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Synthetic Exploitation of the Ring-Opening of 3,4-Dinitrothiophene. Part 7.[1] Access to Disubstituted 1,2,5-Oxadiazole-2-oxides and 2-Phenyl-2*H*-1,2,3-triazole-1-oxides

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Abstract: 1,4-Dialkyl- and 1,4-diaryl-2,3-bis(hydroxyimino)butanes **7**, from reduction of the corresponding 1,4-disubstituted 2,3-dinitro-1,3-butadienes **2**, are transformed with satisfactory yields into 3,4-disubstituted 1,2,5-oxadiazole-2-oxide **5** and 4,5-disubstituted 2-phenyl-2*H*-1,2,3-triazole-1-oxides **6**. Dinitrobutadienes **2** are obtained from the reaction of 3,4-dinitrothiophene with diethylamine and subsequent treatment of the ensuing bis(diethylamino)butadiene **1** with Grignard reagents; thus the overall transformation represents a novel approach to 1,2,5-oxadiazole and 1,2,3-triazole systems via a ring-opening ring-closure strategy. © 1997, Elsevier Science Ltd. All rights reserved.

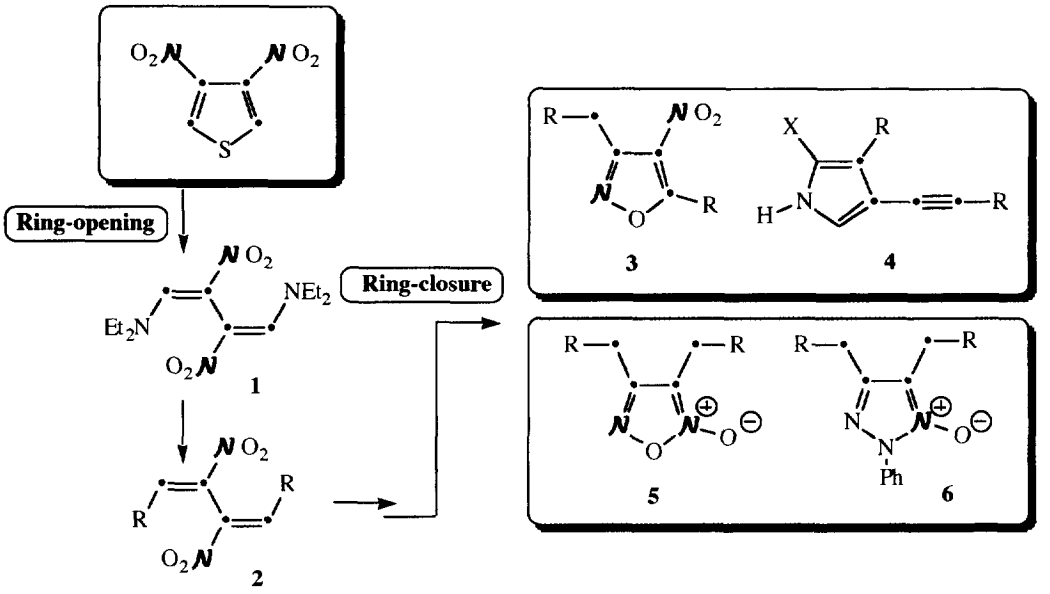
The ring-opening of 3,4-dinitrothiophene with diethylamine and the subsequent reaction of the ensuing 1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene **1** with Grignard reagents[2a,b,e] furnish good overall yields of 1,4-dialkyl- and 1,4-diaryl-2,3-dinitro-1,3-butadienes **2**. In previous papers[2] we have shown some interesting applications of the latter compounds as synthetic building blocks and in particular their transformation, under different conditions, into heterocyclic systems such as the substituted 4-nitroisoxazoles **3**[2c] and 4-ethynylpyrroles **4**.[2d] As depicted in Scheme 1, the overall process corresponds to a 3,4-dinitrothiophene ring-opening with eventual ring-closure to new pentatomic heterocycles whose structure may be not easily available by other means.

We report herein on the extension of such a ring-opening ring-closure strategy to the synthesis of substituted 1,2,5-oxadiazole-2-oxides **5** and 2-phenyl-2*H*-1,2,3-triazole-1-oxides **6**.

RESULTS AND DISCUSSION

On the grounds of the above mentioned ready availability of 1,4-disubstituted 2,3-dinitrobutadienes **2** from 3,4-dinitrothiophene in good overall yields (*ca.* 80%),[2a,b,e] a key step of the synthesis herein is represented by the preparation of the corresponding α-dioximes **7** which, as sketched in Schemes 2 and 3, are the starting materials of the subsequent ring-closing procedures to 1,2,5-oxadiazole and 1,2,3-triazole systems **5** and **6**.

