Chemistry of Heterocyclic Compounds, Vol.35, No. 4, 1999

SYNTHESIS OF MESITYL-SUBSTITUTED 1,3,4-OXADIAZOLES FROM MESITOTRICHLORIDE AND AROMATIC AND HETEROAROMATIC ACID HYDRAZIDES*

L. I. Belen'kii, S. I. Luiksaar, and M. M. Krayushkin

At interaction of 2,4,6-trimethylbenzotrichloride with aromatic (heteroaromatic) acid hydrazides in a mixture of 2,6-lutidine and tert-butanol the processes of alcoholysis and reductive condensation are suppressed. The corresponding 2-aryl- or 2-hetaryl-5-mesityl-1,3,4-oxadiazoles are obtained in high yields. The PMR, IR, and mass spectra of the products are studied.

We previously have proposed efficient methods for preparing symmetric and asymmetric diaryl-1,3,4-oxadiazoles *via* the reaction of trichloromethylarenes (TCMA) and acylhydrazines in mixtures of pyridine and ethanol or methanol [1, 2]. The product yields reached 80%. However, only products of reductive condensation, 2,4,6-trimethylbenzaldehyde arylhydrazones and 2,4,6-trimethylbenzoic acid esters, were produced even under conditions optimal for heterocyclization from reactions of 2,4,6-trimethylbenzotrichloride (I) and acid hydrazides. The yields in several instances reached 85%.

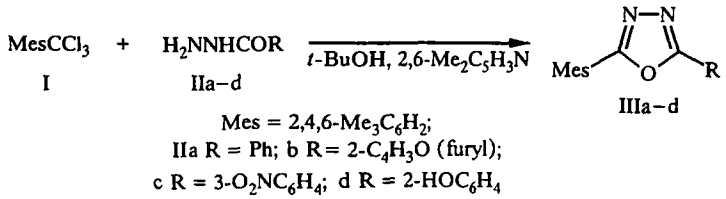
Such specific behavior of mesitotrichloride is undoubtedly related to its structure. On one hand, it easily forms N-(α-chloroarylmethyl)-4-(pyridinio)pyridinium dichlorides or N-(α-chloroarylmethyl)-4-chloropyridinium chlorides upon reaction with pyridine, like other *o,o*-disubstituted benzotrichlorides. The products actually are the primary products of reductive condensation under the examined conditions and react with hydrazine derivatives to give the corresponding N-substituted aromatic aldehyde hydrazones [3, 4]. On the other hand, the cooperative effect of the three methyl groups sharply facilitates nucleophilic substitution of the chlorine atoms of the CCl_3 group. This apparently occurs *via* the S_N1 mechanism [5]. Thus, competition of the nucleophiles in the mixture – pyridine compound, hydrazide, and alcohol – should determine the direction of the reaction. The results obtained demonstrated that the last is the strongest nucleophile.

In the present work, conditions enabling preparation of 2,5-diaryl-1,3,4-oxadiazoles from sterically hindered *o,o'*-disubstituted TCMA are found. The principal task was to block the undesirable processes of alcoholysis and reductive condensation, that is not difficult to prevent, while avoiding pyridine as an acceptor of hydrogen chloride because pyridine is involved in the reduction itself, as was shown previously [3, 4]. We used 2,6-lutidine to bind HCl because it is sterically hindered and cannot form pyridinium salt with mesitotrichloride. Alcoholysis was avoided by replacing the primary alcohols with *tert*-butanol. As a result, I and hydrazides IIa-d react to give 5-aryl(hetaryl)-2-(2,4,6-trimethylphenyl)-1,3,4-oxadiazoles IIIa-d in 50-80% yields.

* Dedicated to Professor Henk van der Plas on his 70th birthday.

N. D. Zelinskii Institute of Organic Chemistry, Moscow 117913, Russia, e-mail: lb@1september.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 557-563, April, 1999. Original article submitted February 23, 1999.

