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Stereoselectivities in $AgBF_4$-Catalyzed and Photoinduced Phenyl-Rearrangement of 2-Chloropropiophenone

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Abstract: (*S*)-2-Phenylpropionic acid was stereoselectively obtained by the $AgBF_4$-catalyzed phenyl-rearrangement of (*S*)-2-chloropropiophenone dimethyl acetal, while the photoirradiation of (*S*)- or (*R*)-2-chloropropiophenone afforded partially racemized (*S*)- or (*R*)-2-phenylpropionic acid, respectively. An intramolecular S_N2 mechanism is suggested for the former rearrangement. The latter result is indicative of the intervention of an ion or radical intermediate in the photoinduced phenyl-rearrangement.

Keywords: anitiinflammatory compounds, photochemistry, rearrangement, stereoselection

The rearrangement of propiophenone derivatives to 2-arylpropionic acid analogue is of great interest in relation to the syntheses of none-steroidal antiinflammatory agents.[1] The reaction of 2-chloropropiophenone (**1**) is one case, and the dimethyl acetal of **1** (**2**) is known to exhibit 1,2-phenyl-migration in the presence of a Lewis acid such as Zn^{2+} or Ag^+.[2,3] The photoirradiation of **1** in a polar solvent is also known to undergo a phenyl-rearrangement and has attracted attention as a conventional one-step 2-phenylpropionic acid (**3**) synthesis.[4,5] Although the stereochemistry at the 2-position of the 2-arylpropionic acid is reported to affect the biological activity,[6] the stereoselectivities of the phenyl-rearrangements of 2-chloropropiophenone have not investigated; the rearrangement of the diastereomeric 2-camphorsulfonyloxy naphthylpropanone dimethyl acetal has only been tested as a similar type of reaction.[7] From this viewpoint, we have investigated the stereoselectivities of the $AgBF_4$-catalyzed phenyl-rearrangement of **2** in methanol and the photoinduced phenyl-rearrangement of **1** in 2,2,2-trifluoroethanol (TFE) for the first time. In this communication, the contractive stereoselectivities between the two phenyl-rearrangements are reported and the reaction mechanisms are discussed based on the results.

The enantiomeric (*S*)- or (*R*)-**1** was obtained by preparative HPLC of its racemate using a chiral column (DAICEL CHIRALCEL-OD). The enantiomeric (*S*)-**1** was also synthesized by the Friedel-Crafts reaction of (*S*)-2-chloropropionyl chloride with benzene. The optical purity of each enantiomeric **1** was confirmed by HPLC analysis with a chiral column and exhibited an enantiomeric excess (e.e.) value of over 96 %. The $AgBF_4$-catalyzed rearrangement of the **2** derived from (*S*)-**1** was performed by heating 20 ml of a methanol solution containing 200 mg of **2** at 60 °C in the presence of 50 mg of $AgBF_4$. The photoinduced phenyl-rearrangement of

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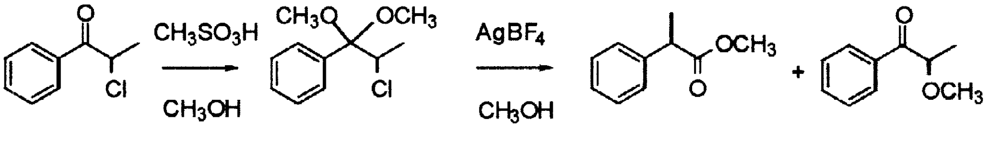
(*S*)- or (*R*)-**1** was carried out as follows. Into 3 ml of TFE, 10 mg of **1** was dissolved together with 100 mg of 2,6-lutidine as a proton buffer. The sample solution was irradiated with a 500 W Xe lamp through a Pyrex filter at 20 °C. The reaction products were analyzed by the following procedure. A portion of the reaction mixture was subjected to preparative HPLC with a silica gel column (Merck Si-60). The purified products were identified by means of the ^{1}H-NMR spectra. The optical purities of the phenyl-rearranged product, as well as the enantiomeric substrate, were determined by HPLC analysis with a chiral column. The absolute stereochemical configurations of the phenyl-rearranged products were determined by the comparison of the ^{1}H-NMR spectra with that of the authentically synthesized sample from commercially available (*S*)-(−)-**3** in the presence of tris-[3-(heptafluorohydroxymethylene)-*d*-campharato] Eu(III) as a shift reagent.

