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Regioselective Synthesis of [1]Benzopyrano[4,3-c]pyrazol-4-(1H)-one and [1]Benzopyrano[3,4-c]pyrazol-4(3H)-one Derivatives

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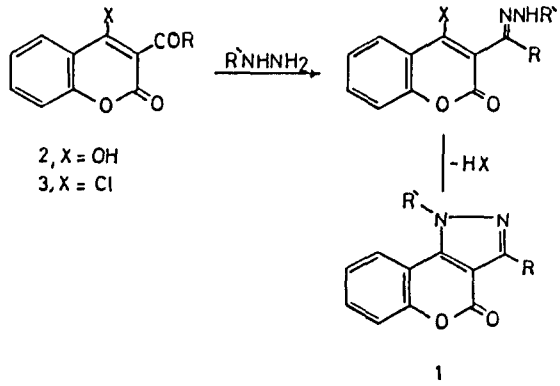
The cycloaddition reaction of N-phenyl-C-cinnamonitrilimine **4** to coumarin leads to the formation of 3-styrylbenzopyrano[4,3-c]pyrazole derivative **6**, whereas 3-phenylsulfonylcoumarin **9** or 3-bromocoumarin **10** or 3-cyanocoumarin **11** gives 1-styrylbenzopyrano[3,4-c]pyrazole derivative **7**. Also, the cycloaddition of **4** to 3-acetylcoumarin **15** and 3-benzoylcoumarin **16** gives the corresponding dihydropyrano[3,4-c]pyrazole adducts **17** and **18** respectively. Oxidation of **17** and **18** gives **7**.

Key words: Nitrilimine, Benzopyrano[4,3-c]pyrazole, Benzopyrano[3,4-c]pyrazole, Coumarin derivatives

INTRODUCTION

Many synthesis of 4-oxobenzopyranopyrazole fused ring system **1** was resulted from cyclization of the hydrazone derivatives of 3-acyl-4-hydroxy-coumarin **2** (Scheme 1) (Mustafa *et al.*, 1965). The other reported method (Moorty *et al.*, 1973) involving the condensation of hydrazines with 3-acyl-4-chlorocoumarin **3** was shown to be implausible one (Chantegrel *et al.*, 1983). In this report, the reaction of coumarin itself and some of its 3-substituted derivatives **9-11**, **15** and **16** with N-phenyl-C-cinnamonitrilimine **4** are investigated. The aim of the present study is on one hand to prepare compounds that might have biological activity and on the other hand to clarify the effect of substituents in coumarin derivatives on the regiochemistry of the cycloaddition process. In addition, this investigation thought interesting since it would provide a one step synthesis for benzopyrano[4,3-c]pyrazole **6** and benzopyrano[3,4-c]pyrazole **7** derivatives.



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Scheme 1.

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MATERIALS AND METHODS

All melting points were determined on Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide on Pye Unicam SP3-300 infrared spectrophotometer. The ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Varian T-60A NMR spectrometer using tetramethylsilane as internal refrence. Elemental analyses were carried out at microanalytical laboratory of University of Cairo, Giza, Egypt. N-Phenyl-C-cinnamohydrazonoyl bromide (Hassaneen *et al.*, 1990), 3-phenylsulfonylcoumarin (Merchant and Shah, 1981), 3-bromocoumarin (Ghiya and Marathey, 1965), 3-cyanocoumarin (Bechert, 1894), 3-acetylcoumarin (Knoevenagel, 1898) and 3-benzoylcoumarin (Knoevenagel and Arnot, 1904) were prepared as previously described in literature.

Synthesis of 3-styryl-1-phenyl[1]benzopyrano[4,3-c] pyrazol-4(1H)-one 6

To a solution of coumarin (0.67 g, 5 mmoles) and N-phenyl-C-cinnamo-hydrazonoyl bromide **5** (1.5 gm,

5 mmoles) in chloroform (50 ml) was added triethylamine (0.7 ml, 5 mmoles) at room temperature. The mixture was refluxed for 12 h, and then cooled. The mixture was washed with water and the organic layer was dried over anhydrous sodium sulfate, then filtered. The solvent was evaporated and the residue was triturated with methanol where it solidified. The latter was collected and crystallized from acetic acid to give compound **6**, mp. 262°C; δ ($CDCl_3$) 7.0-8.2 (m, Ar-H) ppm; ν (KBr) 1730 (C=O), 1585 (C=N) cm^{-1}. Ms.; m/z 364. Anal for $C_{24}H_{16}N_2O_2$ Calcd. C, 79.1; H, 4.4; N, 7.7. Found: C, 79.3; H, 4.3; N, 7.6.