Scheme 1 [a]

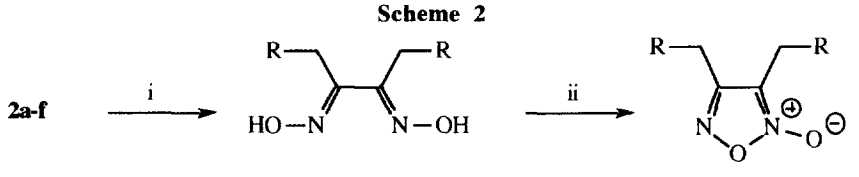


a) The carbons (dots) and nitrogen(s) (emboldened italics) deriving from the parent 3,4-dinitrothiophene are evidenced.

The **2** → **7** transformation was best performed by means of a recently[2b] optimized reduction[3] with lead powder in a mixture of DMF and AcOH at room temperature (see Table 1 for relevant yields of **7**). The 1,4-disubstituted 2,3-bis(hydroxyimino)butanes **7a-f**, obtained in more than satisfactory yields, possess most likely[2b] an (*E*,*E*)-configuration around the carbon-nitrogen double bonds: *i.e.* a configuration not suitable for the subsequent oxidative cyclization (Scheme 2) to the corresponding 1,2,5-oxadiazole-2-oxide derivatives **5a-f**. Anyway the good yields of the latter heterocycles (Table 1) suggest that in the reaction conditions employed (gentle warming in basic ethanol, in order to dissolve compound **7**, followed by treatment at 0 °C with aqueous NaClO) a proper stereomutation of **7** occurs.

Somewhat more complicated is the approach herein to 4,5-disubstituted 1,2,3-triazoles **6a-f** (Scheme 3), which requires the initial transformation of the 1,4-disubstituted 2,3-butanedioximes **7** into the corresponding monoximes **8** via a selective hydrolysis of a single carbon-nitrogen double bond.

Scheme 2



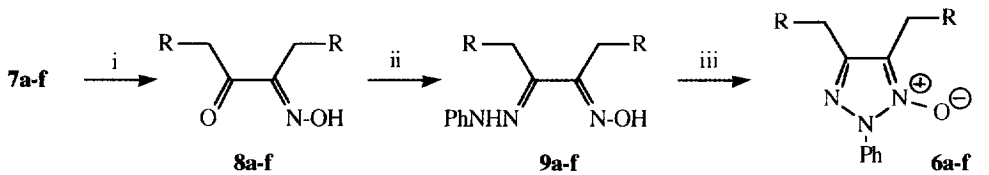
i) DMF-AcOH / Pb powder; ii) EtOH / NaOH / 5% aq. NaClO

Table 1. Results of the synthesis of 3,4-disubstituted 1,2,5-oxadiazole-2-oxides **5a-f** from the corresponding dinitrobutadienes **2**.

2, 5 and 7	R =	2 → 7 *a* Yields (%) *c,d*	7 → 5 *b* Yields (%) *c*	Overall yields (%) of 5 from 2
a	C_6H_5	80	95	76
b	2-MeC_6H_4	70	98	69
c	4-MeC_6H_4	75	71	53
d	4-$MeOC_6H_4$	80	88	70
e	1-naphthyl	70	81	57
f	*cycl*-C_6H_{11}	82	96	79

a) Reduction of **2** with lead powder in DMF/AcOH at 25 °C. *b*) Oxidation of **7** with 5% aqueous hypochlorite in ethanolic sodium hydroxide at 0 °C. *c*) Yields of isolated compounds. *d*) Yields of **7** in agreement with those previously obtained (*cf.* refs 2b and 2e).

Scheme 3



i) Dioxane / diluted HCl, reflux. ii) $PhNHNH_2$ in EtOH / AcOH, reflux. iii) Method A: N-iodosuccinimide in CCl_4, reflux; method B: $CuSO_4$ in aq. pyridine, reflux.

Table 2. Results of the synthesis of 4,5-disubstituted 2-phenyl-2H-1,2,3-triazole-1-oxides **6a-f** from the corresponding bis(hydroxyimino)butanes **7a-f**.

6 - 9	R =	7 → 8 *a* Yields (%) *e*	8 → 9 *b* Yields (%) *e*	9 → 6 *c* Yields (%) *e* A	9 → 6 *c* Yields (%) *e* B	Overall yield (%) of 6 from 7 *d*
a	C_6H_5	80	86	42	97	67
b	2-MeC_6H_4	65	80	55	90	47
c	4-MeC_6H_4	60	88	*f*	96	51
d	4-$MeOC_6H_4$	60	90	*f*	96	52
e	1-naphthyl	63	85	26	82	44
f	*cycl*-C_6H_{11}	77	91	*f*	97	68

a) Hydrolysis with diluted HCl in dioxane at reflux temperature. *b*) Reaction with freshly distilled $PhNHNH_2$ in EtOH/AcOH at reflux temperature. *c*) Reaction performed at reflux temperature with either *N*-iodosuccinimide in CCl_4 (A) or $CuSO_4$ in 15% aq. pyridine (B). *d*) Overall yield calculated for method B. *e*) Yields of isolated products. *f*) Experiments not performed.

