A Simple One Step Synthesis of New 3,5-Disubstituted-4-amino-1,2,4-triazoles

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A number of symmetrically 3,5-disubstituted 4-amino-1,2,4-triazoles have been prepared by the reaction of aromatic nitriles with hydrazine dihydrochloride or sulfate with an excess of hydrazine hydrate in ethylene or diethylene glycol under a nitrogen atmosphere. The structures of the new triazoles derivatives were confirmed by analytical and spectral data.

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Introduction.

As a result of an interest in the synthesis of corrosion inhibitor compounds, we have synthesized new triazoles derivatives. The existing data show that most organic inhibitors act by adsorption on the metal surface. The adsorption of the inhibitor is related to the presence of heteroatoms such as nitrogen, oxygen and sulphur, as well as an aromatic ring in their molecular structure. 4-Amino-1,2,4-triazoles are potentially good inhibitors. In order to test their inhibitory properties, we have synthesized several new 3,5-disubstituted-4-amino-1,2,4-triazoles. Symmetrical 3,5-disubstituted-4-amino-1,2,4-triazoles are accessible by several methods. These compounds can be prepared by the nucleophilic attack of hydrazine or its derivatives on nitriles [1], imidates [2] or amidines [3]. The initial product in each case is the 1,2-dihydro-1,2,4,5-tetrazine which rearranges at elevated temperatures or on treatment with acid to the corresponding 4-amino-1,2,4-triazole. One of these methods [4] involves the reaction between 2-cyanopyridine and hydrazine hydrate. The product was 3,6-bis(2-pyridyl)-1,2-dihydro-1,2,4,5-tetrazine **2n**. This compound was rearranged by further treatment with hydrochloric acid to 3,5-bis-(2-pyridyl)-4-amino-1,2,4-triazole **4n**. One step syntheses involving the reaction of nitriles with hydrazines in the presence of mineral acid were described. The reactions were carried out using hydrogen sulfide-producing compounds [1f] or a high boiling solvent such as ethylene glycol [1g]. 3,5-Diphenyl **4a**, 3,5-bis-(4-chlorophenyl) **4m**, 3,5-bis-(3-aminophenyl) **4f** and 3,5-di-*p*-tolyl-4-amino-1,2,4-triazole **4d** were synthesized by these methods. Later it was also found that 3,5-bis(4-aminophenyl)-4-amino-1,2,4-triazole **4g** is directly obtainable by the reaction of 4-aminobenzonitrile with hydrazine hydrate in the presence of mercaptoethanol and hydrazine dihydrochloride [5].

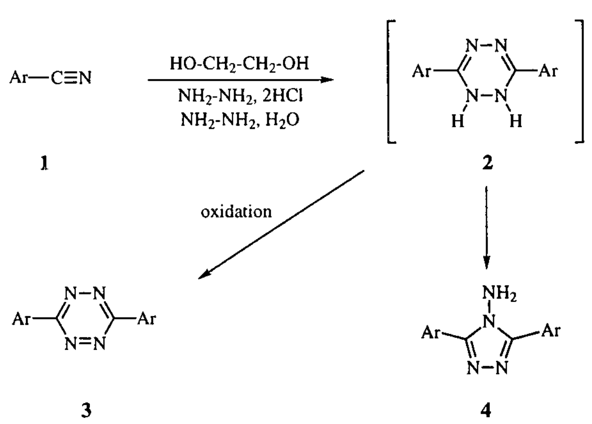
The present paper describes a one step synthesis of new 3,5-disubstituted-4-amino-1,2,4-triazoles **4a-r** by the direct action of hydrazine derivatives on nitriles in a high boiling solvent such as ethylene or diethylene glycol under a nitrogen atmosphere.

Results and Discussion.

In general, the reaction of aromatic nitriles with hydrazine derivatives was performed by heating an equimolar mixture of nitrile and hydrazine dihydrochloride or sulfate with an excess of hydrazine hydrate in ethylene or diethylene glycol at 130° for 2-5 hours. After 20-30 minutes of heating, the reaction mixture became orange, showing the initial formation of the dihydrotetrazine derivative **2**. At the same time, a vigorous evolution of ammonia was observed. After the end of this reaction, addition of water and filtration followed by crystallization from ethanol gave the 3,5-disubstituted-4-amino-1,2,4-triazoles **4** (Scheme 1) in excellent yields (Table 1) and in a good state of purity. The reaction was carried out under a nitrogen atmosphere in order to prevent the subsequent oxidation of intermediate **2** into the red-colored 1,2,4,5-tetrazines **3**.

