Synthesis of substituted dibenz[*b*,*f*]oxepines from 2,4,6-trinitrotoluene*

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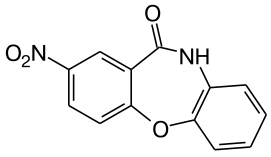
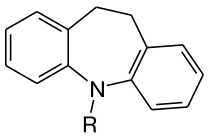
1,3-Dinitro[*b*,*f*]dibenzoxepine undergoes nucleophilic substitution with O- and S-nucleophiles, the nitro group at position 1 (*peri*-nitro group) being selectively replaced. The factors responsible for the selectivity of the reaction are discussed.

Key words: 1,3-dinitrodibenz[*b*,*f*]oxepine, phenolate anions, thiophenolate anions, S_NAr substitution reaction, aromatic nitro compounds.

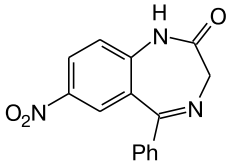
In the course of investigation on the utilization of aromatic polynitro compounds, we turned our attention to the use of these compounds for the synthesis of benzannulated seven-membered heterocycles,[1—4] because some classes of these compounds (in particular, 1,4-benzodiazepines, dibenz[*b*,*f*]azepines, and dibenz[*b*,*f*]oxazepines) are widely used in medicine as agents having an action on the central nervous system.



Sintamil
(antidepressant)



Tricyclic
antidepressants

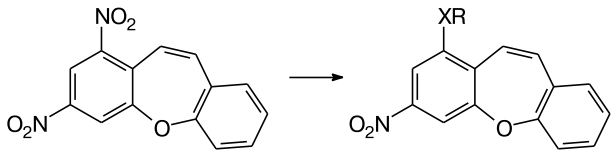


Nitrazepam
(insomnia medication)

The aim of the present study was to synthesize related systems, *viz.*, substituted dibenz[*b*,*f*]oxepines, some of which were also found to have biological activity.[5] The reaction of 2,4,6-trinitrotoluene with salicylaldehyde involves the condensation followed by the intramolecular nucleophilic substitution of the nitro group to form 1,3-dinitrodibenz[*b*,*f*]oxepine.[6] As was shown earlier,[2,7—9] such benzannulated dinitro compounds can further be functionalized by replacing one or both nitro groups with nucleophiles.

We showed that one nitro group in 1,3-dinitrodibenz[*b*,*f*]oxepine (**1**) is replaced with O- and S-nucleophiles (phenolate and thiophenolate anions) (Scheme 1, Table 1).

Scheme 1



1 **2**

Reagents and conditions: RXH, K_2CO_3, DMF, 100 °C.

The reaction is regioselective and results in the substitution of the nitro group at position 1, *i.e.*, of the nitro group nearest to the bridgehead position. The selectivity of substitution was confirmed by the X-ray diffraction study of compound **2a** (Fig. 1).

In the case of S-nucleophiles, the structures of the replacement products were confirmed by the independent synthesis of compound **2m** from 2-[(4-methylphenyl)sulfanyl]-4,6-dinitrotoluene **3** (see Ref. 10) and salicylaldehyde (Scheme 2).

The result of the present study was unexpected. It is known that the nitro group nearest to the bridgehead

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Table 1. Synthesis of substituted dibenz[*b*,*f*]oxepines **2a—m***

Product	RX	*T*/°C	Yield (%)
2a	PhO	100	76
2b	4-MeC_6H_4O	100	75
2c	3-MeC_6H_4O	100	79
2d	4-$MeOC_6H_4O$	100	81
2e	3-$MeOC_6H_4O$	100	64
2f	2-$MeOC_6H_4O$	100	67
2g	4-ClC_6H_4O	100	68
2h	3-ClC_6H_4O	100	76
2i	2,4-$Cl_2C_6H_3O$	100	58
2j	4-BrC_6H_4O	100	69
2k	4-$AcNHC_6H_4O$	100	72
2l	PhS	70	72
2m	4-MeC_6H_4S	70	67

* The reaction time is 3 h.

