

Action of *N,N*-Dimethylformamide Dimethylacetal on Some Oximino- β -dicarbonyl Compounds

Salvatore Plescia*, Giuseppe Daidone and Vincenzo Sprio

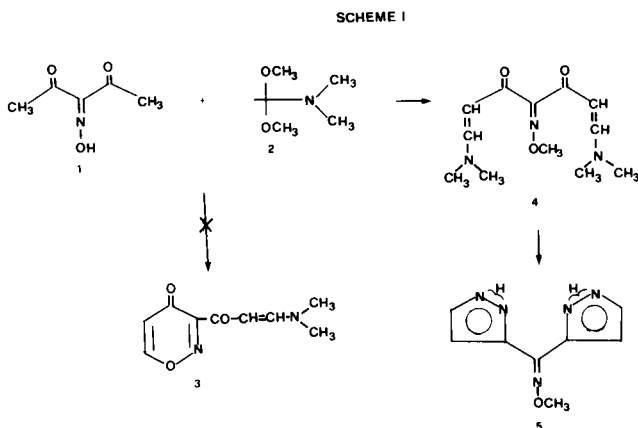
Istituto di Chimica Farmaceutica e Tossicologica della Università, Via Archirafi 32,
90123 Palermo, Italy
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3-Oximino-2,4-pentanedione (**1**) and ethyl 2-oximino-3-oxobutanoate (**6**) reacted with *N,N*-dimethylformamide dimethylacetal (DFDA) to give 1,7-bisdimethylamino-3,5-dioxo-4-methoximinohepta-1,6-diene (**4**) and ethyl 5-dimethylamino-2-methoximino-3-oxo-4-pentenoate (**8**), respectively. When compounds **4** and **8** were treated with hydrazine hydrate, they gave *O*-methylidipyrazol-3(5)-ylketoxime (**5**) and ethyl 2-methoximino-3(5)-pyrazolyethanoate (**9**) together with its corresponding hydrazide **10**, respectively. Upon action of DFDA on 3-oximino-2,4-pentanedione (**1**) at -20° an explosive crystalline product was obtained. On the other hand, the reaction of 3-acetoximino-2,4-pentanedione (**11**) with DFDA at -20° afforded a product which in ethanol solution, spontaneously deacetylated to give 1-dimethylamino-3,5-dioxo-4-oximinohexa-1-ene (**13**). The structures of all the new compounds were assigned on the basis of satisfactory analytical and spectroscopic data.

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We have recently reported that some phenylazo derivatives of β -dicarbonyl compounds react with excess DFDA to give new 1-phenyl-4(1*H*)-pyridazinones, bearing a carbonyl group at C-3, in good yield. These intermediates, in turn, reacted with hydrazine hydrate to give new pyrazolo-[4,3-*c*]pyridazine derivatives (**1**).

Extension of this work led us to explore the potential utility of this route, by reacting some oximino derivatives of β -dicarbonyl compounds **1** and **6** with DFDA, both from the point of view of production of compounds of biological importance incorporating the oxazine nucleus and new interesting oxazinones of type **3** and **7** bearing a carbonyl group at C-3, potentially useful as intermediates (Schemes I and II).



The reaction of 3-oximino-2,4-pentanedione (**1**) and ethyl 2-oximino-3-oxobutanoate (**6**) with DFDA at reflux resulted in the formation of 1,7-bisdimethylamino-3,5-dioxo-4-methoximinohepta-1,6-diene (**4**) and ethyl 5-dimethylamino-2-methoximino-3-oxo-4-pentenoate (**8**), respectively; the expected ring closure to oxazinones **3** and **7** could not be attained (Schemes I and II).

These results indicated that the DFDA attacked, besides the methyl groups of **1** and **6**, also the oximino group, to give the *O*-methyl derivatives **4** and **8**; as a consequence, the desired intramolecular condensation failed. To our knowledge, the DFDA has never been reported to methylate the oximino group.

