Tetrahedron Letters, Vol.22, No.43, pp 4305 - 4308, 1981
Printed in Great Britain

0040-4039/81/434305-04$02.00/0

A NEW METHOD FOR THE SYNTHESIS OF α-ARYLALKANOIC ACIDS BY THE USE OF 1,2-REARRANGEMENT OF THE ARYL GROUP[1)]

Gen-ichi Tsuchihashi,[2)]* Koji Kitajima, and Shuichi Mitamura
Sagami Chemical Research Center
Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Abstract: A simple synthetic method of α-arylalkanoic acids was accomplished by the use of a novel 1,2-rearrangement of the aryl group and this method was applied to the syntheses of some biologically important substances.

α-Arylalkanoic acids are the group which involves many useful compounds. Some of them like α-(4-isobutylphenyl)propionic acid show potent anti-inflammatry and analgesic activities[3)] and some others (α-arylisovaleric acids) are used as the acid moiety of synthetic pyrethroid.[4)] Various kinds of the methods for the preparation of α-arylalkanoic acids were reported. Among them, we are interested in the method using 1,2-rearrangement of the aryl group because of its simple and short synthetic route.[5)] In this letter, we wish to report a novel 1,2-rearrangement of the aryl group and a new convenient method for the synthesis of α-arylalkanoic acids by the use of this rearrangement.

The reaction of α-bromopropiophenone (1) with sodium methoxide in methanol gave an α-hydroxy acetal 2 in 94% yield.[6)] Treatment of 2 with p-toluenesulfonyl chloride in pyridine at room temperature afforded 1-phenyl-2-(p-toluenesulfonyloxy)-1-propanone dimethylacetal (3) in 92% yield. Heating thus obtained α-tosyloxy acetal 3 in an aqueous polar solvent in the presence of a weak base,[7)] followed by usual work-up, yielded a mixture of rearranged products, methyl α-phenylpropionate (4) and 1-phenyl-2-methoxy-1-propanone (5) (see Table 1). Formations of 4 and 5 can be accounted for by the solvolytic

Scheme 1

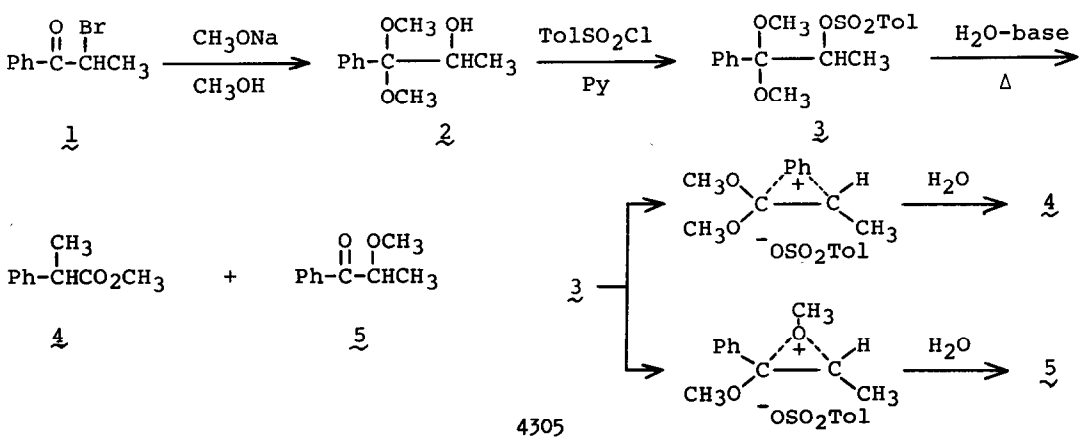


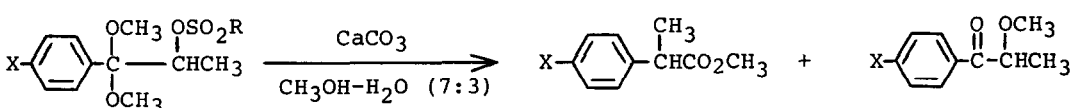
Table 1. Hydrolysis of the α-tosyloxy acetal 3.

Reaction conditions				Yields[c] of products (%)	
Solvent[a]	Base[b]	Temp.	Time (h)	4	5
Dioxane-H_2O (6 : 4)	$CaCO_3$	reflux	64	57	40
DMF-H_2O (6 : 4)	AcOK	reflux	14	56	44
DMSO-H_2O (6 : 4)	$CaCO_3$	100 °C	94	54	40
CH_3OH-H_2O (7 : 3)	$CaCO_3$	reflux	72	66	33

(a) Ratios in parentheses indicate weight ratios of the components of the mixed solvents. (b) An equimolar amount of a base was used. (c) Obtained by GLC using internal standard method.

