Steric factors in the preparation of nitrostilbenes

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The influence of an adjacent methyl group on the conformation of an aromatic nitro group and the consequent effect on the ease of synthesis of nitrostilbenes, has been examined using X-ray crystallographic studies to reveal the extent of the rotation of the nitro group.

Keywords nitrostilbenes, X-ray crystallography

Stilbenes possess a range of potentially useful properties including anti-fungal,[1] nematocidal,[2] and anti-leukemic activity.[3] Some stilbenes have been investigated as liquid crystalline additives to polymers.[4] Pinosylvin and resveratrol are hydroxystilbene phytoalexins which are produced by a number of plants in response to fungal attack.[5] In connection with the synthesis of novel fungicides modelled on these stilbenes, we have examined the preparation of a number of substituted stilbenes bearing electron-donating substituents on one ring and electron-withdrawing substituents on the other.

Stilbenes have been prepared by the condensation of phenylacetic acid esters and aldehydes,[6] by Wittig reactions between benzylphosphonium ylids and aldehydes,[7] by coupling reactions using zinc or low-valency titanium[8] and by the condensation of nitrotoluenes with aldehydes.[9] The latter method was best suited for our work. The recommended catalyst is piperidine in a refluxing benzene solution[10] although recently a microwave method using pyrrolidine as the catalyst, has been reported.[11]

In our work we replaced the benzene with pyridine and retained the piperidine as a catalyst. These conditions which were successful with 2,4-dinitrotoluene and a series of aldehydes, gave *trans*-stilbenes (see Table 1). The alkene coupling constants, typically 16Hz, were characteristic of *trans*-alkenes. 2,6-Dinitrotoluene reacted far less readily and under these conditions gave only mediocre yields after two hours reflux. In prior work[12] a 2,6-dinitrostilbene had been obtained by the reductive elimination of the 4-nitro group of 2,4,6-trinitrostilbenes.

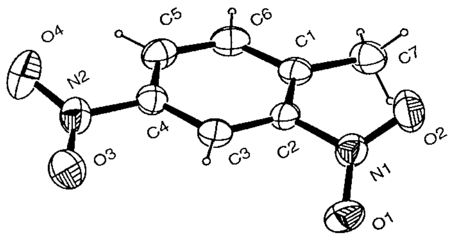

Fig. 1 X-ray crystal structure of 2,4-dinitrotoluene.

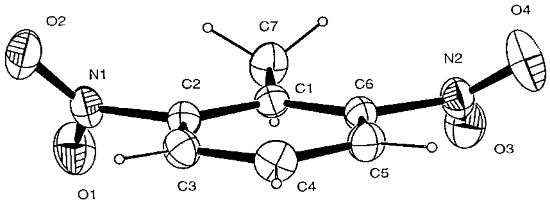

Fig. 2 X-ray crystal structure of 2,6-dinitrotoluene.

Both methyl groups of the dinitroxylenes, 1,3-dimethyl-2, 4-dinitrobenzene[13] and 1,5-dimethyl-2,4-dinitrobenzene[14] are potentially activated by nitro groups. However, 1,3-dimethyl-2,4-dinitrobenzene reacted slowly and only after four hours reflux, did it give a low yield of mono-condensation products. The structure of the compound obtained from *p*-anisaldehyde as 2,4-dinitro-3-methyl-4'-methoxystilbene rather than 2,6-dinitro-3-methyl-4'-methoxystilbene was established by nuclear Overhauser effect (nOe) enhancements, Irradiation of the

