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CYCLOADDITION OF DIPHENYLNITRILIMINE TO COUMARINS. THE SYNTHESIS OF 3a,9b-DIHYDRO-4-OXO-1H-BENZOPYRANO[4,3-c]PYRAZOLE DERIVATIVES[1]

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Abstract - The cycloaddition of diphenylnitrilimine to a series of coumarins occurs with the same regioselectivity in all cases, regardless the nature of the substituent present, to yield the corresponding 3a,9b-dihydro-4-oxo-1H-benzopyrano[4,3-c]pyrazoles 4a-f. Dehydrogenation of 4a yields 4-oxo-1H-benzopyrano[4,3-c]-pyrazole 6. In ethanolic sodium ethoxide solution, the reaction between coumarin and diphenylnitrilimine precursor, namely N-phenylbenzohydrazidoyl chloride 1, affords no cycloadducts, but yields o-(β-ethoxycarbonylvinyl)phenyl N-phenylbenzohydrazidate 10. The regiochemistry of the cycloadducts 4a-f and the reaction sequence leading to 10 are outlined. The structures of the products have been established by spectroscopic methods and independent syntheses wherever possible.

INTRODUCTION

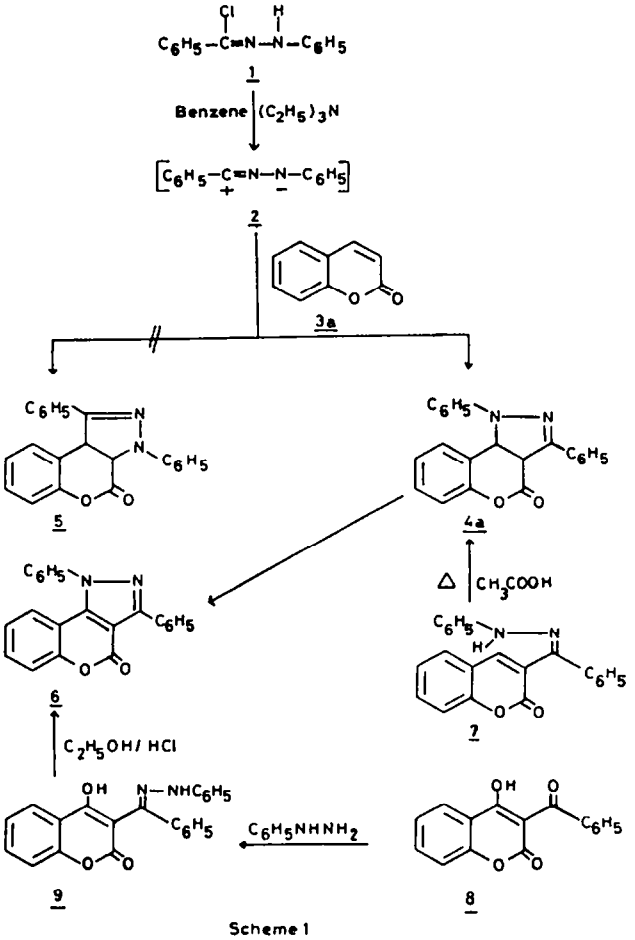
Previous syntheses of the 4-oxo-1H-benzopyrano[4,3-c]pyrazole fused ring system have employed the cyclization of the hydrazone derivatives of 3-acyl-4-hydroxycoumarins.[4-6] The other reported method involving the condensation of hydrazines with 3-acyl-4-chlorocoumarins[7] was recently shown to be an implausible one.[6] Furthermore, although diazoalkanes usually add to alkenes to give the corresponding pyrazoline derivatives, their reactions with coumarins were reported to give 4-alkylcoumarins.[8-12]

In the present study the title compounds have been synthesized by the 1,3-dipolar addition of diphenylnitrilimine to coumarin and some of its substituted derivatives with the two fold objective of preparing compounds with biological activity and of studying the regiochemistry of the process. The coumarin system was considered an attractive platform for this study because : (a) coumarin derivatives are well known for their biological properties, (b) being structurally related to styrene derivatives, the use of coumarins in 1,3-dipolar cycloadditions will shed some light on the effect of the presence of electron-donating and electron-withdrawing groups in direct conjugation with the dipolarophilic double bond on the regioselectivity in these reactions.

