Synthesis of 3-acyl-5-nitroisoxazoles on the base of geminal trinitro- and chlorodinitro-substituted pentan-2-one or 2-oximino-1-phenylbutan-1-one

G. Kh. Khisamutdinov,[a] N. M. Lyapin,[b] V. G. Nikitin,[c] V. I. Slovetskii,[d] and A. A. Fainzil´berg[d]†*

[a]State Scientific Research Institute "Krislall",
6 ul. Zelenaya, 606007 Dzerzhinsk, Nizhny Novgorod Region, Russian Federation.
Fax: +7 (831) 324 4085. E-mail: kristall@sinn.ru
[b]Scientific Research Institute of Chemical Products,
1 ul. Svetlaya, 42002 Kazan, Russian Federation.
Fax: +7 (843 2) 544 1272
[c]Kazan State Technological University,
68 ul. K. Marksa, 420015 Kazan, Russian Federation.
Fax: +7 (843 2) 72 1030
[d]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328

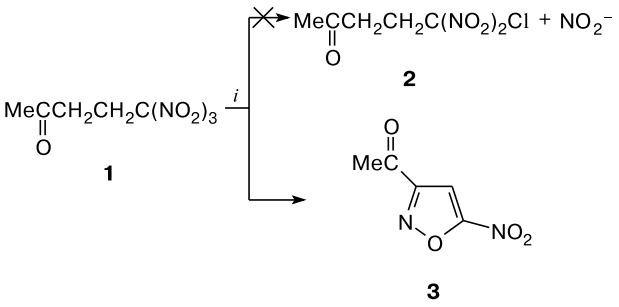
3-Acyl-5-nitroisoxazoles were synthesized by heating 5,5,5-trinitropentan-2-one with LiCl in DMF at 100 °C as well as by heating oximino derivatives of 5,5,5-trinitro-, 5-chloro-5,5-dinitropentan-2-one or 4,4,4-trinitro- and 4-chloro-4,4-dinitro-1-phenylbutan-1-one in organic solvents.

Key words: 5,5,5-trinitro- and 5-chloro-5,5-dinitropentan-2-ones, 4,4,4-trinitro- and 4-chloro-4,4-dinitro-2-oximino-1-phenylbutan-1-ones, 5-nitroisoxazoles, synthesis, intramolecular cyclization, aromatization.

It is known that the reaction of trinitromethane derivatives $(O_2N)_3CX$ (X = NO_2, F, Cl, Br, Me) with alkali halides (KF, RbF, CsF, LiCl, KCl, RbCl, CsCl, KBr, LiBr) and sodium azide in anhydrous polar solvents (DMF, DMSO, acetone) results in the substitution of the halogen atom (F, Cl, Br)[1—7] and the azido group,[1,8,9] respectively, for the nitro group.

In continuation of our research in this field, we studied the reaction of 5,5,5-trinitropentan-2-one (**1**) bearing the electron-withdrawing carbonyl group and the trinitromethyl moiety with lithium chloride, which is the most efficient agent in the reactions with tetranitromethane.[5] In contrast to the compounds studied previously, compound **1** reacts abnormally under these conditions. Instead of expected 5-chloro-5,5-dinitropentan-2-one (**2**), heating of compound **1** in DMF at 100 °C resulted in hitherto unknown 3-acetyl-5-nitroisoxazole (**3**) in 23.6% yield* with complete conversion of the starting **1** (Scheme 1, method *A*).

Scheme 1



i. LiCl, DMF, 100 °C.

No formation of isoxazole **3** was observed upon heating of compound **1** in DMF without LiCl. Probably, in the presence of LiCl, the substitution of the chlorine atom for the nitro group characteristic of polynitromethanes[4—7] occurred initially to give compound **2** and the nitrite ion. The latter denitrates the starting compound providing the anion of 5,5-dinitropentan-2-one (**4**) and N_2O_4; N_2O_4 or its reaction products with LiCl (NOCl),[10] or nitrogen oxides (N_2O_3, N_2O_4), which formed upon thermolysis of

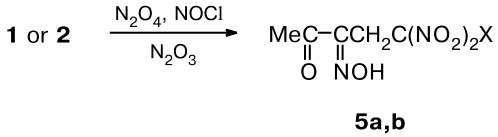
† Deceased.

* No optimization of the yield was performed, the yield could probubly be increased.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2113—2116, October, 2009.

