A Study of the Ferrous Ion-initiated $S_{RN}1$ Reactions of Halogenoarenes with *tert*-Butyl Acetate and *N*-Acylmorpholine Enolates

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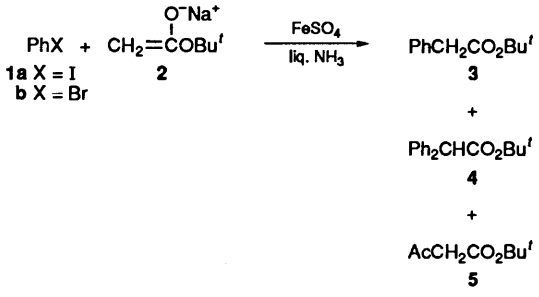
A detailed preparative study is reported of the ferrous ion-initiated $S_{RN}1$ reactions of a range of halogenoarenes with the sodium enolates of *tert*-butyl acetate, *N*-acetylmorpholine and a number of higher *N*-acylmorpholines. Smooth and rapid substitution occurs in many cases, and good to excellent yields were obtained of arylacetic esters or acids, arylacetamides and arylalkanamides. The broad scope and limitations of the process have been defined, and the possible role of the ferrous ion is discussed.

The aromatic $S_{RN}1$ reaction can be a very important process for the substitution of nucleofugic substituents on unactivated aromatic rings, and has been the subject of extensive synthetic and mechanistic investigations.[1–4] Carbon–carbon bond-forming processes are, of course, of particular interest and importance, and $S_{RN}1$ reactions of halogenoarenes with ketone enolates have been studied in considerable detail. Reactions with ester[5,6] and amide[7–9] enolates, by contrast, have been examined only superficially, and almost exclusively under either electrochemical or photostimulation conditions. Moderate to good yields of substitution products were obtained in a few cases with simple halogenoarenes. In principle, successful development of an $S_{RN}1$-based conversion of halogenoarenes into arylacetic esters or amides could constitute an important route to arylacetic acids and, possibly, 2-arylpropionic acids, products of enormous importance as non-steroidal antiinflammatory drugs.[10] In practice, however, photo- and electrochemically stimulated reactions are not very attractive, especially in terms of scale-up.

In 1984, Galli and Bunnett reported that preparatively useful yields of substitution products could be obtained from the ferrous ion-catalysed reactions of bromobenzene or iodobenzene with the enolates of either acetone and/or pinacolone and with diethyl phosphite ion, while reaction of *o*-chloroaniline with acetone enolate gave 2-methylindole in 51% yield.[11] Some evidence was obtained that these reactions were $S_{RN}1$ in nature, although the function of the iron catalyst was unclear. As far as we are aware, Galli and Bunnett's discovery of ferrous ion catalysis of aromatic nucleophilic substitution has not been extended or exploited. We now describe the results of a detailed preparative investigation of the ferrous ion-initiated $S_{RN}1$ reactions of halogenoarenes with the enolates derived from *tert*-butyl acetate and *N*-acylmorpholines, and show that this substitution route represents a simple and convenient method for the preparation of arylacetic and 2-arylpropionic acids from readily available halogenoarenes.

Results and Discussion

Reaction of iodobenzene **1a** with *tert*-butyl sodioacetate **2** in liquid ammonia in the presence of 20 mol % of ferrous sulfate resulted in rapid consumption of the iodobenzene and formation of a mixture of *tert*-butyl phenylacetate **3**, *tert*-butyl diphenylacetate **4** and *tert*-butyl acetoacetate **5** (Scheme 1). The rate of reaction and relative proportions of **3**–**5** varied significantly with the amount of ester enolate **2** used: with 3 equiv. of **2** per equiv. of **1a** the reaction required 45 min to go to completion and gave the products **3**:**4**:**5** in the ratio 66:22:12. With the ratio of reagents **2**:**1a** = 6:1 the reaction was



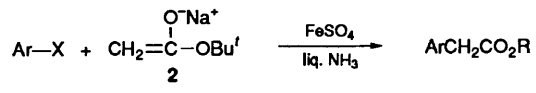
Scheme 1

complete in 20 min and gave the products **3**:**4**:**5** in the ratio 74:4:22; with **2**:**1a** = 9:1 the ratio was 65:3:32. Increasing the concentration of reactants led to a decrease in the amount of **3** and **4** and an increase in the amount of **5**. There was no reaction when *tert*-butyl lithioacetate was used instead of the sodium salt while dimethyl sulfoxide, a solvent which has often been used very successfully for $S_{RN}1$ reactions, was ineffective in the present case, its use at room temperature leading to formation of only very small amounts of **3** together with large amounts of **5**. Reaction of bromobenzene **1b** with *tert*-butyl sodioacetate was, as expected, slower and less efficient than the corresponding reaction with iodobenzene **1a**, but both the rate of reaction and the yield of **3** (see below) were increased substantially when 1 equiv. of ferrous sulfate was used rather than 20 mol %. Chlorobenzene did not react. The apparent unique catalytic activity of simple iron(II) salts for the conversion **1a** → **3** was confirmed by the results of a limited study with other metal salts which can formally act as one-electron transfer agents. Use of the following salts, arranged in order of increasing redox potential, gave the product **3** in the yields shown (%): CuCl (11), $RuCl_3$ (21), $FeCl_2$ (73), Hg_2SO_4 (12), $Ce_2(SO_4)_3$ (9) and $CoSO_4$ (7). Complexation of the iron(II), however, inhibited the activity and only 20% of **3** was obtained after 3 h when $K_4[Fe(CN)_6]$ was used.

