Tetrahedron Vol 46, No 5, pp 1659-1668, 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00
© 1990 Pergamon Press plc

SYNTHESIS OF 3,5-DIARYL-1,2,4-OXADIAZOLES FROM TRICHLOROMETHYLARENES AND ARENEAMIDOXIMES

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 2 August* 1989)

Abstract. The interaction of trichloromethylarnes $ArCCl_3$ [1, Ar = Ph (a), 2,4-$Me_2C_6H_3$ (b), 2,4,6-$Me_3C_6H_2$ (c), 2,4,5-$Me_3C_6H_2$ (d)] with areneamidoximes $Ar'C(NH_2)=NOH$ [2, Ar' = Ph (a), 4-$NO_2C_6H_4$ (b), 4-$MeOC_6H_4$ (c)] was studied. The reaction in the absence of a solvent at 140-150 °C leads to the formation of 3,5-diaryl-1,2,4-oxadiazoles (3). The reaction carried out in solvents (benzene, toluene, nitrobenzene, pyridine) in the broad temperature range (0-150 °C) showed the first stage of the process to be obviously an electrophilic attack of (1) on O-atom of (2), products of which undergo cyclization converting into oxadiazoles (3), or side processes, i.e. rearrangement into N-substituted derivatives, or fragmentation with the formation of nitrile Ar'CN (4) which corresponds to starting amidoxime along with acid ArCOOH (5) corresponding to trichloromethylarene (1), being formed during the treatment of the reaction mixture.

Introduction

Recently various substituted benzotrichlorides have become quite accessible[1-4]. This accounts for their extended use in organic synthesis. For instance, the formation of a number of heterocyclic systems under the action of trichloromethylarenes on aminoalcohols, hydrazines and semicarbazide derivatives was shown[5-10].

As early as 1884, Tiemann and Kruger reported the formation of 3,5-diphenyl-1,2,4-oxadiazole from benzotrichloride and benzamidoxime[11], but they did not present either reaction conditions, or data on the yield. As far as we know, for more than 100 years the reaction under discussion has not been reproduced. Besides, the choice of objects was not optimal due to the easy conversion of benzamidoxime into diphenyl-1,2,4-oxadiazole, for example, under the action of heating and acids[12].

Results and Discussion

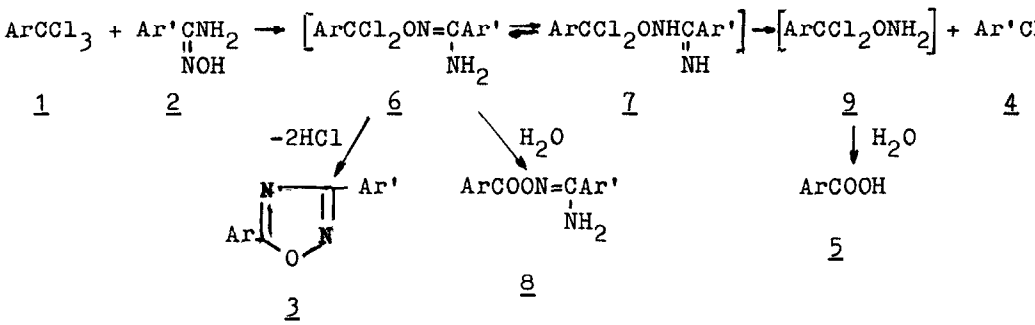
The aim of this paper was to study the perspectives of the synthesis of 1,2,4-oxadiazoles from aryltrichloromethanes and areneamidoximes. It is essential to note that not only benzotrichloride and benzamidoxime but also their derivatives bearing electron-releasing and electron-withdrawing substituents were used. Trichloromethylarenes $ArCCl_3$ [1, Ar = Ph (a), 2,4-$Me_2C_6H_3$ (b), 2,4,6-$Me_3C_6H_2$ (c), 2,4,5-$Me_3C_6H_2$ (d)] were introduced into the reaction with areneamidoximes $Ar'C(NH_2)=NOH$ [2, Ar' = Ph (a), 4-$NO_2C_6H_4$ (b), 4-$MeOC_6H_4$ (c)]. In the course of the reaction of 1a-d with 2b,c in the absence of a solvent at 140-150 °C 3,5-diaryl-1,2,4-oxadiazoles (3) were obtained in 40-60% yields. The end of the hydrogen chloride release served as a criterion for the reaction completion. The products were separated by means of column chromatography. For benzamidoxime 2a the above conditions are too drastic and mainly lead to the product of thermal destruction of 2a, i.e. benzonitrile 4a.

