Tetrahedron Vol. 44, No. 14, pp. 4527 to 4536, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + 00

REGIOCHEMISTRY OF THE CYCLOADDITIONS OF DIPHENYLNITRILIMINE TO COUMARIN, 3-ETHOXYCARBONYL AND 3-ACETYL COUMARINS. A REINVESTIGATION

Toufik FATHI, NGUYEN DINH AN, Gérard SCHMITT,
Ernest CERUTTI and Bernard LAUDE*

Laboratoire de Chimie Organique
Université de Franche-Comté - Besançon
La Bouloie, 16 route de Gray -25030 BESANCON Cedex - FRANCE

(*Received in Belgium* 29 *April* 1988)

Abstract - The cycloaddition reactions of diphenylnitrilimine to coumarin, 3-ethoxycarbonyl and 3-acetylcoumarins were studied. The observed regiochemistry of the reaction with the coumarin 4a was the same as the one suggested by other researchers. For the coumarins 4b and 4c bearing an electron withdrawing group at the 3-carbon atom, our results invalidate the previously reported regiochemistry. The presence of an electron-withdrawing group at the 3-C atom of coumarin derivatives reverses the regioselectivity of cycloaddition of diphenylnitrilimine to the dipolarophilic double-bond.

INTRODUCTION

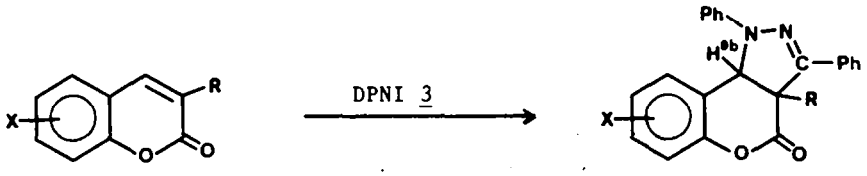
Coumarin derivatives are well known for their biological properties and many syntheses of the 4-oxo-1H-benzopyrano[4,3-c]pyrazole fused ring system 5 resulted from the cyclisation of the hydrazone derivatives 1 or 2[1-3].

Recently, SHAWALI and co-workers[4,5] described the 1,3-dipolar additions of diphenylnitrilimine 3 (DPNI) to coumarin 4a and some of its substituted derivatives 4b-f with the twofold objective of preparing compounds with biological activity and of studying the regiochemistry of the process.

These authors claimed that the regiochemistry of all the reactions is the same and suggested that cycloaddition would proceed "in such a manner that union occurs between C-4 of coumarins 4a-f and the terminal nitrogen atom of diphenylnitrilimine, and between C-3 of coumarins and the cationic carbon terminal of diphenylnitrilimine", thus leading to the cycloadducts 5.

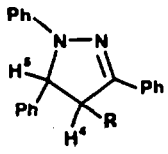
These results were established on the following bases :

- the identity of 5a with an authentic sample prepared by refluxing 3-benzoylcoumarin phenylhydrazone 1 in acetic acid (Scheme 2).



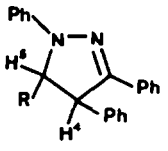
4 5 (assigned structure in ref.5)

a : X = R = H (δH^{9b} = 4.5 or 4.7 ppm)
b : X = H ; R = CO_2Et (δH^{9b} = 5.38 ppm)
c : X = H ; R = $COCH_3$ (δH^{9b} = 5.23 ppm)
d : X = H ; R = COPh (δH^{9b} = 5.35 ppm)
e : X = 6-CH_3 ; R = H (δH^{9b} = 4.45 or 4.75 ppm)
f : X = 7-OCH_3 ; R = H (δH^{9b} = 4.45 or 4.8 ppm)



(A)

R = CO_2Et [6]	R = $COCH_3$ [7]
δH^4 = 4.3 ppm	δH^4 = 4.18 ppm
δH^5 = 5.53 ppm	δH^5 = 5.42 ppm



