The Reaction of Coumarin Derivatives with Nucleophilic Reagents

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Summary: Coumarin-3N-(4-bromo-2-aroylphenyl) carboxamides (II and III) have been prepared from (I) by Friedel-Crafts reaction. Also, the reaction of 3-cyanocoumarin with Grignard reagents was reported.

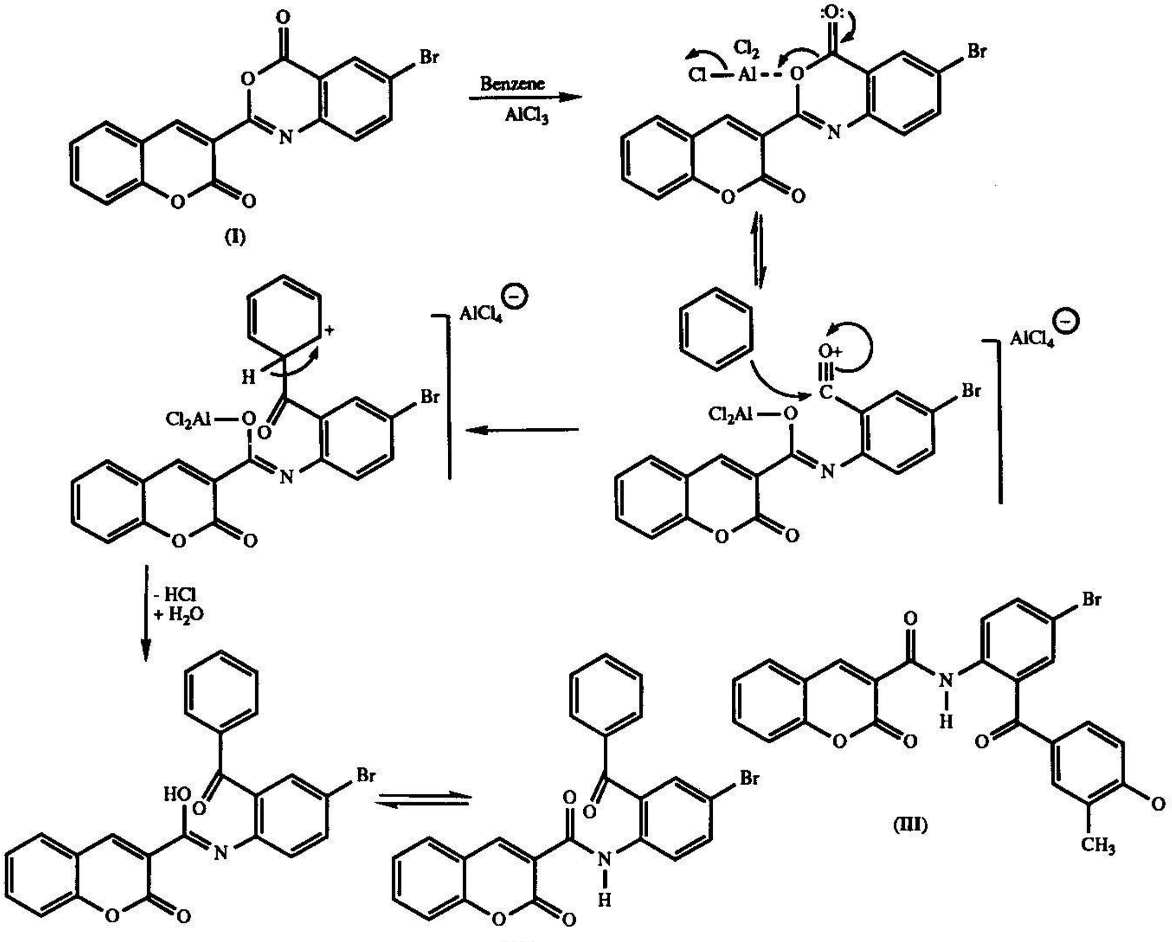
Introduction

Previously Abdalla *et al.*, [1] reported that the reaction of 3-(3,1-benzoxazine-4-one-2-yl) coumarin compounds with aromatic hydrocarbons under Friedel Crafts conditions gave 3-(*o*-aroylphenyl)-3,4-dihydro) coumarin carboxamide derivatives, since hydrogen transfer took place to the C_3-C_4 double bond in the coumarin nucleus. This foundation prompted us for further investigation of such anomalous behaviour. Thus the reaction of (I) [2] with benzene in the presence of anhydrous $AlCl_3$ under Fridel-Crafts reaction condition, gave coumarin-3N-(4-bromo-2-benzoyl-phenyl) carboxamide (II), Scheme 1. IR spectrum for (II) showed νCO at 1721, νAr-H at 3020 and νNH at 3140 cm^{-1}. ^{1}H-NMR spectrum showed the aromatic protons and N-H proton appears as a set of multiplet signals at δ 7.1-8.4. The olefinic proton of the coumarin nucleus resonated as a singlet at 8.8 ppm. The formation of (II) takes place according to the Scheme 1. The reactive electrophile in the Friedel-Crafts reaction is the resonance - stabilized acylium ion which is generated by the reaction of benzoxazone ring and $AlCl_3$.

