One-Pot Synthesis of 3,4-Dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazin-2-one Derivatives from *N*-(2′-Pyridinyl)benzoylacetamide and Nitrosobenzenes

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Abstract: A convenient method leading to fused pyrido[1,2-*a*][1,3,5]triazine-2-ones is described. It consists in a one-pot, two-step reaction of *N*-(2′-pyridinyl)benzoylacetamide with nitrosobenzenes. On the other hand, *N*-(2′-pyridinyl)acetoacetamide provides a C-2 condensation/addition product with nitrosobenzene. *N*-(2′-Pyridinyl)benzoylthioacetamide and *N*-(2′-pyridinyl)acetothioacetamide with nitrosobenzene undergo oxidative heterocyclisation leading to [1,2,4]thiadiazolo[2,3-*a*]pyridine derivatives.

Key words: amides, heterocycles, pyridotriazines, thiadiazolopyridines, cycloadditions

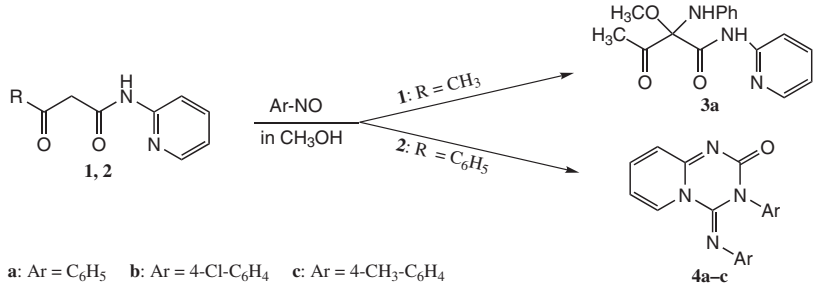
The interest in the pyrido[1,2-*a*][1,3,5]triazine system arises from its wide biological activity,[1,2] which comes from its antagonistic effect upon 5-HT_2 and 5-HT_{2a} serotonin receptors. Such influence can result in: mediating coronary blood flow,[1a] decreasing mean arterial blood pressure,[1b] and the anti-thrombotic effect[1c] in mammals. Other disorders, for whose prophylactic or therapeutic treatment pyrido[1,2-*a*][1,3,5]triazine derivatives can be used, are those involving airway constriction in human or animals: asthma, emphysema, chronic bronchitis, chronic obstructive pulmonary disease,[2] and various psychotic conditions including schizophrenia, depression, anorectic or bulimic eating disorders, and anxiety in humans.[2c]

Since 1952, when a possible approach to this system was mentioned for the first time,[3a] several general methods of synthesis of pyrido[1,2-*a*][1,3,5]triazines have been invented, mostly leading to their oxo derivatives.

Cyclodimerisation of iso(thio)cyanates leads to pyrido[1,2-*a*][1,3,5]triazine-2,4-di(thi)ones.[3b–d] The other methods include: reaction of isocyanates[4a] or active esters of imidodicarbonic[4b] or carbonic[4c] acid with 2-aminopyridine or other amidines and cyclisation of (thio)urea derivatives[3a] or their reaction with isothiocyanate.[4d] Pyrido[1,2-*a*][1,3,5]triazine-4-ones can be obtained from urea derivatives,[5a,b] e.g. by their cyclisation,[5a] or reaction of aryl isocyanates and unsymmetrical carbodiimides containing 2′-pyridine ring.[5c,d] There are only a few examples of the syntheses of pyrido[1,2-*a*][1,3,5]triazine-2-(thi)ones known.[3d,6]

It has recently been shown[7–10] that 2-methoxy-*N*-phenyl-2-phenylaminoacetothioacetamide, which was obtained as the product of the reaction of *N*-phenylacetothioacetamide and nitrosobenzene in methanol, is a compound of particular interest. This compound has got capacity to react as bielectrophilic system on C-2 in various ways, depending on reagents and reaction conditions, and usually leading to heterocyclic systems by new rearrangements.[7,8] These results encouraged us to undertake a study on the reactivity of *N*-(2′-pyridinyl)acetoacetamide (**1**) and *N*-(2′-pyridinyl)benzoylacetamide (**2**) with nitrosobenzenes. Products of such type of reaction had proven useful as good building blocks for constructing various heterocyclic systems.[7,8]

N-(2′-Pyridinyl)acetoacetamide (**1**) furnished the expected product **3a**, in contrast to the reaction of *N*-(2′-pyridinyl)benzoylacetamide (**2**) with nitrosobenzenes. This reaction unexpectedly afforded pyrido[1,2-*a*] [1,3,5]triazin-2-ones **4a–c** (Scheme 1).



