Tetrahedron Vol. 47, No. 3, pp. 447-456, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

REDUCTIVE CONDENSATION OF TRICHLOROMETHYLARENES WITH HYDROXYLAMINE AND HYDRAZINES IN PYRIDINE

L.I.Belen'kii*, D.B.Brokhovetskii, M.M.Krayushkin

N.D.Zelinsky Institute of Organic Chemistry,
USSR Academy of Sciences, 117913, Moscow, USSR

(*Received in UK 6 August* 1990)

Abstract. The interaction of trichloromethylarenes with hydroxylamine in pyridine involves the reductive oximation of aryltrichloromethanes. Further transformations of the oximes in the reaction course can result in the formation of nitriles or 3,5-diaryl-1,2,4-oxadiazoles as final products. The conversion depth depends on reaction conditions and structures of trichloromethylarenes. When hydrazines used instead of hydroxylamine, respective benzaldehyde hydrazones or azines are obtained.

Introduction

Studying the reaction of trichloromethylarenes (TCMAs) with hydroxylamine in ethanol, we have revealed a new way of arenecarbonitrile oxides formation[1]. The reaction proceeds via the corresponding hydroximoyl chlorides, besides hydroxamic and carboxylic esters are formed. The latter fact prompted us to use another solvent which is not capable to react with hydroximoyl chlorides or nitrile oxides giving mentioned esters. It turned out unexpectedly that the replacement of ethanol by pyridine initiated the reductive oximation of TCMA (see a preliminary report[2]) which could be followed by dehydration of the oxime to form the nitrile while further transformation led to 3,5-diaryl-1,2,4-oxadiazoles. The process depth depends on reaction conditions and TCMA structure.

Results and Discussion

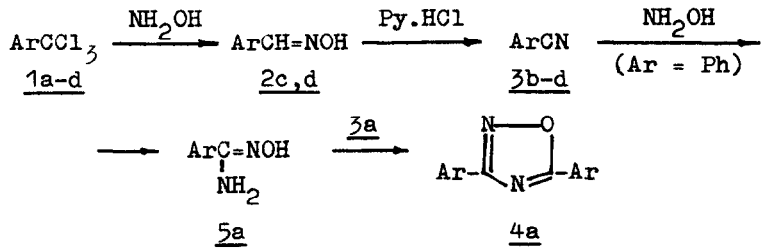
The following trichloromethylarenes $ArCCl_3$ (1, Ar = a Ph, b 2,4-$Me_2C_6H_3$, c 2,4,5-$Me_3C_6H_2$, d 2,4,6-$Me_3C_6H_2$) differing in the presence and number of methyl substituents, i.e. in steric shielding of the reaction centre, were chosen for the investigation.

Boiling trichloromethylmesitylene (1d) solution in pyridine with an excess of $NH_2OH.HCl$ does not lead to the expected hydroximoyl chloride but, instead, affords 2,4,6-trimethylbenzaldehyde oxime (2d) in high yield. The highest yield of the oxime (80%) was achieved with five-fold

excess of hydroxylamine and reaction time of 1 h. A decrease of NH_2OH amount and reaction time lowers the oxime yield. When NH_2OH excess is increased to 10-fold one and the process time to 2 h, 2,4,6-trimethylbenzonitrile (3d) was isolated in 15% yield along with the oxime 2d (45%). The former apparently formed from 2d. It should be pointed out in this connection that the dehydration of oximes to yield nitriles on the action of pyridine hydrochloride was described earlier[3] with both syn- and anti-aldoximes undergoing dehydration. An increase of $NH_2OH.HCl$ amount raises the pyridine hydrochloride concentration and favours dehydration of the oxime 2d which is a mixture of syn- and anti-isomers at a ratio of about 1:1 (PMR, see Table).