RESULTS and DISCUSSION

The cycloaddition of coumarin 3a to diphenylnitrilimine 2, prepared in situ from N-phenylbenzohydrazidoyl chloride 1 in benzene in the presence of triethylamine, was carried out at 80°C for 2 h. The sole product obtained was found to be the cycloadduct 4a (Scheme 1) The other regioisomer 5a was not identified in the reaction mixture as evidenced by TLC analysis. The product 4a can be dehydrogenated to pyrazole derivative 6 by treatment with chloranil in refluxing xylene (Scheme 1). Proof of the structures of 4a and 6 was obtained from their elemental analyses, spectral data (pmr and ir) (see Experimental), and their independent syntheses. On the basis of the coupling constant between 3a and 9b protons in 4a (J = 12 Hz), the latter cycloadduct was assigned the cis-configuration.[13,14]

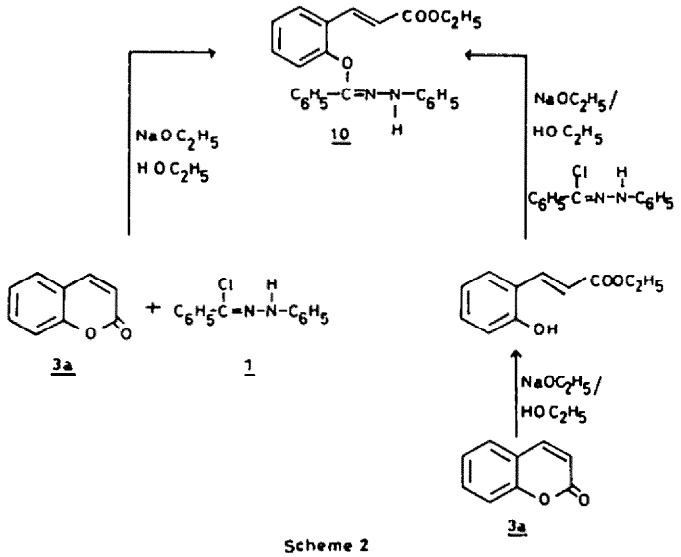
The regiochemistry of the cycloadduct 4a was established by its identity with an authentic sample prepared by refluxing 3-benzoylcoumarin phenylhydrazone 7 in acetic acid for 6 h (Scheme 1). To confirm it further, the dehydrogenation product 6 was independently prepared as follows. 3-Benzoyl-4-hydroxycoumarin 8[15] was converted to its phenylhydrazone derivative 9, followed by cyclization in ethanolic hydrogen chloride (Scheme 1).



Scheme 1

When the reaction of coumarin 3a with N-phenylbenzohydrazidoyl chloride 1 was carried out in ethanol in the presence of sodium ethoxide, the cycloadduct 4a was not obtained, the acyclic hydrazidate ester 10 was formed instead. The structure of the latter product follows its physical and spectral data (see Experimental). The sequence leading to 10 from 3a and 1 under these conditions is outlined in scheme 2

This sequence together with the structure of 10 were established by the alternate synthesis of the latter product from ethyl o-hydroxycinnamate[16] and 1 in ethanol in the presence of sodium ethoxide (Scheme 2). In the light of this finding, the reactions of other coumarins 3b-f with the hydrazidoyl chloride 1 were studied in benzene in the presence of triethylamine.

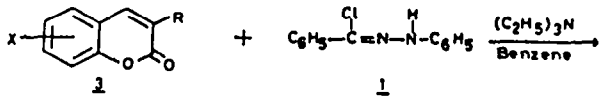


Scheme 2

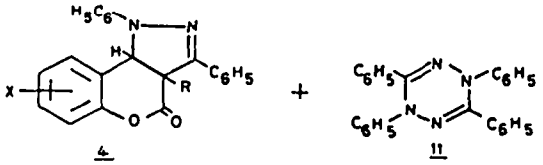
Thus, under such conditions, 6-methyl- and 7-methoxy-coumarins, 3b and 3c react readily with 1 and afford the cycloadducts 4b and 4c respectively (Scheme 3). In these cases, the dihydrotetrazine derivative 11 was identified in the reaction mixture as a by product. The latter is undoubtedly resulted from the dimerization of diphenylnitrilimine involved as an intermediate in these reactions.