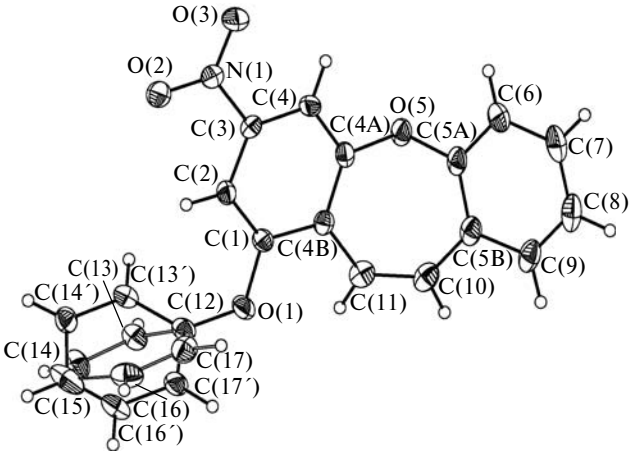
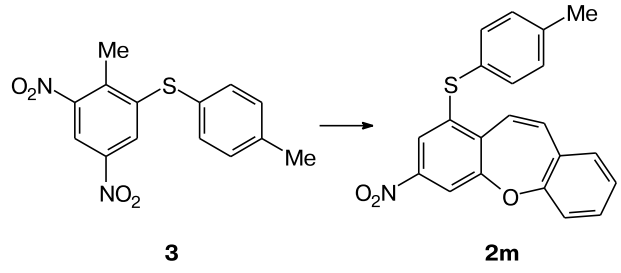
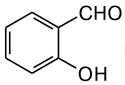


Fig. 1. General view of compound **2a** with displacement ellipsoids drawn at $p = 50\%$. Two positions of the disordered phenyl substituent are shown.

Scheme 2

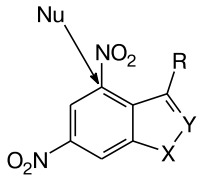


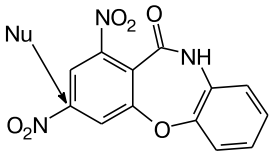
3 **2m**

Reagents and conditions: 

, C_6H_6, piperidine, 80 °C.

position (*peri*-nitro group) is selectively replaced with nucleophiles in dinitro-substituted benzannulated five-membered heterocycles.[11—13] However, the reverse selectivity of substitution is observed in analogous fused seven-membered systems (for example, in dibenzoxazepinone **A**)[2] or, at least, the substitution is nonselective.[14]





A

It was hypothesized[2] that the selective substitution of the nitro group remote from the bridgehead position in dibenzoxazepinone **A** is due to substantial steric hindrance caused by the C=O group to the attack on the *peri* position. From this standpoint, the difference in the regioselectivity between compound **A** and 1,3-dinitrodibenz[*b*,*f*]-oxepine **1** can be attributed to the fact that the C—H group in the latter compound causes much less hindrance to the *peri*-attack than the carbonyl group in compound **A**.[14,15]

Experimental

The ^{1}H NMR spectra were recorded on Bruker AM 300 and Bruker DRX 500 instruments operating at 300.13 and 500.13 MHz, respectively, in DMSO-d_6. The EI mass spectra (70 eV) were obtained on a Kratos MS-30 instrument. 2-[(4-Methylphenyl)-sulfanyl]-4,6-dinitrotoluene **3** was synthesized from 2,4,6-trinitrotoluene according to a known procedure.[10]

The X-ray diffraction data for compound **2a** ($C_{20}H_{13}NO_4$) were measured at −173 °C on an automated three-circle Smart APEX II CCD diffractometer (Mo-Kα, graphite monochromator, ω-scanning technique, $2\theta < 60°$). At −173 °C, the crystals are monoclinic: $a = 4.5725(6)$ Å, $b = 31.849(4)$ Å, $c = 10.5834(14)$ Å, $\beta = 93.539(3)°$, $V = 1538.3(3)$ Å^3, space group $P2_1/c$, $Z = 4$ ($Z' = 1$), M = 331.31, $d_{calc} = 1.431$ g cm^{-3}, $\mu = 1.01$ cm^{-1}, $F(000) = 688$. A total of 20721 reflections were measured ($R_{int} = 0.0807$), of which 4752 independent reflections were used in calculations.

