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METHODS FOR THE SYNTHESIS OF ANTIINFLAMMATORY 2-ARYL PROPIONIC ACIDS

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1. INTRODUCTION

Non-steroidal antiinflammatory (NSAI) agents are one of the largest class of drugs both due to their high number and to their therapeutic interest. All these compounds have a similar mode of action: by cyclooxygenase inhibition they stop the arachidonic acid cascade to prostaglandins and thromboxane A_2 which are responsible for the inflammation mechanism. Non-steroidal anti-inflammatory agents can be classified according to their chemical structure. Except for the latest class of oxicams with piroxicam and isoxicam, most of the more thoroughly studied NSAI agents can be categorized into three main classes.

(1) Benzoic derivatives with: salicylic group where aspirin is often the highlight and with the new diflunisal compound; anthranilic compounds with mefenamic and niflumic acids.

(2) Aryl acetic acid compounds among which the most representative ones are indomethacin, sulindac, ibufenac and diclofenac.

(3) α-Aryl propionic acids with ibuprofen as the first representative.

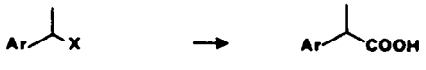
Methyl group introduction into the aliphatic side chain of substituted aryl acetic acids seems beneficial since ibuprofen has a higher activity than ibufenac. This property was widely developed and several derivatives, whose structural formulas are given in Table 1 were marketed.

This success probably explains the proliferation of synthetic methods for these types of structures. The development, at the Fabre Research Center, of an original and potent antiinflammatory compound from this class[1] led us to search various synthetic methods of access to this structure.

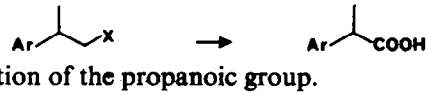
According to the building mode for the aliphatic side chain it was possible to differentiate four main synthetic methods.

(1) Final introduction of methyl radical from phenylacetic acid derivatives.

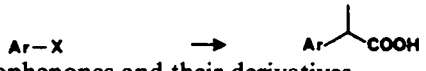
(2) Terminal building of the carboxylic function either by functionalization



or by oxidation.



(3) Simultaneous introduction of the propanoic group.



(4) Transposition of propiophenones and their derivatives.

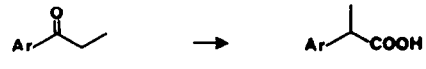
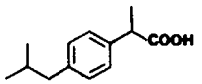
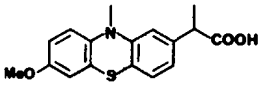
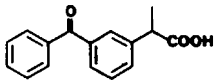
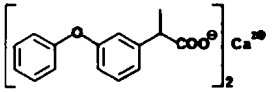
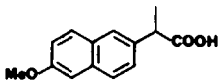
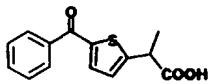
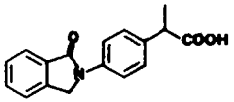
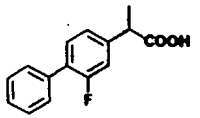
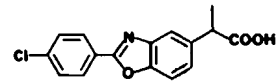
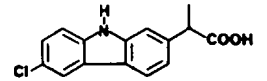
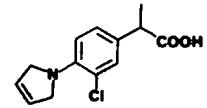
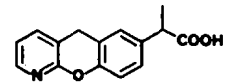
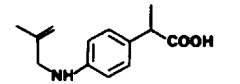
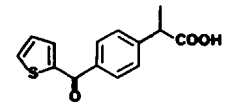
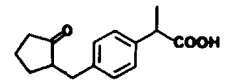


