

Michael Additions using 2-[2-(3-Chloro-4-Methylbenzoyl-vinyl)]-4H-3-p-Tolylquinazolin-4-one

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Summary: The reaction of 2-[2-(3-chloro-4-methylbenzoylvinyl)]-4H-3-p-tolyl-quinazolin-4-one (I) with compounds containing active methylene group under Michael conditions gave addition or cyclic products depending on the nature of the active methylene compounds or the reactions conditions.

Recently [1], it has been reported that the reaction of 2-phenyl-3,1,4-benzoxazine with active methylene compounds in pyridine led to ring opening of the benzoxazine ring.

In the present investigation, we have investigated the reaction of the quinazolinone I with active methylene compounds under Michael conditions, and have found that the product depends upon the nature of the reactants and the reaction conditions.

The quinazoline ring is not opened under Michael conditions, and the active methylene compounds add easily to the α , β -unsaturated system in the side chain.

Thus, reaction of I with such active methylene compounds as diethyl malonate, cyclohexanone, ethyl benzoylacetate, ethyl cyanoacetate and acetylacetone in the presence of aqueous KOH led to addition to the double bond giving the corresponding Michael addition adducts II a-f [2-4].

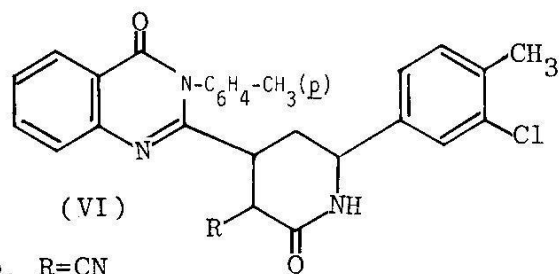
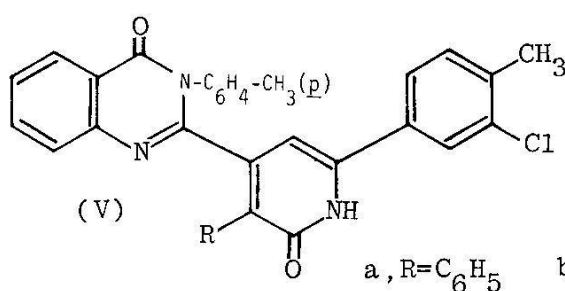
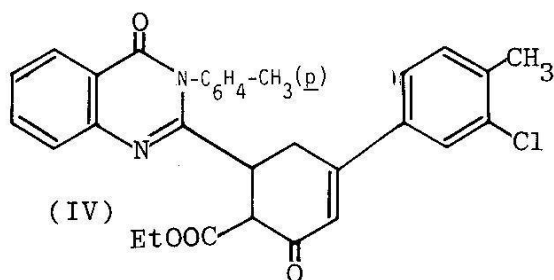
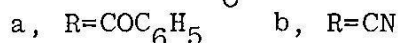
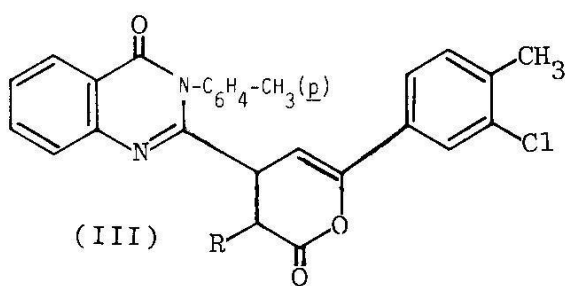
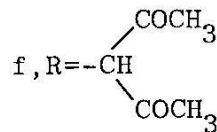
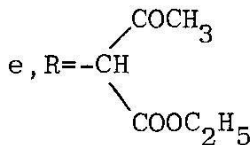
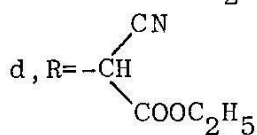
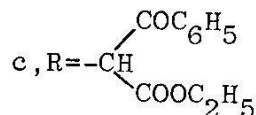
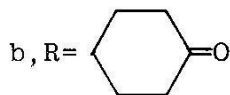
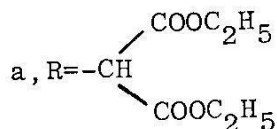
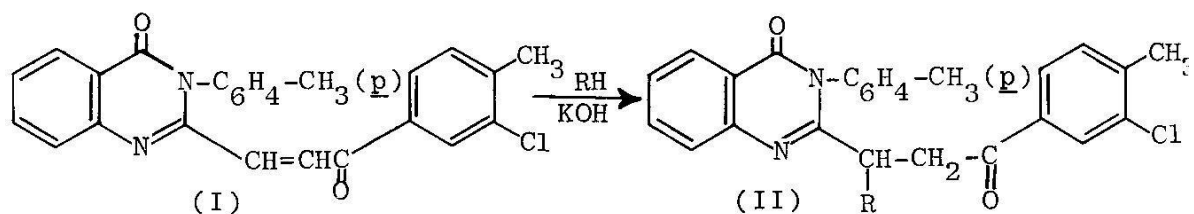
As a point of interest, the fusion of a mixture of I, diethyl malonate or cyclohexanone and sodium methoxide at 150-160°C afforded addition products II a and b respectively.

