Alternative synthesis of 2-arylpropanoic acids from enolate and aryl halides

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Arylpropanoic acids, a type of non-steroidal antiinflammatory drug, have been prepared in liquid ammonia by photo-radical nucleophilic substitution of halogenoarenes with sodium *N*,*N*-dimethylacetamide enolate followed by methylation and hydrolysis. Rapid substitution occurred in many cases with good to excellent yields of arylpropanoic acids. The title compounds have also been prepared by arylation of sodium acetone enolate with methylation and oxidation in a haloform reaction.

Introduction

2-Arylpropanoic acids, good antiinflammatory agents currently used for controlling the pain and inflammation of rheumatic disease,[1] inhibit cylooxygenase and thus stop the arachidonic acid cascade to prostaglandins and thromboxane A_2. Such is the therapeutic efficacy of these compounds that their synthesis has been widely investigated and a number of patents have been registered for compounds such as Ibuprofen **8**, Naproxen **5c** Ketoprofen **5i** and Flurbiprofen **5h**.

The racemic and enantiomeric syntheses of these compounds[2] generally involves either the loss of a methyl group (mode *a* in Fig. 1) or the loss of carboxylic group (mode *b*) and sometimes the breaking of the aryl–alkyl C–C bond (mode *c*). The desired substitution has been obtained by 1,2-aryl migration especially in the synthesis of chiral aryl propanoic acids.[3] Also employed in such work has been the $S_{RN}1$ reaction, a chain process that can be used to introduce an aryl moiety on an aliphatic chain,[4] which requires an initiation[5] such as light, solvated electrons, electrochemical methods, sodium amalgam (Hg/Na)[6] or ultrasound.[7] Other workers have had some success in preparing arylpropanoic acids by radical arylation of propanoide enolates or propanoic-precursor enolates[8] and 2-alkyl-*N*-ethylmorpholine.[9]

As a consequence of related work on the arylation of acetamides 10 in attempts to prepare herbicides, we now report an alternative simple synthesis of 2-arylpropanoic acids and based on an $S_{RN}1$ arylation–alkylation strategy followed by hydrolysis.

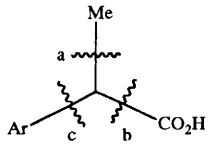
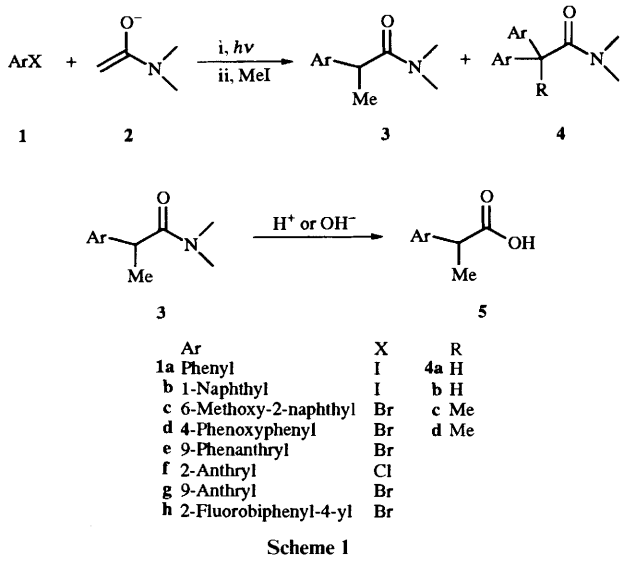


Fig. 1



Scheme 1

Results and discussion

Arylpropanoic acids were synthesized by hydrolysis of arylpropanamides, previously prepared by radical nucleophilic substitution of aryl halides. *N*,*N*-Dimethylacetamide enolate ion was used as a nucleophile since it is more effective then esters or nitriles, in radical nucleophilic substitution. Nitriles are unsuitable because the product-radical anion intermediates decompose and hence lower the yield of substituted product.[11] Acetamides were used in preference to propanoate esters or propanamides since, with the latter, the methyl group attached to the enolate, being a good hydrogen-donor, lowers the product ester yield to *ca.* 5%.[12] Acetamides were used as the starting material as they are relatively cheap, produce no by-products in the key step (introduction of the aryl moiety to the side-chain) and lead to the arylacetamide in 70–90% yield. Since these reactions occur in the presence of an excess of nucleophile, the enolate of the arylacetamide product is formed and alkylation occurs without addition of base. The arylpropanoic acids were prepared as shown in Scheme 1.

