1,3-DIPOLAR CYCLOADDITION OF 2-DIAZOPROPANE TO COUMARIN. THE SYNTHESIS OF DERIVATIVES OF /1/BENZOPYRANO/4,3-c/PYRAZOL-4(3H)-ONE AND /1/BENZOPYRANO/3,4-c/PYRAZOL-4(1H)-ONE

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Abstract - 1,3-Dipolar cycloaddition of 2-diazopropane (2) to unsubstituted coumarin (1) is taking place nonregiospecifically to give a mixture of cycloadducts 3 and 5. These are thermally transformed into cyclopropane derivative 6 and 4-isopropyl derivative 7, respectively. In the presence of potassium hydroxide or 2 substituted pyrazoles 8, 9 and 10 are produced. The oxidation of 3 and 5 with bromine in acetic acid gives tricyclic systems 15 and 16.

The addition of diazoalkanes to coumarins with an electronegative substituent, such as acetyl, benzoyl, cyano, arylsulpinyl and others, at position 3 is usually highly regiospecific. Cyclopropacoumarins, 4-alkyl-substituted derivatives and ring-expansion products are the most common products in this reactions.[1-4]

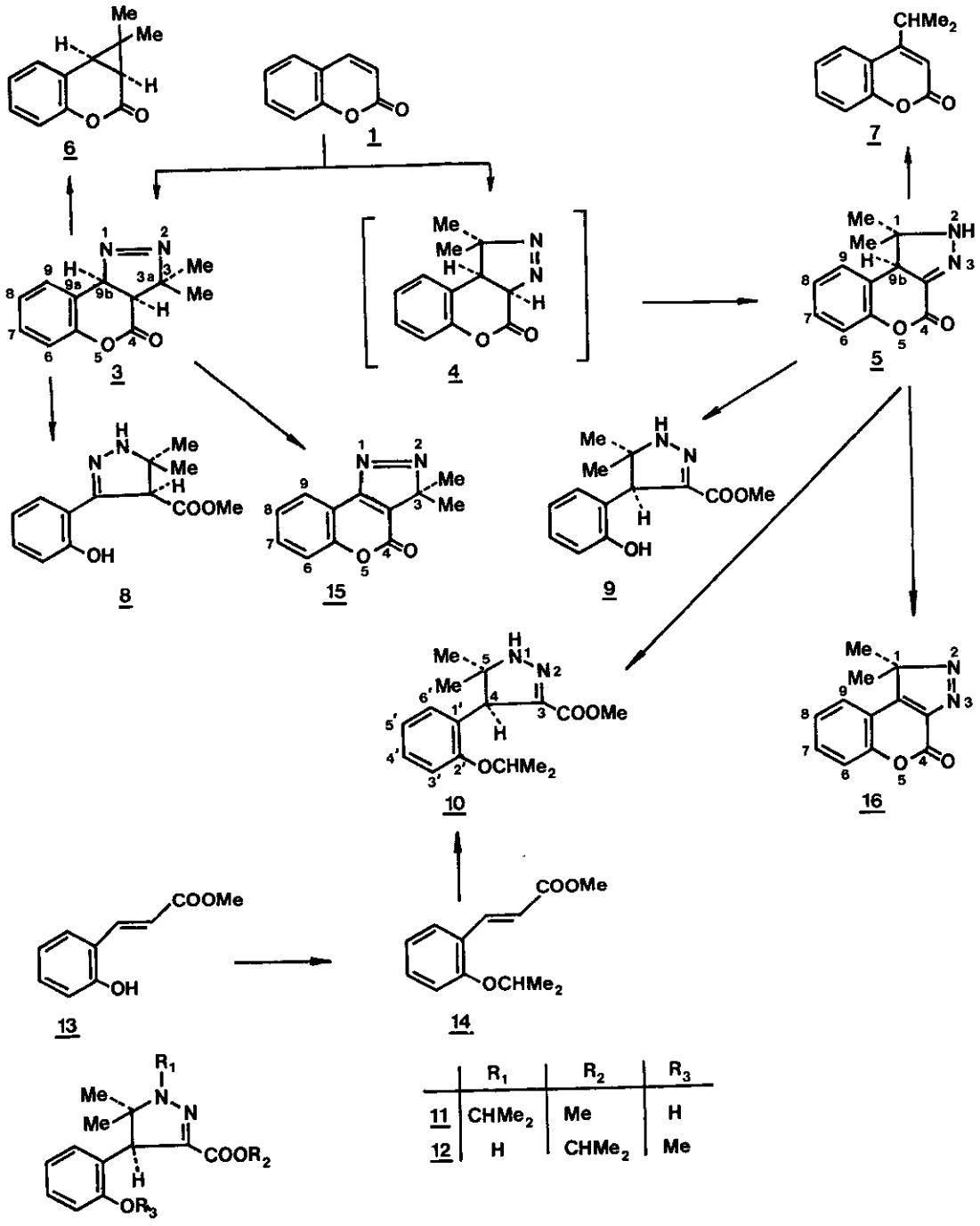
As an extension of our research in the field of 1,3-dipolar cycloadditions of diazoalkanes to heteroaromatic systems[5] we report here on the cycloaddition of 2-diazopropane (2) to unsubstituted coumarin (1) in which cycloaddition occurs across the 3,4-double bond in pyran part of the molecule nonregiospecifically. Two isomeric cycloadducts, 3,3-dimethyl-3a,9-dihydro/1/benzopyrano/4,3-c/pyrazol-4(3H)-one (3) and 1,1-dimethyl-3a,9b-dihydro/1/benzopyrano/3,4-c/pyrazol-4(1H)-one (4), are formed at -25°C. The cycloadduct 3 is stable under the reaction conditions and work-up procedure, while the isomeric cycloadduct 4 isomerizes into the tautomeric 1,1-dimethyl-2,9b-dihydro/1/benzopyrano/3,4-c/pyrazol-4(1H)-one (5).

