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A UNIQUE 1,2-SHIFT SELECTIVITY IN 2-HYDROXYPROPIOPHENONE DIMETHYLACETALS: GENERATION OF NEW METHODOLOGIES FOR METHYL-2-ARYLPROPANOATES AND 1,2-CARBONYL TRANSPOSITION+

H. R. Sonawane*, B. S. Nanjundiah, D. G. Kulkarni and Jaimala R. Ahuja
National Chemical Laboratory, Pune 411 008 (INDIA)

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Abstract: α-Hydroxydimethylacetals I have been shown to undergo two different rearrangements involving highly selective 1,2-shifts under mild conditions. When treated with Ph_3P/CCl_4 in the presence of pyridine, I were cleanly transformed via 1,2-aryl shifts into methyl 2-arylpropanoates, an important class of anti-inflammatory agents; a pronounced substituent effect has been observed in this rearrangement.

On the other hand, treatment of I with catalytic amount of Ph_3P/I_2 in benzene furnished α-methoxy-α-aryl propan-2-ones in excellent yields and culminated in the development of a new methodology for 1,2-carbonyl transposition.

In the past several years, the chemistry of rearrangement reactions involving 1,2-shifts has remained one of the most fascinating areas of organic research.[1] The topic has been approached mostly from its mechanistic aspects, great attention having been focussed on the issue of competitive migratory aptitude[2] (CMA) of atoms or groups. The ratio of the products arising from 1,2-shifts of various migrants is generally considered as a measure of CMA.[2] However, from a synthetic point of view, these rearrangements are not yet considered useful, as effective control over selective migration cannot be easily achieved.[2] In view of these observations, if a fine control over 1,2-selective shift of two potential migrants of diverse nature can be achieved, it would be of great synthetic potential.

In general, the reaction of alcohols with triphenylphosphine in combination with CCl_4/halogens is found to be a very useful method to obtain the corresponding alkyl halides in high yields without rearrangement.[3] In this connection, it may be noted that these reactions are successfully carried out with[4] or without[5] organic bases such as amines along with Ph_3P/halogen; however, the role of such an external base in this transformation is not clearly understood. Nevertheless, it has been pointed out that one of the intermediates, viz. the ylid $Ph_3P{=}CCl_2$ formed by the reaction of Ph_3P and CCl_4 is a strong base and therefore use of an external base is not recommended.[6] α-Hydroxyacetals by virtue of possessing both the masked keto and hydroxy functionalities make potential substrates for rearrangement reactions of synthetic utility. Therefore, it was interesting to subject the readily accessible 2-hydroxypropiophenone dimethylacetals I to the above mentioned halogenation reactions. After extensive experimentation of I with Ph_3P/CCl_4 and Ph_3P/I_2 under a variety of conditions, we were surprised to find that an external base plays a crucial role in diverting the course of the reaction, and culminating in two interesting rearrangements which are described below.

RESULTS

Rearrangement of α-Hydroxyacetals I with Ph_3P/CCl_4 [Rearrangement A]

Treatment of I with Ph_3P/CCl_4 in CH_2Cl_2 in presence of pyridine, instead of affording the corresponding chlorides, surprisingly led to an altogether different type of products, whose spectral data (IR,PMR) indicated the presence of a $-COOCH_3$ and a secondary methyl group at the benzylic carbon. These structural features present in most of the products (vide infra) strongly suggested the occurrence of a rearrangement involving aryl migration. An analysis of their PMR and mass spectral data coupled with the elemental analysis enabled the characterization of the products as methyl 2-arylpropanoates, II (Eqn. 1). These structural assignments were confirmed by an alkaline hydrolysis of the products to the corresponding known 2-arylpropanoic acids. A different type of rearrangement occurred in a few cases leading to 1-methoxy, 1-aryl propan-2-ones, III (vide infra).

