Heterocyclic Letters
Vol. 7| No.2|341-345|Feb-April| 2017
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF NOVEL 2-(HALOGENATED ARYL) PROPANOIC ACIDS VIA PHOTOLYSIS

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Abstract: The present paper presents the simple and efficient synthesis of four novel 2-(Halogenated Aryl) propanoic acids **3a-3d** starting from halogenated propiophenones. These halogenated propiophenones first converted into halogenated α-chloropropiophenones **2a-2d** which on photochemical transformation in presence of acid scavenger furnished 2-(Halogenated Aryl) propanoic acids in moderate yields.

Keywords: 2-(Halogenated Aryl) propanoic acids**,** α-chloropropiophenones**,** Anti-inflammatory, Photolysis

Introduction

2-Arylpropanoic acids have emerged as an important class of non-steroidal anti-inflammatory (NSAI) agents during past two decades.[I] The medicinal activity of 2-Arylpropanoic acids appears to be related to their three key structural features which involve: the propanoic acid side chain, substituents on the phenyl ring and an additional hydrophobic group. In addition to these structural features, the stereochemical disposition of the methyl group is also intimately connected with the activity.[II] Some of the commonly used 2-arylpropanoic acids are Naproxen, Ketoprofen, Ibuprofen, Fluriprofen, Suprofen and Pirprofen.[III] 2-(3'-chlorophenyl) propanoic acid is one of the compound which has also been known for its anti-inflammatory activity.[IV]

In view of the anti-inflammatory activities and wide applications of 2-arylpropanoic acid, several methods have been developed for their synthesis. Among those reported methods, a methodology which involves the synthesis of 2-arylpropanoic acid from the starting material 2-halopropiophenones found to be the most simplest and effective.[V-VII] Rest methods suffered from the drawbacks of multistep reaction sequence and low yield.[VII-XIII] As a part of continuous endeavour to develop new and efficient approach for the synthesis of 2-arylpropanoic acid from 2-halopropiophenones, Sonawane et al developed a single step, efficient photochemical approach which involves carbonyl triplet excited state directed 1, 2-aryl migration of the aryl group.[XIV] Hence it was decided to apply the same methodology for the synthesis of above mentioned bioactive compound 2-(3'-chlorophenyl) propanoic acid

and check the applicability of this method for the synthesis of different derivatives (**Figure 1**).

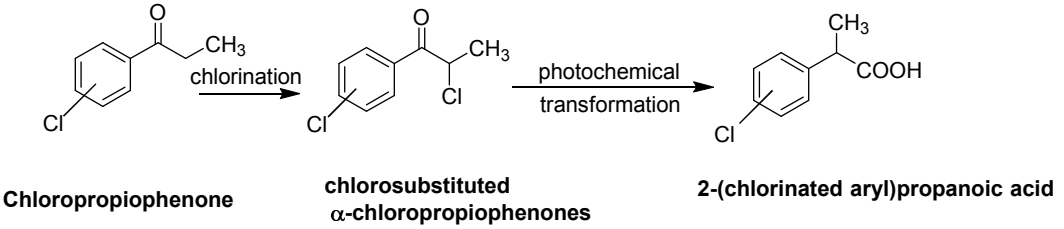
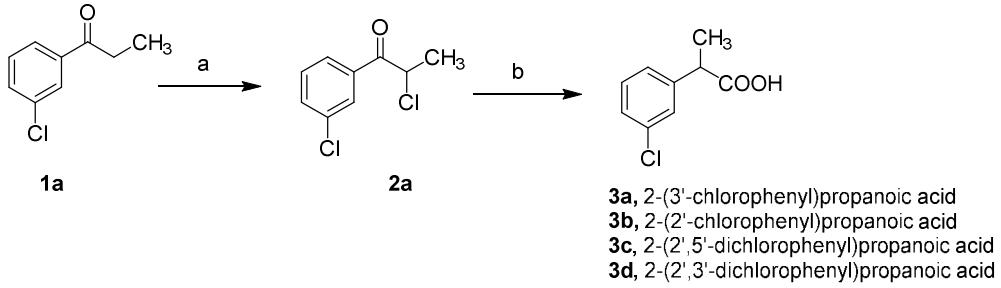


Figure 1. Systematic approach for the synthesis of 2-(chlorinated aryl)propanoic acid

To the best of our knowledge, this is for the first time we have applied this photochemical approach for the synthesis of 2-(chlorinated aryl) propanoic acids **3a-3d** and successfully obtained these acids in moderate yield of 45-50%. Formation of corresponding benzoic acid as a byproduct was also confirmed in this study.

