Synthesis of picryl-substituted 1,3,4-oxadiazoles

*T. K. Shkinyova, I. L. Dalinger, S. I. Molotov, and S. A. Shevelev**

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 117913 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: shevelev@cacr.ioc.ac.ru

A convenient procedure was developed for the synthesis of picryl-substituted 1,3,4-oxadiazoles. The nucleophilic replacement of the nitro group in picroylacylhydrazines under the action of thiophenol was studied.

Key words: 2,4,6-trinitrotoluene (trotyl), 1,3,4-oxadiazoles, picroylacylhydrazines, nucleophilic substitution.

This work was undertaken as part of our continuing studies aimed at using an explosive, *viz.*, 2,4,6-trinitrotoluene (TNT, trotyl), as a readily available versatile starting compound for the production of valuable products for different purposes.[1]

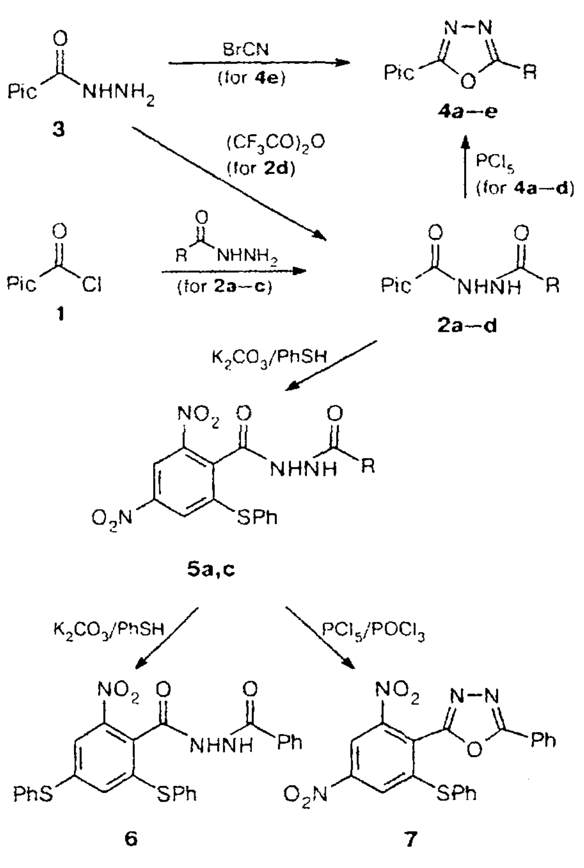
Among organic compounds which can be prepared based on TNT, 2,4,6-trinitrophenyl (picryl) derivatives of aromatic heterocycles may be of particular value as intermediates in organic synthesis. One would expect that the presence of the picryl substituent containing three *meta*-nitro groups will make it possible to perform various functionalizations of the phenyl moiety giving rise to heterocyclic compounds with new combinations of functional groups in the phenyl substituent.

The aim of this work was to develop a procedure for the synthesis of picryl-substituted 1,3,4-oxadiazoles and some of their analogs because aryl-1,3,4-oxadiazoles are of substantial interest both as organic scintillators and intermediates in the synthesis of physiologically active compounds.

Previously,[2] only a few examples of 5-aryl-2-picryl-1,3,4-oxadiazoles have been described. It was of interest to extend the range of picryloxadiazoles by preparing 2-picryl-1,3,4-oxadiazoles containing substituents other than aryl groups (in particular, functional groups) at position 5.

For this purpose, we synthesized the starting compounds, *viz.*, different *N'*-acyl-*N*-(2,4,6-trinitrobenzoyl)hydrazines (**2a—c**), by the reactions of 2,4,6-trinitrobenzoyl chloride (picroyl chloride, **1**) with the corresponding hydrazides. Hydrazine **2d** was prepared according to another procedure involving the reaction of picroylhydrazide (**3**) with trifluoroacetic anhydride (Scheme 1).

Scheme 1



Pic = 2,4,6-(NO$_2$)$_3$C$_6$H$_2$
R = Ph (**a**); 2-ClC$_6$H$_4$ (**b**); Me (**c**); CF$_3$ (**d**); NH$_2$ (**e**)

The drawback of the known procedure for cyclization of diacylhydrazines **2** yielding oxadiazoles **4**[2] is that a large amount of the condensing agent (POCl$_3$) is consumed per mmole of **2** (50 mL). We developed a convenient procedure based on the use of PCl$_5$ in dichloroethane. As a result, we simplified the preparation of oxadiazole **4a** described previously and synthesized for the first time oxadiazoles **4b—d** including those containing the methyl or trifluoromethyl groups.