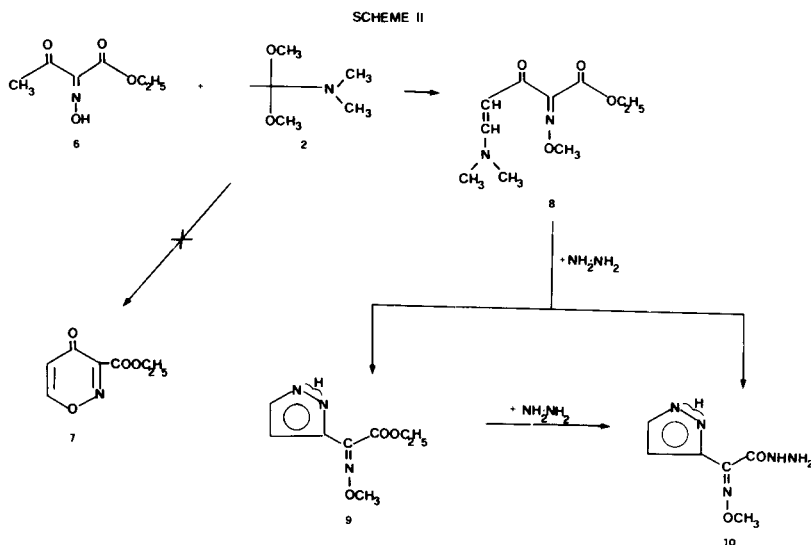
Compounds **4** and **8** were obtained as crystalline materials and were characterized by their ir and ^1H -nmr spectra as well as by elemental analysis and molecular weight determined by mass spectroscopy (see experimental).

The intermediate ethyl 5-dimethylamino-2-methoximino-3-oxo-4-pentenoate (**8**) reacted with hydrazine hydrate to give a mixture of ethyl 2-methoximino-3(5)-pyrazolyethanoate (**9**) and its corresponding hydrazide **10**. Further, the reaction of **9** with hydrazine hydrate in ethanol afforded a product, which was identical in all respects with the 2-methoximino-3(5)-pyrazolyethanohydrazide (**10**).

On the other hand, 1,7-bisdimethylamino-3,5-dioxo-4-methoximinohepta-1,6-diene (**4**) reacted at room temperature with hydrazine hydrate to give *O*-methylidipyrazol-3(5)-ylketoxime (**5**). The presence of the pyrazole moiety in compounds **5**, **9** and **10** was evident based on the infrared spectrum, which showed a broad absorption at $3000\text{--}3400\text{ cm}^{-1}$ (NH) and the pmr spectrum, which exhibited the resonance of the pyrazole NH at δ 13.20-13.30 (1H) and the shifts of the two annular protons H-4 and H-3 (**5**), seen as doublets, at δ 6.50-6.70 and 7.00-7.80 respectively, with a coupling constant of 2.0 Hz, according to literature reported data (2).

This sequence to the synthesis of pyrazoles **5**, **9** and **10**, by utilizing the masked β -ketoaldehyde derivatives **4** and **8**, as intermediates, allowed the cyclization step to occur in temperature conditions extremely mild.

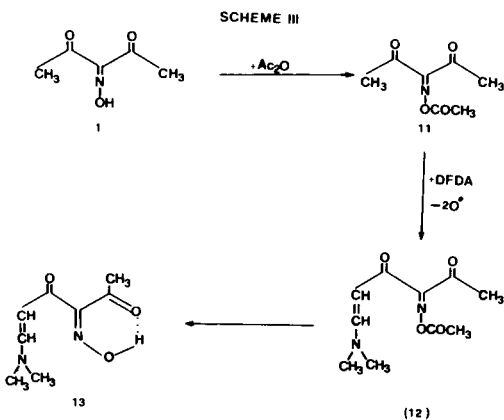
With the goal of avoiding *O*-methylation of oximino



group, compound **1** was treated with DFDA under other conditions. At room temperature, 1,7-bisdimethylamino-3,5-dioxo-4-methoximinohepta-1,6-diene (**4**) has also been obtained. Moreover, DFDA at -20° transformed **1** into a product, not yet identified, which stored in a dessicator, spontaneously **EXPLODED**.

1720 cm^{-1} , as was exhibited by the precursor 3-oximino-2,4-pentanedione (**1**). Instead, an intense absorption at 1680 cm^{-1} resulted from intramolecular hydrogen bonding. Likely, the low frequency band observed at 1630 cm^{-1} was attributable to the stretching of the carbonyl group conjugated with the carbon-carbon double bond, bearing the dimethylamino group. In fact, the position of the α,β unsaturated ketones stretching band in the compounds **4** and **8** occurred at 1630-1640 cm^{-1} .

The structure **13** also supported by inspection of the pmr spectrum, which exhibited a broad absorption at lower field δ 12.40 (1H), than a typical oximino resonance. Some attempts to effect intramolecular cyclocondensation of **13** to oxazinone of type **3** were unsuccessful.



At this point of the work, it was decided to protect the hydroxyl group by acetylating **1** with acetic anhydride.

Thus, when the reaction of 3-acetoximino-2,4-pentanedione (**11**) with DFDA was carried out at room temperature a very complex mixture, from which no product could be isolated, was formed.

