The Cyclisation of (*Z*) and (*E*)-3-Ethoxycarboyl-4(3'-chloro- 6'-methyl-phenyl)-but-3-enoic acid and Synthesis of Poly Substituted Naphthoic Acid

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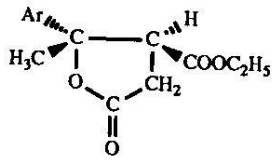
Summary: The condensation of 5-chloro-2-methylacetophenone with diethyl succinate in the presence of potassium *t*-butoxide gave a mixture of (*Z*)- and (*E*)-3-ethoxy-carbonyl-4-(3'-chloro-6'-methylphenyl)but-3-enoic acid. Cyclisation of (*E*)- and (*Z*)-half-esters afforded the naphthalene derivative and oxo-indenyl acid *via* the anhydride formation, respectively. The reaction of (*E*)-anhydride with aromatic hydrocarbons, amines and anhydrous aluminium chloride in acetylene tetrachloride was also investigated. The IR, ^{1}N-NMR and mass spectra of the products were discussed.

Introduction

As a continuation of the recent studies [1-4] during the course of this work it was found that the condensation of 5-chloro-2-methyl acetophenone with diethyl succinate in the presence of potassium *t*-butoxide as a condensing agent, produced predominantly the (*E*)-half-ester 1. The structure (1) was infered from ^{1}H-NMR spectrum (DMSO-d6) which showed the following signals: at δ (ppm) 0.8 (t, 3H, CH_2CH_3), δ 2.1 (s, *3H*, CH_3-Ar), δ 2.4 (s, *3H*, CH_3-C C), δ 3.4 (s, *2H*, CH_2COOH), δ 3.8 (q, *2H*, CH_2CH_3) and δ 6.9 - 7.4 (m, 3*H*, aromatic protons). The mass spectrum of (1) showed the molecular ions with m/e values followed by % of abundance: 296 (8), 252 (30), 237 (10), 222 (10), 206 (12), 195 (6), 187 (12), 178 (100), 153 (6), 143 (70), 128 (86), 115 (66), 102 (10), 91 (52), 77 (15), 63 (15), 55 (11) and 51 (22). Adequate evidence for the structure and (*E*)-configuration of (1) was given by its susceptibility for cyclisation with sodium acetate - acetic anhydride mixture to the corresponding acetoxy ester (**IIa**). The formation of the latter product was confirmed both by its IR and ^{1}H-NMR spectra. Those show ν C=O at 1752 cm^{-1} and 3*H* singlet at δ 2.6 ppm, which indicates the presence of acetoxy group. However, the methoxy carbonyl group exhibit at ν C=O at 1718 cm^{-1} and 3*H* triplet at δ 1.4 and 2*H* quartet at δ 2.1 ppm. The cyclisation of the acidic crude material, obtained from Stobbe condensation, gave also the acetoxy ester (**IIa**) in almost the same yield as obtained from the pure crystalline half-ester (1). This leads the conclusion that the latter is the essential constituent of the condensation product. The predominance of the (*E*)-configuration of the half-ester (1) can be readily interpreted in the light of the currently accepted mechanism [5] concerning steric and/or polar non-bonded interactions involved in the formation of the intermediate δ-lactone (A). The formation of (1) is facilitated both by the tendency of the bulky aryl group to be trans to the carboethoxyl group, as well as by repulsive forces between its π-sextet and the negative field of the carbonyl oxygen in the ester group.



(A)

Saponification of the acetoxy ester (**IIa**) gave 5-chloro-4-hydroxy-1,8-di-methylnaphthalene-2-carbo -xylic acid (**IIb**), whose IR spectrum showed a strong broad band at 3310 cm^{-1} characteristic of OH with polymeric association, absorption in this region disappeared upon conversion of (**IIb**) to methyl-5-chloro-4-methoxy-1,8-dimethylnaphthalene-2-carboxylate (**IIc**) by treatment with dimethyl sulphate. Saponification of latter product gave the methoxy acid (**IId**) whose carbonyl group exibit ν C=O at 1696 cm^{-1}.