The structure of **2a** was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters. An analysis of difference Fourier maps showed that the phenyl substituent is disordered over two equally occupied sites. The atoms of the disordered phenyl substituent were refined isotropically. The hydrogen atoms were positioned geometrically and refined using a riding model. The final *R* factors were $R = 0.0551$ based on 2737 reflections with $I > 2\sigma(I)$, $wR_2 = 0.1412$, GOOF = 0.980 based on all measured reflections. All calculations were carried out with the use of the SHELXTL PLUS 5 program package.

Nucleophilic substitution in 1,3-dinitro[*b*,*f*]dibenzoxepine (general method). Anhydrous K_2CO_3 (0.83 g, 6 mmol) was added to a solution of 1,3-dinitrodibenz[*b*,*f*]oxepine **1** (1.42 g, 5 mmol) and the corresponding phenol (thiophenol) (5.5 mmol) in anhydrous DMF (10 mL). The reaction mixture was stirred at 100 °C for 3 h, cooled to room temperature, and poured into water (150 mL). Then concentrated HCl was added to pH 2. The precipitate that formed was filtered off, dried, and recrystallized; MeCN was used as the solvent for crystallization (unless otherwise stated).

3-Nitro-1-phenoxydibenz[*b*,*f*]oxepine (2a). M.p. 135—137 °C. Found (%): C, 72.28; H, 4.15; N, 3.97. $C_{20}H_{13}NO_4$. Calculated (%): C, 72.50; H, 3.95; N, 4.23. ^{1}H NMR, δ: 7.03 (d, 1 H, J = 11.6 Hz); 7.10 (m, 3 H); 7.26 (m, 2 H); 7.33 (s, 1 H); 7.36 (d, 1 H, J = 7.8 Hz); 7.40 (d, 1 H, J = 8.0 Hz); 7.46 (m, 3 H); 7.90 (s, 1 H). MS, m/z (I_{rel} (%)): 331 $[M]^+$ (100), 179 (80), 163 (58), 77 (78).

1-(4-Methylphenoxy)-3-nitrodibenz[*b*,*f*]oxepine (2b). M.p. 149—151 °C. Found (%): C, 72.70; H, 4.51; N, 3.89. $C_{21}H_{15}NO_4$. Calculated (%): C, 73.03; H, 4.38; N, 4.06. ^{1}H NMR, δ: 2.35 (s, 3 H); 7.01 (d, 2 H, J = 8.0 Hz); 7.05 (d, 1 H, J = 11.5 Hz); 7.09 (d, 1 H, J = 11.5 Hz); 7.26 (m, 4 H); 7.36 (d, 1 H, J = 7.8 Hz); 7.38 (d, 1 H, J = 8.0 Hz); 7.44 (t, 1 H, J = 7.9 Hz); 7.85 (s, 1 H). MS, m/z (I_{rel} (%)): 345 $[M]^+$ (100), 179 (65), 163 (43).

1-(3-Methylphenoxy)-3-nitrodibenz[*b*,*f*]oxepine (2c). M.p. 152—154 °C. Found (%): C, 72.68; H, 4.62; N, 4.00. $C_{21}H_{15}NO_4$. Calculated (%): C, 73.03; H, 4.38; N, 4.06. ^{1}H NMR, δ: 2.37 (s, 3 H); 6.83 (d, 1 H, J = 7.9 Hz); 6.88 (s, 1 H); 7.00 (m, 2 H); 7.04 (d, 1 H, J = 8.1 Hz); 7.21 (t, 1 H, J = 7.9 Hz); 7.31 (m, 4 H); 7.40 (t, 1 H, J = 8.0 Hz); 7.80 (s, 1 H). MS, m/z (I_{rel} (%)): 345 $[M]^+$ (85), 179 (80), 163 (64), 65 (100).

1-[(4-Methoxy)phenoxy]-3-nitrodibenz[*b*,*f*]oxepine (2d). M.p. 177—179 °C. Found (%): C, 69.93; H, 4.02; N, 3.61. $C_{21}H_{15}NO_5$. Calculated (%): C, 69.80; H, 4.18; N, 3.88. ^{1}H NMR, δ: 3.78 (s, 3 H); 7.03 (d, 2 H, J = 8.0 Hz); 7.11 (m, 4 H); 7.22 (s, 1 H); 7.27 (t, 1 H, J = 7.8 Hz); 7.29 (d, 1 H, J = 7.8 Hz); 7.45 (m, 2 H); 7.87 (s, 1 H). MS, m/z (I_{rel} (%)): 361 $[M]^+$ (100), 179 (60), 163 (33).