The structures of 3 and 5 were established on the basis of microanalytical data, ^{1}H nmr spectral characteristics and further chemical transformations. The ^{1}H nmr spectrum of 3 shows two singlets at δ = 1.10 ppm and δ = 1.77 ppm for two nonequivalent methyl groups at position 3, two doublets at δ = 2.95 ppm for H_{3a} and δ = 6.08 ppm

for H_{9b} with the coupling constant J = 10.5 Hz and two multiplets at δ = 6.87-7.38 ppm for H_6, H_7 and H_8 and δ = 7.63-7.87 ppm for H_9, while the ^1H nmr spectrum for 5 whows two singlets at δ = 0.92 ppm and δ = 1.71 ppm for two methyl groups attached at position 1, a singlet at δ = 4.19 ppm for H_{9b}, a multiplet at δ = 6.95-7.50 ppm for H_6, H_7, H_8 and H_9, and a broad singlet at δ = 8.82 ppm for NH, exchangable with deuterium oxide. These data are in full agreement with the proposed structures. This was further confirmed by the following chemical transformations. When 3 was heated in xylene under reflux, thermal elimination of nitrogen from pyrazole part of the molecule was taking place to afford 1,1-dimethyl-1a,7b-dihydrocyclopropa/c//1/benzopyran-2-one (6). The structure determination of this compound is based on microanalytical data and ^1H nmr spectrum which shows again two singlets at δ = 0.95 ppm and δ = 1.58 ppm for two nonequivalent methyl gropus attached to the cyclopropane ring, two doublets at δ = 2.09 ppm for H_{7b} and δ = 2.55 ppm for H_{1a} with the coupling constant J = 7.5 Hz, and a multiplet at δ = 6.79-7.50 ppm for H_4, H_5, H_6 and H_7.

On the other hand, when isomer 5 was heated in xylene or DMF under reflux, elimination of nitrogen occurred to yield 4-isopropylcoumarin (7). The ^1H nmr spectrum of it shows a doublet at δ = 1.33 ppm for two methyl groups of the isopropyl group, a heptuplet at δ = 3.30 for a proton of the isopropyl group with a coupling constant J = 6.5 Hz, a singlet at δ = 6.10 ppm for H_3, and a multiplet at δ = 7.03-7.81 ppm for H_5, H_6, H_7 and H_8. The chemical shift for H_3, which falls in the range δ = 5.90-6.40 ppm, characteristic for other coumarin derivatives[6,7], clearly indicates that isopropyl group is attached at position 4.

When the compounds 3 and 5 were treated with methanolic potassium hydroxide solution at room temperature, the cleavage of the pyran ring took place to produce isomeric methyl 3-(2-hydroxyphenyl)-5,5-dimethyl-4,5-dihydro-1H-pyrazole-4-carboxylate (8) and methyl 4-(2-hydroxyphenyl)-5,5-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxylate (9), respectively. On the other hand, when the compound 5 was treated with 2-diazopropane (2) in a mixture of methanol and diethyl ether, containing a catalytic amount of potassium hydroxide, a product was isolated for which the microanalytical data indicate to have a molecular formula $C_{16}H_{22}N_2O_3$. ^1H nmr spectrum of it shows two singlets, integrating each for 3H, at δ = 0.86 ppm and δ = 1.37 ppm for two methyl groups, a doublet integrating for 6H at δ = 1.35 ppm and a heptuplet integrating for one proton at δ = 4.50 ppm with the coupling constant J = 6.0 Hz for isopropyl



