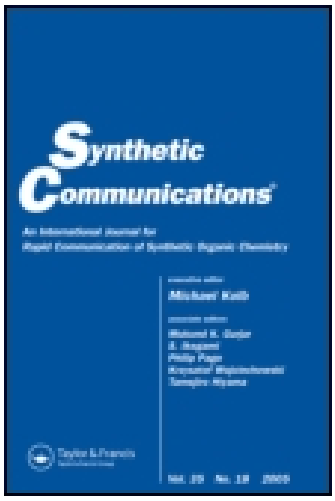

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# Reaction of Oxime Derivatives of β-Diketones and β-Ketoesters with Substituted Hydrazides: Novel Synthesis of Nitroso-*N*-sulfonyl- and Nitroso-*N*-substituted Amino Pyridones

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## ABSTRACT

A novel and efficient method for the synthesis of a new variety of nitroso-*N*-arylsulfonylaminated pyridones and nitroso-*N*-substitutedamino pyridones via the reaction of oxime derivatives of β-diketones and β-ketoesters with *N*-cyanoacetoarylsulfonylhydrazides and substituted cyanoacetohydrazides has been investigated. The synthetic potential of the method is demonstrated.

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*Key Words:* *N*-Amino-pyridones; *N*-Sulfonylaminated-pyridones; Substituted hydrazides; Nitroso pyridones; Ketoesters; Diketones.



In recent reports from our laboratory, we described the preparation of different novel functionalized *N*-substitutedamino pyridones, which revealed antagonistic activity.[1–4] These common features, encouraged us to develop a new straightforward route for the synthesis of these compounds. The present research deals with a novel synthesis of nitroso-*N*-arylsulfonylaminated pyridones and nitroso-*N*-substitutedamino pyridones by the reaction of oxime derivatives of β-diketones and β-ketoesters with cyanoacetoarylsulfonylhydrazides and substituted cyanohydrazides, respectively. Thus, it has been found that cyanoacetoarylsulfonylhydrazides **1** reacted with isonitroso derivatives of β-diketones **3a,b** in boiling ethanolic sodium ethoxide to give the corresponding 5-nitroso-*N*-sulfonylamino-2-pyridones **6**. The structures of **6** were established on the basis of elemental analysis and spectral data (IR, $^1$H NMR, $^{13}$C NMR and MS). The formation of **6** from the reaction of **1** with **3** is assumed to proceed via Michael addition of active methylene of **1** to the double bond in **3**. The formed Michael adduct then cyclized smoothly via elimination of two moles of water to give the final pyridones **6**. Similarly it has been found that reaction of compounds **3** with cyanoacetohydrazide **8** in the presence of sodium ethoxide gave the novel 5-nitroso-*N*-amino-2-pyridones **7**, the structures of which were established on the basis of elemental analysis and spectral evidence. The analytical data for **7a** revealed a molecular formula $C_8H_8N_4O_2$ ($M^+ = 192$), $^1$H NMR spectroscopy was used to confirm this structure for the product. Thus, $^1$H NMR revealed two bands at $\delta$ 2.46 and 2.68 ppm assignable to two methyl groups and a broad singlet at $\delta$ 5.52 ppm assignable for an amino group. The formation of **7** from the reaction of **3** and cyanoacetohydrazide **8** is assumed to proceed via intermediacy of Michael adduct, which cyclized to yield the final pyridones **7**. Reaction of compound **7** with aryl sulfonyl chlorides in refluxing ethanol containing catalytic amounts of piperidine gave the corresponding pyridones **6**. In order to investigate the scope of this reaction further and in order to establish whether the reaction of isonitroso derivatives of β-diketones **3** with activated nitriles could be extended to provide a general approach to nitrosopyridone derivatives, we studied the reaction of **3** with other substituted nitriles. Thus, in a typical experiment, when isonitroso derivatives of β-diketones **3** reacted with 1-cyanoacetyl-4-arylmethylidene-semicarbazide **9** in reluxing ethanolic