Following from the above results, the ferrous sulfate-catalysed reactions of a range of halogenoarenes with *tert*-butyl sodioacetate were examined and the results are summarised in Table 1. In some cases the mixtures of esters **3**–**5** (Scheme 1) were separated chromatographically. In others, and especially in larger scale reactions, it proved advantageous to hydrolyse the crude reaction mixture of **3**–**5** with aqueous toluene-*p*-sulfonic acid. This gave a mixture of arylacetic and diarylacetic acids from which the desired pure arylacetic acid could be readily obtained by simple crystallisation.

The results in Table 1 are largely as expected for an $S_{RN}1$ reaction of halogenoarenes. Iodides react faster and more

Table 1 Ferrous sulfate-initiated substitution of halogenoarenes (1 equiv.) by *tert*-butyl sodioacetate (6 equiv.).

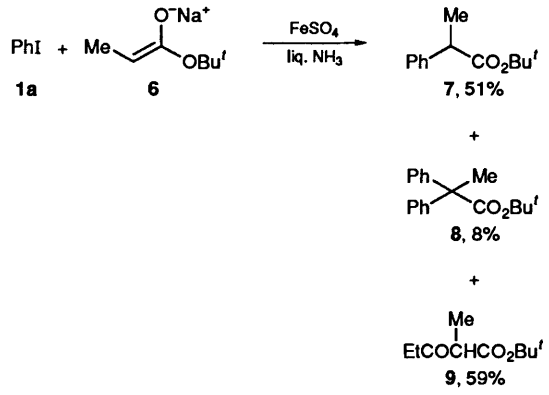


Ar	X	$FeSO_4$ (mol %)[a]	Time (T/min)	R[b]	$ArCH_2CO_2R$[c] %
Ph	Br	100	45	H	69
	I	20	20	H	82
2-MeC_6H_4	I	100	30	H	55
4-MeC_6H_4	Br	100	180	CMe_3	20
	I	100	30	H	63
4-$MeOC_6H_4$	Br	100	120	CMe_3	28
	I	100	45	H	78
4-FC_6H_4	I	20	20	H	81
2-Thienyl	I	100	60	CMe_3	5
3-Thienyl	I	100	45	H	73
2-Pyridyl	Cl	20	45	CMe_3	22
	Br	20	45	CMe_3	89
3-Pyridyl	Br	20	30	CMe_3	51
	I	20	45	CMe_3	59
4-Methyl-2-pyridyl	Br	20	45	CMe_3	18
2-Quinolyl	Cl	20	45	CMe_3	15

[a] Relative to ArX. [b] For R = H, the mixture of crude reaction products was hydrolysed with aqueous toluene-*p*-sulfonic acid; for R = CMe_3 the mixtures of esters (see Scheme 1) were separated chromatographically. [c] Isolated product.

efficiently than bromides. Electron-rich substrates react sluggishly and use of a full equivalent of ferrous sulfate was necessary to achieve complete reaction in a reasonable time. The very marked difference in reactivity between 2- and 3-iodothiophene is difficult to explain, although it is known that 2-bromothiophene reacts less effectively than 3-bromothiophene in the photostimulated $S_{RN}1$ reaction with the acetone enolate.[12] The results with the π-deficient heterocycles were disappointing overall, as very high yields of substitution products have been obtained in many photostimulated reactions of π-deficient halogenoheterocycles with ketone enolates and other nucleophiles.[2] In the case of 2-bromo-4-methylpyridine deprotonation of the 4-methyl substituent might be expected to lead to complications and, in general, Lewis base complexation of the heterocycles with the iron(II) salt may account, at least in part, for the poor yields of substitution products. Some evidence was obtained that nucleophilic addition to the π-deficient ring may also lead to complications. Thus, reaction of 2-chloropyrimidine with *tert*-butyl sodioacetate under the standard conditions led to rapid (< 15 min) consumption of starting material and formation of a highly coloured, complex mixture of products, the NMR spectrum of which showed no aromatic CH signals. There were signals characteristic of aldehyde and vinyl protons, however, implying nucleophilic addition to the ring followed by ring cleavage. Similar reactivity has been recorded for the reaction of 2-chloropyrimidine with acetone enolate.[13]

Minor but undesirable aspects of the reactions listed in Table 1 were the formation of small amounts—usually 3–5%—of disubstituted esters, *cf.* **4**, and significant amounts of the β-keto ester **5**. The latter was usually formed in 10–15% yield, but in the reaction with 2-iodothiophene was obtained in 95% yield. As described, removal of **4** and **5** was trivial but, nevertheless, a nuisance. More importantly, *tert*-butyl sodioacetate is only partially soluble in liquid ammonia, which probably had a yield-limiting effect in the slower reactions. Use of higher solvent volumes was not beneficial, and the problem of poor nucleophile solubility became more apparent when *tert*-butyl sodiopropionate **6** was used as nucleophile with iodobenzene **1a** (Scheme 2). Under the optimum conditions established for



Scheme 2

tert-butyl sodioacetate (**1a**:2 = 1:6, 20 mol% $FeSO_4$) the reaction of **1a** with **6** required 90 min for completion; even with 1 equiv. of ferrous sulfate the reaction took 60 min, but the yield of ester **7** was virtually unchanged (49%).