	R_1	R_2	R_3
11	$CHMe_2$	Me	H
12	H	$CHMe_2$	Me

SCHEME

group attached to a heteroatom, a singlet integrating for 3H at δ = 4.50, a broad singlet for 1H, exchangable with deuterium oxide, at δ = 5.76 ppm and a multiplet for four aromatic protons at δ = 6.59-7.30 ppm. On the basis of these data three structures, 10-12, can be proposed. An independent synthesis starting from methyl o-hydroxycinnamate (13) which was converted with 2-diazopropane (2) through the corresponding isopropoxy derivative 14 into indentical product showed, that the compound is methyl 4-(2-isopropoxyphenyl)-5,5-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxylate (10).

Oxidation of compounds 3 and 5 with bromine in acetic acid produced 3,3-dimethyl /1/benzopyrano/4,3-c/pyrazol-4(3H)-one (15), as a derivative of a novel heterocyclic system, and 1,1-dimethyl/1/benzopyrano/3,4-c/pyrazol-4(1H)-one (16) in 91% and 27% yield, respectively. The latter compound is identical with the compound obtained from 3-(4-methylphenylsulphinyl)-coumarin and 2-diazopropane (2) followed by elimination of sulphenic acid[1,2]. These two isomeric systems can be easily differentiated on the basis of the chemical shifts for H_9 in ^1H nmr spectrum. Namely, H_9 in the compound 15 appears as a multiplet at δ = 8.33-8.57 ppm, approximately for 0.5 ppm lower than H_9 in the isomeric system 16.

EXPERIMENTAL

3,3-Dimethyl-3a,9b-dihidro/1/benzopyrano/4,3-c/pyrazol-4(3H)-one (3) and 1,1-Dimethyl-2,9b-dihydro/1/benzopyrano/3,4-c/pyrazol-4(1H)-one (5). - To a solution of 1 (730 mg, 0.005 mole) in methylene chloride (20 ml) a solution of 2-diazopropane[8] prepared from acetone hydrazone (3 g) was added dropwise at -25°C. The mixture was left in refrigerator at -10°C until the starting coumarin was consumed (approx. 48 h). The volatile components were evaporated in vacuo to give the solid which was separated by flash chromatography (Kieselgel 60, 0.40 - 0.063 mm, E.Merck, 70 g). Elution with a mixture of benzene and diethyl ether (10:1), followed by evaporation of the solvent, gave 3 (444 mg, 41%), mp 116-119°C (from cyclohexane), nmr ($CDCl_3$) δ: 1.10(s, 3-Me), 1.77(s, 3-Me), 2.95(d, H_{3a}, J = 10.5 Hz), 6.08 (d, H_{9b}, J = 10.5 Hz), 6.87-7.37(m, H_6, H_7, H_8), 7.63-7.89(m, H_9). Anal.Calcd.for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.54; H, 5.62; N, 12.95. Further eluation with diethyl ether, followed by evaporation of the solvent in vacuo gave 5 (452 mg, 42%), mp 163-167°C (from a mixture of cyclohexane and ethanol),

nmr (DMSO-d_6) δ: 0.92(s, 1-Me), 1.71(s, 1-Me), 4.19(s, H_{9b}), 6.95-7.50(m, H_6, H_7, H_8, H_9), 8.82(br s, NH). Anal.Calcd.for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.91; H, 5.65; N, 12.94.

1,1-Dimethyl-1a,7b-dihydrocyclopropa/c//1/benzopyran-2-one (6). - A solution of 3 (216 mg, 0.001 mole) in xylene (5 ml) was heated under reflux (2 h). The solvent was evaporated in vacuo to give 6 (180 mg, 95 %), mp 72-74°C (sublimation, 100°C), nmr ($CDCl_3$) δ: 0.95(s, 1-Me), 1.58(s, 1-Me), 2.09(d, H_{7b}, J = 7.5 Hz), 2.55 (d, H_{1a}, J = 7.5 Hz), 6.79-7.50 (m, H_4, H_5, H_6, H_7). Anal.Calcd.for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.55.

4-Isopropylcoumarin (7). - A solution of 5 (216 mg, 0.001 mole) in N,N-dimethylformamide (3 ml) was heated under reflux (3 h). The product was separated by flash chromatography (Kieselgel 60, 0.040-0.063 mm, E.Merck, 20 g and a mixture of benzene/diethyl ether, 20:1 as solvent) to give 7 (104 mg, 55 %), bp 90°C (1 torr), nmr ($CDCl_3$) δ: 1.33(d, 4-CHMe_2, J = 6.7 Hz), 3.30(hept, 4-C$H$$Me_2$, J = 6.7 Hz), 6.30 (s, H_3), 7.03-7.81(m, H_5, H_6, H_7, H_8). Anal.Calcd.for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.62.