The pure crystalline half-ester (1) was hydrolysed with aqueous sodium hydroxide to give the dibasic acid (**III**). The ^{1}H- NMR spectrum (DMSO-d6) of (**III**) showed the signals at δ 2.3 ppm (s, 3H, CH_3-Ar), δ 2.8 (s, 3H, CH_3-C=C). 4.1 (s, 2H, CH_2 COOH) and δ at 7 - 7.2 (m, 3*H*, aromatic protons). This was converted with N,N'-di-cyclohexylcarbodiimide to (*E*)-3-carboxy-4-(3'-chloro-6'-methylphen-

yl)-but-3-enoic anhydride (IV) which exhibit ν C=O at 1810 and 1750 cm^{-1}. The structure of (IV) was constracted on the basis of: a) ^{1}H-NMR spectrum of (IV) showed signals at δ 2.3 ppm (s, 3*H*, CH_3-Ar), δ 2.6 (s, 3*H*, CH_3-C-C), δ 3.7 (s, 2*H*, CH_2CO) and δ 7-7.7 (m, 3*H*, Ar-H), b) The mass spectrum of (IV) showed the molecular ions with m/e values followed by % of abundance; 250 (70), 187 (21), 178 (100), 171 (8), 163 (8), 143 (52), 128 (76), 115 (68), 102 (6), 89 (15), 77 (12), 65 (7), 63 (30) and 51 (62). Acylation of the aromatic amines, namely, aniline, *p*-toluidine, α-naphthylamine and benzylamine with the (*E*)-anhydride (IV) in dry benzene led to a ring cleava -ge at the non-conjugated carbonyl group to give N-aryl-3-carboxy-4-(3'-chloro-6'-methoxyphenyl)-4-methyl -but-3-enoic acid amide (V). The IR spectrum of (V) supports the suggested ring cleavage in as much as it shows strong carbonyl bands at 1678 and 1683 cm^{-1} expected for non-conjugated acid amide and α,β-unsaturated carbonyl groups, respectively. On the other hand, the anhydride (IV) when subjected to reaction with anhydrous aluminium chloride in dry acetylene-tetrachloride, gave (IIb) whereas with aromatic hydro -carbons such as benzene, toluene, and anisole in anhydrous aluminium chloride under the conditions of Friedel-Craft's reaction it gave (VIa-c). Hydrazinolysis of (VIb) in *n*-butanol afforded the acidic product (VII) together with the neutral product (VIII).

The presence of the (Z)-half-ester in the crude condensation products, was revealed from the following sequence of reactions. Saponification of the oily half-ester mixture afforded the dibasic acid (III) together with the oily dibasic acid (IX) which when treated with acetyl chloride, gave the corresponding neutral oily cyclic anhydride (X). Cyclisation of the latter with anhydrous aluminium chloride in acetylene tetrachloride gave 7-chloro-3,4-dimethyl-1-oxo-2-indenyl acetic acid (XI). The assignment of the indenone structure (XI) based beside the analytical data on the following: i) The characteristic yellow colour of indenones, it solubility in sodium carbonate, formation of 2,4-dinitrophenylhydrazone. ii) The IR spectrum exhibits two strong absorptions in the carbonyl region at 1700 cm^{-1} νC=O non-conjugated) and 1682 cm^{-1} (ν C=O of α,β-unsaturated ketone). iii) The ^{1}H-NMR spectrum (DMSO-d_6) of (XI) showed the signals at δ 2.1 ppm (s, 3*H*, CH_3-Ar), δ 2.8 (s, 3*H*, CH_3-C=C), δ 4.0 (2*H*, CH_2COOH) and δ at 7.1-7.3 (br, m, 2*H*, Ar-H).

Compound (XI) reacted with hydrazine hydrate in *n*-butanol and gave the pyridazinone derivative (XII), whose IR spectrum showed carbonyl stretching frequency of cyclic amide at 1680 cm^{-1}, νNH 3300 cm^{-1} (broad) and νC=N at 1598 cm^{-1} which are consistent with the proposed structure. However, when (XI) was allowed to react with phenylhydrazine in boiling ethanol, the corresponding phenylhydrazone (XIII) has been obtained. Structure (XIII) was infered from: i) its solubility in sodium carbonate solution, ii) its IR spectrum showed strong absorption at 3410, 3300, 1705 and 1612 cm^{-1} attributable to ν OH, ν NH, ν C=O and ν C=N , respectively. (The synthesis of various compounds are outlined in schemes 1 and 2).

