Catalysis by Ferrous Ion in Nucleophilic Aromatic Substitution Reactions

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Efficient catalysis is provided by ferrous chloride in the nucleophilic aromatic substitution reaction of several aryl and heteroaryl halides with a ketone enolate ion as the nucleophile in Me_2SO, to give the aryl or heteroaryl ketones in fair to good yields. The enolate ions from pinacolone, acetophenone, cyclohexanone and pentan-3-one behave successfully. A side-reaction is represented in some cases by the hydrodehalogenation of the substrate ArX, and evidence is provided for the intermediacy of both $Ar^{\bullet}$ and Ar^- species. Other significant mechanistic clues acquired include: (i) inhibition by electron and radical scavengers; (ii) entrainment of poor nucleophiles by good ones; (iii) the relative reactivity of two nucleophiles in competition experiments with PhI under Fe^{2+} catalysis having the same value as in the experiments under both photostimulation and spontaneous initiation. All these findings are consistent with an $S_{RN}1$ mechanism of substitution where ferrous ion, in combination with the nucleophile, plays an important rôle in the initiation step.

Aromatic nucleophilic substitutions on aryl halides, which are not activated by electron-withdrawing substituents, have been widely documented in the past two decades.[1] Quite a number of these reactions occur by the radical chain $S_{RN}1$ mechanism, whose initiation step (1) and propagation steps (2)–(4) are shown in Scheme 1, where Y^- is the nucleophile.

$$ArX \xrightarrow{\text{initiation}} ArX^{\bullet -} \qquad (1)$$

$$ArX^{\bullet -} \longrightarrow Ar^{\bullet} + X^- \qquad (2)$$

$$Ar^{\bullet} + Y^- \longrightarrow ArY^{\bullet -} \qquad (3)$$

$$ArY^{\bullet -} + ArX \longrightarrow ArY + ArX^{\bullet -} \qquad (4)$$

Scheme 1

Occasionally, this mechanism comes into action by *spontaneous* initiation in the dark through a thermal process, very likely involving an electron transfer from the nucleophile Y^- to the substrate ArX [eqn. (5)].[2] In most cases, however,

$$ArX + Y^- \longrightarrow ArX^{\bullet -} + Y^{\bullet} \qquad (5)$$

step (1) has to be appropriately provoked. The first reported method of initiation was the addition of solvated electrons to the substrate in liquid ammonia.[1,3] Recently, sodium amalgam was also shown to initiate the reaction.[4] Cathodically generated electrons provide an alternative and efficient method of initiation.[5] Photostimulation is another widely employed method for effecting step (1):[1,6] it is possibly due to an electron transfer within an excited complex of the aryl halide with the anion (an enolate ion) [eqn. (6)].[7]

$$[ArX \cdots Y^-] \xrightarrow{h\nu} [ArX^{\bullet -}\ Y^{\bullet}] \qquad (6)$$

A few years ago, catalysis by iron(II) salts of the reactions of a ketone enolate ion, and of diethyl phosphite ion, with bromo- and iodo-benzene have preliminarily been reported.[8] We have undertaken a re-examination of this catalysis with a two-fold aim: to gain a better understanding of the features governing this new form of initiation and to explore the value of ferrous catalysis in preparative use. In this paper the catalytic efficiency of various iron(II) salts and other inorganic salts, has been compared; the effect of changing the structure of the substrate, as well as that of the enolate ion, has been examined under ferrous ion catalysis; a few mechanistic tests have been performed. The results are consistent with an $S_{RN}1$ mechanism of substitution. A few peculiarities, however, have been disclosed.

Results

In all the reactions reported in this study the following general scheme applies [eqn. (7)], where an aryl halide reacts, without

$$ArX + \underset{\mathbf{1}}{^-CH_2COCMe_3} \xrightarrow{MY_n} ArCH_2COCMe_3 + X^- \qquad (7)$$

illumination, with an excess of a suitable nucleophile under catalysis by an inorganic salt (MY_n). The enolate ion of 3,3-dimethyl-2-butanone (pinacolone), generated *in situ* by the use of Bu^tOK, was chosen as the reference nucleophile since it is known to undergo clean $S_{RN}1$ substitution processes.[1] Most of the reactions were run in dimethyl sulfoxide (Me_2SO), a solvent easier to use than liquid ammonia. Preliminary attempts had shown that in dimethylformamide or in acetonitrile the reaction of eqn. (7) does not occur. The experiments were run under an inert atmosphere (either N_2 or argon), even though no difference was observed by occasionally running the reactions in air. Finally, the formation of products from reaction (7) was monitored by gas chromatography.