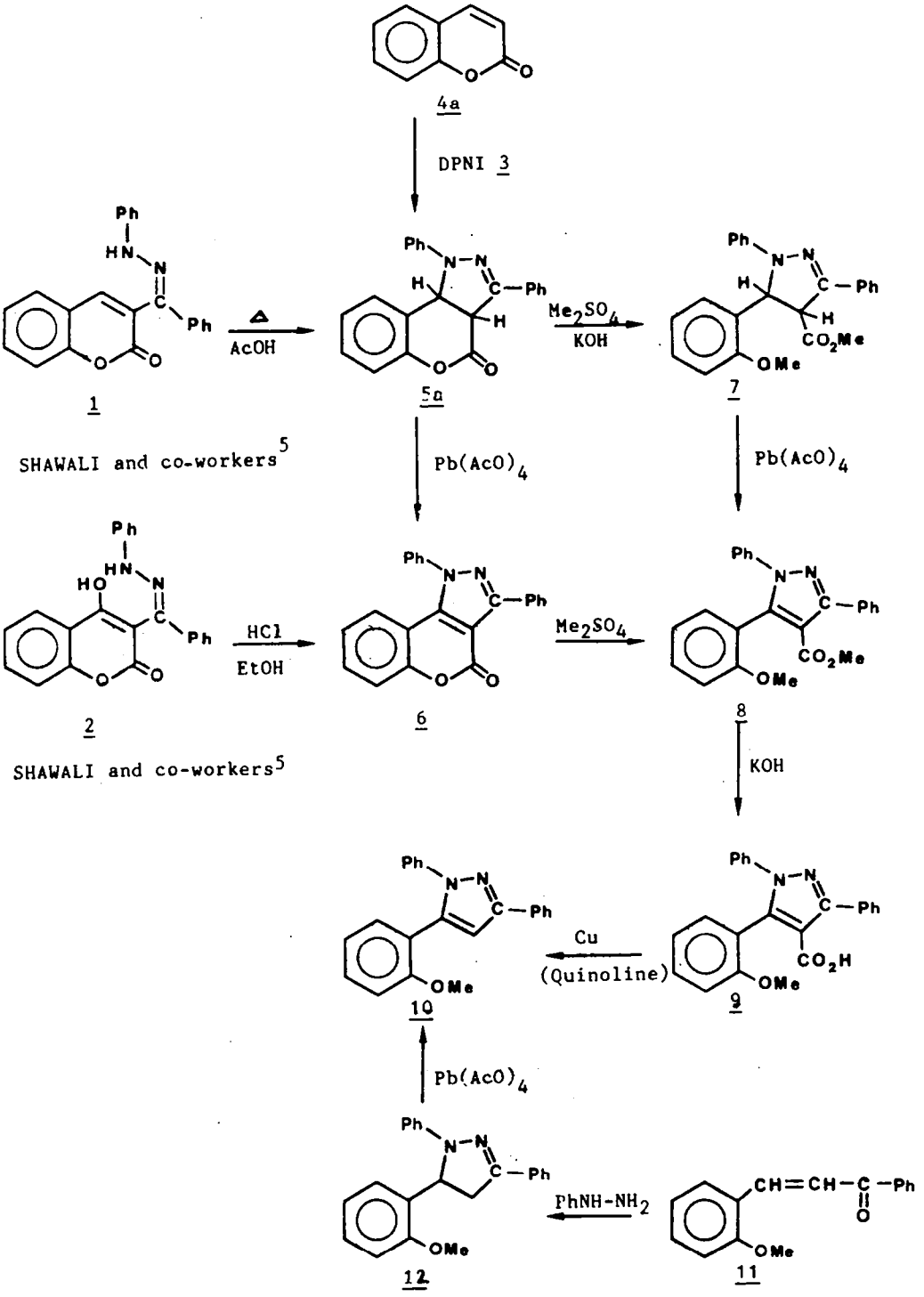
(B)

R = CO_2Et [6]	R = $COCH_3$ [7]
δH^4 = 4.65 ppm	δH^4 = 4.7 ppm
δH^5 = 4.82 ppm	δH^5 = 4.7 ppm

Scheme 1

- the assigned structures 5b-d were supported by analytical and spectral data (pmr and ir) : the regiochemistry of these cycloadducts was established by comparison of the chemical shifts of their 9b-protons with those of 4-CH and 5-CH of the related pyrazolines derivatives (A) and (B), obtained from diphenylnitrilimine and ethyl cinnamate [6] or α,β-unsaturated ketones [7]. The similarity between the chemical shifts of the 9b-proton of 5b-c and the 5-CH in the pyrazolines (A) would substantiate the regiochemistry of the cycloadducts 5b-c as suggested by SHAWALI and co-workers [5].

- finally, the proposed regioselectivity was rationalized in terms of the frontier molecular orbital (FMO) theory [8].


4a
DPNI 3
1
AcOH
5a
Me2SO4
KOH
7
SHAWALI and co-workers5
Pb(AcO)4
Pb(AcO)4
2
HCl
EtOH
6
Me2SO4
8
SHAWALI and co-workers5
KOH
Cu
(Quinoline)
10
9
Pb(AcO)4
PhNH-NH2
12
11

Scheme 2

In our opinion, this extension of the chemically demonstrated regiochemistry of 5a to the cycloadducts from the coumarins 4b-c substituted at C-3 by an electron withdrawing group, is doubtful :

- we already pointed out that the FMO theory did not always give results in good agreement with the experiment[9].

- the comparison with the pyrazolines (A) and (B) is unadvisable because the relative stereochemistry of H-4 and H-5 of these pyrazolines was not specified.

- finally, our previous results[10-12] show that the regiochemistry of cycloaddition of DPNI can be oriented by an ester group fixed on the C-atom of the dipolarophilic double-bond. In any case, the terminal nitrogen atom of DPNI is linked with the C-atom bearing the ester group.

On the basis of these arguments we reinvestigated the regiochemistry of the cycloaddition of DPNI to coumarins 4a-c.

RESULTS AND DISCUSSION

1. Cycloaddition of DPNI to coumarin 4a

The cycloaddition of diphenylnitrilimine 3 (prepared in situ from N-phenylbenzohydrazidoylchloride in benzene in the presence of triethylamine) to the coumarin 4a was carried out at 80°C for 4 hours. The sole product was found to be the cycloadduct 5a (Scheme 2) which can be dehydrogenated to pyrazole 6 by treatment with lead tetraacetate. Proof for the structures of 5a and 6 was obtained by SHAWALI and co-workers[5] from 1 and 2 respectively. We support the structure of 5a in transforming it into 5-orthomethoxyphenyl 1,3-diphenyl 4-methoxycarbonyl pyrazoline 7. Oxydation of this compound leads to the pyrazole 8 which was also obtained by reaction of 6 with dimethylsulfate.