Table 1 Synthesis of nitrostilbenes

Substrates	Products	% Yield
2,4-Dinitrotoluene		
Anisaldehyde	2,4-Dinitro-4'-methoxystilbene	72
Vanillin	2,4-Dinitro-4'-hydroxy-3'-methoxystilbene	68
Isovanillin	2,4-Dinitro-3'-hydroxy-4'-methoxystilbene	65
Veratraldehyde	3',4'-Dimethoxy-2,4-dinitrostilbene	73
Piperonal	2,4-Dinitro-3',4'-methylenedioxystilbene	72
3,5-Dimethoxybenzaldehyde	3′,5′-Dimethoxy-2,4-dinitrostilbene	70
Cinnamaldehyde	1-(2,4-Dinitrophenyl)-4-phenylbutadiene	65
2,6-Dinitrotoluene		
Anisaldehyde	2,6-Dinitro-4'-methoxystilbene	30
Vanillin	2,6-Dinitro-4'-hydroxy-3'-methoxystilbene	30
Piperonal	2,6-Dinitro-3',4'-methylenedioxystilbene	35
1,3-Dimethyl-2,4-dinitrobenzene		
Anisaldehyde	2,4-Dinitro-4'-methoxy-3-methylstilbene	20
Veratraldehyde	3',4'-Dimethoxy-2,4-dinitro-3-methylstilbene	25
1,5-Domethyl-2,4-dinitrobenzene		
Anisaldehyde	1,5-Di(4'-methoxyphenylethen)-2,4-dinitrobenzene	65
Vanillin	1,5-Di(4'-hydroxy-3'-methoxyphenylethene)-2,4-dinitrobenzene	65
Piperonal	1,5-Di(3'4'- methylenedioxyphenylethene)-2,4-dinitrobenzene	67
Veratraldehyde	1,5-Di(3'4'-dimethoxyphenylethene)-2,4-dinitrobenzene	56

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* Correspondence.

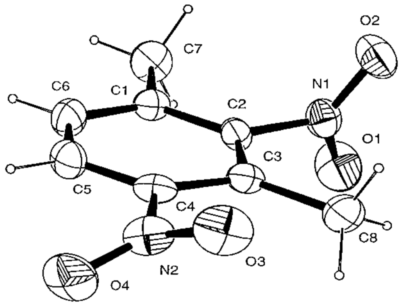

Fig. 3 X-ray crystal structure of 1,3-dimethyl-2,4-dinitrobenzene.

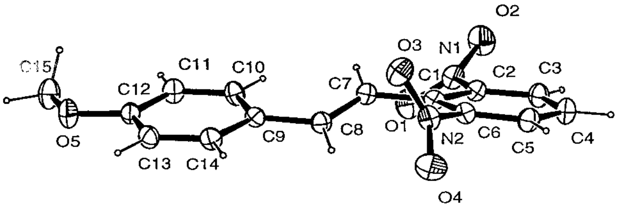

Fig. 4 X-ray crystal structure of 2,6-dinitro-4'-methoxystilbene.

methyl group (δ_H 2.37) produced no enhancements but irradiation of the one-proton aromatic resonance (δ_H 8.07, doublet, *J*=8.8 Hz) produced enhancements of 9.2% of the alkene signal at δ_H 7.59 (doublet, *J*=16Hz) and 1.0% at δ_H 6.68 (doublet, *J*=16 Hz). 1,5-Dimethyl-2,4-dinitrobenzene was more reactive and readily gave bis-condensation products such as 1,5-di(4'-methoxyphenylethene)-2,4-dinitrobenzene (see Table 1).

Comparison of the X-ray crystal structures of 2,4-dinitrotoluene and 1,3-dimethyl-2,4-dinitrobenzene (see Figs 1–3) shows that the nitro groups which are adjacent to the methyl groups are rotated out of the plane of the aromatic ring. The effect of one methyl group is to twist the plane of the nitro group by 45° or 29° in 2,4-dinitrotoluene (there were two independent molecules in the unit cell), 51° and 37° in 2,6-dinitrotoluene and 27° for the 4-nitro group in 1,3-dimethyl-2,4-dinitrobenzene. The two methyl groups of 1,3-dimethyl-2, 4-dinitrobenzene twist the plane of the 2-nitro group to 75° relative to the plane of the aromatic ring. Rotation of the plane of the nitro group away from co-planarity with the aromatic ring, diminishes its electron-withdrawing effect on the methyl group and the resonance stabilisation it provides for the resultant carbanion. Together with steric crowding of the methyl group, this may account for the lack of reactivity of 2.6-dinitrotoluene and of the 3-methyl group of 1,3-dimethyl-2,4-dinitrobenzene.