Reaction Conditions.—In a typical experiment, PhI (0.02 mol dm^{-3}), along with a 40% molar equivalent of anhydrous $FeCl_2$, reacted with a three-fold excess of $^-CH_2COCMe_3$ (**1**; 0.06 mol dm^{-3}) in Me_2SO at room temperature. Disappearance of PhI was observed within 20 min, replaced by 74% of the substitution product, $PhCH_2COCMe_3$, and *ca.* 10% of the disubstitution product, $Ph_2CHCOCMe_3$ (expt. 1, Table 1). In the absence of $FeCl_2$ the reaction was much slower (expt. 2), but, by no means negligible, 8% of phenylpinacolone being formed. This confirms the occurrence of the already reported 'spontaneous initiation' [as in eqn. (5)][2] along with the ferrous-catalysed one. No such spontaneous initiation had been observed in liquid ammonia,[8] while it is documented in other $S_{RN}1$ reactions run in Me_2SO.[1,2] It is important to stress that, in the absence of the enolate ion, no reaction occurred between

Table 1 Cation-induced nucleophilic aromatic substitutions in Me_2SO at room temperature[a]

Expt.	Substrate	Salt	% ArX recovered[b]	$PhCH_2COCMe_3$, yield (%)[b]
1	PhI	$FeCl_2$	4	74[c]
2	PhI	—	89	8
3	PhI	$FeCl_2$[d]	53	50
4	PhBr	$FeCl_2$	90	5
5[e]	PhBr	$FeCl_2$	0	99
6[e]	PhBr	—	89	7
7	PhI	$FeSO_4$	68	34
8	PhI	$Fe(NO_3)_3$	98	3
9	PhI	$Fe(COO)_2$[f]	76	19
10	PhI	Ferrocene	80	2
11	PhI	$CpFe(CO)_2I$[g]	102	2
12	PhI	$K_4Fe(CN)_6$	88	7
13	PhI	$AgNO_3$	93	1
14	PhI	$Ni(OAc)_2$	81	13
15	PhI	$Co(OAc)_2$	84	5
16	PhI	$FeCl_2$/p-$C_6H_4(NO_2)_2$[h]	91	10
17	PhI	$FeCl_2$/p-cymene[i]	95	6

[a] ArX, 0.51 mmol; $^-CH_2COCMe_3$, 1.6 mmol; salt, 0.21 mmol; Me_2SO, 25 cm^3; 20 min reaction time. [b] By GLC, typical uncertainty, ±3%. [c] Plus 10% $Ph_2CHCOCMe_3$. [d] 0.06 mmol. [e] Enolate, 3.2 mmol. [f] Oxalate. [g] Cp for cyclopentadienate ion. [h] 0.20 mmol. [i] 0.22 mmol.

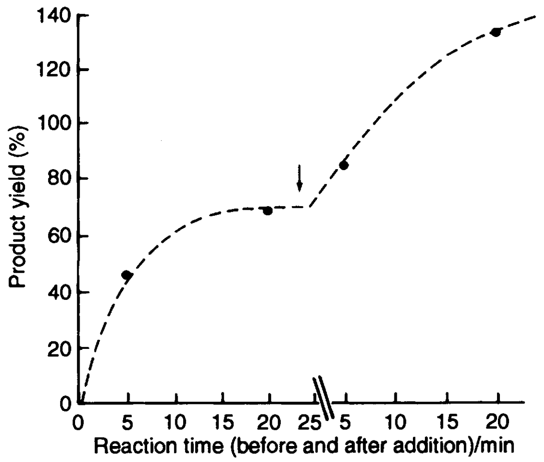

Fig. 1 Catalytic efficiency of $FeCl_2$: the arrow marks the addition of the second aliquot of the reagents (see text)

$FeCl_2$ and PhI: no release of I^-, and no production of PhH or of Ph_2, was observed.

The catalytic rôle played by the iron(II) salt stems from the fact that reaction (7) gains a distinct advantage with respect to the 'spontaneous' conversion (expts. 3 and 2, respectively) even when the $FeCl_2$/substrate molar ratio is as low as 0.12. Further evidence comes from the experiment illustrated in Fig. 1. After a reaction time of 20 min, as in expt. 1, a second aliquot of all the reagents (*i.e.*, PhI, pinacolone, Bu^tOK) except $FeCl_2$ was quickly added to the reaction solution. Samples were withdrawn at various times before and after this addition: the substitution process kept on going with good efficiency in the 'second' period, yet employing the amount of catalyst of the 'first' period.

The Catalyst.—As far as the choice of the catalyst is concerned, a comparison among various salts is shown in Table 1 (expts. 7–15); for higher efficiency, these have to be dried. On the basis of this screening, anhydrous $FeCl_2$ was found to be the best and was used for all further experiments; $FeSO_4$, which performed very well in liquid NH_3,[8] suffers from poor solubility in Me_2SO.