 0009-3122/99/3504-0492$22.00



Mes = 2,4,6-$Me_3C_6H_2$;
IIa R = Ph; b R = 2-C_4H_3O (furyl);
c R = 3-$O_2NC_6H_4$; d R = 2-HOC_6H_4

The synthesis of type III compounds from mesitotrichloride and acid hydrazides has not previously been reported. Only one publication [6] is known on the preparation of 2,5-diaryl-1,3,4-oxadiazoles containing a mesityl residue by cyclization of N-aroyl-N'-mesitoylhydrazines, which are produced from 2,4,6-trimethylbenzoylchloride and hydrazides of the corresponding acids. The method proposed by us is undoubtedly advantageous because it is one-step, uses available starting materials, and is simple.

The structures of IIIa-d were confirmed by elemental analysis (Table 1), IR and PMR spectra (Table 2), and mass spectra (Table 3). Assignments in the IR spectra agree with those summarized earlier [7] for 1,3,4-oxadiazoles (for furyl-substituted IIIb) and furans. Assignment of signals in the PMR spectra was also straightforward. The signals of IIIb are close to those reported for furyl-substituted 1,3,4-oxadiazoles [8, 9].

Mass spectra of several 2,5-diaryl-1,3,4-oxadiazoles were interpreted in detail in our previous work [10]. Based on these data, mass spectra of the mesityl-substituted oxadiazoles IIIa-d, which possess some unique features, could be assigned. The spectra (Table 3) contain intense peaks (66-100 rel. %) for the molecular ions M^+. In the latter the splitting of oxadiazole rings proceeds (Scheme 1) along several parallel paths [11] including breaking the $C_{(5)}$–$N_{(4)}$ and O–$C_{(2)}$ bonds to produce the RCN_2 radical and the $[MesCO]^+$ cation, the O–$C_{(5)}$ and $C_{(2)}$–$N_{(3)}$ bonds to produce the $[RCO]^+$ cation and $MesCN_2$, and the O–$C_{(5)}$ and N–N bonds or the O–$C_{(2)}$ and N–N bonds to produce MesCN, MesCNO, RCN, and RCNO. The peak corresponding to elimination of the nitrogen molecule to produce the cation-radical with the corresponding diaryloxirene structure is weak. As a rule, peaks of $[MesCO]^+$, $[RCO]^+$, $[Mes]^+$, and $[R]^+$ are highly intense. Peaks of medium intensity with *m/z* 117 for $[Mes - 2H]^+$ or $[C_9H_9]^+$, which might have the dimethyldehydrotropylium structure, are also observed.

The fragmentation of the molecular ion of the mesityl-substituted oxadiazoles that involves elimination of N_2 and CO is somewhat specific. A rearrangement with migration of one of the aryl substituents precedes the fragmentation. Elimination of N_2 and CO is accompanied by loss of a hydrogen atom apparently not from the *o*-position of the benzene ring as is postulated for ordinary aryl substituents [12] but from one of the *o*-methyl groups of the mesityl residue (Scheme 2).

