Synthesis of 1-methyl-, 4-nitro-, 4-amino- and 4-iodo-1,2-dihydro-3*H*-pyrazol-3-ones

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Received April 24, 2001

4-Aminopyrazole-3-ones **4b, e, f** were prepared from pyrazole-3-ones **1b-d** in a four-step reaction sequence. Reaction of the latter with methyl *p*-toluenesulfonate gave 1-methylpyrazol-3-ones **2b-d**. Compounds **2b-d** were treated with aqueous nitric acid to give 4-nitropyrazol-3-ones **3b-d**. Reduction of compounds **3b-d** by catalytic hydrogenation with Pd-C afforded the 4-amino compounds **4b, e, f**. Using similar reaction conditions, nitropyrazole-3-ones derivatives **2c, d** were reduced into aminopyrazole-3-ones **5e**, **f**. 4-Iodopyrazole-3-ones **7a**, **7c** and **8** were prepared from the corresponding pyrazol-3-ones **2a**, **2c** and **6** and iodine monochloride or sodium azide and iodine monochloride.

J. Heterocyclic Chem. **38**, 1065 (2001).

Pyrazol-3-ones are versatile compounds [1] that have found application as intermediates and products in analytical [2], agricultural [3], biological [4] and pharmaceutical chemistry [5]. The use of 4-aminopyrazol-3-one derivatives as chromogenic agents for the spectrophotometric determination of phenols has been published recently [6]. We now report the synthesis of these derivatives.

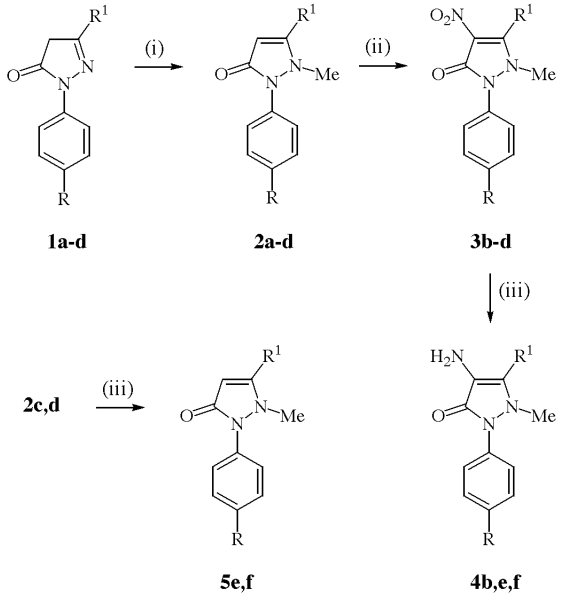
The most common synthesis of 1,2-dihydro-3*H*-pyrazol-3-ones is Knorr's reaction between a β-keto ester and hydrazine hydrate or a mono or disubstituted hydrazine [7-10]. The substituents on the ester and the hydrazine have been greatly varied. All types of alkyl, alicyclic, aralkyl and heterocyclic substituted esters have been used. A large variety of monosubstituted alkyl, aryl and heterocyclic hydrazines have been successfully employed [1].

Alkylation of pyrazole-3-ones at position 1 has been carried out by alkyl halides [11], dialkyl sulfates [12] diazomethane [13] and alkyl *p*-toluenesulfonates [14]. The reaction of pyrazole-3-ones with alkyl *p*-toluenesulfonates at 160° has generally given the highest yields of alkylated products. Pyrazol-3-ones **1a-d** reacted smoothly with methyl *p*-toluenesulfonate to give 1-methylpyrazol-3-ones **2a** [15,16] and **2b-d** in excellent yields.

A well-established route for the introduction of an amino group at position 4 of a pyrazol-3-one is first selective nitration at this position and then reduction of the resulting 4-nitro adduct. Two nitrating methods, 50% aqueous nitric acid [17] and acetic anhydride in fuming nitric acid [18], have been employed. The former conditions give much higher yields and therefore pyrazole-3-ones **2b-d** were treated with 55% aqueous nitric acid at 0 to 80° to give the corresponding 4-nitro derivatives **3b-d** in 80, 78 and 70% yield.