The photostimulated reaction of iodobenzene **1a** with *N*,*N*-dimethylacetamide enolate ion **2** in liquid ammonia for 1 h followed by methylation with MeI afforded *N*,*N*-dimethyl-2-phenylpropanamide **3a** (73%) and non-methylated product **4a** (10%) (Table 1, entry 1). Similar yields of *N*,*N*-dimethyl-2-naphthylpropanamide **3b** and the disubstitution product **4b** were found using 1-iodonaphthalene **1b** as substrate (Table 1, entry 2). The first step in the synthesis of 6-methoxy-2-naphthylpropanoic acid **5c** (Naproxen), a widely used non-steroidal antiinflammatory drug, was the reaction of 6-methoxy-2-naphthyl bromide **1c** with **2** to afford, after 2 h, the propanamide **3c** (52%) and the disubstitution product **4c** (15%); it is noteworthy that the disubstituted product was methylated during the reaction. The yields of **3c** were higher with an excess (10- to 15-fold) of nucleophile (Table 1, entries 3–5).

4-Phenoxyphenyl bromide **1d** was photolysed with **2** and the

Table 1 Photostimulated reactions of **1** with **2** in liquid ammonia

Entry	1 (mmol)	2 (mmol)	MeI (mmol)	Product	
1	**1a** (3.0)	30	45	**3a** (73)[a]	**4a** (10)[a]
2	**1b** (3.0)	30	45	**3b** (60)[a]	**4b** (18)[a]
3	**1c** (3.0)	15	30	**3c** (52)[b]	**4c** (15)[b]
4	**1c** (3.0)	30	45	**3c** (84)[a]	**4c** (10)[b]
5	**1c** (2.0)	30	45	**3c** (92)[a]	**4c** (5)[b]
6	**1d** (3.0)	15	30	**3d** (55)[b]	**4d** (18)[b]
7	**1e** (3.0)	30	45	**3e** (72)[a]	
8	**1f** (3.0)	15	30	**3f** (21)[b]	
9[c]	**1f** (2.0)	20	30	**3f** (77)[d]	
10	**1g** (3.0)	30	45	**3g** (70)[a]	
11	**1g** (3.0)	30		**6** (70)[a]	
12	**1h** (3.0)	15	30	**3h** (18)[a]	

[a] = Quantified by GC. [b] = Isolated yield. [c] = Initiated with 3% (Hg)Na. [d] = Quantified by HPLC.

product methylated to afford **3d** (55%) and **4d** (18%), both methylated at the C-α position (Table 1, entry 6).

Under the same conditions, the substrates **1e** and **1g** afforded the products **3e** and **3g**, respectively, in good yields, without the disubstitution product (Table 1, entries 7 and 10). The photostimulated reaction of 2-anthryl chloride **1f** with **2** followed by methylation of the product yielded only 21% of the corresponding propanamide **3f**, 70% of unchanged substrate being recovered (Table 1, entry 8). This low yield was probably the result of a poor $S_{RN}1$ propagation cycle. We have previously demonstrated that Na amalgam is a good catalyst for these reactions, being an excellent source of electrons which favour the initiation step.[5] The yield of 2-anthryl-*N*,*N*-dimethylpropanamide **3f** increased to 77% when the reaction of **1f** with **2** was catalysed by 3% (Hg)Na (Table 1, entry 9).

The propanoic acids **5a–f**, **h** were obtained by simple acid or basic hydrolysis of compounds **3a–f**, **h** depending on the compatibility of the other functional groups (Table 2).