Published in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 9, pp. 1583—1585, September, 2000.

Table 1. Yields, melting points, and data of elemental analysis and ^1H NMR spectroscopy for the compounds synthesized

Compound	Yield (%)	M.p. /°C	Found/Calculated (%) C	H	N	Molecular formula	^1H NMR (DMSO-d_6), δ
2a	64	275[a] (265—266)[2]	—	—	—	—	7.49—7.63 (m, 3 H, Ph); 7.92—8.00 (m, 2 H, Ph); 9.13 (s, 2 H, Pic); 10.95 (s, 1 H, NH); 11.30 (s, 1 H, NH)
2b	72	298[b]	41.00 41.03	1.95 1.97	17.13 17.10	$C_{14}H_8ClN_5O_8$	7.41—7.60 (m, 4 H, Ph); 9.12 (s, 2 H, Pic); 11.01 (s, 1 H, NH); 11.47 (s, 1 H, NH)
2c	80	182[a]	34.54 34.51	2.22 2.26	22.40 22.37	$C_9H_7N_5O_8$	1.93 (s, 3 H, CH_3); 9.10 (s, 2 H, Pic); 10.57 (s, 1 H, NH); 11.29 (s, 1 H, NH)
2d	89	215[c]	29.41 29.44	1.07 1.10	19.10 19.08	$C_9H_4F_3N_5O_8$	9.18 (s, 2 H, Pic); 11.60 (s, 1 H, NH); 12.3 (br.s, 1 H, NH)
4a	80	245—246[a] (237—238)[2]	—	—	—	—	7.63—7.79 (m, 3 H, Ph); 8.09 (s, 1 H, Ph); 8.12 (s, 1 H, Ph); 9.40 (s, 2 H, Pic)
4b	82	250—251[a]	42.89 42.93	1.52 1.55	17.84 17.88	$C_{14}H_6ClN_5O_7$	7.61—7.80 (m, 3 H, Ph); 8.05 (s, 1 H, Ph); 9.39 (s, 2 H, Pic)
4c	68	125[a]	36.55 36.61	1.73 1.69	23.79 23.73	$C_9H_5N_5O_7$	2.70 (s, 3 H, CH_3); 9.32 (s, 2 H, Pic)
4d	50	220[c]	30.81 30.95	0.60 0.58	20.14 20.06	$C_9H_2F_3N_5O_7$	9.40 (s, 2 H, Pic)
4e	90	222[b]	32.40 32.44	1.33 1.36	28.41 28.38	$C_8H_4N_6O_7$	8.81 (s, 2 H, NH_2); 9.30 (s, 2 H, Pic)
5a	85	238—239[b]	54.73 54.79	3.25 3.22	12.74 12.78	$C_{20}H_{14}N_4O_6S$	7.48—7.73 (m, 8 H, Ph); 7.95—8.10 (m, 2 H, Ph); 7.91 (s, 1 H, Pic); 8.61 (s, 1 H, Pic); 11.00 (s, 1 H, NH); 11.21 (s, 1 H, NH)
5c	87	309—310[b]	47.91 47.87	3.26 3.22	14.91 14.89	$C_{15}H_{12}N_4O_6S$	1.95 (s, 3 H, CH_3); 7.51—7.63 (m, 5 H, Ph); 7.91 (s, 1 H, Pic); 8.60 (s, 1 H, Pic); 10.50 (s, 1 H, NH); 11.08 (s, 1 H, NH)
6	40	283[b]	62.30 62.25	3.80 3.83	8.35 8.38	$C_{26}H_{19}N_3O_4S$	7.49—7.70 (m, 15 H, Ph); 8.08 (s, 1 H, Pic); 8.10 (s, 1 H, Pic); 10.65 (s, 1 H, NH); 10.89 (s, 1 H, NH)
7	61	190[b]	57.07 57.13	2.90 2.88	13.30 13.33	$C_{20}H_{12}N_4O_5S$	7.50—7.60 (m, 3 H, Ph); 7.61—7.73 (m, 5 H, Ph); 8.08 (s, 2 H, Ph); 8.04 (s, 1 H, Pic); 8.80 (s, 1 H, Pic)

[a] From EtOH.
[b] From CH_3CN.
[c] From CF_3COOH.