Scheme 1

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The structure of compounds **4a–c** could not be completely elucidated by IR, ^{1}H NMR, ^{13}C NMR spectra and MS analyses, therefore it was established by X-ray analysis.[11] A perspective view of the molecule of **4a** with the crystallographic numbering scheme of non-hydrogen atoms is shown in Figure 1.

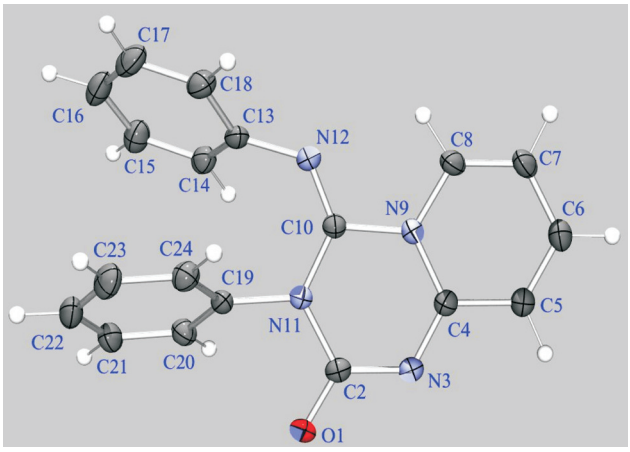


Figure 1 X-ray crystal structure of **4a**

The packing in the crystal structure is dominated by van der Waals interactions with only intramolecular close contacts involving the C8, H108 and N12, and C20, H120 and O1 atoms (Figure 1). These interactions are fairy strong, with D–-A distances equal to 264.9(3)Å and 294.0(3)Å, respectively, and rather angular [D-H.A angles equal 104(2)° and 84(2)°]. Rather than affect the packing, these intramolecular interactions tend to stabilise the molecule's conformation. In fact, the molecular geometry is rather characteristic, because, in good approximation, all atoms lie in three planes: two planes passing through the phenyl moieties and the third one defined by the remaining atoms. Least-squares planes involving the phenyl rings are inclined to each other at an angle of 27.06(8)°, whereas they form angles of about 66° with the plane defined by the heterorings.

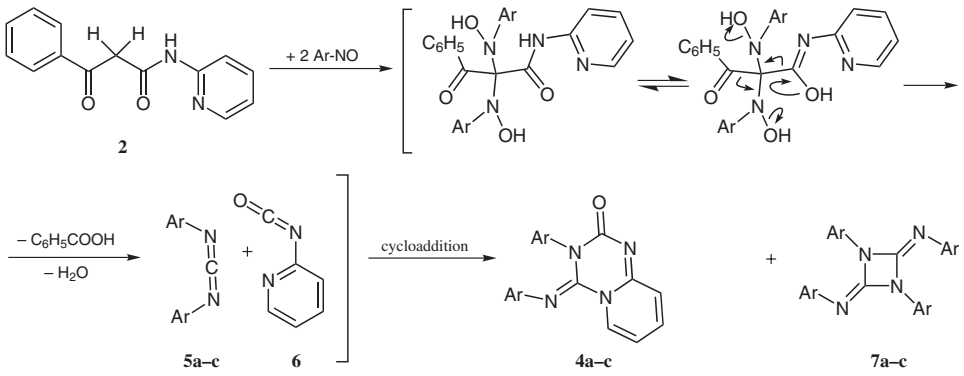
It is noteworthy that using 2 equivalents of the corresponding nitrosobenzene in the reaction with **2** significantly increases the yields of products **4a–c**. This fact suggests a simultaneous attack of two molecules of nitrosobenzene on C2 of **2** followed by splitting of C1–C2 and C2–C3 bonds. This results in forming corresponding carbodiimides **5a–c** and 2′-pyridinylisocyanate **6** (Scheme 2).