The treatment of **2** with $AgBF_4$ in methanol afforded 2-phenylpropionic acid methyl ester (**3a**) and 2-methoxy propiophenone (**4a**) in 47 % and 20 % yield, respectively (Scheme 1). These products were reasonably ascribed to the Ag^+ aided nucleophilic displacement reaction either by a neighboring phenyl group or by the solvent.

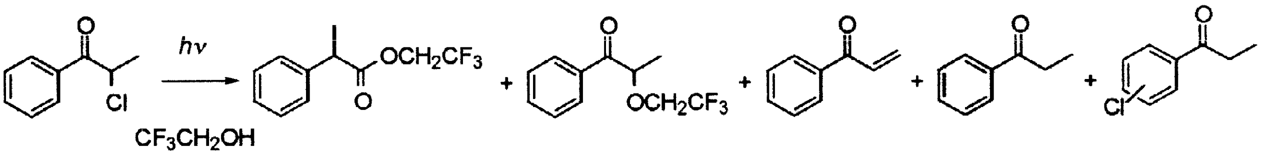


1 **2** **3a** **4a**

Scheme 1

When **2** derived from an enantiomeric (*S*)-**1** was subjected to the $AgBF_4$-catalyzed phenyl-rearrangement, **3a** was obtained as an enantiomeric product at the 2-position. By ^{1}H-NMR and HPLC analyses, the stereochemistry of **3a** was revealed to possess (*S*)-configuration with an e.e. value of 97 % (Table 1). The observed stereoselectivity in the phenyl-rearrangement resulted from inversion of the stereochemistry at the reaction center, and suggests the rearrangement proceeds with the backside phenyl group participation at the C-Cl bond. The nearly complete inversion of the stereoselectivity suggests an intramolecular S_N2 mechanism for the phenyl-rearrangement of **2** as has been proposed for the β-arylalkyl sulfonate solvolyses.[8] These results accommodate the previously illustrated transition state in which the phenyl group participation and the Lewis acid ligation synergeticaly assist the carbon-halogen bond cleavage.

The photoirradiation of **1** in TFE afforded a phenyl-rearranged trifluoroethyl ester (**3b**) in 85 % yield (Scheme 2). The photosolvolysis also gave a trace of a nucleophilic substitution product by TFE (**4b**) in 0.7 % yield. In addition to these C-Cl bond heterolysis products, elimination product (**5**) and hydrogen abstraction products (**6** and **7**) were obtained in 9 and 3 % yields, respectively. The photoreaction of **1** in TFE gave a much larger amount of bond heterolysis products than that obtained in aqueous acetone[2] and the selective C-Cl bond heterolysis is possibly ascribed to the highly polar nature of the TFE.



1 **3b** **4b** **5** **6** **7**

Scheme 2

Table 1 Preferential Configurations and Optical Purities of **3a** and **3b** Obtained by the $AgBF_4$-Catalyzed Phenyl-Rearrangement of **2** in MeOH and by the Photosolvolysis of **1** in TFE

Substrate	Reaction Time / h	Substrate e.e. / %	Preferential Product	Product e.e. / %
(*S*)-**2**	0	98[a]		
	48		(*S*)-**3a**	97
(*R*)-**1**	0	98		
	0.5	94	(*R*)-**3b**	48
	1.0	91	(*R*)-**3b**	50
	1.5	86	(*R*)-**3b**	47
	2.0	82	(*R*)-**3b**	43
	3.0	75	(*R*)-**3b**	40
(*S*)-**1**	0	96		
	0.5	95	(*S*)-**3b**	47
	1.0	93	(*S*)-**3b**	49
	1.5	89	(*S*)-**3b**	48
	2.0	88	(*S*)-**3b**	50
	3.0	80	(*S*)-**3b**	47

[a] Optical purity of the parent 2-chloropropiophenone.