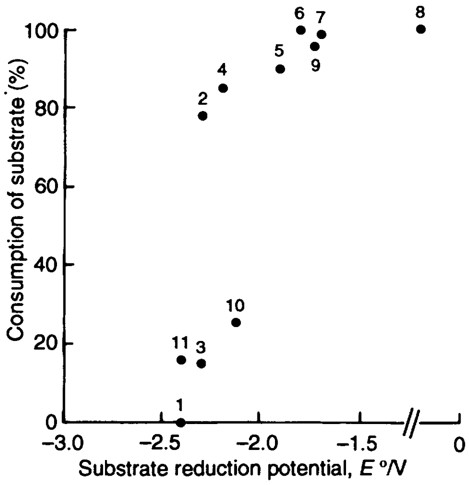

Fig. 2 Qualitative substrate reactivity at 20 min. Substrates: 1, PhBr; 2, 2-BrPy; 3, 4-Br-PhCl; 4, 1-Br-Nph; 5, 2-Br-PhCN; 6, PhI; 7, 1-I-Nph; 8, Ph_2I^+; 9, 9-Br-Anth; 10, 3-BrTy; 11, 4-Br-$PhOCH_3$

Substrate Reactivity.—Bromobenzene is known to be less reactive than PhI in a $S_{RN}1$ substitution.[1,2a] We obtained in fact almost complete recovery of unreacted PhBr (expt. 4) under the conditions where PhI did react; increasing the amount of $FeCl_2$ did not help. However, increase of the excess of enolate up to six-fold (0.13 mol dm^{-3}) with respect to PhBr (0.02 mol dm^{-3}) afforded quantitative formation of the substitution products (expt. 5). The spontaneous reaction was not affected to a comparable extent by this change of concentration (expt. 6).

Other aryl halides, endowed with a less negative reduction potential[9,10] than PhBr, have been tested in the reaction with **1** in the presence of $FeCl_2$ as the catalyst [see eqn. (7)] under the general conditions of expt. 1 (Table 2). Samples of the reaction mixture were withdrawn at different time intervals, depending on the reactivity of the substrate, and analysed by gas chromatography; in case of poor mass balance, titration of the halide ion released was also carried out. The reactions gave a clean product pattern, and complete consumption of the substrate within 1 h was often observed. Along with the substitution product, $ArCH_2COCMe_3$, the product of reductive dehalogenation, ArH, was detected in some cases. The conversion after the same reaction time (20 min) is given in Table 2, to allow a rough discrimination in reactivity among the substrates, whose reduction potential[9,10] is also listed. A crude plot of the percentage of overall consumption of the substrate (*i.e.* 100 − % ArX recovered after 20 min) *vs.* its redox potential is provided in Fig. 2. The conversion for the uncatalysed process of each substrate is also given in Table 2.

Ferrous ion catalysis appears to be a convenient and efficient way to induce nucleophilic substitution on aromatic and heteroatomic halides. The spontaneous process[2] is in general less satisfactory, and competes with the catalysed route only in the case of easily reducible substrates (see expts. 21 and 23). Under the chosen conditions, and within the uncertainty limits of the mass balance, the eleven substrates appear to be crudely discriminated in terms of their electron affinity, which varies widely from Ph_2I^+ down to PhBr, the more easily reducible ones providing higher conversion within the fixed reaction time (see also Fig. 2). From a mechanistic point of view this implies that the reduction potential of the substrate must play a relevant rôle in the ferrous-ion stimulated reaction.

With 4-chlorobromobenzene, both the mono- and (under a larger excess of **1**) the di-substituted products [4-Cl-C_6H_4-CH_2COCMe_3, **2** and 1,4-$C_6H_4(CH_2COCMe_3)_2$, **3**, respectively; expts. 32 and 33] were detected by GC–MS. This

Table 2 Reactivity of substrate with pinacolone enolate ion and of nucleophile (Y^-) with PhI under $FeCl_2$ catalysis in Me_2SO at room temperature for 20 min[a]

					Products yield (%)		
Expt.	Substrate, (ArX)	$E°/V$[b]	Y^-	% ArX recovered	ArY	ArH	X^-
1	PhI	−1.8	$^-CH_2COCMe_3$	4	74[c]	n.d.	n.d.
18	$Ph_2I^+Br^-$	−0.2		0	97[d]	0	n.d.
19	without $FeCl_2$			22[e]	48[f]	n.d.	n.d.
20	9-Br-anthracene	−1.7		4	46	30	97
21	without $FeCl_2$			7	41	19	n.d.
22	1-I-naphthalene	−1.7		1	60	26	n.d.
23	without $FeCl_2$			32	41	12	n.d.
24	2-Br-C_6H_4CN	−1.9		1	46	6	99
25	without $FeCl_2$			34	15	n.d.	n.d.
26	3-Br-thiophene	−2.1		75	10	4	14
27	without $FeCl_2$			59	2	n.d.	n.d.
28	1-Br-naphthalene	−2.2		18	41	25	78
29	without $FeCl_2$[g]			58	33	11	n.d.
30	2-Br-pyridine	−2.3		22	80	0	n.d.
31	without $FeCl_2$			62	36	1	n.d.
32	4-Br-C_6H_4Cl	−2.3		80	*ca.* 20[h]	0[i]	n.d.
33[k]				60	*ca.* 5[h,l]	2[m]	n.d.
4	PhBr	−2.4		90	5	n.d.	n.d.
34	4-Br-C_6H_4OMe	−2.4[n]		84	13[o]	2	n.d.
35	without $FeCl_2$			94	7	n.d.	7
36	PhI		$^-CH_2COPh$	5	75	n.d.	n.d.
37	PhI		$CH_3\bar{C}HCOEt$	12	55	n.d.	n.d.
38	PhI		cyclohexanone[p]	24	39	n.d.	n.d.
39	PhI		indan-2-one[p]	100	0	n.d.	n.d.
40	PhI		$(EtO)_2PO^-$	100	0	n.d.	n.d.