The first representative of 5-amino-1,3,4-oxadiazoles containing the picryl substituent at position 2 (**4e**) was synthesized by the reaction of hydrazide **3** with cyanogen bromide (see Scheme 1).

With the aim of functionalizing 2-picryl-1,3,4-oxadiazoles (taking into account interest in acylhydrazines as possible biologically active compounds), we studied the nucleophilic replacement of the nitro groups in picroylacylhydrazines. We found conditions under which one nitro group in hydrazines **2a,c** is replaced under the action of thiophenol to form only *ortho*-substituted products **5a,c**. The reaction proceeds smoothly at room temperature in a medium of *N*-methyl-2-pyrrolidone (MP) in the presence of solid K_2CO_3 (an equimolar ratio of the reagents) (see Scheme 1).

The second nitro group is replaced only in HMPA. Using hydrazine **5a** as an example, it was found that the second nitro group was also replaced regioselectively, but the replacement occurred at position 4 rather than at position 6, *i.e.*, *ortho-para*-substitution product **6** was formed.

Cyclization of the resulting substituted hydrazine **5a** proceeded under substantially more drastic conditions (only in a medium of $PCl_5/POCl_3$ upon prolonged refluxing (24 h)) compared to those used in the case of

Table 2. ^{13}C NMR spectra (DMSO-d_6) of the compounds synthesized

Compound	δ (*J*/Hz)
4c	10.3; 124.8; 149.8; 166.1
4d*	115.8 (q, *J* = 272.1); 116.6; 125.2; 149.2; 150.2; 155.6 (q, *J* = 44.6); 158.5
4e	117.7; 124.0 (d, *J* = 180); 147.4; 148.9; 149.1; 165.5
5a	116.82; 126.86; 127.73; 128.38; 130.13; 130.37; 130.54; 131.90; 132.20; 133.95; 134.31; 142.50; 147.30; 147.74; 160.86; 165.01
5c	20.51; 116.96; 127.17; 130.14; 130.55; 131.20; 133.69; 134.22; 142.23; 147.16; 147.76; 159.93; 167.04
6	127.39; 127.64; 128.31; 128.94; 129.39; 130.15; 130.43; 131.49; 131.76; 132.40; 133.20; 133.69; 134.20; 139.39; 140.21; 148.14; 163.12; 165.13
7	117.36; 122.05; 126.55; 127.02; 129.27; 129.94; 130.15; 132.41; 133.60; 145.21; 149.16

* ^{19}F NMR (DMSO-d_6). δ: −63.44 ($CFCl_3$ as the standard).

picroylhydrazines **2** and afforded oxadiazole **7** (see Scheme 1).

The structures of the resulting compounds were established by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy (Tables 1 and 2) and were confirmed by the data of elemental analysis (see Table 1), mass spectrometry, and IR spectroscopy ($\nu_{as}(NO_2)$, 1550—1590 cm^{-1}; $\nu_s(NO_2)$, 1350—1390 cm^{-1}; ν(CO), 1630—1680 cm^{-1}).

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C). The ^{19}F NMR spectra were measured on a Bruker AC-200 instrument (188.31 MHz). The melting points of the compounds were determined on a Boetius stage (the rate of heating was 4 deg min^{-1}). The IR spectra were recorded on a Specord M-80 spectrometer (in KBr). The mass spectra were obtained on an MS-30 (Kratos) spectrometer.

Synthesis of *N'*-acyl-*N*-picroylhydrazines (2a—c) (general procedure). Picroyl chloride **1** [2] (0.01 mol) was added to a solution of hydrazide $RCONHNH_2$ (0.01 mol) in EtOH (50 mL) and the reaction mixture was stirred at ~20 °C for 6—8 h. The precipitate that formed was filtered off, washed with EtOH, and dried in air.

