A Facile Synthesis of 2,5-Disubstituted Tetrazoles by the Reaction of Phenylsulfonylhydrazones with Arenediazonium Salts[1]

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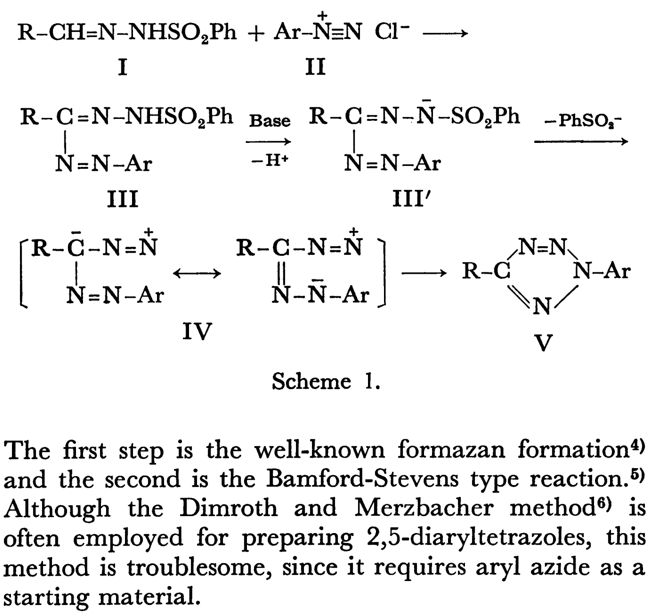
2,5-Disubstituted tetrazoles are obtained in good yields by the reaction of phenylsulfonylhydrazones of aromatic aldehydes (and cinnamaldehyde) with arenediazonium salts. From the synthetic viewpoint for tetrazoles, this method may be of high synthetic utility on account of the availability of starting materials, the simplicity of procedure, and higher yields.

The 1,5-dipolar cyclization[2] is a general method for synthesis of five-membered heterocycles; a typical example of this type of reaction is the cyclization of vinyldiazomethane to pyrazole.[3]

Azodiazomethane, an unknown diazalogue of vinyldiazomethane, can be expected to afford tetrazole through the 1,5-dipolar cyclization. As a synthetic route to azodiazomethane, the following scheme may be reasonable:



Scheme 1.

The first step is the well-known formazan formation[4] and the second is the Bamford-Stevens type reaction.[5] Although the Dimroth and Merzbacher method[6] is often employed for preparing 2,5-diaryltetrazoles, this method is troublesome, since it requires aryl azide as a starting material.

The present paper is concerned with an attempt to prepare 2,5-disubstituted tetrazoles[7] according to the above reaction scheme.[8]

Results and Discussion

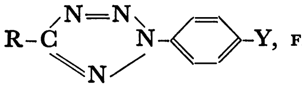
As shown in Table 1, 2,5-disubstituted tetrazoles could be obtained as was expected, in good yields with a few exceptions. Phenylsulfonylhydrazones[9] were allowed to react with one equivalent of arenediazonium salt(II) in alkaline (NaOH) ethanol at 5—2 °C or in pyridine at −10—−15 °C. Extraction of the reaction mixture with chloroform–water gave benzenesulfinic acid and tetrazole(V).[10] When 1.5 equivalents of diazonium salt were used, the yields of tetrazoles increased by a factor of about 1.1.

Attempts to isolate formazan (III) were unsuccessful: the overall reaction generally proceeded fast under these reaction conditions.[11] When the reaction of benzaldehyde phenylsulfonylhydrazone with benzenediazonium salt was carried out in aqueous alkali, there were separated brownish yellow precipitates, which were unstable and changed gradually to a deep red and then to brown mass. This product(mp 40—43 °C) could not be purified by crystallization, but gave 2,5-diphenyltetrazole (5%), 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine[12] (3%), and benzenesulfinic acid (16%) by treatment with hot sodium ethoxide–ethanol solution.

Although formazan(III) could not be isolated and confirmed in this study, the intermediacy of formazan (III) or formazanide anion (III′) should be reasonable from the reaction process.