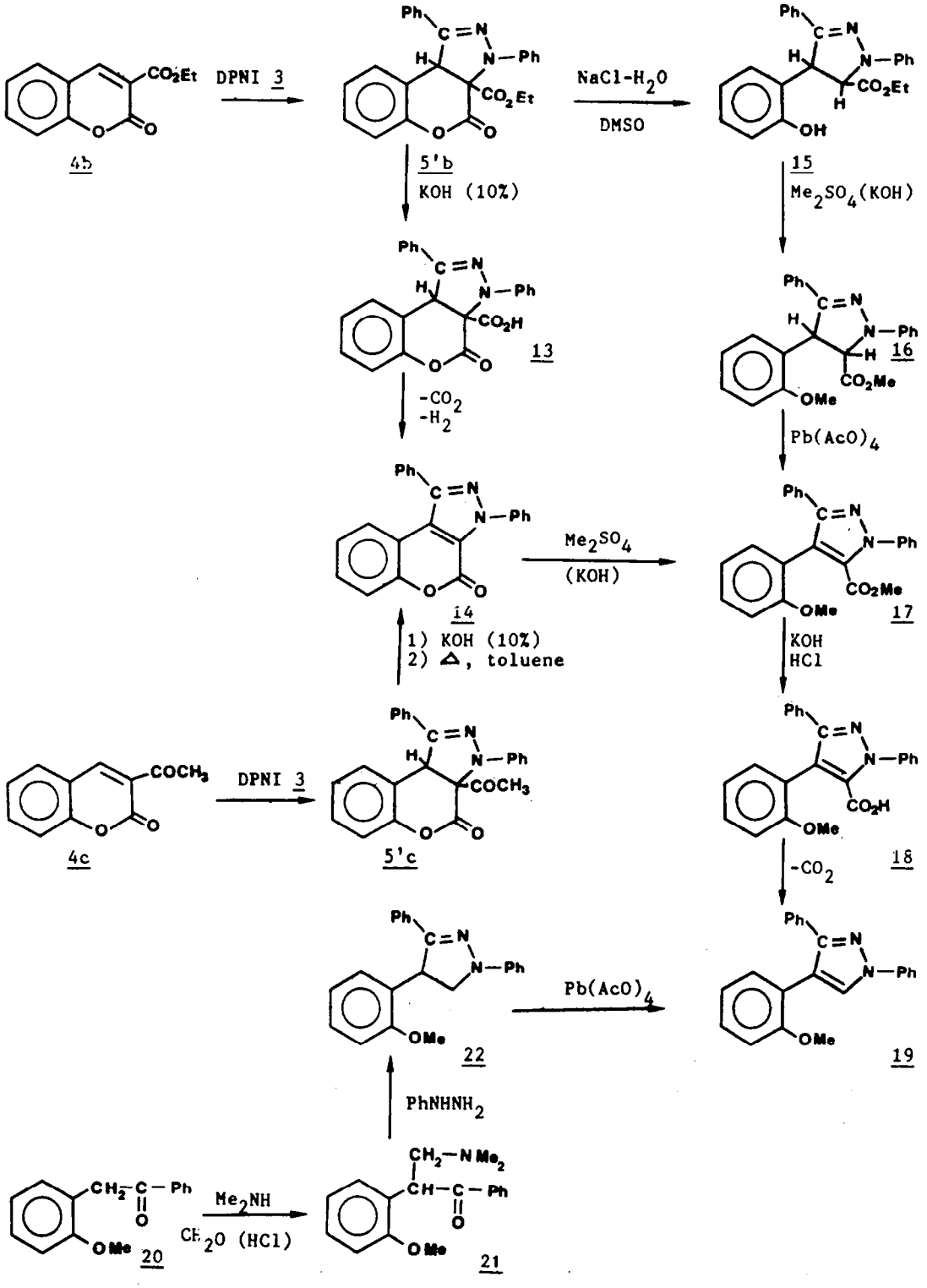
Saponification of the ester 8 gives the acid 9 which decarboxylates to 5-orthomethoxyphenyl 1,3-diphenyl pyrazole 10. The pmr spectrum of 10 shows a one proton singlet at 6.78 ppm, characteristic for a 4-CH proton of the pyrazole ring[13-15].

For further confirmation, the pyrazole 10 was independently prepared as follows : 1-Phenyl 3-orthomethoxyphenyl 1-propenone 11[16,17] was converted to its phenylhydrazone derivative followed by cyclization in refluxing acetic acid to give the pyrazoline 12, which was dehydrogenated to pyrazole 10 by treatment with lead tetraacetate. The cycloadduct 5a is identical with 3a,9b-dihydro-4-oxo-1H-benzopyrano[4,3-c]pyrazole.

This complementary proof of the regiochemistry of 5a may appear superfluous, but it will allow us to compare the pyrazole 10 with product 19 obtained by transforming the cycloadducts 5'b and 5'c issued from the reaction of DPNI with 3-ethoxycarbonyl coumarin 4b and 3-acetyl coumarin 4c.