1-[(3-Methoxy)phenoxy]-3-nitrodibenz[*b*,*f*]oxepine (2e). M.p. 113—116 °C. Found (%): C, 70.04; H, 3.98; N, 4.10. $C_{21}H_{15}NO_5$. Calculated (%): C, 69.80; H, 4.18; N, 3.88. ^{1}H NMR, δ: 3.76 (s, 3 H); 6.68 (d, 1 H, J = 8.1 Hz); 6.75 (m, 1 H); 6.84 (d, 1 H, J = 8.3 Hz); 7.02 (d, 1 H, J = 11.6 Hz); 7.12 (d, 1 H, J = 11.6 Hz); 7.27 (t, 1 H, J = 8.0 Hz); 7.35 (d, 1 H, J = 8.0 Hz); 7.38 (m, 2 H); 7.45 (m, 2 H); 7.93 (s, 1 H). MS, m/z (I_{rel} (%)): 361 $[M]^+$ (100), 179 (30), 163 (29), 120 (38).

1-[(2-Methoxy)phenoxy]-3-nitrodibenz[*b*,*f*]oxepine (2f). M.p. 153—155 °C. Found (%): C, 69.75; H, 4.29; N, 3.55. $C_{21}H_{15}NO_5$. Calculated (%): C, 69.80; H, 4.18; N, 3.88. ^{1}H NMR, δ: 3.78 (s, 3 H); 7.03 (d, 2 H, J = 8.0 Hz); 7.11 (m, 4 H); 7.22 (s, 1 H); 7.27 (t, 1 H, J = 7.8 Hz); 7.29 (d, 1 H, J = 7.8 Hz); 7.45 (m, 2 H); 7.87 (s, 1 H). MS, m/z (I_{rel} (%)): 361 $[M]^+$ (100), 179 (60), 163 (33).

1-(4-Chlorophenoxy)-3-nitrodibenz[*b*,*f*]oxepine (2g). M.p. 158—160 °C. Found (%): C, 65.90; H, 3.15; N, 4.22; Cl, 10.03. $C_{20}H_{12}ClNO_4$. Calculated (%): C, 65.67; H, 3.31; N, 3.83; Cl, 9.69. ^{1}H NMR, δ: 6.98 (s, 2 H); 7.06 (d, 2 H, J = 8.2 Hz); 7.20 (t, 1 H, J = 7.8 Hz); 7.28 (m, 2 H); 7.40 (m, 4 H); 7.83 (s, 1 H). MS, m/z (I_{rel} (%)): 367 $[M]^+$ (29), 365 $[M]^+$ (100), 179 (57), 163 (35).

1-(3-Chlorophenoxy)-3-nitrodibenz[*b*,*f*]oxepine (2h). M.p. 156—158 °C. Found (%): C, 65.79; H, 3.84; N, 4.11; Cl, 9.52. $C_{20}H_{12}ClNO_4$. Calculated (%): C, 65.67; H, 3.31; N, 3.83; Cl, 9.69. ^{1}H NMR, δ: 6.96 (m, 3 H); 7.08 (s, 1 H); 7.21 (m, 2 H); 7.28 (m, 2 H); 7.40 (m, 2 H); 7.45 (s, 1 H); 7.85 (s, 1 H). MS, m/z (I_{rel} (%)): 367 $[M]^+$ (29), 365 $[M]^+$ (100), 179 (55), 163 (40).

1-(2,4-Dichlorophenoxy)-3-nitrodibenz[*b*,*f*]oxepine (2i). M.p. 187—189 °C. Found (%): C, 59.74; H, 2.99; N, 3.26; Cl, 18.10. $C_{20}H_{11}Cl_2NO_4$. Calculated (%): C, 60.02; H, 2.77; N, 3.50; Cl, 17.72. ^{1}H NMR, δ: 7.03 (s, 2 H); 7.18 (d, 1 H, J = 8.3 Hz); 7.22 (m, 2 H); 7.30 (m, 2 H); 7.40 (m, 2 H); 7.61 (d, 1 H, J = 2.1 Hz); 7.84 (d, 1 H, J = 1.8 Hz). MS, m/z (I_{rel} (%)): 401 $[M]^+$ (57), 399 $[M]^+$ (100), 192 (50), 179 (80), 163 (78).