Synthesis of 1-styryl-3-phenyl[1]benzopyrano[3,4-c]pyrazol-4(3H)-one 7

To a mixture of N-phenyl-C-cinnamohydrazonolyl bromide **5** (1.5 gm, 5 mmoles) and 3-phenylsulfonylcoumarin **9** (1.4 gm, 5 mmoles) in dry benzene (40 ml) was added triethylamine (0.7 ml, 5 mmoles) at room temperature. The mixture was refluxed till the hydrazonoyl bromide disappeared (10 h) as indicated by TLC analysis. After cooling to room temperature the precipitated triethylamine hydrobromide was filtered off and the solvent was evaporated. Trituration of the residue with methanol gave a crude solid. The latter was collected, washed with methanol and dried. Crystallization from acetic acid gave compound **7**, mp. 255°C; δ ($CDCl_3$) 7.0-8.0 (m, Ar-H) ppm; ν (KBr) 1730 (C=O), 1590 (C=N) cm^{-1}. Anal. for $C_{24}H_{16}N_2O_2$ Calcd. C, 79.1; H, 4.4; N, 7.7. Found: C, 79.0; H, 4.7; N, 7.8. Compound **7** was also prepared using 3-bromocoumarin (1.1 gm, 5 mmoles) or 3-cyanocoumanrin (0.9 gm, 5 mmoles) in place of 3-phenylsulfonylcoumarin.

Synthesis of 3-phenyl-3a-R-dihydro[1]benzopyrano[3,4-c]pyrazol-4(3H)-one 17 and 18

These compounds were prepared by the same method described for the synthesis of **7** using 3-acetylcoumarin (0.94 gm, 5 mmoles) or 3-benzoyl-coumarin (1.25 gm, 5 mmoles) in place of 3-phenylsulfonylcoumarin. The compounds prepared were crystallized from acetic acid. Compound **17** had mp. 254°C, (DMSO) 2.4 (s, 3H), 5.1 (s, 1H), 6.8-7.8 (m, 16H) ppm; (KBr) 1760 (C=O), 1690 (C=O), 1585 (C=N) cm^{-1}. Anal for $C_{26}H_{20}N_2O_3$ Calcd. C, 76.5; H, 4.9; N, 6.9. Found: C, 76.8; H, 5.1; N, 6.6. Compound 18 had mp. 201°C, δ ($CDCl_3$) 5.2 (s, 1H), 6.9-8.2 (m, 21H) ppm, ν (KBr) 1750 (C=O), 1660 (C=O), 1585 (C=N) cm^{-1}. Anal. for $C_{31}H_{22}N_2O_3$ Calcd. C, 79.1; H, 4.7; N, 6.0. Found C, 79.4; H, 4.6; N, 5.9.

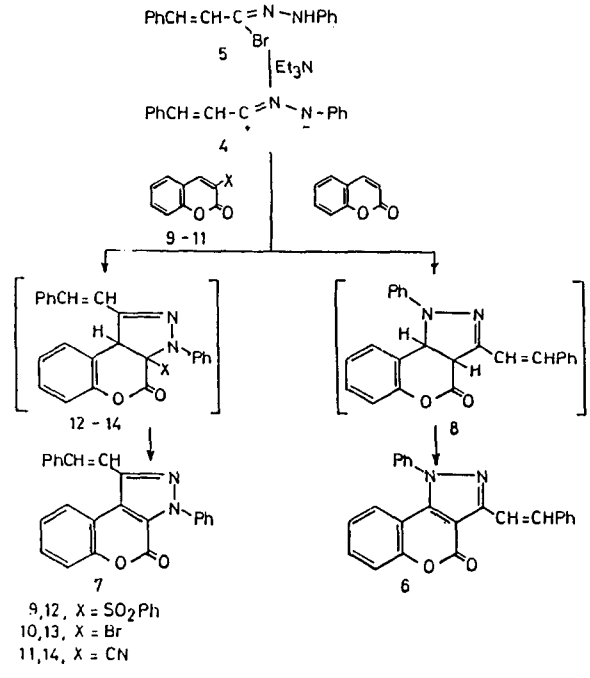
Oxidation of 3-phenyl-3a-R-dihydrobenzopyrano[3,4-c]pyrazol-4(3H)-ones 17 and 18

A suspension of **17** or **18** (2 mmoles) in aqueous potassium hydroxide (10 ml, 10%) was relfuxed for 12 h. The reaction mixture was cooled, poured into water (50 ml) and acidified with hydrochloric acid (1N). The crude product was filtered, washed with water, dissolved in toluene (10 ml) and refluxed for 2 h. After cooling the product that precipitated was collected and crystallized from acetic acid. The pure product had mp. 255°C and was identical in all respects (mp, mmp, IR ^{1}H-NMR) with **7**.

