Homolytic Aromatic Substitution by Heterocyclic Free Radicals. Part IV.[1] Reaction of 5-Substituted Thiazol-2-yl Radicals with Alkylbenzenes

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The relative rates and the partial rate factors of the homolytic thiazolylation of alkylbenzenes by the thiazol-2-yl radical substituted in the 5-position by methyl, bromo, and nitro groups are reported. The radicals were generated by the aprotic diazotization of the corresponding 2-aminothiazoles. The results show a very small substituent effect compared with that observed for substituted phenyl radicals.

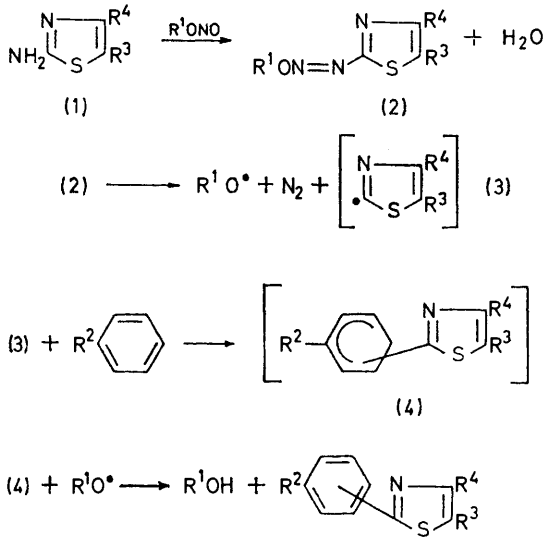
ACCORDING to the theory of polarized radicals the presence of substituents on aromatic free radicals can slightly affect their polarity, rendering them more electrophilic or more nucleophilic by comparison with the phenyl radical. Since little attention has been paid to homolytic reactions of substituted heterocyclic radicals with aryl radicals, we have extended our previous work on the weakly electrophilic thiazol-2-yl radical[1] to include the 4,5-dimethyl-, 5-bromo-, and 5-nitro-substituted derivatives. One simple criterion for deciding whether a given radical is electrophilic or nucleophilic, is to examine a particular series of aromatic substrates in terms of the reactivities at positions of high or low electron availability, all other conditions being equal (resonance stabilization, steric effects, reaction medium). We used this to study quantitatively the effect of substituents on the electrophilic nature of thiazol-2-yl radicals as gauged by their substitution of alkylbenzenes.

RESULTS AND DISCUSSION

Isomer Ratios and Relative Reactivities.—For isomer ratio determinations, 5-substituted thiazol-2-yl radicals were initially generated in single alkylbenzenes (R = Me, Et, Pr^i, and Bu^t) by the aprotic diazotization of the corresponding 2-aminothiazoles (Scheme), according to ref. 2. This method was chosen in preference to the photochemical decomposition of the appropriate 2-iodothiazole to avoid by-products arising from the photoisomerization of 2-arylthiazoles.[1,3] Yields obtained by this method are a little higher than those obtained by the Gomberg method (*ca.* 15—20%). The mixtures were analysed by g.l.c. and the structures of the *ortho*-, *meta*-, and *para*-substituted 2-arylthiazole isomers were established by a chromatographic method based upon relative retention volumes and Kovats indices. The structures of the products were confirmed either by g.l.c.–mass spectroscopy (g.l.c.–m.s.) or by t.l.c.–n.m.r.

Products other than 2-arylthiazoles were also present in the mixtures. Among them, minor amount of dimers arising from hydrogen abstraction from the side chain of the alkylbenzenes (except for t-butylbenzene) were reported earlier.[1] Thiazole (or its 4- or 5-substituted derivatives), and azo-dyes were also formed. In all cases these side reactions did not adversely affect the ring substitution process.

To study quantitatively the effect of polar substituents on the reactivity of the thiazol-2-yl radical the



(5) $R^3 = R^4 = H$ a; $R^2 = H$
(6) $R^3 = R^4 = Me$ b; $R^2 = o; m; p-Me$
(7) $R^3 = Br, R^4 = H$ c; $R^2 = o; m; p-Et$
(8) $R^3 = NO_2, R^4 = H$ d; $R^2 = o; m; p-Pr^i$
e; $R^2 = o; m; p-Bu^t$

SCHEME

competitive method was used, working with an excess of equimolar amounts of benzene and alkylbenzene. Partial rate factor ratios at the *meta*- and *para*-positions (f_m/f_p) were also determined. These results are summarized in Table 1. This Table shows results obtained with thiazol-2-yl radicals generated from various sources; isomer ratios and relative reactivities were the same whatever the source.