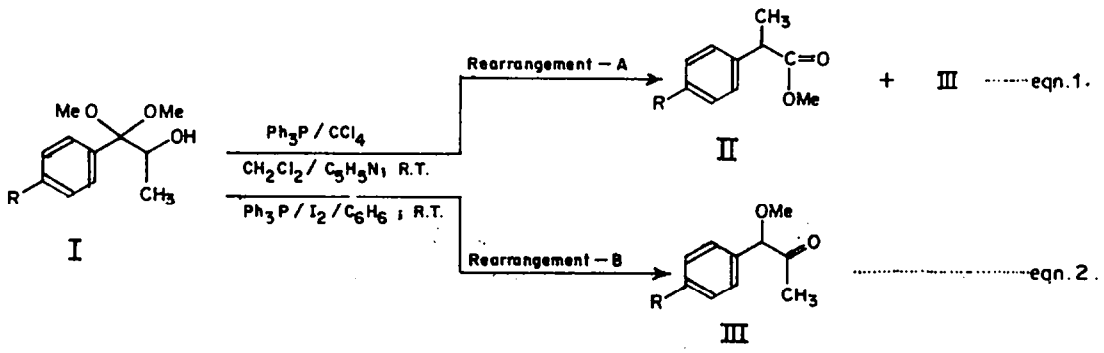
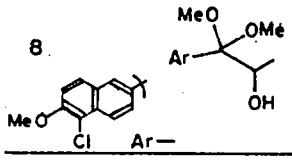
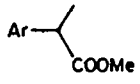
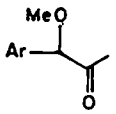


Table: Reaction Conditions for the Rearrangement of 2-Hydroxypropiophenone Dimethylacetals I

Entry Number	I R	Conversion[a] (%)	Rearrangement-A Yield[b] (%) II	III	Rearrangement-B[c] Yield[b] III
1	H	60	36	54	88
2	CH_3	70	75	-	85
3	i-C_4H_9	60	81[d]	-	78
4	OCH_3	80	87	-	82
5	Ph	83	80	-	75
6	Cl	35	36	36	90
7	CN	30	-	73	85
8		80	 85		 85

Notes: (a) Determined by GLC/PMR; (b) Isolated yields based on I consumed; (c) Resulted in high conversions (80-90%); (d) The corresponding acids of II [entry-3] and dehalogenated II [entry-8] are well-known anti-inflammatory agents, Ibuprofen and Naproxen, respectively.

A perusal of the results (Table) reveals that the aryl migration is strongly influenced by the polar effects of the aryl substituents. Electron-releasing methyl, isobutyl, methoxyl and phenyl substituents (entries 2-5) have led exclusively to aryl-migrated products II, the unsubstituted I (R=H) yielded II along with III. The aryl migration was suppressed with the introduction of an electron-withdrawing substituent (entry-6) and was completely absent in the cyano case (entry-7). Regarding the other type of products observed in certain cases (entries 1,6 and 7) the typical spectral features (IR, PMR) for the CH_3CO and Ar-CH-OCH_3 groups suggested the structure III and again, a complete spectral analysis and elemental composition data provided support to this structural assignment.

It is to be emphasized that the selective aryl migration occurring in high yields in the case of I with electron-releasing aryl substituents leading to II, constitutes a new methodology for the synthesis of 2-arylpropanoic acids, an important class of non-steroidal antiinflammatory agents.[7] It is interesting to note that the reaction of I with Ph_3P/I_2 in the presence of pyridine led to the same types of products described above. However, as the Ph_3P/CCl_4 reaction was cleaner, this reaction was resorted to for the study. It is also noteworthy that the reaction of I with Ph_3P/CCl_4 in the absence of pyridine gave a mixture of the corresponding chlorides and 2-chloro propiophenones, the latter obviously arising from the hydrolysis of the corresponding chloroacetals by hydrochloric acid liberated in situ.[8]

Rearrangement of α-Hydroxyacetals I under HI catalysis [Rearrangement-B]

On treatment of I with equimolar amounts of Ph_3P/I_2, the reaction mixture turned highly acidic[8] and gave rise to a mixture of products. Interestingly enough, with the adventitious use of catalytic amount

