The Reaction of *N*-(Phenylsulfonyl)benzohydrazonoyl Chloride with *N*-Substituted Benzamidines, with Benzimidates, and with 2-Aminopyridines*

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(Received December 9, 1976)

4-Alkyl or aryl-3,5-diphenyl-4*H*-1,2,4-triazoles, 3-phenyl-1,2,4-triazolo[4,3-*a*]pyridine, and -pyrimidine are obtained by the title reactions. The reaction may proceed *via* the nucleophilic attack of amidine or imidate on the imidoyl carbon of hydrazonoyl chloride and the subsequent intramolecular cyclization of the intermediate formed in the initial step, with the removal of the amino or alkoxyl and phenylsulfonyl groups.

N-(Phenylsulfonyl)benzohydrazonoyl chloride(**1**) does not function as a 1,3-dipole source for the cyclo-addition reaction because of the strong electron-withdrawing nature of the phenylsulfonyl group.[1] However, since the arylsulfonyl group can be eliminated as an arenesulfinate anion or -sulfonyl cation, and since the imidoyl carbon and amino nitrogen of **1** possess electrophilic and nucleophilic[2] characters respectively, **1** may serve for synthesizing heterocycles.

In the previous paper,[3] we reported the synthesis of 2,5-diaryltetrazoles by the reaction of **1** with arylhydrazine, in which the elimination of the benzenesulfinate ion was observed.

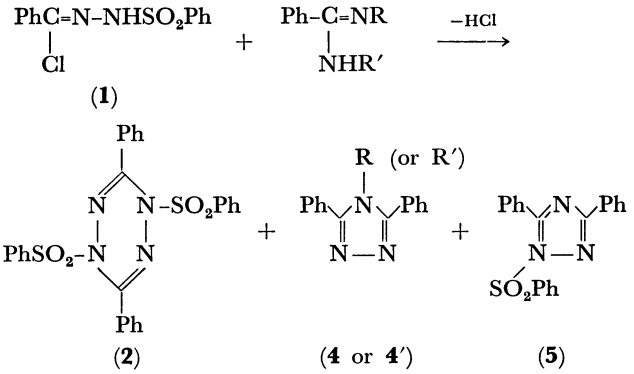
The present paper will deal with the formation of 1,2,4-triazoles from **1** and *N*-substituted benzamidines, benzimidates, or 2-aminopyridines. In this reaction, the phenylsulfonyl group may be removed cationically.

Fusco and Musante[4] reported the preparation of 1-substituted 1*H*-1,2,4-triazoles using *N*-phenylbenzohydrazonoyl chloride and unsubstituted benzamidines. Similarly, Huisgen *et al.*[5] obtained 1,2,4-triazole by the reaction of ethyl acetimidate with *N*-phenylbenzohydrazonoyl chloride in the presence of triethylamine. In these methods, however, *N*-substituted benzamidines or imidates cannot be used, and the resulting triazole bears the *N*-substituent of the starting hydrazonoyl chloride, virtually the phenyl group only, as its 1-substituent.

In contrast, the present method, using various amidines and imidates, gives 4-aryl or alkyl substituted 4*H*-1,2,4-triazoles as well as 1-phenylsulfonyl-1*H*-1,2,4-triazole.

Results and Discussion

Reaction with Benzamidines. The reaction of **1** with benzamidines was carried out in a 1 : 2 mole ratio in THF at room temperature, giving 4-substituted 3,5-diphenyl-4*H*-1,2,4-triazole (**4** or **4'**), and/or 1-phenylsulfonyl-3,5-diphenyl-1*H*-1,2,4-triazole(**5**), and 1,4-dihydro-3,6-diphenyl-1,4-bis(phenylsulfonyl)-1,2,4,5-tetrazine(**2**), together with a trace amount of 3,6-diphenyl-1,2,4,5-tetrazine.[6] The results are summarized in Scheme 1 and Table 1.

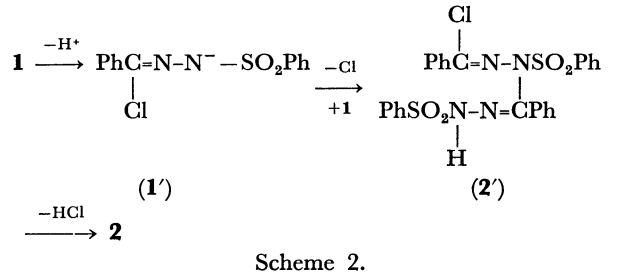


Scheme 1.