Comparison of the ^{1}H NMR spectra of the 2,4-dinitrostilbenes with that of the 2,6-dinitrostilbenes showed that one alkene resonance was significantly shielded in the 2,6-dinitro compounds. The resonance concerned was identified as that of H-8 by means of spin decoupling experiments based on the long-range coupling of the alkene resonances to the aromatic proton resonances. In 2,4-dinitro-4'-methoxystilbene, H-5 was a doublet of doublets of doublets (δ_H 8.41, *J*=8.8, 2.2 and 0.6 Hz) showing a *meta* coupling to H-3 (δH 8.67, *J*=2.2 Hz). Spin decoupling experiments established that the long-range coupling (0.6 Hz) was to the alkene resonance at δ_H 7.31 which was therefore assigned to H-7. Hence H-8 was the alkene signal at δ_H 7.53 (*J*=16.1 Hz). In 2,6-dinitro-4'-methoxystilbene H-4 was a triplet of doublets (δ_H 7.77, *J*=8.2 and 0.6 Hz). Spin decoupling experiments established that the long-range coupling (0.6 Hz) was to the alkene signal at δ_H 7.22 which was assigned to H-7. Hence H-8 was the signal at δ_H 6.58 (*J*=16.6 Hz). There is therefore a significant shielding of this proton ($\Delta\delta_H$ 0.95) between the 2,4- and 2,6-dinitro-4'-methoxystilbenes. The X-ray crystal structure of 2,6-dinitro-4'-methoxystilbene (see Fig.4) shows that whilst the stilbene ring system remains planar, the 2- and 6-nitro groups are rotated out of the plane of the aromatic ring. This has the effect of bringing the H-8 alkene proton within the shielding cone of the nitro group.[15] In conclusion, the rotation of the aromatic nitro groups can affect both the ease of formation of the nitrostilbenes and their properties.

Experimental

General experimental details: Extracts were dried over anhydrous sodium sulfate. IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined in d$_6$-dimethylsulfoxide at 300 MHz. Nuclear Overhauser effect enhancements were determined at 500MHz. Mass spectra were determined on a Fisons Autospec or a Bruker Daltonics Apex III electrospray mass spectrometer.

General procedure for preparing nitrostilbenes: (a) 2, 4-Dinitrotoluene (1.8 g) and aldehyde (1.5 g) were dissolved in pyridine (18 cm^3) and piperidine (2 cm^3) was added. The reaction was heated under reflux for a period of 30 min. The solution was cooled and poured into dil. hydrochloric acid. The product was filtered and recrystallised from glacial acetic acid. Some products required purification with charcoal. The results are given in Table 1. The reactions using 2, 6-dinitroroluene were heated under reflux for 2 hours whilst those using 1,3-dimethyl-2,4-dinitrobenzene were heated for 4 hours. The reactions using 1,5-dimethyl-2,4-dinitrobenzene were heated for 30 min.

The following compounds were obtained:

2,4-Dinitro-4'-methoxystilbene, m.p 163–164°C (lit.,[16] 163°C), ν_{max}/cm^{-1} 1590, 1531, 1512; δ_H (500 MHz) 3.78 (3H, s, OMe), 6.97 (2H, d, *J*=8.8 Hz), 7.31 (1H, dd, *J*=16.1 and 0.6 Hz), 7.53 (1H, d, *J*=16.1 Hz), 7.59 (2H, d, *J*=8.8 Hz), 8.18 (1H, d, *J*=8.8 Hz), 8.41 (1H, ddd, *J*=8.8, 2.2 and 0.6 Hz), 8.67 (1H, d, *J*=2.2 Hz).

2,4-Dinitro-4'-hydroxy-3'-methoxystilbene, m.p 193–194°C (lit.,[17] 193°C), ν_{max}/cm^{-1} 3447, 1582, 1509; δ_H 3.85 (3H, s, OMe), 6.85 (1H, d, *J*=8.1 Hz), 7.13 (1H, d, *J*=8.1 Hz), 7.22 (1H, d, *J*=16.1 Hz), 7.26 (1Hs), 7.55 (1H, d, *J*=16.1 Hz), 8.22 (1H, d, *J*=8.8 Hz), 8.47 (1H, dd, *J*=8.8 and 2.0 Hz), 8.71 (1H, d, *J*=2.0 Hz).

2,4-Dinitro-3'-hydroxy-4'-methoxystilbene, m.p 180–182°C (lit.,[16] 183°C), ν_{max}/cm^{-1} 3479, 1584, 1516; δ_H 3.80 (3H, s, OMe), 6.98 (1H, d, *J*=8.2 Hz), 7.10 (1H, d, *J*=8.2 Hz), 7.13, (1H, s), 7.28 and 7.55 (each 1H, d, *J*=16.1 Hz), 8.23 (1H, d, *J*=8.6 Hz), 8.45 (1H, dd, *J*=8.8 and 2.0 Hz), 8.73 (1H, dd, *J*=2.0 Hz).