A literature survey revealed that, by far, the most reliable method to reduce nitropyrazole-3-ones is catalytic hydrogenation. Although a large variety of catalysts have been used, the best yields have been obtained with 10% Pd-C [19]. Thus 4-nitropyrazol-3-ones **3b-d** were reduced smoothly by hydrogenation at 3 atmospheres and in the presence of 10% Pd-C to afford the corresponding amines **4b**, **e** and **f** in 82, 77 and 78% yield. In a similar manner, nitro derivatives **2c** and **2d** were reduced to amines **5e** and **5f** in 87 and 88% yield, respectively.

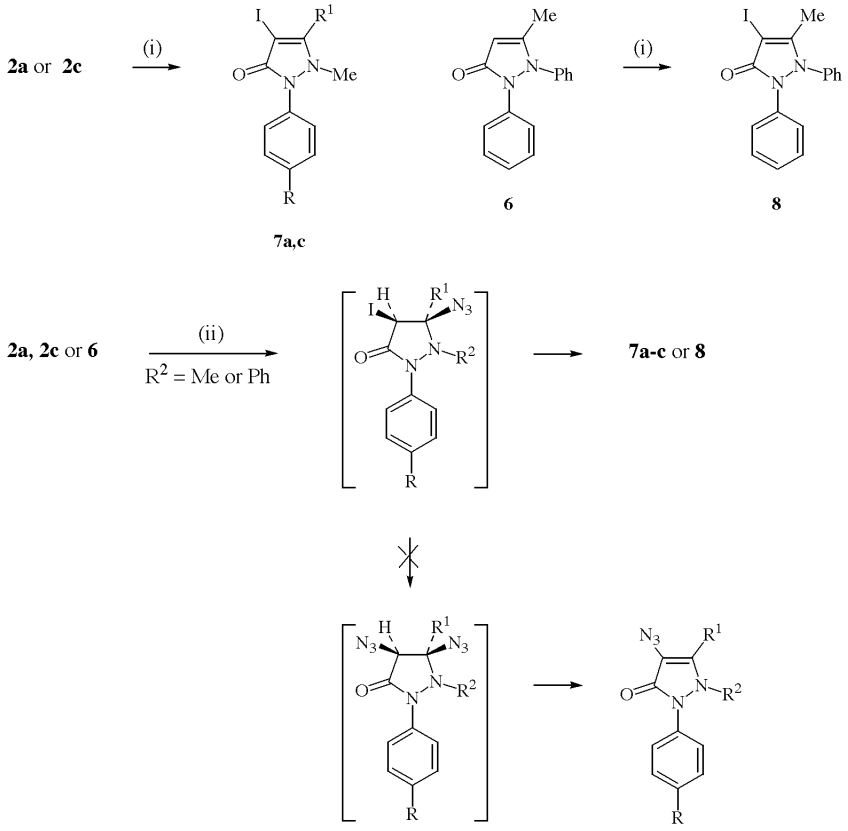
Scheme 1



a, R = H, R^1 = Ph, **b**, R = H, R^1 = 4-ClC_6H_4, **c**, R = H, R^1 = 4-$NO_2C_6H_4$, **d**, R = NO_2, R^1 = Ph, **e**, R = H, R^1 = 4-$NH_2C_6H_4$, **f**, R = NH_2, R^1 = Ph. (i) methyl *p*-toluenesulfonate, (ii) 55% aq. HNO_3, 0-22°, (iii) H_2, 10% Pd-C.

In order to establish a more selective method for the synthesis of 4-aminopyrazol-3-ones, a route *via* 4-halopyrazol-3-ones was investigated. For example, substitution of the halogen atom from 4-halopyrazol-3-ones by sodium azide in the Gabriel reaction would afford the corresponding 4-azidopyrazol-3-ones. Reaction of the latter with tri-*n*-butylphosphine and then hydrolysis of the

Scheme 2



a, R = H, R^1 = Ph, **c**, R = H, R^1 = 4-$NO_2C_6H_4$

(i) ICl, DMF or MeCN, 0 to 22°, (ii) NaN_3, ICl, MeCN, 0-22°.

intermediate iminophosphoranes would selectively yield 4-aminopyrazol-3-ones. For this purpose we selected to synthesize 4-iodopyrazol-3-ones. Halogenation at position 4 of a pyrazol-3-one may be accomplished by a variety of reagents. The products are mono- or dihalogeno derivatives, which are versatile compounds that can provide a further avenue for structural elaboration. In the literature there are fewer 4-iodopyrazol-3-ones than the other halogeno derivatives. Direct iodination [20] of a 4-unsubstituted pyrazole-3-one and replacement of a 4-chloromercuri group [21] with elemental iodine were the first two methods that gave fairly good yields of 4-iodo-pyrazol-3-ones. More recently it was demonstrated that 1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (antipyrine) was iodinated with bis(pyridine)iodonium(I) tetrafluoroborate to give 4-iodoantipyrine in almost quantitative yield [22].