The same compound was obtained in essentially the same yield, when xylene was used instead of DMF.

Methyl 3-(2-Hydroxyphenyl)-5,5-dimethyl-4,5-dihydro-1H-pyrazole-4-carboxylate (8). - To a solution of 3 (216 mg, 0.001 mole) in methanol (20 ml) an aqueous solution of potassium hydroxide (1 %, 1 ml) was added and the mixture was left at room temperature (1 h). The solvent was evaporated in vacuo to give 8 (234 mg, 97 %), mp 111-113°C (from cyclohexane), nmr (DMSO-d_6) δ: 1.21(s, 5-Me), 1.29(s, 5-Me), 3.60 (s, 4-COOMe), 4.02(s, H_4), 6.65-7.26(m, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.31(br s, NH), 10.79 (s, 2'-OH). Anal.Calcd.for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49; N, 11.28. Found: C, 62.62; H, 6.50; N, 11.25.

Methyl 4-(2-Hydroxyphenyl)-5,5-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxylate (9). - To a solution of 5 (216 mg, 0.001 mole) in methanol (50 ml) a solution of aqueous potassium hydroxide (1 %, 1 ml) was added in one portion and, after 1 h, followed by evaporation of solvent in vacuo to give 9 (243 mg, 93 %), mp 153-157°C (from a mixture of n-heptane and ethyl acetate), nmr (DMSO-d_6) δ: 0.77 (s, 5-Me), 1.23 (s, 5-Me), 3.56(s, 3-COOMe), 4.22(s, H_4), 6.31-7.03(m, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 8.20(br s, NH). Anal.Calcd.for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49; N, 11.28. Found: C, 62.99; H, 6.57; N, 11.41.

Methyl 4-(2-Isopropoxyphenyl)-5,5-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxylate (10).- a) To a solution 5 (324 mg, 0.0015 mole in methanol (30 ml) a solution of 2-diazopropane (2)[8], prepared from 4.2 g of acetone hydrazone, was added. The reaction was finished after 10 min. The solvent was evaporated in vacuo to give 10 (174 mg, 40 %), mp 160-163°C (from cyclohexane), nmr ($CDCl_3$) δ: 0.86 (s, 5-Me), 1.35(d, $CHMe_2$, J = 6.0 Hz), 1.37(s, 5-Me), 3.68(s, 3-COOMe), 4.50(s, H_4), 4.50(hept, $CHMe_2$, J = 6.0 Hz), 5.76(br s, NH), 6.59-7.30(m, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$). Anal.Calcd.for $C_{15}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.64. Found: C, 66.28; H, 7.75; N, 9.76.

b) To a solution of methyl o-hydroxycinnamate (13; 178 mg, 1 mole) in a mixture of methylene chloride (60 ml) and ethanol (10 ml) a solution of 2-diazopropane (2)[8], prepared from 12 g of acetone hydrazone, was added and the mixture was left at room temperature (24 h). The solvent was evaporated in vacuo and the solid recrystallized from cyclohexane to give 10 (1.65 g, 57 %).

3,3-Dimethyl/1//benzopyrano/4,3-c/pyrazol-4(3H)-one (15). - To a solution of 3 (216 mg, 0.001 mole) in acetic acid (5 ml) a solution of bromine (160 mg) in acetic acid (2 ml) was added dropwise at room temperature. The mixture was after 5 min poured on crushed ice (20 g) and the solid formed was collected by filtration to give 15 (194 mg, 91 %), mp 156-160°C (from cyclohexane), nmr ($CDCl_3$) δ: 1.66 (s, 3,3-diMe), 7.13-8.00(m, H_6, H_7, H_8), 8.33-8.57(m, H_9). Anal.Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.07. Found: C, 67.11; H, 4.85; N, 12.96.

1,1-Dimethyl/1/benzopyrano/3,4-c/pyrazol-4(1H)-one (16). - To a suspension of 5 (195 mg, 0.0009 mole) in acetic acid (5 ml) a solution of bromine (130 mg) in acetic acid (2 ml) was added and the mixture was heated under reflux (5 min). Water (5 ml) was added in order to dissolve the precipitate formed during cooling and the clear solution was poured on crushed ice (20 g). The precipitate was collected by suction to give 16 (50 mg, 27 %), mp 234-238°C(from a mixture of cyclohexane and ethanol), lit[3] mp 240-241°C, nmr ($CDCl_3$, 60°C) δ: 1.77(s, 1,1-diMe), 7.19-7.91(m, H_6, H_7, H_8, H_9). Anal.Calcd.for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.11; N, 13.07. Found: C, 67.00; H, 4.85; N, 12.98.

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