On the other hand, the fusion of I with ethyl benzoylacetate or ethyl cyanoacetate and sodium methoxide at 150-170°C under Michael conditions provided the corresponding pyrone derivatives III a and b via II c and d as intermediates followed by loss of a molecule of ethanol. Compounds III a and b are derived from ring closure of II c and d.

It is worth pointing out that the fusion of I with ethyl acetoacetate under the same conditions led to formation of the corresponding cyclohexenone derivative [5] IV again through the intermediacy of II, followed by loss of one molecule of water. Compound IV can be obtained alternatively via ring closure of II a.

Recently, the synthesis of pyridone derivatives by the condensation of ethyl cyanoacetate with unsaturated ketones in the presence of excess ammonium acetate has been reported [6,7].

The present work investigated the reaction of ethyl benzoylacetate and ethyl acetoacetate with I in the presence of excess ammonium acetate. The condensation was carried out by heating a mixture of active methylene



compound with I and ammonium acetate (molar ratio 1:I:0.8) at 150-170°C for 6-8 h. the product of condensation proved to be the corresponding pyridone V and hexahydropyridone derivative VI, respectively.

Experimental

The infrared absorption spectra were determined with a Unicam SP 1200 Spectrophotometer using the KBr Wafer technique and the values are listed

with other physical data in Table 1. The NMR spectra were obtained by using a Varian A - 90 Spectrophotometer and are given in Table 2. All melting points are not corrected.

Reaction of I with active methylene compounds

A) In aqueous KOH. Formation of IIa-f
A mixture of I (0.01 mole), active methylene compound, namely diethyl