3',4'-Dimethoxy-2,4-dinitrostilbene, m.p 144–146°C (lit.,[17] 143°C), ν_{max}/cm^{-1} 1584, 1516; δ_H 3.75 and 3.80 (each 3H, s, OMe), 6.98 (1H, d, *J*=8.2 Hz), 7.18 (1H, d, *J*=8.2 Hz), 7.22, (1H, s), 7.30 and 7.55 (each 1H, d, *J*=16.2 Hz), 8.20 (1H, d, *J*=8.6 Hz), 8.44 (1H, dd, *J*=8.8 and 2.0 Hz), 8.71 (1H, dd, *J*=2.0 Hz).

3',5'-Dimethoxy-2,4-dinitrostilbene, m.p 240–206°C (Found: M$^+$ 330.0852, $C_{16}H_{14}N_2O_6$ requires 330.0852), ν_{max}/cm^{-1} 1596, 1520; δ_H 3.80 (6 ,OMe), 6.55 (1H, s), 6.90 (2H, s), 7.05, (2H, s), 8.25 (1H, d, *J*=8.6 Hz), 8.50 (1H, dd, *J*=8.8 and 2.0 Hz), 8.71 (1H, dd, *J*=2.0 Hz)

2,4-Dinitro-3',4'-methylenedioxystilbene, m.p 176–178°C (lit.,[16] 179-180°C), ν_{max}/cm^{-1} 1607, 1594, 1517; δ_H 6.08 (2H, s, OCH_2O), 6.99 (1H, d, *J*=8.1 Hz), 7.28 (1H, d, *J*=8.1 Hz,), 7.33, (1H, s), 7.35 and 7.55 (each 1H, d, *J*=16.1 Hz), 8.21 (1H, d, *J*=8.6 Hz), 8.47 (1H, dd, *J*=8.8 and 2.0 Hz), 8.71 (1H, d, *J*=2.0 Hz).

1-(2,4-Dinitrophenyl)-4-phenylbutadiene, m.p 192–194°C (Found: M$^+$ 296.0797, $C_{16}H_{12}N_2O_4$ requires 296.0797), ν_{max}/cm^{-1} 1587, 1525, 1510; δ_H 6.95–7.4 (7H, overlapping multiplets), 6.97 (2H, t, *J*=16.8 Hz), 8.20 (1H, d, *J*=8.6 Hz), 8.45, (1H, dd, *J*=8.6 and 2.0 Hz), 8.71 (1H, d, *J*=2.0 Hz).

2,6-Dinitro-4'-methoxystilbene, m.p 166–168°C (Found: M$^+$ 300.0746, $C_{15}H_{12}N_2O_5$ requires 300.0746), ν_{max}/cm^{-1} 1634, 1599, 1524; δ_H (500 MHz)$_1$ 3.77 (3H, s, OMe), 6.58 (1H, d, *J*=16.6 Hz), 6.94 (2H, d, *J*=8.8 Hz,), 7.22, (1H, dd, *J*=16.6 and 0.6 Hz), 7.47 (2H, dd, *J*=8.2 and 0.3 Hz), 7.77 (1H, td, *J*=8.2 and 0.6 Hz), 8.28 (2H, d, *J*=8.2 Hz).

2,6-Dinitro-4'-hydroxy-3'-methoxystilbene, m.p 140–142°C (Found: M$^+$ 316.0694, $C_{15}H_{12}N_2O_6$ requires 316.0694), ν_{max}/cm^{-1} 3496, 1628, 1596, 1535; δ_H 3.80 (3 ,OMe), 6.55 (1H, d, *J*=16.5 Hz), 6.82 (1H, d, *J*=8.2 Hz,), 6.98, (1H, d, *J*=8.2 Hz), 7.14 (1H, s), 7.20 (1H, d, *J*=16.5 Hz), 7.78 (1H, t, *J*=8.3 Hz), 8.29 (2H, d *J*=8.3 Hz).

2,6-Dinitro-3',4'-methylenedioxystilbene, m.p 138–140°C (Found: M$^+$ 314.0539, $C_{15}H_{12}N_2O_5$ requires 314.0539), ν_{max}/cm^{-1} 1640, 1604, 1568, 1523; δ_H 6.05 (2H, s, OCH_2O), 6.58 (1H, d, *J*=16.6 Hz), 6.90

(1H, d, J=8.2 Hz,), 6.95, (1H, d, J=8.2 Hz), 7.25 (1H, s), 7.28 (1H, d, J=16.6 Hz), 7.79 (1H, t, J=8.2 Hz), 8.30 (2H, d J=8.2 Hz).