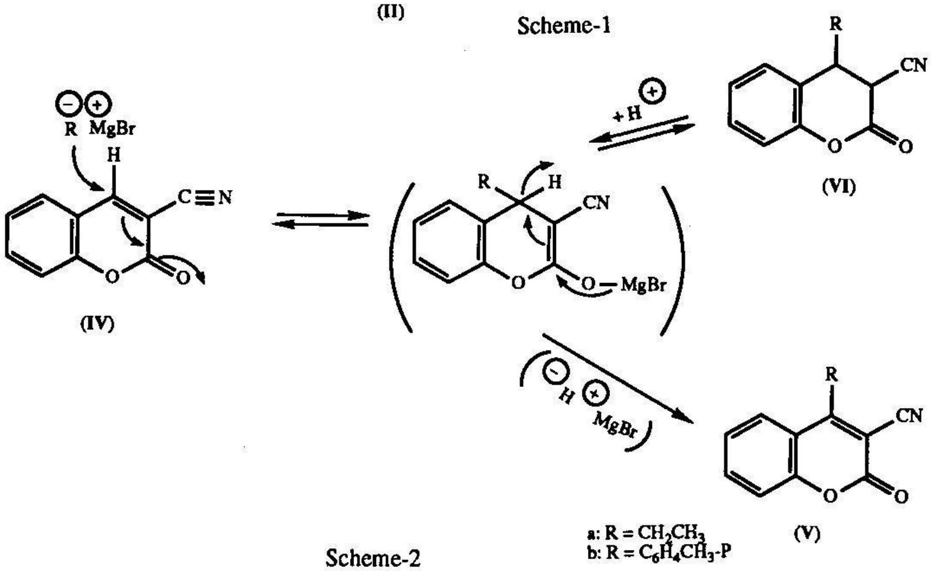
Treatment of (I) with toulene in the presence of anhydrous $AlCl_3$ gave a product (III) which was analyzed for a compound with molecular formula $C_{23}H_{18}BrNO_4$. IR spectrum for this product (III) showed νCO at 1721. Ar-C-H at 3000, νC-H aliphatic at 2875 and NH at 3167 cm^{-1}. ^{1}H- NMR for (III) showed two sharp singlet at δ 2.4 and 2.5, which are assignable for two methyl protons in the phenyl ring (xylene ring), the aromatic protons showed a multiplet at 7.4-8.3, the olefinic proton in the 4- position of the pyran moiety appear as a singlet at 8.8 and a singlet at 11.4 ppm for -CONH- which disappeared with D_2O shake. From the above data, it was decided that the product (III) is formulated as coumarin - 3N[2-(3,4-dimethylbenzoyl-4-bromo)phenyl]carboxamide, which was explained on the basis of Friedel-Crafts acylation beside the disproportionation of tolyl group into 3,4-dimethyl phenyl group under the reaction condition employed. From the above results, we concluded that benzene and toluene reacted with 3-[6-bromo-3,1-benzoxazine-4-one)-2-yl] coumarin (I) under Friedel - Crafts reaction condition without hydrogen transfer reported previously C_3-C_4 double bond in pyrone nucleus, which remained intact.