Thus, the principal process of the reaction is identical with that of the reaction between *N*-phenylsulfonylbenzhydrazonoyl chlorides and arylhydrazines to yield 2,5-diaryltetrazoles.[7]

For the formation of tetrazole(V) from formazan

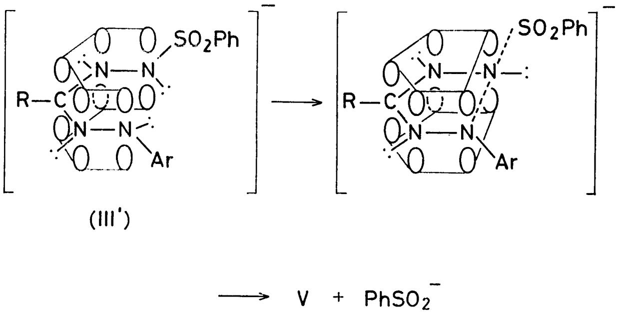
Table 1. 2,5-Disubstituted tetrazoles,  from phenylsulfonylhydrazones and arenediazonium salts

Tetrazole[a,b]		Yield[c,d] (%)	Mp (°C)	Solvent[e]	Molecular formula	Calcd (%)			Found (%)		
R	Y					C	H	N	C	H	N
Ph	H	71 (51)	101—102[f]	E	$C_{13}H_{10}N_4$						
Ph	Me	72	104—105[g]	E	$C_{14}H_{12}N_4$						
Ph	MeO	71	101—102	E	$C_{14}H_{12}N_4O$	66.66	4.79	22.21	66.55	4.79	22.29
Ph	Cl	65	123—124[h]	E	$C_{13}H_9N_4Cl$						
Ph	NO_2	67	185—186 (dec.)[m]	B	$C_{13}H_9N_5O_2$						
p-MeC_6H_4	H	66 (37)	93— 95[i]	E	$C_{14}H_{12}N_4$						
p-MeC_6H_4	Me	69	137—138[m]	E	$C_{15}H_{14}N_4$						

Table 1. (Continued)

