

α, β-UNSATURATED KETONES: REACTIONS WITH ACETOACETANILIDES AND CYANOACETAMIDES

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Reaction of 3,4,5-trimethoxyacetophenone (1) with aromatic aldehydes gave α, β-unsaturated ketones (IIa-c), which upon reaction with acetoacetanilides in presence of sodium methoxide afforded the cyclic β-ketoanilides (IIIa-h). Treatment of III with hydrazines yielded the substituted benzopyrazolones (IVa-c). Reaction of α, β-unsaturated ketones (IIa-c and/or IIa-f) with cyanoacetamide gave the corresponding cyanopyridone derivatives (VIa-e) in a good yield. The structures of the hitherto unknown ring systems have been confirmed by their analytical and spectral data.

Key words: α, β-Unsaturated ketones, Acetoacetanilides, Cyanoacetamides.

Introduction

Many pyrazolones have been recently described to exhibit anti-inflammatory effect [1,2]. In addition, anti-inflammatory activity has been shown to be associated with certain pyridine and pyridone derivatives [3]. The presence of a methoxy group in the aryl moiety caused a significant increase in the analgesic and anti-inflammatory effects of many drugs such as indomethacin [4] and indoxole [5]. Moreover, incorporation of cyclohexenones with some anti-inflammatory drugs e.g. griseofolvin showed higher activity. These observations have prompted us to undertake the synthesis of cyclohexenones, Indazolones and cyanopyridones having three methoxy groups in the same molecule.

Experimental

Melting points (uncorrected) and were determined on Fisher- Johnne electric melting point apparatus. IR spectra as

KBr disc, were recorded on a Pye Unicam SP 1000 infrared spectrophotometer. The ¹H NMR spectra were recorded on Jeol FX 90 Q. spectrometer using TMS as internal standard.

α-Arylidene-3,4,5-trimethoxyacetophenones (IIa-c). The appropriate aromatic aldehyde (0.01 mole) was added with continuous stirring and cooling to a solution of 3,4,5-trimethoxyacetophenone (0.01 mole) in 2.5% solution of sodium hydroxide in ethanol (30 ml). The reaction mixture was stirred at room temperature for 3 hr. The separated solid product was filtered, washed with water, dried and crystallized (Table 1).

5-Aryl-4-arylcarbamoyl-1-(3,4,5-trimethoxyphenyl)cyclohex-1-ene-3-ones (IIIa-h). A mixture of IIa-c (0.01 mole) and acetoacetanilides (0.02 mole) in sodium methoxide solution (0.02 mole) was heated under reflux for 6 hr. After cooling, the reaction mixture was poured into ice-cold water acidified with 10% hydrochloric acid,

TABLE I. CHARACTERIZATION DATA OF COMPOUNDS IIa-c, IIIa-h AND IVa-c.

Compound No.	R	R'	Ar	m.p. °C	Cryst.* solv.	Yield %	Molecular formula [§]
II a	4-NO ₂	—	—	185	—	75	C ₁₈ H ₁₇ NO ₆
b	2-Br	—	—	85	E	80	C ₁₈ H ₁₇ BrO ₄
c	3,4-Cl ₂	—	—	135	E	65	C ₁₈ H ₁₆ Cl ₂ O ₄
III a	4-NO ₂	—	C ₆ H ₅	162	Aq. E	50	C ₂₈ H ₂₆ N ₂ O ₇
b	4-NO ₂	—	2-CH ₃ OC ₆ H ₄	149	Aq. E	55	C ₂₀ H ₂₈ N ₂ O ₈
c	4-NO ₂	—	4-CH ₃ OC ₆ H ₄	115	Aq. E	45	C ₂₉ H ₂₈ N ₂ O ₈
d	4-NO ₂	—	2-CH ₃ C ₆ H ₄	215	Aq. E	60	C ₂₉ H ₂₈ N ₂ O ₇
e	2-Br	—	C ₆ H ₅	175	E	50	C ₂₈ H ₂₆ BrN ₂ O ₅
f	2-Br	—	2-CH ₃ OC ₆ H ₄	95	Aq. E	55	C ₂₉ H ₂₈ BrN ₂ O ₆
g	2-Br	—	2-CH ₃ C ₆ H ₄	218	Aq. E	40	C ₂₉ H ₂₈ BrN ₂ O ₅
h	2-Br	—	4-NO ₂ C ₆ H ₄	120	Aq. E	60	C ₂₈ H ₂₅ BrN ₂ O ₇
IV a	4-NO ₂	H	—	290	E	44	C ₂₂ H ₂₁ N ₃ O ₆
b	4-NO ₂	C ₆ H ₅	—	150	Aq. E	50	C ₂₈ H ₂₅ N ₃ O ₆
c	2-Br	H	—	138	Aq. E	45	C ₂₂ H ₂₁ BrN ₂ O ₄

