Thallium(III)-induced Bromination of *meta*-Substituted Anisoles

By K. L. ERICKSON* and H. W. BAROWSKY

(*Jeppson Laboratory, Clark University, Worcester, Massachusetts* 01610)

Summary Thallium(III)-induced bromination of *meta*-substituted anisoles shows a surprising preference for attack *para* to the ether function even in the presence of bulky *ortho*-substituents in contrast to what is expected on the basis of the presumed steric requirements of the attacking species.

THE bromination of aromatic compounds in the presence of thallium(III) acetate is a convenient method for achieving a high degree of selectivity in direction of attack.[1,2] In monosubstituted benzene derivatives the direction of attack is always *para*. This is attributed to a highly ordered substrate–bromine–thallium(III) acetate complex with large steric requirements.[2]

We have found that in *meta*-disubstituted systems steric factors must be of little importance in directing the position of attack. The thallium(III) acetate-induced bromination of methyl 3-methoxybenzoate[3] and of 3-acetoxytoluene gives one product in each case—that corresponding to bromination *para* to the oxygen substituent.

A series of 3-alkylanisoles were studied in which the size of the alkyl group increased. The results are shown in the Table. The monobrominated products were formed in 70—80% yields (isolated) and were analysed by g.l.c.; resolution of the isomers was thus effected. The minor isomers in the first three cases were not identified but are assumed to be the 6-bromo-3-alkylanisoles in analogy to other work[5,6] and to the 3-t-butylanisole case where the

6-bromo-isomer is the predominant one. The major products and 4-bromo-3-t-butylanisole were identified by spectral comparison with authentic samples.†

TABLE

$Tl(OAc)_3$-*Induced bromination of* 3-*alkylanisoles*, *m*-$R{\cdot}C_6H_4{\cdot}OMe$.

R	% of 4-Bromo-isomer in monobrominated product
Me	96
Et	93
Pr^i	88
Bu^t	*ca.* 40[a,b]

[a] The major isomer formed is the 6-bromo-isomer; overlapping of the peaks necessitated an approximation of the isomer ratio. [b] Ref. 4.

The Table clearly shows the strong preference for attack *para* to the methoxy-group even when a bulky isopropyl substituent is *ortho* to this position. By comparison, bromination of 3-isopropylphenol with elemental bromine affords a mixture of 35% of the 4-bromo-isomer and 40% of the 6-bromo-isomer plus 5% of the 4,6-dibromo-derivative.[6] The relatively small amount of 4-isomer produced is considered a result of steric interaction of the isopropyl group with the bromine when it attacks this position. Similarly, bromination of 3-t-butylphenol with elemental bromine gives exclusively the 6-isomer.[5] In the thallium-induced bromination of 3-t-butylanisole, a 60:40 ratio of the 6-bromo- and 4-bromo-isomer is produced. The formation of substantial amounts of the 4-isomer in this system is striking and suggests that bromination of 3-substituted anisoles in the presence of thallium(III) acetate is subject to remarkable electronic control and minimal steric control.

(*Received, October 15th*, 1971; *Com.* 1787.)

† We thank Professor J. M. A. Baas for spectra of 4-bromo-3-t-butylanisole.

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[2] E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 1970, **3**, 338.
[3] Reference 1 incorrectly reports the product as methyl 4-bromo-3-methoxybenzoate.
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[5] W. W. Kaeding, *J. Org. Chem.*, 1961, **26**, 4851.
[6] J. R. Kilsheimer and H. H. Moorefield, U.S.P. 3,341,401, (1967) (*Chem. Abs.*, 1968, **68**, 12675a).