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Substituent effects on thermal rearrangement of 3-(substituted phenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4*H*)-thiones

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ABSTRACT: The kinetics of the rearrangement of 3-(substituted phenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4*H*)-thiones in solution were determined in the temperature range 160–200 °C. From the correlation of log*k* against σ, it was found that for *m*-Me, *p*-Cl and *p*-CN, the compounds rearrange with the homolytic cleavage of the N—O bond, whereas for *p*-Me, H and *m*-NO_2, the rearrangement occurs with the heterolytic cleavage of the N—O bond. In comparison with the uncatalysed rearrangement, Cu catalysis greatly increased the rate of the rearrangement of 3-(*m*-chlorophenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4*H*)-thione at 166 °C. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: thermal rearrangement; substituent effect; 3-(substituted phenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4H)-thiones

INTRODUCTION

Substituent effects on free radical reactions are more complex than those for polar reactions. Therefore, this area has continued to hold the interest of chemists over the years. Both electron-withdrawing and electron-releasing substituents, when conjugated with a radical centre, can provide stabilization of the radical. Hence polar substituent constants are not appropriate measures of radical stabilization. A number of approaches, which are based on extended Hammett equations, has been made to quantify the effect of substituents on free radical reactions. These frequently contain both radical and polar components since polar effects operate in many radical reactions.

RESULTS AND DISCUSSION

Simamura and co-workers proposed[1] the τ_p scale, which is based on the product distribution for phenyl radical addition to substituted benzenes (Scheme 1). In this reaction, a large kinetic effect is obtained, since *para* substituents are directly conjugated to a cyclohexadienyl radical. However, this model reaction has serious disadventages. The τ values depend on the assumption that all of the intermediate adduct radicals end up as the substitution product, and the reactive phenyl radical is prone to side reactions at the substituent groups.

Yamamoto and Otsu[2] studied the chain transfer reaction between the polystyryl radical and ring-substituted cumenes. They proposed a set of parameters E_R, which represent the resonance stabilization energy of the radical, and in their proposed equation (Scheme 1), the ρ value is chosen as $+0.7$ to agree with the Alfrey–Price *Q/e* system.[3] Because of the empirical nature of the *Q/e* scheme, this agreement is difficult to justify.

Sakura *et al.*[4] examined the reaction of substituted styrene with trichloromethyl radical and developed a delocalization substituent constant E_D (Scheme 1). In this reaction, the formation of a benzylic radical is involved in the rate-determining step. However, the radical character is only partially developed.[5] Therefore, the kinetic effects will be smaller than they would be for complete radical development. Additionally, a polar contribution in this reaction must be important since an electronegative radical is used. A similar reaction of substituted toluenes with trichloromethyl radical is known to proceed on a purely polar basis.[6]

A $\sigma^{\bullet}_F$ scale was derived[7] from the bromination of *para*-substituted 3-cyanotoluenes (Scheme 1).The involvement of a steric effect, interference of side reactions and a polar contribution are all disadvantages in this approach.

Creary's $\sigma^{\bullet}_c$ scale[8–10] was based on the extensive rate data for the rearrangement of methylenearylcyclopropane (Scheme 1). However, the extent of electron decoupling in the transition state of this reaction is not certain.