Table 1. Marketed 2-aryl propanoic acids

I.N.N.	STRUCTURAL FORMULA	TRADE NAME	COUNTRY (YEAR)	MANUFACTURER
IBUPROFEN		BRUFEN®	GB... (1972)	BOOTS
PROTIZINIC ACID		PIROCRID®	FR (1972-80) J	THERAPLIX (RP) MOCHIDA
KETOPROFEN		PROFENID®	FR (1973)	SPECIA (RP)
FENOPROFEN		NALGESIC®	GB... (1974)	DISTA PRODUCTS (LILLY)
NAPROXEN		NAPROZIN®	USA... (1974)	SYNTEX
TIAPROFENIC ACID		SURGAM®	FR (1975)	ROUSSEL
INDOPROFEN		FLOSINT®	IT (1976)	CARLO ERBA
FLURBIPROFEN		FROBEN®	GB... (1977)	BOOTS

I.N.N.	STRUCTURAL FORMULA	TRADE NAME	COUNTRY (YEAR)	MANUFACTURER
BENOXAPROFEN		OPREN®	GB... (1980) suspended in 1983	DISTA PRODUCT (LILLY)
CARPROFEN		IMADYL®	CH... (1981)	HOFFMANN LA ROCHE
PIRPROFEN		RENGASIL®	CH... (1982)	CEIGY
PRANOPROFEN		NIFLAN®	J (1982)	YOSHITOMI
ALMINOPROFEN		MINALFENE®	FR (1983)	BOUCHARA
SUPROFEN		SUPROL®	GB... (1983)	CILAG (JANSSEN)
LOXOPROFEN		LOXONIN®	J (1985-6)	SANKYO

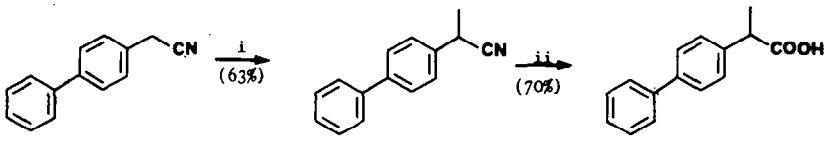
2. METHODS BY METHYL GROUP INTRODUCTION

2.1. *Direct Methylation of Aryl Acetic Acid Derivatives*

Giving relatively easy access to aryl acetic acid derivatives, it seemed the best method to the earlier authors. It was founded on the formation of the aryl acetic acid carbanion of benzylic type stabilized by resonance with the aromatic nucleus, and then reaction with a methylating reagent. The difficulty of this nucleophilic substitution reaction was the dialkylated side product formed by the second alkylation of the tertiary carbanion prepared *in situ*. The techniques described only differed by the type of aryl acetic acid derivatives and the reaction conditions.

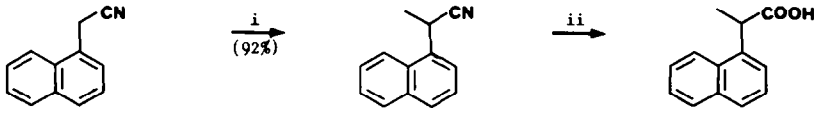
2.1.1. *Aryl acetonitriles*

At first, carbanion formation was carried out in anhydrous conditions with sodium amide or hydride. Most of the time, the reaction product was soiled by the dialkylated derivative; usual alkylating agents were methyl iodide or dimethyl sulfate[2,3] using ether as solvent (Scheme 1). Application to



Scheme 1. Reagents: (i) $NaNH_2$, MeI, Et_2O, reflux 12 h; (ii) H_2SO_4, AcOH, H_2O, reflux 15 h.

the synthesis of ketoprofen[4,5] and naproxen derivatives[6] has been claimed. The monoalkylation reaction was also studied in aqueous solvents by phase transfer catalysis. Using substituted α-naphthyl acetonitriles alkylation was selective and hydrolysis gave expected carboxylic acids in good yields[7] (Scheme 2). This reaction was optimized and adapted to the synthesis of ibuprofen.[8-10]

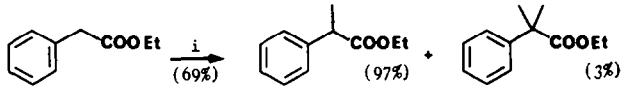


Scheme 2. Reagents: (i) aq 50% NaOH, $PhCH_2N^+Et_3Cl^-$; 5 h at 45°; (ii) NaOH, $HOCH_2CH_2OH$, reflux.