Benzenesulfonamides and *N*-phenylsulfonylated amidine were also obtained. Interestingly, the formation of benzenesulfonyl chloride was observed in the reaction with *N*,*N*-disubstituted benzamidines.[7]

As is shown in Table 1, *N*-arylbenzamidines gave **4** predominantly, and the reaction with benzamidine and its *N*-alkylated derivatives resulted in an increase in the yield of **2**. Aliphatic amidines such as *N*-ethylacetamidine, a stronger base than benzamidines, gave **2** primarily, and a small amount of *N*-(phenylsulfonyl)-*N*-[*N*-(phenylsulfonyl)benzohydrazonoyl]benzohydrazonoyl chloride(**2'**)[8] was isolated in this case.

Since the phenylsulfonyl group is a strong electron-withdrawing group, the amino hydrogen of **1** may be acidic and may be abstracted easily by amidine, a base, and the resulting *N*-(phenylsulfonyl)benzohydrazonoyl chloride anion(**1'**) may be also stable. Considering the isolation of **2'** in the reaction with *N*-ethylacetamidine, the following mechanism involving the nucleophilic attack of **1'** on **1** may be possible for the formation of **2** (Scheme 2).[9] The increased formation of **2** observed in the reaction with benzamidine and its *N*-alkylated derivatives may be attributed to their basicity being stronger than that of *N*-arylbenzamidines.



Scheme 2.

* Presented in part at the Autumnal Joint Meeting of the Tokai Branch of the Chemical Society of Japan and the Chubu Branches of the related Societies, Nagoya, October, 1975.

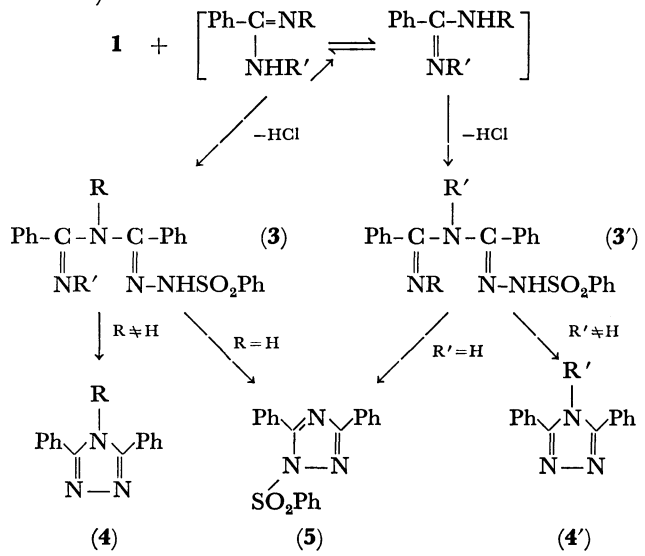
Table 1. The reactions of *N*-(phenylsulfonyl)-benzohydrazonoyl chloride with benzamidines

Ph-C=N-R NHR′		Yields(%) of products[a]			Mp of **4** (°C)
R	R′	**2**	**5**[b]	**4**[c]	
Ph	H	trace	4	82	
Ph	Ph	trace	—	90	291—292[e]
Ph	Me	7	—	70 9(**4′**, R′=Me)[d]	
p-ClC_6H_4	H	4	6	80	266—267[f]
p-MeC_6H_4	H	trace	8	69	291—292[g]
$PhCH_2$	H	10	58	26	223—224[h]
Et	H	22	40	12	159—160[i]
Me	H	16	37	16	248—250[j]
H	H	20	49	—	
Ph-C=NH N=CHPh		12	72	—	

