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Reaction of 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene) propanedinitrile with 1,3-dicarbonyl compounds

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2-(3-Methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene) propanedinitrile (**1**) reacted with indane-1,3-dione (**2**) to give 2-amino-3′-methyl-5,5′-dioxo-1′-phenylspiro[indeno[1,2-*b*]pyran-4(5*H*),4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**3**), 6-amino-3,3′-dimethyl-5′-oxo-1,1′-diphenylspiro[pyrano[2,3-*c*]pyrazole-4(1*H*),4′(5′*H*)-[1*H*]pyrazole]-5-carbonitrile (**6**) and 2′-amino-1,3,5′-trioxospiro[indane-2,4′(5′*H*)-indeno[1,2*b*]pyran]-3′-carbonitrile (**7**). Also **1** reacted with 4-hydroxy-2*H*-chromen-2-one (**8**) to afford 2-amino-3′-methyl-5,5′-dioxo-1′-phenylspiro[4*H*, 5*H*-pyrano-[3,2*c*]-1-chromene-4,4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**9**) together with **6**. While 5,5-dimethylcyclohexane-1,3-dione (**11**) reacted with **1** to give 2-amino-3′,7,7-trimethyl-5,5′-dioxo-1′-phenyl-5,6,7,8-tetrahydrospiro[4*H*-chromene-4,4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**12**) as a solely product.

1. Introduction

The bioactivity of coumarins [1, 2] and indene derivatives [3] is well established. Moreover, Michael adducts of arylideneindandione with coumarins were reported as anticoagulants [4]. Nevertheless, nothing has been reported on spiro pyrazoles incorporating pyranochromenes and with indenopyrans which may lead to the production of compounds with altered/enhanced bioactivity. The coumarin and indene derivatives however have been reported to undergo Michael addition reaction [5, 6]. Few of 2-spiro-compounds of indane-1,3-dione have been reported in the literature and these compounds were prepared from indian-1,2,3-trione [7–9] or 2-(1,3-dioxoindan-2-ylidene) propanedinitrile (**5**) [10, 11].

2. Investigations, results and discussion

In view of these observations, we have now investigated the reaction of **1** with indane-1,3-dione (**2**), 4-hydroxy-2*H*-chromen-2-one (**8**) and 5,5-dimethylcyclohexane-1,3-dione (**11**) to explore the possibility of the formation of a novel spiro system incorporating pyrazole, pyran, pyranobenzopyran and chromene moieties.

In the present paper the reaction of 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene) propanedinitrile (**1**) with 1,3-dicarbonyl compounds is reported. We describe firstly the reaction of **1** with indane-1,3-dione (**2**). A solution of **1** in ethanol when added to a solution of **2** in the same solvent and heated under reflux for 1 h, gave the novel spiro compounds: 2-amino-3′-methyl-5,5′-dioxo-1′-phenylspiro-[indeno[1,2-*b*]pyran-4(5*H*),4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**3**), 6-amino-3,3′-dimethyl-5′-oxo-1,1′-diphenylspiro[pyrano[2,3-*c*]-pyrazole-4(1*H*),4′(5′*H*)-[1*H*]pyrazole]-5-carbonitrile (**6**) and 2′-amino-1,3,5′-trioxospiro[indane-2,4′(5′*H*)-indeno[1,2-*b*]pyran]-3′-carbonitrile (**7**) in 26, 20, and 52% yield, respectively.