2. Cycloaddition of DPNI to coumarins 4b and 4c

Following our previous experiments, the reactions of the coumarins 4b and 4c with N-phenylbenzohydrazidoyl chloride were studied in benzene in the presence of triethylamine in order to point out the effect of the presence of an electron withdrawing group at C-3 in coumarin derivatives on the regioselectivity of cycloaddition (Scheme 3).


4b
DPNI 3
5'b
KOH (10%)
NaCl-H2O
DMSO
15
Me2SO4(KOH)
13
-CO2
-H2
16
Pb(AcO)4
14
Me2SO4
(KOH)
17
1) KOH (10%)
2) Δ, toluene
KOH
HCl
4c
DPNI 3
5'c
18
-CO2
19
22
Pb(AcO)4
PhNHNH2
20
Me2NH
CH2O (HCl)
21

Scheme 3

Thus, the reactions afforded the cycloadducts 5'b and 5'c. The yields (65%) are better than those obtained by SHAWALI and co-workers[5]. The ^{13}C nmr spectra allow us to assign the chemical shifts of the C-3a and C-9b atoms (5'b : δC-3a = 75.25 ppm ; δC-9b = 53.31 ppm ; 5'c : δ C-3a = 79.81 ppm ; δ C-9b = 52.83 ppm). The high values of δ C-3a are inconsistent with the regiochemistry suggested by SHAWALI and co-workers[5] where the corresponding chemical shifts for δC-3a should be lower than 60 ppm[18].

Then, we carried out a chemical study of the cycloadducts 5'b and 5'c, where the target molecule is the pyrazole 19. The sequence from 5'b and 5'c to 19 is outlined in Scheme 3. Treatment of cycloadduct 5'b with an aqueous solution (10%) of potassium hydroxide gives the acid 13 whose decarboxylation is accompanied by dehydrogenation leading to 14. The same compound 14 was obtained by treatment of 5'c with an aqueous solution of potassium hydroxide, followed by heating the crude product in toluene. Methylation of 14 gives the substituted pyrazole 17, which can also be obtained differently from 5'b. Treatment of 5'b with a NaCl-H_2O-DMSO mixture according to KRAPCHO and LOVEY[19] yields the pyrazolinic ester 15 which was transesterified with dimethylsulfate to pyrazolinic methylester and ether 16. This compound was dehydrogenated to pyrazole 17.

Saponification of 17 leads to the acid 18 which decarboxylates to 4-orthomethoxyphenyl 1,3-diphenyl pyrazole 19, an isomer of 10.

The pmr spectrun of 19 exhibits a one proton singlet at 8.1 ppm, corresponding to a 5-CH of the pyrazole ring[13-15].

A comparison between the structures 10 and 19 rejects the regiochemistry suggested by SHAWALI and co-workers[5] for the cycloadducts from DPNI and the coumarins 4b and 4c. These cycloadducts 5'b and 5'c are in fact 3a,9b-dihydro-4-oxo-3H-benzopyrano[3,4-c]pyrazole derivatives.

For further confirmation, the pyrazole 19 was independently prepared as follows : the Mannich base 21, a precursor of an α,β-unsaturated ketone, was synthesized by an adaptation of the literature methods[20-23] starting from orthomethoxydesoxybenzoine 20[24,25]. By treating 21 with phenylhydrazine we obtained the pyrazoline 22 which can be dehydrogenated to give the target molecule 19.

We conclude that the presence of an electron withdrawing group at C-3 of coumarin reverses the regioselectivity of the cycloaddition reaction of DPNI. All the observations which we[10-12] and other researchers[7,26-30] recorded corroborate these results.

EXPERIMENTAL

Melting points (KOFLER Bank) are uncorrected. IR Spectra (KBr) were obtained on BECKMAN spectrophotometer model IR 33, NMR Spectra ($CDCl_3$) were recorded on a BRUKER-SPECTROSPIN AC-200 spectrometer. Chemical-shifts are given in ppm downfield from internal standard tetramethylsilane. Microanalyses were perfomed by the CNRS (Service d'Analyses, VERNAISON, France).

The DPNI 3 was prepared in-situ by a standard method[31]. Coumarin 4a was purchased from ALDRICH. Substituted coumarins 4b[32] 4c[33], chalcone 11[17] and desoxybenzoine 20[24,25] were prepared according to literature methods.

1. Cycloaddition reactions

General procedure : To a solution of coumarin or its derivatives (10 mmol) and N-phenylbenzohydrazidoyl chloride (2.3 g, 10 mmol) in benzene (50 ml) was added triethylamine (1 ml)

and the magnetically stirred mixture was refluxed for 4 hours and then cooled. The reaction mixture was filtered to remove the precipitated triethylamine hydrochlororide. The solvent was evaporated to give the crude product which was crystallized from ethanol.

1,3-diphenyl-3a,9b-dihydro-4-oxo-1H-benzopyrano[4,3-c]pyrazole 5a mp 179°C (lit.[5] : 175-6°C), 65% (lit.[5] : 65%).