Since acidic hydrolysis of **3c** afforded compound **9** rather than **5c**, the latter was obtained by basic hydrolysis (Table 2, entries 3 and 4). Although the 2-(2-anthryl)propanamide **3f** was easily hydrolysed to **5f** (85%) (Table 2, entry 7) attempted hydrolysis of the 2-(9-anthryl)propanamide **3g** failed even under harsh conditions of refluxing HCl (7 mol dm^{-3}), $HClO_4$ (2 mol dm^{-3}), $MeSO_3H$ (1 mol dm^{-3}), $MeCO_2H$ glacial, NaOH (4 mol dm^{-3})–EtOH, Bu^{t}OK (0.122 mol dm^{-3})–H_2O diethyl ether.[13] 2-(9-Anthryl)-*N*,*N*-dimethylacetamide **6**, however, underwent acidic hydrolysis to give the corresponding acid **7**. To obtain 2-(9-anthryl)propanoic acid **5g**, **1g** was photostimulated with the enolate ion **2** to give **6** (70%). This was then subjected to basic hydrolysis to afford compound **7** (97%) whose enolate was methylated with MeI; this afforded the acid **5g** (Table 2, entry 8).

Since Flurbiprofen **5h** and Ketoprofen **5i**, were obtained in only low yield by photolysis followed by methylation, 4-bromo-2-fluorobiphenyl **1h** was allowed to react with compound **2** under $S_{RN}1$ conditions to afford product **3h** (Table 1, entry 12). The low yield of product (18%) was a result of benzyne-generated products **10** and **11** being formed in competition with **3h** (see Scheme 2).

In the synthesis of Ketoprofen **5i**, acetamide enolate **2** was an unsuitable nucleophile since it reacts with the benzophenone carbonyl group.

In the preparation of 2-(2-fluorobiphenyl-4-yl)propanoic acid **5h** and 2-(3-benzoylphenyl)propanoic acid **5i**, the $S_{RN}1$ arylation–alkylation strategy was followed, but using acetone enolate ion as nucleophile (which has a lower pK_a than acetamide)[14] for the introduction of the side chain and the oxidative demethylation (haloform reaction) (Scheme 3).

Table 2 Hydrolysis reactions of **3** to obtain **5**

Entry	3	Yield (%)[a] 5	Overall yield (%) (**1** + **2** ⟶ ⟶ **5**)
1	**3a**[b]	**5a** (97)	71
2	**3b**[b]	**5b** (89)	54
3	**3c**[b]	**9** (95)	88
4	**3c**[c]	**5c** (95)	88
5	**3d**[c]	**5d** (91)	50
6	**3e**[b]	**5e** (95)	69
7	**3f**[c]	**5f** (85)	65
8	**6**[c]	**5g** (87)	61[d]
9	**3h**[c]	**5h** (93)	17

[a] = Isolated yield. [b] = Acid medium. [c] = Basic medium. [d] = Including methylation after hydrolysis.

Table 3 Photostimulated reactions and hydrolyses of **1h** and **1i** with **14** and MeI

Entry	1 (mmol)	14 (mmol)	Yield (%) 15	5	Overall
1	**1h** (1.5)	12	**15h** (62)[a]	**5h** (95)[b]	59
2	**1i** (2.0)	10	**15i** (12)[b,c]	**5i** (95)[b]	11

[a] = Quantified by GC. [b] = Isolated yield. [c] = Dimethylated product was obtained in 32% yield.