[a] Conditions as in Table 1; yields by GC or by titration of X^-. [b] In DMF *vs.* SCE, from ref. 9; in H_2O *vs.* Ag/AgCl for Ph_2I^+, from ref. 10. [c] Plus 10% $Ph_2CHCOCMe_3$. [d] Plus 3% $Ph_2CHCOCMe_3$. [e] As PhI. [f] Plus 8% $Ph_2CHCOCMe_3$. [g] After 60 min. [h] As 4-Cl-$C_6H_4CH_2COCMe_3$, see text. [i] As PhCl. [k] Enolate, 3.2 mmol. [l] Plus *ca.* 10% of *p*-$C_6H_4(CH_2COCMe_3)_2$. [m] As $PhCH_2COCMe_3$. [n] Assumed equal to that of PhBr. [o] As 4-MeO-$C_6H_4CH_2COCMe_3$. [p] Enolate from it.

may be taken as an evidence[1,11] of the intermediacy of the radical anion of the monosubstituted product ($\mathbf{2}^{\bullet -}$), which either fragments in step (10) or acts as a reductant of the substrate in step (11): this evidence is in agreement with a stepwise mechanism of substitution of the $S_{RN}1$ kind.

$$\text{Br-}C_6H_4\text{-Cl}^{\bullet -} \longrightarrow Br^- + {}^{\bullet}C_6H_4\text{-Cl} \tag{8}$$

$$\mathbf{1} + {}^{\bullet}C_6H_4\text{-Cl} \longrightarrow \underset{\mathbf{2}^{\bullet -}}{\text{Cl-}C_6H_4CH_2COCMe_3{}^{\bullet -}} \tag{9}$$

$$\mathbf{2}^{\bullet -} \longrightarrow Cl^- + {}^{\bullet}C_6H_4CH_2COCMe_3 \tag{10}$$

$$\mathbf{2}^{\bullet -} \xrightarrow{BrC_6H_4Cl} \mathbf{2} + BrC_6H_4Cl^{\bullet -} \tag{11}$$

$$\mathbf{1} + {}^{\bullet}C_6H_4CH_2COCMe_3 \longrightarrow \underset{\mathbf{3}^{\bullet -}}{C_6H_4(CH_2COCMe_3)_2{}^{\bullet -}} \tag{12}$$

Hydrodehalogenation represents a more or less strongly interfering pathway, depending on the substrate (Table 2). Such interference is almost absent in NH_3, both in the photostimulated[1] and in the ferrous-ion stimulated[8] processes. Since Me_2SO is a better hydrogen atom donor than NH_3,[12] the detection of ArH [see eqn. (13)] supports the formation of the radical intermediate, $Ar^{\bullet}$, in the ferrous-ion catalysed process in Me_2SO. This is a mechanistic feature complying with the $S_{RN}1$ scheme.

$$Ar^{\bullet} + SH \longrightarrow ArH + S^{\bullet} \tag{13}$$

Inhibition of the Reaction.—Retardation of a process occurring by a $S_{RN}1$ mechanism is observed when radical or electron scavengers are added to the medium.[1] *p*-Dinitrobenzene, a well known electron sink, severely retarded the ferrous-ion induced reaction of PhI with **1** (expt. 16) even when added in modest concentration as also did *p*-cymene (expt. 17), a good hydrogen atom donor.[13] These inhibition experiments once more indicate that (i) the formation of radical intermediates is involved and (ii) electron transfer steps are relevant in the ferrous-ion stimulated process, in agreement with a $S_{RN}1$ mechanistic picture. We observe, however, an additional and unexpected source of inhibition in the ferrous-ion catalysed process. In one of the very first experiments, addition of the gas chromatographic internal standard (biphenyl) to the reagents before starting the reaction, as is common practice,[1b] resulted in a negligible conversion to products. This had not been observed in liquid ammonia.[8] Strangely enough, biphenyl is neither an electron scavenger nor a hydrogen atom donor. As a practical consequence, we had to add the standard later, upon quenching the reactions.