Among the several methods which are in principle suitable to accomplish the **7** to **8** transformation, in our hands the best procedure resulted to be the simple heating of a dioxane solution of **7** with dilute hydrochloric acid until disappearance of the starting material (TLC). 1,4-Disubstituted 3-hydroxyimino-2-butanones **8a-f** were thus obtained (Table 2) in yields ranging between 60 and 80%. The presence of small quantities of 1,4-disubstituted 2,3-butanediones, the products of further hydrolysis of **8**, was always detected (TLC, ^{1}H NMR) in the crude reaction mixture, but only in the case of the hydrolysis of **7a** we took care of the isolation of the relevant 1,4-diphenyl-2,3-butanedione.[4]

The condensation of **8a-f** with phenylhydrazine (step ii, Scheme 3) involved trivial standard procedures and relevant 1,4-disubstituted 3-hydroxyimino-2-phenylhydrazonobutanes **9a-f** were obtained in good yields (Table 2); no investigation was carried out in order to ascertain the configuration around the two carbon-nitrogen double bonds of the latter compounds, which were submitted to the subsequent oxidative cyclization to the corresponding 4,5-disubstituted 2-phenyl-2*H*-1,2,3-triazole-1-oxides **6a-f**.

In order to accomplish the latter transformation the method[6] involving *N*-iodosuccinimide as reagent in refluxing carbon tetrachloride was first attempted. However, as shown by the yields reported in Table 2 (method A), this procedure resulted to be extremely unsatisfactory. The alternative method B consisting in the simple heating of compounds **9** in aqueous pyridine with copper(II) sulfate,[7] on the contrary, furnished excellent yields of the desired 4,5-disubstituted 2-phenyl-2*H*-1,2,3-triazole-1-oxides **6a-f**.

In conclusion, the strategy involving the ring-opening of 3,4-dinitrothiophene and, after proper transformations, the eventual ring-closure furnishes a novel and convenient method for the synthesis of bis(arylmethyl)-substituted 1,2,5-oxadiazole and 2-aryl-1,2,3-triazole systems, compounds of interest both as intermediates and as potentially biologically-active molecules.[7-11] Through an appropriate choice of the reagents, in our opinion, the method herein can be adapted to the synthesis, with some obvious limitations, of a variety of the above cited pentatomic heterocycles whose structure would be cumbersome to obtain by other means. Last but not least, it is worth stressing the easy access, through the exploitation of 3,4-dinitrothiophene as template, to 2-oxooximes **8** of well defined structure: a class of compounds of well known synthetic potentiality.[12]

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini 200 spectrometer; TMS was used as internal standard and chemical shifts are reported as δ values (ppm).

Materials

Petroleum ether and light petroleum refer to the fractions with bp 40-60 °C and 80-100 °C respectively. All reagents were commercial products used as received, but for phenylhydrazine which was freshly distilled before use. 1,4-Disubstituted 2,3-bis(hydroxyimino)butanes **7a-f** were prepared, as previously reported,[2b] by lead powder reduction in DMF/AcOH of the corresponding 1,4-disubstituted 2,3-dinitro-1,3-butadienes **2** (see Table 1 for relevant yields).

Reactions of 1,4-disubstituted 2,3-bis(hydroxyimino)butanes 7a-f with aqueous sodium hypochlorite

A solution of 1 mmol of 1,4-disubstituted 2,3-bis(hydroxyimino)butanes **7a-f** in 33 ml of EtOH and 2 ml of 1 M aqueous KOH was cooled to *ca.* 0 °C. Under magnetic stirring, 13 ml of 5% aqueous NaClO (precooled at 0 °C) were quickly dropped into the reaction mixture, which was then allowed to reach room temperature. After 20 min, another 20 ml aliquot of 5% aq. NaClO was added and the reaction stirred for further 20 min, during

which time precipitation of a white solid was generally observed. The reaction mixture was then extracted with ether and the ether extracts evaporated under reduced pressure, after drying over sodium sulfate.

The residue was finally purified by chromatography (silica gel column, dichloromethane as eluant) and the crude product (but for **5e** and **5f**, see below) crystallized.

The yields of the 1,2,5-oxadiazole-2-oxides obtained are collected in Table 1, while the relevant physical, spectroscopic (^{1}H and ^{13}C NMR) and microanalytical data are reported below.

3,4-Disubstituted 1,2,5-oxadiazole-2-oxides 5a-f

3,4-Dibenzyl-1,2,5-oxadiazole-2-oxide **5a**, mp 71.0-71.4 °C (EtOH-H_2O) (lit.,[13] mp 74-75 °C); ^{1}H NMR ($CDCl_3$) δ 3.64 (2H, s), 3.88 (2H, s), 6.99 (2H, m), 7.12 (2H, m) and 7.27 (6H, m); ^{13}C NMR ($CDCl_3$) δ 28.44, 32.19, 115.21, 127.60, 128.33, 128.63, 128.94, 133.64, 133.94 and 156.59.