* E = Ethanol, Aq. E = aqueous ethanol; § = Satisfactory elemental analyses for C, H, and N were obtained for all compounds.

TABLE 2. CHARACTERIZATION DATA OF COMPOUNDS VIa-e.

Compound No.	Ar	R	m.p. °C	Cryst* solv.	Yield %	Molecular ^s formula
V1a	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	2-BrC ₆ H ₄	138	Aq. E	60	C ₂₁ H ₁₇ BrN ₂ O ₄
b	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	3,4-Cl ₂ C ₆ H ₃	158	Aq. E	50	C ₂₁ H ₁₆ Cl ₂ N ₂ O ₄
c	4-ClC ₆ H ₄	2-ClC ₆ H ₄	115	E	50	C ₁₈ H ₁₀ Cl ₂ N ₂ O
d	4-ClC ₆ H ₄	4-ClC ₆ H ₄	105	E	70	C ₁₈ H ₁₀ Cl ₂ N ₂ O
e	4-ClC ₆ H ₄	4-BrC ₆ H ₄	101	E	65	C ₁₈ H ₁₀ BrClN ₂ O

*E = Ethanol, Aq. E = aqueous ethanol; ^s = Satisfactory elemental analyses for C, H and N were obtained for all compounds.

stirred for 2 hr., and kept in a refrigerator overnight. The precipitated solid was collected by filtration, washed with water, dried and crystallized from the suitable solvent (Table 1).

Compound III d. IR (cm⁻¹): 1670(CONH), 1725(C=O), 3300 (NH); ¹H NMR (CDCl₃) δ: 1.4(s, 3H, CH₃), 3.0, 3.2 (dd, 2H, CH₂-6), 3.6(m, 1H, H-5), 3.75, 3.85 (s, 9H, 3 OCH₃), 4.4 (d, 1H, H-4), 6.6 (s, 1H, H-2), 6.7-6.8 (m, 6H, ArH), 7.4-7.6 (m, 2H, ArH), 8.0-8.15 (m, 2H, ArH).

Compound III b. IR (cm⁻¹): 1660(CONH), 1720 (C=O), 3310(NH); ¹H NMR (CDCl₃) δ: 3.1-3.3 (dd, 2H, CH₂-6), 3.6(m, 1H, H-5), 3.85(m, 12H, 4, OCH₃), 4.25 (m, 1H, H-4), 4.7 (br s, 1H, NH), 6.6(s, 1H, H-2), 6.7-7.1 (m, 6H, ArH), 7.45-7.65 (m, 2H, ArH), 8.1-8.3 (m, 2H, ArH).

3,3a,4,5-Tetrahydro-4-(p-nitrophenyl)-6-(3,4,5-trimethoxy-phenyl)-2-indazole-3-one (IVa) and its 2-phenyl derivative (IVb). To a solution of IIIa-d (0.01 mole) in glacial acetic acid (30 ml), hydrazine hydrate or phenyl hydrazine (0.011 mole) was added. The reaction mixture was heated under reflux for 4 hr. and left overnight at room temperature. The precipitated product was filtered, dried and crystallized (Table 1).