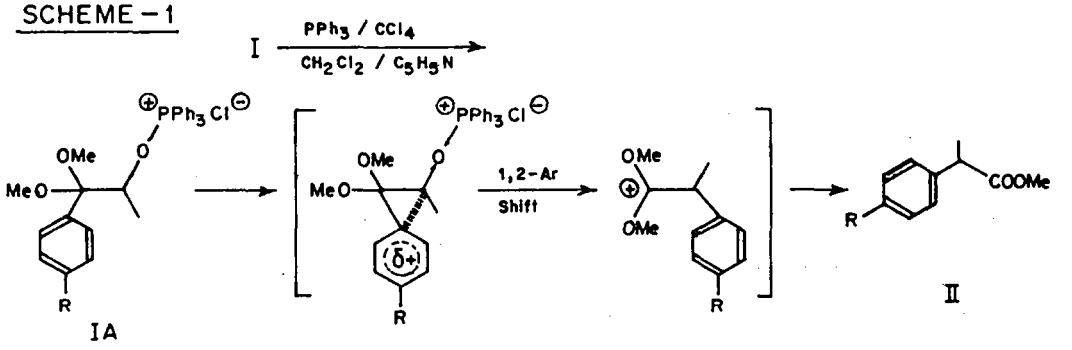
of iodine, the reaction followed an entirely different course and led to the exclusive formation of III (Eqn. 2). It is necessary to point out that surprisingly, Ph_3P was almost quantitatively recovered suggesting that the reaction is catalyzed by HI liberated in situ by the reaction of I with Ph_3P/I_2.[8] A careful analysis of the experimental conditions revealed that only a catalytic amount of HI generated as mentioned above was adequate for an efficient and clean transformation of I to III in high yields (Table). Furthermore, this technique of liberating HI in situ was found to be much superior when compared with the results obtained on addition of aqueous HI (55%) externally to the reaction mixture[9] in that the other competing reactions such as dimerization[10] and hydrolysis of the acetal to the parent ketone[11] were completely eliminated.

DISCUSSION

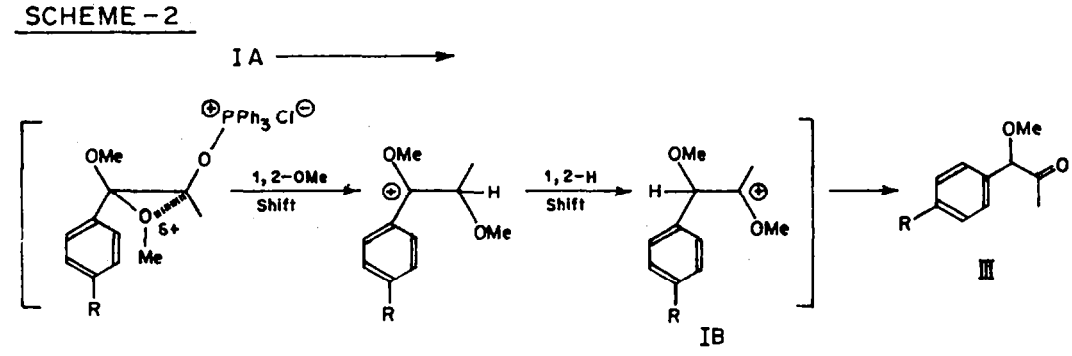
Rearrangement A:

Plausible Pathway: To understand the probable course of this rearrangement, it can reasonably be assumed that the reaction of Ph_3P/CCl_4 with the hydroxyl group in I leads to the corresponding phosphonium salt IA (Scheme 1) as the intermediates;[6] instead of the normal Arbuzov reaction of this salt leading to the alkyl halide, an intramolecular 1,2-aryl migration preferentially occurs resulting in the formation of II with the concurrent loss of triphenylphosphine oxide.