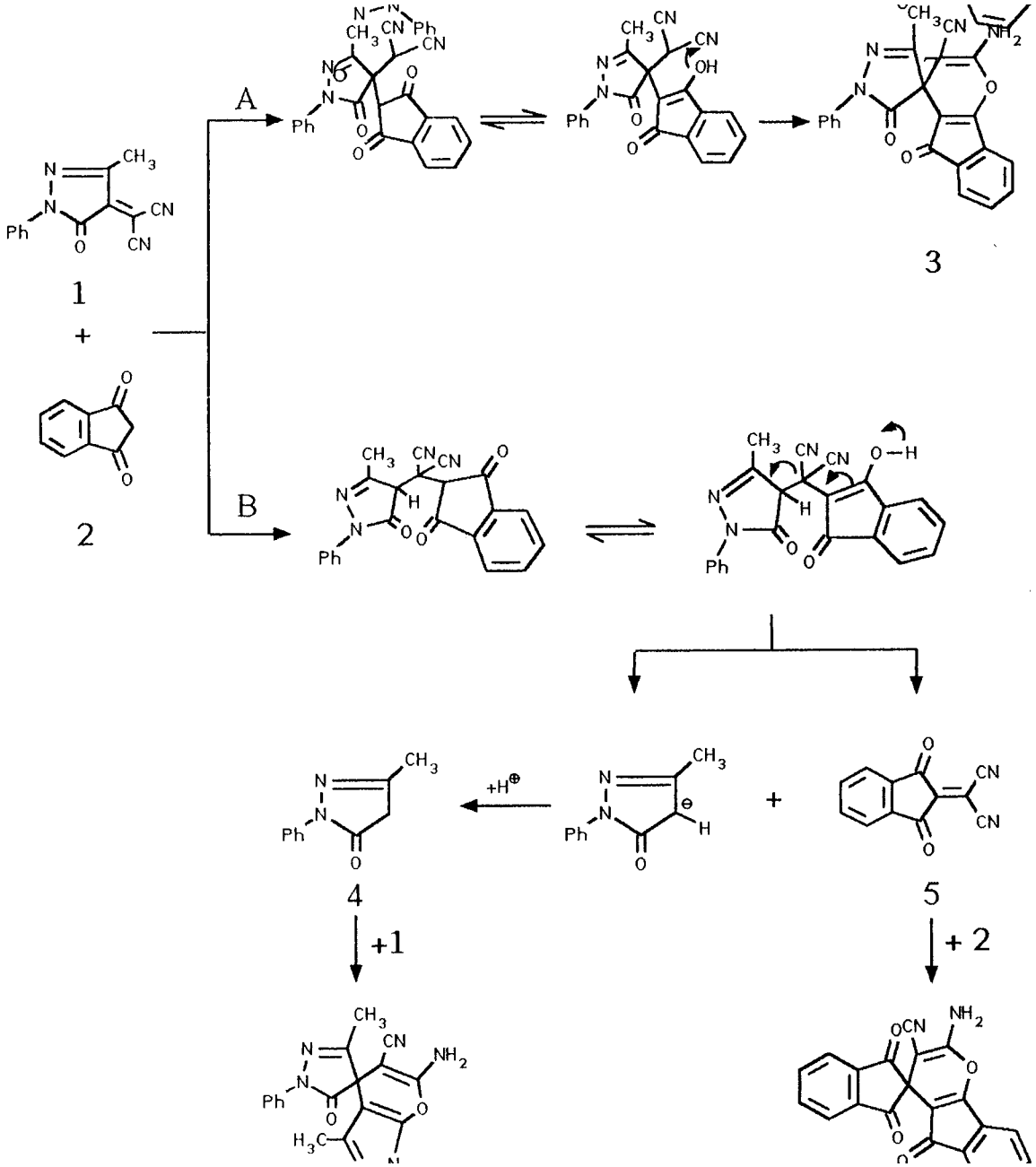
The structures **3, 6** and **7** were confirmed on the basis of spectral data. The IR spectra showed characteristic absorptions between 3400 and 3200 cm^{-1} for the amino group and between 2200 and 2180 cm^{-1} for the cyano group and between 1709 and 1680 cm^{-1} for the carbonyl groups. Also the pyran ether linkage was observed between 1180 and 1178 cm^{-1}. The ^1H NMR spectra displayed aromatic protons in the region 7.32–8.16 ppm and a characteristic signal between 8.03–8.13 ppm corresponding to the amino group (at 5.03 ppm in the case of compound **3**). Moreover, the MS showed the correct molecular ion peaks for the compounds **3, 6** and **7** as $m/z = 382$, 410 and 354 respectively corresponding to their molecular weights.