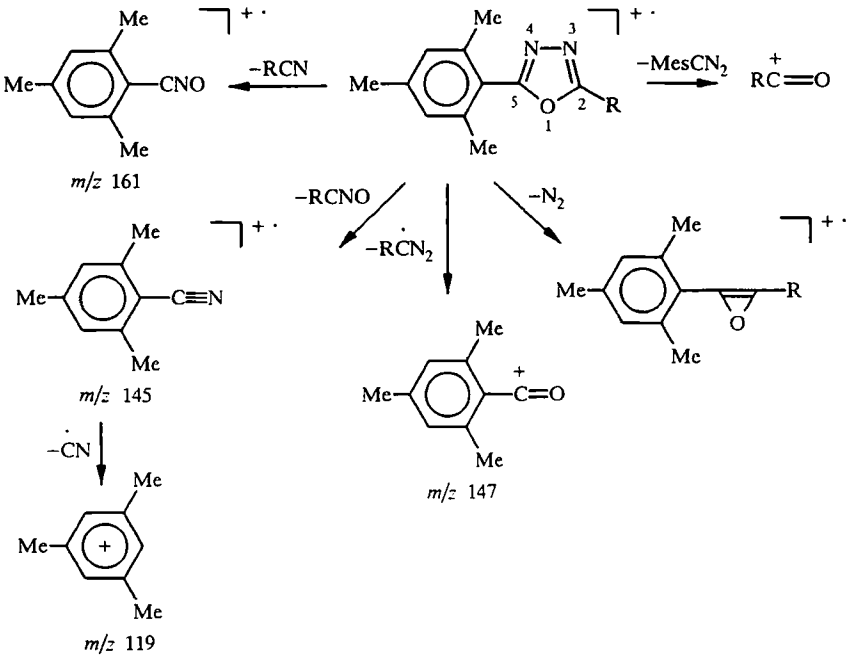
The presence of mesityl residue in the molecule opens additional paths for fragmentation that involve the loss of CH_3 radicals and CO and HCN molecules on various fragmentation steps of the molecular ion. It has been noted [13] that the presence of one or several *o*-methyl groups in 2,5-diaryl-1,3,4-oxadiazole causes several interesting fragmentations. Hypothetically the fragmentation of the molecular ion can be preceded by hydrogen transfer from *o*-methyl group to nitrogen atom of the heterocycle to produce 1,3,4-oxadiazolium structure that then

TABLE 1. Characteristics of 2-Aryl(hetaryl)-5-mesityl-1,3,4-oxadiazoles

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
III*					96...97* (MeOH)	73
IIIb	$C_{15}H_{14}N_2O_2$	70,76 / 70,85	5,53 / 5,55	10,93 / 11,01	112...114 (EtOH)	52
IIIc	$C_{17}H_{15}N_3O_3$	65,89 / 66,01	4,86 / 4,89	13,49 / 13,58	176...177 (dioxane)	80
IIId	$C_{17}H_{16}N_2O_2$	72,78 / 72,83	5,72 / 5,75	9,91 / 10,00	105...106 (EtOH)	77

* Lit. mp 95-96°C [6].

Scheme 1



fragments in two directions (a and b), which are presented in Scheme 3. According to [14] another characteristic of mesityl-substituted oxadiazoles is the $[2,4\text{-}Me_2C_6H_2CN]^+$ ion with m/z = 130, which is produced by elimination of methyl radical from the mesitonitrile cation-radical with m/z = 145.