sodium ethoxide, the 5-nitroso-*N*-arylmethylideneamino-2-oxo-pyridines **13** were obtained in good yields. The structures of **13** were established and confirmed for reaction products on the basis of their elemental analysis and spectral data (IR, $^1$H NMR, $^{13}$C NMR and MS). The analytical data for **13a** revealed a molecular formula $C_{15}H_{11}N_4O_2$ ($M^+ = 280$), $^1$H NMR spectroscopy was used to confirm this structure for the product. Thus, $^1$H NMR revealed two bands at $\delta$ 2.32 and 2.54 ppm assignable for two methyl groups, a multiplet at $\delta$ 6.98–7.87 ppm assigned for aromatic protons and a broad singlet at $\delta$ 8.67 ppm assigned for yildenic CH. The formation of **13** from the reaction of **3** and 1-cyanoacetyl-4-arylmethylidene-semicarbazide **9** is assumed to proceed via intermediacy of Michael adducts, which cyclized to yield the final *N*-aryl-5-nitroso-2-pyridones **13**. Similarly, the reaction of oxime derivatives of β-ketoesters **14** with activated nitriles **1** and **9a** leads to the corresponding 6-hydroxy-5-nitroso-2-oxopyridines **15** and **16**, respectively. The structures of **15** and **16** were established on the basis of elemental analysis and spectral data.

In summary, we have achieved a regiospecific synthesis of interesting nitroso-*N*-arylsulfonylaminated pyridones and nitroso-*N*-substituted-amino pyridones by the reaction of oxime derivatives of β-diketones and β-ketoesters with cyanoacetoarylsulfonylhydrazides and substituted cyanohydrazides, respectively. The compounds obtained seems promising as high potential intermediates for synthesizing antimetabolite agents.

## EXPERIMENTAL

All melting points are uncorrected. The IR spectra were obtained (KBr, disk) on a Perkin Elmer/1650 FT-IR instrument. The $^1$H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ with $SiMe_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

### 5-Nitroso-*N*-phenylsulfonylamino-4-methyl-2-pyridones (6a,b)

General Procedure

A mixture of *N*-cyanoacetophenylsulfonylhydrazide **1** (0.01 mol) and oximes of β-diketones **3a,b** (0.01 mol) in sodium ethoxide (0.01 mol) and ethanol (30 mL) was refluxed for 4 h. The reaction mixture was

cooled and acidified with HCl. The resulting solid product was filtered off and recrystallized from the appropriate solvent.

**6a.** Brown crystals, from DMF, 56% yield, m.p. 300°C. IR ($cm^{-1}$): 3294, 3198 (NH); 2216 (CN); 1663 (CO). $^1$H NMR ($\delta$ ppm): 2.42 (s, 3H, $CH_3$); 2.51 (s, 3H, $CH_3$); 11.00 (s, 1H, NH). $^{13}$C NMR ($\delta$ ppm): 16.34 ($CH_3$); 18.00 ($CH_3$); 110.56 (CN); 164.12 (C-2); 126.32 (C-3); 152.69 (C-4); 138.65 (C-5); 156.11 (C-6). Found: C, 50.8; H, 3.4; N, 17.0%; Calcd. for $C_{14}H_{12}N_4O_4S$ ($m/z = 332$): C, 50.6; H, 3.6; N, 16.9%.

**6b.** Yellow crystals from EtOH/DMF , 50% yield, m.p. 290°C. IR ($cm^{-1}$): 3400, 3320 (NH); 2220 (CN); 1670 (CO). $^1$H NMR ($\delta$ ppm): 2.40 (s, 3H, $CH_3$); 2.58 (s, 3H, $CH_3$); 7.00–7.99 (m, 5H, $C_6H_5$), 11.17 (s, 1H, NH). $^{13}$C NMR ($\delta$ ppm): 16.00 ($CH_3$); 113.00 (CN); 120.43–127.11 (phenyl carbons), 165.19 (C-2); 128.67 (C-3); 150.43 (C-4); 137.10 (C-5); 157.00 (C-6). Found: C, 57.7; H, 3.5; N, 14.4%; Calcd. for $C_{19}H_{14}N_4O_4S$: C, 57.9; H, 3.6; N, 14.2%.

### 5-Nitroso-*N*-phenylsulfonylamino-6-hydroxy-2-pyridones (15a,b)

General Procedure

A mixture of *N*-cyanoacetophenylsulfonylhydrazide **1** (0.01 mol) and oximes of β-ketoesters **14a,b** (0.01 mol) in sodium ethoxide (0.01 mol) and ethanol (30 mL) was refluxed for 4 h. The reaction mixture was cooled and acidified with HCl. The resulting solid product was filtered off and recrystallized from the appropriate solvent.

