Pak. j. sci. ind. res., vol. 33, nos. 1-2, Jan.-Feb. 1990

SOME REACTIONS OF 3-CHLOROKETONES

S.K.El- Sadany, S.M. Sharaf, A.I. Darwish and A.A. Youssef
Department of Chemistry, Alexandria University, Alexandria, Egypt

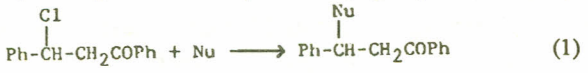
(Received January 14, 1989; revised October 8, 1989)

3-Chloro-3-(*p*-substitued phenyl) propiophenones (I) were allowed to react with diethyl malonate and ethyl acetoacetate in the presence of slight excess of sodium ethoxide to give the corresponding ethyl 2-carbethoxy-3-aryl-4-benzoylbutyrate (III), and ethyl 3-hydroxy-3-phenyl-5-aryl-cyclohexane-1-one-6-carboxylate IV, respectively. The same products were isolated, when p-substituted benzalacetophenones were used instead of the 3-chloroketones. This indicated that, the former reactions proceed by an elimination-addition mechanism. The structure of the products were established.

Key words: Carbanions, Chloroketones, Elimination-addition

Introduction

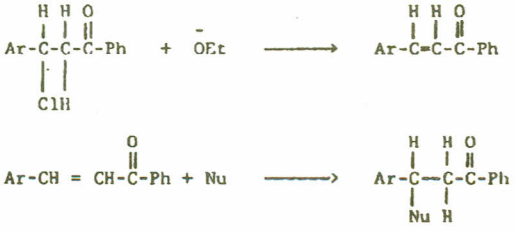
The reaction of equimolecular quantities of 3-chloro-3-phenyl propiophenone I_a and potassium thiocyanate, aniline, *p*-toluidine and hydroxylamine was reported [1] to give the corresponding substitution products (eqn. 1).



(1)

The reaction of two moles of phenylhydrazine with one mole of I_a gave, however, triphenyl pyrazoline. The same product was obtained by konnor [2] from the reaction of equimolar quantities of benzalacetophenone and phenylhydrazine. Both the substitution and elimination products, 3-cyano-3-phenyl propiophenone and benzalacetophenone, were isolated from the reaction with potassium cyanide [1].

The reaction of equimolecular quantities of I_a with sodium ethoxide in the presence of compounds containing active methylene group gave only the corresponding elimination product, benzalacetophenone [3,4]. In the presence of a slight excess of base, however, the formation of benzal acetophenone was followed by addition of the nucleophile to give the corresponding adduct.

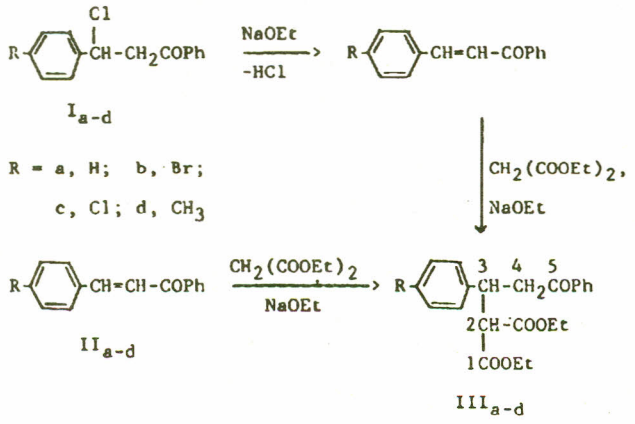


The aim of this work is the study of further reactions of 3-chloro-3-(*p*-substituted phenyl) propiophenones I_{a-d} with different nucleophiles such as diethyl malonate and ethyl acetoacetate. This will lead also to the study of the differently formed cyclic compounds and establish their structures using spectroscopic techniques.

Results and Discussion

3-Chloro-3-(*p*-substituted phenyl) propiophenones I_{a-d} were generally prepared by the reaction of acetophenone with the appropriate *p*-substituted benzaldehyde in the presence of dry hydrogen chloride gas [5]. The ir, uv and ^{1}Hnmr spectra of these compounds I_{a-d} are collected in Table 1. The ^{1}Hnmr spectra show signals of the C_2 methylene protons which are non-equivalent (AB part of an ABX system) that give rise to a multiplet centered at δ 3.70 ppm with two protons intensity. A triplet of one proton intensity for C_3 at δ 5.45-5.72 ppm. The aromatic protons appear as multiplet centered at δ 7.60 ppm.