Next, the reactions of 3-acetyl-, 3-benzoyl-, and 3-ethoxycarbonyl-coumarins 3d-f with 1 were examined in an attempt to investigate the effect of the presence of an electron withdrawing group at C3 in coumarin on the regioselectivity in cycloadditions. Thus, treatment of 3d with 1 in refluxing benzene in the presence of triethylamine afforded the cycloadduct 4d in 32% yield together with the dihydrotetrazine derivative 11 (60%) (Scheme 3). Similarly, compounds 3e and 3f react with 1 under similar conditions and yield the corresponding cycloadducts 4e and 4f but in lower yields (23% and 28%) respectively. The assigned structures 4d-f were supported by analytical and spectral data (pmr and ir) (see Experimental). 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 pyrazoline derivatives obtained from diphenylnitrilimine and ethyl cinnamate and α,β-unsaturated ketones[17] (Table 1). As shown in this table the similarity between the chemical shifts of the 9b-proton in 4d-f and the 5-CH in 4-ethoxycarbonyl- and 4-acetyl-substituted derivatives of 1,3,5-triphenylpyrazolines 13 and 15 respectively, substantiates the assigned regiochemistry of the cycloadducts 4d-f.

The regioselectivity observed in the studied reactions of coumarins 3a-f with diphenylnitrilimine can be rationalized in terms of the frontier molecular orbital (FMO) theory[18] as follows. The FMO energies[18] and coefficients[19] of diphenylnitrilimine are given in literature. The coefficients and energies of FMOs of coumarin 3a and its 3-substituted derivatives 3d-f are calculated in this work by the Huckel molecular orbital (HMO) method.[20] The results are summarized in Table 2. Taking the values of the Coulomb integral $\alpha = -10.5$ eV and the resonance integral $\beta = -3.8$ eV, the values of the energies of the highest occupied and the lowest unoccupied molecula



3 1



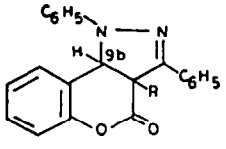
4 11

a, R = X = H
b, R = H, X = 6-CH_3
c, R = H, X = 7-CH_3O
d, R = CH_3CO, X = H
e, R = C_6H_5CO, X = H
f, R = C_2H_5OCO, X = H

Scheme 3

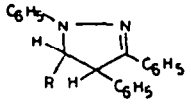
Table 1

4-Oxo-1H-benzopyrano[4,3-c]pyrazolines, 4d-f



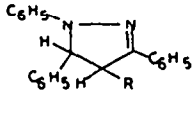
no	R	δH(9b), ppm
4d	CH_3CO	5.23
4e	C_6H_5CO	5.35
4f	C_2H_5OCO	5.38

1,3,4-Triphenyl-5-R-pyrazolines



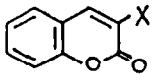
no	R	δ 4-CH	δ 5-CH	Ref.
12	C_2H_5OCO	4.65	4.82	15
13	CH_3CO	4.70	4.70	17