The proposed general method for diaryloxazole (3) synthesis can be considered as an analogue of preparative synthesis of 1,2,4-oxadiazoles from amidoximes and various derivatives of carboxylic acids[13]. It is known that in the process of the reaction between carboxylic acid chlorides and amidoximes the O-acylation of amidoxime is the first stage accompanied by cyclization[14], however the cases of obtaining N-mono- as well as N,O-diacyl-substituted amidoximes were also described[13,14]. Unfortunately, when reactions of trichloromethylarenes with amidoximes were carried out in the absence of a solvent we did not manage to obtain any intermediate products.

To establish the course of the reaction, as well as to carry out syntheses of 3-phenyl-5-aryl-1,2,4-oxadiazoles (from 2a) various solvents (benzene, toluene, pyridine, nitrobenzene) were used. While boiling in benzene trichloromethylarenes 1b-d with 4-fold excess of 2a for HCl neutralization corresponding oxadiazoles (3b-d) in 50-70% yields and benzonitrile (15-20%) were obtained. Under these conditions benzotrichloride (1a) gives 3,5-diphenyl-1,2,4-oxadiazole (3a) in the yield as low as 5%. The temperature growth when the reaction was carried out in boiling toluene allows the increase of the yield for 3a up to 50%. It should be noted that neither 2a nor its hydrochloride while boiling in toluene gives even traces of 3a and this proves the trichloride 1a participation in the formation of 3a under these conditions.

The interaction of trichloromethylarene 1c with 4-methoxybenzamidoxime (2c) in boiling benzene leads after hydrolysis of the reaction mixture to N-acylamidoxime (10) which failed to undergo cyclization into corres-

ponding 1,2,4-oxadiazole. 4-Nitrobenzamidoxime (2b) is insoluble in non-polar solvents, so to carry out the reaction under the same conditions we had to use pyridine which played simultaneously a role of an acceptor for HCl, thus taking advantage of equimolar ratios of components. It was found that while boiling in pyridine amidoximes 2a-c reacted in the same manner, nitriles Ar'CN (4) and acids ArCOOH (5) being the main products of the reaction. In the case of benzamidoxime (2a) along with the above products of fragmentation oxadiazoles (3a-d) were also formed in the yields no more than 20%. In addition, oxadiazoles 3b-d contained some diphenyl-substituted derivative (3a) formed as the result of amidoxime 2a "dimerization". Analogous results were obtained for the interaction of 1b,c with 2b in nitrobenzene (100-120 °C, 3 h with subsequent treatment with water). The properties of the obtained compounds are listed in Table 1. As a whole, the transformations under consideration can be described by Scheme 1.



1 and 5 a) Ar = Ph; b) Ar = 2,4-$Me_2C_6H_3$; c) Ar = 2,4,6-$Me_3C_6H_2$; d) Ar = 2,4,5-$Me_3C_6H_2$.

2 and 4 a) Ar' = Ph; b) Ar' = 4-$NO_2C_6H_4$; c) Ar' = 4-$MeOC_6H_4$.

3 a) Ar = Ar' = Ph; b) Ar = 2,4-$Me_2C_6H_3$, Ar' = Ph; c) Ar = 2,4,6-$Me_3C_6H_2$, Ar' = Ph; d) Ar = 2,4,5-$Me_3C_6H_2$, Ar' = Ph; e) Ar = Ph, Ar' = 4-$NO_2C_6H_4$; f) Ar = 2,4-$Me_2C_6H_3$, Ar' = 4-$NO_2C_6H_4$; g) Ar = 2,4,6-$Me_3C_6H_2$, Ar' = 4-$NO_2C_6H_4$; h) Ar = 2,4,5-$Me_3C_6H_2$, Ar' = 4-$NO_2C_6H_4$; i) Ar = Ph, Ar' = 4-$MeOC_6H_4$; j) Ar = 2,4,5-$Me_3C_6H_2$, Ar' = 4-$MeOC_6H_4$.