3,4-Bis[(2-methylphenyl)methyl]-1,2,5-oxadiazole-2-oxide **5b**, mp 75.3-76.2 °C (petroleum ether); ^{1}H NMR ($CDCl_3$) δ 2.06 (3H, s), 2.10 (3H, s), 3.65 (2H, s), 3.68 (2H, s), 6.74 (1H, d, *J* 7.7 Hz), 6.84 (1H, d, *J* 7.3 Hz) and 7.12 (6H, m); ^{13}C NMR ($CDCl_3$) δ 19.33, 26.77, 29.74, 114.77, 126.32, 126.38, 127.70, 127.82, 128.33, 128.51, 130.69, 130.75, 131.62, 132.24, 136.56, 136.62 and 156.69; Found: C, 73.3; H, 6.1; N, 9.6%. $C_{18}H_{18}N_2O_2$ requires C, 73.4; H, 6.2; N, 9.5%.

3,4-Bis[(4-methylphenyl)methyl]-1,2,5-oxadiazole-2-oxide **5c**, mp 109.6-110.9 °C (light petroleum); ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, s), 2.34 (3H, s), 3.59 (2H, s), 3.83 (2H, s), 6.89 (2H, AA' of AA'BB', *J* 8.1 Hz), 7.01, 7.06 and 7.12 [6H in all, partly overlapped BB' of AA'BB' (*J* 8.1 Hz) and AA'BB' (*J* 8.2 Hz)]; ^{13}C NMR ($CDCl_3$) δ 21.06, 27.98, 31.62, 115.49, 128.26, 128.56, 129.57, 129.67, 130.69, 130.88, 137.31, 137.34 and 156.93; Found: C, 73.6; H, 6.2; N, 9.4%. $C_{18}H_{18}N_2O_2$ requires C, 73.4; H, 6.2; N, 9.5%.

3,4-Bis[(4-methoxyphenyl)methyl]-1,2,5-oxadiazole-2-oxide **5d**, mp 40.8-41.9 °C (pentane); ^{1}H NMR ($CDCl_3$) δ 3.58 (2H, s), 3.78 (3H, s), 3.80 (3H, s), 3.82 (2H, s), 6.78, 6.83, 6.92 and 7.03 (2H each, four half parts of AA'BB', *J* 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 27.58, 31.19, 55.26, 114.30, 114.41, 115.53, 125.69, 125.89, 129.46, 129.73, 157.03 and 159.06; Found: C, 66.1; H, 5.6; N, 8.7%. $C_{18}H_{18}N_2O_4$ requires C, 66.2; H, 5.6; N, 8.6%.

3,4-Bis[(1-naphthyl)methyl]-1,2,5-oxadiazole-2-oxide **5e**, waxy compound; ^{1}H NMR ($CDCl_3$) δ 4.06 (2H, s), 4.08 (2H, s), 6.80 (1H, d, *J* 7.0 Hz), 6.91 (1H, d, *J* 7.0 Hz), 7.09 (2H, m), 7.44 (5H, m), 7.66 (3H, m) and 7.80 (2H, m); ^{13}C NMR ($CDCl_3$) δ 26.76, 29.36, 115,17, 122.84, 122.95, 125.10, 125.98, 126.16, 126.40, 126.49, 126.92, 128.33, 128.52, 128.82, 128.90, 129.16, 129.70, 131.34, 133.78 and 156.84; Found: C, 78.7; H, 5.0; N, 7.5%. $C_{24}H_{18}N_2O_2$ requires C, 78.7; H, 5.0; N, 7.6%.

3,4-Bis(cyclohexylmethyl)-1,2,5-oxadiazole-2-oxide **5f**, oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (10H in all, two partly overlapped m), 1.70 (12H, m), 2.38 (2H, d, *J* 7.2 Hz) and 2.50 (2H, d, *J* 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.88, 25.98, 26.11, 29.99, 33.10, 35.38, 36.21, 115.55 and 157.29; Found: C, 68.9; H, 9.3; N, 10.1%. $C_{16}H_{26}N_2O_2$ requires C, 69.0; H, 9.4; N, 10.1%.

Hydrolysis of 1,4-disubstituted 2,3-bis(hydroxyimino)butanes 7a-f with diluted hydrochloric acid

In a one-neck flask equipped with magnetic bar and reflux condenser, 1,4-disubstituted 2,3-bis(hydroxyimino)butanes **7a-f** (2 mmol) were dissolved in the minimum amount of hot dioxane (60-90 ml). Diluted hydrochloric acid (conc. 3%, 120 ml) was added from the top of the condenser and the solution refluxed until TLC showed complete disappearance of the starting dioxime. In some cases the initial addition of diluted HCl resulted in the precipitation of some substrate, which anyway went into solution with the progress of the reaction.

The usual workup involved pouring of the reaction mixture into brine and extraction with ether. After washing of the ether extracts with aqueous $NaHCO_3$ and with water, they were dried over sodium sulfate and evaporated under reduced pressure. From the crude residue the 1,4-disubstituted 3-hydroxyimino-2-butanones **8a-f** were finally separated by column chromatography on silica gel using petroleum ether/dichloromethane gradients.

The yields of compounds **8a-f** obtained are reported in Table 2, while their physical, ^{1}H NMR and microanalytical data are collected below.