1,3,5-Triphenyl-4-R-pyrazolines

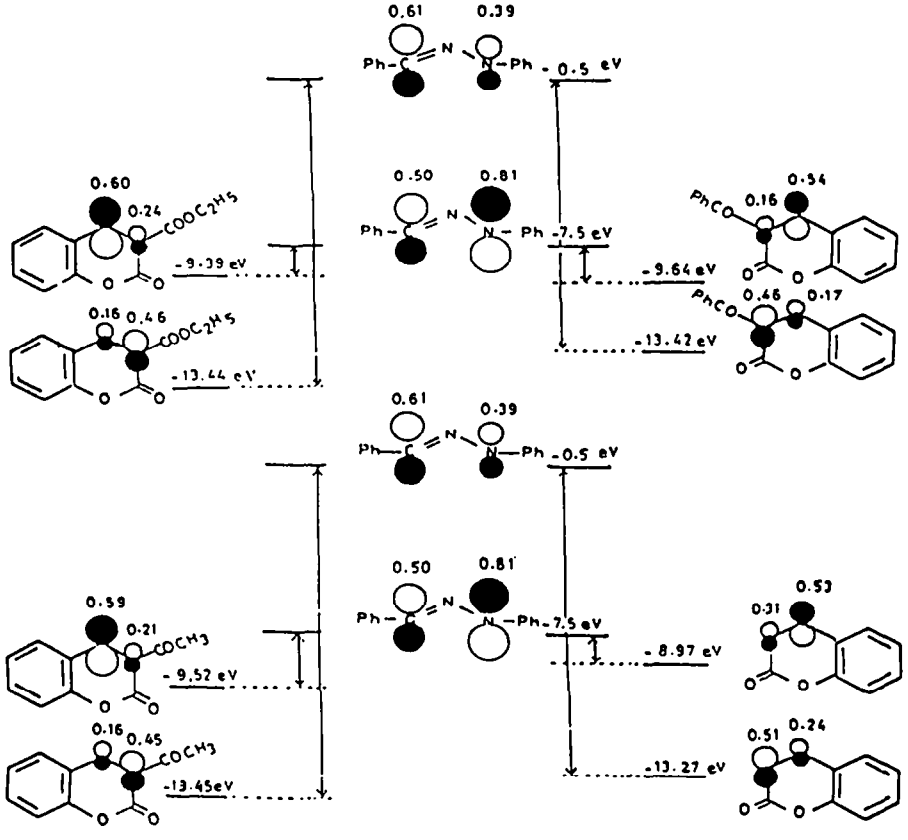


14	C_2H_5OCO	4.30	5.53	15
15	CH_3CO	4.18	5.42	17

Table 2. Orbital coefficients and energies of FMOs of coumarins.



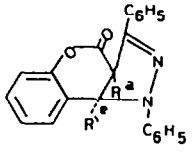
X	HOMO a_3	HOMO a_4	HOMO E	LUMO a_3	LUMO a_4	LUMO E
H	0.51	0.24	$\alpha + 0.728\beta$	0.31	-0.53	$\alpha - 0.401\beta$
$COCH_3$	0.45	0.16	$\alpha + 0.776\beta$	0.21	-0.59	$\alpha - 0.257\beta$
COC_6H_5	0.46	0.17	$\alpha + 0.768\beta$	0.16	-0.54	$\alpha - 0.227\beta$
$COOC_2H_5$	0.46	0.16	$\alpha + 0.773\beta$	0.24	-0.60	$\alpha - 0.291\beta$



Scheme 4. Interaction scheme of Diphenylnitrilimine (DPNI) with coumarin and some of its 3-substituted derivatives. The FMO energies and coefficients of DPNI are given in literature[18,19] and those of coumarins were estimated by HMO method.

orbitals of the coumarins studied will be as shown in scheme 4. As shown in this scheme, the energy difference ($E^{HO}_{DPNI} - E^{LU}_{coumarin}$) is less than ($E^{HO}_{coumarin} - E^{LU}_{DPNI}$), and accordingly the reactions are controlled by HOMO(DPNI) - LUMO(coumarin) interaction. Furthermore, the data in scheme 4 indicate that the largest and the smallest orbital coefficients in diphenylnitrilimine HOMO are on the terminal anionic nitrogen and the cationic carbon atoms, respectively. The LUMO of coumarin (or its 3-substituted derivative) has the largest and the smallest orbital coefficients at C4 and C3 respectively. Thus, according to the greatest energy gain principle, the cycloaddition will proceed in such a manner that union occurs between C4 of coumarins (3a-f) and the terminal nitrogen atom of diphenylnitrilimine, and between C3 of coumarins and the cationic carbon terminal of diphenylnitrilimine, leading thus to the observed regiochemical results.

It should be noted that the cycloadducts prepared may adopt either conformation 16 in which the group R' is pseudoequatorial, or conformation 17 in which the aryl group is pseudoequatorial. For the cycloadducts 4a-f, conformation 16 (where R = acyl or ester group, and R' = H) will be less favourable because it contains the equivalent of a 1,3-diaxial interaction between the pseudo-axial acyl (or ester) group and N-phenyl group.



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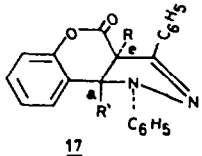

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EXPERIMENTAL

Melting points (Bockmonoscop unit) are uncorrected. IR spectra (KBr) were obtained on Zeiss Infrarot-spectrophotometer model IMT16, PMR spectra ($CDCl_3$) were recorded on a Varian EM-390-90 MHz spectrometer. Chemical shifts δ are given in ppm downfield from internal standard tetramethylsilane. Microanalyses were performed on Perkin Elmer elemental analyzer, model 240-B. Fluka AG silicagel G with 13% gypsum was used for TLC analysis.