Nevertheless monoalkylation selectivity was dependent on the catalyst and temperature.[8] For example, when this reaction was performed using dimethyl sulfate and 50% aqueous sodium hydroxide the best yield was obtained at 20° during 2 h when t-butyl ammonium bromide was added as catalyst. The yield of the reaction was 65 and 10% respectively, for the mono- and dialkylated products, whereas the same composition was obtained at 70° using methyl triphenyl phosphonium iodide. *m*-Benzoyl phenyl acetonitrile could be alkylated in the same way with average yields to give a ketoprofen intermediate.[11-13]

2.1.2. *Aryl acetic acid esters*

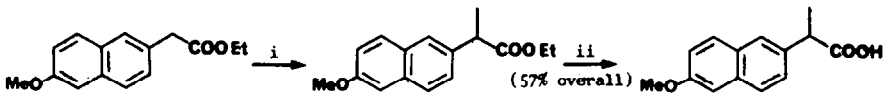
To avoid hydrolysis of the ester the reaction had to be carried out in an anhydrous medium. Alkylation of ethyl phenylacetate was performed by Kenyon *et al.*[14] using sodium amide in a mixture of liquid ammonia and ether. Under such conditions some dimethylated derivative was obtained (Scheme 3). This method was used to synthesize ethyl 2-(3-chloro-4-piperidinophenyl)propionate[15]



Scheme 3. Reagents: (i) $NaNH_2$, liq NH_3, Et_2O, 0.5 h.

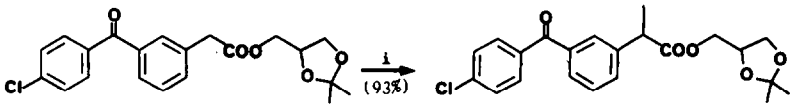
in a similar yield. Alcoholic potash hydrolysis gave the corresponding acid. Yields (86%) and selectivity (100%) were improved when methylation was carried out from ethyl *p*-methoxyphenyl acetate or its equivalent t-butylic ester.[16] The carbanion formation is easier with sodium amide

than with sodium hydride. This process was applied to naproxene synthesis[17,18] with average yields (Scheme 4) and patented.[19,20] 2-(3-Cyclohexylphenyl)propionic acid was formed in the same



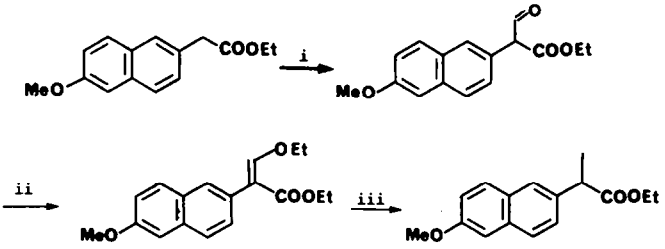
Scheme 4. Reagents: (i) NaH, MeI, $MeOCH_2CH_2OMe$; (ii) KOH, EtOH–H_2O, refluxed 0.5 h.

manner.[21] Powdered potassium hydroxide can be used to generate the carbanion reagent as in the synthesis of 2-(4-(2-thiazolylphenyl))propionic acid.[22] The alkylation reaction seemed more selective when the carbanion was prepared from a lithium compound as in the case of ketoprofen derivatives[23] (Scheme 5) and in the 2-(4-cyclohexyl-2-methoxyphenyl)propionic acid[24] synthesis. In spite of the



Scheme 5. Reagents: (i) BuLi + Et_2NH, THF/HMPT, 0.5 h at −40°, then 20°.

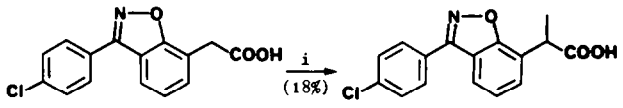
fast hydrolysis of esters in basic medium, alkylation can be successfully conducted in an aqueous mixture by phase transfer catalysis.[25,26] A formylation reaction of ethyl (6-methoxy-2-naphthyl) acetate via an enolether and then hydrogenation over palladium catalyst[27] gave the ethyl ester of naproxene in moderate yield (Scheme 6).