reaction involving intramolecular displacements of the tosyloxy group with the neighboring phenyl group[8] and methoxy group, respectively (see Scheme 1). If the reaction path leading to 4 involves a bridged phenonium ion as shown in Scheme 1, introduction of an electron-donating group at the para position of the phenyl group in 3 should enhance the rate of formation of the product corresponding to 4. In order to examine this substituent effect, several kinds of α-sulfonyloxy acetals 7, bearing substituent X at the para position of the phenyl group, were prepared and subjected to hydrolysis by heating under reflux with an equimolar amount of calcium carbonate in a mixed solvent of methanol and water (weight ratio 7 : 3). Table 2 shows the results. As seen in Table 2, when X is an electron-donating group such as methoxy, acetylamino, or isobutyl group, the 1,2-rearrangement of the substituted phenyl group took place preferentially to give methyl α-arylpropionate 8 in a good to an excellent yield, and enhancement of the reaction rate was also observed.[9] The α-sulfonyloxy acetals 7 can be prepared in excellent yields from α-halo aromatic ketones which can be easily obtained either by halogenation of

Table 2. Hydrolysis of the α-sulfonyloxy acetals 7.



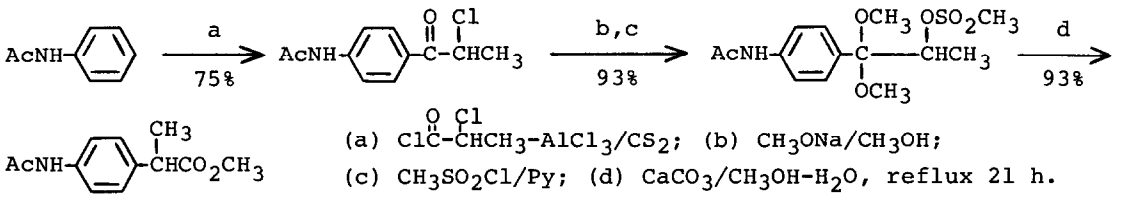
7 8 9

7		Reaction time	Yields[a] of products (%)	
X	R	(h)	8	9
CH_3O	CH_3	20	93	0
AcNH	CH_3	21	93	0
i-Bu	CH_3	72	84[b]	trace
	Ph	10	82	trace
	Tol	22	81	trace
F	CH_3	24	75	20

(a) Isolated yields. (b) Yield of the corresponding acid derived from 8.

aromatic ketones or by the Friedel-Crafts reaction of aromatic compounds with α-haloalkanoyl halides. Thus, together with the easy availability of the starting materials 7, this reaction offers a simple and efficient method for the synthesis of α-arylalkanoic acids having electron-donating substituents in the aryl groups. The simplicity of this method is exemplified by the preparation of methyl α-(4-acetylaminophenyl)propionate[10] starting from acetanilide in 65% over all yield (see Scheme 2).

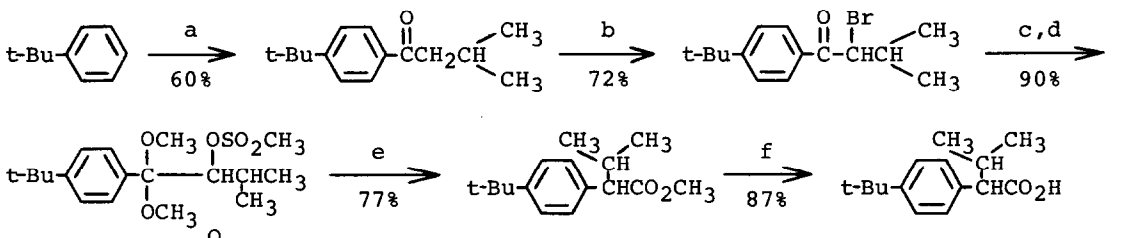
Scheme 2



(a) $ClC(=O)CHClCH_3$-$AlCl_3/CS_2$; (b) CH_3ONa/CH_3OH;
(c) CH_3SO_2Cl/Py; (d) $CaCO_3/CH_3OH$-H_2O, reflux 21 h.

The method is also effective for the synthesis of α-arylisovaleric acids such as α-[4-(tert-butyl)phenyl]isovaleric acid[4] (see Scheme 3).

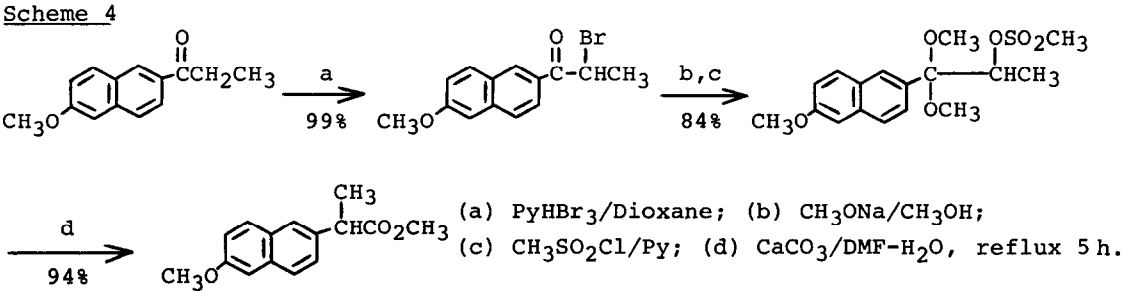
Scheme 3



(a) $ClC(=O)CH_2CH(CH_3)_2$-$AlCl_3/CS_2$; (b) Br_2/Dioxane-Et_2O; (c) CH_3ONa/CH_3OH;
(d) CH_3SO_2Cl/Py; (e) $CaCO_3/CH_3OH$-H_2O, reflux 72 h; (f) KOH/CH_3OH-H_2O.