(I) *Reaction with diethyl malonate.* Reaction of I_a with diethyl malonate in the presence of slight excess of sodium ethoxide gave ethyl2-carbethoxy-3-phenyl-4-benzoylbutyrate IIIa. The same product was previously isolated by Kohler and others [6,7] when benzalacetophenone II_a was used instead of I_a. This indicates that the former reaction presumably proceeded *Via* the formation of benzalacetophenone through dehydrochlorination [3,4,8], followed by nucleophilic addition of the diethyl malonate anion (i.e. the reaction proceed by the elimination-addition mechanism). The 3-(p-Br, p-Cl and p-CH_3) derivatives III_{b-d} behaved similarly as shown in Scheme 1.



Scheme 1

The products III_{a-d} were obtained in good yield by the reaction of *p*-substituted benzalacetophenones II_{a-d} with diethyl malonate in presence of sodium ethoxide. The structures of IIIa-d were confirmed by elemental analyses and spectroscopic methods. The ir spectra show sharp bands at 1680-1685 and 1737-1735 cm^{-1} characteristic of the C=O of the carbonyl group and of the ester group respectively.

The ^{1}Hnmr spectra showed two triplets with six protons intensity centered at δ1.00 and δ1.20 ppm characteristic of the two methyl proton of the unsymmetrical ethyl ester groups, and a multiplet with eight protons intensity centered at δ3.80 ppm characteristic of the C_2, C_3, C_4 protons and the four protons of the methylene groups of the unsymmetrical ethyl ester groups. The aromatic protons appeared as a multiplet centered at δ7.46 ppm. Furthermore, the spectrum of compound III_d shows a singlet appeared at δ2.23 ppm with three protons intensity characteristic of the *p*-methyl protons (Table 1).

The reaction of benzalacetophenones with ethyl phenylacetate in presence of sodium ethoxide had been reported [9-15] to give the corresponding 4-aryl-3,6-diphenyl-3,4-dihydro-2H-pyran-2-ones. The reaction proceeded by Michael addition of the carbanion of ethyl phenylacetate to the α, β-ethylenic ketone to give the corresponding adduct, followed by the lactonization of the intermediate adduct to yield the appropriate lactone. Attempts to affect similar lactonization with the adducts III_{a-d} were unsuccessful. This may be attributed to the existance of III_{a-d} in the resonating structure III'_{a-d} in which a large electron density is centered on the carbon atom of the carbonyl ester group. Accordingly, the nucleophilic attack of the enolate of the benzoyl group on the carbonyl ester group is rendered difficult.

TABLE 1. SPECTRAL DATA FOR COMPOUNDS I_{A-D}, III_{A-D}, IV_{A-D} AND V_{a-d}..