Compound IVa. IR (cm⁻¹): 1650 (C=O), 3350 (NH); ¹H NMR (CDCl₃) δ: 3.2 (dd, 2H, CH₂-5), 3.6 (d, 1H, H-3a), 3.76-3.86(s, 9H, 3OCH₃), 4.35 (m, 1H, H-4), 6.6 (s, 2H, ArH), 6.8(s, 1H, ArH), 7.4 (d, 2H, ArH), 8.1 (d, 2H, ArH).

3,3a,4,5-Tetrahydro-4-(o-bromophenyl)-6-(3,4,5-trimethoxyphenyl)-2-indazole-3-one (IVc). This compound was prepared from IIIe-h (0.01 mole) and hydrazine hydrate (0.011 mole) in glacial acetic acid (30 ml), as mentioned for IVa,b (Table 1).

4,6-Diaryl-3-cyano-2-pyridones (VIa-e). Method (A). A mixture of IIb-f (0.05 mole) and cyano acetamide (0.05 mole) and few drops of piperidine, was heated under reflux in an oil bath at 140-150° for 6 hr. After cooling, the reaction mixture was triturated with hot ethanol, and the solid mass obtained was collected and crystallized (Table 2).

Method (B). A mixture of IIb-f (0.05 mole), ethyl cyanoacetate (0.05 mole) and ammonium acetate (0.5 g) in glacial acetic acid (30 ml) was heated under reflux for 6 hr.

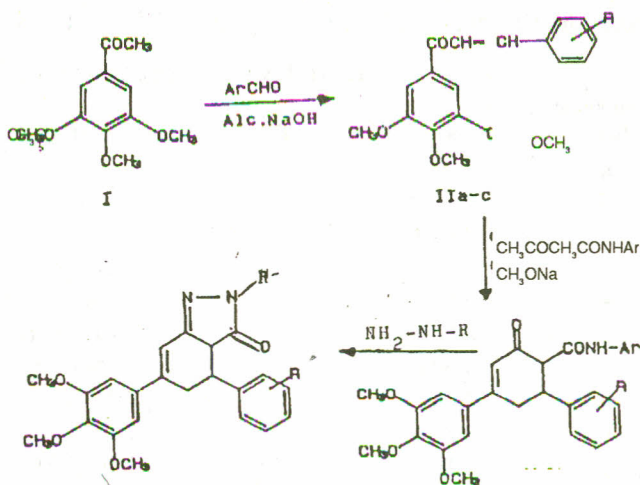
After cooling, the solid products that separated were filtered and crystallized (Table 2).

The IR spectrum of compounds VIa-e showed bands at 1635 cm⁻¹ (C=O of the pyridone) and 2235 cm⁻¹ (C=N); ¹H NMR of compound VIa (DMSO-d₆) δ: 3.8, 3.88 (s, 9H, 3 OCH₃), 6.8-8.0 (m, 7H, ArH); compounds VIa-e showed peaks at δ7.2-8.5 (m, 10H, ArH and NH).