Triazoles structures **4a-r** were consistent with elemental analyses (Table 2) and mass spectra. The melting points of the known triazoles agree with those reported in the literature (Table 1).

Scheme 1



1, 4a	Ar = C_6H_5	1, 4j	Ar = 4-HOC_6H_4
b	Ar = 2-$CH_3C_6H_4$	k	Ar = 3-CH_3O, 4- OHC_6H_3
c	Ar = 3-$CH_3C_6H_4$	l	Ar = 4-$CH_3OC_6H_4$
d	Ar = 4-$CH_3C_6H_4$	m	Ar = 4-ClC_6H_4
e	Ar = 2-$H_2NC_6H_4$	n	Ar = 2-pyridyl
f	Ar = 3-$H_2NC_6H_4$	o	Ar = 3-pyridyl
g	Ar = 4-$H_2NC_6H_4$	p	Ar = 4-pyridyl
h	Ar = 2-HOC_6H_4	q	Ar = 2-pyrazinyl
i	Ar = 3-HOC_6H_4	r	Ar = 2-thienyl

Because of the ready availability of reactants and its experimental simplicity, the "one pot" approach reported here seems to be a convenient alternative synthetic method to prepare symmetrical 3,5-diaryl-4-amino-1,2,4-triazoles **4**.

1,2-Dihydro-1,2,4,5-tetrazines **2** are usually differentiated from 4-amino-1,2,4-triazoles **4** by oxidation of the former to the highly colored tetrazines. However, a further reliable basis of differentiaton is their pmr spectra. The nitrogen protons of dihydrotetrazine appear at much lower field δ 8.9-9.5 [1e] than do those of 4-amino-1,2,4-triazoles δ 6.0-6.75 (Table 3). The nitrogen protons for compounds **4m** and **4q** appear at much lower field than expected probably due to hydrogen bonding between the triazolyl amino group and the pyridyl or pyrazinyl nitrogen atoms.

The ^{13}C nmr spectra for compounds **2** and **4** are similar. The signals for the carbons are situated approximately within the same range except for the carbon in **2** which resonated at much lower field (approximately 10 ppm) in compound **2**.

A suggested mechanism is given in Scheme 2.

Scheme 2

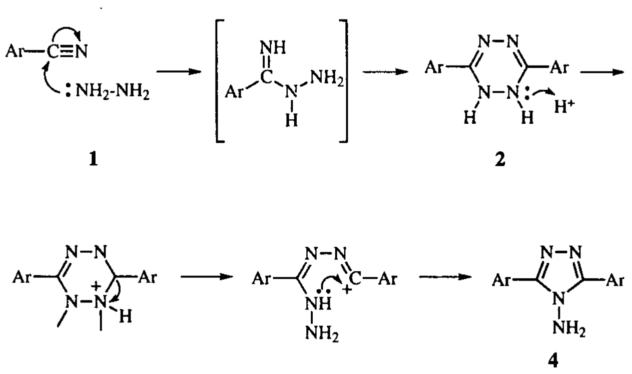


Table 1

3,5-Diaryl-4-amino-1,2,4-triazoles **4a-r**

Compound No.	Ar	Yield %	Lit Yield %	Mp °C	Lit Mp °C	References
4a	C_6H_5	97	95	265	263	[1f]
4b	2-$CH_3C_6H_4$	76		132		
4c	3-$CH_3C_6H_4$	80		168		
4d	4-$CH_3C_6H_4$	80	75	295	295	[1f]
4e	2-$H_2NC_6H_4$	83		218-219		
4f	3-$H_2NC_6H_4$	85	72	240	241	[1f]
4g	4-$H_2NC_6H_4$	90	75	226	225-227	[5]
4h	2-HOC_6H_4	79	77	259-261	260	[1g]
4i	3-HOC_6H_4	89		292		
4j	4-HOC_6H_4	93		296		
4k	3-CH_3O, 4-OHC_6H_3	82		228		
4l	4-$CH_3OC_6H_4$	86		277		
4m	4-ClC_6H_4	96	79	289	290	[1g]
4n	2-pyridyl	85		185-186	186	[4]
4o	3-pyridyl	82		275		
4p	4-pyridyl	80		340		
4q	2-pyrazinyl	83		310		
4r	2-thienyl	72		286		