Interception of Intermediates.—The formation of hydrodehalogenation products (ArH in Table 2) results from interception of the reactive intermediate $Ar^{\bullet}$ by the solvent [eqn. (13)]. To check this point further, the reaction of 1-bromonaphthalene with **1** and $FeCl_2$ was run in $[^2H_6]Me_2SO$. By GC–MS analysis both naphthalene-D and naphthalene-H were found, along with the substitution product. Although adventitious abstraction of an H atom from sources other than the solvent cannot be excluded, we are more inclined to suggest a reduction of $Naph^{\bullet}$ to $Naph^-$: proton abstraction would then become feasible [*e.g.* from Bu^tOH produced by reaction of Bu^tOK; eqn. (14)].

$$Ar^{\bullet} \xrightarrow{\text{reductant}} Ar^- \xrightarrow{SH} ArH + S^- \tag{14}$$

Table 3 Relative reactivities of nucleophiles with PhI in Me_2SO at room temperature from competition experiments

Expt.	Nucleophile from	Relative rate[a]	Initiation
	Pinacolone	1.00	
41	$(EtO)_2PHO$	2.4	$FeCl_2$
42	$(EtO)_2PHO$	2.2	*hv*
43	Acetophenone	1.5	$FeCl_2$
44	Pentan-3-one	1.4[b]	$FeCl_2$
45	Cyclohexanone	0.49[c]	$FeCl_2$
46	Indan-2-one	0.29	$FeCl_2$
47	Indan-2-one	0.34	*hv*

[a] Average of two experiments; reproducibility within ±10%. [b] Spontaneous initiation gave 1.4; from ref. 2*b*. [c] Spontaneous initiation gave 0.67; from ref. 2*b*.

A similar feature had already been observed by Savéant *et al.*[12b] Reduction of $Ar^{\bullet}$ should be easy, its reduction potential being of the order of -0.3 V.[14] In any $S_{RN}1$ reaction, a possible reductant of $Ar^{\bullet}$ is the radical anion of the product,[5,15] in a step competing with step (4). In our case, however, another possible reductant is Fe^{2+}, and this could increase the incidence of termination steps of the kind of eqn. (14) (compare a 30% yield of ArH in expt. 20 with a 19% yield in the uncatalysed expt. 21).

Spectroscopic Investigation.—Infrared observation of the reacting system reveals that addition of Bu^tOK to the Me_2SO solution of pinacolone causes the appearance of an absorption band at 1550 cm^{-1}, probably due to the formation of the enolate ion. The addition of $FeCl_2$ leads to the disappearance of that band: we take this as evidence of the Fe^{2+}/enolate complexation. Subsequent addition of PhI shows the appearance of a new band at 1510 cm^{-1} within 20 min. We explain the latter as being due to the absorption of the enolate ion of phenylpinacolone, *i.e.* the substitution product of the reaction. The enolate ion of phenylpinacolone has been independently generated and showed the same IR absorption.

Reactivity of Nucleophile.—Besides **1**, other nucleophiles have been employed in reaction with PhI under $FeCl_2$ catalysis (see Table 2; expts. 36–40). The enolate ions from cyclohexanone, pentan-3-one, and acetophenone gave rise to their substitution products in fair to good yields after 20 min. On the contrary, the enolate ion from indan-2-one and diethyl phosphite ion, $(EtO)_2PO^-$, did not react at all, no consumption of the substrate occurring either. This is odd, because $(EtO)_2PO^-$ did react very well with PhI in NH_3 under $FeSO_4$ catalysis.[8]

Table 3 shows the results of competition experiments run between each of the above nucleophiles and **1** as the reference reagent. It is noteworthy that even the two above mentioned 'unreactive' nucleophiles did react in competition with **1** (expts. 41 and 46), showing a very strong example of entrainment: this is a typical feature of a chain process such as the $S_{RN}1$ reaction.[1,16] Diethyl phosphite ion became the most reactive in the series of the competing nucleophiles! It is likely that the initiation step due to $(EtO)_2PO^-$, or also to the enolate ion of indan-2-one, is inefficient when they react alone with $FeCl_2$; in the competition experiment they exploit instead the initiation provided by **1** and enter the propagation chain reacting more or less efficiently with the $Ph^{\bullet}$ intermediate.

Our reactivity ratios from the competition of pentan-3-one *vs.* **1** and of cyclohexanone *vs.* **1** are in good agreement with previous determinations[2b] obtained for the same pairs of nucleophiles under 'spontaneous' initiation in Me_2SO. Similarly, we obtain good agreement between the reactivity ratios of the pairs $(EtO)_2PO^-$/**1** and indan-2-one/**1** under $FeCl_2$ initiation *and* under photostimulation. The consistency of these results among three different initiation techniques strongly supports production of $PhI^{\bullet -}$ in all cases; fragmentation to $Ph^{\bullet}$ would ensue, which diffuses free in solution and becomes available to attack by the competing nucleophiles, both the efficient and the 'inefficient' ones, without any memory effect of the specific initiation technique. These findings, along with the observed entrainment between nucleophiles, are also contrary to any possibility of 'in cage' radical–radical combination [eqn. (15)].

$$\mathrm{PhI} + \mathrm{Y}^- \longrightarrow \mathrm{PhI}^{\bullet -}\mathrm{Y}^{\bullet} \longrightarrow \left[\mathrm{Ph}^{\bullet}\ \begin{matrix}\mathrm{I}^-\\ \mathrm{Y}^{\bullet}\end{matrix}\right] \longrightarrow \mathrm{PhY} + \mathrm{I}^- \qquad (15)$$

Strangely enough, while we obtain entrainment between nucleophiles, we do not observe entrainment between substrates. It is reported[2a] that increase of the release of Br^-, in the spontaneous reaction of PhBr with **1** in Me_2SO, occurs on the addition of tiny amounts of PhI. This was attributed to entrainment of the 'poor' substrate by the 'good' one in the radical chain. Under $FeCl_2$ catalysis, on the contrary, PhI was the only one to react in competition, PhBr being recovered unchanged. This finding is at odds with the 'normal' $S_{RN}1$ behaviour.