a) Yields(isolated) as mole per cent based on **1** used. Satisfactory analytical data (±0.3% for C,H,N) were obtained for all the known products in the table. b) Colorless needles. Mp 145—147 °C (EtOH). Found: C, 66.56; H, 4.10; N, 11.72%. Calcd for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.19; N, 11.63%. c) The 4-substituent corresponds to the N^2-substituent of the starting amidine shown in the table. d) Identical with 4(R=Me). e) Lit, mp 291—292 °C: Y. A. Levin and M. S. Skorobagotova, *Khim. Geterotsikl. Soedin*, **1967**, 339; *Chem. Abstr.*, **67**, 100076f(1967). f) Lit, mp 252.5—254 °C: *idem.*, *ibid.* g) Lit, mp 291—292 °C: *idem.*, *ibid.* h) Lit, mp 229 °C: T. Curtius and G. Ehrhart, *Ber.*, **55**, 1559 (1922); "Beilsteins Handbuch der Organischen Chemie," E2, Bd. XXVI (1954), p. 49. i) Lit, mp 163.5—164.5 °C: L. A. Lee, R. Evans, and J. W. Wheeler, *J. Org. Chem.*, **37**, 343 (1972). j) Lit, mp 242—243 °C: L. A. Lee and J. W. Wheeler, *ibid.*, **37**, 348 (1972).

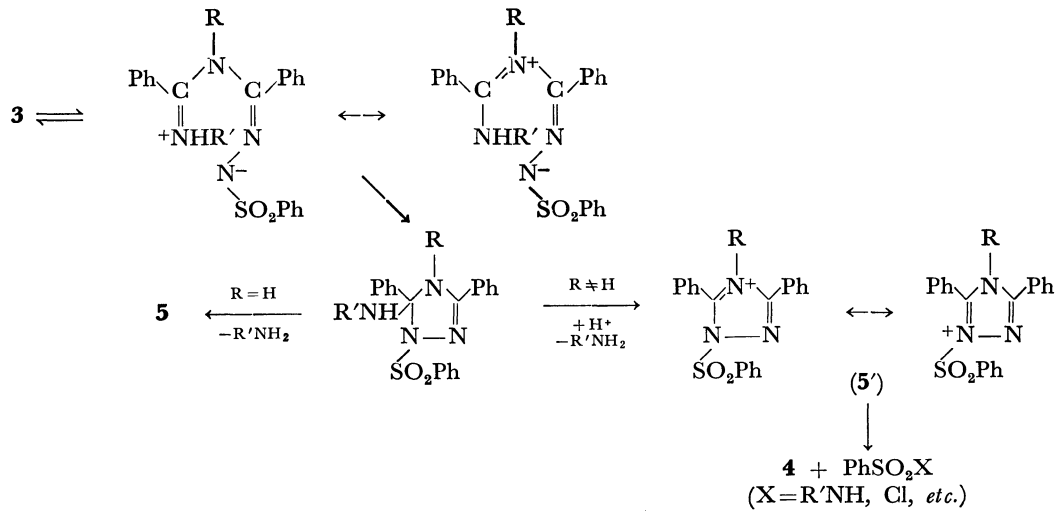
The attempted reactions of **1** with a number of dipolarophiles in the presence of a base *via* the 1,3-dipolar cyclo-addition were unsuccessful, but resulted in the formation of **2** in all cases. The reactivity of **1** different from that of *N*-phenylbenzohydrazonoyl chloride is probably due to the fact that the negative-charge delocalizability of the phenylsulfonyl group is superior to that of the phenyl group: the charge on the amino nitrogen of **1′** is delocalized by the phenylsulfonyl group, so **1′** does not release the chloride anion to form a 1,3-dipole.

Thus, the 1,3-dipolar cyclo-addition mechanism may not be applicable to the reaction of **1** with amidines, and a step-by-step mechanism involving the nucleophilic attack of amidine on **1**, followed by the intramolecular cyclization of the resultant *N*-hydrazonoylbenzamidine (**3** or **3′**)[10] *via* the nucleophilic attack of amino group on the imino carbonyl carbon of the original amidine moiety, can be postulated as more probable (Schemes 3 and 4):



Scheme 3.