Compound **3** was formed by a Michael addition through the route A (Scheme 1). The Michael adduct of **1**, having an electron attracting group on the exomethylene carbon atom is interesting, as it can afford either a Michael adduct which can exist as such or this adduct can be enolised and converted into the spiro-pyran system of C-4 of pyrazole i.e. compound **3**. On the other hand **1** may react with **2** through route B. This is probably by a Michael addition reaction through the addition of **2** on the α-carbon atom of **1** to give a Michael adduct. This adduct can undergo cleavage in a malononitrile exchange reaction giving 3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (**4**) and 2-(1,3-dioxoindan-2-ylidene) propanedinitrile (**5**). In turn compound **4** reacts with **1** to give **6**, while compound **5** reacts with **2** to five **7**. Such an exchange of the malononitrile residue has been previously reported [12]. This means that **1** which is an α, β-unsaturated nitrile may react by the α-carbon atom in the route B and by the β-carbon atom in the route A. (see Scheme 1).

Similarly like **2**, 4-hydroxy-2*H*-chromen-2-one (**8**) reacts with **1** to afford two products, 2-amino-3′-methyl-5,5′-dioxo-1′-phenylspiro[4*H*,5*H*-pyrano-[3,2*c*]-1-chromene-4,4′(5′*H*)-[1*H*]pyrazole]-3-carbonitrile (**9**) and **6** in 53 and 15% yield respectively. The IR spectra of **9** showed characteristic absorptions at 3385 and 3265 cm^{-1} for the amino group and at 220 cm^{-1} for the cyano group, and at 1728 and 1645 cm^{-1} for the carbonyl groups. The ^1H NMR showed aromatic protons in the region 7.23 to 7.94 ppm and a characteristic signal at 8.15 ppm for the amino group. The MS showed the correct molecular ion peak of **9** as $m/z = 398$ corresponding to its molecular weight. The structure of the second product **6** was identified by comparison of its melting point with both that reported in the literature [12] and that from the product of the reaction of **1** with **2**. Neither the 2-(1,3-dioxo-2*H*-1-benzopyran-3(4*H*)-ylidene) propanedinitrile (**10**) nor its adduct with **8** was obtained from the reaction mixture, this may be due to the instability of **10** which undergoes cleavage to malononitrile and **8** under the reaction conditions. Thus the reaction of **1** with the nucleophiles like **2** and **8** may involve both addition in the β-position to the carbonyl group and the β-position to the cyano groups.

Next, the reaction of a non-fused 1,3-dicarbonyl compound dimedone **11** with **1** was investigated in order to

Schema 1



compare its reactivity with **2** and **8** towards **1**. On heating the ethanolic solutions of **11** and **1** under reflux for 1 h, the novel spiro compound 2-amino-3′,7,7-trimethyl-5,5′-dioxo-1′-phenyl-5,6,7,8-tetrahydrospiro[4*H*-chromene-4,4′(5′*H*)-[1*H*]-pyrazole]-3-carbonitrile (**12**) was obtained as a solely product in 68% yield; no malononitrile exchange reaction with **1** was observed. The structure **12** was confirmed on the basis of spectral data and elemental analysis. Thus from the above findings it may be concluded that the indane-1,3-dione (**2**) and the 4-hydroxy-2*H*-chromen-2-one (**8**) have a more acidic CH_2 group than of the dimedone **11**. Therefore it is obvious that the reactivity of 2-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene) propanedinitrile (**1**) towards 1,3-dicarbonyl compounds depends strongly on the nature of the CH acidic component.