SCHEME – 1



SCHEME – 2



Use of pyridine appears to be responsible for directing the course of the reaction in favour of the observed rearrangement (Eqn. 1). A likely explanation for this may be found in the relative ease of the Arbuzov reaction under two different circumstances. In the absence of pyridine, the reaction medium becomes sufficiently acidic due to the liberation of HCl and α-ketophosphonium salts are formed as a result of the hydrolysis of the acetal group. In such α-ketophosphonium salts, the Arbuzov reaction involving a bimolecular nucleophilic attack (S_N2 pathway) is expected to be greatly accelerated due to the α-keto group;[12] whereas in the presence of pyridine, this accelerating effect of the keto group vanishes as the acetal group remains very much intact. In such a circumstance, the intramolecular aryl participation[13] assumes competitive importance leading to observed rearranged products, II.

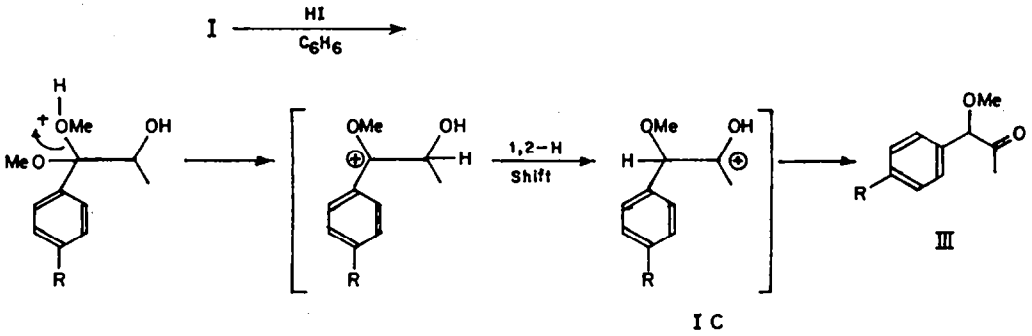
The same phosphonium salt IA responsible for the formation of II, may be imagined to lead to the products III (Scheme-2). While the aryl migration may lead to II, a competitive 1,2-methoxyl migration,[14] followed by a 1,2-hydride shift can result in the carbocation IB, the precursor of III.

It may be pointed out that the transformation of I to II and III constitute fine examples of selective 1,2-migrations, controlled by the nature of the aryl substituents. It can be recalled that the electron-releasing substituents in the phenyl ring have led to the products II, arising from exclusive aryl migration. Both aryl and methoxyl migrations have occurred in the case of unsubstituted and chloro-substituted I. In the case of the highly electron-withdrawing cyano-substituted I, methoxyl migration becomes the exclusive pathway.

Rearrangement B:

It should be emphasized that with almost quantitative recovery of triphenylphosphine and use of catalytic amounts of iodine, this reaction gets catalyzed by HI.

SCHEME – 3



I C

Formation of III in this reaction may probably be ascribed to a rearrangement (Scheme-3) involving acid-catalyzed loss of methanol[15] from I and subsequent 1,2-hydride shift leading to the carbocation, IC, the likely precursor of III. This overall mechanistic scheme appears to be reminiscent of the well-known pinacol rearrangement. It may be noted here that this reaction, unlike the previous one (vide Supra) is free from polar effects of the aryl substituents and offers III in high yields.

1,2-Carbonyl transposition is an extremely useful operation practised in synthetic organic chemistry and many methods are available in literature for this transformation.[16] Particularly, the transformation of propiophenones into 1-aryl-2-propanones has attracted considerable attention; for example, Corey,[17] Paquette,[18] Larson[19] and Shono[20] have devised different methodologies towards this goal. In view of this, it may be pointed out that our methodology achieves this transformation in a relatively simple and convenient manner.

In conclusion, α-hydroxyacetals I have been shown to be excellent probes to check the occurrence of selective 1,2-shifts; and we continue to explore the synthetic potential of these reactions in other areas.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. All solvent extracts were finally washed with brine before drying over Na_2SO_4.

IR spectra were recorded as Smears or Nujol mulls (solids) on a Perkin-Elmer Infracord model 137E. PMR were taken in $CDCl_3$ solution on a Varian FT-80A instrument using TMS as internal standard. Mass spectra were recorded on a CEC mass spectrometer, model 21-110B, using an ionization potential of 70eV. GLC analyses were carried out on a Hewlett Packard-700 machine using a column, 180 cm x 0.6 cm packed with 20% FFAP (Carbowax-20M treated with terphthalic acid).

