Relative Reactivities of Thiophen, Furan, and Pyrrole Rings in Electrophilic Substitutions: Trifluoroacetylation

By S. CLEMENTI, F. GENEL, and G. MARINO*
(*Istituto Chimico, Università di Trieste, Italy*)

IN connection with our current studies on electrophilic substitutions in five-membered heterocyclic compounds,[1,2] we are now able to report the relative rates of substitution of furan, thiophen, pyrrole, and several of their derivatives in the trifluoroacetylation reaction.

Trifluoroacetic anhydride is an interesting electrophilic reagent, in that it is able to acylate a reactive aromatic compound in the absence of any added Friedel–Crafts catalyst.[3] This avoids the complications arising from the interactions of pyrrole with such catalysts.[4]

Reactions were carried out at 75° in dichloroethane solution and the relative rates were determined using a competitive procedure. Standard solutions of two heterocyclic substrates were treated with a deficient amount of trifluoroacetic anhydride in the same solvent. The reaction mixtures were quenched and the products analysed by vapour-phase chromatography.

Under the conditions used for the competitive experiments the α-trifluoroacetyl derivative is the only reaction product in all cases.

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-methylthiophen, 2-methylfuran, and 2-methoxythiophen. The relative rate of trifluoroacetylation of *N*-methylpyrrole was also determined.

The results are summarised in the Table.

TABLE

Relative rates of trifluoroacetylation

Thiophen	1
Furan	$1{\cdot}5 \times 10^{2}$
2-Methylthiophen	3×10^{2}
2-Methylfuran	$3{\cdot}5 \times 10^{4}$
2-Methoxythiophen	1×10^{6}
Pyrrole	1×10^{8}
N-Methylpyrrole	2×10^{8}

As far as we know, this is the first reported quantitative comparison of the reactivities of furan, thiophen, and pyrrole in an electrophilic substitution. The reactivity of furan is intermediate between those of thiophen and pyrrole, but much closer to the former than to the latter.

The general reactivity pattern observed in this reaction has been confirmed in a completely different electrophilic substitution, *i.e.*, bromination of the 2-methoxycarbonyl derivatives (see the following Communication).

Inspection of the data in the Table reveals another point of interest. The acylation by trifluoroacetic anhydride in the absence of catalysts is one of the most selective electrophilic substitutions known. The introduction of a methyl group in an α-position of the thiophen ring increases the reactivity of the other α-position by a factor of *ca.* 600, an effect similar to that observed in bromination by molecular bromine.[5]

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