1-Trifluoroacetyl-2-(2,4,6-trinitrobenzoyl)hydrazine (2d). Hydrazide **3** [2] (0.9 g, 3.6 mmol) was added to trifluoroacetic anhydride (1 mL, 7.4 mmol) and the reaction mixture was stirred at ~20 °C for 6 h. The precipitate that formed was filtered off, washed with water, and dried in air.

Preparation of 2-(2,4,6-trinitrophenyl)-1,3,4-oxadiazoles (4a—d) (general procedure). Diacylhydrazine **2a—d** (1.3 mmol) was added to a solution of PCl_5 (3.3 mmol) in dry dichloroethane (25 mL) and the reaction mixture was refluxed (for 8 h in the case of **4a,b** and for 6 and 16 h in the synthesis of **4c** and **4d**, respectively). Then the mixture was concentrated to dryness and triturated with water. The precipitate that formed was washed with a 3% KOH solution and water and dried in air.

5-Amino-2-(2,4,6-trinitrophenyl)-1,3,4-oxadiazole (4e). Cyanogen bromide (0.16 g, 1.5 mmol) was added to a suspension of picroylhydrazide **3** (0.4 g, 1.5 mmol) in EtOH (5 mL) and the reaction mixture was stirred at 40—50 °C for 5 h. Then a solution of $NaHCO_3$ (0.12 g, 1.5 mmol) in water (4 mL) was added and the mixture was stirred at this temperature for 2 h. The precipitate was filtered off and washed with water. The filtrate was concentrated to dryness and treated with a small amount of water. The precipitate was filtered off. Then the precipitates were combined. MS (EI, 70 eV), *m/z*: 296 $[M]^+$.

Preparation of substituted hydrazines 5 (general procedure). Thiophenol (1.83 mL, 16 mmol) was added to a suspension of K_2CO_3 (2.21 g, 16 mmol) in MP (200 mL) at ~20 °C and the reaction mixture was stirred for 0.5 h. Then a solution of hydrazine **2** (16 mmol) in MP (64 mL) was added dropwise and the mixture was stirred at ~20 °C for 8 h. The reaction mixture was poured into ice water (800 mL) and acidified with concentrated HCl to pH 5—6. The precipitate that formed was filtered off, washed with water, and dried in air.

2-Benzoyl-1-[6-nitro-2,4-di(phenylthio)benzoyl]hydrazine (6). Thiophenol (0.20 mL, 2 mmol) was added to a suspension of K_2CO_3 (0.28 g, 2 mmol) in HMPA (5 mL) and the reaction mixture was stirred for 0.5 h. Then hydrazine **5a** (0.88 g, 2 mmol) was added. The reaction mixture was stirred at ~20 °C for 4 days, poured into ice water (80 mL), and acidified with concentrated HCl to pH 5—6. The precipitate that formed was filtered off, washed with water, and dried in air. MS (EI, 70 eV), *m/z*: 501 $[M]^+$.

5-(4,6-Dinitro-2-phenylthio)phenyl-2-phenyl-1,3,4-oxadiazole (7). Hydrazine **5a** (0.6 g, 1.4 mmol) was added to a solution of PCl_5 (1.8 g, 8.6 mmol) in $POCl_3$ (12 mL). The reaction mixture was refluxed for 24 h and poured into water. Then a 3% KOH solution was added to pH 7—8. The precipitate that formed was filtered off, washed, and dried in air. MS (EI, 70 eV), *m/z*: 420 $[M]^+$.

This work was financially supported by the International Science and Technology Center (ISTC) (Project No. 419).

References

1. V. A. Tartakovsky, S. A. Shevelev, M. D. Dutov, A. Kh. Shakhnes, A. L. Rusanov, L. G. Komarova, and A. M. Andrievsky, *Problems of Trotyl (TNT) Processing into Condensation Monomers, Polymers, and Dyes*, in *Conversion Concepts for Commercial Applications and Disposal Technologies of Energetic Systems*, Ed. H. Krause, Kluwer Academic Publishers, Dordrecht, 1997, 137.
2. G. P. Sharnin, B. I. Buzykin, and R. Kh. Fassakhov, *Khim. Geterotsikl. Soedin.*, 1977, 741 [*Chem. Heterocycl. Compd.*, 1977 (Engl. Transl.)].

Received March 4, 2000;
in revised form May 19, 2000