1,4-Disubstituted 3-hydroxyimino-2-butanones 8a-f

3-Hydroxyimino-1,4-diphenyl-2-butanone **8a**, mp 146.0-147.0 °C (light petroleum-toluene) (lit.,[5] mp 146.5-147.0 °C); ^{1}H NMR ($CDCl_3$) δ 3.90 (2H, s), 4.09 (2H, s), 7.22 (10H, m) and 7.88 (1H, s).

3-Hydroxyimino-1,4-bis(2-methylphenyl)-2-butanone **8b**, mp 108.0-109.0 °C (light petroleum-toluene); ^{1}H NMR ($CDCl_3$) δ 2.15 (3H, s), 2.31 (3H, s), 3.89 (2H, s), 4.13 (2H s), 6.91 (1H, d, *J* 6.5 Hz), 7.08 (7H, m) and 8.04 (1H, s); Found: C, 76.7; H, 6.8; N, 5.1%. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%.

3-Hydroxyimino-1,4-bis(4-methylphenyl)-2-butanone **8c**, mp 115.0-115.8 °C (light petroleum-toluene); ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s), 2.31 (3H, s), 3.85 (2H, s), 4.03 (2H, s), 7.01 (2H, AA' of AA'BB', *J* 7.7 Hz), 7.08 [6H, overlapped BB' of AA'BB' (*J* 7.7 Hz) and app. s] and 7.85 (1H, s); Found: C, 76.7; H, 6.7; N, 5.0%. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%.

3-Hydroxyimino-1,4-bis(4-methoxyphenyl)-2-butanone **8d**, mp 120.0-121.0 °C (light petroleum-toluene); ^{1}H NMR ($CDCl_3$) δ 3.76 (3H, s), 3.78 (3H, s), 3.82 (2H, s), 4.01 (2H, s), 6.75 (2H, AA' of AA'BB', *J* 8.7 Hz), 6.81 (2H, AA' of AA'BB', *J* 8.6 Hz), 7.08 (2H, BB' of AA'BB', *J* 8.6 Hz), 7.14 (2H, BB' of AA'BB', *J* 8.7 Hz) and 7.90 (1H, br s); Found: C, 68.8; H, 6.2; N, 4.6%. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%.

3-Hydroxyimino-1,4-bis(1-naphthyl)-2-butanone **8e**, mp 116.6-118.0 °C (light petroleum-toluene); ^{1}H NMR ($CDCl_3$) δ 4.38 (2H, s), 4.55 (2H, s), 7.21 (3H, m), 7.39 (5H, m), 7.70 (3H, app t), 7.81 (2H, m) and 8.07 (2H, overlapped br s and m); Found: C, 81.4; H, 5.3; N, 4.1%. $C_{24}H_{19}NO_2$ requires C, 81.6; H, 5.4; N, 4.0%.

1,4-Dicyclohexyl-3-hydroxyimino-2-butanone **8f**, mp 76.6-76.9 °C (EtOH-H_2O); ^{1}H NMR ($CDCl_3$) δ 1.10 (10H, m), 1.63 (11H, m), 1.87 (1H, m), 2.46 (2H, d, *J* 7.1 Hz), 2.63 (2H, d, *J* 6.9 Hz) and 7.52 (1H, s); Found: C, 72.4; H, 10.4; N, 5.5%. $C_{16}H_{27}NO_2$ requires C, 72.4; H, 10.25; N, 5.3%.

Condensation of 1,4-disubstituted 3-hydroxyimino-2-butanones 8a-f with phenylhydrazine

A solution of phenylhydrazine (0.49 ml, 5 mmol) in 2.3 ml of acetic acid was added, under magnetic stirring, to 1 mmol of hydroxyiminobutanones **8a-f** dissolved in 7.9 ml of absolute ethanol in a 25 ml two-neck flask. The latter was equipped with a dropping funnel (with pressure equalizing side-arm) filled with 4 Å molecular sieves and surmounted by a reflux condenser with silica gel valve.

After heating at reflux temperature until TLC showed complete disappearance of the substrate (generally 1-2h), the reaction mixture was poured into ice-water and left overnight at room temperature in order to obtain a crystalline precipitate. The product was finally filtered on a Buchner funnel, washed with water on the filter, dried in the air and crystallized from ethanol.

The yields of compounds **9a-f** are collected in Table 2, while their physical, ^{1}H NMR and microanalytical data are reported below.

1,4-Disubstituted 3-hydroxyimino-2-phenylhydrazonobutanes 9a-f

3-Hydroxyimino-1,4-diphenyl-2-phenylhydrazonobutane **9a**, mp 185.3-186.4 °C (EtOH); ^{1}H NMR (CD_3COCD_3) δ 4.12 (2H, s), 4.26 (2H, s), 6.80 (1H, m), 7.21 (12H, m), 7.41 (2H, m), 8.93 (1H, s) and 10.47 (1H, s); Found: C, 76.7; H, 6.2; N, 12.3%. $C_{22}H_{21}N_3O$ requires C, 76.9; H, 6.2; N, 12.2%.