The behaviour of substituted thiazol-2-yl radicals in these reactions is very similar to that of the unsubstituted radical; no substantial change is encountered in the *ortho*-isomer distribution whose decreasing proportion

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from toluene to t-butylbenzene reflects the steric effect of bulky alkyl groups. However the existence of a small substituent effect can be seen from relative reactivities and the f_m/f_p ratios.

The presence of an electron-withdrawing group in the thiazol-2-yl radical ($R^3 = NO_2$) leads to an increase in its electrophilic character. The reverse effect is observed with an electron-releasing group such as methyl. The small effect observed with the bromo-group may be due to two opposite effects, an inductive, electron-withdrawing effect and an electron-releasing conjugation.

TABLE 1

Experimental isomer distribution, relative reactivities (k), and f_m/f_p ratios, for homolytic thiazol-2-ylation and 5-substituted thiazol-2-ylation of alkylbenzenes

Substrates	5-Substituents	Isomer ratios (±1) *o*	*m*	*p*	k_M	f_m/f_p
Toluene	H	65·8	19·3	14·9	2·2	0·65
	Me	66·5	19·5	14·0	2·1	0·7
	Br	64·5	19·4	16·1	2·3	0·60
	NO_2	62·5	19·7	17·8	2·6	0·55
Ethylbenzene	H	56·5	25·4	18·1	1·8	0·7
	Me	56·5	26·8	16·7	1·6	0·8
	Br	52·5	27·7	19·8	1·9	0·7
	NO_2	51·0	27·7	21·3	2·2	0·65
Isopropylbenzene	H	46·0	33·2	20·8	1·45	0·8
	Me	43·5	36·4	20·1	1·4	0·9
	Br	41·5	35·3	23·2	1·55	0·76
	NO^2	40·2	35·3	24·5	1·9	0·72
t-Butylbenzene	H	21·5	50·5	28	1·12	0·9
	Me	20·0	52·4	27·6	1·08	0·95
	Br	22·5	47·8	28·7	1·25	0·85
	NO_2	21·0	48·6	30·4	1·6	0·8

An increase of the f_m/f_p ratios from toluene to t-butylbenzene is observed whatever the polar nature of the radical. This result is not in qualitative agreement with expectation on the basis of the behaviour of increasingly electron-releasing substrates towards electrophilic attack. This general phenomena has been observed for other heterocyclic radicals and this result has not been explained.

These results strongly support the hypothesis of low polar character of heteroaromatic radicals and their low selectivity which is quite similar to that observed in homolytic arylations. The influence of substituents on these radicals agrees with their polar character but this effect is generally much smaller than the effect of the substituents in aromatic or heteroaromatic substrates.

EXPERIMENTAL

Analytical Methods.—G.l.c. All mixtures were analysed with an Intersmat IGC 15 gas chromatograph equipped with a flame ionization detector. An Intersmat IGC 12 was used in conjunction with the Camag–Diochrom apparatus for g.l.c.–t.l.c. Peak areas were measured using a Vidar Autolab integrator. Percentages are based on the areas of peaks of isomer mixtures only because signal areas are identical within experimental error. Relative reactivities have been determined as described in previous papers.[1] Difficulty was experienced in finding a suitable column to separate *m*- and *p*-tolylthiazoles. The best separation was obtained on a column packed with 10% Apiezon L on Chromosorb W HMDS 80—100 mesh previously coated with 3% potassium hydroxide (column A). Other columns were: 10 ft × 1/8 in Carbowax 4000 on silanised Chromosorb G 80—100 mesh (column B); 6 ft × 1/8 in 5% SE 30 on Chromosorb W HMDS 60—80 mesh. The detector temperature was 240 °C; carrier gas, hemixal; flow rate 20 ml min^{-1}.