**15a.** Yellow crystals, from EtOH, 62% yield, m.p. >300°C. IR ($cm^{-1}$): 3490–3370 (OH, NH); 2230 (CN); 1680 (CO). $^1$H NMR ($\delta$ ppm): 2.30 (s, 3H, $CH_3$); 11.00 (s, 1H, NH), 12.09 (s, br, $^1$H, OH). Found: C, 46.9; H, 3.1; N, 17.0%; Calcd. for $C_{13}H_{10}N_4O_5S$: C, 46.7; H, 3.0; N, 16.8%.

**15b.** Yellow crystals, from DMF-MeOH, 60% yield, m.p. 295°C. Found: C, 54.4; H, 2.8; N, 14.3%; Calcd. for $C_{18}H_{12}N_4O_5S$: C, 54.5; H, 3.0; N, 14.1%.

### 5-Nitroso-*N*-amino-2-pyridones (7a,b)

General Procedure

A mixture of oximes **3a,b** (0.01 mol) and cyanoacetohydrazide **8** (0.01 mol) was refluxed in sodium ethoxide solution (0.01 mol) and

ethanol (30 mL) for 5 h. The reaction mixture was cooled, poured over ice/water mixture and neutralized with dil. HCl. The precipitated product was collected by filtration and recrystallized from ethanol.

**7a.** Brown crystals, 50% yield, m.p. $>300^{\circ}$C. IR ($cm^{-1}$): 3420, 3250 ($NH_2$, NH); 2210 (CN); 1680 (CO). $^1$H NMR ($\delta$ ppm): 2.46 (s, 3H, $CH_3$); 2.68 (s, 3H, $CH_3$); 5.52 (s, br, 2H, $NH_2$). Found: C, 50.1; H, 4.4; N, 29.0%; Calcd. for $C_8H_8NO_2$ ($m/z = 192$): C, 50.0; H, 4.2; N, 29.2%.

**7b.** Yellow crystals, 55% yield, m.p. 285°C. Found: C, 61.6; H, 4.1; N, 22.1%; Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.4; H, 3.9; N, 22.0%.

## 5-Nitroso-*N*-arylmethylideneamino-4-methyl-2-pyridones (13a–f)

General Procedure

To a mixture of 1-cyanoacetyl-4-arylmethylidenesemicarbazide **9** and oximes of β-diketones **3a,b** (0.01 mol), sodium ethoxide (0.01 mol) in ethanol (30 mL) was added. The reaction mixture was heated under reflux for 4 h. The resultant product was acidified with HCl. The precipitate formed was collected by filtration, dried and then recrystallized from ethanol.

**13a.** Yellow crystals, 40% yield, m.p. 300°C. IR ($cm^{-1}$): 2216 (CN); 1663 (CO). $^1$H NMR ($\delta$ ppm): 2.32 (s, 3H, $CH_3$); 2.54 (s, 3H, $CH_3$); 6.98–7.87 (m, 5H, $C_6H_5$), 8.67 (s, 1H, CH). Found: C, 64.5; H, 4.1; N, 19.8%; Calcd. for $C_{15}H_{12}N_4O_2$ ($m/z = 280$): C, 64.3; H, 4.3; N, 20.0%.

**13b.** Brown crystals, 50% yield, m.p. 290°C. IR ($cm^{-1}$): 2220 (CN); 1670 (CO). $^1$H NMR ($\delta$ ppm): 2.37 (s, 3H, $CH_3$); 2.54 (s, 3H, $CH_3$); 7.11–8.00 (m, 5H, $C_6H_4$), 9.05 (s, 1H, CH). Found: C, 57.3; H, 3.6; N, 17.5%; Calcd. for $C_{15}H_{11}N_4O_2$: C, 57.2; H, 3.5; N, 17.8%.

**13c.** Brown crystals, 60% yield, m.p. $>300^{\circ}$C. Found: C, 65.4; H, 4.6; N, 19.2%; Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.3; H, 4.8; N, 19.0%.

**13d.** Brown crystals, 48% yield, m.p. 279°C. Found: C, 61.7; H, 4.4; N, 18.3%; Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.9; H, 4.5; N, 18.1%.

**13e.** Yellow crystals, 40% yield, m.p. $>300^{\circ}$C. Found: C, 70.9; H, 4.3; N, 15.9%; Calcd. for $C_{21}H_{16}N_4O_2$: C, 70.8; H, 4.5; N, 15.7%.