Discussion

The experiments reported in this paper do suggest the occurrence of a mechanism of nucleophilic substitution of the $S_{RN}1$ kind under iron(II) catalysis. In fact (i) the reaction occurs on unactivated aryl halides, (ii) aryl iodides are more reactive than the bromides, (iii) substitution occurs with retention of the aromatic ring position (see for example expts. 32 and 34). Therefore, the operation of alternative mechanisms, such as the elimination–addition (benzyne) or the S_NAr mechanism, may be excluded. In favour of the $S_{RN}1$ mechanism are also the observed inhibition by radical and electron scavengers. Further evidence of the intermediacy of $Ar^{\bullet}$ comes from the trapping experiment in $[^2H_6]Me_2SO$.

Ferrous chloride and, in liquid ammonia, also $FeSO_4$,[8] are the best catalysts for the present process. The synthetic value of the procedure is documented by the wide range of substrates successfully employed, by the possible variety of nucleophiles, and by the satisfactory yields obtained under mild and convenient conditions within very short reaction times: an easy functionalization of an aromatic compound *via* C–C bond formation is therefore provided, without the need for photochemical or electrochemical equipment. The interference by the hydrodehalogenation pathway, which may have some relevance in Me_2SO, is suppressed or minimized by working in NH_3. We are presently trying to extend the synthetic scope of the ferrous-ion catalysis.

As far as the nature of the ferrous-ion induced initiation is concerned, we are now able to exclude some mechanistic possibilities that in the preliminary paper[8] had been tentatively advanced, but left unchecked, in lieu of the $S_{RN}1$ route. Ferrous ion is a modest reductant (0.10 V in Me_2SO *vs.* SCE; our determination), and direct reduction of the substrate [eqn. (16)]

$$\mathrm{Fe}^{2+} + \mathrm{ArX} \longrightarrow \mathrm{Fe}^{3+} + \mathrm{ArX}^{\bullet -} \qquad (16)$$

appears unlikely because it is largely endoergonic (*ca.* 30 kcal mol^{-1}).*,† Besides that, in the absence of the nucleophile we do

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* 1 cal = 4.184 J

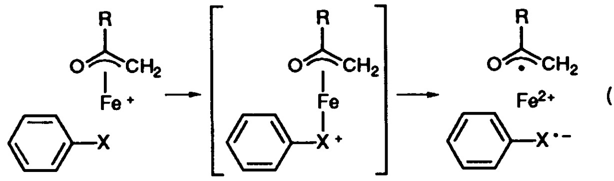
† Value derived from the oxidation potential of 0.1 V for Fe^{2+} and a reduction potential of -1.9 V for ArX.

not observe any hydrodehalogenation product, ArH, nor coupling product, Ar_2, which could arise [following eqn. (16)] from fragmentation of $ArX^{\bullet -}$ into $Ar^{\bullet}$. The possibility that complexation with the enolate ion affects the reduction potential of iron(II), transforming it into a much more powerful reductant, was checked electrochemically and found inconsistent. Capture of halide atom [eqn. (17)] can also be excluded

$$ArX + Fe^{II} \longrightarrow Ar^{\bullet} + Fe^{III}X \qquad (17)$$

because we do not find any product derived from ArX when the nucleophile is either absent or an 'unreactive' one (see expts. 39 and 40). Equally inconsistent with our findings would be any concerted[13,17] or bond-insertion[18,19] mechanism not leading to a 'free' radical species. In fact, the good agreement between the relative reactivity of some pairs of nucleophiles obtained under photostimulation, under spontaneous initiation and under Fe^{2+} catalysis, does support the view[8,16] that the nucleophiles compete with each other in the attack to the same intermediate, very likely $Ph^{\bullet}$, in the bulk of the solution, irrespective of the initiation technique and without any cage effect.