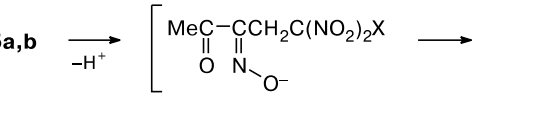
anion **4**, as in the case of other ketones[11] can nitrosate both unconsumed compound **1** and initially formed product **2** to give oximino derivatives **5a,b** (Scheme 2).

Scheme 2



X = NO_2 (**a**), Cl (**b**)

Oximino derivatives **5a,b** bearing the oxime and the polynitromethyl groups underwent intramolecular ring closure to give 3-acetyl-5,5-dinitroisoxazoline (**6**) (Scheme 3). This pathway resembled that for the synthesis of dinitroalkyl nitrolates from the dinitroalkane salts,[12,13] which according to the published data[14] followed the radical ion chain mechanism with one-electron transfer. In the next step analogously to other azolines,[8,15] aromatization of compound **6** occurred affording **3**.



Scheme 3

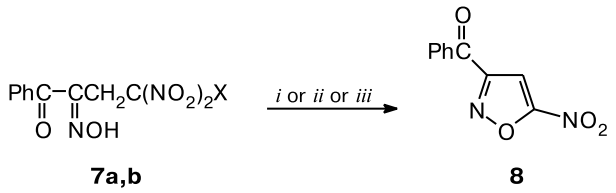
X = NO_2 (**a**), Cl (**b**)

The proposed mechanism was confirmed by the formation of 1-chloro-1-oximinoacetone by the reaction of tetranitromethane with LiCl in acetone documented earlier,[5] by thermal decomposition of polynitromethane anions in DMF accompanied by evolution of nitrogen oxides,[5] and as well as by the preparation of isoxazole **3** by treatment of **1** in DMF with N_2O_4 in the presence of LiCl (method *B*) or sodium nitrite in the presence of conc. HCl (method *C*) (these reactants are typically used for the conversion of ketones into oximino derivatives[16,17]), by treatment of compound **1** with dilute nitric acid (method *D*), by heating of the specially prepared 5,5,5-trinitro-3-oximinopentan-2-one (**5a**) in 95% methanol at 30—35 °C (method *E*), or acetonitrile and DMF at 50—60 °C (method *F*) and by treatment of **5a** with a solution of KOH in 90% methanol at room temperature (method *G*) in 25, 37, 5.6, 70, 72, and 75% yields, respectively.

Compound **5a** was synthesized by the reaction of **1** (see Ref. 18) with methyl nitrite in anhydrous diethyl ether in the presence of hydrogen chloride or by treatment with nitrosyl sulfuric acid in AcOH in 64 and 72% yield, respectively.

Other geminal polynitroalkyl oximino ketones can also undergo ring closure yielding the isoxazole ring. For example, hitherto unknown 3-benzoyl-5-nitroisoxazole (**8**) was prepared by heating 4,4,4-trinitro-2-oximino-1-phenylbutan-1-one (**7a**) and 4-chloro-4,4-dinitro-2-oximino-1-phenylbutan-1-one (**7b**) in organic solvents (methods *E* and *F*), or by treatment of **7a,b** with solution of KOH in 90% methanol (method *G*) in 70—75% yields (Scheme 4).

Scheme 4



Reagents and conditions: *i*. 95% MeOH, 30—35 °C; *ii*. MeCN or DMF, 50—60 °C; *iii*. KOH in 90% MeOH, 20 °C.

Compounds **7a,b** were prepared by nitrosation of 4,4,4-trinitro-1-phenylbutan-1-one (**9**)[19] and 4-chloro-4,4-dinitro-1-phenylbutan-1-one (**10**), which in turn was prepared by chlorination of 4,4-dinitro-1-phenylbutan-1-one potassium salt (**11**)[20] with gaseous chlorine following the procedure described for compound **5a** (method *A*).

It is of note that prior to our research only one publication[21] devoted to the synthesis of 3,5-dinitroisoxazole and its 4-methyl-substituted analog from 1,1,1,3-tetranitropropane by treatment with dilute mineral acids (sulfuric or nitric) or water at 80—90 °C in the yields of 70 and 50%, respectively, was published. From our viewpoint, the mechanism, which is given in the publication cited, is of low probability, as it suggested the attack by the methine carbon atom bearing the negative charge on the electron-negative oxygen atom of the nitro group. We believe that the reaction mentioned as well as the reactions un-

der study proceed *via* oximino derivatives formed upon their reactions with nitric acid or nitrogen oxides produced at high temperatures, namely, *via* nitrolic acids. The latter following the mechanism of one-electron transfer from the oximate anion to the trinitromethyl group underwent ring closure to give 3,5,5-trinitroisoxazoline derivatives, which then transformed into 3,5-dinitroisoxazole and its derivative.

