

A FACILE AND SOLVENT-FREE SYNTHESIS OF 3,5 -DISUBSTITUTED-4-AMINO-1,2,4-TRIAZOLES BY REACTIONS OF AROMATIC NITRILES WITH HYDRAZINE

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Abstract : A variety of 3, 5-disubstituted-4-amino-1,2,4-triazoles were prepared by reactions of aromatic nitriles with hydrazine monohydrate. The structure of 3,5-diphenyl-4-amino-1,2,4-triazole was established by an X-ray analysis.

4-Amino-1,2,4-triazoles derivatives have rather interesting activities such as fungicides (1a-c), herbicides and pesticides (2), and more recently, have been used as organic electroluminescent material and devices (1d). 4-Amino-1,2,4-triazoles have been prepared by a number of methods (2).

Previously, we reported preparation of a variety of 3,6-diaryl-1, 2, 4, 5-tetrazines and their inverse electron demand Diels-Alder reaction with cyclooctyne (3).

During the course of preparation of a variety of 3,6-diaryl-1, 2, 4, 5-tetrazines from aromatic nitriles and hydrazine, we obtained colorless solids when a mixture of these was vigorously refluxed (4). Fortunately, one of the compounds formed a single crystal which was subjected to an X-ray analysis and was unambiguously proven to be 3,5-diphenyl-4-amino-1,2,4-triazole (5). Therefore, we describe below briefly a facile and solvent-free synthesis of 3,5-disubstituted-4-amino-1,2,4-triazoles **3** by reactions of aromatic nitriles **1** with hydrazine monohydrate **2**.

The reaction procedure is extremely simple: for example, a mixture of benzonitrile **1a** (4.95g, 0.048 mol) with hydrazine monohydrate **2** (14.447g, 0.288 mol) was refluxed for 48 h. The colorless precipitates were separated by filtration which were dried under vacuum giving crude 3,5-diphenyl-4-amino-1,2,4-triazole **3a** in 74 % yield (4.2 g) (6). The analytically pure sample was obtained by recrystallizing from ethanol.

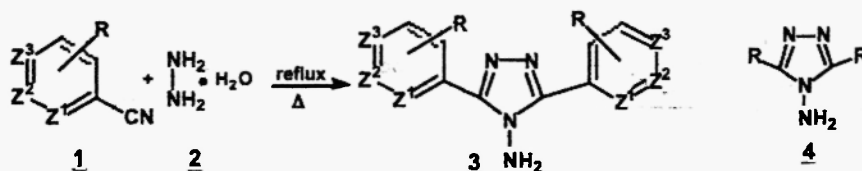
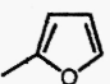
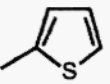
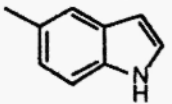
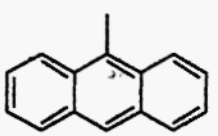
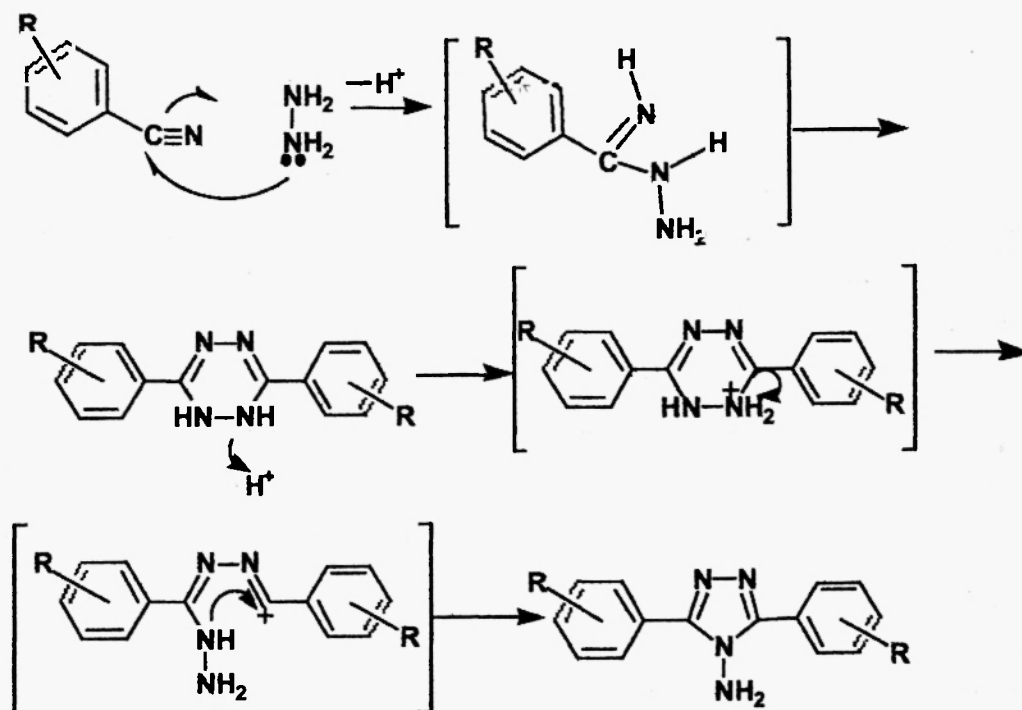