8 a) Ar = 2,4,6-$Me_3C_6H_2$, Ar' = Ph; b) Ar = 2,4,6-$Me_3C_6H_2$, Ar' = 4-$MeOC_6H_4$.

Scheme 1

We did not succeed in isolation of intermediate dichlorides (6). The isolation of the product resulting from hydrolysis of of one of such dichlorides, i.e. O-mesitoylbenzamidoxime (8a) in 30% yield along with

oxadiazole 3c (40%) when the reaction time was unsufficient (1.5 h) can be regarded as the confirmation of the existence of similar compounds in the reaction mixture. When the reaction was carried out during 3 h the yield of 3c rised to 68%. Our unsuccessful attempts to carry out the cyclization of 8a as well as of specially prepared O-benzoylbenzamidoxime and O-benzoyl-4-methoxybenzamidoxime when boiling their benzene solutions indirectly prove the fact that compounds of the type 8 are not intermediate heterocyclization products. We consider rather dichlorides 6 or their tautomers 7 to be the intermediates. It is natural that the structures of non-identified products (6, 7, 9) are suggestive, the real intermediates could be formed also as a result of nucleophilic substitution of not one but two or three chlorine atoms of starting trichloromethylarene 1.

The formation of N-acylated amidoxime (10) while boiling 1c with 2c in benzene can be accounted for transalkylation of the initially formed O-substituted derivative of the types 6 or 7. Hydrolysis products of the latter, i.e. O-mesitoyl-4-methoxybenzamidoxime (8b) was identified when the reaction of 1c with 2c was carried out in pyridine at 0 °C. The presence of an electron-releasing substituent in 8b should promote the transalkylation (Scheme 2).

$$\left[\underline{6} \rightleftharpoons \underline{7} \longrightarrow ArCCl_2NHCAr' \atop \| \atop NOH\right] \xrightarrow{H_2O} ArCONHCAr' \atop \| \atop NOH$$

10

Ar = 2,4,6-$Me_3C_6H_2$, Ar' = 4-$MeOC_6H_4$

Scheme 2

The presence of nitriles (4) in the products of the reaction proved unexpected, though it is known that during thermal decomposition of the amidoxime 2a nitrile 4a and benzamide were the main products[15]. A possibility of the formation of nitriles from amidoximes 2a-c or from oxadiazole 3h while boiling in pyridine in the presence of pyridine hydrochloride was not confirmed. This allows the conclusion that nitriles (4) and acids (5) can be formed from dichlorides of the type 7 which are tautomers of 6. The presence of a base in the reaction medium should promote an equilibrium shift to the tautomeric form 7 and, naturally, facilitate the formation of fragmentation products 4 and 5. The increase in the yield of 4a from 15-20% in benzene up to 50-65% in pyridine proves the above. The fragmentation can proceed via intermediate formation of an O-substituted hydroxylamine (9). It should be noted that the fragmentati-

on was not observed when the interaction of areneamidoximes with acyl chlorides instead of trichloromethylarenes was carried out in pyridine[16].

As it was mentioned above, an N-acyl derivative of amidoxime 2c (10) was not obtained in pyridine but the reaction gave the nitrile (4c) with an admixture of O-acylated 4-methoxybenzamidoxime (8b). We failed to obtain neither N-, nor O-substituted derivatives of amidoxime 2b in its reactions with 1a-d. However the isolation of 4-nitrobenzonitrile (4b) and corresponding carboxylic acids (5b,c) when the reaction was carried out not only in pyridine, but also in nitrobenzene allows the electrophilic attack to be directed on the oxygen atom of the amidoxime group.

Both structures and compositions of the obtained compounds were confirmed by PMR, IR, mass spectra as well as by elmental analysis. Mass spectra of oxadiazoles 3 contained peaks corresponding to the fragmentation according to the scheme of 1,3-dipolar cycloreversion, the latter, as known for 1,2,4-oxadiazoles, leading to ArCN and Ar'CNO[17]. IR spectra of 3 contain a set of bands characteristic of aryl-substituted 1,2,4-oxadiazoles (1608-1612, 1555-1576, 1448-1552, 1350-1370 cm^{-1})[18]. PMR data are given in Table 2.