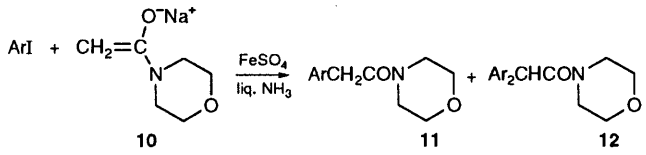
The above problems were addressed by change in nucleophile from ester to amide enolate. Rossi and Alonso have reported that the sodium enolate of *N*-acetylmorpholine (**10**, Table 2) is completely soluble in liquid ammonia and that it reacts very well with both chlorobenzene and bromobenzene when photostimulated.[7] Moreover, **10** would not be expected to undergo self-condensation (*cf.* **2** → **5**) and this proved to be the case. Using the basic conditions established for the conversions in Table 1, the reactions of a range of iodoarenes with the sodium enolate of *N*-acetylmorpholine in the presence of ferrous sulfate were examined and the results are summarised in Table 2. These follow the same general trends as those in Table 1. Reactions of the iodoarenes with the amide enolate **10** were noticeably slower than those with the ester enolate **2**. As expected, chlorobenzene did not react, nor did 4-methoxybromobenzene, while bromobenzene gave a best yield of **11** (Ar = Ph) of 46%. 2-Bromopyridine reacted satisfactorily to give **11** (Ar = 2-C_5H_4N) in 65% yield. As found for the reactions in Table 1, reductive dehalogenation, a side reaction characteristic of $S_{RN}1$ processes, occurred in virtually all cases (and most noticeably with 2-fluoroiodobenzene), but as before no attempt was made to quantify the reduction products in the cases of volatile arenes. The poor yields obtained with 4-*tert*-butyliodobenzene and 4-iodobiphenyl and the lack of reaction with 2-iodo-6-methoxynaphthalene appear to be due primarily to the low to negligible solubility of the substrates in liquid ammonia.

As a final aspect of the preparative study, and in the particular context of 2-arylpropionic acid synthesis, we examined the reactions of a few iodoarenes with higher *N*-acylmorpholine enolates. The results are given in Table 3. Very small amounts (*ca.* 2%) of disubstituted products were formed in most cases (NMR) but these were not quantified.

Some or all of the features noted in earlier experiments were evident here also: significant reductive dehalogenation (entries 1, 6–8), poor (entries 2–4) to negligible (entry 5) solubility of the enolate, and poor substrate solubility (entries 7, 8) leading to recovery of starting material. Even so, reasonable yields of pure products were obtained in all but one case, and entries 7 and 8 are of interest, as the products are the morpholineamides of the non-steroidal anti-inflammatory agents ibuprofen and fenoprofen.

Our study shows that many arylacetic and 2-arylpropionic acids, esters and amides are easily accessible in good yield from the ferrous ion-initiated substitution of halogenoarenes with the enolates of *tert*-butyl acetate and *N*-acetyl- and *N*-propionylmorpholine, and that the process can usefully be extended to certain higher 2-arylalkanoic acid amides. The reactions are

Table 2 Ferrous sulfate-initiated substitution of iodoarenes (1 equiv.) by the sodium enolate of *N*-acetylmorpholine **10** (6 equiv.)[a]

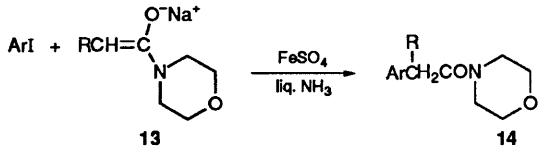


10 11 12

Ar	$FeSO_4$ (mol %)[b]	11 (%)[c]	12 (%)[c]	Other (%)
Ph	25	70	4	—
2-MeC_6H_4	100	62	Trace	—
3-MeC_6H_4	25	73	8	—
4-MeC_6H_4	50	65	5	—
2,6-$Me_2C_6H_3$	100	44	—	—
4-$Me_3CC_6H_4$	100	40	4	$ArNH_2$, trace, ArH, 10
2-$C_6H_5C_6H_4$	50	71	Trace	ArH, 12
4-$C_6H_5C_6H_4$	50	45	16	ArH, 22
2-$MeOC_6H_4$	25	57[d]	5[d]	—
3-$MeOC_6H_4$	25	31	15	$ArNH_2$, 10
4-$MeOC_6H_4$	100	60	6	$ArNH_2$, trace
2-F	25	9	Trace	—
3-F	25	45	11	$ArNH_2$, 12
4-F	25	64	12	—
3-Thienyl	100	27	8	—
1-Naphthyl	50	65	6	ArH[e]
6-Methoxy-2-naphthyl	50	0	0	—[f]

[a] Reaction time for iodobenzene: 45 min; for all other iodoarenes: 90 min. [b] Relative to ArI. [c] Isolated product. [d] Determined by NMR. [e] Not quantified. [f] Starting material recovered (90%).

Table 3 Ferrous sulfate (50 mol %)-initiated reactions of iodoarenes (1 equiv.) with sodium enolates of *N*-acylmorpholines **13** (6 equiv.)[a]



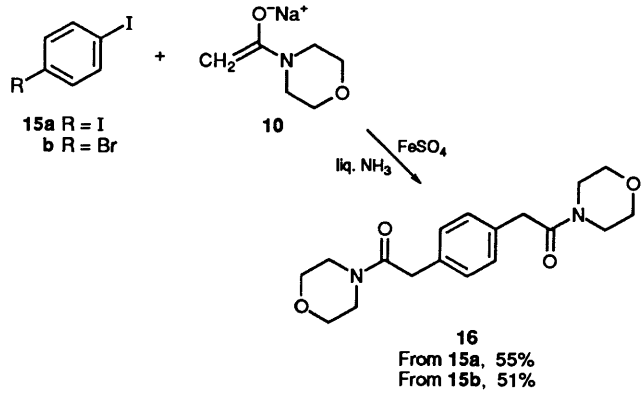
13 14

Entry	Ar	R	14 (%)[b]
1	Ph	Me	57
2		Et	60
3		Pr^i	63
4		C_4H_9	44
5		C_8H_{17}	4
6	4-MeC_6H_4	Me	61
7	4-$Bu^iC_6H_4$	Me	42[c]
8	3-$PhOC_6H_4$	Me	47[d]

[a] Reaction time: 90 min. [b] Isolated product. [c] Starting material (18%) and isobutylbenzene (13%) also isolated. [d] Diphenyl ether (33%) and 3-aminodiphenyl ether (8%) also isolated.

clean and are simple to perform, and the broad scope and limitations of the process have been defined. From the few comparative data available it is clear that higher yields can be obtained from the corresponding photostimulated reactions, but the preparative value of that method remains to be established and the practical advantages of ferrous ion-initiated reactions compensate, at least in part, for the somewhat lower yields.

