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ELECTROPHILIC AROMATIC SUBSTITUTION BY PUMMERER REACTION OF α-SULFINYLACETATE

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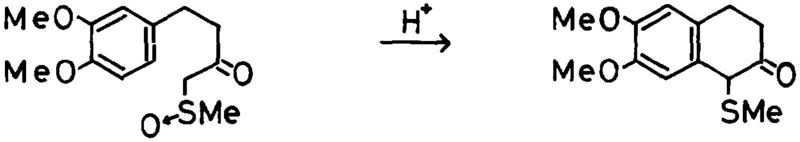
Summary: Treatment of a mixture of aromatic compound and ethyl α-(methylsulfinyl)acetate (5) with p-toluenesulfonic acid under continuous removal of separated water brought about an intermolecular aromatic substitution to give ethyl α-(methylthio)arylacetate (6). Similar treatment of acylmethyl phenethyl sulfoxide (8) led to cyclization into 1-acylisothiochroman (9).

Synthetic utility of the Pummerer reaction for the formation of carbon-carbon bonds on aromatic rings was first demonstrated by Oikawa and Yonemitsu in 1971: the reaction consists of treating β-ketosulfoxide having aromatic ring with such strong acid as p-toluenesulfonic acid or trifluoroacetic acid to induce cyclization (e.g., 1→2).[1] A key step of this cyclization is the intramolecular nucleophilic attack of an aromatic ring on the intermediary α-thiocarbocation (3) derived from β-ketosulfoxide (1). If this type of α-thiocarbocation can react intermolecularly with aromatic rings, the method would have preparative value in the synthesis of aromatic compounds being substituted by carbon atom. Recently, Bates has reported that the reaction of 4-bromophenylsulfinylacetate (4) with



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$$\mathrm{Me\overset{+}{S}{=}CHCO(CH_2)_2Ar \longleftrightarrow MeS\overset{+}{C}HCO(CH_2)_2Ar}$$

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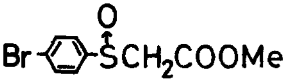

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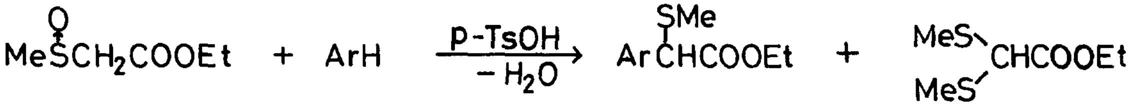
aromatic compound does not occur under the usual Pummerer conditions, but gives the expected products under neutral thermal conditions.[2] The latter successful reaction, however, is unsatisfactory as a preparative method because the yields of the products are low, and the reaction is restricted to reactive aromatics such as anisole or p-xylene. We have now found that the intermolecular reaction of α-(methylsulfinyl)acetate (5) and aromatic compounds efficiently takes place in the presence of anhydrous p-toluenesulfonic acid with continuous removal of the water produced during the reaction to afford α-(methylthio)arylacetate (6a-h) in good yields. As in our previous work[3] on the Friedel-Crafts synthesis of α-(methylthio)arylacetate (6), the present reaction would also afford a useful synthetic way to the arylacetate through reductive desulfurization of the methylthiogroup of 6.



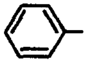
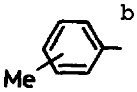
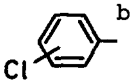
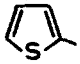
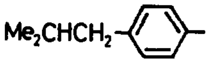
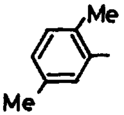
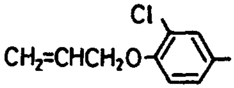
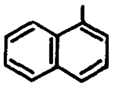
$$\mathrm{Me\overset{O}{S}CH_2COOEt} + \mathrm{ArH} \xrightarrow[-\mathrm{H_2O}]{p\text{-}\mathrm{TsOH}} \mathrm{Ar\overset{SMe}{C}HCOOEt} + \mathrm{(MeS)_2CHCOOEt}$$