We now report that iodination of **2a**, **2c** or **6** [23] with iodine monochloride [24] gave the corresponding 4-iodo derivatives **7a**, **7c** and **8** in 70, 55 and 75% yield. However any attempts to substitute iodine anion by azide anion in these compounds failed giving back unreacted starting material.

Alternatively, the synthesis 4-azidopyrazol-3-ones directly from compounds **2a**, **2c** or **6**, by a method similar to that used for the preparation of α-azidovinyl-ketones, was investigated. This work has been carried out by Hassner and co-workers [25] who reported the *trans* addition of iodine azide, prepared *in situ* by the reaction of sodium azide and iodine monochloride, to a variety of unsaturated systems. Thus α,β-unsaturated ketones and esters were postulated to give intermediate iodo azide adducts where iodine anion is substituted by excess azide anion to afford diazido intermediates. *Trans* elimination of hydrazoic acid from the diazido adducts is reported to give unsaturated α-azides. However upon reaction of compounds **2a**, **2c** or **6** with sodium azide and iodine monochloride the corresponding 4-iodo compounds **7a**, **7c** and **8** were obtained in 45, 38 and 44% yield, respectively. A plausible

explanation for this result is that after the addition of *in situ* generated iodine azide to **2a**, **2c** or **6**, hydrazoic acid elimination from the intermediate iodo azide adducts occurred faster than substitution of iodine anion by azide anion.

At present we are continuing our studies towards the selective introduction of an amino group at position 4 of 1,2-dihydro-3*H*-pyrazol-3-ones.

EXPERIMENTAL

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 783-B spectrometer solids were taken as Nujol mulls between sodium chloride discs. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Nuclear magnetic resonance spectra were measured at 400 MHz on a Brüker AMX 400 spectrometer using tetramethylsilane as internal standard. Purity verification and mass spectra were obtained by (i) an HPLC Waters system, type 616 with a Nova-Pak C_{18}, 4 μm (3.9 mm x 15 cm, Waters 36975) column at 25° with ms detector (Waters Integrity System, Milford MA). The ionization was made at 70 eV, the source was at 230° and the temperature of the PB (Particle Beam) interface set at 88° and (ii) a Thermo Separation gradient pump HPLC system, with Supelco, Supelcosil LC-18-DB, 3 μm (2.1 mm x 25 cm) at 25° with an APCI (Atmospheric Pressure Chemical Ionization) Finnigan MAT LCQ ion trap mass spectrometer. The ionization was made in APCI temperature of 450° with the corona discharge at -5.5 kV negative ionization (NI). Ms-ms spectra of the corresponding molecular ions are also collected. Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Solvents and reagents were of analytical grade and were used as received from the manufacturers.

General Procedure for the Methylation of Pyrazol-3-ones **1b-d** with Methyl *p*-Toluenesulfonate.

A stirred mixture of the appropriate of pyrazole-3-one **1b-d** (30 mmoles) and methyl *p*-toluenesulfonate (50 mmoles) was heated at 130-160° for 6-7 hours. The temperature of the reaction mixture was lowered to 80°, water (20 ml) added and then left stirring at that temperature for 20 minutes. The reaction mixture was cooled to room temperature and then brought to pH 8-9 by the addition of 40% aqueous sodium hydroxide. The crude precipitate was filtered off, washed with water and crystallized from an appropriate solvent to give 1-methylpyrazole-3-ones **2b-d** in 78, 70 and 83% yield, respectively.

5-(4-Chlorophenyl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**2b**).

This compound was obtained as yellow crystals (isopropyl alcohol), mp 167-168°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 3.19 (s, 3H, CH_3), 5.79 (s, H, 4-H), 7.22-7.69 ppm (m, 9H, benzene protons); APCI(-)ms: m/z 285(100), 283(50); APCI(-) ms-ms (283): m/z 263 (40), 243 (15), 196 (30).

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.57; H, 4.78; N, 9.65.