IR (KBr) : ν(C=O) = 1735 cm^{-1}
PMR ($CDCl_3$) : δ = 4.45 ppm (d,1H,J=12Hz) H-3a ; 4.75 ppm (d,1H,J=12Hz) H-9b ; 6.8-8 ppm (m,14H).
^{13}C nmr (selected values) : δ C-3a = 48.28 ppm (d,J=141Hz) ; δ C-9b = 67.61 ppm (d,J=143Hz).

1,3-diphenyl-3a-ethoxycarbonyl -3a,9b-dihydro-4-oxo-3H-benzopyrano[3,4-c]pyrazole 5'b: mp 137°C (lit.[5] : 134-5°C), 65% (lit.[5] : 28%).

IR (KBr) : ν(C=O) = 1725 and 1745 cm^{-1}
PMR ($CDCl_3$) : δ = 1.1 ppm (t,3H,J=7Hz) ; 4.2 ppm (AB part of an ABX_3, 2H) ; 5.38 ppm (s,1H) H-9b ; 6.8-7.9 ppm (m,14H).
^{13}C nmr (selected values) : δ CH_3 = 13.4 ppm (q,J=133Hz) ; δ CH_2 = 62.96 ppm (t,J=146Hz) δ C-9b = 53.51 ppm (d,J=142.5Hz) ; δ C-3a = 75.25 ppm (s).

1,3-diphenyl-3a-acetyl-3a,9b-dihydro-4-oxo-3H-benzopyrano[3,4-c]pyrazole 5'c : mp 186°C (lit.[5] : 182-3°C), 65% (lit.[5] : 32%).

IR (KBr) : ν(C=O) = 1710 and 1770 cm^{-1}
PMR ($CDCl_3$) : δ = 2.34 ppm (1,3H) ; 5.23 ppm (s,1H) H-9b ; 6.9-7.9 ppm (m,14H)
^{13}C nmr (selected values) : δ CH_3 = 26.3 ppm (q,J=130Hz) ; δ C-9b = 52.83 ppm (d,J=141Hz) ; δ C-3a = 79.81 ppm (s).

2. Dehydrogenation reactions with lead tetracetate

General procedure : 7.5 mmol of $Pb(AcO)_4$ -preliminary washed with pentane- were added to a solution of 5 mmol of each product (5a, 7, 12, 16 or 22) in 10 ml of dichloromethane. The mixture was magnetically stirred at room temperature for 12 hours. The excess of lead tetracetate was destroyed with a little acetic acid and hydrazine hydrate. The solution was dried over anhydrous potassium carbonate, filtered and the solvent evaporated. The crude solid was then crystallized from ethanol (EtOH) or acetic acid (AcOH).

- Dehydrogenation of 5a gives 1,3-diphenyl-4-oxo-1H-benzopyrano[4,3-c]pyrazole 6 : AcOH, mp 258°C (lit.[5] : 232-3°C) ; 83% (lit.[5] : 60%) ; IR (KBr) : ν(C=O) = 1720 cm^{-1} ; PMR ($CDCl_3$) δ = 6.9-8.3 ppm (m,ar.H).

- Dehydrogenation of 7 yields 1,3-diphenyl-5-orthomethoxyphenyl-4-methoxycarbonyl pyrazole 8 : EtOH, mp 130°C, 80% ; IR (KBr) : ν(C=O) = 1710 cm^{-1} ; PMR ($CDCl_3$) : δ = 3.35 ppm (s,3H) OCH_3 ; 3.58 ppm (s,3H) OCH_3 ; 6.8-7.9 ppm (m,14H). Anal. Calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98 ; H, 5.24 ; N, 7.29. Found : C, 74.68 ; H, 5.32 ; N, 7,42%.

- Dehydrogenation of 12 yields 1,3-diphenyl-5-orthomethoxyphenyl pyrazole 10 : EtOH, mp 144°C ; 88% ; PMR ($CDCl_3$) : δ 3.36 ppm (s,3H) OCH_3 ; 6.8-8 ppm (m,14H) ; 6.78 ppm(s,1H) 4-CH. Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.95 ; H, 5.56 ; N, 8.58. Found : C, 81.03 ; H, 5.62 ; N, 8.42%.

- Dehydrogenation of 16 yields 1,3-diphenyl-4-orthomethoxyphenyl-5-methoxycarbonyl pyrazole 17 : EtOH, mp 170°C, 84% ; IR (KBr) : ν(C=O) = 1725 cm^{-1} ; PMR ($CDCl_3$) : δ 3.6 ppm (s,3H) OCH_3 ; 3.64 ppm (s,3H) OCH_3 ; 6.9-7.8 ppm (m,14H). Anal. Calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98 ; H,5.24 ; N,7.29. Found : C, 74.87 ; H, 5.37 ; N, 7.52%.

- dehydrogenation of 22 yields 1,3-diphenyl-4-orthomethoxyphenyl pyrazole 19 : EtOH, mp 96°C, 85% ; PMR ($CDCl_3$) ; δ = 3.36 ppm (s,3H) OCH_3 ; 6.8-7.9 ppm (m,14H) ; 8.1 ppm (s,1H) 5-CH. Anal. calcd. for $C_{22}H_{18}N_2O$: C, 80.95 ; H, 5.56 ; N, 8.58. Found : C, 81.22 ; H, 5.32 ; N,8.72%.