Tetrazole[a,b] R	Tetrazole[a,b] Y	Yield[c,d] (%)	Mp (°C)	Solvent[e]	Molecular formula	Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
p-MeC_6H_4	MeO	55	112—114	E	$C_{15}H_{14}N_4O$	67.65	5.30	21.04	67.55	5.28	20.98
p-MeC_6H_4	Cl	60	142—143	E	$C_{14}H_{11}N_4Cl$						
p-MeC_6H_4	NO_2	78	171—172 (dec.)[m]	B	$C_{14}H_{11}N_5O_2$						
p-*i*-PrC_6H_4	H	60 (42)	44— 45	M	$C_{16}H_{16}N_4$	72.70	6.10	21.20	72.81	6.04	20.88
p-*i*-PrC_6H_4	Me	65	50— 51	M	$C_{17}H_{18}N_4$	73.35	6.52	20.13	73.51	6.32	20.34
p-*i*-PrC_6H_4	MeO	51	84— 86	M	$C_{17}H_{18}N_4O$	69.37	6.16	19.03	69.63	6.20	19.04
p-*i*-PrC_6H_4	Cl	62	98— 99	M	$C_{16}H_{15}N_4Cl$	64.32	5.06	18.75	64.26	5.08	18.66
p-*i*-PtC_6H_4	NO_2	76	158—159 (dec.)	EB	$C_{16}H_{15}N_5O_2$	62.13	4.89	22.64	61.90	4.80	22.91
p-$MeOC_6H_4$	H	66 (44)	106—107[j]	E	$C_{14}H_{12}N_4O$						
p-$MeOC_6H_4$	Me	74	111—112[m]	E	$C_{15}H_{14}N_4O$						
p-$MeOC_6H_4$	MeO	59	123—125	E	$C_{15}H_{14}N_4O_2$	63.82	5.00	19.85	63.71	5.03	19.86
p-$MeOC_6H_4$	Cl	71	140—142[m]	EB	$C_{14}H_{11}N_4ClO$						
p-$MeOC_6H_4$	NO_2	69	182—184 (dec.)[m]	EB	$C_{14}H_{11}N_5O_3$						
p-$Me_2NC_6H_4$	H	38 (18)	111—112	M	$C_{15}H_{15}N_5$	67.91	5.70	26.40	67.94	5.73	26.41
p-$Me_2NC_6H_4$	Me	28	150—151	M	$C_{16}H_{17}N_5$	68.80	6.13	25.07	68.61	5.97	24.92
p-$Me_2NC_6H_4$	MeO	10	138—139	M	$C_{16}H_{17}N_5O$	65.07	5.80	23.71	64.82	5.80	24.06
p-$Me_2NC_6H_4$	Cl	52	177—178 (dec.)	EB	$C_{15}H_{14}N_5Cl$	60.10	4.71	23.36	59.96	4.68	23.36
p-$Me_2NC_6H_4$	NO_2	63	180—181 (dec.)	C	$C_{15}H_{14}N_6O_2$	58.06	4.55	27.08	57.90	4.61	26.86
p-ClC_6H_4	H	75 (50)	110—111[k]	E	$C_{13}H_9N_4Cl$						
p-ClC_6H_4	Me	65	141—142[m]	E	$C_{14}H_{11}N_4Cl$						
p-ClC_6H_4	MeO	73	156—157	E	$C_{14}H_{11}N_4ClO$	58.65	3.87	19.54	58.50	3.78	19.46
p-ClC_6H_4	Cl	68	176—177 (dec.)[m]	EB	$C_{13}H_8N_4Cl_2$						
p-ClC_6H_4	NO_2	75	184—185 (dec.)[m]	B	$C_{13}H_8N_5ClO_2$						
p-$O_2NC_6H_4$	H	82 (13)	199—201 (dec.)[l]	B	$C_{13}H_9N_5O_2$						
p-$O_2NC_6H_4$	Me	82	173—174[m]	B	$C_{14}H_{11}N_5O_2$						
p-$O_2NC_6H_4$	MeO	69	199—200 (dec.)	B	$C_{14}H_{11}N_5O_3$	56.57	3.73	23.56	56.24	3.70	23.63
p-$O_2NC_6H_4$	Cl	82	189—190 (dec.)[m]	B	$C_{13}H_8N_5ClO_2$						
p-$O_2NC_6H_4$	NO_2	71	202—203 (dec.)[m]	B	$C_{13}H_8N_6O_4$						
2-C_4H_3O	H	60 (19)	87— 88	M	$C_{11}H_8N_4O$	62.26	3.80	26.40	62.25	3.75	26.49
2-C_4H_3O	Me	63	83— 84	E	$C_{12}H_{10}N_4O$	63.71	4.46	24.76	63.76	4.49	24.87
2-C_4H_3O	MeO	59	92— 93	E	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13	59.45	4.13	23.29
2-C_4H_3O	Cl	68	120—122	E	$C_{11}H_7N_4ClO$	53.57	2.86	22.71	53.42	2.84	22.47
2-C_4H_3O	NO_2	30	163—164	B	$C_{11}H_7N_5O_3$	51.37	2.74	27.23	51.32	2.79	27.36
PhCH=CH	H	36 (21)	90— 91	E	$C_{15}H_{12}N_4$	72.56	4.87	22.57	72.78	4.98	22.60
PhCH=CH	Me	54	96— 97	E	$C_{16}H_{14}N_4$	73.26	5.38	21.36	73.29	5.39	21.46
PhCH=CH	MeO	48	123—124	E	$C_{16}H_{14}N_4O$	69.05	5.07	20.13	68.73	5.07	19.87
PhCH=CH	Cl	51	137—138	E	$C_{15}H_{11}N_4Cl$	63.72	3.92	19.82	63.56	3.87	19.93
PhCH=CH	NO_2	31	183—184 (dec.)	B	$C_{15}H_{11}N_5O_2$	61.43	3.78	23.88	61.55	3.75	23.84

a) Satisfactory analytical data (±0.3% for C,H,N) were also obtained for all known compounds in the table. b) 2-C_4H_3O: 2-Furyl. c) Yields (isolated) in the reaction of equimolar quantities of reactants. d) Figures in parentheses are yields in the reaction in sodium hydroxide–ethanol system, and others those in pyridine. e) Solvent for recrystallization. B: benzene, E: ethanol, EB: ethanol–benzene, C: chloroform, M: Methanol. f) Lit, mp 101.5—102.0°: O. Dimroth and S. Merzbacher, *Ber.*, **40**, 2402 (1907). g) Lit, mp 103°: D. Jercher and H. Fischer, *Chem. Ber.*, **89**, 563 (1956). h) Lit, mp 120.5—121.5°: Soon-Yung Hong and J.E. Baldwin, *Tetrahedron*, **24**, 3787 (1968). i) Lit, mp 92.0—93.0°: *idem., ibid.* j) Lit, mp 105.0—105.5°: *idem., ibid.* k) Lit, mp 108.0—108.5°: *idem., ibid.* l) Lit, mp 199.0—200.0°: E. Wedekind, *Ber.*, **31**, 478 (1898). m) The uncorrected mps of the identical tetrazoles prepared from *N*-phenylsulfonylbenzhydrazonoyl chlorides and arylhydrazines were reported in the preceding paper. (Ref. 7).