The hydrazidoyl chloride 1[21] and substituted coumarins 3c[22], 3d[23], 3e[24] and 3[25] were prepared by standard methods. Coumarin 3a and its 6-methyl derivative 3b were purchased from BDH.

1,3-Diphenyl-3a,9b-dihydro-4-oxo-1H-benzopyrano[4,3-c]pyrazoles 4a-f. General Procedure - To a solution of coumarin or its derivative (5 mmol) and N-phenylbenzohydrazidoyl chloride 1 (1.15 g, 5 mmol) in benzene (50 ml) was added triethylamine (0.7 ml) and the mixture was refluxed for 2-3 h and then cooled. The reaction mixture was filtered to remove the precipitated triethylamine hydrochloride. The solvent was then evaporated to give the crude product. In some cases, chromatographic separation on silicagel preceeded crystallization of the product. In this way the following compounds were prepared.

Compound 4a had mp. 175-176°C (ethanol), 65%, IR (KBr) $\bar{\nu}$ 1735 (C=O), 1230 (lactone C-O-C) cm^{-1}; PMR ($CDCl_3$) δ 4.5 (d, 1H, J = 12 Hz), 4.7 (d, 1H, J = 12 Hz), 7.0-8.0 (m, 14H) ppm. Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.6 ; H, 4.7 ; N, 8.2 . Found : C, 77.6; H, 4.7 ; N, 8.4 %.

Compound 4b had mp. 174-175°C (ethanol), 35%; IR (KBr) $\bar{\nu}$ 1760 (CO), 1220 (lactone C-O-C) cm^{-1}; PMR ($CDCl_3$) δ 2.2 (s,3H), 4.45 (d, 1H, J = 12 Hz), 4.75 (d, 1H, J = 12 Hz), 6.8-8.0 (m, 13H) ppm. Anal. Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.9 ; H, 5.1 ; N, 7.9 . Found : C, 77.5; H, 5.0; N, 7.8 %.

Compound 4c had mp. 181-182°C (ethanol); 40%; IR (KBr) $\bar{\nu}$ 1745 (CO), 1630 (C=N), 1280 (C-O-C), 1230 (Ar-O-C) cm^{-1}; PMR ($CDCl_3$) δ 3.8 (s, 3H), 4.45 (d, 1H, J = 10 Hz), 4.8 (d, 1H, J = 10 Hz), 6.5-8.0 (m, 13H) ppm. Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.5; H, 4.9 ; N, 7.6 . Found : C, 74.4 ; H, 4.8 ; N, 7.7 %

Compound 4d had mp. 182-183°C (ethanol), 32%, IR (KBr) $\bar{\nu}$ 1770, 1710 (CO), 1618 (C=N), 1150 (lactone C-O-C) cm-1; PMR ($CDCl_3$) δ 2.3 (s, 3H), 5.23 (s, 1H), 6.9-7.9 (m, 14H) ppm. Anal. Calcd. for $C_{24}H_{18}N_2O_3$: C, 75.3 ; H, 4.7 ; N, 7.3 . Found : C, 75.2 ; H, 4.6 ; N, 7.3 %.

Compound 4e had mp. 180-181°C (ethanol), 23%; IR (KBr) $\bar{\nu}$ 1775, 1670 (C=O), 1230 (C-O-C) cm^{-1}; PMR ($CDCl_3$) δ 5.35 (s, 1H), 6.9-8.3 (m, 19H) ppm. Anal. Calcd. for $C_{29}H_{20}N_2O_3$: C, 78.4 ; H, 4.5 ; N, 6.3 . Found : C, 78.4 ; H, 4.5 ; N, 6.3 %.

Compound 4f had mp. 134-135°C (ethanol), 28%; IR (KBr) $\bar{\nu}$ 1750, 1730 (C=O), 1230, 1180 (C-O-C) cm^{-1}; PMR ($CDCl_3$) δ 1.15 (t, 3H, J= 7 Hz), 4.28 (q, 2H, J = 7 Hz), 5.38 (s, 1H), 6.8-7.9 (m, 14H) ppm. Anal. Calcd. for $C_{25}H_{20}N_2O_4$: C, 72.8 ; H, 4.9 ; N, 6.8 . Found : C, 72.7 ; H, 4.8 ; N, 6.9 %.