All of the evidence available, much of which is given above, indicates that most, if not all, of the ferrous ion-initiated substitutions are $S_{RN}1$ in nature. Further important observations indicative of the $S_{RN}1$ mechanism come from reactions of dihalogenoarenes. As mentioned previously, chlorobenzene is unreactive in the ferrous sulfate method. 4-Fluoroiodobenzene reacts very well by displacement only of the iodine substituent (Tables 1 and 2). 1,4-Diiodobenzene **15a** undergoes disubstitution (Scheme 3), but 4-chloroiodobenzene **15b** reacts similarly



Scheme 3

and just as efficiently. Production of **16** from **15a** by stepwise formation of the monosubstitution product, *i.e.* 4-chlorophenylacetylmorpholine, is not acceptable in view of the unreactivity of simple chloroarenes. An explanation for the reactivity of **15b** is, however, readily available on the basis of an $S_{RN}1$ mechanism [eqns. (1)–(6)].[3,14] Thus, for the 4-halogenoiodoarenes $S_{RN}1$ substitution of an iodine leads to the radical anion $[XC_6H_4Nu]^{\bullet -}$ [eqns. (1)–(3)]. Two pathways are then possible [eqn. (4)]: (a) expulsion of an electron and formation of XC_6H_4Nu,

$$XC_6H_4I \xrightarrow{+e^-} [XC_6H_4I]^{\bullet -} \text{ initiation} \quad (1)$$

$$[XC_6H_4I]^{\bullet -} \xrightarrow{-I^-} XC_6H_4^{\bullet} \text{ propagation} \quad (2)$$

$$XC_6H_4^{\bullet} + Nu^- \longrightarrow [XC_6H_4Nu]^{\bullet -} \quad (3)$$

$$[XC_6H_4Nu]^{\bullet -} \begin{cases} \xrightarrow{-e^-} XC_6H_4Nu \\ \xrightarrow{-X^-} {}^{\bullet}C_6H_4Nu \end{cases} \quad (4)$$

$$\cdot C_6H_4Nu + Nu^- \longrightarrow [NuC_6H_4Nu]^{\cdot -} \quad (5)$$

$$[NuC_6H_4Nu]^{\cdot -} + XC_6H_4I \longrightarrow NuC_6H_4Nu + [XC_6H_4I]^{\cdot -} \quad (6)$$

which is the pathway followed by 4-fluoroiodobenzene, or (b) where X is a good leaving group (Cl, I) expulsion of halogen and formation of the radical [$\cdot C_6H_4Nu$]. Reaction of the latter with more nucleophile generates the new radical anion $[NuC_6H_4Nu]^{\cdot -}$ [eqn. (5)] which can react further in the $S_{RN}1$ chain sequence [eqn. (6)]. A similar 'mono- *vs.* di-substitution' argument has been used by Bowman *et al.* to distinguish a photostimulated $S_{RN}1$ reaction from a copper-catalysed nucleophilic aromatic substitution reaction.[15]

Reactions of halogenoarenes with nucleophiles in liquid ammonia can proceed by the elimination–addition mechanism. Treatment of bromobenzene with the sodium enolate of either *tert*-butyl acetate or *N*-acetylmorpholine in liquid ammonia in the *absence* of ferrous sulfate did not result in any reaction, and we have no firm evidence for an elimination–addition mechanism for most of the conversions listed in Tables 1–3. *With 3-iodo*anisole (Table 2), 3-fluoroiodobenzene (Table 2) and 3-iododiphenyl ether (Table 3), however, the formation of significant amounts of anilines (10, 12 and 8% respectively) suggests that both the benzyne and the $S_{RN}1$ mechanisms may be operative in these cases.

There remains the question of the role of the ferrous ion. Galli and Bunnett[11] tentatively suggested three possible functions for the iron ion: (a) electron transfer from Fe^{II} to ArI; (b) iron-mediated electron transfer from the nucleophile to ArI; or (c) direct capture of iodine from ArI, with formation of Ar$^\cdot$. In all of the reactions in the present study addition of ferrous sulfate to the nucleophile solution/suspension resulted in rapid darkening of the mixture, which we suggest may be indicative of formation of an iron enolate, decomposition of which would lead to a ketyl-like enolate, ferrous ion and an electron which can be transferred to the halogenoarene [eqns. (7) and (8)]. The

$$NaCH_2COR + Fe^{2+} \longrightarrow [FeCH_2COR]^+ + Na^+ \quad (7)$$

$$[FeCH_2COR]^+ \longrightarrow Fe^{2+} + \cdot CH_2COR + e^- \quad (8)$$

formation of iron enolates and their potential to undergo electron transfer reactions has been postulated for the iron-induced reductive dehalogenation of α-halogeno ketones.[16,17] We have, however, been unable to find further precedent for ferrous ion catalysis which might shed some light on the precise and intriguing role of the ferrous ion in the reactions described above.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. Microanalyses were determined by Mr A. W. R. Saunders of the University of East Anglia, as were EI mass spectra, which were performed with a Kratos MS25 spectrometer. ^1H NMR spectra were recorded on a JEOL PMX 60 spectrometer at 60 MHz and ^{13}C NMR spectra on a JEOL EX90 spectrometer at 22.5 MHz. All NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. Analytical GLC was performed on a Philips PU4500 chromatograph with a flame ionisation detector using a column packed with 4% silicon rubber SE30 on Chromosorb G support between 150–220 °C and with 2-methylnaphthalene as internal standard. Atmospheric pressure column chromatography was carried out on silica gel Merck 7734 (200–600 Mesh) and flash column chromatography on silica gel May and Baker Sorbsil C60.