3. Experimental

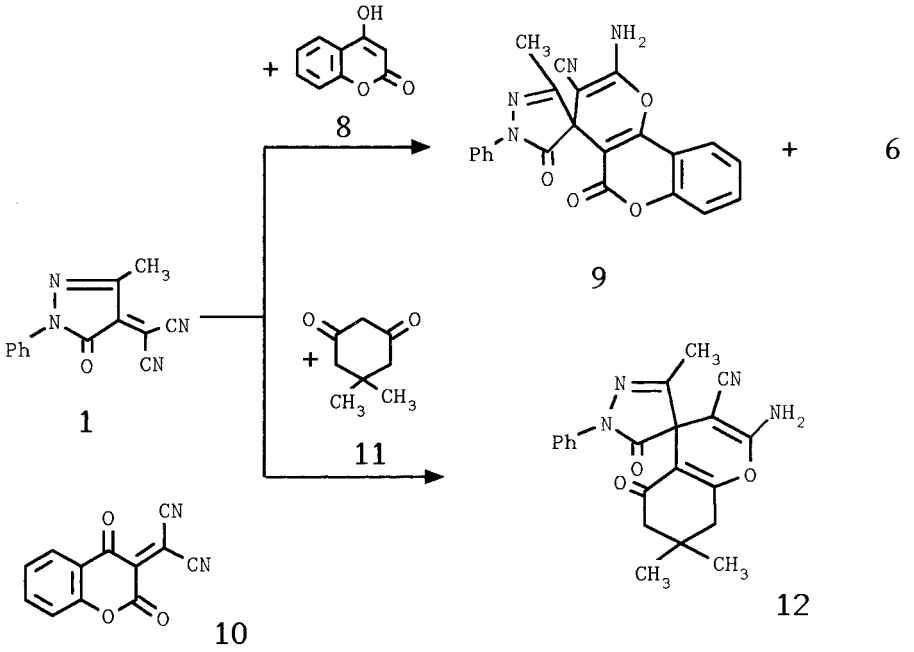
3.1. Materials

Indane-1,3-dione (**2**) (Riedel-de Haën), 4-hydroxy-2*H*-chromen-2–one (**8**) (Aldrich) and dimedone (**11**) (Merck) were used as received. 2-(3-Methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene) propanedinitrile (**1**) was prepared according to literature procedures [13].

3.2. Measurements

The uncorrected melting points were determined on a Griffin & George apparatus. Elemental analyses were carried out by Microanalysis Center at Cairo University. All the results were in an acceptable range. The IR spectra (KBr) were recorded on a Shimadzu 470 spectrophotometer. The 270 MHz ^{1}H NMR spectra were observed on a Bruker AC 270. The MS (70 eV, electron impact mode) were recorded on an AMD 604 instrument at Duisburg University. Preparative layer chromatography (plc) used air dried 1.0 mm thick layers of slurry applied silica gel Merck PF_{254} on

Schema 2



48 cm wide and 20 cm high glass plates and toluene-ethyl acetate (2 : 1) as developing solvent. Zones were detected by their color or by quenching of indicator fluorescence upon exposure to 254 nm light and eluted with acetone or ethyl acetate.

3.3. Reaction of indane-1,3-dione (**2**)*, 4-hydroxy-2H-chromen-2-one* (**8**) *and dimedone* **11** *with* **1** *(general procedure)*

To a mixture of **1** (1 mmol) and the respective 1,3-dicarbonyl compound (1 mmol) in ethanol a few drops of piperidine were added. The reaction mixture was heated under reflux for 1 h and then allowed to cool. The precipitate product (only in the case of **11**) was filtered off, dried and recrystallised from ethanol to give **12**. The reaction mixture was dried in vacuo and subjected to plc using toluene-ethyl acetate as 2 : 1. The main zones in every case contained **3**, **6**, **7**, **9** and **10**.