Highly reactive intermediate symmetrical carbodiimides **5a–c** spontaneously react with 2′-pyridinylisocyanate (**6**), formed in situ, via [4π + 2π] heterocycloaddition between the N=C–N=C moiety of **6** as 4π component and the C=N moiety of **5a–c** as 2π component to yield pyrido[1,2-*a*][1,3,5]triazin-2-one derivatives **4a–c** as major products. At the same time dimerisation of carbodiimide occurs, leading to four-membered ring of 1,3-diazetine. The corresponding 1,3-diaryl-2,4-diarylimino-1,3-diazetines **7a–c** were isolated by chromatography of reaction mixtures remaining after separating the main products **4a–c** which did not need purification. Another fact that confirms the proposed [4π + 2π] cycloaddition mechanism is the 4*Z* configuration of compounds **4a–c**.

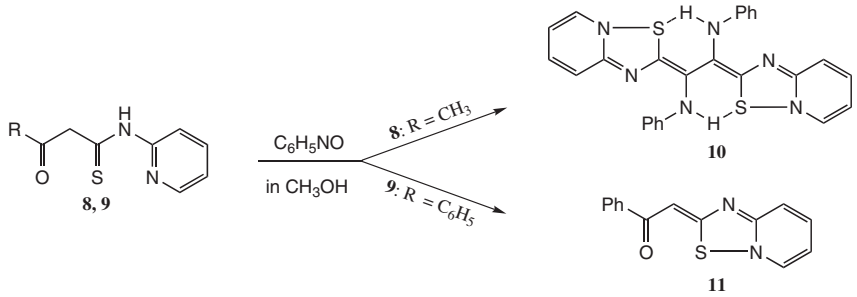
Previously reported methods[5c,d] using [4π + 2π] heterocycloaddition lead mostly to pyrido[1,2-*a*][1,3,5]triazin-4-ones, because the pyridine ring was a part of carbodiimide and not isocyanate.

Under the same conditions *N*-(2′-pyridinyl)acetothioacetamide (**8**) and *N*-(2′-pyridinyl)benzoylthioacetamide (**9**) underwent oxidative cyclisation by the treatment with nitrosobenzene. Oxidative ring closure of **8** takes place between the nitrogen atom of the pyridine ring and the sulfur atom of the thioamide moiety forming a 1,2,4-thiadiazolo[2,3-*a*]pyridine derivative **10** with elimination of the acetyl fragment. In this case, however, using 2 equivalents of nitrosobenzene did not increase the yield. The structure of compound **10** was established on the basis of IR, ^{13}C NMR, ^{1}H NMR, and MS analyses and microanalyses. On the other hand *N*-(2′-pyridinyl)benzoylthioacetamide (**9**) gave the known 1-phenyl-2-(2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyridin-2-yliden)ethanone (**11**)[12a] (Scheme 3). Such oxidation is a common way of obtaining [1,2,4]thiadiazolo[2,3-*a*]pyridine derivatives,[13a,b,c] which constitute a new family of potassium channel openers,[13b] and exhibit excellent endothelin receptor antagonistic activity.[13d] They are also the subject of theoretical research.[13c,e]

In conclusion, we have demonstrated a convenient one-pot preparation of (4*Z*)-3-phenyl-4-(phenylimino)-3,4-di-



Scheme 2



Scheme 3

hydro-2*H*-pyrido[1,2-*a*][1,3,5]triazin-2-ones **4a–c** starting from simple, cheap and easily available *N*-(2′-pyridinyl)benzoylacetamides **2** and variously substituted nitrosobenzenes which work as oxidizing reagents. It is an experimentally straightforward and particularly suitable way for obtaining pure and easily isolable new examples of the pyrido[1,2-*a*][1,3,5]triazin-2-one system. It should be stressed that, in contrast to many known ways leading to 4-oxo and 2,4-dioxo derivatives of pyrido[1,2-*a*][1,3,5]triazine, only a few examples for syntheses of pyrido[1,2-*a*][1,3,5]triazin-2-one derivatives have been reported.[6]

Mps were determined on an electrothermal IA9000 digital mp apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS 48 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX 500 NMR spectrometer at r.t. Chemical shifts are given in ppm. Yields are given for pure products. 4-Chloronitrosobenzene and 4-methylnitrosobenzene were prepared according to the known procedure.[14]

***N*-(2′-Pyridinyl)acetoacetamide (1); Typical Procedure**

A solution of ethyl acetylacetate (17.3 mL, 0.1 mol) in xylene (70 mL) was heated to boil. To the boiling mixture was added 2-aminopyridine (9.4 g, 0.1 mol) in portions during 1 h, and the liberated EtOH was removed by distillation. Traces of EtOH were removed by codistilling with xylene (20 mL). Cooling the mixture at 0 °C afforded the product, which was collected by filtration under suction; yield: 14.24 g (80%); colourless needles; mp 113–114 °C (Lit.[12e] mp 111–112 °C).