In conclusion, it appears conceivable that iron(II), associated with the enolate ion, acts as an electron relay between the enolate and ArX, improving the ease of the electron transfer, which could otherwise occur through the spontaneous route [eqn. (5)] but with lower efficiency. Complexes of iron(II) with various ligands, including ketone enolates, have indeed been isolated and characterized by X-ray diffraction.[20,21] Perhaps the octahedral coordination of iron(II),[22] which is shared by nickel(II) (see expt. 14), provides a ligand arrangement well suited to enhance the feasibility of the above electron transfer within the complex of substrate, Fe^{2+} and enolate ion [eqn. (18)]. One could then understand why bulky complexes of iron(II) are less reactive or even unreactive as catalysts (see Table 1). The weakness of diethyl phosphite ion lies instead in its weaker basicity (pK_a 15)[23] compared to an enolate ion: presumably, it is a worse reductant as well. In fact, $(EtO)_2PO^-$, a good nucleophile under photostimulation, is unable to undergo any dark (i.e., spontaneous) $S_{RN}1$ reaction.[1,16] If the ferrous-ion induced initiation [eqn. (18)] is more similar to the spontaneous step [eqn. (5)] than to the photostimulated one [eqn. (6)], one could understand why a complex between Fe^{2+} and $(EtO)_2PO^-$ is unreactive with PhI (expt. 40).



(18)

At variance with the general picture of a $S_{RN}1$ reaction (Scheme 1), we believe that step (4) does not take place in the ferrous-ion induced process. In fact, a better acceptor of the extra electron of $ArY^{\bullet -}$ is iron(II), either as such or as the complex in eqn. (18), rather than ArX. By interception of this

$$ArY^{\bullet -} + Fe^{II} \longrightarrow ArY + \text{'}Fe^{I}\text{'} \qquad (19)$$

electron, an iron(I) species could even be generated and continue the process, strengthening the catalytic effect. The absence of entrainment between *substrates* could originate from replacement of step (4) by step (19): in fact, ferrous ion [and perhaps even iron(I)] in combination with the enolate is a worse reductant than $ArY^{\bullet -}$ toward the 'poor' substrate PhBr (see expt. 4). This new propagation step would also be inhibited by electron scavengers.

In a future paper we plan to address further the point of a possible relationship between relative reactivity of nucleophiles and their strength as reducing species.

Experimental

Instrumentation.—^1H NMR spectra were taken at 80.13 MHz in $CDCl_3$ on a Bruker WP 80 SY instrument. IR spectra were recorded with a Nicolet 510 FT-IR instrument. GLC analyses were performed on two columns, namely, a 25 m × 0.20 mm methyl silicone gum capillary column and a 10 m × 0.53 mm SE-30 wide bore capillary column. Quantitative analyses were done by the internal standard method, authentic samples being employed for the determination of the response factors. GC–MS analyses were performed on a HP 5980 gas chromatograph equipped with a 12 m × 0.20 mm methyl silicone gum capillary column, coupled to a HP 5970 mass selective detector. Electrochemical determinations were carried out with a Amel 5000 potentiostat, using a platinum working electrode (planar disk, ϕ 1 mm) and a SCE reference electrode.

Materials.—Iodobenzene, 1-iodonaphthalene and $(EtO)_2$-PHO were distilled from CaH_2; 4-chlorobromobenzene was sublimed. All the other substrates were commercially available and were used as received. The ketones were distilled from anhydrous K_2CO_3; indan-2-one was recrystallized from diethyl ether. Freshly sublimed Bu^{t}OK was used to generate the anions. Ammonia was distilled from sodium directly into the reaction flask. The iron salts, and also the salts of other cations to be used as catalysts, were dried in a drying pistol over P_2O_5 at 110 °C under vacuum. Commercial Me_2SO (C. Erba RPE, 99.5%) was flushed with argon for 1 h prior to use: distillation of the solvent from CaH_2 under vacuum provided instead a less satisfactory reaction medium. Commercial $[^2H_6]Me_2SO$ (Janssen, 99.9% of D) was also flushed with argon.

General Procedure.—Dimethyl sulfoxide (25 cm^3, previously flushed with argon), sublimed Bu^{t}OK (0.25 g, 2.2 mmol) and 1.6 mmol of pinacolone (*ca.* 200 mm^3, taken by a weighed syringe) were mixed under N_2 in a three-necked reaction flask. After 10 min, $FeCl_2$ (28 mg, 0.21 mmol) was added and, after an additional 10 min, 0.51 mmol of substrate were quickly added by weighed syringe, or by paper funnel if solid: this marked the beginning of the reaction. Samples (*ca.* 5 cm^3) were taken at intervals, quenched with acidic solution, the internal standard (biphenyl) added, and extracted with diethyl ether; GLC determination of the reaction product(s) followed. For preparative purposes, the whole reaction mixture was quenched with acidic solution and worked up with ether. Isolation of the reaction product(s) was done by chromatography on silica gel with $CHCl_3$/light petroleum (b.p. 40–70 °C) 1:1 or 1:2 or, directly, by distillation of the crude. In a few cases, the reaction was carried out in liquid ammonia in a similar way, to prevent competing hydrodehalogenation of the substrate. In the preparative cases, the amount of the reagents was *ca.* ten times that given above, in a volume of solvent of 50–100 cm^3. Occasional determination of the halide ion released was carried out by standard potentiometric titration with $AgNO_3$ at a silver electrode, care being taken to quench the reaction with NH_4NO_3 or HNO_3 solutions. The experiments where pinacolone ion was replaced by the other nucleophiles, were run in a strictly comparable way.