Experimental

PMR spectra were recorded on JEOL FX-90Q (90 MHz) and Bruker WM-250 (250 MHz) spectrometers in $CDCl_3$. IR spectra (tablets in KBr) were obtained on Perkin-Elmer 577 and Specord M-80 instruments. Mass spectra were recorded on Varian MAT CH-6 spectrometer at ionization energy of 70 eV with the direct introduction of a sample into the ionic source. Melting points were determined on a Boetius heated plate.

Starting trichloromethylarenes were prepared according to the procedures described in[1,4], the syntheses of areneamidoximes were performed as described in[12].

Synthesis of 3,5-Diaryl-1,2,4-oxadiazoles (3a-j)

Method A. Areneamidoxime (2b,c) (0.2 mol) was added by portions to 0.1 mol of trichloromethylarene (1a-d) heated up to 120 °C. Then the mixture was heated up to 140-145 °C and maintained at this temperature until the end of HCl evolution (time is given in Table 1). The reaction being completed, the products were extracted with chloroform, the extract was evaporated and the residue separated by means of column chromatography on silica, eluent - benzene.

Method B. Benzamidoxime (2a) (0.4 mol) was dissolved while heating in benzene (50 ml). Then 0.1 mol of trichloromethylarene (1a-d) was added. The reaction mixture was boiled during the time given in Table 1. The reaction control was carried out by TLC on Silufol, eluent - chloroform.

On the reaction completion hydrochloride of 2a was filtered off, the benzene solution was washed with water, then evaporated. The products were separated as described in Method A.

Interaction of Trichloromethylarenes with Areneamidoximes in Pyridine

Amidoxime (2a-c) (0.1 mol) was dissolved in pyridine (15 ml), 0.1 mol of trichloromethylarene (1a-d)was then added. The reaction mixture was refluxed for 3 h. Then pyridine was distilled off and the residue was separated using column chromatography on silica (hexane - ethyl acetate, 3:1 as eluent). The following products were successively eluted: nitriles (4a-c), oxadiazoles (3a-d) and, finally, a resinous coloured product, hydrolysis of which (conc. H_2SO_4) leads to carboxylic acids (5a-d). The yields of the products are listed in Table 3.

Synthesis of Acylamidoximes

a) In the interaction of 1c with 2a under the conditions similar to those described in Method B, but during 1.5 h, after alkaline hydrolysis (aqueous NaOH) along with 40% of oxadiazole 3c, O-mesitoylbenzamidoxime (8a) was obtained in 30% yield, m.p. 133-140 °C, M^+ 282. Found, %: C 72.23; H 6.31; N 9.75. $C_{16}H_{18}N_2O_2$. Calcd., %: C 72.34; H 6.38; N 9.93. IR spectrum, cm^{-1}: 3480, 3330 (NH_2), 1735 (CO).

b) Under similar conditions 25% of N-mesitoyl-4-methoxybenzamidoxime (10), m.p. 198-199 °C, M^+ 312 was obtained from 1c and 2c after the reaction completion (1 h) followed by the treatment with water and column chromatography (silica, eluent - benzene). Found, %: C 69.14; H 6.40; N 9.06. $C_{18}H_{20}N_2O_3$. Calcd., %: C 69.23; H 6.41; N 8.97. IR spectrum, cm^{-1}: 3208, 3120, 1696.

c) 4-Methoxybenzamidoxime (0.1 mol) was dissolved in pyridine (10 ml), cooled to 0 °C. Then 0.1 mol of trichloromethylarene 1c was added. The reaction mixture was stirred for 3 h at 0 °C, pyridine was then distilled off in vacuum. Along with nitrile 4c (60%) O-mesitoyl-4-methoxybenzamidoxime (8b) was separated by means of column chromatography of residue on silica (hexane - ethyl acetate, 3:1), yield 10%, m.p. 172-180 °C, M^+ 312. Found, %: C 69.30; H 6.40; N 8.90. $C_{18}H_{20}N_2O_3$. Calcd., %: C 69.23; H 6.41; N 8.97. IR spectrum, cm^{-1}: 3500, 3350 (NH_2), 1735 (CO).

d) O-Benzoylbenzamidoxime (m.p. 151-155 °C) and O-benzoyl-4-methoxybenzamidoxime (m.p. 140-148 °C) were obtained from benzoyl chloride and corresponding amidoximes according to the procedure given in [19]. IR spectra contain characteristic bands: ca. 3505, 3375 (NH_2) and 1730 (CO) cm^{-1}.