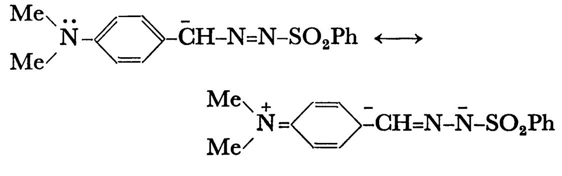


Scheme 2.

(III), a mechanism which involves the S_N1 type separation of benzenesulfinate ion from formazanide ion (III′) and the 1,5-dipolar cyclization of arylazoaryldiazomethane (IV) to tetrazole (V), given in Scheme 1, may be possible. However, the possibility of neighboring-group participation by nitrogen may be conceivable as observed in substitution reactions of δ-haloalkylamines.[13] Thus, the intramolecular displacement may be represented as the most possible mechanism by considering the participation of the lone-pair orbital of arylazo α-nitrogen atom with a planar quasi-aromatic[14] configuration of formazanide anion in the transition state (Scheme 2). Since formazan and formazanide anion are isoelectronic with pentadienide anion, their most favored configuration should be the planar U-shaped form,[15] in which the π-system may gain some quasi-aromatic stabilization. This stabilization would compensate the weak nucleophilicity of azo group.

As shown in Table 1, pyridine resulted in higher yields of tetrazoles than sodium hydroxide–ethanol system. The principal reason for this results should be chiefly attributed to the fact that the hydrazones are not sufficiently soluble in cold alkaline ethanol in contrast in pyridine.

As for the reaction of benzaldehyde hydrazones in pyridine, it may be said that increase in the electrophilicity of diazonium ion generally increases the yields of tetrazoles.[16] The difficulty of obtaining triarylformazans with *p*-dimethylamino or *p*-hydroxyl substituent in the *C*-phenyl group was attributed to the preferential azo-coupling to the activated aromatic ring.[17] This might be questionable[18] and is not adoptable for the present results. The low yields in the case of *p*-(dimethylamino)benzaldehyde hydrazone can be accounted for by the antagonistic resonance effect of *p*-(dimethylamino)phenyl group on the azo-carbanion structure of hydrazonide anion.[19]



That is to say, the electron-donating nature of dimethylamino group should be responsible for the decreased nucleophilicity of α-carbon of aldehyde moiety of hydrazone.

In the present method, the starting materials are readily available, the procedure is simple, and the yield of product is high in general. In conclusion, this method possesses the higher synthetic utility for 2,5-diaryltetrazoles.

Experimental[20]

Preparation of Phenylsulfonylhydrazones (I). General Procedure: Aldehyde (0.1 mol) dissolved in a small amount of hot ethanol (liquid aldehydes were used directly) was mixed with the solution of phenylsulfonylhydrazine (17.2 g, 0.1 mol) in ethanol (100 ml). After being allowed to stand for 30 min, the mixture was cooled and diluted with water. The separated crystalline product was filtered, washed with aqueous ethanol, and air dried. Yield: 79—97%. *p*-Tolualdehyde hydrazone, 92%, mp 124—125 °C. Found: C, 61.32; H, 5.17; N, 10.17%. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21%. *p*-Cumaldehyde hydrazone, 89%, mp 132—133 °C, Found: C, 63.38; H, 6.05; N, 9.16%. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.27%.

Reaction of Phenylsulfonylhydrazones (I) with Arenediazonium Salts (II). General Procedure: Diazonium salt solutions were prepared as follows: A cooled solution of sodium nitrite (5 mmol) in 2 ml of water was added to a solution of aniline (5 mmol) and 1.3 ml of concentrated hydrochloric acid in 8 ml of 50% ethanol below 5 °C.