It should be noted in summary that the literature data and the data obtained in the present work allow prediction of the synthetic pathways toward novel isoxazole and isoxazoline derivatives with electron-withdrawing substituents in the ring.

Experimental

The IR spectra were recorded on a UR-10 spectrometer in KBr pellets, the ^{1}H NMR spectra were obtained on a Perkin—Elmer-12 instrument (60 MHz) relative to hexamethyldisiloxane (internal standard).

4-Chloro-4,4-dinitro-1-phenylbutan-1-one (10). Gaseous chlorine was passed through a stirred suspension of salt **11** (5 g, 0.02 mol) in anhydrous diethyl ether (50 mL) at 20—22 °C until the yellow color of the starting salt disappeared. The reaction mixture was kept at room temperature for 2 h, the precipitate that formed was filtered off, the solvent from the filtrate was removed *in vacuo*, the resulting product was recrystallized from ethanol or *n*-hexane to give compound **10** in a yield of 4 g (81%), m.p. 72—73 °C (EtOH). Found (%): C, 44.14; H, 3.41; Cl, 13.14. $C_{10}H_9ClN_2O_5$. Calculated (%): C, 44.03; H, 3.30; Cl, 13.02. IR, ν/cm^{-1}: 1690 (C=O), 1595, 1310 (Cl(NO$_2$)$_2$C). ^{1}H NMR (CD_3CN), δ: 3.25 (m, 4 H, CH_2CH_2); 7.20 (m, 5 H, Ph).

3-Oximino compounds 5a and 7a,b (general procedure). ***A.*** Dry gaseous HCl and methyl nitrite generated by the known procedure[22] were passed simultaneously through a solution of compound **1**, **9**, or **10** (0.05 mol) in anhydrous diethyl ether (70 mL) at such a rate that the reaction mixture gently boiled. After passage of the calculated amount of methyl nitrite, HCl was introduced for additional 15 min, and then the reaction mixture was kept at room temperature for 4—6 h; during this time, the color of the reaction mixture changed from dark cherry to light yellow. The solvent was removed *in vacuo*, the resulting residue was recrystallized from carbon tetrachloride or dichloroethane.

5,5,5-Trinitro-3-oximinopentan-2-one (5a). The yield was 64%, light yellow crystals, m.p. 94—95 °C (CCl_4). Found (%): C, 23.83; H, 2.55; N, 22.55. $C_5H_6N_4O_8$. Calculated (%): C, 24.00; H, 2.40; N, 22.40. IR, ν/cm^{-1}: 1600, 1305 (C(NO$_2$)$_3$), 1720 (C=O), 3350 (=NOH). ^{1}H NMR (DMSO-d$_6$), δ: 4.20 (m, 2 H, CH_2); 1.98 (s, 3 H, Me); 12.80 (s, 1 H, =NOH).

4,4,4-Trinitro-2-oximino-1-phenylbutan-1-one (7a). The yield was 70%, colorless crystals, m.p. 92 °C (dichloroethane). Found (%): C, 38.06; H, 2.45; N, 17.40. $C_{10}H_8N_4O_8$. Calculated (%): C, 38.46; H, 2.56; N, 17.95. IR, ν/cm^{-1}: 1600, 1300 (C(NO$_2$)$_3$), 1690 (C=O), 3365 (=NOH). ^{1}H NMR (DMSO-d$_6$), δ: 4.15 (m, 2 H, CH_2); 7.08 (m, 5 H, Ph); 10.80 (s, 1 H, =NOH).

4-Chloro-4,4-dinitro-2-oximino-1-phenylbutan-1-one (7b). The yield was 74%, light yellow crystals, m.p. 99—100 °C (CCl_4). Found (%): C, 39.16; H, 2.14; Cl, 11.48. $C_{10}H_8ClN_3O_6$. Calculated (%): C, 39.80; H, 2.65; Cl, 11.77. IR, ν/cm^{-1}: 1600, 1310 (ClC(NO$_2$)$_2$), 1685 (C=O), 3370 (=NOH). ^{1}H NMR (DMSO-d$_6$), δ: 4.50 (d, 2 H, CH_2, $J_{H,H}$ = 14 Hz); 7.15 (m, 5 H, Ph); 9.40 (s, 1 H, =NOH).