On boiling of 2,4,5-trimethylbenzotrichloride (1c) solution in pyridine with a 10-fold excess of hydroxylamine hydrochloride during 2 h, 2,4,5-trimethylbenzaldehyde oxime (2c) and respective nitrile (3c) were isolated in 30% and 35% yields, respectively. A higher yield of the nitrile 3c than isomeric nitrile 3d was apparently caused by lesser steric shielding of the oximino group in 2c as compared with 2d, as a result of which dehydration of the oxime 2c was facilitated. This keeps in line with the 2,4-dimethylbenzotrichloride (1b) reaction results: on boiling with 5-fold excess of $NH_2OH.HCl$ in pyridine, 1b converts to 2,4-dimethylbenzonitrile (3b) in 50% yield, the latter obviously being formed from the respective aldoxime.

In the conditions described above for the chloride 1b benzotrichloride (1a) as the substrate unexpectedly gives 3,5-diphenyl-1,2,4-oxadiazole (4a) which is probably formed via benzamidoxime (5a). The interaction between nitriles and hydroxylamine can serve as general method for the synthesis of amidoximes[4], the latter thereby formed can be converted into oxadiazoles 4 on action of benzonitrile[5], another benzamidoxime molecule[4] or benzotrichloride[6]. On the basis of our results[6] one may suggest that the most probable way of the oxadiazole 4a formation under the conditions of reductive oximation (boiling in pyridine) consists of the reaction of amidoxime with nitrile. Thus, the reaction of TCMAs with hydroxylamine in pyridine may be presented by the following scheme:



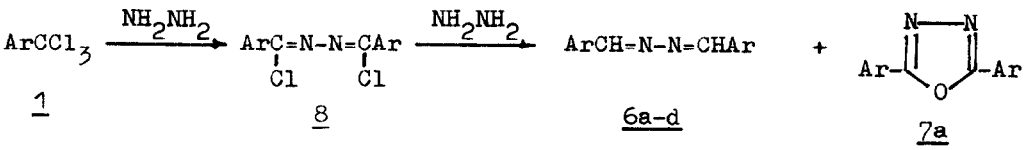
The scheme presented does not explain in what manner the reductive oximation of TCMAs itself occurs. First of all, an attempt was made to evaluate the role of pyridine in the transformations. Benzotrichloride is known to enter Fujiwara reaction with pyridine which involves the substitution of one or two chlorine atoms and the formation of respective pyridinium salts; the cleavage of the pyridine ring in the latter under the action of an alkali leads to glutaconic aldehyde derivatives[7,8]. Since there was no alkali in conditions used by us, a possibility of further transformations of the pyridinium salts under the action of hydroxylamine in pyridine was checked. However the formation of type 2-4 products was not observed, which made it possible to reject the reductive oximation of benzotrichlorides to proceed *via* their interaction with pyridine. It is noteworthy that pyridine is not an unique solvent for the reductive oximation and further transformations: the corresponding nitriles were isolated from products of reactions of benzotrichloride 1a and 2,4,6-trimethylbenzotrichloride 1d with hydroxylamine in triethylamine or quinoline, although we were not succeeded in analysing complex mixtures formed in detail. Thus, the nature of pyridine being a nitrogen-containing base plays an essential part in the reaction pathway; newertheless, its role should not be only the liberation of NH_2OH from its hydrochloride.

Inasmuch as hydroxylamine is a reducing reagent, it may be suggested that the reaction involves benzotrichloride reduction to respective benzylidene dichlorides as the first stage followed by the formation of 2-4 type products. We have compared reactions of 2,4,6-trimethylbenzotrichloride 1d and 2,4,6-trimethylbenzylidene dichloride with $NH_2OH.HCl$ runned under similar conditions (boiling in pyridine); the reactions were monitored by GLC which showed both reactions to proceed at comparable rates. In both cases the main product proved to be respective oxime 2d while the formation of 2,4,6-trimethylbenzylidene dichloride from trichloromethylmesitylene 1d was not observed, which did not corroborate the possibility of intermediate dichloromethylarene formation in the course of reductive oximation.

