Pergamon

Tetrahedron, Vol. 53, No. 49, pp. 16789-16794, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10081-3

MEDIA CONTROLLED PHOTO - FAVORSKII TYPE REARRANGEMENT OF α-CHLORO ACETOPHENONES: SYNTHESIS OF PHENYLACETIC ACIDS†

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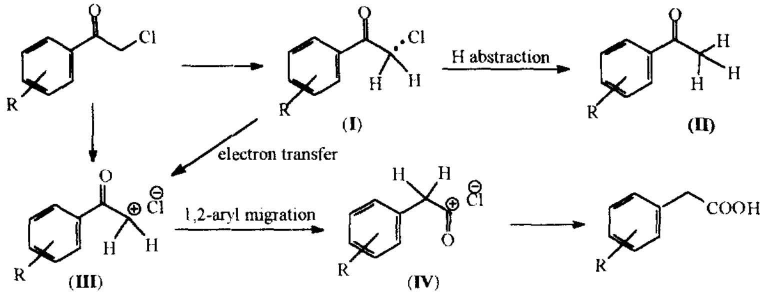
Abstract: Photolysis of substituted α-chloro acetophenones has been studied in different solvent systems wherein 1,2-aryl migration is found to be media controlled. Effect of substituents on the migratory aptitude and a direct access to phenylacetic acids, in practical yields, has been described.

Amongst α-arylalkanoic acids, the importance of phenylacetic acids as key intermediates in the drug, agrochemical industries and as antiinflammatory agents is well known[1]. The earlier synthetic approaches to this class of compounds were confined to Willgerodt reaction[2], Darzens reaction[3] and carbonylation of benzyl halides[4]. In recent years, synthetic aspect of 1,2-aryl migration reactions observed in α-haloalkyl aryl ketones in the presence of metal catalyst, leading to the formation of α-aryl alkanoic acids, has acquired a great interest[5]. Although, an analogous photo-induced 1,2-aryl migration in α-substituted alkyl aryl ketones which is reminiscent of the Favorskii rearrangement[6] is known, its synthetic applicability to α-aryl alkanoic acids has received a limited attention. The reports[7] on photobehavior of α-substituted ketones reveal that the success of 1,2-aryl migration is influenced by number of other competitive photoprocesses such as photo-reduction, solvolysis and Norrish type I and II reactions. The efficiency of product distribution is dependent on (a) the type of α-substituent (α-halo, α-tosyloxy, α-mesyloxy, α-acetoxy) to carbonyl group[8] (b) the nature and position of the substituent in phenyl ring[7] and (c) the reaction medium[7f]. The mechanistic investigation for different type of photo-processes[7d, 7e] (**Scheme 1**) envisages an initial step as the C-Cl bond homolysis (**I**) which manifests as a common source for both types of products. If the radical is intercepted by a hydrogen atom source, the process leads to a reduction product (**II**). On the other hand, an electron transfer in the radical pair leads to an ionic intermediate (**III**) which undergoes either nuclophilic attack of the solvent to give solvolysis product or 1,2-aryl rearrangement to give (**IV**) followed by attack of solvent to afford photo-Favorskii product (**V**).

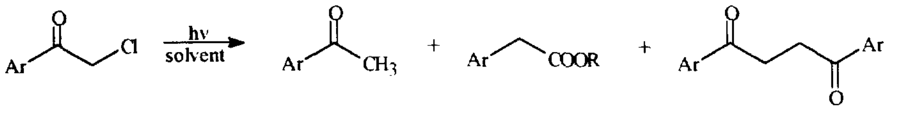
We thought that, if such carbocationic species (**III**) is the likely intermediate for such rearrangement, then dispersal of the developing positive charge will certainly provide much of the driving force for the formation of both ionic species (**III and IV**) and hence the rearranged product. As a continuation of our interest in the synthesis of α-aryl alkanoic acids[7f, 7g, 9], we have now studied the synthetic aspects of photochemical reaction of α-chloro acetophenones in different solvent systems and demonstrated that the photoprocess of α-chloro acetophenones in polar media, could be directed in a more specific way towards 1,2-aryl migration leading to the formation of phenylacetic acids in preparative yields.



Scheme 1

The photolysis of 2% degassed solution of α-chloro acetophenones **1a-d**[10] in methanol was re-examined using Rayonet RPR 208 photoreactor fitted with 300nm lamp and propylene oxide as a halogen acid scavenger[7f, 11]. After 4h of irradiation, the products were isolated by standard chromatographic techniques. The results, as depicted in **Table 1**, indicate that the substrates **1a-d** have shown major proclivity for the formation of acetophenones **2a-d** (reduction product) and this far supersedes the formation of 1,2-aryl rearrangement products **3a-d**[12] (**eq. 1**). The irradiation of α-chloro acetophenones **1a-d** was first studied in 1,4-dioxane-water (95:5)[13]. The use of water as cosolvent, which can act as a nucleophile as well, will lead directly to phenylacetic acids whereas when alcohols are used esters are produced which have to be hydrolyzed, if the acid is required. However, during this photolysis the starting compounds **1a-d** were recovered up to ~90% yields even after the irradiation for 12h. In an attempt to study the photoreactivity in more polar medium, photo-reactions of **1a-d** were performed in acetone-water (95:5)[13] wherein, significantly, the overall photo-reactivity and in particular the efficiency of rearrangement process i.e. formation of phenyl acetic acids **4a-d,** had been increased and that of **2a-d** had been suppressed (**Table 1**). In addition, the reaction led to the formation of a new dimeric product **5a-d** in low yield, probably resulting from the radical-radical coupling of homolytically cleaved C-Cl bond (**eq. 1**).