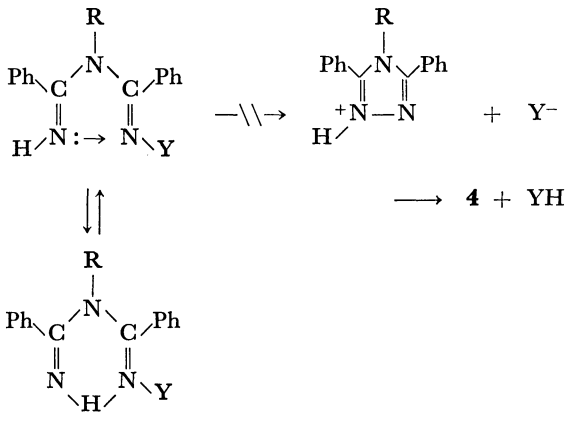
Amidines are a tautomeric compound, so that the nucleophilic attack of amidine on the imidoyl carbon of **1** may take place in two ways. Since the nucleophilicity of imino nitrogen of amidine is stronger than that of amino nitrogen, the predominant formation of **4** in the reaction with *N*-arylbenzamidines indicates that the amidines exist preferentially as arylimino tautomers. This preference is probably a result of the



Scheme 4.

conjugation between the aryl and imino groups.[11] On the other hand, *N*-alkylbenzamidines gave **5** as the major product: presumably, this result is due to the steric hindrance of the *N*-alkyl group.

Since the arylsulfonamido group is also workable as a leaving group, as may be seen in the diazo-transfer reaction with tosyl azide,[12] an alternative process involving the direct replacement of the sulfonamido group, given in Scheme 5, is conceivable for the cyclization of **3** or **3'**; in such a case, R'=H in **3** or R=H in **3'**.



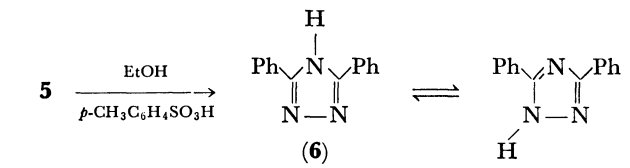
(**3**, R'=H) : Y=$PhSO_2NH$
(**7**) : Y=$PhSO_2$

Scheme 5.

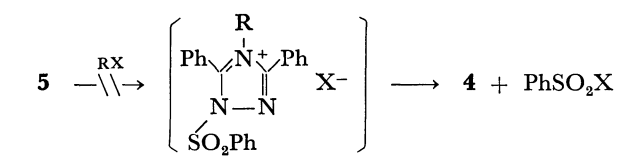
In this route, benzenesulfonamide should be the only product carrying a phenylsulfonyl group. Actually, however, *N*-phenylsulfonylated amidine and amine were mainly obtained, and benzenesulfonamide was a minor product. Consequently, this reaction route is improbable.[13]

Stirring the reaction mixture obtained in the first step of the reaction of **1** with amidine with potassium carbonate after the removal of the precipitates led to the formation of 3,5-diphenyl-4*H*-1,2,4-triazole(**6**) in part, which must have been derived from 1-phenylsulfonyl-3,5-diphenyl-1*H*-1,2,4-triazole(**5**). The combined yield of the two products were almost invariable.

The transformation of **5** to **6** proceeded excellently when the ethanolic solution of **5** was refluxed in the presence of a catalytic amount of *p*-toluensulfonic acid.



Attempts to derive **5** to **4** by alkylation with alkyl halide were, however, unsuccessful.

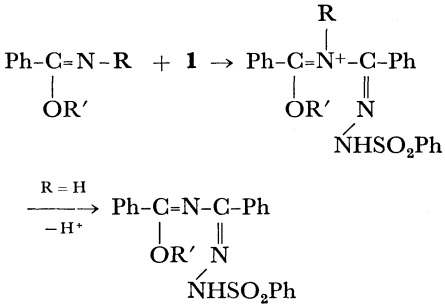


N-Benzylidenebenzamidine gave **5** upon the removal of the benzylideneamine moiety, and the elimination of benzenesulfinic acid from the primary intermediate could not be observed in the presence of alkali.

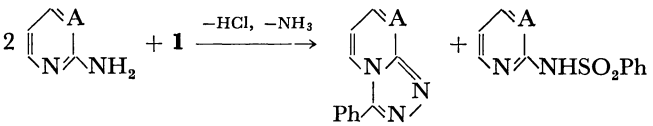
Table 2. 3,5-diphenyl-1,2,4-triazoles from benzimidates(Ph-C(=NR)-OR')

Benzimidate R	Benzimidate R'	Triazole (Yield, %)	
H	Et	**5**	(95)
Ph	Et	**4**(R=Ph)	(25)
Me	Me	**4**(R=Me)	(33)

Reaction with Benzimidates. The reaction of **1** with benzimidates took place analogously with the removal of the alkoxyl group to give triazoles (Table 2). With a slight modification of Schemes **3** and **4** by replacing R'NH by R'O, the reaction route can be represented. In the case of *N*-substituted benzimidates, the reaction proceeded slowly and gave **2** as the main product; this may be due to the uneasy formation of an intermediate because of the lack of a hydrogen atom to be removed as a proton in the imidates.