3. Methylation reactions with dimethylsulfate

General procedure : To a mechanically stirred and refluxing solution of 10 mmol of each compound (5a, 6, 14 or 15) in 20 ml of aqueous normal potassium hydroxide solution (with a little ethanol to complete the dissolution), we alternatively added dropwise 40 mmol of dimethylsulfate and 25 ml of aqueous normal potassium hydroxide solution. After these additions, the reflux was continued for one hour and the mixture was cooled and extrated with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate and filtered. Dichloromethane was evaporated and the residue crystallized from ethanol.

- Methylation of 5a yields 1,3-diphenyl-5-orthomethoxyphenyl-4-methoxycarbonyl pyrazoline 7 : mp 120°C, 76% ; IR (KBr) : ν(C=O) = 1735 cm^{-1} ; PMR ($CDCl_3$) : δ 3.75 ppm (s,3H, OCH_3) ; 3.95 ppm (s,3H) OCH_3 ; 4.15 ppm (d,1H,J=6.7Hz) 4-CH ; 5.9 ppm (d,1H,J=7Hz) 5-CH ; 6.75-7.9 ppm (m,14H). Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59 ; H, 5.74 ; N, 7.25. Found C, 74.46 ; H, 5.82 ; N, 7.42%.

- Methylation of 6 yields 1,3-diphenyl-5-orthomethoxyphenyl-4-methoxycarbonyl pyrazole 8 : mp 130°C, 65%.

- Methylation of 15 yields 1,3-diphenyl-4-orthomethoxyphenyl-5-methoxycarbonyl pyrazoline 16 : mp 64°C, 75% ; IR (KBr) : ν(C=O) = 1735 cm^{-1} ; PMR ($CDCl_3$) : δ = 3.75 ppm (s,3H) OCH_3 ; 3.9 ppm (s,3H) OCH_3 ; 4.65 (d,1H,J=4.7Hz) ; 5.3 ppm (d,1H,J=4.7Hz) ; 6.75-7.75 ppm (m,14H). Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59 ; H, 5.74 ; N, 7.25. Found : C, 74.72 ; H, 5.57 ; N, 7.37%.

- Methylation of 14 yields 1,3-diphenyl-4-orthomethoxyphenyl-5-methoxycarbonyl pyrazole 17 : mp 170°C, 80%.

4. Saponification of compounds 8 and 17 yields the acids 9 and 18 - Decarboxylation of the acids 9 and 18 to pyrazoles 10 and 19.

General procedure for the saponification reactions : 5 mmol of each ester 8 or 17 were dissolved in 20 ml of methanol, then 5 ml of methanolic solution of potassium hydroxide (2N) were added. After refluxing for 30 minutes, the reaction mixture was poured into 50 ml of cold water and acidified with HCl 2N. The crude solid was filtered, washed, dried and recrystallized from acetic acid. Yields are quantitative.

1,3-diphenyl-5-orthomethoxyphenyl pyrazole-4-carboxylic acid 9 : mp 140°C ; IR (KBr) : ν (C=O) = 1680 cm^{-1} ; ν(OH) = 2400-3400 cm^{-1} ; PMR ($CDCl_3$) : δ = 3.6 ppm (s,3H) OCH_3 ; 6 ppm (wide s,1H) OH ; 6.8-7.9 ppm (m,14H). Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.78 ; H, 4.9 ; N, 7.56. Found : C, 74,72 ; H, 4.87 ; N, 7.47%.

1,3-diphenyl-4-orthomethoxyphenyl pyrazole-5-carboxylic acid 18 : mp 191°C ; IR (KBr): ν (C=O) = 1700 cm^{-1} ; ν (OH) = 2400-3500 cm^{-1} ; PMR ($CDCl_3$);δ=3.5 ppm (s,3H) OCH_3 ; 6.9-7.7 (m, 15H, 14 arom. H and OH). Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58 ; H, 4.9 ; N, 7.56. Found : C, 74.82 H, 4.78 ; N, 7.63%.

General procedure for the decarboxylation : 2 mmol of each acid 9 or 18 were added to 15 ml of quinoline and 0.14 g of Cu powder. The magnetically stirred mixture was refluxed for 4 hours, then cooled and poured in 100 ml of HCl 1N. The solution was extracted with dichloromethane. The organic layer was washed and dried over anhydrous sodium sulfate and then filtered. The solvent was evaporated and the residue dissolved in a little chloroform. Filtration on silica gel (Merck 70-230 mesh) gives after evaporation of the solvent a solid residue which was recristallized from ethanol.

- Decarboxylation of 9 yields 10 : mp 144°C, yield 75%.

- Decarboxylation of 18 yields 19 : mp 96°C, yield 80%.

