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SILVER ASSISTED REARRANGEMENT OF PRIMARY AND SECONDARY α-BROMO-ALKYLARYLKETONES

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Abstract The silver assisted rearrangement of primary and secondary α-bromo-alkylarylketones is reported for the first time. The influence of the acidity on the reaction selectivity is discussed

The considerable importance of α-arylalkanoic acids in the industry of fine chemicals is well known [2] A potential general method of synthesis of α-arylalkanoic acids is related to the rearrangement of α-halo-alkylarylketones.[3-5] Previous attempts to obtain the rearrangement from primary and from non-benzylic secondary α-halo-alkylarylketones were unsuccessful.[6] Now we wish to report on a new method of synthesis of α-arylalkanoic acids,of practical interest,based on the silver ions assisted methanolysis of primary and secondary α-bromo-alkylarylketones,subsequent hydrolysis of methylesters,so obtained,provides the corresponding acids.The method arose from the observation(done for the first time by us)that in the silver ions($AgBF_4$)assisted methanolysis of 2-bromo-4'-methoxyacetophenone 1e,both substitution(formation of 2e)and rearrangement (formation of 3e)processes occur[7] and that the ratio 3e to 2e is strongly affected by the acidity of the reaction medium.The study of this phenomenon led us to develop a new method,of synthetic value for the preparation of α-arylalkanoic acids 4 from primary and secondary α-bromo-alkylarylketones 1.Among the acidic systems investigated the BF_3 $2CH_3OH$ complex showed to be the acid as well as the solvent of choice.As a matter of fact,it allows the use of relatively unexpensive and available silver compounds such as silver carbonate and silver oxide,which by reacting with BF_3.$2CH_3OH$ complex provide a reactive and soluble silver salt.Thus,the method consists of adding at 15°C bromoketone 1(0 1 mol)to a solution of silver ions,obtained by dissolving silver carbonate(0 06 mol)in BF_3 $2CH_3OH$ complex(100 ml).The free acid 4 can be isolated easily after hydrolysis of the reaction crude.The reaction has shown to be of general character for primary and secondary α-bromo-alkylarylketones(Table).Generally,with tertiary α-bromo-alkylarylketones the formation of α,β-unsaturated ketones strongly prevails on the rearrangement.This is the only method which allows the direct conversion of primary and secondary α-bromo-alkylarylketones into the corresponding methylesters of α-arylalkanoic acids Two effects concerning the acidity of the reaction medium can be envisaged 1)the acid catalyzes the formation of ketals,it has been verified by NMR analysis that a certain amount of ketal is in equilibrium,at low values of acid concentration,with the corresponding ketone.Actually,the rearrangement is quite selective towards esters formation starting from α-bromo-alkylarylketals.[3,5,8] Thus,at low acid concentra-

tion it is likely that ketals and hemiketals strongly contribute to esters formation. ii)at high acid concentration($BF_3.2CH_3OH$ complex as reaction solvent),where no ketal is present, α-bromoketones must be directly involved in the reaction,this because ethers 2,under the reaction conditions, are not converted into esters 3.At high acid concentration the formation of esters 3 would prevail on the ethers 2 owing to the decreased nucleophilicity of the solvent As far as the reaction is concerned,the results of the Table,indicating that aryl migration is favoured by electron-releasing groups,suggest an electrophilic character of the reaction center in the transition state.

a) $Ag_2CO_3 \xrightarrow{BF_3.2CH_3OH} 2\,Ag^+ + CO_2 + H^+$

b) $Ar\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{R}{\underset{|}{CH}}\text{-}Br + Ag^+ \xrightarrow{CH_3OH \text{ or } BF_3.2CH_3OH} Ar\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{R}{\underset{|}{CH}}\text{-}OCH_3 + Ar\text{-}\underset{R}{\underset{|}{CH}}\text{-}COOCH_3 + AgBr + H^+$

(1) (2) (3)

c) 3 $\xrightarrow{1)\ OH^-\quad 2)\ H^+}$ $Ar\text{-}\underset{R}{\underset{|}{CH}}\text{-}COOH$ (4)

Entry[9]	Ar	R	4:yield%[10]	mp°C(solvent)	Lit.	Ratio 3 2[11]
a	6'-methoxy-2'-naphthyl-	CH_3	85	153-154(acetone-hexane)	150-151[12]	15
b	4'-methoxy-phenyl-	CH_3	78	55(petrol. ether)	56-57[13]	9
c	4'-biphenylyl-	C_2H_5	41	125-126(acetic acid)	123-125[14]	1.5
d	phenyl-	CH_3	51	16(petrol. ether)	16[15]	2
e	4'-methoxy-phenyl-	H	58	86-88(water)	83-84[16]	5
f	4'-methyl-phenyl-	H	22	89-90(benzene)	91[17]	0 75
g	phenyl-	H	8	77(petrol. ether)	77[18]	0.2
h	4'-chloro-phenyl-	H	4	104-106(water)	105[19]	0.15

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2)T.Y.Shen,Angew.Chem.Int.Ed.,6,460(1972). 3)J.P.Bêguê,D.Bonnet,Tetrahedron,30,141(1974) 4)D.J. Pasto,J P.Sevenair,J.Am.Chem.Soc.,93,711(1971). 5)D.Baudry,M Charpentier-Morize,Tetrahedron Lett. 3013(1973). 6)D.J.Pasto,K.Garves,J.Org.Chem.,32,778(1967),A.Nadar,G.Gnanasekaran,J.Chem.Soc.Perkin II,1893(1976),A.L.Fry,Y Migron,Tetrahedron Lett ,3357(1979). 7)2-bromo-4'-methoxyacetophenone 1e(10 mmol)was added,at 15°C,to a solution of silver tetrafluoroborate(10 mmol)in methanol(10 ml).The reaction mixture was stirred in the dark,at 15°C,for 2h The reaction mixture was filtered,diluted with water,added with benzylacetate(as internal standard),extracted with diethyl-ether and analyzed by GLC methylester of 4'-methoxyphenylacetic acid 3e(2 8 mmol:yield 28%)and 2-methoxy-4'methoxyacetophenone 2e(3 mmol,yield 30%) 8)C.Giordano,G.Castaldi,J.Org.Chem.,submitted for publication. 9)Reaction time 20h,reactions were carried out in the dark. 10)Yields are calculated on the pure isolated acids and are based on the starting bromoketones. 11)Ratio 3 2 was determined by NMR and/or by GLC on the reaction crude. 12)I.T.Harrison,B Lewis,R.Ruszkowki,A.Tomolonis,J.H.Fried,J.Med.Chem.,13,203(1970). 13)W.M.Lauer,L.I Hansen,J.Am.Chem.Soc ,61,3039(1939). 14)F.F.Blicke,N.Grier,J.Am.Chem.Soc.,65,1725(1943). 15)A.Fredga,S.Wideqvist, Acta Chem Scand.,1,860(1947). 16)J.A.King,F.H.McMillan,J Am.Chem Soc.,68,2335(1946). 17)K.Kindler,W.Metzendorf,Dschi-yin-kwok,Chem.Ber.,76,308(1943). 18)L.Kofler,A.Kofler,"Termo-Mickro Methoden"(1945),Ed.Weinheim. 19)J.F.Dippy,F.R.Williams,J.Chem.Soc.,161(1948).

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