1-(4-Bromophenoxy)-3-nitrodibenz[*b*,*f*]oxepine (2j). M.p. 160—162 °C. Found (%): C, 58.78; H, 3.12; N, 3.23; Br, 19.15. $C_{20}H_{12}BrNO_4$. Calculated (%): C, 58.56; H, 2.95; N, 3.41; Br, 19.48. ^{1}H NMR, δ: 6.99 (m, 4 H); 7.21 (t, 1 H, J = 7.7 Hz); 7.29 (m, 2 H); 7.40 (m, 2 H); 7.54 (d, 2 H, J = 8.3 Hz); 7.84 (s, 1 H). MS, m/z (I_{rel} (%)): 411 $[M]^+$ (47), 409 $[M]^+$ (52), 255 (48), 192 (49), 179 (100), 163 (87).

1-[(4-Acetylamino)phenoxy]-3-nitrodibenz[*b*,*f*]oxepine (2k). M.p. 242—244 °C. Found (%): C, 67.69; H, 4.15; N, 7.40. $C_{22}H_{16}N_2O_5$. Calculated (%): C, 68.04; H, 4.15; N, 7.21. ^{1}H NMR, δ: 2.05 (s, 3 H); 6.97 (m, 3 H); 7.06 (d, 1 H, J = 11.7 Hz); 7.20 (t, 1 H, J = 7.7 Hz); 7.28 (m, 3 H); 7.38 (t, 1 H, J = 7.9 Hz); 7.68 (d, 1 H, J = 8.0 Hz); 7.74 (s, 1 H). MS, m/z (I_{rel} (%)): 388 $[M]^+$ (100), 346 (67), 255 (20), 179 (15).

3-Nitro-1-(phenylsulfanyl)dibenz[*b*,*f*]oxepine (2l). M.p. 199—200 °C (benzene). Found (%): C, 68.88; H, 3.95; N, 4.16, S, 8.90. $C_{20}H_{13}NO_3S$. Calculated (%): C, 69.15; H, 3.77; N, 4.03; S, 9.23. ^{1}H NMR, δ: 7.03 (d, 1 H, J = 11.4 Hz); 7.10 (d, 1 H, J = 11.4 Hz); 7.20 (t, 1 H, J = 7.7 Hz); 7.28 (m, 2 H); 7.42 (m, 6 H); 7.60 (s, 1 H); 7.88 (s, 1 H). MS, m/z (I_{rel} (%)): 347 $[M]^+$ (100), 346 (41), 271 (37), 163 (30).

1-[(4-Methylphenyl)sulfanyl]-3-nitrodibenz[*b*,*f*]oxepine (2m). M.p. 207—209 °C (benzene). Found (%): C, 70.16; H, 3.90; N, 4.04; S, 8.81. $C_{21}H_{15}NO_3S$. Calculated (%): C, 69.79; H, 4.18; N, 3.88; S, 8.87. ^{1}H NMR, δ: 2.42 (s, 3 H); 7.04 (d, 1 H, J = 11.0 Hz); 7.09 (d, 1 H, J = 11.0 Hz); 7.20 (t, 1 H, J = 7.7 Hz); 7.28 (m, 4 H); 7.35 (d, 2 H, J = 8.0 Hz); 7.38 (t, 1 H, J = 7.9 Hz); 7.59 (s, 1 H); 7.83 (s, 1 H). MS, m/z (I_{rel} (%)): 361 $[M]^+$ (100), 271 (30), 163 (41).

Independent synthesis of compound 2m. A solution of 2-[(4-methylphenyl)sulfanyl]-4,6-dinitrotoluene **3** (1.52 g, 5 mmol), salicylaldehyde (0.61 g, 5 mmol), and piperidine (0.51 g, 6 mmol) in benzene (5 mL) was refluxed for 5 h, cooled, and diluted with MeOH (10 mL). The precipitate was filtered off, washed with ethanol (1 mL), and dried. The yield was 73%. The melting point and the ^{1}H NMR spectrum of the reaction product are identical to those of the above-described compound **2m**.

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