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

Yukio Ikemi,[a] Naoto Hayashi,[a] Akikazu Kakehi[b] and Kiyoshi Matsumoto,*[a]
[a] Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan
[b] Faculty of Engineering, Shinshu University, Nagano 380-8553, Japan

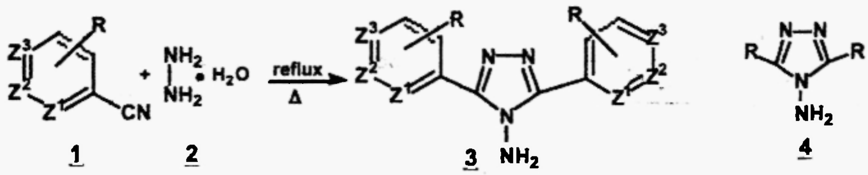
Abstract : A variety of 3, 5-disubstituted-4-amino-1,2,4-triazoles were prepared by reactions of aromatic nitriles with hydrazine monohydrate. The structure of 3,5-diphenyl-4-amino-1,2,4-triazole was established by an X-ray analysis.

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 benzonirile **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.

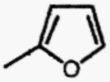
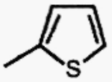
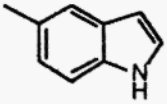
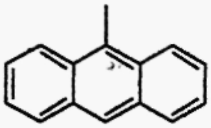


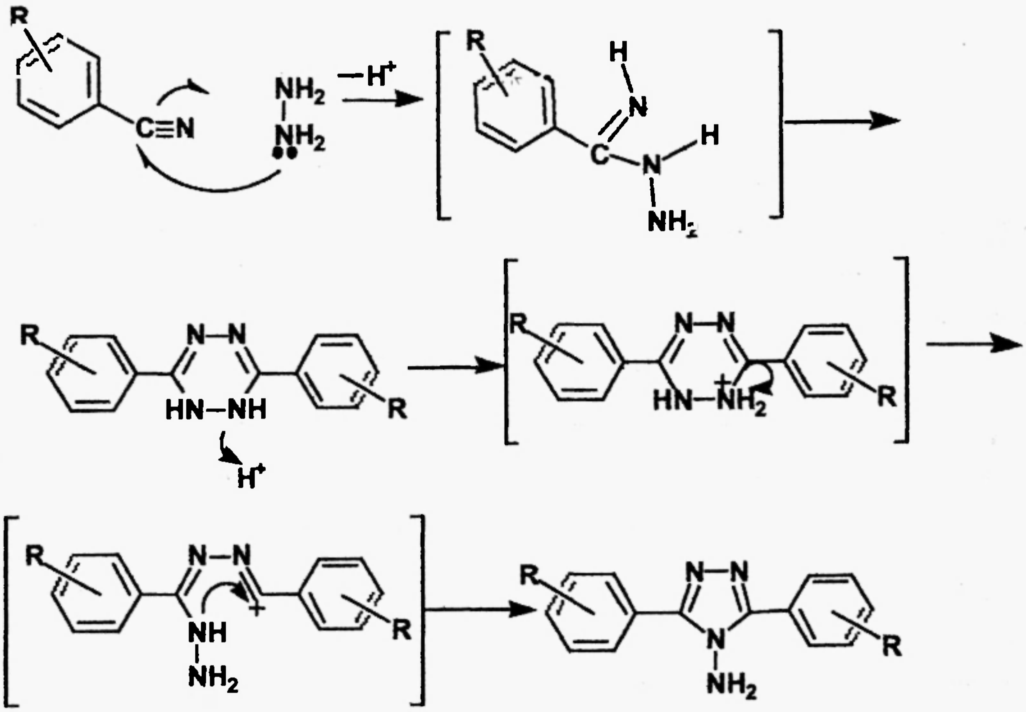
1 **2** **3** **4**

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

	R	Z1	Z2	Z3	Reaction Times(h)	**3** Yield(%)	mp(℃)
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--NO2	CH	CH	CH	72	38	200-201
l	3--NO2	CH	CH	CH	75	46	229-230
m	4--NO2	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-Disubustituted 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-terazines 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.

ACKNOWLEDGMENTS

This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors are also grateful to the Ministry of Education, Culture, Sports, Science, and Technology, Japan for purchasing the high-field NMR instruments (JEOL JNM-A500 and JNM-EX270) by the special fund to K. M. in 1992. Thanks are also extended to Mr. Shozo Ohnishi (Analytical Application Lab., Shimadzu Corporation, Kyoto, Japan) who kindly performed measurement of mass spectra in this work.

REFERENCES AND NOTES

1. (a) C. Stehmann, M. A. de Waard, *Pestic. Sci.*, 1995, **44**, 183; (b) N. F. Eweiss, A. A. Bahajaj and E. A. Elsherbini, *J. Heterocycl. Chem.*, 1986, **23** , 1451; (c) B. N. Goswami, J. C. S. Kataky 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 (Cl.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 Doushisha, March, 1998.
5. Data were collected at T=20° C on a Rigaku AFC5S diffractometer; **3a** :$C_{14}H_{12}N_4$, 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)$Å^3$, Z=4, Dc=1.375gcm^{-3}, F(000)=496. Mo-Kα radiation (λ =0.71069 Å), μ= 0.081mm^{-1}, ω-2 sacn mode with ω sacn width=1.34 + 0.30 tanθ, 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 2θmax=55.0° . The final difference map maximum and minimum were 0.26 and -0.41e$Å^{-3}$, 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℃ (lit.(7) mp 263℃) ; IR(KBr)1457,1654,3045,3215,3276,3362 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 4.83(s,2H), 7.54~7.57(m,6H), 7.92~7.97(m,4H): Mass: m/z 236(M^+); Anal. calcd. $C_{14}H_{12}N_4$: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.

Received on April 10, 2002