Scheme 2

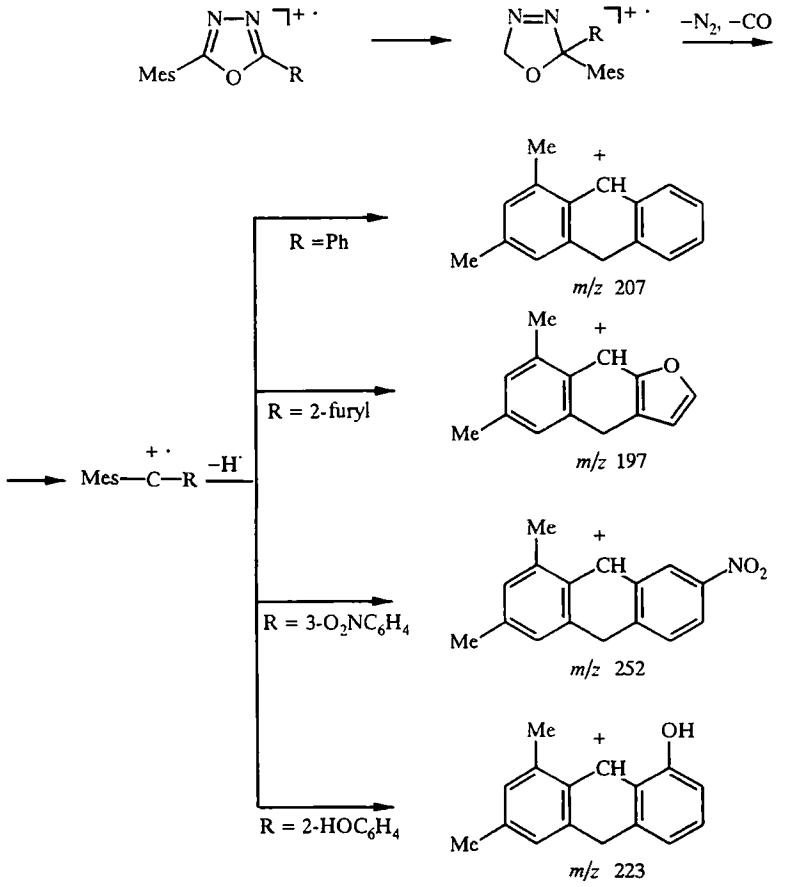


TABLE 2. IR and PMR Spectral Characteristics of 2-Aryl(hetaryl)-5-mesityl-1,3,4-oxadiazoles

Compound	IR spectrum, ν, cm^{-1}					PMR spectrum, δ, ppm		
						mesityl residue		
	C–H_{arom}	CH_3	C=N C=C	C–O–C	other vibrations	CH_3, s	H_{arom} s, (2H)	R
IIIa	3062 3024	2954 2922	1610 1568 1553 1483	1078 1054 1030	787, 760, 735, 713, 700 (CH_{arom})	2,32 (6H) 2,33 (3H)	6,99	8,11 (2h, M, *o*-H) 7,52 (3H, m, *m*- and *p*-H)
IIIb	3139 3120	2963 2925	1634 1615 1573 1521	1051 1019	782, 761, 740, 720 (CH_{arom})	2,30 (6H) 2,35 (3H)	6,99	6,61 (1H, dd, 4'-H, J = 3,4 and 3,6 Hz) 7,19 (1H, d, 3'-H, J = 3,4 Hz) 7,66 (1H, br. s, 5'-H)
IIIc	3084	2988 2927 2870	1615 1597 1580 1552	1057 1034	1533, 1358, 1349 (NO_2) 750, 727, 715 (CH_{arom})	2,34 (6H) 2,38 (3H)	7,02	8,91 (1H, s, 2'-H); 8,49 (1H, d, 4'-H) 8,41 (1H, d, 6'-H) 7,75 (1H, t, 5'-H, J ~ 8 Hz)
IIId	3050 3014	2964 2923 2860	1631 1617 1598 1592 1548	1055 1038	3165 (OH) 1265, 1260, 1244 (C–OH) 753, 725, 711 (CH_{arom})	2,34 (6H) 2,38 (3H)	7,02	10,27 (1H, br. s, OH); 7,79 (1H, d, 6'-H) 7,46 (1H, t, 4'-H); 7,18 (1H, d, 3'-H) 7,02 (1H, br. t, 5'-H, J ~ 8 Hz)

TABLE 3. Mass Spectral Characteristics of 2-Aryl(hetaryl)-5-mesityl-1,3,4-oxadiazoles

Compound	Ion, *m/z* (relative intensity, %)										
	$\frac{[M+1]^+}{[M]^{+\cdot}}$	$\frac{\Phi_1}{\Phi_2}$	$\frac{\Phi_3}{\Phi_4}$	$\frac{\Phi_5}{\Phi_6}$	$\frac{\Phi_7}{\Phi_8}$	$\frac{\Phi_9}{\Phi_{10}}$	$\frac{\Phi_{11}}{\Phi_{12}}$	$\frac{\Phi_{13}}{\Phi_{14}}$	$\frac{\Phi_{15}}{\Phi_{16}}$	$\frac{\Phi_{17}}{\Phi_{18}}$	other ions
IIIa	265 (11) 264 (100)	236 (12) —	207 (6) 161 (9)	147 (52) 146 (30)	145 (13) 133 (10)	132 (3) 130 (5)	* 119 (10)	118 (5) —	105 (27) 103 (13)	91 (15) 77 (29)	192 (9) $[M-N_2-CO-CH_3]^*$
IIIb	255 (11) 254 (74)	— 225 (3)	197 (9) 161 (9)	147 (100) 146 (82)	145 (7) 133 (20)	132 (6) 130 (16)	109 (3) 119 (24)	118 (11) 117 (30)	95 (35) 93 (5)	91 (16) 67 (4)	169 (20), 148 (21)
IIIc	310 (40) 309 (94)	281 (3) 280 (6)	252 (2) 161 (36)	147 (92) 146 (100)	145 (22) 133 (30)	132 (7) 130 (9)	164 (3) 119 (50)	118 (53) 117 (42)	150 (12) 148 (11)	91 (30) —	279 (7) $[M-N_2-2H]^+$, 254 (9), 192 (12) 160 (17) [M–RCN–H]; 145 (22) [MesCO–2H] 104 (19) [PhCNH]
IIId	281 (20) 280 (66)	— 251 (6)	223 (14) 161 (18)	147 (63) 146 (33)	145 (8) 133 (22)	132 (65) 130 (24)	135 (4) 119 (14)	118 (24) 117 (39)	121 (100) *	91 (40) 93 (17)	209 (29) $[M-N_2-CO-CH_3]^+$, 159 (18), 122 (19)