Materials: The solvents used in the present study were purified by standard procedures. Aldrich-made triphenylphosphine and freshly sublimed iodine were employed. Pyridine was refluxed over KOH pellets and distilled before use. The starting 2-hydroxypropiophenone dimethylacetals, I, were prepared from the corresponding 2-chloropropiophenones by a reported method;[21] these hydroxyacetals gave satisfactory elementary analysis and spectral data.

General procedures for the rearrangement reactions:

RearrangementA: To a premixed solution of I (5 mmol), Ph_3P (7.5 mmol), pyridine (10 mmol) in CH_2Cl_2 (10 ml), dropwise addition of CCl_4 (25 mmol) was made at room temperature, while stirring. The reaction mixture was further stirred at R.T. for 15 hr. and treated with water, extracted with CH_2Cl_2 (10 ml x 3). The organic extract was successively washed with cold dil. HCl (1:1), water and brine, then dried over anhydrous Na_2SO_4. The crude product obtained by the evaporation of the solvent, was chromatographed over SiO_2. Initial elution with 95:5 n-hexane:ethylacetate mixture broughtforth the product II which was distilled under reduced pressure. Further elution yielded almost equimolar (with respect to I) quantity of triphenylphosphine oxide.

Hydrolysis of methyl 2-aryl propanoates II: A mixture of II (10 mmol) and 2N sodium hydroxide (25 ml) was stirred at 80-85° for 3 hr. The reaction mixture was cooled to room temperature and acidified with conc. HCl, then extracted with ethylacetate (3 x 30 ml). The organic phase was washed with brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent under reduced pressure furnished the corresponding 2-aryl propanoic acids in 80-90% yields.

Rearrangement B: To a solution of I (5 mmol) and Ph_3P (75 mg) in benzene (10 ml), iodine (65 mg) was added at R.T. and the solution was stirred for 15 hr. Benzene was stripped off on water bath and the crude product obtained was chromatographed on SiO_2; distillation under reduced pressure afforded pure III.

Characterization of products

(a) Methyl 2-aryl propanoates (II): These compounds were subjected to alkaline hydrolysis as described above and the corresponding 2-aryl propanoic acids were obtained.

Physical data of 2-aryl propanoic acids (See Table): 2-Phenyl propanoic acid (R=H), m.p. 16°C (hexane) (Lit.[22] m.p. 16°C); 2-(4-methylphenyl) propanoic acid (R=CH_3), m.p. 38-39° (hexane), (Lit.[23] m.p. 36-37°C); 2-(4-isobutylphenyl) propanoic acid, m.p. 76°C (hexane) (Lit.[22] m.p. 75-77°C); 2-(4-methoxyphenyl) propanoic acid, (R = OCH_3), m.p. 57°C (hexane) (Lit.[22] 56-57°C); 2-(biphenyl) propanoic acid (R = Ph), m.p. 146°C (Lit.[23] m.p. 146.5°C), 2-(4-chlorophenyl) propanoic acid (R = Cl), m.p. 57°C (hexane) (Lit.[24] 57-58°C); 2-(6-methoxy, 5-chloro-2-naphthyl) propanoic acid, m.p. 151-3°C (acetone-hexane) (Lit.[25]).

(b) 1-Methoxy-1-aryl-2-propanones, III: 1-Methoxy-1-phenyl-2-propanone (R=H), b.p. 120° (bath)/3 mm (Lit.[26] 110-112°/0.8 mm); IR: 1715 and 1105 cm^{-1}; PMR: 2.06 (s, 3H), 3.38 (s, 3H), 4.58 (s, 1H) and 7.30 (s, 5H); Mass: m/e 164 (M^+, 4%), 135 (38%) and 121 (100%); $C_{10}H_{12}O_2$ requires C 73.14; H 7.37; Found C 73.01; H 7.15.