3.3.1. 2-Amino-3′-methyl-5,5′-dioxo-1′-phenylspiro[indeno[1,2-b]pyran-4(5H),4′(5′H)-[1H]-pyrazole]-3-carbonitrile (**3**)

Colorless crystals from ethyl acetate-cyclohexane. Yield 100 mg, 26%, m.p. 200 °C. IR(KBr): ν = 3350, 3180 (NH_2), 2200 (CN), 1709 and 1652 (C=O), 1180 cm^{-1} (C−O) str. ^1H NMR ($CDCl_3$) δ = 1.67 (s, 3 H, CH_3), 5.03 (br, 2 H, NH_2), 7.34–8.16 (m, 9 H, aromatic-H). MS: m/z 382 (M^+, 22%), 355 (8), 249 (15), 236 (27), 208 (65), 174 (96), 152 (65), 146 (19), 132 (15), 104 (46), 91 (67), 77 (100).
$C_{22}H_{14}N_4O_3$

3.3.2. 6-Amino-3,3′-dimethyl-5′-oxo-1,1′-diphenylspiro[pyrano[2,3-c]pyrazole-4(1H),4′(5′H)-[1H]pyrazole]-5-carbonitrile (**6**)

Colorless crystals from ethyl acetate. Yield 80 mg, 20% m.p. 260 °C (lit. [12] 262 °C). IR(KBr) ν = 3359, 3180 (NH_2), 2200 (CN), 1655 (C=O), 1180 cm^{-1} (C−O) str. ^1H NMR (DMSO) δ = 1, 89 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 7.28–7.87 (m, 10 H, aromatic-H), 8.03 (s, 2 H, NH_2). MS: m/z 410 (M^+, 1%), 383 (7), 344 (8), 315 (4), 236 (45), 210 (11), 174 (41), 132 (7), 105 (23), 91 (40), 77 (100).

3.3.3. 2′-Amino-1,3,5′-trioxospiro[indane-2,4′(5′H)-indeno[1,2-b]pyran]-3′-carbonitrile (**7**)

Yellow crystals from ethanol. Yield 184 mg, 52% m.p. 238–240 °C. IR(KBr) ν = 3390, 3235 (NH_2), 2195 (CN), 1701, 1665 (C=O), 1178 cm^{-1} (C−O) str. ^1H NMR (DMSO) δ = 7.32–7.63 (m, 8 H, aromatic-H), 8.15 (br, 2 H, NH_2). MS: m/z 354 (M^+, 10%), 326 (4), 290 (5), 208 (84), 180 (19), 146 (79), 104 (100), 91 (4), 77 (15).
$C_{21}H_{10}N_2O_4$

3.3.4. 2-Amino-3′-methyl-5,5′-dioxo-1′-phenylspiro[4H,5H-pyrano[3,2-c]-1-chromene-4,4′(5′H)-[1H]pyrazole]-3-carbonitrile (**9**)

Colorless crystals from ethanol. Yield 210 mg, 53% m.p. 252–254 °C. IR(KBr) ν = 3385, 3265 (NH_2), 2200 (CN), 1709, 1680 (C=O), 1170 cm^{-1} (C−O) str. ^1H NMR ($CDCl_3$) δ = 2.07 (s, 3 H, CH_3), 7.23 to 7.94 (m, 9 H, aromatic-H), 8.15 (s, 2 H, NH_2). MS: m/z 398 (M^+, 15), 369 (8), 344 (37), 327 (7), 236 (54), 210 (15), 162 (30), 120 (42), 105 (14), 91 (29), 77 (100).
$C_{22}H_{14}N_4O_4$

3.3.5. 2-Amino-3′,7,7-trimethyl-5,5′-dioxo-1′-phenyl-5,6,7,8-tetrahydrospiro[4H-chromene-4,4′(5′H)-[1H]pyrazole]-3-carbonitrile (**12**)

Colorless crystals from ethanol. Yield 254 mg, 68% m.p. 243–245 °C. IR(KBr) ν = 3420, 3300 (NH_2), 2200 (CN), 1700, 1680 cm^{-1} (C=O). ^1H NMR (DMSO) δ = 1.04 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 2.26 (d, 1 H-a), 2.30 (d, 1 H-b, J = 13.50 Hz, CH_2), 2.60 (s, 2 H, CH_2), 7.20–7.80 (m, 7 H, aromatic-H and NH_2). MS: m/z 376 (M^+, 94), 347 (66), 334 (10), 307 (5), 243 (18), 236 (16), 216 (100), 160 (11), 105 (7), 77 (43).
$C_{21}H_{20}N_4O_3$

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