Experimental

All melting points are uncorrected. IR spectra were measured on Unicam SP (1200), using KBr Wafer technique. ^{1}H-NMR spectra were measured on Varian EM-390 at 90 MHz, with TMS as internal lock and reference compound. Mass spectra were determined with A.E.I. M.S., 12 single focusing mass spectrometer.

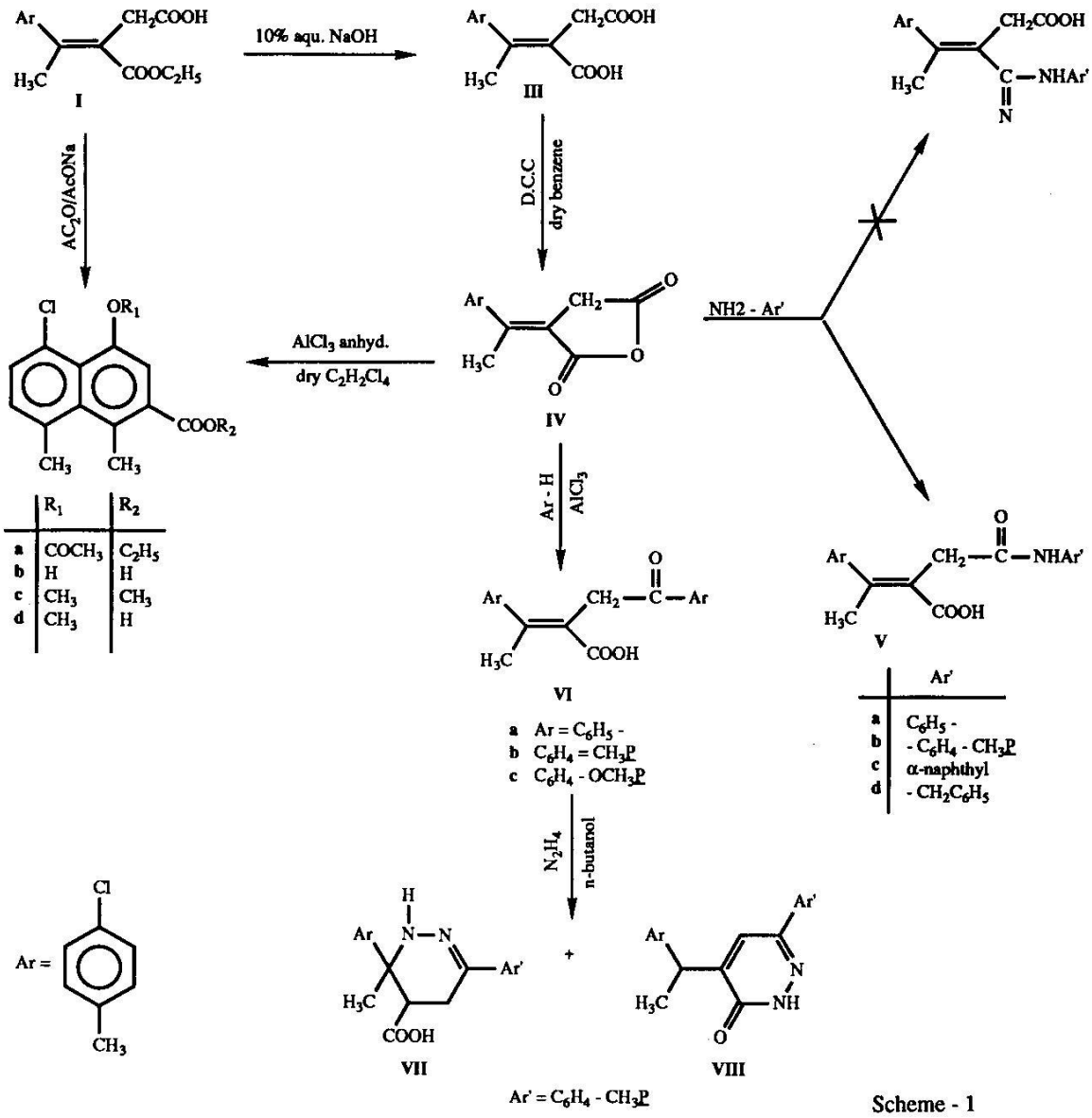
(E) and (Z)-Ethoxycarbonyl-4-(3'-chloro-6'-methyl-phenyl)-but-3-enoic acids

A mixture of 5-chloro-2-methylacetophenone (16.9 g, 0.1 mol.) and diethyl succinate (34 g, 0.2 mol.) in t-butyl alcohol (150 ml) was gradually added during 1 hr. to a heated solution of potassium *t*-butoxide at 70-75°. The temperature was maintained for a further 2 hr., then the mixture was worked up in the usual manner [5]. The acidic product (*ca* 21 g) was separated into two fractions by extraction with boiling benzene.