Arnold and co-workers suggested a $\sigma^{\bullet}_\alpha$ scale[11,12] based

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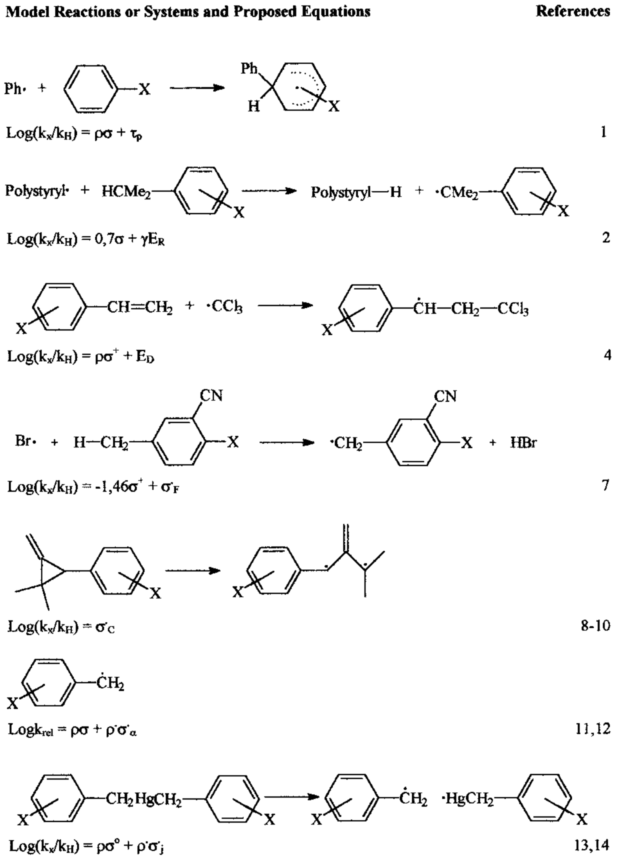
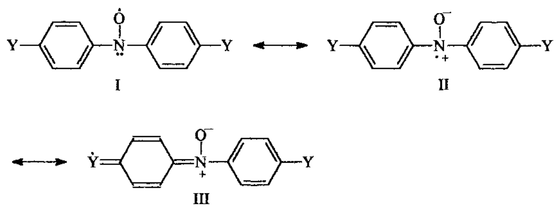


Scheme 1

on the reduction of the exocyclic α C—H coupling constant by stabilizing substituents in benzyl radical (Scheme 1). The advantage of this scheme is the absence of problems associated with side reactions and that the radical character is, of necessity, fully developed. Possible disadvantages include the uncertainty of whether stabilization by different types of substituents is linearly related to the reduction of the coupling constants (a_H).

The thermal decomposition of dibenzylmercurials was chosen[13,14] as a model reaction for the σ_J scale (Scheme 1). The advantage of this reaction is that the full stabilizing effect of a *para* substituent on a benzyl radical comes into play in the transition state, and gives a reasonably large kinetic effect. Additionally, side reactions should be less important, since the main fate of the benzyl radicals is dimerization. The difficulties of this scheme are experimental. Some dibenzylmercurials with conjugating electron-withdrawing groups are difficult to prepare, and some of the compounds have limited solubility in the solvents normally used for the kinetic experiments.

Recently, an hfsc $= \rho^X\sigma^X + \rho^\bullet\sigma^\bullet$ equation was obtained[15] from ESR coupling constants for bis(*p*-Y-substituted phenyl)aminoxyl radicals. The delocalization of unpaired electrons in the aminoxyl radical may be represented by the structures **I, II** and **III** (Scheme 2).



Scheme 2

In this system, the variation in the α_N coupling constant is small (maximum 1.27 G), leading to a coarsely graduated scale. However, it is interesting that the aminoxyl radical is stabilized by both electron-withdrawing and electron-releasing substituents.

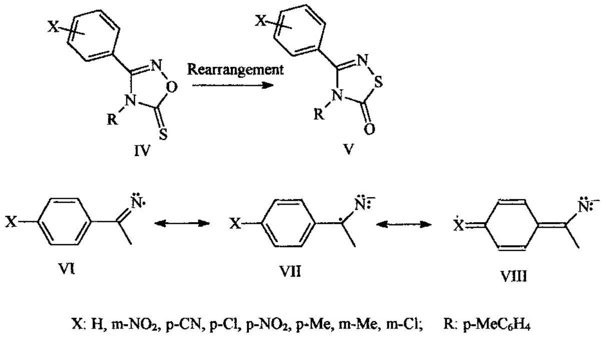
Since the aminoxyl radical is stabilized by a wide range of the substituents, we expected that the rate of the thermal rearrangement of 3-substituted phenyl-4(*p*-tolyl)-1,2,4-oxadiazole-5(4*H*)-thiones (**IV**) to the corresponding 5-ones (**V**) would be similarly enhanced by both electron-withdrawing and electron-releasing *para* substituents through the structures **VI, VII** and **VIII** (Scheme 3).