3-Hydroxyimino-1,4-bis(2-methylphenyl)-2-phenylhydrazonobutane **9b**, mp 160.5-161.6 °C (EtOH-H_2O); ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 2.49 (3H, s), 4.01 (2H, s), 4.24 (2H, s), 6.86 (4H, m), 7.17 (10H, m) and 7.53 (1H, s); Found: C, 77.6; H, 6.6; N, 11.2%. $C_{24}H_{25}N_3O$ requires C, 77.6; H, 6.8; N, 11.3%.

3-Hydroxyimino-1,4-bis(4-methylphenyl)-2-phenylhydrazonobutane **9c**, mp 181.4-182.2 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.30 (6H, s), 3.98 (2H, s), 4.23 (2H, s), 6.86 (1H, app t), 7.04 (8H, m), 7.28 (5H, m) and 7.73 (1H, s); Found: C, 77.5; H, 7.0; N, 11.4%. $C_{24}H_{25}N_3O$ requires C, 77.6; H, 6.8; N, 11.3%.

3-Hydroxyimino-1,4-bis(4-methoxyphenyl)-2-phenylhydrazonobutane **9d**, mp 154.0-155.2 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 3.76 and 3.77 (6H in all, two partly overlapped s), 3.96 (2H, s), 4.20 (2H, s), 6.82 (5H, m), 7.03 (4H, m), 7.24 (3H, m), 7.35 (2H, BB' of AA'BB', *J* 8.8 Hz) and 7.72 (1H, s); Found: C, 71.6; H, 6.4; N, 10.6%. $C_{24}H_{25}N_3O_3$ requires C, 71.4; H, 6.2; N, 10.4%.

3-Hydroxyimino-1,4-bis(1-naphthyl)-2-phenylhydrazonobutane **9e**, mp 188.2-189.4 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 4.53 (2H, s), 4.79 (2H, s), 6.72 (2H, m), 7.06 (2H, m), 7.38, 7.58, 7.74 and 7.90 (15H in all, four partly overlapped m), 8.15 (1H, m) and 8.38 (1H, m); Found: C, 81.4; H, 5.9; N, 9.6%. $C_{30}H_{25}N_3O$ requires C, 81.2; H, 5.7; N, 9.5%.

3-Hydroxyimino-1,4-dicyclohexyl-2-phenylhydrazonobutane **9f**, mp 164.2-165.0 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.15 (10H, m), 1.68 (12H, m), 2.45 (2H, d, *J* 7.0 Hz), 2.72 (2H, d, *J* 7.0 Hz), 6.90 (1H, m), 7.10 (2H, m), 7.29 (3H, m) and 7.63 (1H, s); Found: C, 74.3; H, 9.4; N, 12.0%. $C_{22}H_{33}N_3O$ requires C, 74.3; H, 9.4; N, 11.8%.

Cyclization of 1,4-disubstituted 3-hydroxyimino-2-phenylhydrazonobutanes 9a-f to the corresponding 2-phenyl-2H-1,2,3-triazole-1-oxides 6a-f

A) With N-iodosuccinimide.[14] — A magnetically stirred solution of 0.5 mmol of 3-hydroxyimino-2-phenylhydrazonobutanes **9a-f** and *N*-iodosuccinimide (1 mmol) in 17 ml of anhydrous carbon tetrachloride, was heated at reflux temperature under argon.

After 2h (TLC checking for disappearance of the substrate) the reaction mixture was cooled, diluted with carbon tetrachloride and washed, in a separatory funnel, with 5% aqueous sodium sulfite. The organic phase was then dried over sodium sulfate and the solvent evaporated under reduced pressure. From the crude residue the triazole derivatives **6a-f** were then isolated by column chromatography (silica gel, dichloromethane as eluant).

B) With copper(II) sulfate.[14] — 3-Hydroxyimino-2-phenylhydrazonobutanes (0.5 mmol) were added to 15% aqueous pyridine (8 ml) in a two-neck flask equipped with reflux condenser and magnetic bar. The mixture was heated at reflux temperature under magnetic stirring for a few minutes: a small quantity of the substrate remained as undissolved material. A solution of copper(II) sulfate (1.25 mmol) in water (1.5 ml) was added while stirring, and heated to reflux: with the progress of the reaction the undissolved substrate went into solution. After heating for 1h, the reaction mixture was cooled to room temperature, acidified with diluted hydrochloric acid and extracted with dichloromethane. The extracts were washed with water, dried over sodium sulfate and concentrated to small volume. Such dichloromethane solution of the crude reaction product was usually filtered through a short silica gel column to give, after evaporation of the solvent, essentially pure 4,5-disubstituted 2-phenyl-2*H*-1,2,3-triazole-1-oxides **6a-f**.

The yields of compounds **6a-f** are collected in Table 2, while their physical, ^1H and ^{13}C NMR and microanalytical data are reported below.