5 6a-h 7

In a typical procedure, a solution of the sulfoxide (5)[4] (2 mmol) and anhydrous p-toluenesulfonic acid (4 mmol) in benzene (15 ml) was refluxed for 1 hr with continuous removal of the water produced by means of a Dean-Stark water separator. The reaction mixture was washed with water to remove p-toluenesulfonic acid, and dried. The solvent was evaporated off, and the residue was chromatographed on silica gel using benzene as an eluent to give ethyl α-(methylthio)phenylacetate (6a) in 88% yield. When the reaction was carried out with reduced amount of p-toluenesulfonic acid or without water-separation, the formation of 6a decreased and instead the formation of dithioacetal (7)[5] increased.[6] This may suggest that the excess amounts of p-toluenesulfonic acid hold the water formed during the reaction, preventing the formation of 7. The reaction can be proceeded in an inert solvent with each equal amount of 5 and aromatic compound. Thus, refluxing a solution of 5 (2 mmol), isobutylbenzene (2 mmol) and p-toluenesulfonic acid (4 mmol) in dichloroethane (15 ml) using a Dean-Stark apparatus gave ethyl α-methylthio-(p-isobutylphenyl)acetate (6e) in yield of 58%, along with 7 (9% based on 2 mol of 5).

The results of the reaction of 5 and aromatic compounds are summarized in Table.

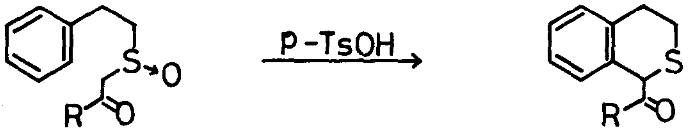
Table. Acid-catalized Reaction of Sulfoxide (5) with Aromatic Compounds.

	reaction conditions				product (6)		
ArH[ArH/(5) ratio]	solv.	p-TsOH/(5) ratio	temp.	time min	No.	Ar in (6)	yield %
benzene[a]	—	2	refl.	60	6a		88
toluene[a]	—	2	refl.	60	6b	 b)	89
chlorobenzene[a]	—	2	refl.	60	6c	 b)	60
thiophene[a]	—	1	70°	30	6d		56
isobutyl-benzene (1)	$(CH_2Cl)_2$	2	refl.	60	6e		58
p-xylene (1)	$(CH_2Cl)_2$	2	refl.	60	6f		55
o-allyloxy-chlorobenzene (1)	$(CH_2Cl)_2$	2	refl.	40	6g		74
naphthalene (1)	$(CH_2Cl)_2$	2	refl.	60	6h		62

a) an excess of the reactant was used as a solvent

b) a mixture of o- and p-isomers

The reaction condition employed herein was shown to be also effective for an intramolecular cyclization of the acylmethyl phenethyl sulfoxides (8a,b). Thus, refluxing a benzene solution of the sulfoxide (8a) in the presence of two equivalents of p-toluenesulfonic acid gave 1-(ethoxycarbonyl)isothiochroman (9a) in yield of 78%. In this case, operation of the water-removal during the reaction is not always necessary. In a similar manner, the sulfoxide (8b) gave 9b in yield of 86%.



8a,b

a, R=OEt
b, R=Ph

9a,b

References and Notes

1 Y. Oikawa and O. Yonemitsu, *Chem. Comm.*, 1971, 555; idem, *Tetrahedron*, 30, 2653 (1974); idem, *J. Org. Chem.*, 41, 1118 (1976); idem, *J. Chem. Soc. Perkin I*, 1976, 1479; idem, *Heterocycles*, 5, 233 (1976).

2 D.K. Bates, *J. Org. Chem.*, 42, 3452 (1977).

3 Y. Tamura, H. Shindo, J. Uenishi and H. Ishibashi, *Tetrahedron Lett.*, 1980, 2547.

4 J.J.A. van Asten and R. Louw, *Tetrahedron Lett.*, 1975, 671.

5 The formation of this type of compound has been previously observed in the reaction of α-(phenylsulfinyl)acetic acid with acetic acid, W.J. Kenney, J.A. Walsh and D.A. Davenport, *J. Am. Chem. Soc.*, 83, 4019 (1961), and see also ref. 1.

6 When one equivalent of p-toluenesulfonic acid was used in this reaction, nearly equal amount of 6a and 7 were formed.

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