This type of thione–thiol rearrangement was found to proceed through a free radical mechanism. A transient free-radical species has been detected[16] by ESR measurements in the thermal rearrangement of oxime thionocarbamates to thioxime carbamates.

The rearrangements were carried out on ca $(5–8) \times 10^{-3}$ M solutions in *n*-pentadecane in individual degassed ampoules, and the reactions were monitored by HPLC analysis of the remaining thiones. No deviations from first order were noted, and the results are summarized in Table 1.

The first-order rate constants obtained at 180 °C gave, as expected, no good overall correlation with any of the polar substituent constants σ, σ^+ or σ^-. Plots of log$k$ against σ show, however, that *m*-Me, *p*-Cl, *m*-Cl and *p*-CN substituents lie close to a line of small gradient; $\rho = 0.15$ (Fig. 1), indicating that *homolysis* of the N—O bond occurs (Scheme 4).

Since both electron-withdrawing and electron-releasing substituents are involved, this can be explained by the



Scheme 3

Table 1. Kinetic data for the thermal rearrangement of 3-(substituted phenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4*H*)-thiones

Substituent	T (°C)	$10^{-3}k$ (s^{-1})	E (kcal mol^{-1})
H	180	15.89	
m-NO_2	180	1.98	
p-CN	180	36.32	
p-Cl	180	29.46	
p-NO_2	180	12.44	
p-Me	180	29.94	
m-Me	180	28.49	
m-Cl	160	7.35	
	180	32.31	23.08
	200	74.13	
m-Cl	166	105.04 (with Cu catalysis)	

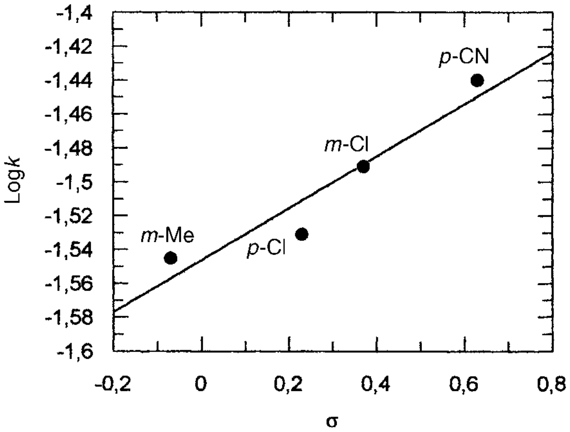


Figure 1. Plots of log*k* for *m*-Me, *p*-Cl, *m*-Cl and *p*-CN against σ

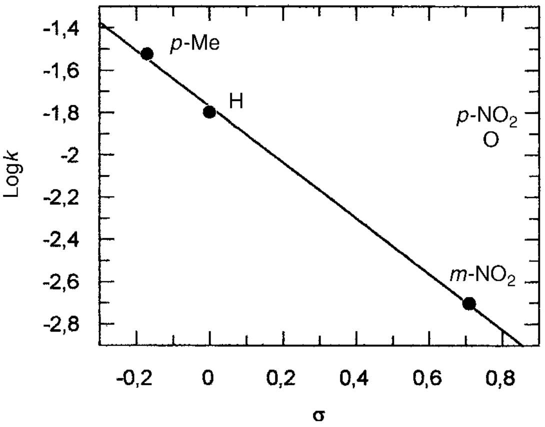
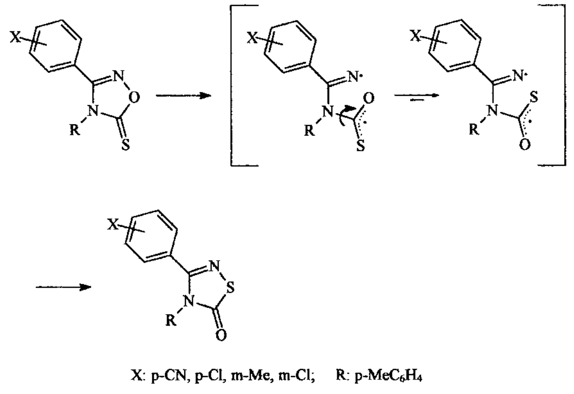
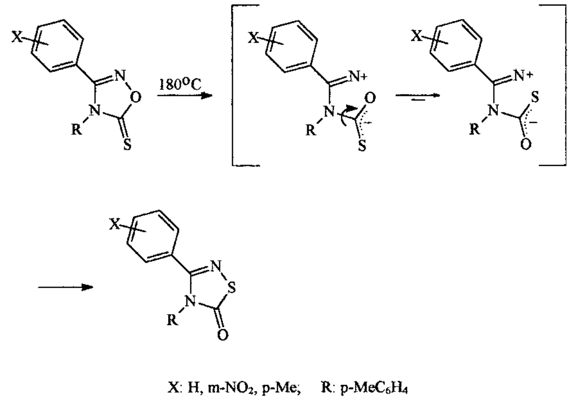