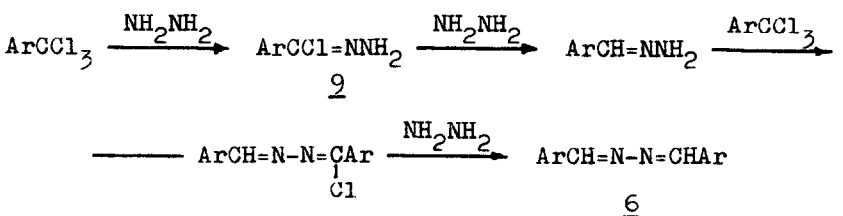
Another possible way of aldoxime formation from TCMAs in pyridine includes intermediate formation of hydroximoyl chlorides, like in reactions using ethanol as the solvent[1]. The possibility of such an unusual oxime preparation by the reduction of hydroximoyl chlorides with hydroxylamine in pyridine was confirmed experimentally. So, boiling of 2,4,6-trimethylbenzhydroximoyl chloride with 4-fold excess of NH_2OH in pyridine leads to 60% yield of 2,4,6-trimethylbenzonitrile 3d instead of expected substitution product, i.e. hydroxyamidoxime (Cf.[4]). This fact is in agreement with the following reaction sequence:

$$ArCCl_3 \xrightarrow[-2HCl]{NH_2OH} ArCCl{=}NOH \xrightarrow{NH_2OH} ArCH{=}NOH \xrightarrow[-H_2O]{Py.HCl} ArCN$$

The transformations considered prompted us to study the interaction between TCMAs and hydrazines which are also reducing agents, using pyridine as the solvent. It is known that reactions of benzotrichlorides with hydrazines in methanol produce 2,5-diaryl-1,3,4-triazoles and 1-amino-2,5-diaryl-1,3,4-triazoles[9]. We have found that the boiling of TCMAs 1b-d with 5-fold excess of hydrazine hydrochloride in aqueous pyridine for 30 to 45 min gives completely different results: respective methyl-substituted benzaldazines (6b-d) are obtained in 45-65% yield. Under similar conditions, benzotrichloride 1a produces benzaldazine (6a, 10%) and 2,5-diphenyl-1,3,4-oxadiazole (7a, 20%). The formation of aldazines 6a-d and oxadiazole 7a can be presented by the following scheme:



The formation of oxadiazole 7a from dichloride 8a under the action of water which is present in the reaction mixture is in agreement with known data[10] on the synthesis of 1,3,4-oxadiazoles, however sequential reaction of TCMA with one amino group of hydrazine molecule followed by the product (9) reduction cannot be excluded:



It is possible that, in the case of sterically unhindered benzotrichloride 1a, the interaction between one molecule of hydrazine and two TCMA molecules to form dichloride 8a is more probable; the dichloride is further reduced to azine 6a or cyclized giving oxadiazole 7a whereas sterically hindered TCMAs 1b-d react in accordance to the above scheme yielding azines 6b-d as the only products. This assumption keeps in line with the lack of 1,3,4-oxadiazoles in products formed in reactions of compounds 1b-d with hydrazine.

The possibility of the chlorides 8 and 9 to be reduced with hydrazine have been supported by the interaction of N-phenylbenzhydrazonoyl chloride and 4-fold excess of hydrazine in pyridine which leads to benzaldehyde phenylhydrazone in 40% yield:

$$PhC(Cl)=NNHPh \xrightarrow{NH_2NH_2} PhCH=NNHPh$$

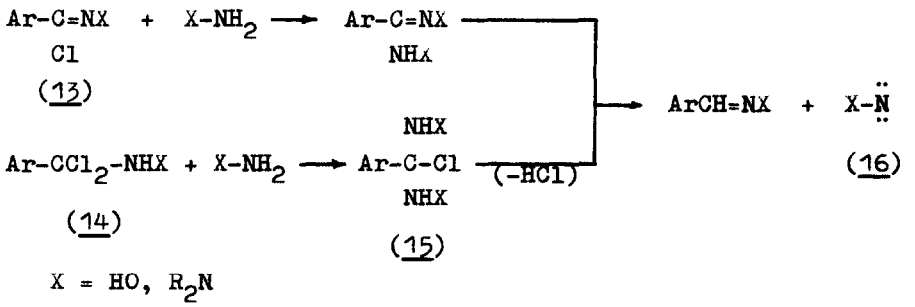
With the aim to clarify the generality of the reaction found we have also studied the interaction between TCMAs and substituted hydrazines unable to form azines, namely acetylhydrazine and N,N-dimethylhydrazine. Reaction of trichloromethylmesitylene 1d with excess acetylhydrazine in pyridine does not afford 1,3,4-oxadiazole (as in the known reaction in ethanol[11]) but, instead, gives 2,4,6-trimethylbenzaldehyde acetylhydrazone (10) in 50% yield. In addition, the azine 6d was isolated (11%), however its formation mechanism requires an additional study.