Table 1

3,5-Diaryl-1,2,4-oxadiazoles (3)

Compound	M.p., °C (solvent for recrystallization)	Method of preparation (see experimental)	Reaction time, h	Yield, %	M^+	Found, %			Formula	Calcd., %		
						C	H	N		C	H	N
3a	106-107* (EtOH)	B	16	50	222	-	-	-	$C_{14}H_{10}N_2O$	-	-	-
3b	83-84 (MeOH)	B	18	50	250	77.03	5.80	11.08	$C_{16}H_{14}N_2O$	76.80	5.60	11.20
3c	56-57 (MeOH)	B	3	68	264	77.25	6.04	10.49	$C_{17}H_{16}N_2O$	77.27	6.06	10.60
3d	99.5-101 (MeOH)	B	6	50	264	77.42	5.98	10.59	$C_{17}H_{16}N_2O$	77.27	6.06	10.60
3e	194** (EtOH)	A	1	50	267	-	-	-	$C_{14}H_9N_3O_3$	-	-	-
3f	165-167 (EtOH)	A	1	55	295	63.51	4.30	13.91	$C_{16}H_{13}N_3O_3$	63.79	4.32	13.95
3g	183-184 (EtOH)	A	1	60	309	66.36	4.74	13.40	$C_{17}H_{15}N_3O_3$	66.39	4.88	13.50
3h	170-172 (EtOH)	A	1	55	309	66.21	4.82	13.45	$C_{17}H_{15}N_3O_3$	66.39	4.88	13.50
3i	97-98*** (EtOH)	A	2	40	252	-	-	-	$C_{15}H_{12}N_2O_2$	-	-	-
3j	116-118 (EtOH)	A	2	45	294	73.20	6.01	9.32	$C_{18}H_{18}N_2O_2$	73.47	6.12	9.52

*Ref. [20]: m.p. 108 °C. **Ref. [21]: m.p. 195 °C. ***Ref. [22]: m.p. 98 °C.

Table 2

PMR Spectra of 3,5-Diaryl-1,2,4-oxadiazoles (3)* and Acylamidoximes (8a,b, 10)**

Compound	Group Ar, , ppm					Group Ar', , ppm					Me, ppm
	H^2	H^3	H^4	H^5	H^6	$H^{2'}$	$H^{3'}$	$H^{4'}$	$H^{5'}$	$H^{6'}$	
3a	- - -	- - - -	8.21m (5H)	- - - -		- - - -	- - -	7.55m (5H)	- - -	- - -	-
3b	-	7.19s broad.	-	7.19s broad.	8.02d	8.24dd	- - - -	7.58m (3H)	- - -	8.24dd	2.40s, 2.68s
3c	-	6.98s	-	6.98s	-	8.24dd	- - - -	7.58m (3H)	- - -	8.24dd	2.27s (6H), 2.36s (3H)
3d	-	7.11s broad.	-	-	7.88s broad.	8.24dd	- - - -	7.58m (3H)	- - -	8.24dd	2.35s (6H), 2.64s (3H)
3e	8.25dd	- - -	7.72m (3H)	- - -	8.25dd	-	8.40s	-	8.40s	-	-
3f	-	7.18s broad.	-	7.18s broad.	8.07d	-	8.39s	-	8.39s	-	2.43s, 2.73s
3g	-	7.03s	-	7.03s	-	-	8.38s	-	8.38s	-	2.34s (6H), 2.38s (3H)
3h	-	7.15s broad.	-	-	7.95s broad.	-	8.39s	-	8.39s	-	2.35s (6H), 2.71s (3H)
3i	8.23dd	- - -	7.56m (3H)	- - -	8.23dd	8.14d	7.03d	-	7.03d	8.14d	-
3j	-	7.11s broad.	-	-	7.88s broad.	8.18d	7.05d	-	7.05d	8.18d	2.32s (6H), 2.63s (3H)
8a	-	6.90s	-	6.90s	-	7.76dd	- - - -	7.42m (3H)	- -	7.76dd	2.31s (3H), 2.38s (6H)
8b	-	6.90s	-	6.90s	-	7.69d	6.93d	-	6.93d	7.79d	2.31s (3H), 2.39s (6H)
10	-	6.91s	-	6.91s	-	7.38d	6.85d	-	6.85d	7.38d	2.39s (9H)