In another attempt performed at -20° , DFDA transformed **11** yielding a product **12**, which during crystallization from ethanol, deacetylated to 1-dimethylamino-3,5-dioxo-4-oximinohepta-1,6-diene (**13**). The structure was assigned on the basis of elemental analysis, ^1H -nmr, ir spectral data and molecular weight by ms. Compound **13** is believed to exist in the form indicated in the Scheme III due to the fact that ir spectrum lacked a free carbonyl absorption at

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. The ir spectra were determined in hexachlorobutadiene (unless otherwise specified) with a Perkin-Elmer Infrared 299 spectrophotometer. A Jeol-JMS-01-SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra. The nmr spectra were obtained with a Varian EM-360 60 MHz spectrometer (TMS as internal reference).

Action of DFDA on 3-Oximino-2,4-pentanedione (**1**) and Ethyl 2-Oximino-3-oxobutanoate (**6**). Ethyl 5-Dimethylamino-2-methoximino-3-oxobutanoate (**8**).

A suspension of ethyl 2-oximino-3-oxobutanoate (**6**) (3) (60 mmoles) in DFDA (50 ml) was refluxed for 25 minutes and then cooled at -20° . After standing at -20° overnight the precipitate was filtered, washed with light petroleum and recrystallized. The product melted at 118-120° (ethanol), yield 35%; ms: m/e 228 (M^+); ir: cm^{-1} 1640 and 1740 (carbonyl bands); nmr (deuteriochloroform): δ 1.30 (t, CH_3 , 3H, $J = 6$ Hz), 2.90-3.20 (2s, $2 \times \text{CH}_2$, 6H), 4.00 (q, CH_2 , 2H, $J = 6$ Hz), 5.70 (d, CH, 1H, $J = 12$ Hz), 7.80 (d, CH, 1H, $J = 12$ Hz).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.60; H, 7.12; N, 12.27.

1,7-Bisdimethylamino-3,5-dioxo-4-methoximinohepta-1,6-diene (**4**).

A suspension of 3-oximino-2,4-pentanedione (**1**) (**4**) (30 mmoles) in DFDA (25 ml) was refluxed for 25 minutes. The mixture was concentrated *in vacuo*, the last traces of DFDA were removed by adding chloroform and successive evaporation. The residual oil was chromatographed on silica gel (385 g) column with ethyl acetate (4 l) and then with ethanol (900 ml). The ethyl acetate fractions and the first 400 ml of ethanol solution were neglected. The successive ethanol fractions (500 ml) were evaporated under reduced pressure to leave a residue, which was recrystallized. The product melted at 176-178° (benzene), yield 25% ms: m/e 253 (M⁺); ir: cm⁻¹ 1630 and 1640 (carbonyl bands); nmr (deuteriochloroform): δ 3.10 (s, 4 × CH₃, 12H), 4.00 (s, CH₃, 3H), 5.20 (d, CH, 1H, J = 12 Hz), 5.70 (d, CH, 1H, J = 12 Hz), 7.40 (d, CH, 1H, J = 12 Hz), 7.80 (d, CH, 1H, J = 12 Hz).

Anal. Calcd. for C₁₂H₁₉N₃O₅: C, 56.90; H, 7.56; N, 16.59. Found: C, 56.77; H, 7.57; N, 16.48.

Action of Hydrazine Hydrate on Ethyl 5-Dimethylamino-2-methoximino-3-oxo-4-pentenoate (**8**).

A suspension of **8** (7 g) in ethanol (35 ml) and 3.1 ml of hydrazine hydrate was stirred at room temperature for 24 hours. The mixture was allowed to stand at -20° overnight. The crystalline product, which separated, was collected and purified by column chromatography over silica gel (ethanol as eluent) to give ethyl 2-methoximino-3(5)-pyrazolylethylhydrazide (**10**), mp 177-179° (ethanol); yield 60%; ms: m/e 183 (M⁺); ir: cm⁻¹ 1650 (CO) 3000-3300 (multiple bands) (NH and NHNH₂); nmr (DMSO-d₆): δ 3.85 (s, CH₃, 3H), 4.40 (s, NH₂, 2H, exchangeable), 6.50 (d, CH, 1H, J = 2 Hz), 7.80 (d, CH, 1H, J = 2 Hz), 9.70 (broad, NH, 1H, exchangeable), 13.20 (broad, NH, 1H, exchangeable).

Anal. Calcd. for C₈H₁₂N₄O₂: C, 39.34; H, 4.95; N, 38.24. Found: C, 39.38; H, 4.82; N, 38.12.