***N*-(2′-Pyridinyl)benzoylacetamide (2)**

Compound **2** was prepared in an analogous way as **1**, starting from ethyl benzoyl acetate;

yield: 73%; colourless needles; mp 114–115 °C (Lit.[12e] mp 113–114 °C).

2-Methoxy-2-phenylamino-*N*-(2-pyridinyl)acetoacetamide (3)

To a stirred solution of **1** (1.78 g, 0.01 mol) in MeOH (20 mL), nitrosobenzene (1.07 g, 0.01 mol) and solid NaOH (0.02 g) (as a catalyst) were added and the mixture was stirred overnight. The product was suction filtered and dried; yield: 1.80 g (60%); white powder; mp 152–153 °C.

IR (KBr): 3363, 3108, 1683 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 11.75 (s, 1 H, CONH), 8.20–7.01 (m, 9 H, CH_{arom}), 4.74 (s, 1 H, NH), 3.46 (s, 3 H, OCH_3), 2.44 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 204.2 ($COCH_3$), 168.2 (CONH), 148.1, 138.4, 129.2, 128.9, 124.8, 123.5, 121.3, 120.7, 114.6 (9 C_{arom}), 92.8 (C-2), 50.7 (OCH_3), 22.6 (CH_3).

MS (EI): *m*/*z* (%) = 225 (12, M$^+$ – Ph), 121 (97, 2-PyNHCO), 93 (84, 2-PyNH), 77 (100, Ph).

Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.55; H, 5.50; N, 13.77.

(4*Z*)-3-Aryl-4-(arylimino)-3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazin-2-ones 4; General Procedure

Compound **2** (0.48 g, 2 mmol) was dissolved in MeOH (20 mL) at 40 °C and one drop of 25% aq solution of NaOH (as a catalyst) was added. To the stirred solution, the corresponding nitrosobenzene was added (4 mmol) in several portions during 5 min. The nitrosobenzene dissolved readily in the solution, which changed its color from green to orange-brown. After 2h, the product was collected by filtration under suction.

(4*Z*)-3-Phenyl-4-(phenylimino)-3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazin-2-one (4a)

Yield: 0.33 g (52%); orange plates; mp 231–232 °C.

IR (KBr): 1703, 1648, 1553 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.88 (ddd, 1 H, *J* = 7.3, 1.5, 0.8 Hz), 7.85 (ddd, 1 H, *J* = 9.0, 6.8, 1.9 Hz), 7.09–7.06 (m, 3 H), 7.01–6.96 (m, 3 H), 6.93 (ddd, 1 H, *J* = 7.0, 6.8, 1.5 Hz), 6.82 (t, 2 H, *J* = 7.8 Hz), 6.60 (tt, 1 H, *J* = 7.3, 1.1 Hz), 6.40 (dd, 2 H, *J* = 8.5, 1.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 155.3, 143.9, 141.4, 136.1, 135.3, 130.1, 129.7, 127.7, 127.5, 127.2, 122.9, 121.1, 120.5, 112.5.

MS (EI): *m*/*z* (%) = 314 (2, M$^+$), 222 (35, M$^+$ – PhN), 194 [100, retro Diels–Alder reaction fragment (RDA)], 120 (4, RDA).

Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.48; H, 4.46; N, 17.74.

(4*Z*)-3-(4-Chlorophenyl)-4-[(chlorophenyl)imino]-3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazin-2-one (4b)

Yield: 0.31 g (40%); yellow-orange plates; mp 230–232 °C.