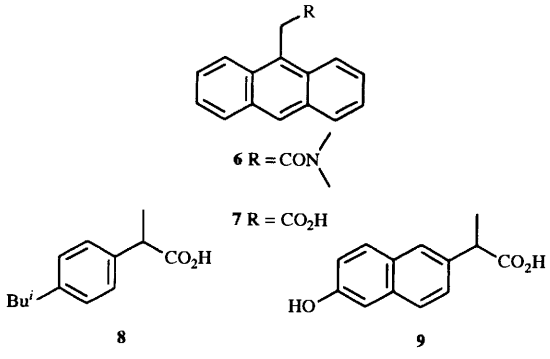


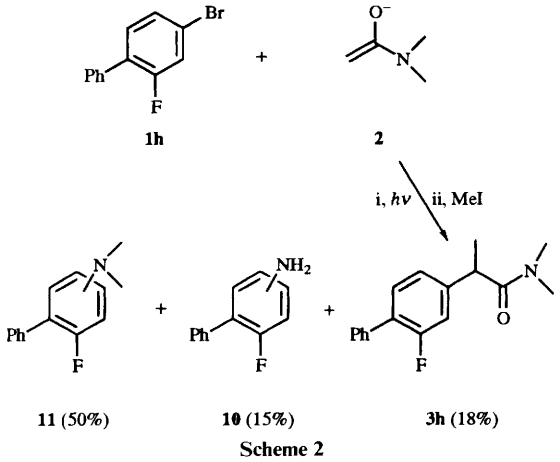
Fig. 2

The photostimulated reaction of 2-fluorobiphenyl-4-yl bromide **1h** with acetone enolate ion **12** in liquid ammonia followed by methylation with MeI, yielded the 3-(2-fluorobiphenyl-4-yl)butan-2-one **13h** (62%). The reaction of **13h** with sodium hypochlorite yielded Flurbiprofen (95%) (Table 3, entry 1). Following the same approach, the reaction of 3-chlorobenzophenone with **12** yielded product **13i** (12%) and the unavoidable methylation product 3-(3-benzoylphenyl)-3-methylbutan-2-one (32%). Nevertheless, Ketoprofen was obtained in high yield (95%) from **13i** by the haloform reaction (Table 3, entry 2).

Conclusions

The $S_{RN}1$ arylation–alkylation–hydrolysis (oxidation) sequence has proved to be an efficient method for the preparation of aryl propanoic acids using simple reagents.

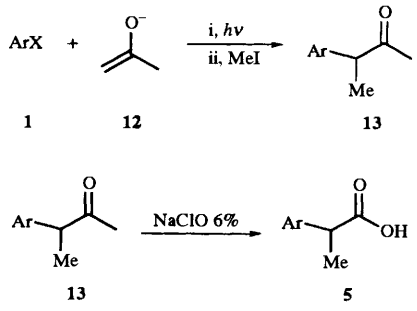
Several commercial non-steroidal antiinflammatory drugs have been synthesized in good yield (70–90% overall yield). Other aryl propanoic acids (and propanamides), interesting synthetic intermediates, were prepared by the same method in good yields.



1h **2**

11 (50%) **10** (15%) **3h** (18%)

Scheme 2



1 **12** **13**

13 **5**

1h Ar = 2-Fluorobiphenyl-4-yl, X = Br
1 Ar = 3-Benzoylphenyl, X = Cl

Scheme 3

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 200 MHz FT-nuclear magnetic spectrometer. Mass spectral measurements were obtained with a Finnigan Model 3300 FT-100 mass spectrometer. *J* values in Hz. Gas chromatographic analyses were performed on a Konik instrument with a flame ionization detector using a column packed with 3% SE30 on Chromosorb P or 5% OV17 on Chromosorb P or 3% OV101 on Chromosorb W-AW. HPLC chromatographic analyses were performed on a Konik instrument with a UV–VIS detector at 254 nm using a Spherisorb ODS-2 5 μm column. Irradiation was conducted in a reactor equipped with two 400 W lamps with maximal emission at 350 nm (Philips model HPT, water refrigerated).