Competition Experiments of Different Nucleophiles.—The general procedure already described[16] was followed. Three samples of the reacting mixture containing the two nucleophiles and PhI were taken at intervals, the internal standard (biphenyl) solution added, and the solution worked up with diethyl ether, and analysed by GLC. The standard equation[16] for competitive reactions was employed to calculate the relative reactivity from the concentrations of the two products formed. The relative reactivities reported in Table 3 are the average of the values from the three samples, which were constant within experimental error. In the case of the enolate of indan-2-one, which was unreactive when alone (expt. 39), its substitution product, *i.e.* 1-phenylindan-2-one, was observed only in the competition experiment with **1**. In order to calculate the relative reactivity of that anion (expts. 46 and 47) we used the GC response factor of $Ph_2CHCOCH_3$, which is structurally very similar and was available from a previous investigation.[8]

Characterization of the Reaction Products.—This was done by NMR and by GC–MS. Phenylpinacolone, $Ph_2CHCOCMe_3$, $PhP(O)(OEt)_2$, 3,3-dimethyl-1-(9-anthryl)butan-2-one and 3,3-dimethyl-1-(α-naphthyl)butan-2-one were available from previous investigations.[16,24] Phenylacetophenone was from Fluka. A brief description of the other compounds follows.

3,3-*Dimethyl*-1-(3-*thienyl)butan*-2-*one*. It was synthesized in Me_2SO from 3-bromothiophene according to the general procedure. ν/cm^{-1} 1710 (C=O). All the other data matched those previously published.[24]

3,3-*Dimethyl*-1-(2-*pyridyl)butan*-2-*one*. It was synthesized in liq. NH_3 from 2-bromopyridine. B.p. 100–110 °C at 12–15 Torr (lit.,[25] b.p. 51–53 °C at 0.15 Torr). *m*/*z* 177 (M^+). ν/cm^{-1} 1710 (C=O). δ_H 15.4 (s, 1 H, enolic OH), 8.6 and 7.0–8.0 (m, 4 H), 5.4 (s, 1 H, enolic CH), 4.0 (s, 2 H, CH_2CO), 1.3 (s, 9 H, CMe_3).

3,3-*Dimethyl*-1-(2-*cyanophenyl)butan*-2-*one*. It was synthesized in liq. NH_3 from 2-bromobenzonitrile. M.p. 30–35 °C. *m*/*z* 201 (M^+). ν/cm^{-1} 1712 (C=O) and 2229 ($C\equiv N$). δ_H 7.2–7.6 (m, 4 H), 4.0 (s, 2 H, CH_2CO), 1.2 (s, 9 H, CMe_3). (Found: C, 77.25; H, 7.65; N, 6.75. Calc. for $C_{13}H_{15}NO$: C, 77.58; H, 7.74; N, 6.96).

3,3-*Dimethyl*-1-(4-*methoxyphenyl)butan*-2-*one*. It was synthesized in Me_2SO from 4-bromoanisole. ν/cm^{-1} 1707 (C=O) and 1249 (ArOR). The other data matched those already published.[26]

3,3-*Dimethyl*-1-(4-*chlorophenyl)butan*-2-*one*. It was obtained in minute amounts from 4-chlorobromobenzene, *m*/*z* 210 (M^+), but it was not very pure. ^1H NMR confirmed a *para* pattern. We have used GC response factors taken from compounds of similar structure to give the approximate yields of compounds **2** and **3** in Table 2.

2-*Phenylpentan*-3-*one*. It was synthesized in Me_2SO from PhI and pentan-3-one according to the general procedure. B.p. 124–126 °C at 38–40 Torr (lit.,[27] 92–94 °C at 4 Torr). *m*/*z* 162 (M^+). δ_H 7.0–7.4 (m, 5 H), 3.8 (q, 1 H, CHCO), 2.3 (t, 2 H, $COCH_2Me$), 1.4 (d, 3 H), 1.0 (t, 3 H). ν/cm^{-1} 1713 (C=O).

2-*Phenylcyclohexan*-1-*one*. It was synthesized in Me_2SO from PhI and cyclohexanone. B.p. 120 °C at 15 Torr. M.p. 41–43 °C (lit.,[28] 53 °C). *m*/*z* 174 (M^+). δ_H 7.0–7.5 (m, 5 H), 3.6–3.7 (dd, 1 H, CHCO), 1.5–2.8 (m, 8 H). ν/cm^{-1} 1712 (C=O).

Electrochemical Determinations.—These were carried out in Me_2SO at room temperature under Ar with 0.2 mol dm^{-3} $NaClO_4$ as the supporting electrolyte. The concentration of $FeCl_2$ was 1×10^{-3} mol dm^{-3}. When the determination was carried out with the concomitant presence of the enolate of pinacolone, the latter was 2×10^{-3} mol dm^{-3}: no shift of the Fe^{2+}/Fe^{3+} wave was observed in this case, even though it became blurred.

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