B. A solution of compound **1** (11 g, 0.05 mol) in glacial acetic acid was maintained at 15—17 °C (40 mL) while a suspension of nitrosyl sulfuric acid (prepared from sodium nitrite (10.75 g, 0.15 mol), conc. sulfuric acid (20 mL), and 18% fuming sulfuric acid (2 mL)) was added portionwise with vigorous stirring. The reaction mixture was kept at 15—17 °C for 40—60 min and poured onto ice. The precipitate that formed was filtered off, washed with cold water, and dried on air. Compound **5a** was obtained in a yield of 9 g (72%), m.p. 94—94.5 °C (CCl_4). The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

3-Acetyl-5-nitroisoxazole (3). ***A.*** A mixture of compound **1** (3 g, 13.5 mmol) and LiCl (0.58 g, 14 mmol, freshly calcined) in anhydrous DMF (60 mL) was heated to 90 °C with stirring. Evolution of nitrogen oxides and elevation of the temperature to 100 °C were observed. The reaction mixture was stirred for 2 h at 100 °C, cooled to room temperature, and poured into water (200 mL). The mixture was extracted with diethyl ether (2×50 mL), the combined organic layers were washed with water (3×40 mL) and dried with $MgSO_4$. Removal of the solvent *in vacuo* and recrystallization of the solid residue from *n*-hexane with freezing out afforded isoxazole **3** (0.5 g, 23.6%), m.p. 71—72 °C. Found (%): C, 38.47; H, 2.86; N, 17.90. $C_5H_4N_2O_4$. Calculated (%): C, 38.45; H, 2.56; N, 17.93. IR, ν/cm^{-1}: 1720 (C=O), 1600 (C=N), 1555 and 1362 (NO$_2$). Mol. weight: found, 154 (cryoscopy in benzene); calculated, 156. ^{1}H NMR (CD_3CN), δ: 7.30 (s, 1 H, =CH); 2.68 (s, 3 H, Me).

B. To a solution of compound **1** (3 g, 13.5 mmol) and LiCl (0.58 g, 14 mmol) in anhydrous DMF (60 mL), N_2O_4 (0.86 mL, 14 mmol) was added at 5—10 °C with stirring. The reaction mixture was stirred for 0.5 h at 5—10 °C, warmed up to 60 °C, and kept at this temperature for 1 h. Work up as described for the method *A* afforded compound **3** in a yield of 0.53 g (25%), m.p. 69—70 °C. The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

C. To a solution of compound **1** (3 g, 13.5 mmol) and conc. HCl (2 mL) in DMF (60 mL), $NaNO_2$ (1 g, 14.5 mmol) was added at 5—10 °C with stirring. The reaction mixture was stirred for 30 min at 5—10 °C, then warmed up to 60 °C, and stirring was continued for 1 h. Compound **3** was isolated as described above (method *A*) in a yield of 0.57 g (26.7%), m.p. 69—71 °C. The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

D. To a mixture of 98% nitric acid (25 g) and water (25 mL), compound **1** (11 g, 0.05 mol) was added in small portions at room temperature. During addition, the reaction temperature elevated to 30 °C. After 1 h, the reaction mixture was poured onto ice, the precipitate that formed was filtered off, washed with water, and recrystallized from ethanol. Compound **3** was obtained in a yield of 0.44 g (5.6%), m.p. 70—71 °C. The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

E. A solution of compound **5a** (2.5 g, 10 mmol) in 95% MeOH (30 mL) was stirred at 30—35 °C for 2 h and the solvent was removed *in vacuo*. Recrystallization of the residue from *n*-hexane afforded compound **3** (1.09 g, 70%), m.p. 70—71 °C. The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

F. A solution of compound **5a** (2.5 g, 10 mmol) in acetonitrile or DMF (30 mL) was heated at 50—60 °C for 5 h. Compound **3** was isolated as described for the method *A* in a yield of 1.12 g (72%), m.p. 71 °C. The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

G. A solution of compound **5a** (2.5 g, 10 mmol) was treated with a 5% solution of KOH in 90% MeOH at 20 °C for 30 min. The product was isolated as described for the method *E* to give compound **3** in a yield of 1.17 g (75%), m.p. 70—71 °C. The IR spectrum of the product was identical to that of the sample synthesized by the method *A*.

3-Benzoyl-5-nitroisoxazole (8) was prepared from compounds **7a,b** by the methods *E*—*G* in the yields of 75—85%, m.p. 86 °C (EtOH). Found (%): C, 56.34; H, 3.00; N, 14.25. $C_9H_6N_2O_3$. Calculated (%): C, 56.84; H, 3.15; N, 14.73. IR, ν/cm^{-1}: 1660 (C=O), 1615 (C=N), 1095 (C—O—N), 1550, 1360 (NO_2). Mol. weight: found, 187 (cryoscopy in benzene); calculated, 190.