1-Methoxy-1-(p-methylphenyl)-2-propanone: (R = CH_3): b.p. 130° (bath)/3-4 mm; IR: 1720, 1600 and 1100 cm^{-1}; PMR: 2.05 (s, 3H), 2.31 (s, 3H), 3.32 (s, 3H), 4.57 (s, 1H) and 7.23 (s, 4H); Mass: m/e 178 (M^+, 3.5%), 1.51 (61%), 135 (100%). $C_{11}H_{14}O_2$ requires C 74.13; H 7.92; found C 74.26; H 7.51.

1-Methoxy-1-(4-isobutylphenyl)-2-propanone: (R = $i\text{-}C_4H_9$): b.p. 148° (bath)/4 mm; IR: 1718, 1600 and 1110 cm^{-1}; PMR: 0.88 (d, J = 9Hz, 6H), 1.65-2.05 (m, 1H), 2.08 (s, 3H), 2.43 (d, J=9Hz, 2H), 3.32 (s,3H), 4.58 (s, 1H) and 7.05-7.25 (m, 4H); Mass: 220 (M^+, 1%), 192 (8%), 177 (100%), 161 (14%), and 150 (22%). $C_{14}H_{20}O_2$ requires C 76.32; H 9.15; found C 76.47; H 8.89.

1-Methoxy-1-(4-methoxyphenyl)-2-propanone: (R= OCH_3): b.p. 136° (bath)/4 mm; IR: 1720, 1610, 1125 and 1105 cm^{-1}; PMR: 2.03 (s, 3H), 3.30 (s, 3H), 3.72 (s, 3H), 4.51 (s, 1H) and 6.75-7.35 (m, 4H); Mass: m/e 194 (M^+, 4%), 166 (14%), 151 (97%) and 135 (100%); $C_{11}H_{14}O_3$ requires C 68.02; H 7.27; found C 68.12; H 7.21.

1-Methoxy-1-(biphenyl)-2-propanone: (R=Ph): Thick syruppy material; IR: 1718, 1600, 1490 and 1108 cm^{-1}; PMR: 2.08 (s, 3H), 3.31 (s, 3H), 4.60 (s, 1H) and 7.2-7.6 (m, 9H); Mass: m/e 240 (M^+, 2%), 197 (100%) and 181 (42%). $C_{16}H_{16}O_2$ requires C 79.97; H 6.71; found C 80.15; H 6.51.

1-Methoxy-1-(4-chlorophenyl)-2-propanone: (R = Cl): b.p. 126°C (bath)/3 mm; IR: 1720, 1595 and 1115 cm^{-1}; PMR: 2.08 (s, 3H), 3.35 (s, 3H), 4.57 (s, 1H) and 7.33 (s, 4H); Mass: m/e 200 (<1%), 198 (<1%), 157 (25%), 156 (72%) and 139 (100%). $C_{10}H_{11}O_2Cl$ requires C 60.44; H, 5.58 and Cl 17.85; found C 59.94; H 5.55 and Cl 17.63.

1-Methoxy-1-(4-cyanophenyl)-2-propanone: (R=CN): b.p. 135°C (bath)/4 mm; IR: 2200, 1710, 1600 and 1100 cm^{-1}; PMR: 2.09 (s, 3H), 3.38 (s, 3H), 4.65 (s, 1H) and 7.2-7.8 (m, 4H); Mass: m/e 189 (M^+, 2%), 161 (6%), 146 (100%) and 130 (13%). $C_{11}H_{11}NO_2$ requires C 69.82; H 5.86, and N 7.40; found C 69.45; H 5.91 and N 7.03.

1-Methoxy-1-(6-methoxy-5-chloro-2-naphthyl)-2-propanone: Thick syruppy material; IR: 1710, 1600, 1155 and 1080 cm^{-1}; PMR: 2.08 (s, 3H), 3.37 (s, 3H), 3.85 (s, 3H), 4.64 (s, 1H) and 7.2-8.1 (m, 5H); Mass m/e 280 (M^+, 1%); 278 (M^+, 1%), 260 (5%), 237 (45%), 235 (100%) and 184 (35%). $C_{15}H_{15}ClO_3$ requires C 64.62; H 5.43; Cl 12.73; found C 64.33; H 5.30; Cl 12.44.

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