$$ArCCl_3 + AcNHNH_2 \longrightarrow \underset{10}{ArCH=NNHAc} + \underset{6d}{ArCH=N-N=CHAr}$$

On boiling of TCMAs 1b-d in pyridine with 5-fold excess of N,N-dimethylhydrazine for 2 h 50-60% yields of dimethylhydrazones of respective aldehydes (11b-d) have been obtained. Benzotrichloride 1a does not react under the same conditions. The assumed formation of the reduction products (11) from hydrazonoyl chlorides 12 was not corroborated: both 2,4,6-trimethylbenzhydrazonoyl chloride 12d and the corresponding bromide do not produce, on boiling with N,N-dimethylhydrazine in pyridine, the hydrazone 11d, which makes us to consider the possible reduction in a preliminary stage:

$$ArCCl_3 + H_2NNMe_2 \longrightarrow ArCCl_2\text{-}NHNMe_2 \not\longrightarrow \underset{12}{ArCCl=NNMe_2}$$
$$\downarrow [H] \qquad\qquad \downarrow \not$$
$$ArCHCl\text{-}NHNMe_2 \longrightarrow \underset{11}{ArCH=NNMe_2}$$

As to the mechanism of the reduction act itself, one of possible schemes might include intermediate formation of diimide known for reductions using hydrazine[12]. However, the fact that hydroxylamine and N,N-dimethylhydrazine which are not able to generate diimide can also play a role of reducing agents allow the suggestion of nitrene mechanism [13,14]. In such mechanism the role of pyridine as a solvent is determined by its basic properties which, owing to pyridinium salt formation, promote the dissociation of C-Cl bond in hydroximoyl chlorides, hydrazonoyl chlorides (13) and intermediates like 14, 15. Unfortunatelly, the attempts to trap nitrenes 16 were unsuccessful and the scheme below is only hypothetic one:



Experimental

PMR spectra were recorded on JEOL FX-90Q (90 MHz) and Bruker WM-250 (250 MHz) spectrometers in $CDCl_3$. IR spectra were obtained on Perkin-Elmer 577 and Specord M-80 instruments (disks with KBr and, for liquids, solutions in $CHCl_3$). Mass spectra were recorded on a Varian MAT CH-6 spectrometer (direct introduction of the sample, ionizing energy 70 eV, emission current 100 μA). Cardinal spectral characteristics of oxime 2d, azines 6b-d, and hydrazones 10, 11b-d are listed in the Table.

The preparative chromatography was carried out on columns packed with silica L 40 (100 μ). Melting points were obtained from a microscopic Boetius heated plate.

Interaction between trichloromethylarenes 1a-d and hydroxylamine

A. To a solution of 20 mmol of $NH_2OH.HCl$ in 20 ml of pyridine 4 mmol of trichloride 1 was added, the mixture was then boiled for 1 h, poured into 100 ml of cooled water, and crystals precipitated filtered off and recrystallized from ethanol.