1. The insoluble product (9.0 g) was crystallized from dilute acetic acid and gave the *E*-half-ester (1).
2. Evaporation of the benzene mother liquor left a dark brown viscous oil (10.8 g) which was identified as a mixture of (Z)- and (*E*)-half-esters.

Ethyl-4-acetoxy-5-chloro-1,8-dimethylnaphthalene-2-carboxylate (IIa)

2.6 g (0.01 mol.) of (1) was added to a mixture of sodium acetate (0.8 g, 0.01 mol.) and acetic anhydride (15 ml) and left overnight at room temperature, this mixture was refluxed for 6 hr., and finally the



neutral crystallization product isolated as usual [5]. The solidified product crystallised from a suitable solvent to give the acetoxy ester (**IIa**) as light brown crystals.

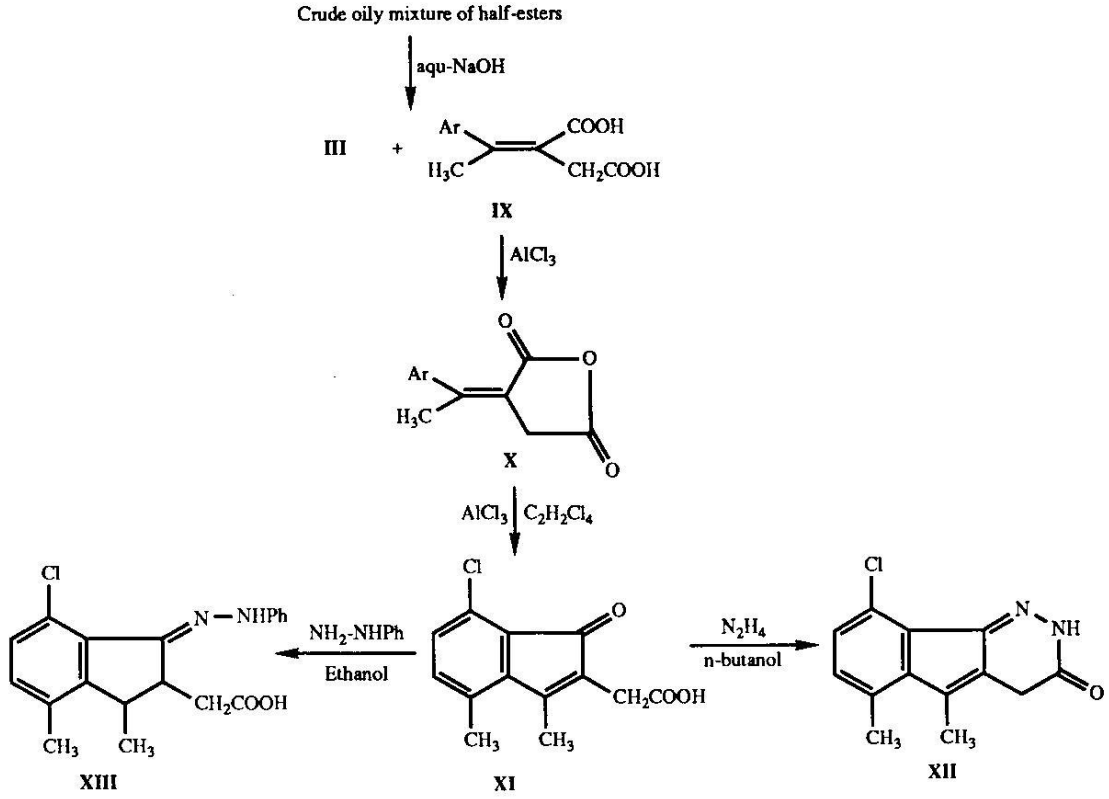
5-Chloro-4-hydroxy-1,8-dimethylnaphthalene-2-carboxylic acid (**IIb**)

Method (1):

3.2 g (0.01 mol.) of (**IIa**) were hydrolysed with aqueous alcoholic potassium hydroxide solution (30 ml), 2 hr. reflux. The phenolic acid (**IIb**) obtained was crystallized from the proper solvent as pale yellow needles.