Materials

The reagents, all commercially available, were purified by standard procedures. Na(Hg) amalgam (3% w/w) was prepared and its concentration determined as reported.[15]

Photostimulated reaction of *N,N*-dimethylacetamide enolate ions with iodobenzene and iodomethane

This reaction is representative of the procedure followed in all reactions. Ammonia was condensed (300 cm^3) into a three-necked, 500 cm^3 round-bottomed flask, equipped with a cold-finger condenser charged with liquid nitrogen and alcohol, a dry nitrogen inlet, and a magnetic stirrer. $NaNH_2$ (30 mmol) was prepared by addition of Na metal (30 mmol) and a catalytic amount of $FeCl_3$ to the ammonia. *N,N*-Dimethylacetamide (30 mmol) and iodobenzene (3 mmol) were then added to the reaction flask and the resulting solution was irradiated for 2 h. The reaction was quenched by addition of iodomethane (45 mmol) after which the ammonia was allowed to evaporate. Water (100 cm^3) was added to the residue and the mixture extracted with dichloromethane (3 × 50 cm^3). Work-up followed by preparative radial thin layer chromatography with diethyl ether as eluent afforded *N,N*-dimethyl-2-phenylpropanamide **3a** as a liquid (387.6 mg, 2.2 mmol). $\delta_H(CDCl_3)$ 1.41 (3 H, d, *J* 7.0), 2.88 (3 H, s), 2.95 (3 H, s), 3.87 (1 H, q, *J* 7.0), 7.28 (5 H, s); and *N,N*-dimethyl-2,2-diphenylacetamide **4a** (37.95 mg, 0.15 mmol), mp 125.5–127 °C;[10] $\delta_H(CCl_4)$ 2.90 (6 H, s), 5.03 (1 H, s) and 7.15–7.27 (10 H, m); *m/z* 239 (M$^+$, 8%), 183 (8), 167 (37), 105 (11), 77 (12) and 72 (100).

In the case of entry 9, in Table 1, 3% sodium amalgam (8 mmol) was added and the resulting solution was stirred for 4 h but not irradiated. In the case of entry 11, in Table 1, the reaction was quenched by adding an excess of ammonium nitrate to afford 9-anthryl-*N,N*-dimethylacetamide **6**.

Hydrolysis of *N,N*-dimethyl-2-phenylpropanamide

2-Phenylpropanoic acid. This reaction is representative of the procedure followed for all hydrolyses. Into a round-bottomed flask (50 cm^3), equipped with a condenser and a magnetic stirrer, and charged with aq. HCl (7 mol dm^{-3}; 10 cm^3) was added *N,N*-dimethyl-2-phenylpropanamide (1 mmol); the resulting solution was heated for 18 h. Work-up followed by preparative radial thin layer chromatography eluted with diethyl ether–light petroleum (bp 60–80 °C) (80:20) afforded the title compound **5a** as a liquid (compared with a commercial sample obtained from Aldrich), $\delta_H(CDCl_3)$ 1.51 (3 H, d, *J* 7.1), 3.80 (1 H, q, *J* 7.1), 7.47 (5 H, s) and 9.73 (1 H, s).

2-(1-Naphthyl)propanoic acid 5b. Mp 148–150 °C (lit.,[16] mp 149–150.5 °C); $\delta_H(CDCl_3)$ 1.65 (3 H, d, *J* 7.1), 4.57 (1 H, q, *J* 7.1), 7.33–8.28 (7 H, m,) and 9.10 (1 H, s); *m/z* 200 (M$^+$, 36%), 155 (100), 141 (6), 128 (9) and 115 (8).

2-(6-Hydroxy-2-naphthyl)propanoic acid 9. Mp 179–181 °C; $\delta_H(CCl_4)$ 1.50 (3 H, d, *J* 7.1), 3.87 (1 H, q, *J* 7.1), 7.08–7.21 (2 H, m), 7.41 (1 H, dd), 7.59–7.80 (3 H, m) and 8.60 (1 H, s) [lit.,[17] ([$^2H_6$]Acetone) 1.49 (3 H, d, *J* 7), 3.83 (1 H, q, *J* 7), 7.03–7.20 (2 H, m), 7.36 (1 H, dd) and 7.55–7.80 (3 H, m); *m/z* 216 (M$^+$, 41%), 171 (100), 153 (9), 141 (9), 128 (14), 115 (18) and 28(90).