Table-1: The physical properties and infrared spectra of new compounds

Compound	m.p. °C	Solvent *	Yield %	Formula (M.Wt.)		Analysis %		Group frequencies (KBr, cm ⁻¹)		
						Found	Required			
IIa	200	P	75	C ₃₂ H ₃₁ O ₆ N ₂ Cl (574.5)	C	66.47	66.84	ν C=O (ketone) 1710 ν C=N 1630	ν C=O (ester) 1710 ν C=C 1590	ν C=O (aroyl) 1710 1690 ν CH ₂ ² 2980
					H	5.16	5.39			
					N	4.52	4.87			
					Cl	6.19	6.17			
IIb	205	P	68	C ₃₁ H ₂₉ O ₃ N ₂ Cl (512.5)	C	72.21	72.58	ν C=O 1730 ν C=N 1620	ν C=O 1700 ν C=C 1600	ν C=O 1680 ν CH ₂ 2940, 2830
					H	5.56	5.65			
					N	5.24	5.46			
					Cl	6.87	6.92			
IIc	160	P/B	65	C ₃₆ H ₃₁ O ₅ N ₂ Cl (606.5)	C	70.87	71.22	ν C=O 1725 ν C=N 1620	ν C=O 1710 ν C=C 1580	ν C=O 1660 ν CH ₂ 2940
					H	5.18	5.11			
					N	4.52	4.61			
					Cl	5.66	5.85			
IIId	214	B	72	C ₃₀ H ₂₆ O ₄ N ₃ Cl (527.5)	C	67.91	68.24	ν C=O 1715 ν C=N 1630	ν C=O 1690 ν C=N 2220	ν C=O 1670 ν CH ₂ 2940
					H	4.62	4.92			
					N	7.83	7.96			
					Cl	6.41	6.72			
IIe	190	B	77	C ₃₁ H ₂₉ O ₅ N ₂ Cl (544.5)	C	68.20	68.31	ν C=O 1720 ν C=N 1635	ν C=O 1700 ν C=N 1600	ν C=O 1680 ν CH ₂ 2960, 2920
					H	5.36	5.32			
					N	4.87	5.14			
					Cl	6.43	6.51			
IIIf	201	B	64	C ₃₀ H ₂₇ O ₄ N ₂ Cl (514.5)	C	69.71	69.97	ν C=O 1725 ν C=N 1640	ν C=O 1700 ν C=N 1590	ν C=O 1670 ν CH ₂ 2930 ^c
					H	5.11	5.24			
					N	5.05	5.44			
					Cl	6.38	6.89			
IIIa	185	B	60	C ₃₄ H ₂₅ O ₄ N ₂ Cl (560.5)	C	73.11	72.79	ν C=O 1710 ν C=N 1650	ν C=O 1690 ν C=C 1600	ν C=O 1680
					H	4.23	4.46			
					N	4.64	4.99			
IIIb	192	P	60	C ₂₈ H ₂₀ O ₃ N ₃ Cl (481.5)	C	69.34	69.78	ν C=O 1700 ν C=C 1600	ν C=O 1680 ν C=N 2205	ν C=N 1650
					H	4.10	4.15			
					N	8.55	8.72			
					Cl	7.18	7.37			
IV	208	B	64	C ₃₁ H ₂₇ O ₄ N ₂ Cl (526.5)	C	70.76	70.65	ν C=O 1720 ν C=C 1590	ν C=O 1670 ν CH ₂ 2960 ²	ν C=N 1625
					H	5.15	5.12			
					N	5.21	5.31			
Va	140	P	39	C ₃₃ H ₂₄ O ₂ N ₃ Cl (529.5)	C	74.40	74.78	ν C=O 1730 ν C=C 1600	ν C=O 1680 ν NH 3300, 3200	ν C=N 1640
					H	4.32	4.53			
					N	7.68	7.93			
					Cl	6.66	6.70			
Vb	150	P	42	C ₂₈ H ₁₉ O ₂ N ₄ Cl (478.5)	C	70.28	70.21	ν C=O 1720 ν C=C 1605	ν C=O 1680 ν NH 3460, 3440	ν C=N 1630
					H	3.71	3.97			
					N	11.56	11.70			
					Cl	7.20	7.41			
VIa	230	B	50	C ₃₃ H ₂₈ O ₂ N ₃ Cl (533.5)	C	73.71	74.22	ν C=O 1720 ν C=C 1600	ν C=O 1680 ν CH ₂ 2890	ν C=N 1630 ν NH 3440
					H	5.18	5.24			
					N	7.66	7.87			
					Cl	6.41	6.65			
VIb	125	B	40	C ₂₈ H ₂₃ O ₂ N ₄ Cl (482.5)	C	69.41	69.63	ν C=O 1710 ν C=C 1600	ν C=O 1680 ν CH ₂ ² 2930 ²	ν C=N 1635 ν NH 3380
					H	4.73	4.76			
					N	11.46	11.60			
					Cl	7.38	7.35			

*B=Benzene

P*=Petroleum (b.p. 100-120°C)