1-Methyl-5-(4-nitrophenyl)- 2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**2c**).

This compound was obtained as light-brown crystals (isopropyl alcohol/ether), mp 182-183°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 2.95 (s, 3H, CH_3), 5.88 (s, 1H, 4-H), 7.26-7.49 (m, 5H, phenyl protons), 7.69 (d, 2H, nitrophenyl β-protons, J = 9.1 Hz), 8.30 ppm (d, 2H, nitrophenyl α-protons, J = 9.1 Hz); APCI(-)ms: m/z 295 (30), 294 (100); APCI(-) ms-ms (295): m/z .272 (60), 255 (50), 185 (10), 99 (20).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.09; H, 4.57; N, 14.10.

1-Methyl-2-(4-nitrophenyl)- 5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**2d**).

This compound was obtained as light-brown crystals (ethyl acetate/methanol), mp 191-193°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 2.97 (s, 3H, CH_3), 5.81 (s, 1H, 4-H), 7.47-7.54 (m, 5H, phenyl protons), 7.73 (d, 2H, nitrophenyl β-protons, J = 9.1 Hz), 8.30 ppm (d, 2H, nitrophenyl α-protons, J = 9.1 Hz); APCI(-)ms: m/z 295 (20), 294 (100); APCI(-) ms-ms (295): m/z 280 (90), 265 (60), 170 (50).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.10; H, 4.67; N, 14.05.

General Procedure for the Nitration of Pyrazol-3-ones **2b-d** with Nitric acid.

To a stirred solution of 55% aqueous nitric acid (4 ml) at 0° was added portion-wise the appropriate pyrazole-3-one **2b-d** (4.8 mmoles). After the addition was complete the temperature of the reaction mixture was raised to 70° and then stirring was continued at that temperature for 6 hours. After cooling the reaction mixture was poured onto ice (50 g) and the resulting precipitate filtered, washed with water and crystallized from an appropriate solvent to give 4-nitropyrazole-3-ones **3b-d** in 80, 78 and 70% yield, respectively.

5-(4-Chlorophenyl)-1-methyl-4-nitro-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**3b**).

This compound was obtained as light brown crystals (isopropyl alcohol/petroleum ether bp 40-60°), mp 86-89°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 3.14 (s, 3H, CH_3), 7.36-7.50 (m, 9H, phenyl and nitrophenyl protons); APCI(-) ms: m/z 330 (100), 328 (45); APCI(-) ms-ms (328): m/z .298 (80), 285 (50), 243 (15), 196 (30).

Anal. Calcd. for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.35; H, 3.79; N, 12.38.

1-Methyl-4-nitro-5-(4-nitrophenyl)- 2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**3c**).

This compound was obtained as orange-red crystals (methanol/isopropyl alcohol), mp >260°; ir: CO 1670, NO_2 1525, 1510 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.17 (s, 3H, CH_3), 7.56-7.65 (m, 5H, phenyl protons), 7.8 (d, 2H, nitrophenyl α-protons, J = 8.9), 8.45 ppm (d, 2H, nitrophenyl α-protons, J = 8.9); APCI(-)ms: m/z 340 (100), 339 (45); APCI(-) ms-ms (340): m/z .279 (35), 250 (30), 185 (50), 117 (35), 99 (10).

Anal. Calcd. for $C_{16}H_{12}N_4O_5$: C, 56.47; H, 3.55; N. 16.46. Found: C, 56.55; H, 3.87; N, 16.29.

1-Methyl-4-nitro-2-(4-nitrophenyl)- 5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one **3d**.

This compound was obtained as orange-red crystals (methanol), mp 230-232°; ir: CO 1670, NO_2 1525, 1515 cm^{-1}; ^1H nmr: δ 3.18 (s, 3H, CH_3), 7.47-7.59 (m, 5H, phenyl protons), 7.61 (d, 2H, nitrophenyl β-protons, J = 8.9), 8.36 ppm (d, 2H, nitrophenyl α-protons, J = 8.9); APCI(-)ms: m/z 340 (100), 339 (60); APCI(-) ms-ms (340): m/z 311 (40), 265 (60), 235 (90), 201 (60), 171 (30), 134 (25).

Anal. Calcd. for $C_{16}H_{12}N_4O_5$: C, 56.47; H, 3.55; N. 16.46. Found: C, 56.62; H, 3.79; N, 16.31.