4,5-Disubstituted 2-phenyl-2H-1,2,3-triazole-1-oxides 6a-f

4,5-Dibenzyl-2-phenyl-2H-1,2,3-triazole-1-oxide **6a**, mp 80.0-81.6 °C (EtOH-H_2O); ^1H NMR ($CDCl_3$) δ 3.89 (2H, s), 3.93 (2H, s), 7.20 (10H, m), 7.50 (3H, m) and 7.98 (2H, m); ^{13}C NMR ($CDCl_3$) δ 28.52, 32.89, 122.70, 126.94, 128.64, 128.73, 129.00, 135.41, 136.00, 136.67 and 144.10; Found: C, 77.5; H, 5.4; N, 12.2%. $C_{22}H_{19}N_3O$ requires C, 77.4; H, 5.6; N, 12.3%.

4,5-Bis[(2-methylphenyl)methyl]-2-phenyl-2H-1,2,3-triazole-1-oxide **6b**, mp 100.6-101.7 °C (EtOH-H_2O); ^1H NMR ($CDCl_3$) δ 2.14 (3H, s), 2.19 (3H, s), 3.74 (2H, s), 3.89 (2H, s), 6.87 (2H, m), 7.12 (6H, m), 7.48 (3H, m) and 7.98 (2H, m); ^{13}C NMR ($CDCl_3$) δ 19.49, 19.55, 26.52, 30.53, 122.67, 126.05, 126.12, 126.41, 127.00, 127.13, 128.58, 128.62, 129.00, 130.36, 130.44, 133.62, 134.75, 135.43, 136.50, 136.57 and 143.96; Found: C, 77.9; H, 6.4; N, 11.5%. $C_{24}H_{23}N_3O$ requires C, 78.0; H, 6.3; N, 11.4%.

4,5-Bis[(4-methylphenyl)methyl]-2-phenyl-2H-1,2,3-triazole-1-oxide **6c**, mp 71.3-72.1 °C (petroleum ether); ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 2.33 (3H, s), 3.84 (2H, s), 3.89 (2H, s), 7.06 (8H, m), 7.45 (3H, m) and 7.97 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.04, 28.06, 32.45, 122.71, 127.14, 128.53, 128.95, 129.31, 129.36, 132.95, 133.62, 135.38, 136.50 and 144.31; Found: C, 78.0; H, 6.4; N, 11.2%. $C_{24}H_{23}N_3O$ requires C, 78.0; H, 6.3; N, 11.4%.

4,5-Bis[(4-methoxyphenyl)methyl]-2-phenyl-2H-1,2,3-triazole-1-oxide **6d**, oil; ^1H NMR ($CDCl_3$) δ 3.77 (3H, s), 3.79 (3H, s), 3.83 (2H, s), 3.87 (2H, s), 6.77 and 6.82 (4H in all, two partly overlapped half parts of AA'BB', *J* 8.8 Hz), 7.07 (4H in all, app d), 7.46 (3H, m) and 7.97 (2H, m); ^{13}C NMR ($CDCl_3$) δ 27.66, 32.05, 55.26, 114.06, 114.12, 122.73, 127.25, 128.60, 128.71, 128.98, 129.66, 135.40, 144.40 and 158.58; Found: C, 71.6; H, 5.9; N, 10.6%. $C_{24}H_{23}N_3O_3$ requires C, 71.8; H, 5.8; N, 10.5%.

4,5-Bis[(1-naphthyl)methyl]-2-phenyl-2H-1,2,3-triazole-1-oxide **6e**, mp 139.2-140.1 °C (light petroleum); ^1H NMR ($CDCl_3$) δ 4.14 (2H, s), 4.37 (2H, s), 6.97 (2H, m), 7.15 (2H, m), 7.46 (7H, m), 7.68 (3H, m), 7.83 (2H, m) and 7.98 (3H, m); ^{13}C NMR ($CDCl_3$) δ 26.62, 30.25, 122.78, 123.46, 123.63, 125.21, 125.72, 125.90, 126.09, 126.26, 126.56, 126.66, 127.67, 127.92, 128.69, 129.04, 131.34, 131.62, 131.76, 132.22, 133.79, 133.84, 135.45 and 144.17; Found: C, 81.6; H, 5.3; N, 9.6%. $C_{30}H_{23}N_3O$ requires C, 81.6; H, 5.2; N, 9.5%.

4,5-Bis(cyclohexylmethyl)-2-phenyl-2H-1,2,3-triazole-1-oxide **6f**, oil; ^1H NMR ($CDCl_3$) δ 1.15 (10H, m), 1.70 (12H, m), 2.52 (4H, t, *J* 6.5 Hz), 7.45 (3H, m) and 7.95 (2H, m); ^{13}C NMR ($CDCl_3$) δ 26.05, 26.15, 26.26, 26.33, 30.21, 33.19, 33.27, 33.87, 35.84, 37.39, 122.63, 127.18, 128.34, 128.91, 135.51 and 144.78; Found: C, 74.7; H, 8.9; N, 12.0%. $C_{22}H_{31}N_3O$ requires C, 74.7; H, 8.8; N, 11.9%.