Starting Materials.—Halogenoarenes were either commercially available or were prepared by standard literature procedures. Liquid ammonia was distilled directly from the cylinder into the reaction vessel and used without any drying. *N*-Acylmorpholines were prepared by literature procedures. Ferrous sulfate was finely ground and dried *in vacuo* for 5 h prior to use.

General Procedure for the Reactions of Halogenoarenes with tert-*Butyl Sodioacetate.*—A 250 cm^3 three-necked flask was equipped with a nitrogen inlet, a solid CO_2 condenser and a magnetic stirrer and flame dried under a stream of nitrogen. The coolant well was filled with a solid CO_2–acetone mixture and the flask immersed in a solid CO_2–acetone bath. Ammonia (150 cm^3) was distilled into the flask and sodium amide (4.8 g, 0.12 mol) added to it. *tert*-Butyl acetate (13.4 g, 0.12 mol) was added slowly by syringe to the stirred suspension and the resulting mixture was stirred at −70 °C for 30 min. The cooling bath was then removed and ferrous sulfate (Table 1) and the halogenoarene (0.02 mol) were added in quick succession. The reaction mixture was rapidly stirred for 20–120 min (Table 1) and then quenched by the gradual addition of small portions of ammonium chloride (20 g). The ammonia was allowed to evaporate and the residue was extracted with diethyl ether (3 × 75 cm^3). The combined extracts were washed with water (50 cm^3), 5% hydrochloric acid (3 × 50 cm^3) and brine (50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product mixture. This was first analysed by GLC and/or NMR and then pure products were isolated either by (a) standard column or flash chromatography using graded mixtures of light petroleum (b.p. 40–60 °C), methylene dichloride and ethyl acetate; or (b) by hydrolysis as follows: toluene-*p*-sulfonic acid (1.2 g, 6.3 mmol) was added to a suspension of the crude product mixture in water (20 cm^3) and the resulting mixture was heated at reflux for 4 h. It was then cooled and extracted with diethyl ether (4 × 75 cm^3). The combined extracts were washed with brine (50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude arylacetic acids which were purified by crystallisation. All products except *tert*-butyl 2- and 3-pyridylacetate have been described previously.

tert-*Butyl 2-pyridylacetate.* Colourless oil, ν_{max}(film)/cm^{-1} 1735; δ_H 1.43 (s, 9 H, CMe_3), 3.76 (s, 2 H, PyrCH_2CO), 7.00–7.81 (m, 3 H, 3,4,5-Pyr-H) and 8.45–8.64 (m, 1 H, 6-Pyr-*H*); *m*/*z* 193 (M^+), 138 ($M^+ - 55$), 120 ($PyrCH_2CO^+$) and 92 ($PyrCH_2^+$) (Found: C, 68.3; H, 7.8; N, 7.1. Calc. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%).

tert-*Butyl 3-pyridylacetate.* Colourless oil, ν_{max}(film)/cm^{-1} 1735; δ_H 1.44 (s, 9 H, CMe_3), 3.51 (s, 2 H, PyrCH_2CO), 7.06–7.33 (m, 1 H, 4-Pyr-H), 7.47–7.71 (m, 1 H, 5-Pyr-H) and 8.18 (m, 2 H, 2,6-Pyr-H) (Found: C, 68.2; H, 7.7; N, 7.05. Calc. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%).

General Procedure for the Reactions of Halogenoarenes with N-*Acylmorpholine Enolates.*—The same general procedure was used as above with liquid ammonia (100 cm^3), sodium amide (3.0 g, 75 mmol) and the *N*-acylmorpholine (77 mmol). The mixture was stirred at −70 °C for 10–15 min and then the solid CO_2 bath was removed. Ferrous sulfate (Tables 2 and 3) and the halogenoarene (12.7 mmol) were added in quick succession to the mixture, which rapidly turned black, and was stirred in the dark for the appropriate time (Tables 2 and 3). Crude products were isolated as described above and analysed by NMR, and pure products obtained by flash chromatography using graded eluent mixtures of light petroleum (b.p. 40–60 °C) and ethyl acetate from 3:1 to 1:3. Arene and arylamine by-products were identified and quantified by GLC and NMR.