Results and Discussion

To accomplish our projected synthesis, we started with 3'-chloropropiophenone (**1a**). First is the side chain chlorination of 3'-chloropropiophenone (**1a**) to obtain 1-(3'-chlorophenyl)-2-chloro-1-propanone (**2a**) which undergoes photochemical transformation to yield desired compound 2-(3'-chlorophenyl)propanoic acid (**3a**) (**Scheme 1**).



Scheme 1: a) Chlorine, EDC, $AlCl_3$, 95-98%; b) Aqueous acetone, propylene oxide, sunlight, N_2, 40-45%

Compound **2a** was obtained by reacting **1a** with chlorine in dichloromethane in the presence of aluminium chloride at room temperature. The reaction was completed in 2 h and an oily product obtained with b.p. 256-258 °C. In the IR spectrum a band of 1707 cm^{-1} indicates the presence of ketocarbonyl group and shifting of carbonyl frequency from 1684 to 1707 cm^{-1} confirms the introduction of chlorine at 2 position. The yield of product was 98%. Photochemical transformation of compound **2a** into **3a** was done by exposing it to sunlight for 16 h in the presence of propylene oxide in aqueous acetone. Crude product obtained was subjected to column chromatography. In initial fractions a thick liquid was obtained which was correctly analyzed for $C_9H_9ClO_2$. In IR spectrum the band of 3300-2500 cm^{-1} indicates the presence of acid group and the band at 1710 cm^{-1} confirms the presence of acid carbonyl group. Further structure confirmation was done on the basis of PMR spectra. The yield of the compound was ~47%. On further elution with the same solvent, a white solid was obtained with m.p. 157 °C. The compound was dissolved in sodium bicarbonate solution and precipitated after acidification. Elemental analysis suggested the compound formula $C_7H_5ClO_2$. Band at 3430-2500 and 1688 cm^{-1} in IR spectra indicates the presence of acid group. On the basis of above data, the obtained compound was confirmed as *m*-chlorobenzoic acid. The yield of this byproduct was ~22%.

To check the generality of this method, different derivatives of chloropropiophenones like 2'-chloropropiophenone, 2',5'-dichloropropiophenones and 2',3'-dichloropropiophenones have studied. In all cases, the desired 2-aryl propanoic acids were obtained from corresponding 2-chloropropiophenones in 45-50% yield and the formation of corresponding benzoic acids in 20-25% yield as a byproduct was also confirmed.

Plausible mechanism for the formation of 2-arylpropanoic acid from corresponding chloro propiophenones has already been discussed by Sonawane et al.[XV] Possible mechanism for the formation of unexpected benzoic acids as a byproduct is outlined below. One possibility is the involvement of both $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ triplets (**Figure 2**). The genesis of the formation of chlorobenzoic acid can be due to the oxygenation of the triplet states. Such photooxygenation of triplet excited states has been discussed earlier also.[XVI, XVII]

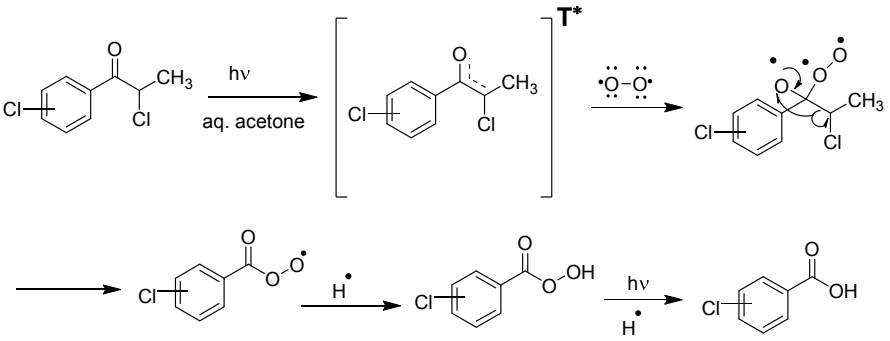


Figure 2: Oxygentaion of the triplet states to form chlorobenzoic acid

Second could be the typical Norrish type-I; α-cleavage (**Figure 3**). Norrish type-I cleavage leads to the formation of acyl and ethyl chloride radical. The reaction of acyl radical with ground state triplet oxygen is responsible for the formation of chlorobenzoic acids.

