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ELECTROPHILIC SUBSTITUTION IN FIVE-MEMBERED HETEROCYCLIC SYSTEMS—VIII

RELATIVE RATES OF TRIFLUOROACETYLATION[1,2]

S. CLEMENTI and G. MARINO*

Istituto di Chimica Organica, Università di Perugia, Italy

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Abstract—The relative rates for the reaction of thiophene (1), selenophene (6·5), furan ($1{\cdot}4 \times 10^2$) and pyrrole ($5{\cdot}3 \times 10^7$) with trifluoroacetic anhydride at 75° in 1,2-dichloroethane have been determined using a competitive procedure.

THE determination of the relative reactivities of 5-membered heteroaromatic rings towards electrophiles is of considerable theoretical interest since it permits the testing of the validity of the many different reactivity indices that have been calculated for these systems using different quantum mechanical approaches.[3] Accordingly, a research programme in this field was started several years ago in this laboratory.

In a previous paper,[4] the relative rates of reaction of furan and thiophene in the iodine- and tin tetrachloride-catalysed acetylations were determined. Pyrrole could not be examined since it interacts with the catalysts under the experimental conditions used.[5]

In a subsequent paper,[6] the relative reactivities of all three fundamental systems (furan, thiophene and pyrrole) were compared in the bromination by molecular bromine. The comparison was then extended to selenophene.[1] However, the peculiarities of the bromination reaction prevented, in this case, the direct comparison of the reactivities of the unsubstituted rings: therefore, rates for the 2-methoxycarbonyl derivatives have been determined.

In continuation of these studies, we are now able to report new data which permit a direct comparison of the α-reactivities of all the four unsubstituted rings: furan, thiophene, selenophene and pyrrole. The data refer to the trifluoroacetylation by trifluoroacetic anhydride in dichloroethane.

Trifluoroacetylation is an interesting electrophilic reaction for several reasons. Firstly, it is a clean reaction and all the examined heterocyclic compounds (pyrrole included) are converted into the monotrifluoroacetylated derivatives without any appreciable formation of by-products. Secondly, it is an acylation reaction which does not require Friedel–Crafts catalysts:[7] this avoids complications arising from interactions of pyrrole with such catalysts.[5] Finally, it is a very selective reaction and therefore particularly suitable for the study of structure–reactivity relationships.

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* To whom correspondence should be addressed.

RESULTS AND DISCUSSION

Each compound examined was first individually treated in dichloroethane with a solution containing an equimolecular amount of trifluoroacetic anhydride. The mixtures were kept at 75° for times ranging from a few minutes (pyrrole and N-methylpyrrole) to several days (thiophene).

The reaction products were then examined by VPC. In all cases the chromatograms exhibited, beside the peak of the starting substance, only a sharp peak corresponding to the α-trifluoroacetyl derivative (identification of isomers was made using NMR spectra).

The relative rates were determined using a competitive procedure which has been used successfully in previous, related, studies.[1,4] Known amounts of two substrates of comparable reactivity were dissolved in dichloroethane and treated at 75° with a deficient amount of the anhydride. After appropriate intervals of time, the reaction solutions were quenched and an inert internal standard was added to permit the estimation of the actual amounts of reaction products present. The relative rates were then calculated using the appropriate formula.[8] The applicability of the formula was tested by varying the initial concentrations of the reactants, and by stopping the reaction at different times corresponding to different percentages of reaction.

Since the difference in reactivity between furan and pyrrole is very large, it was impracticable to determine the relative rate from a direct competitive experiment. The relative rate was therefore determined indirectly with the aid of some substrates exhibiting intermediate reactivity: 2-methylthiophene, 2-thiometoxythiophene, 2-methylfuran and 2-methoxythiophene.

A total of 36 independent competitive experiments was carried out. The average values for the relative rates for each pair of substrates examined are reported in Table 1.

TABLE 1. COMPETITIVE EXPERIMENTS OF TRIFLUOROACETYLATION

Compound I	Compound II	n Experiments	k_I/k_{II}
Selenophene	Thiophene	3	6·5
Furan	Selenophene	2	22
2-Methylthiophene	Furan	6	1·3
2-Methylthiophene	Selenophene	2	28
2-Thiomethoxythiophene	2-Methylthiophene	2	14
2-Methylfuran	2-Thiomethoxythiophene	3	45
2-Methoxythiophene	2-Methylfuran	5	7·6
Pyrrole	2-Methoxythiophene	5	58
N-Methylpyrrole	Pyrrole	4	1·9

The average deviations from the means are quite large (10–12%). However, in view of the very large range in reactivity covered (~ 10^8), the relatively low accuracy of the method adopted does not introduce any major difficulty in the consideration of the results.

The reactivities, relative to the reference compound (thiophene) have been calculated and are reported in Table 2.

TABLE 2. RELATIVE RATES OF TRIFLUOROACETYLATION AT 75°

Compound	k/k_o
THIOPHENE	1
SELENOPHENE	6·5
FURAN	$1{\cdot}4 \times 10^2$
2-Methylthiophene	$1{\cdot}9 \times 10^2$
2-Thiomethoxythiophene	$2{\cdot}6 \times 10^3$
2-Methylfuran	$1{\cdot}2 \times 10^5$
2-Methoxythiophene	$9{\cdot}1 \times 10^5$
PYRROLE	$5{\cdot}3 \times 10^7$
N-Methylpyrrole	$1{\cdot}0 \times 10^8$

In some cases the values obtained are somewhat different from those published in the preliminary note.[2] This fact is due to the use of a larger number of "bridges", i.e. compounds exhibiting intermediate reactivity, which has now permitted a more precise determination of the relative rates. The method of competitive reactions is, in fact, not accurate when the relative rates differ by a factor of 100 or greater.

