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Homolytic Aromatic Substitutions of Pentatomic Heteroaromatics with Electrophilic Carbon Radicals Generated by Alkyl Halides and Triethylborane.

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Abstract: An efficient homolytic aromatic substitution of pyrroles, furan and thiophene by $\cdot CH_2CO_2Et$ and $\cdot CH(CH_3)CO_2Et$ has been carried out, the radicals being generated by autoxidation of BEt_3 in the presence of XCH_2CO_2Et and $XCH(CH_3)CO_2Et$ (X=Br, I).

Key Words: *Triethylborane autoxidation, Homolytic Aromatic Substitutions, 2-Heteroarylacetic Acids, Electrophilic Carbon Radicals.*

In the last two decades, free radical reactions leading to carbon-carbon bond formation have emerged as a very powerful tool for the synthesis of a large variety of organic compounds.[1] Thus, studies concerning the development of methods thereby carbon radicals can be generated and reacted with suitable substrates raise continuous interest.

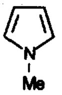
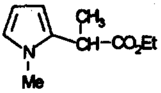
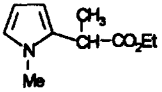
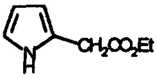
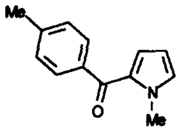
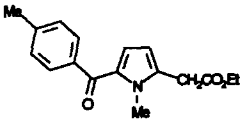
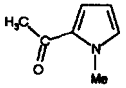
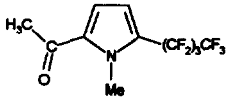
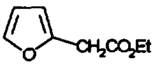
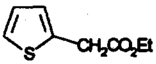
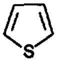
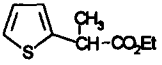
$$R_3B + O_2 \longrightarrow R_2BO_2^{\bullet} + R^{\bullet} \qquad (1)$$

The formation of carbon radicals by trialkylborane autoxidation (eq. 1) is long known;[2] however, only few reports have recently dealt with the possible use of this reaction to generate other carbon radicals by means of the reaction of R·, formed in eq. 1, with an alkyl bromide or iodide (eq. 2).

$$R^{\bullet} + R'X \rightleftharpoons R'^{\bullet} + RX \qquad (2)$$

When R'· is sufficiently more stable than R·, equilibrium (2) is driven to the right and reactions promoted by R'· can be accomplished. Thus, the BEt_3/RX system has been employed to obtain the malonyl radical (eq. 2, R=Et, $R'=CH(CO_2Me)_2$, X=Br) for the malonylation of 2-benzoylpyrrole,[3] and to generate a number of alkyl radicals (eq. 2, R=Et, R'=*t*-Bu, *i*-Pr, CH_2I, *n*-C_6H_{13}) which are then reacted with vinyl ketones.[4]

Table. Homolytic Aromatic Substitutions of Pentatomic Heteroaromatics Promoted by BEt_3 and Alkyl Halides in DMSO.[a]

entry	Substrate	Alkyl halide	Product	yield (%)[b]
1		$ICH(CH_3)CO_2Et$		54
2		$BrCH(CH_3)CO_2Et$		39
3		$BrCH_2CO_2Et$		47
4		ICH_2CO_2Et		55[c]
5		$I(CF_2)_3CF_3$		55
6		ICH_2CO_2Et		60[d,e,f]
7		ICH_2CO_2Et		56[d]
8		$BrCH(CH_3)CO_2Et$		47[d]

[a] A 1.0 M solution of BEt_3 in hexane (1 ml) is added, at room temperature, to an open-air stirred mixture of the substrate (10-30 mmol), the alkyl halide (1.0 mmol) in the appropriate solvent (5 ml) which is either benzene or DMSO for pyrrole and its derivatives and DMSO for furan and thiophene. With the latter two heteroaromatics 1 mmol of $Fe_2(SO_4)_3 \cdot H_2O$ was also added. After 45 min additional BEt_3 was added (1 ml). When the halide is bromide, three further additions of BEt_3 were necessary. The mixture was diluted with brine and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The products were then isolated by column chromatography. All products had spectroscopic data in agreement with the corresponding literature data.[5a,b] The mass balance is good and the unreacted substrate can be recovered (exception is the unsubstituted pyrrole that underwent partial decomposition).