Table 1. Syntheses of 3,5-Disubstituted 4-Amino-1,2,4-Triazoles **3**

	R	Z1	Z2	Z3	Reaction Times(h)	3 Yield(%)	mp(°C)
a	H	CH	CH	CH	48	74	273-274
b	2-Me	CH	CH	CH	120	33	85-86
c	3-Me	CH	CH	CH	72	60	175-176
d	4-Me	CH	CH	C	72	76	303-304
e	4-OEt	CH	CH	C	72	83	217-218
f	2-OH	CH	CH	CH	72	68	246-247
g	3-OH	CH	CH	CH	72	71	296-297
h	4-OH	CH	CH	C	72	72	324-325
i	3-Cl	CH	CH	CH	72	52	226-227
j	4-Cl	CH	CH	C	79	33	273-274
k	2-NO ₂	CH	CH	CH	72	38	200-201
l	3-NO ₂	CH	CH	CH	75	46	229-230
m	4-NO ₂	CH	CH	H	72	47	110-111
n	—	N	CH	CH	72	5	186-187
o	—	CH	N	CH	76.5	33	283-284
p	—	CH	CH	N	72	8	358-359

Table 2. Syntheses of 3,5-Disubstituted 4-Amino-1,2,4-Triazoles **4**

	R	Reaction Times(h)	4 Yield(%)	mp (°C)
a		72	24	246-257
b		48	39	293-294
c		48	51	331-332
d		72	35	224-225



Scheme 1

The generality of the present reaction is illustrated in Table 1. As a matter of course, this procedure is amenable to heteroaromatic as well as condensed aromatic nitriles as depicted in Table 2. In some cases, the isolated yields were quite low, but the extremely simple and solvent free (9) procedure would make up for this drawback.

Since it is well known that dihydrotetrazines undergo oxidation to 1,2,4,5-tetrazines as well as undergo isomerization with acids to 1,2,3-triazoles (1, 8), a plausible mechanism for this one pot synthesis is considered as shown in Scheme 1.

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REFERENCES AND NOTES

- (a) C. Stehmann, M. A. de Waard, *Pestic. Sci.*, 1995, **44**, 183; (b) N. F. Eweiss, A. A. Bahaja and E. A. Elsherbini, *J. Heterocycl. Chem.*, 1986, **23**, 1451; (c) B. N. Goswami, J. C. S. Katoky and J. N. baruah, *J. Heterocycl. Chem.*, 1986, **23**, 1439; (d) M. Tamano, S. Onikubo and S. Okutsu, *Jpn. Kokai Tokkyo Koho*, JP 2000. 68, 059 (CI.H05B 33/14), 3 Mar 2000, Appl. 1998/236.702, 24 Aug 1998.

17pp. Japan.

2. Review: (a) K. T. Pott, *Chem. Rev.*, 1961, **61**, 87(), (b) K. T. Potts (Ed. by A. R. Katritzky and C. W. Rees) *Comprehensive Heterocyclic Chemistry* vol. 5 p733, 1984. (c) V. V. Kuzmenko and A. F. Pozharskii, *Adv. Heterocycl. Chem.*, 1992, **53**, 85.
3. Y. Ikemi, A. Okada, H. Katsura, S. Otani and K. Matsumoto, *Heterocyclic Commun.*, 1999, **4**, 53.
4. K. Matsumoto and Y. Ikemi *et al.*, Presented at the Annual Meeting of the Chemical Society of Japan, No.1D501, Abstract II, p.953, University of Doshisha, March, 1998.
5. Data were collected at T=20° C on a Rigaku AFC5S diffractometer; **3a**: C₁₄H₁₂N₄, M=236.28, white plate, dimensions 0.040 x 0.320 x 0.620 mm, orthorhombic, space group=Pnma(#62), a =11.222(4) Å, b= 26.174(8) Å, c=3.886(8) Å, U=1141(2) Å³, Z=4, Dc=1.375gcm⁻³, F(000)=496. Mo-Kα radiation (λ =0.71069 Å), μ= 0.081mm⁻¹, ω-2 θ scan mode with ω scan width=1.34 + 0.30 tan θ, ω scan speed 16.0deg min⁻¹, 1605 reflections were collected in the range 6.0 < 2θ < 55.0. The structure was solved by direct methods using full-matrix least squares on F for all non-hydrogen atoms using Lorenz polarization and absorption corrections to give R=0.077, and Rw=0.079 for 632 independent observed reflections with I >2.00σ(I) and 94 variables for 2θ max=55.0°. The final difference map maximum and minimum were 0.26 and -0.41eÅ⁻³, respectively. The atomic scattering factors for all atoms and the anomalous dispersion correction factors for atoms other than hydrogen were taken from the literature. All calculations were performed using TEXAN crystallographic software package of Molecular Structure Corporation.
6. mp 273~274°C (lit.(7) mp 263°C) : IR(KBr)1457,1654,3045,3215,3276,3362 cm⁻¹; ¹H NMR(CDCl₃) δ 4.83(s,2H), 7.54~7.57(m,6H), 7.92~7.97(m,4H); Mass: m/z 236(M⁺); Anal. calcd. C₁₄H₁₂N₄:C,71.17; H, 5.12; N, 23.71. Found: C, 71.42; H, 6.45; N, 23.86.
7. A. Kotone, M. Hoda T. Hori and Y. Nakane, German Patent, 1974, No. 2,248,257
8. D. D. Libman and R. Slack, *J. Chem. Soc.*, 1956, 2253; J.F. Geldard and F. Lions, *J. Org. Chem.*, 1965, **30**, 318; R. A. Boowie, M. D. Gardner, D. G. Neilson, K. M. Watson, S. Mahmood and V. Ridd, *J. C. S. Perkin Trans. 1*, 1972, 2395.
9. For an excellent review on solvent-free organic synthesis: K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025.

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