Method (2):

To a stirred ice-cold solution of the (*E*)-anhydride (**IV**) (2.5 g, 0.01 mol.) in dry acetylene tetrachloride (30 ml), powdered aluminium chloride anhydrous (3 g) was added in one portion and stirring was continued for 2 hr. The reaction mixture was left aside overnight at room temperature, then worked out as usual.



Scheme-2

Methyl-5-chloro-1,8-dimethyl-4-methoxynaphthalene-2- carboxylate (**IIc**)

2.5 g (0.01 mol) of (**IIb**) were refluxed for 18 hr. with (15 ml) dimethyl sulphate and 3 g anhydrous potassium carbonate in acetone (50 ml). This gave the methoxy ester (**IIc**).

5-Chloro-1,8-dimethyl-4-methoxynaphthalene-2-carboxylic acid (**IId**)

1.3 g (0.008 mol.) of (**IIc**) were hydrolysed with aqueous alcoholc potassium hydroxide solution by refluxing for 3 hr. The produced methoxy acid (**IId**) was crystallised from a suitable solvent.

(E)-3-Carboxy-4-(3'-chloro-6'-methylphenyl)-but-3-enoic acid (**III**)

5 g (0.02 mol.) of the half-ester (**1**) were hydrolysed with 10% aqueous sodium hydroxide (10 ml/g of the half-ester) for 3 hr. The crude half-ester gave on hydrolysis the above dibasic acid (**III**) together with the oily dibasic acid which identified to be the (*Z*)-dibasic acid (**IX**).

(E)-3-carboxy-4-(3'-chloro-6'-methylphenyl)-but-3-enoic anhydride (**IV**)

A mixture of the diacid (**III**) N,N'-dicyclohexyl carbodiimide (D.C.C.) (1:1 mol.) in excess dry benzene was stirred at room temperature for 2 hr. and left to stand overnight, then worked up as usual [2,6].

(E)-N-aryl-3-carboxy-4(3'-chloro-6'-methylphenyl)-4-methyl-but-3-enoic acid amide (**Va-d**)

A solution of (**IV**) (0.01 mol.) in 50 ml dry benzene was refluxed for 2 hr. with (0.01 mol.) of amines, namely, aniline, *p*-toluidine, α-naphthylamine and benzylamine. The solid formed after cooling was crystallized from a suitable solvent to give (**Va-d**).

Reaction of (**IV**) *with aromatic hydrocarbons: Formation of* (**VIa-c**)

A solution of (**IV**) (0.01 mol.) in (100 ml) of dry aromatic hydrocarbon, namely, benzene, toluene or anisole was added gradually to a cold suspension of anhydrous aluminium chloride (0.02 mol.) in a large excess of aromatic hydrocarbon (50 ml). The