As we reported before [3], the reaction of Grignard reagents on 3-cyano-4-methylcoumarin and 3-cyano-5,6 benzocoumarin gave 1,4-addition at the pyran moiety followed by 1,2-addition on the cyano group. We decided to investigate the behaviour of 3-cyano coumarin (IV) toward ethyl and *p*-tolyl Grignard reagents. Thus treatment of (IV) with ethereal solution containing ethyl magnesium iodide and after decomposition gave a product which was identified as 3-cyano-4-ethyl coumarin (Va), scheme 2. The proposed structure was confirmed by correct elemental analysis. IR spectrum showed νCO at 1720, CN at 2250 cm^{-1} and ^{1}H- NMR spectrum (60 MHz, DMSO d_6) gave three absorption signals (ratio 3:2:4) at δ 1.5 (3H, t, J = 12 Hz, CH_3), 3.28 (2H, q, J = 12Hz, CH_2) and 7.4-8.1 (4H, m, Ar-H).

Interaction of 3-cyanocoumarin (IV) with excess of *p*-tolymagnesium bromide in dry benzene furnished a single product (Vb). Elemental analysis of this product (Vb) indicates that one mole of the Grignard reagent was consumed, IR showed νCO at 1710 and CN at 2140 cm^{-1}. ^{1}H-NMR for (Vb) showed two signals (ratio 3:8) which is corresponding to methyl protons and aromatic protons at δ 2.55 and 7.5-8.5 ppm. From ^{1}H-NMR spectra for compounds (Va and b), showed the absence of absorption signals of the protons at 3,4-positions for the expected product 3-



Scheme-1



Scheme-2

Table 1

Comp.	m.p. °C	Solvent of cryst	Yield %	Analysis Formula M.wt.	Required Found C	H	N
(II)	360	ACOH	65	$C_{23}H_{14}BrNO_4$	61.74	3.13	3.13
				(447)	61.50	2.90	3.00
(III)	185	ACOH	75	$C_{25}H_{18}BrNO_4$	63.16	3.79	2.95
				(475)	62.80	3.60	2.80
(Va)	136	EtOH	73	$C_{12}H_9NO_2$	72.36	4.51	7.06
				(199)	71.10	4.20	6.80
(Vb)	141	pet.ether	79	$C_{17}H_{11}NO_2$	78.16	4.21	5.36
		(60-80)		(261)	78.00	4.10	5.20

cyano-4-substituted 3,4-dihydrocoumarin (VI). Also, these spectra showed the absence of the absorption signal for the methine proton (H_4) of the pyran ring for the starting material (IV) at 8.9 ppm. Hence, on the basis of the above studies, the formation of (Va and b) took place as shown in scheme 2 through 1,4-addition leaving the cyano group intact followed by 1,4-elimination of HMgBr [2].

Experimental

All melting points are not corrected. IR spectra were measured on Perkin Elmer and Pye-Unicam spectrophotometer using KBr technique. ^{1}H-NMR spectra were measured on Varian EM-360-60 MHz at Department of Chemistry, Al-Azhar University.

Synthesis of coumarin-3N-(4-bromo-2-benzoyl-phenyl) carboxamide and its derivative (I and II)

A suspension of (I) in benzene or toluene (50 ml) was added with stirring to a cold suspension of anhydrous $AlCl_3$ (9.5 g) in benzene or toluene (50 ml). The reaction mixture was stirred for 1 hr at room temperature, then for 3 hrs at 100°C and then decomposed with dilute HCl (250 ml). The organic layer was evaporated, the products separated and recrystallized to give (II and III), Table 1.

Reaction of Grignard reagents with 3-cyanocoumarin (IV)

Ethylmagnesium iodide or p-tolyl magnesium bromide (0.03 mole) in dry ether (50 ml) was added to a solution of 3-cyanocoumarin (IV) (0.01 mole) in dry ether (50 ml). The reaction mixture was heated under reflux for 2 hr followed by decomposition with dilute H_2SO_4. The organic layer was separated and evaporated and the product formed was recrystallized from the proper solvent to give (Va and b), Table 1.

References

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