Table 2

Elemental Analyses of **4a-r**

Compound No.	Molecular Formula	Calcd.			Found		
		C	H	N	C	H	N
4a	$C_{14}H_{12}N_4$	71.18	5.08	23.73	71.01	5.01	23.91
4b	$C_{16}H_{16}N_4$	72.73	6.06	21.21	72.82	5.96	21.40
4c	$C_{16}H_{16}N_4$	72.73	6.06	21.21	72.90	6.10	21.12
4d	$C_{16}H_{16}N_4$	72.73	6.06	21.21	72.63	6.09	21.25
4e	$C_{14}H_{14}N_6$	63.16	5.26	31.58	63.09	5.31	31.62
4f	$C_{14}H_{14}N_6$	63.16	5.26	31.58	63.06	5.29	31.65
4g	$C_{14}H_{14}N_6$	63.16	5.26	31.58	63.22	5.30	31.43
4h	$C_{14}H_{12}N_4O_2$	62.69	4.48	20.89	62.44	4.55	20.98
4i	$C_{14}H_{12}N_4O_2$	62.69	4.48	20.89	62.51	4.42	21.02
4j	$C_{14}H_{12}N_4O_2$	62.69	4.48	20.89	62.78	4.39	20.81
4k	$C_{16}H_{16}N_4O_4$	58.54	4.88	17.07	58.50	4.79	17.17
4l	$C_{16}H_{16}N_4O_2$	64.86	5.40	18.12	64.71	5.32	18.20
4m	$C_{14}H_{10}N_4Cl_2$	55.10	3.28	18.37	54.98	3.34	18.43
4n	$C_{12}H_{10}N_6$	60.50	4.20	35.29	60.61	4.38	35.18
4o	$C_{12}H_{10}N_6$	60.50	4.20	35.29	60.72	4.40	35.20
4p	$C_{12}H_{10}N_6$	60.50	4.20	35.29	60.82	4.18	35.19
4q	$C_{10}H_8N_8$	50.00	3.33	46.67	49.82	3.23	46.60
4r	$C_{10}H_8N_4S_2$	48.39	3.23	22.58	48.30	3.15	22.65

Table 3

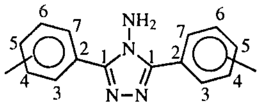
PMR Data (δ values, dimethyl-d_6 sulfoxide) for 3,5-Diaryl-4-amino-1,2,4-triazoles **4a-r**