When an enantiomeric (*R*)- or (*S*)-**1** was photolyzed in TFE, **3b** was obtained as a partially racemized product at the 2-position whereas the racemization of the substrate was negligibly small. The ^{1}H-NMR and HPLC analyses elucidated that (*S*)-**3b** was preferentially obtained by the photoreaction of (*S*)-**1**; the photoreaction of (*R*)-**1** predominantly afforded (*R*)-**3b**. As summarized in Table 1, the stereoselectivities in the phenyl-rearrangements exhibited e.e. values of 40 to 50 % and were nearly independent of the irradiation time. The slight decease in the optical purity of **3b** with the irradiation is possibly ascribed to the minor photoracemization of **1**. The stereoselectivities of ca. 50 % e.e. independent of irradiation time suggest the racemization in the product intrinsically results from the phenyl-rearrangement and not from the racemization of the enantiomeric substrate or product under the photosolvolytic condition. Thus, the racemized **3b** is indicative of the intervention of an ion or radical intermediate in the photoinduced phenyl-rearrangement of **1**. The *partial* racemization in **3b** further suggests the involvement of the intermediate as a geminate pair, the reaction center of which retains the same stereochemical configuration as that of the enantiomeric substrate. This chiral geminate pair undergoes rearrangement through the backside phenyl group participation at the C-Cl bond to afford **3b** with the inverted stereochemistry at the 2-position. The racemized **3b** is possibly derived from the racemization or dissociation of the chiral geminate pair followed by the phenyl-rearrangement. The partial racemization in **3b** is explained as due to the comparable rate constants of the phenyl-rearrangement and the racemization or dissociation of the chiral geminate pair.

As noted above, only a small amount of racemization of the enantiomeric **1** was observed during the photoreaction. The photoracemization of **1** is explained as the result of the recombination of the racemized geminate pair or the dissociated intermediates, and also evidences the intervention of intermediates in the photoreaction. The small amount of photoracemization of **1** is rationalized by the slow recombination of the geminate pair or the dissociated intermediate compared to the phenyl-rearrangement.

In the photosolvolytic phenyl-rearrangement of **1**, an ionic species is a possible intermediate for the geminate pair. The formation of the destabilized α-carbonyl cation and less nucleophilic mesylate anion and the considerable amount of their recombination is shown for the solvolyses of α-carbonyl mesylates in trifluoroacetic acid or hexafluoroisopropanol.[9] The α-carbonyl cation and nucleophilic chloride, if formed in TFE, are also expected to undergo recombination. In contrast, the less apparent recombination of the geminate pair shown in the photoreaction of **1** in TFE elucidated that the characteristics of the photochemically generated geminate pair are somewhat different from that of the ionic intermediate obtained in the solvolyses. A radical species is another plausible intermediate for the photogenerated geminate pair, as often shown in the photosolvolysis of alkyl halides,[10] although the evidence for the intervention of a radical pair and the mechanism of its transformation to the ionic intermediate is now under investigation.

In conclusion, the $AgBF_4$-catalyzed phenyl-rearrangement of **2** proceeded with inversion of the stereochemistry at the reaction center in high stereoselectivity of over 97 % e.e. The result suggested an Ag^+ aided, phenyl-assisted intramolecular S_N2 mechanism for the rearrangement. The photoinduced phenyl-rearrangement of **1** also proceeded with inversion of the stereochemistry but in much lower stereoselectivity of ca. 50 % e.e independent of the irradiation time. The partial racemization in the photoinduced phenyl-rearrangement indicated the intervention of an ion or radical geminate pair which retains the same stereochemical configuration as that of the enantiomeric substrate. The recombination of the geminate pair was less apparent as shown by the small amount of substrate racemization. The present results suggest the characteristics of the photogenerated geminate pair are different from those of the ion pair obtained in the solvolysis of α-carbonyl mesylate.

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