References

1. M. J. Kamlet, H. Adolph, *J. Org. Chem.*, 1968, **33**, 3073.
2. US Pat. 3127736; *Chem. Abstrs*, 1964, **61**, 5445n.
3. G. Kh. Khisamutdinov, V. I. Slovetskii, M. Sh. L´vova, O. G. Usyshkin, M. A. Besprozvannyi, A. A. Fainzil´berg, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1970, 2553 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1970, **19**, 2397].
4. A. A. Fainzil´berg, G. Kh. Khisamutdinov, V. I. Slovetskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1969, 476 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1969, **18**, 476].
5. G. Kh. Khisamutdinov, V. I. Slovetskii, A. A. Fainzil´berg, M. Sh. L´vova, *Izv. Akad. Nauk SSSR, Ser. Khim*, 1971, 1073 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1971, **20**, 976].
6. A. L. Fridman, B. D. Surkov, S. S. Novikov, *Usp. Khim.*, 1980, **49**, 2159 [*Russ. Chem. Rev.* (*Engl. Transl.*), 1980, **49**].
7. S. S. Novikov, G. A. Shveikhgeimer, V. V. Sevost´yanova, V. A. Shlyapochnikov, *Khimiya alifaticheskikh i alitsiklicheskikh nitrosoedinenii* [*Chemistry of Aliphatic and Alicyclic Nitro Compounds*], Khimia, Moscow, 1974, 120 pp. (in Russian).
8. G. Kh. Khisamutdinov, V. I. Slovetskii, Yu. M. Golub, S. A. Shevelev, A. A. Fainzil´berg, *Izv. Akad. Nauk*, *Ser. Khim.*, 1997, 338 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1997, **46**, 324].
9. US Pat. 4476311; *Ref. Zh. Khim.* [*Russian Journal of Abstracts, Chemistry*], 1985, 13N276P (in Russian).
10. L. J. Beckham, W. A. Fessler, V. A. Kise, *Chem. Rev.*, 1951, **48**, 320.
11. L. I. Khmel´nitskii, S. S. Novikov, T. I. Godovikova, *Khimiya furoksanov. Stroenie i sintez* [*Chemistry of Furoxanes. Structure and Synthesis*], Nauka, Moscow, 1984, 173; 180 (in Russian).
12. A. I. Ivanov, L. A. Ustynyuk, V. I. Slovetskii, S. A. Shevelev, A. A. Fainzil´berg, S. S. Novikov, *Zh. Org. Khim.*, 1966, **2**, 763 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1966, **2**, 476].
13. L. A. Ustynyuk, S. A. Shevelev, A. A. Fainzil´berg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966, 930 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1966, **15**].
14. V. F. Selivanov, V. K. Shchedrova, B. V. Gidaspov, *Zh. Org. Khim.*, 1972, **8**, 1543 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1972, **8**].
15. A. T. Baryshnikov, V. I. Erashko, N. N. Zubareva, B. I. Ugrak, S. A. Shevelev, A. A. Fainzil´berg, V. V. Semenov, *Izv. Akad. Nauk*, *Ser. Khim.*, 1992, 2123 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.* (*Engl. Transl.*), 1992, **41**, 1657].
16. L. I. Khmel´nitskii, S. S. Novikov, T. I. Godovikova, *Khimiya furoksanov. Stroenie i sintez* [*Chemistry of Furoxans. Structure and Synthesis*], Nauka, Moscow, 1984, 162; 165 (in Russian).
17. *The Chemistry of the Nitro and Nitroso Groups*, Ed. H. Feuer, Wiley, New York—London—Sydnay—Toronto, 1969.
18. O. M. Lerner, V. V. Perekalin, *Dokl. Akad. Nauk SSSR*, 1962, **145**, 804 [*Dokl. Chem.* (*Engl. Transl.*), 1962].
19. S. S. Novikov, I. S. Korsakova, N. N. Bulatova, *Zh. Obshch. Khim.*, 1959, **29**, 3659 [*J. Gen. Chem. USSR* (*Engl. Transl.*), 1959, **29**].
20. D. J. Glover, M. J. Kamlet, *J. Org. Chem.*, 1961, **26**, 4734.
21. E. L. Golod, G. N. Novatskii, L. I. Bagal, *Zh. Org. Khim.*, 1973, **9**, 1111 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1973, **9**].
22. *Organic Syntheses, Collective Volume 2*, Wiley, New York, 1946, **X**—**XIX**.

Received March 25, 2009;
in revised form August 17, 2009