IR (KBr): 1721, 1663, 1550 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.87 (d, 1 H, *J* = 7.0 Hz), 7.86 (ddd, 1 H, *J* = 9.0, 7.0, 1.5 Hz), 7.14–7.08 (m, 5 H), 6.94 (td, 1 H, *J* = 7.0, 1.5 Hz), 6.90 (d, 2 H, *J* = 8.5 Hz), 6.44 (d, 2 H, *J* = 8.5 Hz).

^{13}C NMR (DMSO-d_6): δ = 154.6, 152.4, 143.7, 141.6, 135.9, 135.0, 132.2, 131.7, 130.1, 127.9, 127.4, 125.3, 122.9, 122.4, 112.7.

MS (EI): *m*/*z* (%) = 382 (81, M$^+$), 262 (14, RDA), 120 (11, RDA).

Anal. Calcd for $C_{19}H_{12}Cl_2N_4O$: C, 59.55; H, 3.16; N, 14.62. Found: C, 59.39; H, 2.94; N, 14.50.

(4*Z*)-3-(4-Methylphenyl)-4-[(methylphenyl)imino]-3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazin-2-one (4c)

Yield: 0.33 g (48%); light orange plates; mp 228–229 °C.

IR (KBr) = 1704, 1647, 1556 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.86 (d, 1 H, *J* = 7.5 Hz), 7.83 (t, 1 H, *J* = 7.8 Hz), 7.05 (d, 1 H, *J* = 9.0 Hz), 6.91 (t, 1 H, *J* = 7.5 Hz), 6.89 (d, 2 H, *J* = 8.5 Hz), 6.77 (d, 2 H, *J* = 8.0 Hz), 6.62 (d, 2 H, *J* = 7.5 Hz), 6.24 (d, 2 H, *J* = 8.0 Hz), 2.12 (s, 3 H), 2.09 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 154.6, 142.2, 141.3, 136.5, 133.6, 130.1, 129.6, 129.3, 128.1, 127.8, 122.8, 120.3, 112.3, 30.6, 30.5.

MS (ESi): *m*/*z* = 343 (M^+), 223 (RDA).

Anal. Calcd for $C_{19}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.63; H, 5.38; N, 16.57.

_N_-[1,3-Diaryl-4-(arylimino)-1,3-diazetidin-2-ylidene]-_N_-phenylamines 7; General Procedure

The filtrate from the preparation of **4** (see the general procedure above) was evaporated, after the removal of **4**. The brownish residue was chromatographed (SiO_2/$CHCl_3$). The first fraction gave the product.

_N_-[1,3-Diphenyl-4-(phenylimino)-1,3-diazetidin-2-ylidene]-_N_-phenylamine (7a)

Yield: 22%; pale yellow needles; mp 162–163 °C. (Lit.[15] mp 165–166 °C).

^{1}H NMR and ^{13}C NMR analyses agree with the known data for **7a**.[15]

_N_-{1,3-Bis(4-chlorophenyl)-4-[(4-chlorophenyl)imino]-1,3-diazetidin-2-ylidene}-_N_-(4-chlorophenyl)amine (7b)

Yield: 30%; pale yellow needles; mp 155–156 °C.

^{1}H NMR ($CDCl_3$): δ = 8.24 (d, 4 H, *J* = 9.0 Hz), 8.15 (d, 4 H, *J* = 8.5 Hz), 7.47 (d, 4 H, *J* = 9.0 Hz), 7.44 (d, 4 H, *J* = 8.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 142.2, 138.1, 135.2, 129.0, 129.0, 127.0, 123.7.

_N_-{1,3-Bis(4-methylphenyl)-4-[(4-methylphenyl)imino]-1,3-diazetidin-2-ylidene}-_N_-(4-methylphenyl)amine (7c)

Yield: 30%; pale yellow needles; mp 152–153 °C.

^{1}H NMR ($CDCl_3$): δ = 8.18 (d, 4 H, *J* = 8.5 Hz), 8.11 (d, 4 H, *J* = 8.5 Hz), 7.29 (d, 4 H, *J* = 8.5 Hz), 7.28 (d, 4 H, *J* = 8.5 Hz), 2.44 (s, 6 H, 2 CH_3), 2.42 (s, 3 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 141.9, 141.9, 140.0, 129.3, 129.3, 125.6, 122.2, 21.5, 21.3.