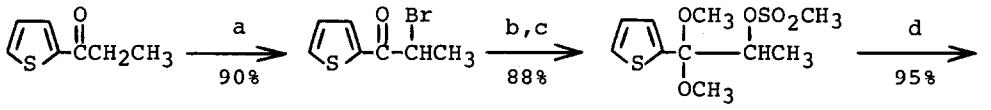
The method can be applied to fused-aromatic and hetero-aromatic systems. Schemes 4 and 5 show the syntheses of methyl α-(6-methoxy-2-naphthyl)propionate and α-(2-thienyl)propionic acid, respectively.[10] In both cases, exclusive rearrangements of the aryl groups occurred to give the desired compounds in excellent yields.

Scheme 4



(a) PyHBr$_3$/Dioxane; (b) CH_3ONa/CH_3OH;
(c) CH_3SO_2Cl/Py; (d) $CaCO_3$/DMF-H_2O, reflux 5 h.

Scheme 5



(a) Br_2/Et_2O; (b) CH_3ONa/CH_3OH; (c) CH_3SO_2Cl/Py; (d) $CaCO_3/CH_3OH$-H_2O, reflux 21 h, followed by addition of NaOH.

Thus, the present method is particularly suitable for the synthesis of alkanoic acids bearing electron-donating aromatic groups at the α-positions. In this type of alkanoic acids, there are many biologically important substances and useful intermediates for the syntheses of these substances.[10]

References and Notes

1) The work described in this letter was presented at the 43rd annual meeting of the Chemical Society of Japan, April 1, 1981.

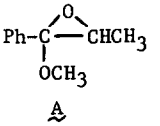
2) Present address; Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223, Japan.

3) T. Y. Shen, Angew. Chem. Int. Ed., 11, 460 (1972).

4) For example, α-(4-chlorophenyl)isovaleric acid is an acid moiety of a recently developed insecticide "fenvalerate"; H. Yoshioka, J. Synthetic Org. Chem. Japan, 38, 1151 (1980). α-[4-(tert-Butyl)phenyl]isovaleric acid is also used for this purpose; Japan Kokai, 80-104252; Chem. Abstr., 94, 78448n (1981).

5) In the methods so far reported, thallium (III) nitrate or diphenyl phosphorazidate [$(PhO)_2P(O)N_3$] was needed for the 1,2-rearrangement; see, a) A. McKillop, B. P. Swann, and E. C. Taylor, J. Amer. Chem. Soc., 95, 3340 (1973), b) T. Shioiri and N. Kawai, J. Org. Chem., 43, 2936 (1978).

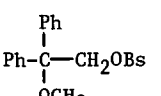
6) The reaction of α-bromo ketone 1 with sodium methoxide in methanol seems to proceed via an intermediary epoxy ether A, whose ring openning by methanol in the presence of sodium methoxide gives the α-hydroxy acetal 2. Almost similar result was obtained in the reaction of the corresponding α-chloro ketone. See, C. L. Stevens, W. Malik, and R. Pratt, J. Amer. Chem. Soc., 72, 4758 (1950).



A

7) As the reaction proceeds, p-toluenesulfonic acid is produced. Neutralization of the acid by an appropriate base is necessary to prevent the acid-catalyzed decomposition of the acetal moiety in 3.

8) Similar rearrangement of the phenyl group in solvolysis of 2-methoxy-2,2-diphenylethyl p-bromobenzenesulfonate (B) was reported; S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, J. Amer. Chem. Soc., 75, 147 (1953).



B

9) In contrast to the dramatical effect of the substituent X on the reaction, no significant change in the yield was observed by varying R of the sulfonyloxy group in 7 from methyl to p-tolyl and phenyl groups although the reaction became fast.

10) The products described in Schemes 2,4 and 5 are known to be potent anti-inflammatry agents or their synthetic intermediates; a) G. Nannini, P. N. Giraldi, G. Molgora, G. Biasoli, F. Spinelli, W. Logemann, E. Dradi, G. Zanni, A. Buttinoni, and R. Tommasini, Arzneim.-Forsch., 23, 1090 (1973). b) I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, J. Med. Chem., 13, 203 (1970). c) F. Clemence, O. L. Martret, R. Fournex, G. Plassard, and M. Dagnaux, Eur. J. Med. Chem.-Chim. Ther., 9, 390 (1974).

(Received in Japan 16 July 1981)