Result and Discussion

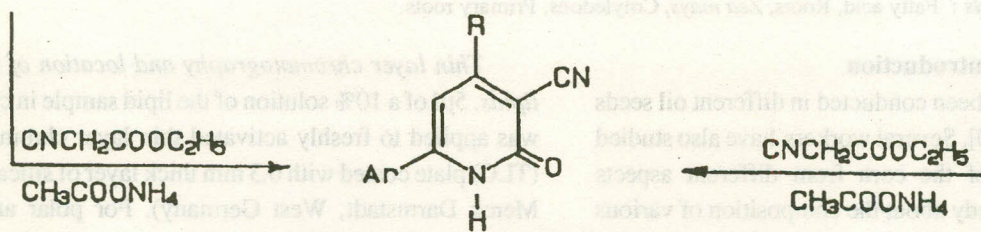
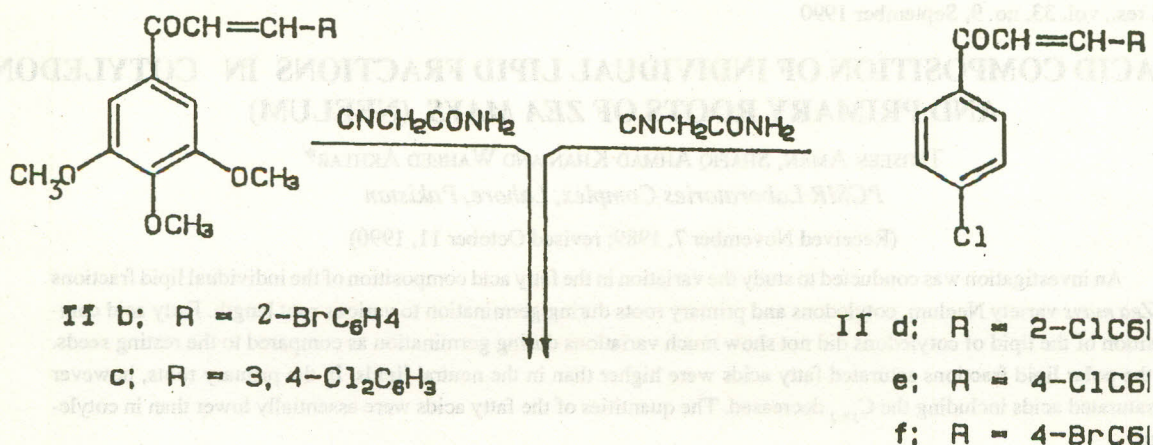
Condensation of 3,4,5-trimethoxyacetophenone (I) with different aldehydes in presence of alcoholic sodium hydroxide afforded the corresponding α, β-unsaturated ketones (IIa-c) which were readily reacted with cyanoacetanilides in presence of sodium methoxide to give the corresponding cyclic β-ketoanilides; namely: 5-aryl-4-arylcarbonyl-1-(3,4,5-trimethoxyphenyl) cyclohex-1-en-3-ones (IIIa-h) (Scheme 1). The formation of compounds III were guided by our previous reports [7] and supported from the correct analytical data, IR and ¹H NMR spectra.

Treatment of β-ketoanilides IIIa-d (R=4-NO₂) with hydrazine hydrate or phenyl hydrazine in presence of



IVa, R' = H, R = 4-NO₂
 IVb, R' = C₆H₅, R = 4-NO₂
 IVc, R' = H, R = 2-Br

Scheme 1



Scheme 2.

glacial acetic acid yielded 3,3a,4,5-tetrahydro-4-(p-nitrophenyl)-6-(3,4,5-trimethoxyphenyl)-2-indazole-3-one (IVa) and its 2-phenyl derivative (IVb), respectively. Infrared and ¹H NMR spectra of IVa, b are consistent with the assigned structures and supported by their correct analytical data, and supported by the fact that all compounds IIIa-d gave one compound (m,p, nmr and TLC) when treated with hydrazine hydrate and one compound with phenyl hydrazine (Scheme 1).

Compounds IIIe-h (R=2Br) react in a similar manner with hydrazine hydrate to give 3,3a, 4,5-tetrahydro-4-(2-bromo-phenyl)- 6-(3,4,5-trimethoxyphenyl)-2-indazole-3-one (IVc) (Scheme 1).

Heating α, β-unsaturated ketones (IIb,c and/or IId-f) with cyanoacetamide in presence of piperidine afforded the corresponding 4,6-diaryl-3-cyano-2-pyridone derivatives (VIa-e), which could be obtained by heating α, β-unsaturated ketones (IIb- f) with ethyl cyanoacetate in presence of ammonium acetate (Scheme 2). The structures of VI were

confirmed by their correct analytical data, IR and ¹H NMR spectra.

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