The mother liquors were mixed with silical gel (10 g) and chromatographed on a column of silica gel (310 g). Elution with ethyl acetate (F₂₀₋₃₂, each 25 ml) removed the product **9**, mp 120-121° (ethyl acetate), yield 17%; ms: m/e 197 (M⁺); ir: cm⁻¹ 1740 (CO); nmr (deuteriochloroform): δ 1.35 (t, CH₃, 3H, J = 6 Hz), 4.10 (s, CH₃, 3H), 4.40 (q, CH₂, 2H, J = 6 Hz), 6.70 (d, CH, 1H, J = 2 Hz), 7.80 (d, CH, 1H, J = 2 Hz).

Anal. Calcd. for C₈H₁₁N₃O₃: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.84; H, 5.55; N, 21.35.

Ethyl 2-Methoximino-3(5)-pyrazolylethylhydrazide (**10**).

A solution of **9** (250 mg) in 10 ml of ethanol containing 1.5 ml of hydrazine hydrate was stirred at room temperature for 4 days. The solid, which separated, was filtered and recrystallized from ethanol, yield 50%. The product was identical (ms, R_f, mp) with ethyl 2-methoximino-3(5)-pyrazolylethylhydrazide described above.

O-Methylpyrazol-3(5)-ylketoxime (**5**).

A solution of **4** (1 g) in 15 ml of ethanol containing 400 mg of hydrazine hydrate was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure to dryness to give a residue, which was recrystallized from benzene. The product melted at 139-141°; yield 60%; ms: m/e 191 (M⁺); ir: cm⁻¹ 3100-3400

(multiple bands, NH); nmr (DMSO-d₆): δ 4.00 (s, CH₃, 3H), 6.70 (d, CH, 1H, J = 2 Hz), 7.00 (d, CH, 1H, J = 2 Hz), 7.80 (multiple bands, 2 × CH, 2H), 13.30 (broad, 2 × NH, 2H, exchangeable).

Anal. Calcd. for C₈H₉N₃O: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.44; H, 4.74; N, 36.57.

3-Acetoxyimino-2,4-pentanedione (**11**).

A mixture of 3-oximino-2,4-pentanedione (**1**) (**4**) (30 g) and acetic anhydride (100 ml) was heated at 100° for 1 hour. Excess of acetic anhydride was evaporated *in vacuo* and the residual oil was purified by distillation under reduced pressure, yield 70%; ms: m/e 171 (M⁺); ir: cm⁻¹ 1700, 1730 and 1800 (carbonyl bands); nmr (neat liquid): δ 2.24 (s, CH₃, 3H), 2.35 (s, CH₃, 3H), 2.50 (s, CH₃, 3H).

Anal. Calcd. for C₇H₉NO₄: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.27; H, 5.48; N, 8.33.

Action of DFDA on 3-Acetoxyimino-2,4-pentanedione (**11**).

Both compounds **11** (2 g) and DFDA (5 ml) were cooled at -20° and then mixed. The mixture was maintained at -20° for 6 days. The crude solid material, which separated was filtered, spread on a porous plate and stored in a desiccator. We believed this product to be **12** due to the fact that it, in deuteriochloroform solution, showed nmr signals at: δ 2.20 (s, CH₃, 3H), 2.42 (s, CH₃, 3H), 3.00 (s, CH₃, 3H), 3.20 (s, CH₃, 3H), 5.70 (d, CH, 1H, J = 12 Hz), 7.85 (d, CH, 1H, J = 12 Hz). Further, when the product, which was not characterized, was crystallized from ethanol and allowed to stand at room temperature in contact with the mother liquors was converted, after three days, completely into 1-dimethylamino-3,5-dioxo-4-oximinohexa-1-ene (**13**), mp 153-155° dec (ethanol); ms: m/e 184 (M⁺); ir: cm⁻¹ 2500-3000 (broad bands, OH) 1630 and 1680 (carbonyl bands); nmr (DMSO-d₆): δ 2.30 (s, CH₃, 3H), 2.80 (s, CH₃, 3H), 3.15 (s, CH₃, 3H), 5.10 (d, CH, 1H, J = 12 Hz), 7.20 (d, CH, 1H, J = 12 Hz), 12.40 (broad, OH, 1H, exchangeable).

Anal. Calcd. for C₈H₁₂N₂O₃: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.34; H, 6.57; N, 15.10.

Action of DFDA on 3-Oximino-2,4-pentanedione (**1**). CAUTION!

To a solution of 3-oximino-2,4-pentanedione (**1**) (**4**) (10 g) in dry diethyl ether (400 ml) cooled at -20° was added DFDA (50 ml) dissolved in dry diethyl ether (50 ml) at -20°, in three portions. The crystalline product, which separated, was rapidly filtered and stored in a desiccator, when the product **EXPLODED**. This compound, not identified, was water-soluble and by acidification of its aqueous solution with hydrochloric acid and successive extraction with diethyl ether the starting material **1** was obtained.

REFERENCES AND NOTES

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