Table 4 Physical data for arylacetylmorpholinamides **11**

Ar (Mol. formula)	% Found/(% Calc.) C	H	N	M.p. (°C) (B.p. °C/mmHg)[a]	δ_H[b,c] Arom	Other	δ_C[d,e] CH_2	Arom	Other	m/z[f]
2-MeC_6H_4 ($C_{13}H_{17}NO_2$)	71.40 (71.21)	7.82 (7.81)	6.37 (6.39)	68–69	7.11 (s, 4 H)	2.24 (s, 3 H, Me)	38.22	126.16, 127.01, 128.70 130.33, 133.55, 136.25	19.57	219 (M^+, 49.6%), 114 (100), 105 (32.4), 70 (50.1)
3-MeC_6H_4 ($C_{13}H_{17}NO_2$)	71.46 (71.21)	7.72 (7.81)	6.57 (6.39)	(170–180/0.6)	6.8–7.2 (m, 4 H)	2.30 (s, 3 H, Me)	40.58	125.52, 127.51, 128.55 129.22, 134.72, 138.22	21.28	219 (M^+, 37.1%), 114 (100), 105 (29.7), 70 (28.8)
4-MeC_6H_4 ($C_{13}H_{17}NO_2$)	71.07 (71.21)	7.94 (7.81)	6.19 (6.39)	80–81.5	7.15 (s, 4 H)	2.34 (s, 3 H, Me)	40.29	128.39, 129,38, 131.77 136.27	20.95	219 (M^+, 25.7%), 114 (100), 105 (40.3)
2,6-$Me_2C_6H_3$ ($C_{14}H_{19}NO_2$)	71.94 (72.07)	8.27 (8.21)	5.94 (6.00)	130–131	7.02 (s, 3 H)	2.24 (s, 6 H, Me)	33.28	126.36, 127.66, 132.65, 136.45	19.89	233 (M^+, 45.6%), 119 (39.1), 114 (100), 70 (48.9)
4-$Me_3CC_6H_4$ ($C_{16}H_{23}NO_2$)	73.74 (73.53)	8.93 (8.87)	5.30 (5.36)	(190–195/0.5)	7.09, 7.31 (AA'BB', 4 H, J 8.1)	1.29 (s, 9 H)	40.09	125.57, 128.23, 131.73, 149.60	31.30	261 (M^+, 23.0%), 114 (100), 70 (31.3)
2-$C_6H_5C_6H_4$ ($C_{18}H_{19}NO_2$)	76.80 (76.84)	7.04 (6.81)	5.10 (4.98)	(200–220/0.7)	7.1–7.4 (m, 9 H)		37.64	126.62, 126.91, 127.33, 127.95, 128.80, 129.35, 129.68, 132.31, 140.84, 141.37		281 (M^+, 38.0%), 167 (29.4), 165 (31.3), 114 (100), 70 (38.4)
4-$C_6H_5C_6H_4$ ($C_{18}H_{19}NO_2$)	76.62 (76.84)	6.78 (6.81)	4.96 (4.98)	122.5–123.5	7.1–7.6 (m, 9 H)		40.16	126.88, 128.70, 127.30, 129.02, 133.89, 139.64, 140.53		281 (M^+, 33.4%), 167 (36.5), 114 (100), 70 (38.1), 57 (32.5) 49 (27.0)
2-$MeOC_6H_4$ ($C_{13}H_{17}NO_3$)	66.40 (66.36)	7.32 (7.28)	5.93 (5.95)	67.5–68.5	6.7–7.4 (m, 4 H)	3.74 (s, 3, H, OMe)	33.72	110.03, 120.34, 123.16, 127.77, 129.50, 156.19	54.98	235 (M^+, 48.6%), 121 (56.4), 114 (100), 91 (53.9), 70 (57.9)
3-$MeOC_6H_4$ ($C_{13}H_{17}NO_3$)	65.98 (66.36)	7.55 (7.28)	6.14 (5.95)	(150–160/0.5)	6.7–6.9 (m, 3 H) 7.1–7.4 (m, 1 H)	3.76 (s, 3 H, OMe)	40.81	112.33, 114.24, 120.83, 129.72, 136.35, 159.95	55.14	235 (M^+, 37.8%), 121 (29.6), 114 (100), 70 (55.0)
4-$MeOC_6H_4$ ($C_{13}H_{17}NO_3$)	66.20 (66.36)	7.50 (7.28)	6.15 (5.95)	(225/0.2)	6.83, 7.15 (AA'BB', 4 H, J 8.7)	3.76 (s, 3 H, OMe)	39.75	114.15, 126.84, 129.58 158.49	55.18	235 (M^+, 19.5%), 121 (100)
2-FC_6H_4 ($C_{12}H_{14}FNO_2$)	64.55 (64.56)	6.37 (6.32)	6.19 (6.27)	93–94	6.8–7.4 (m, 4 H)		33.09 (d, J 2.4)	115.30 (d, J^2 22.2), 122.19 (d, J^2 15.4), 124.33 (d, J^3 3.7), 128.80 (d, J^3 8.4), 130.96 (d, J^3 4.0), 160.53 (d, J^1 244.8)		223 (M^+, 23.5%), 114 (100), 109 (35.2), 70 (42.8)
3-FC_6H_4 ($C_{12}H_{14}FNO_2$)	64.66 (64.56)	6.48 (6.32)	6.27 (6.27)	(185–190/0.5)	6.8–7.3 (m, 4 H)		40.14	113.79 (d, J^2 20.5), 115.76 (d, J^2 21.3), 124.50 (d, J^4 2.9), 130.18 (d, J^3 8.1), 137.47 (d, J^3 8.1), 162.92 (d, J^1 246.2)		223 (M^+, 25.3%), 114 (100), 109 (36.0), 70 (43.8)
4-FC_6H_4 ($C_{12}H_{14}FNO_2$)	64.56 (64.56)	6.32 (6.32)	6.17 (6.27)	86–86.5	6.8–7.3 (m, 4 H)		39.61	115.53 (d, J^2 21.3), 130.28 (d, J^3 8.1), 130.51 (d, J^4 3.3), 161.78 (d, J^1 245.1)		223 (M^+, 16.5%), 114 (100), 109 (41.1), 70 (55.4)
3-Thienyl ($C_{10}H_{13}NO_2S$)	57.12 (58.85)	6.37 (6.20)	6.43 (6.63)	89.5–91	6.9–7.4 (m, 3 H)		35.54	121.91, 126.06, 128.01 134.62		211 (M^+, 60.4%), 114 (100), 97 (44.7), 70 (66.2)

[a] Kugelrohr distillation. [b] δ_H for $ArCH_2$(s): 3.65 ± 0.1 [c] δ_H for morpholine CH_2 groups (m): 3.4 and 3.6 except for Ar = 2-$C_6H_5C_6H_4$: 2.9 and 3.5. [d] δ_C for morpholine CH_2 groups: 42 ± 0.3; 46 ± 0.5; 66.4 ± 0.3. [e] $\delta_{C=O}$ in range 168.65–169.85. [f] M^+ and peaks > 25% R.A. only.