2-(6-Methoxy-2-naphthyl)propanoic acid 5c. Mp 154–155 °C (lit.,[18] mp 155 °C); $\delta_H(CCl_4)$ 1.53 (3 H, d, *J* 7.1), 3.89 (1 H, q, *J* 7.1), 3.91 (3 H, s), 7.15–7.19 (2 H, m), 7.40 (1 H, dd) and 7.68–7.73 (3 H, m); $\delta_C(CDCl_3)$ 18.13, 45.17, 55.30, 105.65, 119.03, 126.14, 126.18, 127.23, 129.29, 133.84, 134.90, 157.75 and 179.99; *m/z* 230 (M$^+$, 49%), 185 (100), 170 (20), 153 (13), 141 (23), 128 (6), 115 (23) and 45 (10).

2-(4-Phenoxyphenyl)propanoic acid 5d. Mp 67–69 °C (lit.,[19] mp 68–69 °C); $\delta_H(CCl_4)$ 1.50 (3 H, d, *J* 7.1), 3.65 (1 H, q, *J* 7.1), 6.84–7.08 (5 H, m) and 7.20–7.35 (4 H, m); $\delta_C(CDCl_3)$ 18.16, 44.61, 118.83, 119.03, 123.36, 128.90, 129.73, 134.41, 156.65, 157.04 and 180.48; *m/z* 243 (M$^+$, 32%), 198 (100), 149 (6), 91 (28), 77 (36) and 43 (52).

2-(9-Phenanthryl)propanoic acid 5e. Mp 184–186 °C (lit.,[20] mp 182–184 °C); $\delta_H(CDCl_3)$ 1.75 (3 H, d, *J* 7.1), 4.55 (1 H, q, *J* 7.1), 7.50–8.78 (5 H, m), 7.85–7.90 (1 H, m), 8.11–8.19 (1 H, m), 8.68 (1 H, d) and 8.75–8.80 (1 H, m); δ_C([$^2H_6$]Acetone) 18.29, 42.25, 123.38, 124.29, 124.99, 126.18, 127.35, 127.55, 127.71, 129.36, 130.74, 131.58, 131.74, 132.62, 136.77 and 175.93; *m/z* 251 (M$^+$, 53%), 206 (100), 191 (22), 178 (23), 165 (26) and 45 (10).

2-(2-Anthryl)propanoic acid 5f. Mp 208–209 °C; $\delta_H(CDCl_3)$ 1.59 (3 H, d, *J* 7.1), 3.98 (1 H, q, *J* 7.1), 7.46–7.54 (3 H, m), 7.99–8.08 (5 H, m) and 8.55 (2 H, s); δ_C([$^2H_6$]DMSO) 18.19, 44.95, 125.45, 125.55, 125.60, 125.76, 126.00, 127.99, 128.05, 128.28, 130.34, 131.13, 131.17, 131.43, 138.29 and 175.31; *m/z* 251 (M$^+$, 51%), 205 (100), 189 (10), 179 (22), 165 (9) and 44 (67).

2-(2-Fluorobiphenyl-4-yl)propanoic acid 5h. Mp 115–117 °C (lit.,[21] mp 115 °C); $\delta_H(CDCl_3)$ 1.55 (3 H, d, *J* 7.1), 3.71 (1 H, q, *J* 7.1), 6.90–7.05 (2 H, m), 7.20–7.50 (6 H, m).

Hydrolysis of *N,N*-dimethyl(9-anthryl)acetamide

Into a round-bottomed flask (50 cm^3), equipped with a condenser and a magnetic stirrer and charged with Claisen reagent [10 cm^3; prepared by KOH (17.6 g), H_2O (13 cm^3) and MeOH (50 cm^3)] was added *N,N*-dimethyl(9-anthryl)acetamide **6** (2 mmol); the resulting solution was heated under reflux for 36 h. After this the solution was acidified with conc. hydrochloric acid and extracted with dichloromethane (3 × 30 cm^3). After work-up the product was recrystallized from dichloromethane to afford a solid, mp 203–205 °C; δ_H([$^2H_6$]Acetone) 4.75 (2 H, s), 7.50–7.68 (4 H, m), 8.10 (2 H, d), 8.44 (2 H, d) and 8.60 (1 H, s); these results are consistent with the product being 2-(9-anthryl) acetic acid **7**. This material was used for the following reaction.