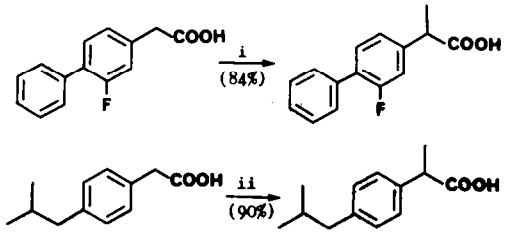
Scheme 6. Reagents: (i) NaH, HCOOEt; (ii) EtOH, TosOH, reflux; (iii) H_2, Pd/C, EtOH.

2.1.3. *Aryl acetic acids*

The lithium salt of substituted aryl acetic acids was able to generate a benzylic carbanion when it was reacted with lithium diisopropylamide as a base. The heterocyclic derivative[28] (Scheme 7) was obtained in lower yield, but this alkylation reaction was optimized in the synthesis of flurbiprofen[29] and ibuprofen[30,31] (Scheme 8).



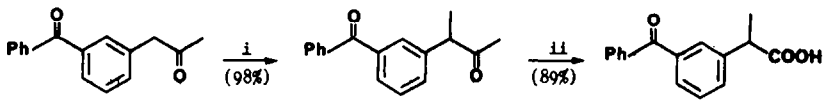
Scheme 7. Reagents: (i) i-Pr_2NH, BuLi, HMPT/THF −30° MeI, then 1.5 h at 5°.



Scheme 8. Reagents: (i) i-Pr_2NH, BuLi, HMPT/THF −20°; MeI 2 h at 20°; (ii) i-Pr_2NH, BuLi, THF, 0° then MeI 25°.

2.1.4. *Alkylation of aryl propanones*

1-Aryl 2-propanones generally obtained by aryl halide condensation with acetyl acetone in strong basic media were selectively methylated either under phase transfer catalysis in a heterogeneous aqueous system or in an anhydrous media using an alcoholate as a base to give intermediary 3-aryl 2-butanones easily oxidized to substituted hydratropic acid in high yield. This reaction was used to synthesize ketoprofen[32] (Scheme 9), naproxen,[33] ibuprofen[34,35] and flurbiprofen.[36]



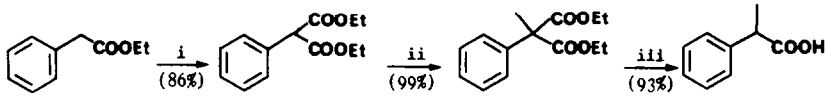
Scheme 9. Reagents: (i) MeI, PhH; 50% aq NaOH, $PhCH_2NEt_3Cl$; (ii) ClONa/MeOH, $-10°$ then 5 h at $-5°$.

2.2. *Indirect Methylation of Aryl Acetic Acid Derivatives*

The introduction of an attracting functional group on the benzylic carbon of an aryl acetic acid derivative permitted the easy formation of a tertiary carbanion. In such conditions the reaction was unequivocal and only led to the monoalkylated derivative.

2.2.1. *From aryl malonic and α-aryl cyanoacetic acid derivatives*

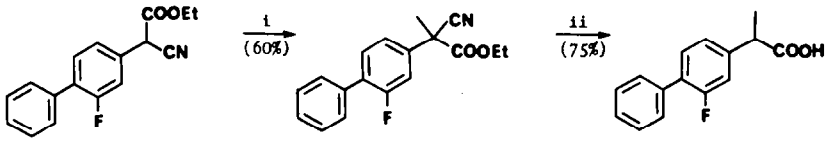
It was a classical and unequivocal method to synthesize hydratropic acids. Diethyl α-aryl malonates were easily prepared by aryl acetate carboxylation using ethyl carbonate[37,38] or oxalate[39] and sodium ethanolate as a base. The tertiary carbanion formed *in situ* reacted with the alkylating methyl iodide or bromide and then the dialkylated malonic derivative was hydrolysed and decarboxylated to hydratropic acid[40] (Scheme 10) in excellent yield. This type of reaction was applied to