Note.

$\Phi_1 = [M-N_2]^{+\cdot}$; $\Phi_2 = [M-N_2-H]^{+\cdot}$;

$\Phi_3 = [M-N_2-CO-H]^{+\cdot}$; $\Phi_4 = [MesCNO]^{+\cdot}$;

$\Phi_5 = [MesCO]^+$; $\Phi_6 = [M-RCN_2H]^{+\cdot}$;

$\Phi_7 = [MesCN]^{+\cdot}$; $\Phi_8 = [M-RCN-CO]^{+\cdot}$;

$\Phi_9 = [M-RCN-CO-H]^+$; $\Phi_{10} = [MesCN-CH_3]^+$;

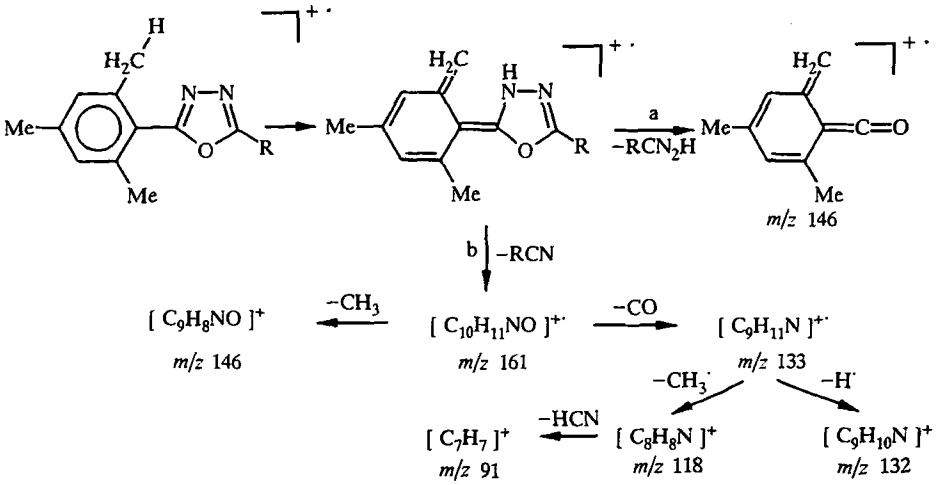
$\Phi_{11} = [RCNO]^{+\cdot}$; $\Phi_{12} = [Mes]^+$; $\Phi_{13} = [M-RCN-CO-CH_3]^+$;

$\Phi_{14} = [Mes-2H]^+$; $\Phi_{15} = [RCO]^+$; $\Phi_{16} = [RCN]^{+\cdot}$;

$\Phi_{17} = [C_7H_7]^+$; $\Phi_{18} = [R]^+$

Peaks for which *m/z* corresponds to that of $\varphi_{12} = [Mes]^+$ are denoted by an asterisk.