Reaction of 2-(9-anthryl)acetic acid 7 with iodomethane

Ammonia (300 cm^3) was condensed into a three-necked, 500 cm^3 round-bottomed flask, equipped with a cold finger condenser charged with liquid nitrogen and alcohol, a dry nitrogen inlet, and a magnetic stirrer. Na (8 mmol) and a catalytic amount of $FeCl_3$ were added to the ammonia to give $NaNH_2$ (8 mmol). 2-(9-Anthryl)acetic acid **7** (2 mmol) was added to the flask after which the mixture was stirred for 1 h. After this iodomethane (20 mmol) was added to the mixture which was then stirred for 1 h. Ammonia was then allowed to evaporate and the residue was acidified with conc. hydrochloric acid. The mixture was then extracted with dichloromethane (3 × 50 cm^3). Work-up followed by column chromatography gave 2-(9-anthryl)propanoic acid **5g**, mp 255–256 °C; δ_H([$^2H_6$]Acetone) 1.76 (3 H, d, *J* 7.1), 5.33 (1 H, q, *J* 7.1), 7.46–7.60 (4 H, m), 8.08–8.13 (2 H, m), 8.34–8.38 (2 H, d) and 8.53 (1 H, s); δ_C([$^2H_6$]Acetone) 17.84, 39.69, 125.07, 125.69, 126.72, 127.75, 130.24, 130.40, 132.79, 135.23 and 177.39; *m/z* 250 (M^+, 54%), 205 (100), 190 (8), 178 (15), 165 (4) and 45 (9).

Photostimulated reaction of acetone enolate ions with 2-fluoro-4-bromobiphenyl and iodomethane

The reaction of acetone enolate ions was carried out in the same manner as the reaction of *N,N*-dimethylacetamide enolate ions. Sodium *tert*-butoxide was prepared by addition of *tert*-butyl alcohol and Na metal to the ammonia. The products were isolated by preparative radial thin layer chromatography with diethyl ether as eluent, yielding 3-(2-fluorobiphenyl-4-yl)butan-2-one **13h** as a liquid: δ_H($CDCl_3$) 1.45 (3 H, d, *J* 7.1), 2.12 (3 H, s), 3.80 (1 H, q, *J* 7.1), 7.00–7.12 (2 H, m) and 7.45–7.58 (6 H, m); δ_C($CDCl_3$) 17.12, 28.41, 53.08, 115.70, 123.77, 123.83, 127.71, 128.44, 128.88, 128.94, 131.07, 131.15 and 207.95; *m/z* 243 (M^+, 13%), 200 (99), 185 (15), 180 (18), 152 (6), 77(14) and 43 (100).

Oxidation of 3-(2-fluorobiphenyl-4-yl)butan-2-one 13h [22]

To commercial aqueous sodium hypochlorite (6% available chlorine; 5 cm^3) in a two-necked flask (50 cm^3) provided with a mechanical stirrer and a reflux condenser, was added 3-(2-fluorobiphenyl-4-yl)butan-2-one **13h** (0.4 mmol). The resulting solution was heated at 70 °C for 15 h after which sodium bisulfite was added to destroy the excess of hypochlorite. The solution was then acidified with conc. hydrochloric acid and extracted with dichloromethane (3 × 50 cm^3). Work-up followed by preparative radial thin layer chromatography eluting with diethyl ether–light petroleum (bp 60–80 °C) (60:40) afforded 2-(2-fluorobiphenyl-4-yl)propanoic acid **5h**.

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