[b] Isolated yield, with respect to the alkyl halide.

[c] No reaction with $BrCH_2CO_2Et$.

[d] 1 equivalent of $Fe_2(SO_4)_3 \cdot H_2O$ was added.

[e] The yield is 20% in the absence of $Fe_2(SO_4)_3 \cdot H_2O$.

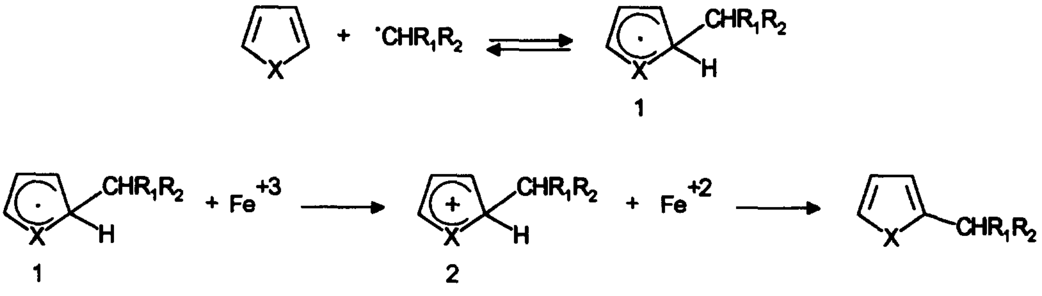
[f] The yield is 19% with ethyl bromoacetate.

We have therefore considered of interest to investigate whether the above approach could represent a viable and general method alternative to that recently developed for the homolytic substitutions of electron-rich aromatic compounds by electrophilic carbon radicals.[5]

The results presented here (Table) show that this is the case and, in particular, that BEt_3, in combination with XCH_2CO_2Et or $XCH(CH_3)CO_2Et$ (X=Br, I) in DMSO provides us with an useful system for the synthesis of the very important 2-heteroarylacetic acids. The procedure is simple and very mild conditions (air is the oxidant!) are used. Even though the yields (not optimized) are slightly lower than those obtained in the previously studied Fe^{+2}/H_2O_2 system,[5a] the present method has the additional advantage that, in several cases, it works well with the less expensive bromoacetic and 2-bromopropionic acids ethyl esters, as the alkyl halides, in the place of the corresponding iodides.

With pyrrole (or N-methylpyrrole) the reaction takes place also when electron-withdrawing groups are present, as shown by the efficient synthesis of the ethyl ester of Tolmetin (Table, entry 4); moreover, it can also be applied to the synthesis of perfluoroalkylpyrroles (Table, entry 5). With the less reactive furan and thiophene, lower yields are obtained under the same conditions used for pyrrole and its derivatives. However, with these substrates too, an efficient reaction is possible when an equimolar amount (with respect to the alkyl halide) of $Fe_2(SO_4)_3{\cdot}H_2O$ is added (Table, entries 6, 7, 8).

Probably, the role of Fe^{+3} is that of easing the oxidation of the intermediate radical σ-complex (Scheme, X=O, S, R_1=CO_2Et, R_2=H, CH_3) to the final substitution product. In the absence of Fe^{+3}, 1 can revert back to the reactants. Perhaps, with pyrrole and N-methylpyrrole Fe^{+3} is not necessary, presumably owing to the much higher stability of the cationic σ-complex 2 when X=NH or NCH_3 than when X=O or S. Thus, a reasonable hypothesis is that in the case of pyrrole derivatives oxidation of the σ-radical can be so easy as to be efficiently accomplished by air. The oxidation of the intermediate σ-complex is probably very difficult also in the perfluoroalkylation reaction. Accordingly, using perfluoroalkyl iodide no perfluoroalkylation of furan and thiophene has been possible, even in the presence of $Fe_2(SO_4)_3{\cdot}H_2O$.



Scheme

Work is under way to extend the scope of this methodology to the homolytic substitution of homoaromatic systems[6] as well as to other reactions of carbon radicals.

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6. Preliminary experiments have shown that an efficient reaction takes place with anisole.

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