It is interesting to note that during photolysis, α-chloro acetophenones **1a-d** reacted in aqueous acetone and not in aqueous dioxane although water is present in excess. Presumably, this change in photoreactivity is due to the polarity of the acetone media compared to 1,4-dioxane. As the electrostatic interaction energy (repulsion) between the dipoles C=O and C-Cl is inversely proportional to dielectric constant (ε)[14], it was expected that this energy would be reduced in solvents with high ε which could lead to a preferred conformation of α-chloro acetophenone to favour 1,2-aryl migration. We have therefore examined the effect of acetonitrile as the solvent on the photo-rearrangement process as ε of acetonitrile (37.5) is more than that of acetone (20.7) and of 1,4-dioxane (2.2). Thus, when **1b** was photolysed in acetonitrile-water (95:5)[13] for 4h, indeed the phenylacetic acid **4b** was isolated in 70% yield; while photoreduction **2b** and dimerisation **5b** products were obtained in low yields (**Table 1**). Accordingly, the photo-behavior of number of substituted α-chloro acetophenone **1a-j** in aqueous acetonitrile was investigated. The results depicted in **Tables 1** and **2** indicate the preponderance of photo-Favorskii type rearrangement in aqueous acetonitrile furnishing higher yields of phenylacetic acids as compared to aqueous acetone as the reaction medium. The photo-reaction in aqueous acetonitrile was also examined using sunlight as the light source in pyrex tube wherein, as exemplified for **1b** and **1e** the corresponding acids **4b** and **4e** were obtained in 84% and 78% yield.



eq. 1

1a-j **2a-j** **3a-d** R=CH3; **4a-j** R=H **5a-d**

Table 1. Photolysis of α-Chloro Acetophenones **1a-d** - Effect of Reaction Medium[a] on Product Distribution

Entry	Substrate		Photolysis products (% yield)[b]							
	1	Ar	In methanol		In aq. acetone			In aq. acetonotrile		
			2	**3**	**2**	**4**	**5**	**2**	**4**	**5**
1	**a**	phenyl	60 (53)[c]	00 (00)[c]	37	24	29	14	**47**	18
2	**b**	4-methyl phenyl	62 (58)[c]	06 (04)[c]	24	47	23	14	**70**	11
3	**c**	4-methoxy phenyl[d]	35 (30)[c]	34 (32)[c]	16	43	14	09	**54**	08
4	**d**	4-chloro phenyl[e]	60 (55)[c]	00 (00)[c]	10	14	31	06	**35**	18

[a] During the photoreaction in aq. dioxane ~90% of starting material was recovered [b]Yields refered to isolated products. [c]Yields reported by Anderson and Reese. [d]4-methoxy chlorobenzene was isolated: in methanol - 17%, in aq. acetone - 19%, in aq. acetonitrile - 19%. [e] Starting material was recovered: in methanol 30%, in aq. acetone 34%, in aq. acetonitrile 33%.

Table 2. Photolysis of **1e-j** in Acetonitrile-Water (95:5): Synthesis of Phenylaceticacids:

Entry	Substrates		Photolysis products (% yield)[a]		
	1	Ar	**2**	**4**	**5**
1	**e**	4 -hydroxy phenyl	05	**75**	10
2	**f**	4 -ethyl phenyl	07	**81**	08
3	**g**	4 -isobutyl phenyl	10	**72**	05
4	**h**	4 -cyclohexyl phenyl	06	**68**	07
5	**i**	2,4 -dimethoxy phenyl[b]	05	**52**	-
6	**j**	2,4,6 -trimethyl phenyl[c]	22	**32**	-

[a] Yields refer to isolated products. [b] 2,4-Dimethoxy chlorobenzene was isolated in 32%.
[c] 5,7-Dimethyl-1-indanone was isolated in 25%.

A noticeable substituent effect on the propensity for 1,2 aryl migration in aq. acetonitrile was also observed. Thus, the para-alkyl-(**1b, 1f, 1g, 1h**) and para-hydroxy-(**1e**) substituents in phenyl ring significantly favour the rearrangement process; while in case of para-methoxy-(**1c**) and 2,4-dimethoxy-(**1i**) substituent, the formation of 4-methoxy chlorobenzene and 2,4-dimethoxy chlorobenzene, respectively, was found to be a competitive process-lowering the yield of corresponding acid. The photo-behavior of the acetophenone (**1j**) shows the effect of the *ortho*-methyl group. Here photo-induced enolisation is equally probable process[7d] leading to the formation of 5,7-dimethyl-1-indanone in comparable yield. This substituent effect could be rationalized on the phenomenon of "state switching" of the exited triplet states (n-π^* or π-π^*) as described earlier[7c, 7f].