B. The synthesis was carried out as above using 40 mmol of $NH_2OH.HCl$ and reaction time of 2 h.

The following compounds were obtained from 1a-d, respectively:

a) 3,5-diphenyl-1,2,4-oxadiazole (4a), 37% yield, m.p. 107-108 °C (lit.: see Ref.[15]), M^+ 222 (method A);

b) 2,4-dimethylbenzonitrile (3b), 50% yield, m.p. 23-24 °C (hexane) (lit.: see Ref.[16]), M^+ 131, ν_{CN} 2220 cm^{-1} (method A);

c) 2,4,5-trimethylbenzonitrile (3c), 35% yield, m.p. 56-57 °C (lit.: see Ref.[17]), M^+ 145, ν_{CN} 2220 cm^{-1} and 2,4,5-trimethylbenzaldoxime (2c), 30% yield, m.p. 109-111 °C (lit.: see Ref.[18]), M^+ 163, IR: 3225 (OH), 1608 (C=N) cm^{-1} (method B);

d) 2,4,6-trimethylbenzaldoxime (2d), 80% yield, m.p. 115-143 °C, which is a mixture of E- and Z-isomers in a ratio ca. 1:1 (PMR) (lit.[19]: m.p. 179 °C for E- and 124 °C for Z-isomer) (method A); oxime 2d, 45% yield and 2,4,6-trimethylbenzonitrile (3d), 15% yield, m.p. 53-54 °C (lit.: see Ref.[20]), M^+ 145, ν_{CN} 2220 cm^{-1}; products 2d and 3d were separated by

column chromatography (ethyl acetate - hexane, 1:3) (method B).

Reaction of trichloromethylarenes 1a-d with hydrazine

To a solution of 10 mmol of hydrazine hydrochloride in 5 ml of pyridine and 1 ml of water chloride 1 (2 mmol) was added. The mixture was boiled for 30 to 45 min, poured into 50 ml of cooled water, and extracted with ether. After distilling of the solvent, the residue was chromatographed on a column packed with silica (benzene as eluent) to give, respectively:
a) benzaldazine (6a), m.p. 92-93 °C (lit.: see Ref.[21]), 10% yield and 2,5-diphenyl-1,3,4-oxadiazole (7a), m.p. 139-140 °C (ethanol) (lit.: see Ref.[22]), 20% yield;
b) 2,4-dimethylbenzaldazine (6b), 50% yield, m.p. 116-117 °C (ethanol) (lit.: see Ref.[23]);
c) 2,4,5-trimethylbenzaldazine (6c), 45% yield, m.p. 178-180 °C (lit.: see Ref.[21]);
d) 2,4,6-trimethylbenzaldazine (6d), 65% yield, m.p. 169-170 °C (lit.: see Ref.[24]).

Reaction of trichloromethylmesitylene (1d) with acetylhydrazine

To a solution of 1.2 g (17 mmol) of acetylhydrazine in 5 ml of pyridine (prepared with heating) 0.8 g (3.4 mmol) of trichloride 1d was added with subsequent boiling for 1 h. After distilling off pyridine, column chromatography on silica (benzene) afforded 0.12 g (11%) of azine 6d and 0.42 g (50%) of 2,4,6-trimethylbenzaldehyde acetylhydrazone 10, m.p. 181-183 °C (ethanol). Found, %: C 70.62, H 7.95, N 13.53. $C_{12}H_{16}N_2O$. Calcd., %: C 70.56, H 7.90, N 13.72.

Reaction of trichloromethylarenes 1b-d with N,N-dimethylhydrazine

To a solution of 20 mmol of N,N-dimethylhydrazine in 10 ml of pyridine 4 ml of trichloromethylarene 1b-d was added. The mixture was boiled during 2 h, and then poured into 50 ml of cooled water with subsequent extraction with chloroform. Column chromatography (SiO_2, benzene) furnished respective dimethylhydrazones (DMH):
2,4-Dimethylbenzaldehyde DMH (11b), b.p. 85-87 °C (5 mm Hg), n_D^{20} 1.5782, 48% yield. Found, %: C 74.80, H 9.20, N 16.01. $C_{11}H_{17}N_2$. Calcd., %: C 74.95, H 9.16, N 15.89.
2,4,5-Trimethylbenzaldehyde DMH (11c), m.p. 66-67 °C (ethanol), 50% yield. Found, %: C 75.59, H 9.70, N 14.73. $C_{12}H_{18}N_2$. Calcd., %: C 75.74, H 9.53, N 14.73.
2,4,6-Trimethylbenzaldehyde DMH (11d), b.p. 107-109 °C (5 mm Hg), n_D^{20} 1.5653, 60% yield. Found, %: C 75.94, H 9.57, N 15.03. $C_{12}H_{18}N_2$. Calcd., %: C 75.74, H 9.53, N 14.73.