**13f.** Brown crystals, 60% yield, m.p. $>300^{\circ}$C. IR ($cm^{-1}$): 2220 (CN); 1690 (CO). $^1$H NMR ($\delta$ ppm): 2.44 (s, 3H, $CH_3$); 3.99 (s, 3H, $OCH_3$); 6.90–8.23 (m, 9H, $C_6H_5$, $C_6H_4$), 8.90 (s, 1H, CH). Found: C, 67.9; H, 4.2; N, 14.9%; Calcd. for $C_{21}H_{16}N_4O_3$: C, 67.7; H, 4.3; N, 15.1%.

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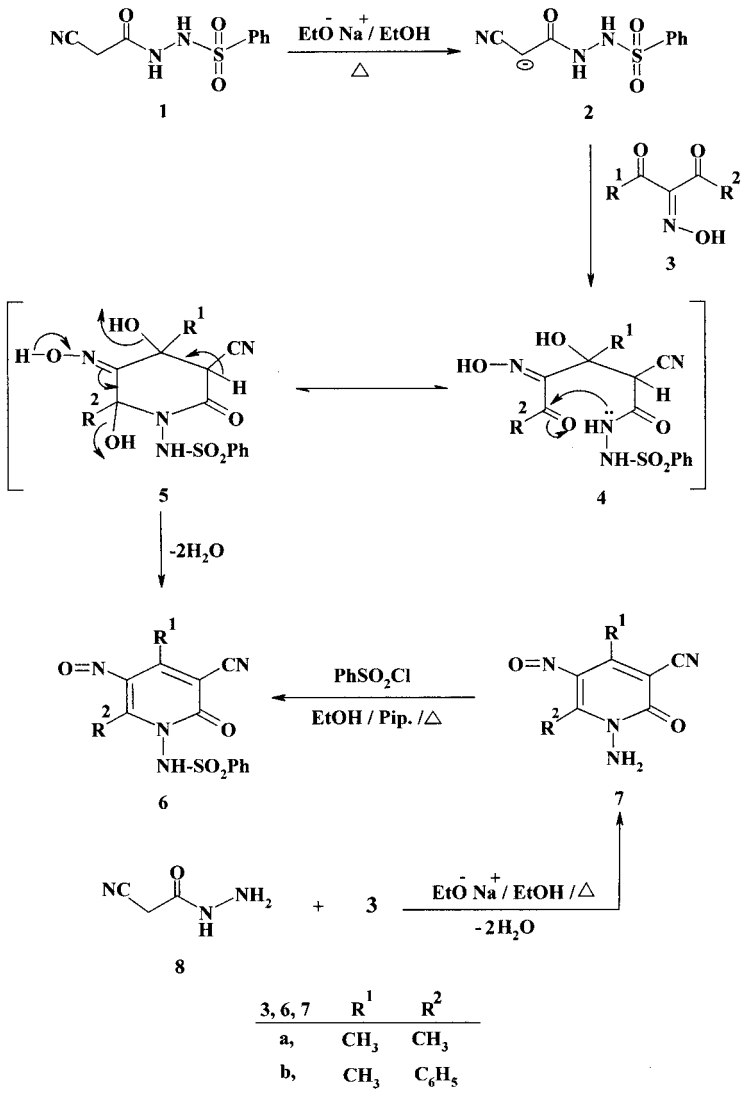