Scheme 10. Reagents: (i) $O{=}C(OEt)_2$, EtOH/EtONa, reflux; (ii) EtOH/EtONa, $-10°$, then MeI; 0.5 h at 20°; (iii) KOH, $EtOH/H_2O$, reflux 3 h.

the synthesis of ibuprofen[41] and analogues,[42] flurbiprofen,[43,44] ketoprofen,[45] isoprofen[46] and then to the 2-(2-(2,4-dichlorophenoxy)phenyl)propionic acid.[47]

The carbonation of commercial aryl acetonitriles leads to α-aryl cyanacetate intermediates which can be easily methylated, saponified and decarboxylated in a process similar to the one described above. Generally methyl iodide was used as alkylating agent as in the preparation of flurbiprofen[48] (Scheme 11), naproxen,[49] ketoprofen[50] and their derivatives[51] and gave good yields but dimethyl sulfate was also advised.[52,53]

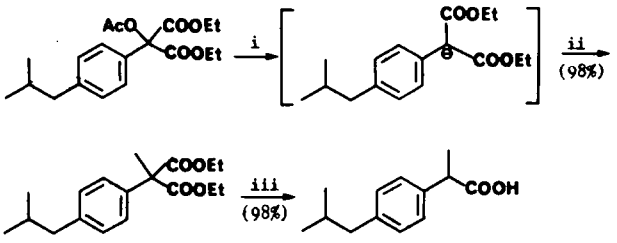


Scheme 11. Reagents: (i) Na/EtOH, MeI, reflux 2 h; (ii) H_2SO_4, H_2O, reflux 3.5 h.

2.2.2. *From α-acetoxy α-aryl malonic acid esters*

Diethyl ketomalonate reacted selectively with aromatic substrates according to a Friedel–Crafts type reaction using stannic chloride as catalyst to give, after acetylation, diethyl α-acetoxy α-aryl malonates.[54] These lose the acetoxy group on reaction with sodium to give a carbanion allowing the

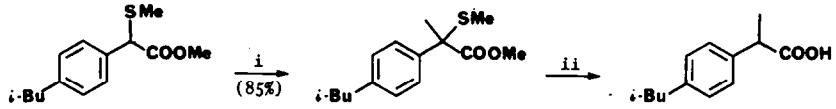
methylation reaction. This method was successfully applied to synthesize ibuprofen in good yields[54] (Scheme 12).



Scheme 12. Reagents: (i) Na, HMPT, 1-(dimethylamino)naphthalene, PhH, 20°, 15 h; (ii) MeI, 20°, 0.5 h; (iii) KOH/H_2O, reflux 4 h.

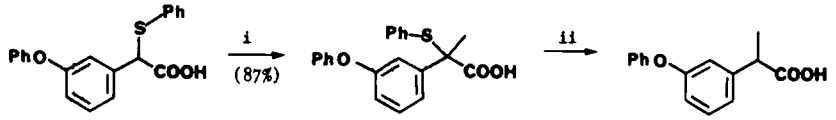
2.2.3. *From α-alkyl (or α-aryl) thio aryl acetic acids*

Condensation of aromatic aldehydes with methyl methylthiomethyl sulfoxide (MMTS) led easily to α-aryl α-methylthio acetic acids. These derivatives could be alkylated in good to excellent yields with methyl iodide after carbanion formation by reaction of sodium hydride or amide.[55] Desulfuration was carried out with nascent hydrogen (Scheme 13). For the fenoprofen syn-



Scheme 13. Reagents: (i) NaH, MeI, aq DMF; (ii) NaOH, MeOH/H_2O, reflux; Zn/AcOH, reflux 40 h.