In conclusion, photo-Favorskii type rearrangement of α-chloro acetophenones is found to be media controlled and facilitated in aq. acetonitrile. The present methodology thus provides an easy and direct access for the synthesis of phenlyacetic acids under environmentally friendly and mild conditions.

Experimental:

^{1}H NMR (200 MHz) spectra were recorded on Brucker AC 200 spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are reported in ppm (δ) relative to internal standard Me_4Si. IR spectra were obtained with Perkin-Elmer 1600 spectrophotometer. Carbon and Hydrogen analyses were performed on a Hosli Carbon-Hydrogen analyzer. Melting points were measured with Thomas Hoover capillary melting point apparatus and are uncorrected. The photo-reactions were conducted in oven-dried glassware under dry N_2 using Rayonet RPR-208 photoreactor fitted with 300nm lamp. On work up, the solvents were evaporated at reduced pressure with Buchi rotary evaporator. Thin layer chromatography was performed on 0.25 mm precoated silica gel polygram Sil G/UV 254. Flash chromatography was carried out on silica gel (200-400 mesh). All solvents, methanol, acetone, acetonitrile, benzene, dichloroethane, diethyl ether, petroleum ether (pet. ether, 60-80°C fraction), ethyl acetate were purified and dried before use. The starting α-chloro acetophenones **1a-j** were prepared by Friedel Craft acylation of correspondingly substituted aromatic compounds using chloro acetyl chloride, in the presence of $AlCl_3$, as per literature procedures[10]. The controlled experiments in the dark indicated no change in the starting compound even after 48h[7f]. Photolysis of α-chloro acetophenones **1a-d** in methanol was performed as reported method[12]. ***Caution:*** *All the α-chloro acetophenones are lachrymators and should be handled carefully in a good ventilated hood.*

Photochemical synthesis of phenyl acetic acids 1a-j; General procedure: A 2% solution of α-chloro acetophenone **1a-j** (1.0g, in 50mL) in 5% aqueous acetone or aqueous. acetonitrile was degassed by passing N_2 gas for 15 minutes, followed by addition of propylene oxide (3mL). The solution was irradiated in a Rayonet photoreactor with 300nm light. In case of sunlight experiment irradiation was carried for 8h. The progress of the reaction was monitored by periodic TLC of aliquots at different intervals of time. Generally, after an irradiation for 4h (in case of 1h and 1j for 6h), the solvent was evaporated at reduced pressure and residue was extracted in ether (40mL). The ether layer was extracted with 10% sodium bicarbonate solution (3x5mL) and alkaline layer was acidified with 3N HCl. The ether layer was kept aside for further work up. The solid that separated on acidification of the alkali layer was extracted in ether (3x10mL), ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the ether gave solid which was identified as corresponding phenyl acetic acid based on IR and NMR spectral and physical data and comparison with reported one. The ether layer which was kept aside was concentrated and residue obtained was subjected to chromatographic separation. Elution first with pet. ether and then with pet. ether/ethyl acetate (98:2) afforded two major products: acetophenones[15] and dimeric products[16] which were characterized through identity of IR and NMR spectral properties. In case of **1c** and **1i** corresponding chlorobenzene derivatives; while in case of **1j** 5,7-dimethyl-1-indanone was isolated and were identified by IR and NMR spectral data and comparison with authentic data. Photolysis of **1a-j** (1.0g) in acetonitrile/water (95:5), as described above, afforded corresponding phenyl acetic acid **4a-j**.

4a, 0.41g, (47%); mp 75-77°C (Lit.,[10] mp 77°C).
4b, 0.62g, (70%); mp 87°C (Lit.,[10] mp 89-90°C).
4c, 0.48g, (54%); mp 86°C (Lit.,[10] mp 86-88°C).
4d, 0.32g, (35%); mp 102°C (Lit.,[10] mp 104-106°C).
4e, 0.66g, (75%); mp 147°C (Lit.,[17] mp 149-151°C).
4f, 0.72g, (81%); mp 85°C (Lit.,[17c] mp 88-89°C).
4g, 0.66g, (72%); mp 85°C (Lit.,[17c] mp 85-87°C).
4h, 0.63g, (68%); mp 75°C (Lit.,[17c] mp 76-77°C).
4i, 0.47g, (52%); mp 111°C (Lit.,[17d] mp 113°C).
4j, 0.28g, (32%); mp 171°C (Lit.,[17c] mp 172°C).

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† Dedicated to Prof. M. S. Wadia on the occasion of his 60th birthday.

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Acknowledgements: We are thankful to University Grants Commission, New Delhi for Teacher Fellowship to Vasant P. Mali and All India Council for Technical Education (AICTE), New Delhi for financial support.

(*Received in UK* 7 *August* 1997; *revised* 15 *September* 1997; *accepted* 18 *September* 1997)