Firstly, the relative reactivities of the unsubstituted fundamental rings may be compared. The reactivity order is: thiophene < selenophene < furan ≪ pyrrole. This is in agreement with bromination[6] and hydrogen–deuterium exchange[9] data. We wish to draw particular attention to the relative reactivities of furan and pyrrole. In many textbooks[10] it is reported that furan is slightly more reactive than pyrrole towards electrophiles; this shows that it may be misleading to draw conclusions concerning the relative reactivities from qualitative examinations of heterogeneous data.

The very high reactivity of pyrrole cannot be ascribed to a reaction of the anion $C_4H_4N^-$ since N–methylpyrrole (for which ionization cannot be hypothesized) is still more reactive than pyrrole by a factor of about 2.

As regards the reactivities of the 2-substituted derivatives, the main features of the results are:

(1) The reactivities of the thiophene derivatives are, at least qualitatively, those foreseen on the basis of the known electronic effects from a conjugative position (H < Me < SMe < OMe).

(2) The effect of a Me group in the α-position increases the reactivity of the other α-position by a factor of 380 in the thiophene ring and 1720 in the furan ring; this seems to indicate a greater sensitivity of the latter ring to structural changes.

The present study will be extended to other substituted derivatives of furan, thiophene, selenophene and pyrrole with the aim of determining the different selectivities of these four heteroaromatic rings.

EXPERIMENTAL

Starting materials. Thiophene (b.p. 83–84°), furan (32°), 2-methylthiophene (112·5°), 2-methylfuran (62·5°), pyrrole (131°) and N-methylpyrrole (114°) were pure grade commercial samples, purified by distillation at atm press.

Selenophene,[11] 2-methoxythiophene[12] (63°/20 mm) and 2-thiometoxythiophene[13] (73·6° at 20 mm) have been prepared according to the literature. All the samples used for competitive experiments were examined by VPC and proved to be at least 99·5% pure.

Trifluoroacetic anhydride was a commercial product (Fluka), distilled over P_2O_5, b.p. 39°. 1,2-Dichloroethane (C. Erba) was dried over $CaSO_4$ and fractionated through a Todd column; the medium fraction boiling at 83–83·5° was used.

Trifluoroacetyl derivatives. The 2-trifluoroacetyl derivatives of thiophene[14] and pyrrole[7] are known compounds. 2-Trifluroacetylfuran, 2-methyl-5-trifluoroacetylfuran, 2-methyl-5-trifluoroacetylthiophene, 1-methyl-2-trifluoroacetylpyrrole and 2-trifluoroacetylselenophene have been characterized in previous papers.[1,15]

2-Methoxy-5-trifluoroacetylthiophene and 2-thiomethoxy-5-trifluoroacetylthiophene are new compounds and were prepared by reaction of 2-methoxy and 2-thiomethoxythiophene with trifluoroacetic anhydride in dichloroethane on a preparative scale. After some hr at room temp the reaction mixtures were poured into $NaHCO_3$aq. The solvent was separated, dried and removed by distillation; the residues were distilled at reduced press.

2-Methoxy-5-trifluoroacetylthiophene. b.p. 110–112°/17 mm is a low melting solid which was further purified by sublimation, m.p. 54–54·5°. (Found: C, 40·18; H, 2·54. Calc. for $C_7H_5O_2F_3S$: C, 40·00; H, 2·40%). The structure was confirmed by a PMR spectrum ($\delta = 4{\cdot}04$ ppm (S, OMe); 6·90 (D, 3H), 7·77 (M, 4H).

2-Thiomethoxy-5-trifluoroacetylthiophene is a light yellow liquid, b.p. 148°/20 mm. (Found: C, 37·27; H, 2·14. Calc. for $C_7H_5F_3OS_2$: C, 37·16; H, 2·23%); ($\delta = 2{\cdot}66$ ppm (S, SMe); 6·92 (D, 3H), 7·77 (M, 4H).

Competitive experiments. The competitive reactions were carried out at 75° for times ranging from a few min (pyrrole and N-methylpyrrole) to several days (thiophene and selenophene). The procedure used is that described;[4] in the case of the less reactive substrates the reactions were carried out in sealed tubes.

Gas chromatographic analyses were accomplished on a Mod. B Erba fractometer equipped with a thermistor detector. A 2 m × 6 mm stainless steel column packed with Craig Polyester succinate supported on C-22 Firebrick, was used for all the analytical determinations. The column temp was 120–200° according to the volatility of the compounds.

The areas of the product peaks were compared with the area of the internal standard peak (acetophenone or bromobenzene) and the amounts of trifluoroacetyl derivatives formed were determinated by application of the Eastman expression.[16] This procedure was tested by the analysis of synthetic mixtures containing acetophenone and 2-trifluoroacetylthiophene.

The relative rates were then calculated from the equation[8]

$$\frac{k_A}{k_B} = \frac{\log (A^\circ - X_A)/A^\circ}{\log (B^\circ - X_B)/B^\circ}$$

where A° and B° refer to the initial moles of the competing heterocycles and X_A and X_B refer to the final moles of the corresponding trifluoroacetyl derivatives.

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