; N, 21.38. Found: C, 72.95; H, 5.55; N, 21.50.

3,6-Bis(4-methylphenyl)-1,2,4,5-tetrazine (2d). mp 229-231 ℃) lit[19] mp 230-234 ℃): ^{1}H NMR ($CDCl_3$) δ 8.58-8.48 (m, 4H), 7.46-7.36 (m, 4H), 2.46 (s, 6H); Mass m/z 262 (M^+, 33), 117 (100), 92 (20), 90 (65), 89 (6); Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.28; H, 5.34; N, 21.38. Found: C, 72.30; H, 5.65; N, 21.68.

3,6-Bis(4-bromophenyl)-1,2,4,5-tetrazine (2f). mp 295-310 ℃ (lit.[20], 290-292): ^{1}H NMR (DMSO-d_6) δ 8.54-8.44 (m, 4H), 7.92-7.82 (m, 4H); Mass m/z 394 (M^+, 100), 396 (55), 395 (39), 314 (13); Anal. Calcd for $C_{14}H_8N_4Br_2$: C, 42.88; H, 2.04; N, 14.29. Found: C, 42.85; H, 2.10; N, 14.23.

3,6-Bis(4-chlorophenyl)-1,2,4,5-tetrazine (2h). mp 123 ℃ (lit[21], mp 228-231 ℃): ^{1}H NMR (DMSO-d_6) δ 8.44-8.41 (m, 4H), 7.58-7.46 (m, 4H); Mass m/z 304 (M^+, 3), 305 (1), 139 (33), 138 (33), 102 (26); Anal. Calcd for $C_{14}H_8N_4Cl_2$: C, 55.45; H, 2.64; N, 18.48. Found: C, 55.49; H, 2.54; N, 18.49.

3,6-Bis(4-methoxyphenyl)-1,2,4,5-tetrazine (2j). mp 221-223 ℃) lit[19] mp 151 ℃): ^{1}H NMR ($CDCl_3$) δ 8.64-8.41 (m, 4H), 7.15-7.05 (m, 4H), 3.93 (s, 6H); Mass m/z 294 (M^+, 3), 268 (20), 134 (30), 133 (100); Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.31; H, 4.76; N, 19.05. Found: C, 65.62; H, 4.97; N, 19.03.

3,6-Bis(2'-pyridyl)-1,2,4,5-tetrazine (2k). mp 222 ℃ (lit[22]., mp 224 ℃); NMR ($CDCl_3$-DMSO-d_6) δ 8.80-7.45 (m, 8H); Mass m/z 236 (M^+, 10), 105 (12), 104 (100), 77 (18). Anal. Calcd for $C_{12}H_8N_6$: C, 61.02, H, 3.39; N, 35.59. Found: C, 61.05; H, 3.38; N, 35.57.

3,6-Bis(4'-pyridyl)-1,2,4,5-tetrazine (2l). mp 254 ℃ (lit[22]., mp 256 ℃): ^{1}H NMR ($CDCl_3$-DMSO-d_6) δ 9.00-8.93 (m, 4H), 8.55-8.47 (m, 4H); Mass m/z 236 (M^+, 12), 105 (15), 104 (100), 77 (18); Anal. Calcd for $C_{12}H_8N_6$: C, 61.02; H, 3.39; N, 35.59. Found: C, 61.07; H, 3.41; N, 35.52.

3,6-Dibenzyl-1,2,4,5-tetrazine (2m). mp 74 ℃ (lit[23], mp 74 ℃): ^{1}H NMR ($CDCl_3$) δ 7.30-7.20 (broad singlet, 10H), 4.56 (s, 4H); Mass m/z 262 (M^+, 1), 117 (100), 90 (54); Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.28; H, 5.34; N, 21.37. Found: C, 73.32; H, 5.65; N, 21.33.

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Alcoholysis of Primary Amides to Esters by Sodium Nitrite or *t*-Butyl Nitrite/Chlorotrimethylsilane Pairs

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Amides are very stable and one of the least reactive acid derivatives. Although unsubstituted carboxamides are readily prepared from the corresponding more reactive acid halides and esters, the reverse transformation is often difficult.[1] The existing methods for the hydrolysis of amides usually call for a treatment with a strong acid or base under reaction conditions generally incompatible with sensitive substrates.[1] Alcoholysis of carboxamide to esters are even more difficult. Strong acids or bases in alcohol solvents are required for the alcoholysis.[1,2]

A number of nitrosating agents were reported to be effective for the hydrolysis of amides. Nitrogen tetroxide,[3] butyl