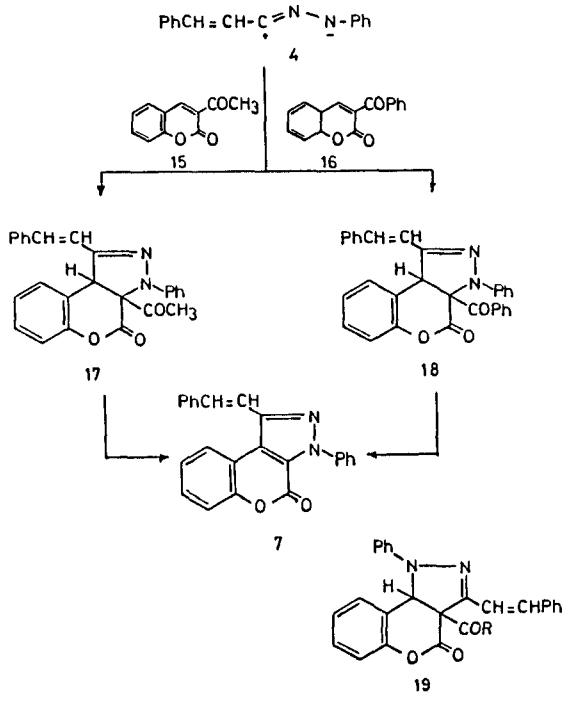
RESULTS AND DISCUSSION

The cycloaddition of coumarin to N-phenyl-C-cinnamonitrilimine **4**, prepared in situ from N-phenyl-C-cinnamohydrazonoyl bromide **5** in chloroform in the presence of triethylamine, was carried out at reflux for 12 h, the sole product obtained was found to be an oxidation product of the cycloadduct **8** (Scheme 2). The other regioisomer **7** was not identified in the reaction mixture as shown by TLC analysis. The structure of **6** was established by elemental analysis, ^{1}H-NMR spectrum and Mass spectrum. The absence of the two doublets in the ^{1}H-NMR spectrum of the product **6** isolated indicates that the cycloadduct **8** is aromatized as it is formed to give the benzopyrano[4,3-c]pyrazole **6**. 2-Pyrazolines are known to be easily aromatized by autoxidation even in the absence of oxygen (Sustman *et al.*, 1967).

Refluxing of **5** with 3-phenylsulfonylcoumarin **9** in beenzene in the presence of triethylamine gave only one isolable product **7** which was analyzed correctly for $C_{24}H_{16}N_2O_2$. The ^{1}H-NMR spectrum of **7** revealed



Scheme 2.



Scheme 3.

the absence of the methine 9b proton in the cycloadduct **7** (Scheme 2). These results indicate that the cycloadduct **12** undergoes simultaneous elimination of benzenesulfinic acid as soon as it is formed to give 3-phenyl-1-styryl[1]benzopyrano[3,4,-c]pyrazol-4(3H)-one **7**. The structure of the product was shown to be **7** by comparison with an authentic sample of the isomeric 3-styryl-1-phenyl[1]benzopyrano[4,3-c]pyrazol-4(1H)-one **6**. Compound **7** was also formed via cycloaddition of **4** to 3-bromocoumarin **10** or 3-cyanocoumarin **11**. The product **7** results undoubtedly via thermal elimination of hydrogenk bromide or hydrogen cyanide from the corresponding cycloadducts **13** and **14**, respectively (Scheme 2).

Threatment of **4** with 3-acetylcoumarin **15** and 3-benzoylcoumarin **16** in refluxing chloroform afforded the 1,3-dipolar cycloadducts **17** and **18**, respectively in 70-80% yield (Scheme 3). The assigned structures of the latter were supported by analytical and spectral data. In their ^{1}H-NMR spectra the cycloadducts **17** and **18** have characteristic signals due to 9b proton resonance near δ 5.1 and 5.2 ppm, respectively. These chemical shifts seem to be compatible with structures **17** and **18** and exclude the possibility of the other regioisomer **19**. The structure of **17** and **18** were confirmed by their conversion to **7**. Thus, refluxing of **17** or **18** in aqueous potassium hydroxide followed by heating the crude product in toluene gave in both cases compound **7** (Hassaneen *et al.*, 1989) (Scheme 3).

The foregoing results indicate that the presence of electron withdrawing groups at C-3 of coumarin reverses the regioselectivity of the cycloaddition of N-phenyl-C-cinnamonitrilimine.

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