| 3, 6, 7 | $R^1$ | $R^2$ |
|---|---|---|
| a, | $CH_3$ | $CH_3$ |
| b, | $CH_3$ | $C_6H_5$ |

*Chart 1.*

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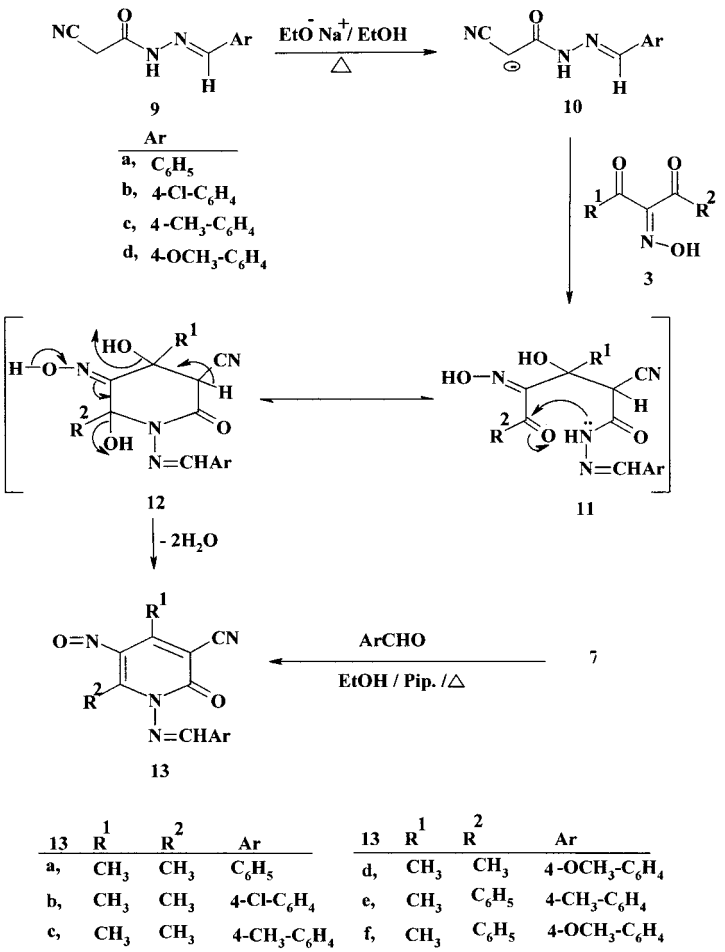


| 13 | $R^1$ | $R^2$ | Ar |
|---|---|---|---|
| a, | $CH_3$ | $CH_3$ | $C_6H_5$ |
| b, | $CH_3$ | $CH_3$ | 4-Cl-$C_6H_4$ |
| c, | $CH_3$ | $CH_3$ | 4-$CH_3$-$C_6H_4$ |
| d, | $CH_3$ | $CH_3$ | 4-$OCH_3$-$C_6H_4$ |
| e, | $CH_3$ | $C_6H_5$ | 4-$CH_3$-$C_6H_4$ |
| f, | $CH_3$ | $C_6H_5$ | 4-$OCH_3$-$C_6H_4$ |

*Chart 2.*

## 6-Hydroxy-4-methyl-5-nitroso-*N*-phenylmethylideneamino-2-pyridone (16)

General Procedure

To a mixture of 1-cyanoacetyl-4-phenylmethylidenesemicarbazide **9a** and oxime **14** (0.01 mol), sodium ethoxide (0.01 mol) in ethanol (30 mL) was added. The reaction mixture was heated under reflux for 4 h. The

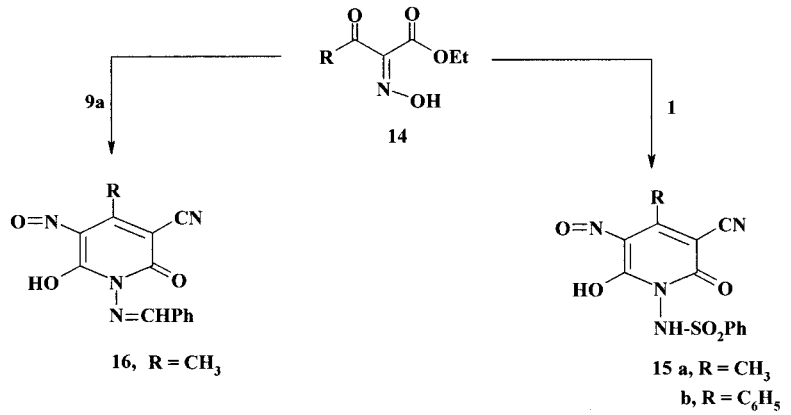


*Chart 3.*

resultant product was acidified with HCl. The precipitate formed was collected by filtration, dried and then recrystallized from ethanol.

**16.** Yellow crystals, 50% yield, m. p. 295°C. 3490, 3400 (OH), 2210 (CN); 1675 (CO). $^1$H NMR ($\delta$ ppm): 2.30 (s, 3H, $CH_3$); 7.09–8.11 (m, 5H, $C_6H_5$), 8.88 (s, 1H, CH), 11.98 (s, br, 1H, OH). Found: C, 60.7; H, 4.3; N, 18.8%; Calcd. for: $C_{15}H_{12}N_4O_3$: C, 60.8; H, 4.1; N, 18.9%.

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