5. Saponification of the cycloadduct 5'b and decarboxylation of the acid 13

A suspension of 10 mmol of 5'b in 10 ml of an aqueous solution of potassium hydroxide (10%) was refluxed for 1 hour. The reaction mixture was cooled, poured into 150 ml of water and acidified with HCl N. The crude solid product was extracted with diethylether, the organic layer washed, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the residue crystallized from pentane to give 1,3-diphenyl-3a-4b-dihydro-4-oxo-3H-benzopyrano[3,4-c]pyrazole-3a-carboxylic acid 13 : mp 101°C, 80% ; IR (KBr) : ν(C=O) = 1710 and 1740 cm^{-1} . PMR ($CDCl_3$) : δ = 7-7.79 ppm (m). Anal. Calcd. for $C_{23}H_{16}N_2O_4$: C, 71.86 ; H, 4.19 ; N, 7.29. Found : C, 71.72 ; H, 4.27 N, 7.47%.

The decarboxylation of acid 13 was performed by heating to the melting point until gas evolution ceased. After cooling, the solid residue was recrystallized from acetic acid to give 1,3-diphenyl-4-oxo-3H-benzopyrano[3,4-c]pyrazole 14 : mp 248°C, 98% ; IR (KBr) : ν (C=O) = 1730 cm^{-1} PMR ($CDCl_3$) : δ 7.2-7.8 ppm (m). Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.1 ; H, 4.17 ; N, 8.28. Found : C, 78.22 ; H, 4.32 ; N, 8.47%.

6. Treatment of cycloadduct 5'b with a NaCl-H_2O-DMSO mixture

To a solution of 10 mmol of 5'b in 10 ml of DMSO, we added 10 mmol of NaCl and 0.6 ml of H_2O. The magnetically stirred mixture was heated up to 150°C under N_2 for 2 hours. After cooling, 0.5 ml of H_2O was added (under N_2) and stirring was continued for 0.5 hours. The mixture was extracted with ether and the extracts washed successively with water, aqueous sodium carbonate (10%), and water. After drying over anhydrous sodium sulfate, the solvent was evaporated. The oily residue was filtered on silica gel (Merck 70-230 mesh) with chloroform as eluant. Evaporation of the solvent gives an oil (yield 60%) which was directly submitted to methylation yielding the compound 16.

7. Treatment of cycloadduct 5'c by KOH followed by heating

A suspension of 10 mmol of 5'c in 10 ml of an aqueous solution of potassium hydroxide (10%) was refluxed for 1 hour. The reaction mixture was cooled, poured into 100 ml of water and acidified with HCl N. The crude solid product was filtered, washed and dissolved in 10 ml of toluene. This solution is refluxed for 2 hours. After cooling, a product crystallized from the toluene solution. It was filtered and recrystallized from acetic acid. The pure product had mp 248°C and was identifical in all respects (mp, mixed mp and spectra) with 14 (yield : 72%).

8. Synthesis of 1,3-diphenyl-5-orthomethoxyphenyl pyrazoline 12

A solution of 10 mmol of chalcone 11[17] in 20 ml of glacial acetic acid was added to 15 mmol of freshly distilled phenylhydrazine. The solution was refluxed for 6 hours and the product 12 crystallized on cooling. Recrystallized from ethanol, mp 134°C, 78% ; PMR ($CDCl_3$) : δ 3 ppm (dd, 1H,J=17Hz,J=12Hz) ; 3.85 ppm (dd,1H,J=17Hz,J=6.3Hz) ; 3.92 ppm (s,3H) OCH_3 ; 5.10 ppm (dd,1H,J=12Hz, J=6.3Hz) 5-CH ; 6.75-7.75 ppm (m,14H). Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46, H, 6.14 ; N, 8.53. Found : C, 80.57 ; H, 5.97 ; N, 8.59%.

9. Synthesis of 1,3-diphenyl-4-orthomethoxyphenyl pyrazoline 22

Mannich base 21 : To a solution of 13.3 moles of desoxybenzoine 20[25] in 20 ml ethanol, we added 13.3 mol of dimethylamine chlorhydrate, 2g of paraformaldehyde and 1 ml of HCl 12N. The magnetically stirred mixture was refluxed for one hour, and 1.2 g of paraformaldehyde were added and then refluxed for 20 hours. The solvent was evaporated and the residue added to water.

The mixture was extracted with diethylether, the organic layer washed with a saturated aqueous solution of sodium carbonate and dried over anhydrous sodium sulfate.

The solvent was evaporated and the crude oil obtained submitted to the reaction with phenylhydrazine without further purification. Yield 50% ; PMR ($CDCl_3$) : δ=2.3 ppm (s,6H) N $(CH_3)_2$; 2.44 ppm (dd,1H,J=12.4Hz,J=4.6Hz) ; 3.32 ppm (dd,1H,J=12.4Hz,J=8.9Hz) ; 3.94 ppm (s,3H) OCH_3 ; 5.37 ppm (dd,1H,J=8.9Hz,J=4.6Hz) ; 6.7-8.1 ppm (m,9H).

1,3-diphenyl-4-orthomethoxyphenyl pyrazoline 22 : the previous Mannich base 21 (5 mmol) was dissolved in 10 ml of ethanol with 6 mmol of freshly distilled phenylhydrazine and 1 ml of HCl 12N. After refluxing for 0.5 hour, the mixture was cooled and the solvent evaporated. The residue was extracted with dichloromethane, washed with water and dried over Na_2SO_4.