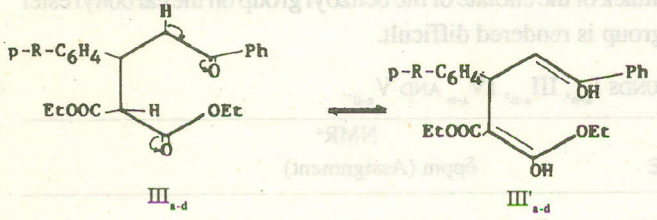
Cpd. No.	m.p. °C	Yield %	IR[a] C=O	IR[a] COOEt	IR[a] OH	UV[b] λmax.	UV[b] ε	NMR[c] δppm (Assignment)
I_a	112	78	1700			210	13900	δ3.36-4.10 (CH_2,2H); 5.45 (CH, 1H);
						244	13900	7.16-7.90 (Ar.H, 1OH)
I_b	90	77	1680			210	17100	δ3.40-4.10 (CH_2,2H); 5.40 (CH,1H);
						239	20650	7.20-8.10 (Ar.H, 9H)
I_c	72	83	1670			210	13700	δ-3.30-4.00(CH_2,2H;5.45(CH,1H);
						236	15900	7.10-7.90 (Ar.H, 9H)
I_d	84	81	1690			210	15500	δ2.53 (*p*-CH_3,3H); 3.56-4.26 (CH_2,2H);
						244	15800	5.72 (CH, 1H); 7.20-8.20 (Ar.H, 9H)
III_a	71	81	1680	1730		210	13400	δ1.00 & 1.20(2CH_3, 6H); 3.33-4.26(2CH_2 &
						244	12060	$^2CH_2$-^{3}CH-^{4}CH,8H); 7.00-7.83(Ar.H,1OH).
III_b	107	85	1685	1735		210	16000	δ1.05 & 1.20(2CH_3,6H); 3.50-4.30(2CH_2&
						232	15400	$^2CH_2$-^{3}CH-^{4}CH,8H); 6.96-7.90 (Ar.H,qH)
III_c	97	84	1685	1735		210	12900	δ1.00 & 1.20(2CH_3,6H); 3.30-4.23(2CH_2 &
						223	14000	$^2CH_2$.^{3}CH.^{4}CH,8H); 7.00-7.82(Ar.H, 9H)
III_d	68	83	1685	1730		210	14400	δ1.00 &1.22(2CH_3,6H); 2.23 (*p*-CH_3,3H);
						244	13400	3.30-4.25(2CH_2& $^2CH_2$.^{3}CH. ^{4}CH,8H);
								6.83-7.86 (Ar. H, 9H).
IV_a	120	88	1680	1740	3400			δ1.10-1.30 (CH_3,3H); 2.00 (OH, 1H); 2.35 ($^2CH_2$,2H); 3.30-3.35 ($^4CH_2$,2H); 3.80-4.30 CH_2&^{5}CH-^{6}CH,4H); 7.20-7.80 (Ar.H, 1OH).
IV_b	129	75	1700	1735	3490			δ1.20-1.25 (CH_3,3H); 2.00(OH, 1H); 2.25 $^2CH_2$,2H); 3.20-3.50 ($^4CH_2$,2H); 3.80-4.30 (CH_2&^{5}CH-^{6}CH,4H); 7.10-7.90 (Ar. H, 9H).
IV_c	127	78	1710	1735	3400			δ1.05-1.20(CH_3,3H); 2.10 (OH,1H); 2.30 ($^2CH_2$,2H); 3.20-3.50 ($^4CH_2$,2H); 3.80-4.30 (CH_2 & ^{5}CH-^{6}CH,4H); 7.10-7.90 (Ar.H, 9H)
IV_d	154	80	1700	1740	3400			δ1.10-1.20(CH_3,3H); 1.90(OH,1H); 2.30 ($^2CH_2$,2H); 2.40(p-CH_3,3H); 3.30-3.40 ($^4CH_2$,2H); 3.80-4.30(CH_2 & ^{5}CH-^{6}CH,4H); 6.90-7.90 (Ar. H, 9H)

Contd. Table 1.

Contd.Table 1

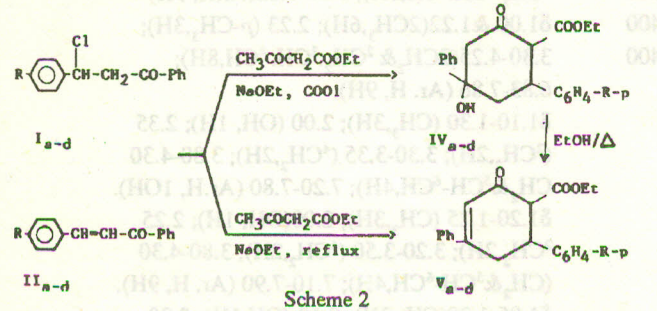
Cpd. No.	m.p. °C	Yield %	IR[a] C=O	IR[a] COOEt	IR[a] OH	UV[b] λmax.	UV[b] ε	NMR[c] δppm (Assignment)
V_a	111	81	1675	1750		210	1700	δ0.90(CH_3, 3H); 2.90($^4CH_2$,2H); 3.60-3.80
						286	19000	^{5}CH-^{6}CH,2H); 3.85 (CH_2,2H); 6.46 (2CH,1H); 7.20-7.60 (Ar.H, 1OH).
V_b	154	86	1670	1750		220	21000	δ1.00(CH_3,3H); 2.90($^4CH_2$,2H); 3.60-3.80
						286	18400	(^{5}CH-^{6}CH, 2H); 3.90 (CH_2, 2H), 6.43 (^{2}CH, 1H); 7.00-7.60 (Ar.H, 9H).
V_c	140	78	1670	1775		220	21000	δ1.00 (CH_3, 3H); 2.90 ($^4CH_2$, 2H); 3.60-3.80
						286	19200	(^{5}CH-^{6}CH, 2H); 3.90 (CH_2, 2H); 6.45 (^{2}CH,1H); 7.10-7.70 (Ar.H, 9H).
V_d	155	85	1680	1760		210	15900	δ1.00 (CH_3, 3H); 2.32 (p-CH_3, 3H); 2.90
						286	17200	($^4CH_2$,2H); 3.60-3.80(^{5}CH-^{6}CH,2H); 3.90 (CH_2,2H); 6.43(^{2}CH,1H), 7.00-7.70 (Ar.H,9H)