Figure 2. Plots of log*k* for *p*-Me, H and *m*-NO_2 against σ

operation of a polar factor, and shows no effect of conjugation (spin delocalization) from the radical centre to the substituents, such as in Scheme 3 (structure **VIII**). In Fig. 2, plots of log*k* for *p*-Me, H and *m*-NO_2 substituted compounds against σ lie in a line, but with a high negative slope; $\rho = -1.3$. This strongly indicates that rearrangement of the thiones with these substituents occurs via the heterolysis of the N—O bond, so placing a positive charge on nitrogen atom (Scheme 5).



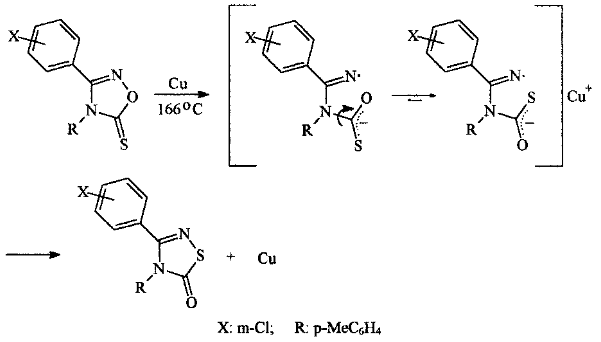
Scheme 4



Scheme 5

The point for the *p*-NO_2 substituted compound lie above the line in Fig. 2. We think that the rearrangement of this proceeds through a more complex mechanism.

The rate of thermal rearrangement of 3-(*m*-chlorophenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4*H*)-thiones was greatly increased when a catalytic amount of copper powder was present. (Table 1). We interpret this as being



Scheme 6

due to the formation of the thione–copper complex in the transition state (Scheme 6), which should lower the activation energy for the reaction.

EXPERIMENTAL

The preparation of 1,2,4-oxadiazole-5-thiones and their rearrangement produces (1,2,4-thiadiazole-5-ones) has been reported previously.[17,18] The compounds were recrystallized before use.

Solutions of $(5–8) \times 10^{-3}$ M 1,2,4-oxadiazole-5-thiones in *n*-pentadecane were prepared. A 1 ml volume of each solution was transferred using a 1 ml bulb pippette into Pyrex ampoules. Each ampoule was degassed and sealed under vacuum. The ampoules were wrapped in aluminium foil and wound round with copper wire to prevent the foil from being removed and to ensure that the ampoule would sink in the oil-bath.

The oil-bath was filled with silicone oil as the thermostat fluid. The heater was controlled by a Variac and a relay contact thermometer, respectively. The fluid was agitated by a steel paddle stirrer. Kinetic studies were carried out at 160, 166, 18O and 200 °C. On removal from the oil-bath each ampoule was cooled to room temperature, opened, and the contents were transferred to sample tubes. Analysis of the remaining 1,2,4-oxadiazole-5-thiones was carried out by HPLC using a Novapak C_{18} column, expressed in terms of the peak area, and these data were analysed for the best fit to the first-order rate equation by regression analysis, using a computer.

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