2,4-Dinitro-4'-methoxy-3-methylstilbene, m.p 142–144°C (Found: M$^+$ 314.0903, $C_{16}H_{14}N_2O_5$ requires 314.0903), ν_{max}/cm^{-1} 1605, 1579, 1512; δ_H 2.37 (3H, s, Ar–Me), 3.78 (3H, s, OMe), 6.68 (1H, d, J=16.1 Hz,), 6.97 (2H, d, J=8.2 Hz), 7.57 (1H, d, J=8.2 Hz), 7.59 (1H, d, J=16.1), 8.07 (1H, t, J=8.8 Hz), 8.19 (1H, d J=8.8 Hz).

3',4'-Dimethoxy-2,4-dinitro-3-methylstilbene, m.p 152–154°C (Found: M$^+$ 344.1010, $C_{17}H_{16}N_2O_6$ requires 344.1008), ν_{max}/cm^{-1} 1629, 1593, 1514; δ_H 2.35 (3H, s, Ar–Me), 3.80 and 3.85 (each 3H, s, OMe), 6.57 (1H, d, J=16.1 Hz), 6.90 (1H, d, J=8.1 Hz), 7.00 (1H, s), 7.20 (1H, d, J=8.1 Hz), 7.57 (1H, d, J=16.1 Hz), 8.10 (1H, d J=8.4 Hz), 8.21 (1H, d J=8.4 Hz).

1,5-Di(4'-methoxyphenylethene)-2,4-dinitrobenzene, m.p 190–192°C (Found: M$^+$ 432.1324, $C_{24}H_{20}N_2O_6$ requires 432.1321), ν_{max}/cm^{-1} 1623, 1585, 1512; δ_H 3.80 (6H, s, OMe), 6.99 (4H, d, J=8.7 Hz), 7.42, (2H, d, J=16.1 Hz), 7.63 (4H, d, J=8.7 Hz), 7.65 (2H, d, J=16.1 Hz), 8.36 (1H, s), 8.61 (1H, s).

1,5-Di(4'-hydroxy-3'-methoxyphenylethene)-2,4-dinitrobenzene, m.p 258–260°C (Found: M$^+$ 464.1219, $C_{24}H_{20}N_2O_8$ requires 464.1219), ν_{max}/cm^{-1} 3533, 1621, 1572, 1508; δ_H 3.80 (6H, s, OMe), 6.80 (2H, d, J=8.3 Hz), 7.03, (2H, d, J=8.3 Hz), 7.23 (2H, s), 7.37 (2H, d, J=16.1 Hz), 7.55 (2H, d, J=16.1 Hz), 8.25 (1H, s), 8.56 (1H, s)

1,5-Di(3',4'-methylenedioxyphenylethene)-2,4-dinitrobenzene, m.p 214–216°C (lit.,[18] 215°C), ν_{max}/cm^{-1} 1622, 1587, 1570, 1504; δ_H 6.15 (4H, s, OCH_2O), 6.98 (2H, d, J=8.4 Hz), 7.16, (2H, d, J=8.4 Hz), 7.30 (2H, s), 7.41 (2H, d, J=16.1 Hz), 7.59 (2H, d, J=16.1 Hz), 8.30 (1H, s), 8.61 (1H, s).

1,5-Di(3',4'-dimethoxyphenylethene)-2,4-dinitrobenzene, m.p 226–228°C (Found: M$^+$ 492.1532, $C_{26}H_{24}N_2O_8$ requires 492.1532), ν_{max}/cm^{-1} 1620, 1580, 1504; δ_H 3.78 and 3.80 (each 6H, s, OMe), 6.99 (2H, d, J=8.3 Hz), 7.20, (2H, d, J=8.3 Hz), 7.23 (2H, s), 7.41 (2H, d, J=16.1 Hz), 7.58 (2H, d, J=16.1 Hz), 8.30 (1H, s), 8.58 (1H, s).