Table

PMR, Mass and IR Spectra of Oxime 2d, Azines 6b-d, Acylhydrazone 10 and N,N-Dimethylhydrazones 11b-d

Compound	Chemical shifts, ppm*						M^+	ν, cm^{-1}
	Methyl groups		Benzene ring protons			CH		
	Me_{arom}	Me_2N	H^3	H^5	H^6			
2d	2.27 2.30 2.40	-	6.90	6.90	-	7.65** 8.44**	163	3260 (OH) 1612 (C=N)
6b	2.36 2.53	-	7.07	7.10***	7.97***	8.98	264	1608 (C=N)
6c	2.30 (12H) 2.50 (6H)	-	7.02	-	7.86	8.98	292	1608 (C=N)
6d	2.33 (6H) 2.53 (12H)	-	6.39	6.93	-	9.00	292	1608 (C=N)
10****	2.30 (3H) 2.35 (3H) 2.48 (6H)	-	6.92	6.92	-	8.18	204	3180, 3080 (OH), 1680 (C=O), 1607 (C=N)
11b	2.34 (3H) 2.42 (3H)	2.99	6.98	7.04***	7.72***	7.47	176	1608 (C=N)
11c	2.24 (3H) 2.26 (3H) 2.38 (3H)	2.98	6.93	-	7.58	7.45	190	1608 (C=N)
11d	2.30 (3H) 2.41 (6H)	2.97	6.92	6.92	-	7.48	190	1608 (C=N)

*Signals are singlets if otherwise not mentioned.

**A mixture of E- and Z-isomers (ca. 1:1), OH 8.20 ppm (broad.).

***Doublet, J = 8 Hz.

****NH 9.92 ppm (broad.).

Reduction of 2,4,6-trimethylbenzhydroximoyl chloride

To a solution of 16 mmol of $NH_2OH.HCl$ in 5 ml of pyridine 4 mmol of 2,4,6-trimethylbenzhydroximoyl chloride[1] was added, the mixture was boiled for 45 min, poured into 50 ml of cooled water and extracted with chloroform. Column chromatography (SiO_2, benzene) gave 60% of 2,4,6-trimethylbenzonitrile (3d) which melting point and spectral data corresponded to those previously reported[20] as well as to the above data.

Reduction of N-phenylbenzhydrazonoyl chloride

To a solution of 7.5 mmol of $NH_2NH_2.2HCl$ in 5 ml of pyridine and 1 ml of water 2 mmol of N-phenylbenzhydrazonoyl chloride[25] was added. The mixture was boiled for 30 min, poured into water and extracted with chloroform. After distilling off chloroform, column chromatography (SiO_2, hexane - ethyl acetate, 3:1) gave 40% of benzaldehyde phenylhydrazone, m.p. 154-156 °C, M^+ 196 (lit.: see Ref.[26]).

N,N-Dimethyl-2,4,6-trimethylbenzhydrazonoyl chloride (12d)

To a solution of 1 mmol of 2,4,6-trimethylbenzaldehyde N,N-dimethylhydrazone 11d in 5 ml of CH_2Cl_2 a solution of 1.1 mmol of chlorine in 5 ml of CH_2Cl_2 was added, the mixture was then stirred at 20 °C for 4 h. The solvent was removed by distillation to afford chloride 12d (70%), m.p. 132-137 °C (benzene). PMR spectrum ($CDCl_3$, ppm): 2.20 s (3H, Me), 2.24 s (3H, Me), 2.27 s (3H, Me), 3.20 s (6H, Me_2N), 6.87 s (2H, H_{arom}). Found, %: C 64.02, H 7.60, Cl 16.07, N 12.23. $C_{12}H_{17}ClN_2$. Calcd., %: C 64.13, H 7.63, Cl 15.77, N 12.47.