a, KBr; b, CH_3CH_2OH; c, $CDCl_3$



III_{a-d} III'_{a-d}

(II) Reaction with ethyl acetoacetate. The products obtained from the reaction of either 3-chloroketones Ia-d or benzalacetophenones II_{a-d} with ethyl acetoacetate in the presence of sodium ethoxide were found to depend entirely on the temperature used for the reactions. When the reactions were carried out at a low temperature, the hydroxy compounds, ethyl 3-hydroxy-3-phenyl-5-aryl-cyclohexane-1-one-6-carboxylate IV_{a-d} were isolated and characterised. On the other hand, when the reactants were refluxed the olefinic products ethyl 3-phenyl-5-aryl-cyclohex-2-ene-1-one-6-carboxylate V_{a-d} were obtained (Scheme 2), which are identical with those obtained by Samour [16] and others [17].



Scheme 2

The structures of the products are established from their spectral data. Thus ir spectra of compounds IV_{a-d} show bands at 1680-1710 (C=O), 1735-1740 (C=O of the ester group), and 3400-3490 (OH) cm^{-1}. The ir spectra of V_{a-d} show the absence of the OH band, besides the presence of other characteristics bands. Further support for the assigned structures comes from the ^{1}Hnmr spectra. The ^{1}Hnmr spectra of IV_a show a triplet (3H, CH_3 of the ester group) at δ1.02 ppm, a singlet (1H, OH) at δ2.00 ppm, a singlet (2H, C_2) at δ2.35 ppm, a doublet (2H, C_4) at δ3.30 ppm, a multiplet (4H, CH_2-O, C_5, C_6 protons) at δ3.80-4.30 ppm and multiplet at δ7.60 ppm for the aromatic protons. The ^{1}Hnmr of Va show a singlet at δ 6.46 ppm for the C_2 vinylic proton, other values are almost similar to IV_a. The signal corresponding to the OH proton at C_3 disappeared. The uv spectra of compounds V_{a-d} gave further support to their structures. (Table 1).

Experimental

Infrared and ultraviolet spectra were record on Unicam SP-1025 and 1805 respectively. ^{1}Hnmr spectra were recorded at Varian A (90 MHz) instrument. Microanalyses were performed in Cairo University Microanalytical Laboratories, Cairo, Egypt. All compounds gave correct elemental analysis within experimental error. Melting points and percentage yield are collected in Table 1.

3-Chloro-3-(p-substituted phenyl) propiophenones I_{a-d}. Dry hydrogen chloride gas was bubbled into a cold mixture of the appropriate *p*-substituted benzaldehyde (0.1 mole) and acetophenone (0.1 mole) until saturation (30 min.). The solid separated was filtered, washed, dried and crystallised from benzene.

p-Substituted benzalacetophenones II_{a-d}. These compounds were obtained as reported earlier [18-20] by the reaction of equimolecular amounts of acetophenone and the appropriate *p*-substituted benzaldehydes.