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REFERENCES AND NOTES

1. Synthetic Exploitation of the Ring-Opening of 3,4-Dinitrothiophene, Part 6: see ref. 2e.
2. *a*) Dell'Erba, C.; Mele, A.; Novi, M.; Petrillo, G.; Stagnaro, P. *Tetrahedron Lett.* **1990**, *31*, 4933. *b*) Dell'Erba, C.; Mele, A.; Novi, M.; Petrillo, G.; Stagnaro, P. *Tetrahedron* **1992**, *48*, 4407. *c*) Dell'Erba, C.; Novi, M.; Petrillo, G.; Stagnaro, P. *J. Heterocycl. Chem.* **1994**, *31*, 861. *d*) Dell'Erba, C.; Giglio, A.; Mugnoli, A.; Novi, M.; Petrillo, G.; Stagnaro, P. *Tetrahedron* **1995**, *51*, 5181. *e*) Dell'Erba, C.; Novi, M.; Petrillo, G.; Spinelli, D.; Tavani, C. *Tetrahedron* **1996**, *52*, 3313. *f*) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. Synthetic Exploitation of the Ring-Opening of 3,4-Dinitrothiophene. In *Topics in Heterocyclic Systems - Synthesis, Reactions and Properties*, Attanasi, O. A.; Spinelli, D.; Eds., Research Signpost: Trivandrum, India, Vol. 1, in press.
3. The method is an adaptation of the procedure reported for the analogous reduction of 1-nitro-1-alkenes: Sera, A.; Yamauchi, H.; Yamada, H.; Itoh, K. *Synlett* **1990**, 477.
4. A sample of 1,4-diphenyl-2,3-butanedione[5] (mp 84.5-85.5 °C) was obtained in 62% yield by exhaustive hydrolysis of the dioxime **7a** with concentrated hydrochloric acid in aqueous formaldehyde. In $CDCl_3$ the isolated compound appeared, by ^1H NMR analysis, as a mixture (*ca.* 4:1) of the diketonic (**dk**) and of the monoenolic (**me**) form; **dk**: δ 4.01 (4H, s), 7.11 (4H, m) and 7.27 (6H, m). **me**: δ 4.16 (2H, s), 6.60 (1H, s), 7.25 (8H, m) and 7.83 (2H, m); under the used conditions the enolic proton of **me** could not be detected.
5. Ruggli, P.; Zeller, P. *Helv. Chim. Acta* **1945**, *28*, 741.
6. Talapatra, S. K.; Chaudhuri, P.; Talapatra, B. *Heterocycles* **1980**, *14*, 1279.
7. Begtrup, M.; Holm, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 503.
8. Paton, R. M. 1,2,5-Oxadiazoles and their Benzo Derivatives, in *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W.; Potts, K. T.; Eds., Pergamon Press: Oxford, 1984, vol. 6, ch. 4.22, p. 393. Ghosh, P.; Ternai, B.; Whitehouse, M. *Med. Chem. Rev.* **1981**, *1*, 159. Stuart, K. L. *Heterocycles* **1975**, *3*, 651.
9. Civelli, M.; Giossi, M.; Caruso, P.; Razzetti, R.; Bergamaschi, M.; Bongrani, S.; Gasco, A. *Br. J. Pharmacol.* **1996**, *118*, 923. Sorba, G.; Ermondi, G.; Fruttero, R.; Galli, U.; Gasco, A. *J. Heterocycl. Chem.* **1996**, *33*, 327. Hwang, K.-J.; Jo, I.; Shin, Y. A.; Yoo, S.; Lee, J. H. *Tetrahedron Lett.* **1995**, *36*, 3337. Fruttero, R.; Boschi, D.; Di Stilo, A.; Gasco, A. *J. Med. Chem.* **1995**, *38*, 4944 and references cited in these papers.
10. Wamhoff, H. 1,2,3-Triazoles and their Benzo Derivatives, in *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W.; Potts, K. T.; Eds., Pergamon Press: Oxford, 1984, vol. 5, ch. 4.11, p. 669. Finley, K. T. Triazoles: 1,2,3, in *The Chemistry of Heterocyclic Compounds*, Weissberger, A.; Taylor, E. C.; Montgomery, J. A.; Eds., Wiley: New York, 1980. Dorlars, A.; Schellhammer, C.-W; Schroeder, J. *Angew. Chem. Internat. Edit.* **1975**, *14*, 665. Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33.
11. Begtrup, M.; Vesdø, P. *Acta Chem. Scand.* **1996**, *50*, 549. Begtrup, M.; Vesdø, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 625. Butler, R. N.; Cunningham, D.; Marren, E. G.; McArdle, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3321 and references cited in these papers.
12. For recent applications see: San Martin, R.; Olivera, R.; Martinez de Marigorta, E.; Dominguez, E. *Tetrahedron* **1995**, *51*, 5361. Tillyer, R. D.; Boudreau, C.; Tschaen, D.; Dolling, U.-H.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 4337.
13. De Sarlo, F.; Guarna, A.; Brandi, A.; Mascagni, P. *Gazz. Chim. Ital.* **1980**, *110*, 341.
14. Methods A (with *N*-iodosuccinimide)[6] and B [with copper(II) sulfate][7] are appropriate modifications of those reported in literature.

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