X-ray crystallographic data and structure determinations

(a) *2,4-dinitrotoluene*, $C_7H_6N_2O_4$, M_r 182.14, monoclinic, space group $P2_1/n$ (No.14), a = 8.0057(7), b = 15.1273(18), c = 12.8853(13) Å, $\alpha = \gamma = 90°$, β = 95.877(6)°, V = 1552.3(3) Å^3, Z = 4, D_{calc}= 1.56 g cm^{-3}, μ = 0.13 mm^{-1}, F(000) = 752. Data were collected using a crystal of size 0.30 × 0.20 × 0.20 mm^3 on a KappaCCD diffractometer. A total of 8345 reflections were collected for $3.72 < \theta < 25.01°$ and $-9 \le h \le 9$, $-17 \le k \le 17$, $-15 \le l \le 13$. There were 2698 independent reflections and 1922 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [I>2σ (I)] R_1 = 0.044, wR_2 = 0.102 and (all data) R_1 = 0.070 and wR_2 = 0.116. The goodness-of-fit on F^2 was 1.039 and the largest difference peak and hole was 0.21 and –0.20 e Å^{-3}. There were two independent molecules in the unit cell.

(b) *2,6-dinitrotoluene*, $C_7H_6N_2O_4$, M_r 182.14, orthorhombic, space group $P2_12_12_1$ (No.19), a = 7.2244(1), b = 7.7856(2), c = 13.6711(3) Å, $\alpha = \beta = \gamma = 90°$, V = 768.95(3) Å^3, Z = 4, D_{calc}= 1.57 g cm^{-3}, μ = 0.13 mm^{-1}, F(000) = 376. Data were collected using a crystal of size 0.2 × 0.2 × 0.2 mm^3 on a KappaCCD diffractometer. A total of 10299 reflections were collected for $3.85 < \theta < 27.49°$ and $-9 \le h \le 9$, $-10 \le k \le 10$, $-17 \le l \le 17$. There were 1749 independent reflections and 1654 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [I>2σ (I)] R_1 = 0.030, wR_2 = 0.083 and (all data) R_1 = 0.033 and wR_2 = 0.086. The goodness-of-fit on F^2 was 1.032 and the largest difference peak and hole was 0.23 and –0.14 e Å^{-3}.

(c) *1,3-dimethyl-2,4-dinitrobenzene*, $C_8H_8N_2O_4$, M_r 196.16, triclinic, space group $P\bar{1}$ (No.2), a = 7.5579(5), b = 8.2416(5), c = 8.6652(6) Å, α = 62.898(4)°, β = 70.5565(3)°, γ = 66.147(3)° , V = 432.07(5) Å^3, Z = 2, D_{calc}= 1.51 g cm^{-3}, μ = 0.12 mm^{-1}, F(000) = 204. Data were collected using a crystal of size 0.10 × 0.10 × 0.02 mm^3 on a KappaCCD diffractometer. A total of 4449 reflections were collected for $4.38 < \theta < 25.00°$ and $-8 \le h \le 8$, $-9 \le k \le 9$, $-10 \le l \le 10$. There were 1498 independent reflections and 929 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [I>2σ (I)] R_1 = 0.059, wR_2 = 0.112 and (all data) R_1 = 0.119 and wR_2 = 0.137. The goodness-of-fit on F^2 was1.020 and the largest difference peak and hole was 0.22 and –0.24 e Å^{-3}.

(d) *2,6-dinitro-4'methoxystilbene*, $C_{15}H_{12}N_2O_5$, M_r 300.27, monoclinic, space group $P2_1/c$ (No.14), a = 8.2041(2), b = 15.4170(3), c = 10.9410(3) Å, $\alpha = \gamma = 90°$, β = 105.179(1)°, V = 1335.57(6) Å^3, Z = 4, D_{calc}= 1.49 g cm^{-3}, μ = 0.11 mm^{-1}, F(000) = 624. Data were collected using a crystal of size 0.20 × 0.15 × 0.15 mm^3 on a KappaCCD diffractometer. A total of 15925 reflections were collected for $3.83 < \theta < 27.49°$ and $-10 \le h \le 10$, $-20 \le k \le 19$, $-14 \le l \le 12$. There were 3048 independent reflections and 2339 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [I>2σ (I)] R_1 = 0.042, wR_2 = 0.102 and (all data) R_1 = 0.062 and wR_2 = 0.119. The goodness-of-fit on F^2 was1.044 and the largest difference peak and hole was 0.28 and –0.27 e Å^{-3}.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCD 225823 – 6).

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