Ethyl 2-carbethoxy-3-phenyl-4-benzoylbutyrate III_{a-d}. The title compounds were obtained when:

(a) A solution of the appropriate 3-chloro-3-(*p*-substituted phenyl) propiophenone I_{a-d} (0.0025 mole) in 10 ml of absolute ethanol was refluxed for 4 hr. with diethyl malonate

(0.003 mole) in the presence of sodium ethoxide (0.003 mole). The reaction-mixture was filtered while hot to remove the separated sodium chloride, and then left overnight at room temperature. The separated solid was filtered, washed and dried. The solid was crystallised from ethanol to give the corresponding products III_{a-d}.

(b) The corresponding *p*-substituted benzalacetophenone II_{a-d} (0.0025 mole) was dissolved in 10 ml of absolute ethanol and allowed to react with diethyl malonate (0.0030 mole) in the presence of a catalytic amount of sodium ethoxide. The reaction mixture was refluxed on a water bath for 4 hr., and left overnight at room temperature. The separated solid was filtered, washed, dried and crystallised from ethanol.

Ethyl 3-hydroxy-3-phenyl-5-aryl-cyclohexane-1-one 6-carboxylate IV_{a-d}. The title compounds were obtained when:

(a) A cold mixture of the appropriate 3-chloroketone I_{a-d} (0.0025 mole) and ethyl acetoacetate (0.003 mole) was added to 10 ml of absolute ethanol and sodium ethoxide (0.003 mole). The reaction-mixture was kept in the ice-box overnight. The precipitated solid was filtered, washed dried and crystallized from ethanol.

(b) The corresponding *p*-substituted benzalacetophenones (0.0025 mole) were treated with ethyl acetoacetate (0.0030 mole) in the presence of a catalytic amount of sodium ethoxide following the previous procedure (a).

Ethyl 3-phenyl-5-aryl-cyclohex-2-ene-1-one-6-carboxylates V_{a-d}. The title compounds were obtained when the previous experiment for the preparation of IV_{a-d} was carried out at reflux. After work up the separated solid was crystallized from ethanol.

References

1. H. Rupe and F. Schneider, Ber., **37**, 957 (1904).
2. L. Konnor, Ber., **21**, 1209 (1888).
3. T.I. Crowell, R.T. Kemp, R.E. Lutz and A.A. Wall, J. Am. Chem. Soc., **90**, 4638 (1968).
4. T.I. Crowell and L. Hwang, J. Am. Chem. Soc., **98**, 4315 (1976).
5. L. Claisen and Claparede, Ber., **14**, 2463 (1881).
6. F.H. Al-Hajjar and Y.A. Al-Farkh, J. Chem. Eng. Data., **25**(1), 85 (1980).
7. E.P. Kohler, Am. Chem. J., **46**, 482 (1911).
8. W. Hanhart and C.K. Ingold, J. Chem. Soc., 997 (1927).
9. Y.A. Al-Farkh, F.H. El-Hajar and H.S. hamoud, J. Heterocyclic Chem., **16**, 1 (1979).
10. W. Borsche, Ber., **42**, 4497 (1909); Meerwein, J. Prakt. Chem., **97**, 274 (1918).
11. F.H. El-Hajjar, Y.A. Al-Farkh, H.S. Hamoud and Y. Al-Sultan, Chem. Pharm. Bull., **27** (11), 2767 (1979).
12. Y.A. Al-Farkh, F.H. El-Hajjar, H.S. Hamoud and Y. Al-Sultan, Annu-Res. Rep-Kuwait Inst. Sci. Res., 180 (1978), C.A., **89**, 146554t (1978).
13. L. Fisnerova and B. Kakac, Kraus, Biochem., Prague, Gech, *Collect. Czech. Chem. Coomun.*, *41* (2), 326 (1976).
14. W. Borsche, Ber., **42**, 4406 (1909).
15. A. Sammour M.I.B. Selim and M.S. Abdel Halim, Egypt J. Chem., **15**, 23 (1972).
16. A. Sammour, M.T. El-Zimaity and A. Abdel -Maksoud, J. Chem., UAR, **12** (4), 481 (1969).
17. G.A. Hanson, Bull. Soc. Chem. Belges., **66**, 654 (1927); ibid. **65**, 1024 (1956).
18. V. Hanzlik and A. Bianchi, Ber. **32**, 2282 (1899).
19. E. Weitz and A. Schefer, Ber., **54**, 2338 (1921).
20. W. Davey and J.R. Cwilt, J. Chem. Soc., 1008 (1957).