Reaction with 2-Aminopyridine and -Pyrimidine. 2-Aminopyridine(**8a**) and -pyrimidine(**8b**), cyclic amidines known to exist as amino tautomers, reacted with **1** in a manner similar to that above to give 3-phenyl-1,2,4-triazolo[4,3-*a*]pyridine and -pyrimidine(**9**) respectively in fairly good yields (Table 3).



(**8a**: A=CH, **8b**: A=N) (**9**)

The main phenylsulfonylated products were 2-(phenylsulfonylamino)pyridine and -pyrimidine. These results indicate that the initial hydrazonoylation took place at the ring nitrogen, and that the 2-amino group was removed. No product *via* the alternative process could be isolated.

Since several methods for preparing 4-substituted 3,5-diaryl-4*H*-1,2,4-triazoles are available,[14] the present method is not always useful from the synthetic point of view. On the other hand, for preparing 1,2,4-triazolopyridines, known to be useful anti-convulsants and tranquilizers, the reaction of 2-hydrazinopyridine with carboxylic acid[15] may be the only available method. Thus, because of the ready availability of starting materials, the simplicity of procedure, and the comparatively higher yield of products, this reaction might be useful in obtaining this type of compound.

Table 3. Preparation of 3-phenyl-1,2,4-triazolo[4,3-*a*]pyridines(**9**)

9 A	Yield (%)	Mp (°C)	IR (ν_{max}^{KBr}, cm^{-1})	^{1}H-NMR(δ, ppm, $CDCl_3$)[a]				
				C-4	C-5	C-6	C-7	Ph
CH	54	174—177[b] (EtOH)	1630, 1495, 1461, 1375, 1309, 1176, 1135, 1163, 1010, 751	8.32 brd	6.86 dt	7.28 brt	[d]	7.50—8.00 m
				$J_{4,5}=J_{5,6}=7.0$, $J_{5,7}=1.5$, $J_{6,7}=8.0$ Hz				
N[c]	42	190—193 (EtOH)	1616, 1507, 1442, 1417, 1379, 1347, 1293, 1226, 1172, 1123, 766	8.92 dd	7.09 q	8.86 dd	—	8.30—8.50 m (2H) 7.40—7.70 m (3H)
				$J_{4,5}=6.0$, $J_{4,6}=1.5$, $J_{5,6}=4.5$ Hz				

a) Abbreviations of the NMR spectral patterns are as follows: d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; dt, double triplet; br, broad. b) Lit, mp 173—174 °C: S. Takase and T. Demura, *Kogyo Kagaku Zasshi*, **69**, 1417 (1966). Found: C, 75.32; H, 4.60; N, 21.45%. c) Almost colorless leaflets. Found: C, 67.02; H, 4.12; N, 28.27%. Calcd for $C_{11}H_8N_4$: C, 67.33; H, 4.11; N, 28.56%. d) Overlapped with C-3 phenyl-proton.

Experimental

The melting points were determined with a Yanagimoto micromelting point apparatus, Model MP-S3, and are uncorrected. The microanalysis was performed on a Perkin-Elmer elemental analyzer, Model 240. The IR and NMR spectra were recorded with a JASCO DS-301 spectrometer and a JEOL C60-HL spectrometer respectively.

The *N*-(phenylsulfonyl)benzohydrazonoyl chloride(**1**) was prepared by the previously reported method,[3] while the benzamidines were obtained from ethyl benzimidate hydrochloride or *N*-substituted benzimidoyl chlorides according to methods described in the literature. The products were identified by means of their analytical and spectral data and by comparison with authentic specimens prepared by other synthetic methods.