Table 1: Characterization Data of various Compounds prepared

Compd	M.P. °C and Solvent	Mol. formula and Mol.Wt.	Analysis, Required/Found C	H	N	Cl
(I)	115-17	$C_{15}H_{17}O_4Cl$	60.7	5.7	-	11.97
	AcOH	(296.5)	60.6	5.5	-	12.1
(IIa)	103-5	$C_{17}H_{17}O_4Cl$	63.7	5.3	-	11.1
	L.P	(320.5)	63.5	5.6	-	11.2
(IIb)	243-5	$C_{13}H_{11}O_3Cl$	62.3	4.4	-	14.2
	E	(250.5)	62.0	4.6	-	14.0
(IIc)	165-7	$C_{15}H_{15}O_3Cl$	64.6	5.4	-	12.7
	Bz	(278.5)	64.7	5.7	-	12.2
(IId)	202-4	$C_{14}H_{13}O_3Cl$	63.5	4.9	-	13.4
	E	(264.5)	63.5	5.0	-	13.8
(III)	230	$C_{13}H_{13}O_4Cl$	58.1	4.8	-	13.2
	E	(268.5)	58.3	4.4	-	13.0
(IV)	145	$C_{13}H_{11}O_3Cl$	62.3	4.4	-	14.2
	Bz	(250.5)	62.6	4.7	-	14.1
(Va)	182	$C_{19}H_{18}NO_3Cl$	66.4	5.2	4.1	10.3
	Bz	(343.5)	66.5	5.2	4.3	10.1
(Vb)	174	$C_{20}H_{20}NO_3Cl$	67.1	5.6	3.9	9.9
	(tol)	(357.5)	67.2	5.6	4.2	10.1
(Vc)	210	$C_{23}H_{20}NO_3Cl$	70.1	5.1	3.6	9.0
	(Tol)	(393.5)	70.3	5.1	3.8	9.1
(Vb)	163	$C_{20}H_{20}NO_3Cl$	67.1	5.6	3.9	9.9
	(Bz)	(357.5)	67.1	5.6	4.0	10.1
(VIa)	202	$C_{19}H_{17}O_3Cl$	69.4	5.2	-	10.8
	(E)	(328.5)	69.3	5.3	-	10.9
(VIb)	213	$C_{20}H_{19}O_3Cl$	70.1	5.5	-	10.4
	(E)	(342.5)	70.2	5.5	-	10.6
(VIc)	192	$C_{20}H_{19}O_4Cl$	66.9	5.3	-	9.9
	(E)	(358.5)	67.0	5.4	-	9.7
(VII)	230-2	$C_{20}H_{21}N_2O_2Cl$	67.3	5.9	7.9	10.0
	(E)	(356.5)	67.3	5.8	8.2	10.1
(VIII)	133-5	$C_{20}H_{19}N_2OCl$	70.9	5.6	8.3	10.5
	(Bz)	(338.5)	70.7	5 6	8.3	10.7
(XI)	260-2	$C_{13}H_{11}O_3Cl$	62.3	4.4	-	14.2
	(Bz-E)	(250.5)	61.9	4.4	-	14.2
(XI)	280	$C_{19}H_{15}N_4O_6Cl$	52.9	3.5	13.0	8.2
(D.N.P)	(Tol)	(430.5)	53.1	3.8	13.0	8.5
(XII)	215-7	$C_{13}H_{11}N_2OCl$	63.3	4.5	11.4	14.4
	(Tol)	(246.5)	63.3	4.6	11.41	14.0
(XIII)	290.2	$C_{19}H_{17}N_2O_2Cl$	66.9	4.99	8.2	10.4
	(E)	(340.5)	66.8	5.0	8.4	10.1

Bz = benzene, E = ethanol, Tol = toluene and L.P. light petroleum (b.p. 80-100°C).

temperature of the mixture was not allowed to rise above 30°. The suspension was stirred at room temperature for 8 hr. The whole mixture was worked up as usual [2]. The viscous oil obtained was triturated with benzene and the product was crystallised from the proper solvent.

Reaction of (VIb) with hydrazine hydrate: Formation of (VII) and (VIII)

A solution of (VIb) (0.01 mol.) and hydrazine hydrate (0.05 mol.) in (50 ml) *n*-butanol was refluxed for 16 hr. The excess *n*-butanol was evaporated. The product extracted with ether and sodium carbonate solution followed by acidification of the inorganic layer gave the acidic product (VII). Slow evaporation of ether left the neutral product as pale yellow crystals (VIII).

Conversion of the oily diacid (IX) to the corresponding oily anhydride (X)

The diacid (IX) (10 g) was refluxed with acetyl chloride (100 ml) for 3 hr. Excess acetyl chloride was then removed by distillation to give the neutral oily product (X).

7-Chloro-3,4-dimethyl-1-oxo-2-indenyl acetic acid (XI)

To a solution of anhydride (X) (5 g) in dry acetylene tetrachloride (50 ml), powdered aluminium chloride anhydrous (8 g) was added in one portion and stirring was continued for 6 hr. The reaction mixture was left aside for 2 days at room temperature with stirring, then worked out as usual [1-6]. The yellow acidic product was crystallized from ethanol to give the indenyl acid (XI) (*ca* 60% yield).

Formation of (XII) and (XIII)

A solution of (XI) (1.4 g, 0.005 mol.) hydrazine hydrate or phenylhydrazine (0.005 mol) in *n*-butanol or ethanol (30 ml) was refluxed for 3 hr. The reaction mixture was concentrated and cooled, the separated solids were crystallised from the suitable solvent and gave the pyridazinone (XII) and the phenylhydrazone (XIII) (The results are listed in Table 1).

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