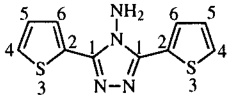
Compound No.	Aromatic Signals	NH_2 (tirazole)	Substituent
4a	7.55 (6H, m), 8.06 (4H, m)	6.31 (2H, s)	
4b	7.39 (4H, m), 7.85 (4H, m)	6.15 (2H, s)	2.60 (6H, s) CH_3
4c	7.39 (4H, m), 7.82 (2H, d), 7.84 (2H, s)	6.22 (2H, s)	2.39 (6H, s) CH_3
4d	7.35 (4H, d), 7.92 (4H, d)	6.31 (2H, s)	2.35 (6H, s) CH_3
4e	7.00 (4H, m), 7.40 (2H, d), 8.00 (2H, d)	6.31 (2H, s)	6.10 (4H, s) NH_2
4f	6.68 (2H, m), 7.17 (6H, m)	6.07 (2H, s)	5.26 (4H, s) NH_2
4g	6.65 (4H, d), 7.70 (4H, d)	6.00 (2H, s)	5.50 (4H, s) NH_2
4h	7.05 (4H, m), 7.42 (2H, m), 8.06 (2H, d)	6.16 (2H, s)	11.25 (2H, s) OH
4i	6.91 (2H, d), 7.32 (2H, t), 7.48 (4H, m)	6.22 (2H, s)	9.75 (2H, s) OH
4j	6.91 (4H, d), 7.84 (4H, d)	6.12 (2H, s)	9.96 (2H, s) OH
4k	7.15 (2H, d), 7.70 (2H, d), 7.79 (2H, s)	6.39 (2H, s)	4.07 (6H, s) OCH_3, 9.73 (2H, s) OH
4l	7.07 (4H, d), 7.93 (4H, d)	6.15 (2H, s)	3.82 (6H, s) OCH_3
4m	8.1 (4H, d), 8.5 (4H, d)	6.75 (2H, s)	
4n	7.58 (2H, m), 8.06 (2H, m), 8.21 (2H, m), 8.79 (2H, m)	7.82 (2H, s)	
4o	7.62 (2H, m), 8.40 (2H, m), 8.73 (2H, d), 9.05 (2H, s)	6.45 (2H, s)	
4p	8.08 (4H, d), 8.80 (4H, d)	6.54 (2H, s)	
4q	8.84 (4H, m), 9.39 (2H, s)	7.02 (2H, s)	
4r	7.25 (2H, m), 7.75 (2H, m), 7.97 (2H, m)	6.49 (2H, s)	

Table 4

^{13}C NMR Data (δ values, dimethyl-d_6 sulfoxide) for 3,5-Diaryl-4-amino-1,2,4-triazoles **4a-r**

The formula of the parent aminotriazole with numbering of the atoms are given below so as to meet the substituent or the heteroatom soon as possible.





Compound No.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	Substituent
4a	154.3	127.2	128.5	128.4	128.4	129.6	128.5	
4b	154.8	125.9	136.4	130.5	131.2	130.2	128.9	19.8
4c	154.2	127.1	128.8	137.7	130.1	128.3	125.4	21.0
4d	154.1	124.5	129.0	128.1	139.1	128.1	129.0	20.9
4e	151.5	93.5	118.1	115.2	133.9	116.0	132.3	
4f	154.7	115.0	113.7	148.7	115.7	127.8	128.8	
4g	153.1	111.1	129.7	113.2	151.1	113.2	129.7	
4h	153.0	112.6	156.0	116.5	131.6	119.1	129.8	
4i	154.1	128.3	115.2	157.3	116.5	129.5	119.0	
4j	153.9	118.1	129.8	115.2	158.6	115.2	129.8	
4k	154.6	119.1	113.0	148.6	148.1	116.0	122.1	56.4
4l	153.7	119.7	129.6	113.8	160.1	113.8	129.6	55.2
4m	153.6	126.0	128.7	130.1	134.6	130.1	128.7	
4n	148.6	147.0	-	148.8	124.5	137.8	122.8	
4o	150.8	125.3	152.6	-	154.8	125.7	137.7	
4p	153.0	134.0	122.0	150.1	-	150.1	122.0	
4q	149.7	142.5	-	145.3	144.3	-	144.0	
4r	150.7	128.1	-	129.0	128.0	128.0	-	

EXPERIMENTAL

Melting points were determined on an electrothermal apparatus and are uncorrected. Elemental analyses for C, H, N were performed by the service central d'analyse du CNRS, Vernaison, France. The nmr spectra were determined on a Bruker F.T. AC 200 spectrometer. Mass spectra were obtained with Finnigun a MAT Vision 2000 MALDI-TOF spectrometer (Laser desorption). All starting materials were commercial products.

3,5-Diaryl-4-amino-1,2,4-triazoles **4a-r**.

A mixture of aromatic nitrile **1a-r** (0.1 mole), hydrazine dihydrochloride or hydrazine sulfate (0.1 mole) and hydrazine hydrate (0.3 mole) in ethylene or diethylene glycol (50 ml) was heated at 130° with stirring under nitrogen for 2-5 hours. After cooling, the reaction mixture was diluted with water (100 ml). The precipitate thus obtained was filtered, washed with water, dried and recrystallized from ethanol. Yields, melting points, elemental analysis and nmr spectra of triazoles **4a-r** are given in Tables 1-4.

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