(A) Reaction in Pyridine. The solution of arenediazonium chloride (II) was added dropwise over a period of 30 min to a stirred solution of I (5 mmol) in 30 ml of pyridine at -10—-15 °C. The reaction mixture was extracted with chloroform and water. The chloroform layer was washed with dilute hydrochloric acid followed by water and dried. After removal of the solvent from the chloroform extract, the resulting residue was chromatographed on a silica gel (10 g) column using benzene as the eluent to give the corresponding tetrazole, which was purified by recrystallization. The results are summarized in Table 1.

(B) Reaction in Sodium Hydroxide–Ethanol System. The diazonium salt solution was added to a cooled solution of sodium hydroxide (20 mmol) and I (5 mmol) in 40 ml of ethanol at 5—2 °C in a similar manner as above. The successive working-up was the same as that of (A). The results are summarized in Table 1.

The alkaline water layer was neutralized and extracted with chloroform to give unaltered I. The yields of recovered hydrazones (crude) were as follows: hydrazone of benzaldehyde, 38; *p*-tolualdehyde, 44; *p*-cumaldehyde, 35; *p*-anisaldehyde, 39; *p*-dimethylaminobenzaldehyde, 26; *p*-chlorobenzaldehyde, 38; *p*-nitrobenzaldehyde, 71%.

Identification of Benzenesulfinic Acid. The aqueous extract from the reaction mixture, in the reaction between benzaldehyde hydrazone and benzenediazonium chloride in sodium hydroxide–ethanol, was acidified, saturated with sodium chloride, and then extracted with dichloromethane. The dichloromethane extract was dried over sodium sulfate and treated with diphenyldiazomethane to afford phenyl benzhydryl sulfone,[21] mp 188—189 °C (Ref.[22] mp 188 °C), yield: 0.34 g (44% based on the 2,5-diphenyltetrazole obtained). (Found: C, 73.92; H, 5.17%).

References

1) A preliminary communication of portions of this study has appeared: S. Ito, Y. Tanaka, A. Kakehi, and K. Kondo, *Chem. Lett.*, **1973**, 1071.

2) For leading references, see (a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **7**, 321 (1968); b) H. Reimlinger,

Chem. Ber., **103**, 1900 (1970); (c) J. Elguero, *Bull. Soc. Chim. Fr.*, **1971**, 1925.

3) (a) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, **1935**, 286. (b) C. D. Hurd and S. C. Lui, *J. Am. Chem. Soc.*, **57**, 2656 (1935). (c) G. L. Closs and W. Boll, *Angew. Chem.*, **75**, 640 (1963). (d) R. K. Bartlett and T. S. Stevens, *J. Chem. Soc., C*, **1967**, 1964.

4) H. von Pechmann, *Ber.*, **25**, 3175 (1892). *Cf.* A. W. Nineham, *Chem. Rev.*, **55**, 355 (1955).

5) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, **1952**, 4735.

6) O. Dimroth and S. Merzbacher, *Ber.*, **40**, 2402 (1907). Concerning the synthetic methods for tetrazoles, see F. R. Benson in "Heterocyclic Compounds," Vol. 8, Chap. 1, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York (1967).

7) S. Ito, Y. Tanaka, and A. Kakehi, *Bull. Chem. Soc. Jpn.*, **49**, 762 (1976).

8) 2,5-Diaryltetrazoles were obtained by the oxidation of *N*-amidino- or *N*-carbamoylformazan with nitric acid, potassium permanganate, or NBS: E. Wedekind, *Ber.*, **31**, 473 (1898); V. A. Grakauskas, A. J. Tomasewski, and J. P. Horwits, *J. Am. Chem. Soc.*, **80**, 3155 (1958); W. Ried and H. Hillenbrand, *Justus Liebigs Chem. Ann.*, **590**, 128 (1954). These reactions should proceed *via* the formation of tetrazolium salts followed by their hydrolysis.

9) Since aliphatic aldehyde hydrazones could not be obtained in a pure state, none of them were used in the present study: aliphatic aldehydes such as propion- and butyraldehyde reacted with phenylsulfonylhydrazone to yield oily products, which decomposed with an evolution of gas on standing. Bartlett and Stevens also reported that formaldehyde *p*-tolylsulfonylhydrazone decomposed when crystallization was attempted: Ref. 3d.