General Procedure for the Reduction of Nitropyrazol-3-ones **2c,d** and **3b-d**.

A solution of 4-nitropyrazol-3-ones **3b-d** (6 mmoles) in methanol (150 ml) was hydrogenated at 3 atmospheres for 24 hours over 10% palladium-on-charcoal (0.2 g). After removal of the catalyst by filtration, evaporation of methanol *in vacuo* gave a residue. Crystallization of the residue from an appropriate solvent gave **4b,e,f** and **5e,f** in 82, 77, 86, 88 and 87% yield, respectively.

4-Amino-5-(4-chlorophenyl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**4b**).

This compound was obtained as off-yellow needles (methanol/diethyl ether), mp 86-89°; ir: NH_2 3420, 3360, CO 1670 cm^{-1}; ^1H nmr: δ 2.91 (s, 3H, CH_3), 3.36 (s, 2H, NH_2), 7.40-7.67 ppm (m, 9H, *p*-chlorophenyl and phenyl protons); APCI(-)ms: m/z 299 (25), 298 (100); APCI(-) ms-ms (299): m/z 298 (50), 285 (50), 263 (30), 243 (15).

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N. 14.02. Found: C, 64.28; H, 4.79; N, 13.81.

4-Amino-1-methyl-5-(4-aminophenyl)- 2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**4e**).

This compound was obtained as colorless crystals (chloroform/petroleum ether bp 40-60°), mp 148-150°; ir: NH_2 3390, 3320, 3220, CO 1670 cm^{-1}; ^1H nmr: δ 2.68 (s, 3H, CH_3), 3.42 (s, 2H, 4-NH_2), 5.23 (s, 2H, *p*-$NH_2C_6H_4$), 6.72 (d, 2H, benzene α-protons, J = 8.3), 7.56 (d, 2H, benzene β-protons, J = 8.36), 7.15-7.41 ppm (m, 5H, phenyl protons); APCI(-)ms: m/z 280 (15), 279 (100); APCI(-) ms-ms (280): m/z 255 (40), 185 (5), 99 (20). PB(EI) ms: m/z 280 (60), 160 (30), 133 (70), 120 (100).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N. 19.99. Found: C, 68.69; H, 5.83; N, 19.74.

4-Amino-1-methyl-2-(4-aminophenyl)- 5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**4f**).

This compound was obtained as colorless needles (ethyl acetate/petroleum ether bp 40-60°), mp 175-178°; ir: NH_2 3390, 3340, 3220, CO 1670 cm^{-1}; ^1H nmr: δ 2.64 (s, 3H, CH_3), 3.51 (s, br, 4H, 4-NH_2 and $NH_2C_6H_4$), 6.69 (d, 2H, benzene α-protons, J = 8.6), 7.28 (d, 2H, benzene β-protons, J = 8.6), 7.27-7.50 ppm (m, 5H, phenyl protons); APCI(-)ms: m/z 280(10), 279(100); APCI(-) ms-ms (280): m/z 279(85), 265(100), 171(40).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N. 19.99. Found: C, 68.59; H, 5.79; N, 19.89.

5-(4-Aminophenyl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**5e**).

This compound was obtained as colorless crystals (methanol/diethyl ether), mp 154-155.5°; ir: NH_2 3320, 3220, CO 1670 cm^{-1}; ^1H nmr: δ 2.86 (s, 3H, CH_3), 3.85 (s, 2H, NH_2), 5.55 (s, 1H, 4- H), 7.11-7.42 (m, 5H, phenyl protons), 6.61 (d, 2H, benzene α-protons, J = 8.5), 7.21 (d, 2H, benzene β-protons, J = 8.5); APCI(-)ms: m/z 265 (40), 264 (100), PB(EI) ms: m/z 265 (100), 250 (25), 222 (20), 173 (35), 117 (45).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N. 15.84. Found: C, 72.65; H, 5.63; N, 15.52.

2-(4-Aminophenyl)-1-methyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**5f**).