Identification by g.l.c. The identification of 2-arylthiazoles bearing alkyl groups in the *ortho-*, *meta-*, and *para*-positions is based upon g.l.c. data for 2-phenylthiazole and the retention increments (α_r or ΔI) of each alkyl group in the *ortho-*, *meta-*, and *para*-positions. According to Martin's additivity principle, these values (on a given column and at a given temperature) are the same whatever the molecule bearing the aryl group. The mean of these values for the four series examined, reported in Table 2, is in good agreement with that reported for arylbenzenes.[1]

TABLE 2

Relative retention volume of 2-alkylphenylthiazoles with or without substituents in the 5-position

R^2 in (5)—(8)	α_r (Columns and temperature)[a] SE 30 (C) 195 °C	Apiezon L (A) 210 °C	Carbowax 4000 (B) 210 °C
o-Me	1·22	1·17	1·1
m-Me	1·46	1·46	1·35
p-Me	1·5	1·55	1·41
o-Et	1·44	1·25	1·12
m-Et	2·0	1·92	1·63
p-Et	2·12	2·18	1·81
o-Pr^i	1·55	1·33	1·15
m-Pr^i	2·3	2·2	1·73
p-Pr^i	2·64	2·65	2·04
o-Bu^t	1·80	1·6	1·5
m-Bu^t	2·80	2·6	1·96
p-Bu^t	3·44	3·45	2·5

[a] $\alpha_r = (d'_R)_{(RC_6H_4)_2Th}/(d'_R)_{Ph_2Th}$ where d'_R represents the retention distance. ΔI For these groups has been given previously.[1]

G.l.c.–m.s. Combined g.l.c.–m.s. analyses were satisfactory for identification. These analyses were performed using Aerograph Model 1400 and Varian MAT 111 instruments at 80 eV, source temperature 200 °C, acceler-

ating voltage 820 V, and trap current 270 μA; column conditions: 10 ft × 1/8 in, steel column 3% SE 30 on 60—80 mesh Varaport, flow rate 15 ml min^{-1} (helium), column temperature 200 °C. Major peaks corresponding to the M^+, $(M - RC_6H_4CN)^+$, and $(M - Me)^+$ ions and their relative intensity of 24 2-arylthiazoles and 2-aryl-4,5-dimethylthiazoles bearing alkyl substituents in the *ortho*-, *meta*-, and *para*-positions are reported in Supplementary Publication SUP No. 20675 (5 pp.).* The general scheme of ring cleavage in these molecules is characteristic of the thiazole nucleus [4,5] and of alkylbenzenes.[6]

T.l.c. To determine isomer ratios more accurately, 2-arylthiazoles were separated from by-products by preparative t.l.c. on silica gel $PF_{254+366}$, according to Stahl's standard procedure, benzene as eluant. The desired fraction (localized mainly in the middle of the plate) was extracted and examined again at high sensitivity by g.l.c.

Thiazolylation Procedure.—2-Aminothiazole (0·01 mol) or a 5-substituted derivative, isoamyl nitrite (0·015 mol), and an alkylbenzene (1 mol) were kept at 60—70° in a thermostatted bath for 6 h with vigorous stirring. After leaving overnight at room temperature, excess of solvent was evaporated under vacuum and the residue was analysed by g.l.c. and then separated by preparative t.l.c. as described above. Extracts from the plates were analysed by g.l.c. under the following conditions: 2-arylthiazoles, 5-bromo-, and 4,5-dimethyl-2-arylthiazoles, on columns A and B at 190—200 °C, 5-nitro 2-arylthiazoles, on column C at 200 °C.

Syntheses.—2-Aminothiazoles were synthesized as described in the literature.[7-9] M.p.s were in the range reported; 2-amino-4,5-dimethylthiazole, 220; 2-amino-5-bromothiazole, 94; 2-amino-5-nitrothiazole, 203 °C. Some 2-aryl-4,5-dimethylthiazoles were prepared by Hantzsch's method by refluxing (for 10 h) appropriately substituted thiobenzamides [1] with 3-bromobutanone in alcohol in the presence of piperidine. In these reactions the corresponding 2-aryl-4-ethylthiazoles, arising from condensation of 4-bromobutanone with thiobenzamides, were also obtained (*ca.* 20%). These compounds were separated by g.l.c.–t.l.c. 5-Bromo- and 5-nitro-2-phenylthiazoles were prepared by thermal decomposition of the corresponding substituted 2-aminothiazole in benzene in the presence of isoamyl nitrite. Pure samples were obtained by preparative t.l.c.

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (items less than 10 pp. are supplied as full-size copies).

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