N,N-Dimethyl-2,4,6-trimethylbenzhydrazonoyl bromide was obtained and isolated similarly to chloride 12d in 68% yield, m.p. 147-150 °C. PMR spectrum ($CDCl_3$, ppm): 2.26 s (3H, 4-Me), 2.30 s (6H, 2- and 6-Me), 2.70 s (6H, Me_2N), 6.84 s (2H, H_{arom}). Found, %: C 53.47, H 6.44, Br 29.35, N 10.28. $C_{12}H_{17}BrN_2$. Calcd., %: C 53.54, H 6.37, Br 29.68, N 10.41.

Only starting compounds could be returned in the interactions between chloride 12d or respective bromide and 4-fold excess of N,N-dimethylhydrazine in boiling pyridine during 2 h.

References

1 Brokhovetskii D.B.; Belen'kii L.I.; Krayushkin M.M. Izv. Akad. Nauk SSSR. Ser. Khim. 1990, No. 7, 1692-1693.

2 Brokhovetskii D.B.; Belen'kii L.I.; Krayushkin M.M. Izv. Akad. Nauk SSSR. Ser. Khim. 1989, No. 3, 748.

3 Hauser C.R.; Vermillion G. J. Am. Chem. Soc. 1941, 63, 1224-1227.

4 Eloy F.; Lenaers R. Chem. Rev. 1962, 62, 155-183.

5 Yarovenko V.N.; Zavarzin I.V.; Krayushkin M.M. Izv. Akad. Nauk SSSR. Ser. Khim. 1986, No. 5, 1213.

6 Belen'kii L.I.; Brokhovetskii D.B.; Krayushkin M.M. Tetrahedron 1990, 46, 1659-1668.
7 Uno T.; Okumura K.; Kuroda Y. J. Org. Chem. 1981, 46, 3175-3178.
8 Okumura K.; Wada T.; Kuroda Y. Chem. Pharm. Bull. 1984, 32, 174-178.
9 Suzuki T.; Mitsuhashi K. Seikei Daigaku Kugakubu Kogaku Hokoku 1976, 22, 1579-1580; C.A. 1977, 86, 139916.
10 Nesynov E.L.; Grekov A.P. Usp. Khim. 1964, 33, 1184-1197.
11 Golfier M.; Milcent R. Synthesis 1979, No. 12, 946-948.
12 Furst A.; Berlo R.C.; Hooton S. Chem. Rev. 1965, 65, 51-68.
13 Ioffe B.V.; Kuznetsov M.A.; Potekhin A.A. Khimiya Organicheskikh Proizvodnykh Gidrazina Khimiya Publ., Leningrad, 1972, 224 p.p.
14 Kuznetsov M.A.; Ioffe B.V. Usp. Khim. 1989, 58, 1271-1297.
15 Goetz N.; Zeeh B. Synthesis 1976, No. 4, 268-269.
16 Birch S.F.; Deen R.A.; Fidler F.A.; Lowry R.A. J. Am. Chem. Soc. 1949, 71, 1362-1369.
17 Haller S. Ber. 1885, 18, 89-94.
18 Lowe G.; Torto F.G.; Weedon B.C.L. J. Chem. Soc. 1958, No. 5, 1855-1861.
19 Hantzsch A.; Lucas A. Ber. 1895, 28, 744-753.
20 Houben J; Fischer W. Ber. 1933, 66, 339-349.
21 Schapiro N. Ber. 1933, 66, 1103.
22 Folpmers T. Rec. trav. chim. 1915, 34, 5234-5277.
23 Curtius T. J. prakt. Chem. /2/, 1900, 62, 83-126.
24 Nauta W.T.; Wuis P.J. Rec. trav. chim. 1938, 57, 41-60.
25 Pechmann H; Seeberger L. Ber. 1894, 27, 2121-2125.
26 Grammaticakis P. Compt. rend. 1947, 224, 1568-1569.