Table 5 Physical data for bis(arylacetylmorpholinamides) **12**

Ar (Mol. formula)	% Found/(% Calc.) C	H	N	M.p. (°C)	δ_H [a,b] Arom	Other	δ_C [c,d,e] Arom	Other	m/z [f]
3-MeC_6H_4 ($C_{20}H_{23}NO_2$)	77.45 (77.64)	7.63 (7.49)	4.56 (4.53)	131.5–132.5	6.9–7.3 (m, 8 H)	2.31 (s, 6 H)	126.06, 127.82, 128.44, 129,67, 138.11, 139.25	21.46	309 (M^+, 2.7%), 219 (32.4), 114 (100), 105 (32.7), 70 (46.9)
4-MeC_6H_4 ($C_{20}H_{23}NO_2$)	77.37 (77.64)	7.54 (7.49)	4.51 (4.53)	131–133	7.13 (s, 8 H)	2.31 (s, 6 H)	128.76, 129.25, 136.55	21.02	309 (M^+, 4.1%), 195 (100)
4-$Me_3CC_6H_4$ ($C_{26}H_{35}NO_2$)	79.00 (79.35)	9.00 (8.96)	3.51 (3.56)	187–189	7.13, 7.33 (AA'BB', 8 H, J 8.7)	1.28 (s, 18 H)	125.48, 128.50, 136.26, 149.73	31.33 34.42	393 (M^+, 3.2%), 279 (89.0), 174 (100), 159 (81.9)
4-$C_6H_5C_6H_4$ ($C_{30}H_{27}NO_2$)	83.23 (83.11)	6.20 (6.28)	3.23 (3.23)	156–158	7.2–7.6 (m, 18 H)		126.94, 127.27, 128.67, 129.32 138.27, 140.00, 140.52		433 (M^+, 6.5%), 320 (30.7), 319 (100), 69 (51.0), 43 (28.3), 32 (38.3)
3-$MeOC_6H_4$ ($C_{20}H_{23}NO_4$)	70.23 (70.36)	7.02 (6.79)	3.97 (4.10)	84–86	6.7–6.9 (m, 6 H) 7.1–7.4 (m, 2 H)	3.71 (s, 6 H, OMe)	112.36, 114.98, 121.31, 129.51 140.58, 159.77	55.14	341 (M^+, 15.1%), 227 (58.2), 165 (51.0), 123 (79.5), 114 (54.0), 78 (33.2), 70 (47.9), 63 (34.3), 43 (100)
4-$MeOC_6H_4$ ($C_{20}H_{23}NO_4$)	69.75 (70.36)	7.13 (6.79)	3.83 (4.10)	gum	6.79, 7.12 (AA'BB', 8 H, J 8.4)	3.72 (s, 6 H, OMe)	113.92, 129.74, 131.66, 158.49	55.14	341 (M^+, 2.7%), 227 (100)
3-FC_6H_4 ($C_{18}H_{17}F_2NO_2$)	67.98 (68.13)	5.36 (5.40)	4.39 (4.41)	88–89	6.8–7.4 (m, 8 H)		114.16 (d, J^2 21.3), 115.82 (d, J^2 22.7), 124.37 (d, J^4 2.9), 129.99 (d, J^3 8.1), 140.94 (d, J^3 7.3), 162.69 (d, J^1 246.2)		317 (M^+, 2.8%), 139 (51.0), 114 (100), 111 (47.8), 70 (40.0), 43 (54.3)
4-FC_6H_4 ($C_{18}H_{17}F_2NO_2$)	68.19 (68.13)	5.16 (5.40)	4.37 (4.41)	139–140	6.8–7.4 (m, 8 H)		115.56 (d, J^2 21.3), 130.42 (d, J^3 8.1), 134.97 (d, J^4 3.3), 161.94 (d, J^1 246.2)		317 (M^+, 4.0%), 203 (38.5), 114 (100), 70 (42.2)
3-Thienyl ($C_{14}H_{15}NO_2S_2$)	57.42 (57.31)	5.11 (5.15)	4.77 (4.77)	114–116	6.9–7.3 (m, 6 H)		122.38, 125.90, 127.95, 139.38		293 (M^+, 23.6%), 179 (100), 125 (38.1), 114 (58.9), 111 (94.7), 97 (30.7), 86 (35.5), 84 (55.9), 70 (94.9)
1-Naphthyl ($C_{26}H_{23}NO_2$)	81.48 (81.86)	6.16 (6.08)	3.57 (3.67)	227–229	7.1–8.1 (m, 14 H)		127.40, 128.08, 129.09, 131.34, 133.94, 134.27		381 (M^+, 4.1%), 155 (29.1), 149 (45.1), 114 (63.9), 91 (25.6), 86 (63.1), 84 (100), 70 (62.5), 57 (26.5), 32 (29.0)

[a] δ_H for Ar_2CH (s): 5.1 ± 0.1 except for 3-thienyl (5.30) and 1-naphthyl (6.54). [b] δ_H for morpholine CH_2 groups (m): 3.4, 3.6. [c] δ_C for Ar_2CH in range 53.01–54.73 except for 3-thienyl (45.22) and 1-naphthyl (45.57). [d] δ_C for morpholine CH_2 groups: 42.5 ± 0.1; 46.3 ± 0.2; 66.4 ± 0.5. [e] $\delta_{C=O}$ in range 169.10–170.83 [f] M^+ and peaks > 25% R.A. only.