10) The tetrazoles obtained were identified by their analytical and spectral data and, in the case of known compounds, by comparison with authentic specimens prepared by other synthetic methods. In the IR spectra, all the tetrazoles exhibit four characteristic peaks at 1260—1290 (weak), 1060—1080 (weak), near 1010 (medium to strong), and near 990 $\mathrm{cm^{-1}}$ (medium to strong). The absorption at 1260—1290 $\mathrm{cm^{-1}}$ can be assigned to the cyclic N–N=N group in analogy with other tetrazoles and triazoles [(a) E. Lieber and T. Enkoji, *J. Org. Chem.*, **26**, 4472 (1961); (b) E. Lieber, C. N. R. Rao, T. S. Chao, and H. Rubinstein, *Can. J. Chem.*, **36**, 1441 (1958)], and those at near 1070, 1010, and 990 $\mathrm{cm^{-1}}$ to the tetrazole ring system [(a) E. Lieber, D. R. Leverring, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951); (b) C. W. Roberts, G. F. Fanta, and J. D. Martin, *J. Org. Chem.*, **24**, 654 (1959); (c) C. W. Roberts and M. L. Maskaleris, *ibid.*, **24**, 926 (1959)].

11) The reaction was exothermic. When the diazonium salt solution was added all at once and the reaction mixture was worked up immediately, tetrazoles could be obtained in a decreased yield by a factor of only about 0.2. On the other hand, cinnamaldehyde phenylsulfonylhydrazone remained unchanged when treated with alkali under the same reaction condition as that in the present procedure.

12) The dimerized product of *N*-phenylbenzonitrilimine which might be formed directly from the intermediate precursor of formazan.

13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York (1960), p. 570.

14) Lloyd and Marshall have proposed the definition of the term "quasi-aromatic": D. Lloyd and D. R. Marshall, *Angew. Chem. Int. Ed. Engl.*, **11**, 404 (1972). In the present paper, the term "quasi-aromatic......" is used in the usual sense.

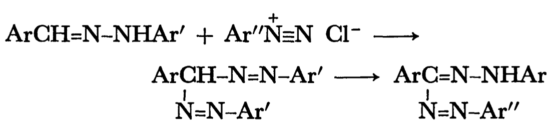
15) R. Hoffmann and R. A. Olofson, *J. Am. Chem. Soc.*, **88**, 943 (1966).

16) This tendency is pronounced in the reaction with *p*-(dimethylamino)benzaldehyde hydrazone.

17) D. D. Libman, A. W. Nineham, and R. Slack, *J. Chem. Soc.*, **1954**, 1565.

18) Experimental data unfit for this explanation were reported: *e.g.* F. R. Fichter and J. Frohlich, *Chem. Zentr.*, **1903**, II. 426; Beilstein's "Handbuch der Organischen Chemie," Hw. Bd. XVI (1933), p. 27.

19) According to the recent study of the mechanism of formazam formation by the action of diazonium salt on arylhydrazone, the reaction intermediate is to be the ***gem***-bis(arylazo) compound, $\mathrm{ArCH(-N{=}NAr')(-N{=}NAr'')}$, whose rearrangement to formazan is an azo-hydrazone conversion: [A. F. Hegarty and F. L. Scott, *Chem. Commun.*, **1966**, 622].



$$\mathrm{ArCH{=}N{-}NHAr'} + \mathrm{Ar''\overset{+}{N}{\equiv}N\ Cl^-} \longrightarrow \underset{\mathrm{N{=}N{-}Ar'}}{\mathrm{ArCH{-}N{=}N{-}Ar'}} \longrightarrow \underset{\mathrm{N{=}N{-}Ar''}}{\mathrm{ArC{=}N{-}NHAr'}}$$

20) Melting points were determined with a Yanagimoto micro-melting point apparatus Model MP-S3 and are corrected. The micro-analysis was performed on a Perkin-Elmer elemental analyzer Model 240. The IR spectra were recorded with a JASCO DS-301 spectrometer.

21) M. Kobayashi, H. Minato, and H. Fukuda, *Bull. Chem. Soc. Jpn.*, **46**, 1266 (1973).

22) R. Knoll, *J. Prakt. Chem.*, **113**, 40 (1926); *Chem. Abstr.*, **20**, 2669 (1926).