Reaction of **1** *with Amidines. General Procedure*: A solution of amidine(0.01 mol) in THF(15 ml) was added, drop by drop, to a solution of **1**(0.005 mol) in THF(15 ml) at room temperature. Within a few minutes, precipitates began to separate. The reaction mixture was stirred for 2 h and then allowed to stand overnight. The separated precipitates were filtered and washed with THF. The filtrate combined with the washings was concentrated and then chromatographed on a silica gel(20 g) column, using benzene as the eluent, to give dihydrotetrazine, benzenesulfonamides, *N*-phenylsulfonylamidine, and 1,2,4-triazole. Benzenesulfonyl chloride, when formed, was obtained as the first eluate. Most of the 4-substituted 3,5-diphenyl-4*H*-1,2,4-triazole was obtained in a fairly pure state by washing the precipitates above separated with water, followed by cold ethanol. The results are summarized in Tables 1 and 3.

Reaction of **1** *with Benzimidates.* The reaction was conducted in a manner similar to that used with amidines. The results are summarized in Table 2.

References

1) S. Ito, Y. Tanaka, and K. Yoshida, Abstracts of the Meeting of the Tokai Branch of the Chemical Society of Japan, Matsumoto, November 1972, p. 1; Abstracts of the 28th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1973, Vol. III, p. 1371.

2) Phenylsulfonylamino nitrogen may function also as an electrophilic center with the elimination of the benzenesulfinate ion; see Ref. 3.

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

4) R. Fusco and C. Musante, *Gazz. Chim. Ital.*, **68**, 147 (1938).

5) R. Huisgen, R. Grashey, E. Aufderhaar, and R. Kunz, *Chem. Ber.*, **98**, 642 (1965).

6) Amine and amidine hydrochloride separated as precipitates in the reaction.

7) This fact might support the possible and potential intermediacy of **5'**(Scheme 4), which may be a strong phenylsulfonylating agent.

8) Compound **2'**: mp 160—162 °C(dec), IR(KBr, cm^{-1}), 3190(ν_{NH}), 1370; 1350; 1170(ν_{SO_2}). Found: C, 56.79; H, 3.79; N, 10.12%. Calcd for $C_{26}H_{21}N_4S_2O_4Cl$: C, 56.47; H, 3.83; N, 10.13%.

9) Wawzonek and Kellen obtained 1,4-dihydro-3,6-diphenyl-1,4-bis(*p*-tolylsulfonyl)-1,2,4,5-tetrazine by treating *N*-(*p*-tolylsulfonyl)benzohydrazonoyl chloride with triethylamine, and suggested the same reaction route for this dehydrochlorodimerization(S. Wawzonek and J. N. Kellen, *J. Org. Chem.*, **38**, 3627 (1973)).

10) The overall reaction generally proceeded easily at room temperature, and the primary product or intermediate, **3** or **3'**, could not be isolated. However, **1** is able to function as a hydrazonoylating agent: for example, the formation of **2'** should be ascribed to the hydrazonoylation of **1'** with **1**, and the reaction of **1** with arylhydrazines[3] proceeds *via* the *N*-hydrazonoylation of hydrazine with **1**. Therefore, the postulation of **3** or **3'** is reasonable.

11) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. I, W. A. Benjamin, New York (1965), p. 178.

12) M. Regitz, *Angew. Chem.*, **79**, 786 (1967).

13) In order to obtain some mechanistic information, the ring closure of N^1-phenyl-N^1-benzimidoyl-N^2-(phenylsulfonyl)-benzamidine(**7**, prepared from *N*-(phenylsulfonyl)benzimidoyl chloride and *N*-phenylbenzamidine, mp 222—225 °C) to **4** was examined. However, even under reflux in xylene in the presence of alkali, no remarkable change was observed, and most of the **7** was recovered. The concerted 1,5-*cis* elimination of benzenesulfinic acid should not be possible because of the anti-aromaticity of the transition state; in the intramolecular S_N2-type route(Scheme 5), the separation of an unlike charge is required for the activation process; the most stable configuration of **7** may be the U-shaped form with hydrogen-bonding. These seem to be the reasons for the unreactivity of **7**.

14) *E.g.*, R. Stolle, *J. Prakt. Chem.*, **73**, 288(1906); G. Scheuing and B. Walach, German Patent 543026; *Chem. Abstr.*, **26**, 3263 (1932).

15) J. B. Bicking, U. S. Patent 2917511; *Chem. Abstr.*, **54**, 8854e (1960).