1,3-Diphenyl-4-oxo-1H-benzopyrano[4,3-c]pyrazole 6. Method A - A Mixture of 4a (0.18 g, 5 mmol) and chloranil (0.15 g, 6 mmol) in dry xylene (30 ml) was refluxed for 12 h during which all 4a disappeared as evidenced by TLC analysis using silicagel as adsorbent and benzene : ethyl acetate mixture (9.5 : 0.2, v/v) respectively as eluent. The reaction mixture was extracted with sodium hydroxide solution (5%) and the organic layer was collected, dried over anhydrous sodium sulfate, and then filtered. Xylene was evaporated and the oil residue solidified on cooling. The crude solid was collected and crystallized from ethanol-chloroform mixture to give 6 in 60% yield, mp. 232-233°C, IR (KBr) $\bar{\nu}$ 1730 (CO), 1615 (C=C), 1215 (C-O-C) cm^{-1}; PMR ($CDCl_3$) δ 6.9-8.5 (m, ArH) ppm. Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.1 ; H, 4.1 ; N, 8.3 . Found : C, 78.2 ; H, 4.2 ; N, 8.2 %.

Method B - A mixture of 3-benzoyl-4-hydroxycoumarin 8[15] (1.33 g, 5 mmol) and phenylhydrazine (0.6 g, 5.5 mmol) in ethanol (30 ml) was refluxed for 1 h and cooled. The precipitated hydrazone was collected and was added to 4% ethanolic hydrogen chloride. The mixture was refluxed for 8 h. After evaporation of the solvent, the solid residue was crystallized from ethanol-chloroform. The pure crystalline product had mp. 232°C and was identical in all respects (mp., mixed mp. and spectra) with 6.

Cyclization of 3-benzoylcoumarin phenylhydrazone - 3-Benzoylcoumarin phenylhydrazone (1.7 g, 5 mmol) was dissolved in acetic acid (30 ml) and the solution was refluxed for 8 h, then cooled. The mixture was poured on crushed ice with stirring. The precipitated solid was collected and dried. Crystallization from ethanol gave a product identical in all respects (mp., mixed mp., and spectra) with 4a.

Preparation of the hydrazidate ester 10. Method A - To an ethanolic sodium ethoxide solution (prepared by dissolving sodium metal (0.115 g, 5 mmol) in absolute ethanol (50 ml) was added coumarin 3a (0.73 g, 5 mmol) and the mixture was heated on water bath to effect dissolution of coumarin. To the resulting hot yellow solution was added the chloride 1 (1.15 g, 5 mmol) and the mixture was refluxed for 3 h and then cooled. TLC analysis using silicagel as adsorbent and the solvent system : toluene, ethyl acetate and acetic acid in the ratio 24 : 8 : 1 (v/v) respectively as eluent indicated the presence of two major products. The first of these was identified as 1,3,4,6-tetraphenyl-1,4-dihydrotetrazine 11, mp. 203°C (acetic acid) (Lit. mp. 203-204°C)[26], mixed mp. with an authentic sample prepared from thermolysis of 2,5-diphenyltetrazole[26] showed no depression.

The second product had mp. 140-141°C (methanol) and was identified as o-(β-ethoxycarbonylvinyl)phenyl N-phenylbenzohydrazidate 10, 55%, IR (KBr) $\bar{\nu}$ 3320 (NH), 1695 (CO), 1630 (C=C) or (C=N), 1245, 1260 (C-O-C) cm^{-1}; PMR ($CDCl_3$) δ 1.3 (t, 3H, J = 7 Hz), 4.3 (q, 2H, J = 7 Hz), 6.9-7.9 (m, 15H) ppm. Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.6 ; H, 5.7 ; N, 7.2 . Found : C, 74.3 ; H, 5.5 ; N, 7.0 %.

Method B - Ethyl o-hydroxycinnamate (0.384 g, 2 mmol), prepared from coumarin 3a and sodium ethoxide in ethanol[16], was added to an ethanolic sodium ethoxide solution, prepared from sodium metal (0.047 g, 2 mmol) and absolute ethanol (40 ml). To the stirred mixture was added the chloride 1 (0.461 g, 2 mmol) and the mixture was refluxed for 1 h and left at room temperature overnight, then filtered. Work up of the reaction mixture as above in method A, yielded 65% of the ester 10, identical in all respects (mp., mixed mp., spectra) with the product obtained by method A.

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