Table 6 Physical data for 2-alkylarylacetylmorpholineamides **14**

R Ar (Mol. formula)	% Found/(% Calc.) C	H	N	B.p. °C/mmHg[a] (M.p., °C)	δ_H[b] CHCO	Arom	Other	δ_C[c,d] CHCO	Arom	Other	m/z[e]
Me C_6H_5 ($C_{13}H_{17}NO_2$)	71.19 (71.21)	7.93 (7.81)	6.27 (6.39)	150–160/0.5	3.84 (q, *J* 7.0)	7.2–7.3 (m, 5 H)	1.45 (d, 3 H, *J* 7.0, Me)	43.04	126.81, 127.10, 128.89, 141.88	20.58	219 (M^+, 22.4%), 114 (100), 105 (41.1), 70 (45.4), 32 (28.7)
Et C_6H_5 ($C_{14}H_{19}NO_2$)	72.02 (72.07)	8.27 (8.21)	6.07 (6.00)	125–130/0.07	3.65 (q, *J* 6.0)	7.23 (s, 5 H)	0.87 (t, 3 H, *J* 7.2, Me), 1.5–2.4 (m, 2 H)	50.50	126.87, 127.75, 128.76, 140.19	12.34 27.93	233 (M^+, 35.3%), 114 (100), 91 (34.3)
$CHMe_2$ C_6H_5 ($C_{15}H_{21}NO_2$)	72.88 (72.84)	8.78 (8.56)	5.64 (5.66)	(61–62)	3.30 (d, *J* 10.8)	7.28 (s, 5 H)	0.70, 1.04 (d, 6 H, *J* 6.9, Me), 2.2–2.8 (m, 1 H, C*H*Me_2)	55.97	126.75, 128.11, 128.38, 138.76	20.09 21.95 31.68	247 (26.9%), 205 (48.7), 133 (26.1), 114 (100), 91 (68.7), 70 (37.4)
C_4H_9 C_6H_5 ($C_{16}H_{23}NO_2$)	73.37 (73.53)	9.12 (8.87)	5.64 (5.36)	145–155/0.1	3.64 (t, *J* 7.2)	7.17 (s, 5 H)	0.8–2.4 (m, 9 H, C_4H_9)	48.80	126.88, 127.75, 128.83, 140.45	13.94, 22.69, 30.02, 34.67	261 (M^+, 7.4%), 205 (74.4), 114 (100), 91 (60.5)
C_8H_{17} C_6H_5 ($C_{20}H_{31}NO_2$)	75.95 (75.67)	9.78 (9.84)	4.16 (4.41)	gum	3.64 (t, *J* 6.6)	7.23 (s, 5 H)	0.7–2.4 (m, 17 H)	48.84	126.89, 127.72, 128.83, 140.43	14.08, 22.65 27.84, 29.27, 29.45, 29.63, 31.86, 34.91	317 (M^+, 8.0%), 205 (100), 114 (95.7), 91 (60.5), 70 (26.7)
Me 4-MeC_6H_4 ($C_{14}H_{19}NO_2$)	71.73 (72.07)	8.31 (8.21)	6.35 (6.00)	160–170/0.3	3.81 (q, *J* 6.3)	7.08 (s, 4 H)	1.42 (d, 3 H, *J* 6.3, Me)	42.72	127.04, 129.64, 136.32, 138.92	20.64, 20.93	233 (M^+, 24.8%), 119 (100), 114 (66.3) 70 (32.3)
Me 4-i-$C_4H_9C_6H_4$ ($C_{17}H_{25}NO_2$)	74.11 (74.14)	9.40 (9.15)	5.03 (5.09)	(89.5–81.5)	3.81 (q, *J* 6.6)	7.08, 7.12 (AA′BB′, 4 H, *J* 8.1)	0.88 (d, 6 H, *J* 6.4, Me), 1.44 (d, 3 H, *J* 6.8, Me), 1.8–1.9 (m, 1 H)	42.87	126.86, 129.66, 139.09, 140.24	20.45, 22.32, 30.15, 44.98	275 (M^+, 21.1%), 161 (100), 114 (56.1)
Me 3-$C_6H_5OC_6H_4$ ($C_{19}H_{21}NO_3$)	73.28 (73.29)	6.94 (6.80)	4.54 (4.50)	180–190/0.06	3.83 (q, *J* 6.6)	6.8–7.4 (m, 9 H)	1.45 (d, 3 H, *J* 6.6, Me)	42.97	117.22, 117.85, 118.80, 121.97, 123.37, 129.78, 130.29, 143.89, 157.08	20.47	311 (M^+, 21.4%), 114 (100), 70 (36.0)

[a] Kugelrohr distillation. [b] δ_H for morpholine CH_2 groups (m): 3.1, 3.8. [c] δ_C for morpholine CH_2 groups: 42.2 ± 0.3; 46.2 ± 0.3; 66.5 ± 0.3. [d] $\delta_{C=O}$ in range 171.42–172.29. [e] M^+ and peaks >25% R.A. only.

Physical and spectroscopic data for new amides **11**, **12** and **14** are given in Tables 4–6.

4,4'-(p-*Phenylenedimethylenedicarbonyl*)*morpholine* **16**. M.p. 184–186 °C; δ_C 40.25, 42.16, 46.48, 66.44, 66.71, 129.01, 133.48 and 169.46; *m*/*z* 332 (M^+, 5.0%), 114 (98.2), 88 (100), 70 (45.8), 58 (67.8), 43 (27.2), 31 (29.0) and 29 (26.9) (Found: C, 65.0; H, 7.4; N, 8.2. Calc. for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43%).

Acknowledgements

We should like to thank Andeno B.V., Venlo, The Netherlands, for generous financial support of this work.

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Paper 3/02787B
Received 17*th May* 1993
Accepted 28*th June* 1993