_N_-(2′-Pyridinyl)acetothioacetamide (8) and _N_-(2′-Pyridinyl)benzoylthioacetamide (9)

Compounds **8** and **9** were prepared according to the known procedure.[12a–d]

_N_-(2′-Pyridinyl)acetothioacetamide (8)

Yield: 42%; light yellow needles; mp 84–86 °C (Lit.[12a] mp 83.5–84 °C).

_N_-(2′-Pyridinyl)benzoylthioacetamide (9)

Yield: 35%; yellow needles; mp 90–91 °C (Lit.[12a] mp 91–92 °C).

{_N,N′_-Diphenyl-1,2-bis-[1,2,4]thiadiazolo[2,3-_a_]pyridin-2-yliden}ethane-1,2-diamine (10)

To a stirred solution of **8** (0.29 g, 1.5 mmol) in MeOH (5 mL) were added nitrosobenzene (0.16 g, 1.5 mmol) and one drop of 25% aq solution of NaOH (as a catalyst). After 2 h, the product was collected by suction filtration; yield: 39%; white powder; mp 234–235 °C (dec.).

IR (KBr): 3348, 3317, 1629, 1600, 1564, 1546, 1496 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.67 (s, 2 H, 2 NH), 7.86 (dt, 2 H, *J* = 7.0, 1.0 Hz), 7.71 (dt, 2 H, *J* = 9.0, 1.0 Hz), 7.41 (ddd, 2 H, *J* = 9.0, 7.0, 1.0 Hz), 7.09 (d, 4 H, *J* = 8.0 Hz), 7.00 (td, 2 H, *J* = 7.0, 1.0 Hz), 6.73 (tt, 2 H, *J* = 7.2, 1.0 Hz), 6.45 (dt, 4 H, *J* = 7.5, 1.0 Hz).

^{13}C NMR (DMSO-d_6): δ = 144.8, 141.9, 132.2, 129.2, 125.9, 125.5, 123.5, 119.0, 117.1, 113.6, 113.0.

MS (EI): *m*/*z* (%) = 238 [100, (1/2 M^+ – 2 H)], 137 [29, $C_6H_4N_2S$ (thiadiazolopyridine moiety) + 1].

Anal. Calcd for $C_{26}H_{20}N_6S_2$: C, 64.98; H, 4.19; N, 17.49. Found: C, 64.76; H, 4.18; N, 17.39.

1-Phenyl-2-(2_H_-[1,2,4]thiadiazolo[2,3-_a_]pyridin-2-yliden)ethanone (11)

To a stirred solution of **9** (0.51 g, 2 mmol) in MeOH (30 mL) was added nitrosobenzene (0.21 g, 2 mmol). After 2 h, the product was collected by suction filtration and recrystallised from cyclohexane; yield: 54%; pale yellow needles; mp 229–231 °C. (Lit.[12a] mp 228–229 °C.

IR (KBr), ^{1}H NMR,^{13}C NMR and MS (EI) analyses and elemental analyses agree with the known data for **11**.[12a]

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(11) Compound **4a** ($C_{19}H_{14}N_4O$) crystallises in the monoclinic system, space group $P2_1/c$, with unit cell parameters a = 1558.71 (5), b = 1331.37 (3), c = 727.70 (2) Å, β = 83.728 (1)°, V = 1.50108 (7) × 10^9 pm^3, Z = 4. The X-ray diffraction data were collected on a KappaCCD (Bruker-Nonius) single-crystal diffractometer using MoKα radiation (55 kV, 30 mA). A total of 11584 reflections were collected and merged to give 3004 independent reflections [R(int) = 0.051] on a single-crystal sample (size 0.3 × 0.2 × 0.15 mm). The structure was solved in space group $P2_1/c$ by direct methods using the SHELXS86 program and refined by full-matrix least-squares method with SHELXL 97. The differential Fourier map of electron density was featureless with no chemically significant peaks. All hydrogen atoms were located on a difference Fourier map of electron density. Final R indices for I>2σ(I) were equal to *R*1 = 0.055, *wR*2 = 0.109, and *R*1 = 0.0856, *wR*2 = 0.1240 for all data. The final difference Fourier map of electron density was featureless with the largest peak and hole at 1.7 × 10^{-7} and –1.5 × 10^{-7} e·pm^{-3}, respectively. The structural data have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 250196.

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