* Coupling constants: J_{56} = 8 Hz (in 3b,f), $J_{23} = J_{2'3'} = J_{56} = J_{5'6'}$ = 7.5 Hz; $J_{26} = J_{2'6'}$ = 1.5 Hz. Chemical shifts (MeO in 3i,j): 3.89 and 3.90 (s). ** Chemical shifts of MeO: 3.84s; of NH_2 (in 8a,b): 5.13, 5.06 resp. (s, broad.); of NH in 10: 9.30s (broad.); of OH in 10: 10.55s (broad.).

Table 3

Yields of Products Formed from Trichloromethylarenes and Areneamidoximes in Pyridine Solution

Starting compounds		Yields of reaction products, %		
Trichloromethyl-arene (1)	Areneamid-oxime (2)	Oxadiazoles (3)	Nitrile (4)	Acid (5)
1a	2a	3a, 20	4a, 65	5a, 32
1b	2a	3b, 15 + 3a, 10	4a, 50	5b, 24
1c	2a	3c, 20 + 3a, 10	4a, 50	5c, 27
1d	2a	3d, 15 + 3a, 15	4a, 60	5d, 30
1b	2b	-	4b, 45	5b, 30
1c	2b	-	4b, 45	5c, 35
1b	2c	-	4c, ~100	5b, 70
1c	2c	-	4c, ~100	5c, 57

References

1 Hart H.; Fish R.W. J. Am. Chem. Soc. 1961, 83, 4460-4466.

2 US Pat.4,575,565 (1986); Chem. Abstr. 1986, 105, 6305.

3 US Pat. 4,419,514 (1983); Chem. Abstr. 1984, 100, 85412.

4 Belen'kii L.I.; Brokhovetsky D.B.; Krayushkin M.M. Chem. Scripta 1989, 29, 81-84.

5 US Pat. 3,402,178 (1968); Chem. Abstr. 1968, 69, 96750.

6 Suzuki T.; Mitsuhashi K. Seikei Daigaku Kugakubu Kogaku Hokoku 1976, 22, 1579-1580; Chem. Abstr. 1977, 86, 139916.

7 Ger. Offen. 2,619,547 (1977); Chem. Abstr. 1978, 88, 62380.

8 Golfier M.; Millicent R. Synthesis 1979, 946-948.

9 Hasaneen H.M.; Shetta A.H.: Elwan N.M.; Shawali A.S. Heterocycles 1982, 19, 1477-1482.

10 Barbero M.; Cadamuro S. Synthesis 1986, 1074-1076.

11 Tiemann F.; Kruger P. Ber. 1884, 17, 1685-1698.

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

13 Clapp L.B. Adv. Heterocycl. Chem. 1976, 20, 65-116.

14 Poplavskaya I.A.; Kurmangalieva R.G. Khimiya Amidoksimov (Amidoxime Chemistry), Nauka, Alma-Ata, 1988, 142 p.

15 Leandri G.; Rebora P. Ann. Chim. (Roma) 1956, 46, 953-959; Chem. Abstr. 1957, 51, 6607f.

16 Chiou Sh.; Shine H.J. J. Heterocycl. Chem. 1989, 26, 125-128.

17 Selva A.; Zerılli L.F.; Cavalleri B.; Fallo F. Org. Mass Spectr. 1974, 9, 558-566.
18 Physical Methods ın Heterocyclic Chemıstry, Ed. A.R.Katrıtzky, Vol. 2, Academic Press, New York - London, 1963, p. 232.
19 Clarke K. J. Chem. Soc. 1954, 4251-4253.
20 Beılst., H. 27, S. 587.
21 Bergmann E.D.; Bendas H.: D'Avılla V. J. Org. Chem. 1953, 18, 64-69.
22 Leandrı G.; Palottı M. Ann. Chım. (Roma) 1957, 47, 376-384.