This compound was obtained as colorless crystals (ethyl acetate/petroleum ether bp 40-60°), mp 129-130°; ir: NH_2 3370, 3220, CO 1670 cm^{-1}; ^1H nmr: δ 2.92 (s, 3H, CH_3), 3.72 (s, 2H, NH_2), 5.71 (s, 1H, 4-H), 6.70 (d, 2H, benzene α-protons, J = 8.6), 7.21 (d, 2H, benzene β-protons, J = 8.6), 7.41-7.45 ppm (m, 5H, phenyl protons); APCI(-) ms: m/z 265 (90), 264 (30), 263 (100), PB(EI) ms: m/z 265 (100), 236 (95), 222 (10), 195 (20), 160 (15), 118 (90), 108 (30), 92 (20), 79 (25), 65 (25).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N. 15.84. Found: C, 72.56; H, 5.99; N, 15.57.

General Procedure for the Iodination Pyrazol-3-ones **2a,c** and **6** Iodine monochloride.

To a stirred and cooled (0°) solution of pyrazol-3-one **2a** [16], **2c** or **6** (0.80 mmoles) in acetonitrile (5 ml), iodine monochloride (1.1 mmoles) was added portionwise. The temperature was allowed to reach room temperature and then stirring was continued for 18 hours. The reaction mixture is poured into cold water (50 ml) and extracted with chloroform (3 x 15 ml). The combined organic layers were treated with a 5% aqueous solution of sodium hydrogen sulfide, the organic layer separated and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a residue. The residue was crystallized from an appropriate solvent to give **7a,c** and **8** in 75, 55 and 75% yield, respectively.

4-Iodo-1-methyl-2,5-diphenyl-1,2-dihydro-3*H*-pyrazol-3-one (**7a**).

This compound was obtained as colorless needles (chloroform/petroleum ether bp 40-60°), mp 176-178°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 2.91 (s, 3H, CH_3), 7.25-7.49 ppm (m, 10H, phenyl protons); PB(EI) ms: m/z 376 (75), 284 (20), 178 (25), 129 (90), 118 (80), 105 (30), 91 (55), 77 (95) 63 (40), 51 (100).

Anal. Calcd. for $C_{16}H_{13}IN_2O$: C, 51.08; H, 3.48; N. 7.45. Found: C, 51.11; H, 3.65; N, 7.13.

4-Iodo-1-methyl-5-(4-nitrophenyl)-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**7c**).

This compound was obtained as colorless needles (chloroform/diethyl ether), mp 133-135°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 2.94 (s, 3H, CH_3), 7.28-7.50 (m, 5H, phenyl protons), 7.69 (d, 2H, benzene β-protons, J = 8.7), 8.31 ppm (d, 2H, benzene α-protons, J = 8.7); APCI(-) ms: m/z 420 (100), 419 (30).

Anal. Calcd. for $C_{16}H_{12}IN_3O_3$: C, 45.63; H, 2.87; N. 9.98. Found: C, 45.66; H, 3.09; N, 9.72.

4-Iodo-5-methyl-1,2-diphenyl-1,2-dihydro-3*H*-pyrazol-3-one (**8**).

This compound was obtained as colorless needles (ethanol/water), mp 114.5-116°; ir: CO 1670 cm^{-1}; ^1H nmr: δ 2.10 (s, 3H, CH_3), 6.92-7.27 (m, 10H, phenyl protons); PB(EI) ms: m/z 376 (65), 219 (50), 178 (35), 130 (60), 101 (80), 89 (70), 75 (100).

Anal. Calcd. for $C_{16}H_{13}IN_2O$: C, 51.08; H, 3.48; N. 7.45. Found: C, 51.19; H, 3.69; N, 7.35.

General Procedure for the Treatment of Pyrazol-3-ones **2a,c** and **6** with Sodium azide and Iodine monochloride.

To a stirred and cooled (0°) solution of pyrazol-3-one **2a,c** or **6** (1 mmole) in acetonitrile (5 ml), sodium azide (2.5 mmoles) and iodine monochloride (1.1 mmoles) were added portionwise. (**Caution!** Explosions have been reported on evaporation of solutions of iodine azide to dryness. Mixtures containing unreacted iodine azide should be washed with sodium bisulfite). The work-up that followed was similar to the previous General Procedure and gave **7a,c** and **8** in 45, 38 and 44% yield, respectively. Compounds **7a,c** and **8** were in all respects identical to authentic samples.

Acknowledgements

The authors wish to thank the General Secretariat of Research and Technology, Athens for financial support (PAVE grant no. 92BE121) and Dr. A. Troganis for NMR spectra measured on a Brüker AMX 400 spectrometer financed by the University of Ioannina.

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