The solvent was evaporated and the solid residue recrystallized in ethanol : mp 105°C, 50% ; PMR ($CDCl_3$) δ = 3.89 ppm (s,3H) OCH_3 ; 3.82 ppm (dd,1H,J=9.9Hz,J=5Hz) ; 4.13 ppm (dd,1H, J=11.7Hz,J=9.9Hz) ; 5.14 ppm (dd,1H,J=11.7Hz,J=5Hz) ; 6.75-7.8 ppm (m,14H). Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46 ; H, 6.14 ; N, 8.53. Found : C, 80.37 ; H, 6.27 ; N, 8.47%.

REFERENCES

1 N.S. VULFSON and R.S. AHURIN, Zh. Obshch. Khim., 11, 3381 ; Chem. Abstr., 1962, 57, 4631.

2 A. MUSTAFA, O.H. HISMAT, A.A. NAWAR and D.M.A. KHALIL, Justus Liebigs, Ann. Chem.,1965, 684, 194.

3 B. CHANTEGRAL, A.I. NADI and S. GELIN, Tetrahedron Lett., 1983, 24, 381.

4 A.S. SHAWALI, B.A. ELTAWIL and H.A. ALBAR, Tetrahedron Lett., 1984, 25, 4139.

5 A.S. SHAWALI, B.A. ELANADOULI and H.A. ALBAR, Tetrahedron, 1985, 41, 1877.

6 T. UKITA, T. TAMURA, R. MATSUDA and KASHIWABARA, J. Expl. Med. Japan, 1949, 20, 109.

7 G. BIANCHI, R. GANDOLFI and C. DE MICHELI, J. Chem. Res.(S), 6 ; (M), 1981, 135.

8 K.N. HOUK, J. SIMS, C.R. WATTS and L.J. LUSKUS, J. Am. Chem. Soc., 1973, 95, 730.

9 B. LAUDE, M. SOUFIAOUI and J. ARRIAU, J. Heterocycl. Chem., 1977, 14, 1183.

10 K. TSHIAMALA, S. KITANE, J. VEBREL and B. LAUDE, Bull. Soc. Chim. Belg., 1986, 95 1083.

11 S. KITANE, K. TSHIAMALA, B. LAUDE, J. VEBREL and E. CERUTTI, Tetrahedron, 1985, 41, 3737.

12 F. HLIMI, K. TSHIAMALA, J. VEBREL and B. LAUDE, J. Chem. Res. (S), 1986, 266.

13 J. ELGUERO, R. JACQUIER and J.L. IMBACH, J. Chim. Phys., 1965, 62, 643.

14 J. ELGUERO, R. JACQUIER and G. TARRAGO, Bull. Soc. Chim. Fr., 1966, 2981.

15 L.G. TENSMEYER and C. AINSWORTH, J. Org. Chem., 1966, 31, 1878.

16 LE QUOC KHANH and B. LAUDE, C.R. Acad. Sci., 1973, 276, 109.

17 G.A. GOLBERG and J. AXBERG, Acta. Chem. Scand., 1963, 17, 967.

18 F.W. WEHRLI and T. WIRTHLIN, Interpretation of Carbon-13 nmr Spectra, Heyden and Son, New-York, 1976, p. 34.

19 A.P. KRAPCHO and A.J. LOVEY, Tetrahedron Lett., 1973, 957.

20 J.J. DENTON, R.J. TURNER, W.B. NEIER, V.A. LAWSON and H.P. SHEDL, J. Am. Chem. Soc., 1949, 71, 2048.

21 H.M.E. CARDWELL, J. Chem. Soc., 1950, 1056.

22 F. POPPELSDORF and S.J. HOLT, J. Chem. Soc., Perkin Trans.1, 1954, 1124.

23 H.O. HOUSE, D.J. REIF and R.L. WASSON, J. Am. Chem. Soc., 1957, 79, 2490.

24 A. SPETZ, Acta. Chem. Scand., 1956, 10, 1422.

25 C.E. SPIVAK and F.L. HARRIS, J. Org. Chem., 1972, 37, 2494.

[26] G. BIANCHI, C. DE MICHELI, R. GANDOLFI, P. GRUNANGER, P. VINTA FINZI and O. VASNA DE PAVA, J. Chem. Soc., Perkin Trans.1, 1973, 1148.

[27] M. CRISTL and R. HUISGEN, Chem. Ber., 1973, 106, 3345.

[28] R. HUISGEN, R. SUSTMANN and G. WALLBILLICH, Chem. Ber., 1967, 100, 1786.

[29] K.N. HOUK, Y.M. CHANG, R.M. STROZIER and P. CARAMELLA, Heterocycles, 1977, 7, 793.

[30] P. CARAMELLA and P. GRUNANGER, 1,3-Dipolar Cycloaddition Chemistry, edited by A. PADWA, J. Wiley and Sons, New-York, Vol.1, 1984, 291, and references cited therein.

[31] R. HUISGEN, M. SEIDEL, G. WALLBILLICH and M. KNUPFER, Tetrahedron, 1962, 17, 3.

[32] E.C. HORNING, M.G. HORNING and D.A. DIMING, Org. Synth., J. Wiley and Sons, New-York, Coll. Vol. 3, 1955, 715.

[33] K.N. TRIVEDI, J. Sci. Ind. Res., 1956, 18B, 308 ; Chem. Abstr., 1960, 54, 6708d.