Scheme 3



EXPERIMENTAL

PMR spectra were recorded on a Bruker WM-250 (250 MHz) radiospectrometer in $CDCl_3$. IR spectra were taken on a Perkin–Elmer 577 spectrometer in KBr pellets. Mass spectra were obtained on a Kratos MS-30 spectrometer with direct probe sample introduction into the ion source, ionizing potential 70 eV, emission current 0.1 mA, and ionization chamber temperature 250°C. Melting points were measured on a Boetius microscope stand and are uncorrected.

Commercially available benzhydrazide (IIa) was used. Hydrazides IIb [15] and IIc,d [16] were prepared by boiling methyl or ethyl esters of the corresponding acids with hydrazine hydrate in alcohol. 2,4,6-Trimethylbenzotrichloride I was synthesized by electrophilic trichloromethylation of mesitylene using the literature method [17].

Reaction of Mesitotrichloride I with Acid Hydrazides. Compound I (1 g, 4.2 mmol) was added dropwise to solution of hydrazide (4.2 mmol) in *t*-butanol (5 ml) and 2,6-lutidine (2 ml). The resulting mixture was boiled for 1 h. The solvent was distilled off. The residue was treated with water (50 ml) and extracted with $CHCl_3$. The extract was separated, dried over $CaCl_2$, and evaporated in a rotary evaporator. The residue was ground with ether (10 ml) on cooling. The crystals were filtered off, washed with cold ethanol, and recrystallized from the solvent indicated in Table 1.

REFERENCES

1. I. S. Poddubnyi, L. I. Belen'kii, and M. M. Krayushkin, *Khim. Geterotsikl. Soedin.*, No. 5, 686 (1994).
2. I. S. Poddubnyi, L. I. Belen'kii, and M. M. Krayushkin, *Izv. Akad. Nauk, Ser. Khim.*, No. 5, 1246 (1996).
3. L. I. Belen'kii, I. S. Poddubnyi, and M. M. Krayushkin, *Tetrahedron Lett.*, **36**, 5075 (1995).
4. L. I. Belen'kii, I. S. Poddubnyi, and M. M. Krayushkin, *Khim. Geterotsikl. Soedin.*, No. 6, 830 (1995).
5. I. F. Dvorko, N. Yu. Evtushenko, and V. N. Zhovtyak, *Zh. Org. Khim.*, **57**, 1157 (1987).
6. V. M. Feygelman, J. K. Walker, A. R. Katritzky, and Z. Dega-Szafran, *Chem. Scripta*, **29**, 241 (1989).
7. A. R. Katritzky (ed.), *Physical Methods in Heterocyclic Chemistry*, Academic, New York (1963).
8. R. A. Karakhanov, V. I. Kelarev, V. N. Koshelev, G. V. Morozova, and Ammar Dibi, *Khim. Geterotsikl. Soedin.*, No. 2, 238 (1995).
9. H. Saihashi, N. Shimojo, and Y. Uehara, *Chem. Pharm. Bull.*, **20**, 1663 (1972).

10. L. I. Belen'kii, S. I. Luiksaar, I. S. Poddubnyi, and M. M. Krayushkin, *Izv. Akad. Nauk, Ser. Khim.*, No. 11, 2309 (1998).
11. T. Nakano, V. E. Marquez, M. T. DiParsia, and C. Suarez, *Org. Mass Spectrom.*, **13**, 236 (1978).
12. R. L. Ushakova, A. I. Mikaya, V. G. Zaikin, V. I. Kelarev, and G. A. Shvekhgeimer, *Khim. Geterotsikl. Soedin.*, No. 4, 539 (1986).
13. A. Selva, F. Zerilli, B. Cavalleri, and G. G. Gallo, *Org. Mass Spectrom.*, **9**, 558 (1974).
14. S. Morrocchi, A. Ricca, A. Selva, and A. Zanarotti, *Gazz. Chim. Ital.*, **99**, 565 (1969).
15. M. J. Cook and E. J. Forbes, *Tetrahedron*, **24**, 4501 (1968).
16. H. Meyer and J. Mally, *Monatsh. Chem.*, **33**, 400 (1912).
17. H. Hart and R. W. Fish, *J. Am. Chem. Soc.*, **83**, 4460 (1961).