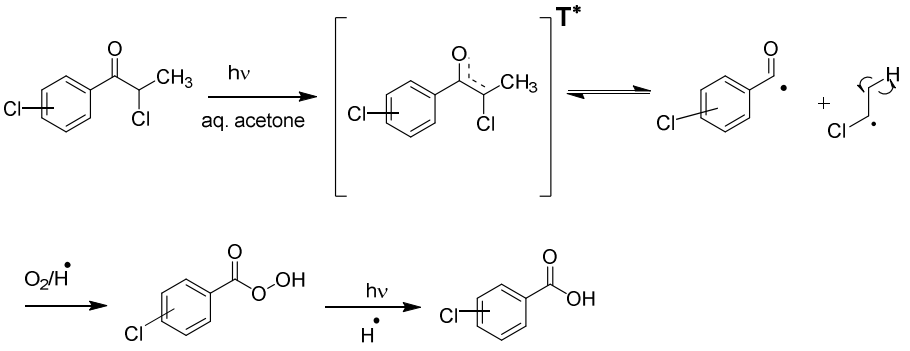


Figure 3: Formation of chlorobenzoic acid via Norrish type-I cleavage

Experimental Section

General

All melting points recorded are uncorrected and are measured in degree Celsius with a Thomas Hoover Capillary melting point apparatus. NMR spectra were recorded on Joel FX 90Q (90 MHz) and Varian Mercury 300 (300 MHz) spectrometers using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on FT IR-Perkin Elmer 1600 instrument. Elemental analysis was obtained using Hoslis's and Perkin Elmer 2400 carbon-hydrogen analyzer. All studies were done at Department of Chemistry, University of Pune.

General procedure for the preparation of chlorosubstituted α-chloropropiophenones (2a-2d)

A suspension of anhydrous aluminium chloride (0.0022 mol) and chloropropiophenone **(1a-1d)** (0.059 mol), in dry dichloromethane (50 ml) was stirred at room temperature for 0.5 hr. Chlorine gas was purged into a solution over a period of 2 hr. At room temperature (monitored by G.C) and the reaction mixture is poured into ice cold water. The organic layer was separated and aqueous layer extracted with dichloromethane (25 ml). The combined organic layer was washed with water and dried over Na_2SO_4. Evaporation of solvent gave an oily product which on distillation provided chlorosubstituted α-chloropropiophenones.

General procedure for the preparation of 2-(chlorinated aryl propanoic acids (3a-3d)

A solution of chlorosubstituted α-chloropropiophenone (0.0025 mol) in acetone: water (95:5, 45 ml) was degassed by passing N_2 for 15 minutes followed by addition of propylene oxide (2.7 ml). The solution was exposed to sunlight for 16 h. (monitored by TLC). The solvent was evaporated under reduced pressure and the residue obtained was extracted with ether (5 ml x 2) and the aqueous layer was acidified with 10 % hydrochloric acid. The precipitated product was extracted with ether (5 ml x 3). The ether layer was washed with water and dried over Na_2SO_4. Evaporation of the ether layer gave a gummy mass which was chromatographed over a silica gel using hexane: ethyl acetate (9: 1) as an eluent to give 2-aryl propanoic acids.

2-(3'-chlorophenyl)propanoic acid, 3a: Thick oil; [Found: C, 58.30; H, 4.93 $C_9H_9ClO_2$ requires C, 58.55; H, 4.91%]; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.22-7.36 (m, 4H, Ar-H), 3.72(q, 1H, -C**H**CH_3, J=6.9Hz), 1.52(d, 3H, -CH**CH_3,** J=6.9Hz); IR (KBR); 3300-2500, 1710 cm^{-1}.

2-(2'-chlorophenyl)propanoic acid, 3b: m.p. 85-86 °C; [Found: C, 58.65; H, 4.86 $C_9H_9ClO_2$ requires C, 58.55; H, 4.91%]; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.2-7.4 (m, 4H, Ar-H), 4.28(q, 1H, -C**H**CH_3, J=6.9Hz), 1.54(d, 3H, -CH**CH_3,** J=6.9Hz); IR (KBR); 3400-2550, 1703 cm^{-1}.

2-(2',5'-dichlorophenyl)propanoic acid, 3c: White solid, m.p. 110-112 °C; [Found: C, 49.20; H, 3.78 $C_9H_8Cl_2O_2$ requires C, 49.34; H, 3.68 %]; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.2-7.35 (m, 3H, Ar-H), 4.21(q, 1H, -C**H**CH_3, J=6.2Hz), 1.52(d, 3H, -CH**CH_3,** J=6.9Hz); IR (KBR); 3300-2500, 1705 cm^{-1}.

2-(2',3'-dichlorophenyl)propanoic acid, 3d: White solid, m.p. 108-110 °C; [Found: C, 49.40; H, 3.72 $C_9H_8Cl_2O_2$ requires C, 49.34; H, 3.68 %]; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.18-7.34 (m, 3H, Ar-H), 4.21(q, 1H, -C**H**CH_3, J=6.9Hz), 1.52(d, 3H, -CH**CH_3,** J=6.9Hz); IR (KBR); 3300-2500, 1707 cm^{-1}.

Conclusion

Photolysis of chlorosubstituted α-chloropropiophenones in aqueous acetone is proved as an efficient and potential one step method for the production of 2-(chlorophenyl) propanoic acids in moderate yields.

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Received on February 17, 2017.