Table-2: The NMR spectra of some new compounds

Compound	Solvent	δ values	Group
IIa	CDCl ₃	6.90 - 8.00	11 aromatic hydrogens
		4.40	4 H of 2 - CH ₂ - in - COOCH ₂ CH ₃
		3.85	1H of - CH (COOCH ₂ CH ₃) ₂
		3.65	1 H of - CH - CH ₂
		3.30	2 H of - CO - CH ₂
		2.35 - 2.30	6 H of 2 - CH ₃ in 2 phenyl groups.
		1.60	6 H of 2 - CH ₃ in 2 - COOCH ₂ CH ₃
IIIf	CDCl ₃	7.05 - 7.85	11 aromatic hydrogens
		6.65	1 H of - CH(COCH ₃) ₂
		3.60	1 H of - CH - CH ₂
		3.50	2 H of - CH ₂ - CO -
		2.45	6 H of 2 - CO- CH ₃
		2.30 - 2.20	6 H of 2 - CH ₃ in 2 phenyl groups.
IIIb	CDCl ₃	6.85 - 7.70	11 aromatic hydrogens
		7.40	1 H of - CH - CN
		6.90	1 H of - CH - CH - C in pyrone
		6.60	1 H of - CH - in pyrone ring
		2.30 - 2.25	6 H of 2 - CH ₃ in 2 phenyl groups
IV	CDCl ₃	7.40 - 8.10	11 aromatic hydrogens
		6.25	1 H of - CH - CH ₂ - in cyclohexenone
		4.30	2 H of - CH ₂ - in ² - COOCH ₂ CH ₃
		3.60	1 H of - CH ₂ - COOCH ₂ CH ₃
		2.60	2 H of - CH ₂ - in cyclohexenone
		2.35 - 2.20	6 H of 2 - CH ₃ in phenyl groups
		1.80	3 H of - CH ₃ in - COOCH ₂ CH ₃
Va	CDCl ₃	7.15 - 7.80	11 aromatic hydrogens
		6.20	1 H of CH - in pyridone ring.
		3.20	1 H of - NH - in pyridone ring.
		2.40 - 2.30	6 H of 2 - CH ₃ in phenyl groups.
VI _b	DMSO	6.95 - 7.70	11 aromatic hydrogens
		7.20	1 H of - CH - CN
		6.15	1 H of - CH - CH ₂ in pyridone
		3.25	1 H of - NH in pyridone
		2.55	2 H of - CH ₂ - in pyridone
		2.45 - 2.30	6 H of 2 - CH ₃ in phenyl groups.

malonate, cyclohexanone, ethyl benzoylacetate, ethyl acetoacetate or acetylacetone (0.012 mole) and 2 g KOH in 20 ml. water was heated at 40°C for 30 minutes and left to stand at room temperature overnight. The reaction mixture poured into water and the solid product formed was recrystallized to give the corresponding Michael addition products IIa-f as yellow crystals.

Alternate preparation of II a and b

A mixture of I (0.01 mole), diethyl malonate or cyclohexanone (0.01 mole) and sodium methoxide solution (prepared from 0.35 g. of sodium in 15 ml. of absolute methanol) (0.015 mole) was fused in a round bottom flask attached to an air condenser at 170°C for 8 h. The reaction mixture was poured into water, the solid product formed was recrystallized, the product proved to be IIa and b by melting and mixture melting point determinations.

B) In sodium methoxide solution. Formation of IIIa and b and IV

A mixture of I (0.01 mole) ethyl benzoylacetate, ethyl cyanoacetate or ethyl acetoacetate (0.01 mole) and sodium methoxide solution (prepared from 0.35 g of metallic sodium in 15 ml. of absolute methyl alcohol) (0.015 mole), was fused in a round bottom flask attached with an air condenser at 170°C for 8 h. The reaction mixture was poured into water, and the solid product formed was recrystallized to give the corresponding cyclic Michael adducts IIIa, IIIb and IV as yellow crystals respectively.

C) In ammonium acetate. Formation of V and VI

A mixture of I (0.01), ethyl benzoylacetate or ethyl cyanoacetate (0.01 mole) and ammonium acetate 5 g was heated in an oil bath at 130-140°C for 6 h. The reaction mixture was poured into water, the solid obtained was found to contain two products. They were collected and separated by extraction with boiling petroleum ether (b.p 100-120) giving V and the remaining insoluble solid was crystallized from benzene giving VI as yellow crystals.

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