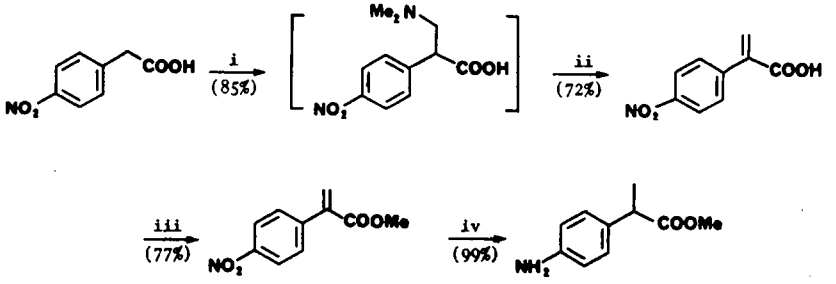
thesis, the reaction occurred with the more easily accessible α-arylthio α-aryl acetic acid[56] (Scheme 14) or with the nitrile analogue in the case of ketoprofen.[57] Alkylsulfur elimination could also be achieved by using Ni–Al alloy[58] or the sodium salt of ethanethiol.[59]



Scheme 14. Reagents: (i) $NaNH_2/NH_3$ −40°, 1 h; MeI/Et_2O; (ii) Zn/AcOH, reflux.

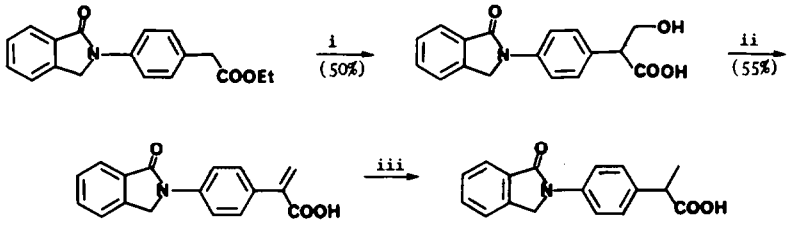
2.2.4. *From α-(dimethylaminomethyl) aryl acetic acids*

Mannich's reaction applied to aryl acetic acids gave α-(dimethylaminomethyl) aryl acetic acids whose dealkylamination led to α-aryl acrylic acids in good yields and then catalytic hydrogenation furnished hydratropic acid as in the synthesis of an alminoprofen intermediate[60] (Scheme 15).



Scheme 15. Reagents: (i) HCHO, Me_2NH, 50°, 0.5 h; (ii) H_3O^+, reflux 1 h; (iii) APTS, MeOH, reflux 16 h; (iv) H_2, Pd/C, MeOH.

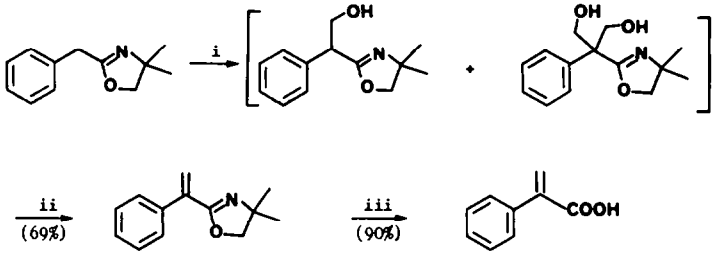
When piperidine was used in place of dimethylamine, the yield was lowered.[61] Avoidance of organic base gave the corresponding substituted tropic acid directly but the yields were lower as in the synthesis of indoprofen[62] (Scheme 16). This latest process was claimed for the production of



Scheme 16. Reagents: (i) HCHO, DMSO/EtOH, 20°, 0.25 h; NaOH, aq EtOH, reflux 8 h; (ii) 50% aq NaOH, reflux 1 h; aq HCl, 20°, 16 h; (iii) H_2, Pd/C, EtOH.

ibuprofen[63] and naproxen.[64] Better yields were obtained when the reaction was carried out with potassium bicarbonate as base, quaternary ammonium salt as catalyst and heating for 3 h at 80°. Thus ethyl atropate was obtained in 74% yield from ethyl phenylacetate.[65] When the carboxylic function was protected as 2-oxazoline, the reaction proceeded with less selectivity[66] and a dialkylated side product was obtained (Scheme 17).

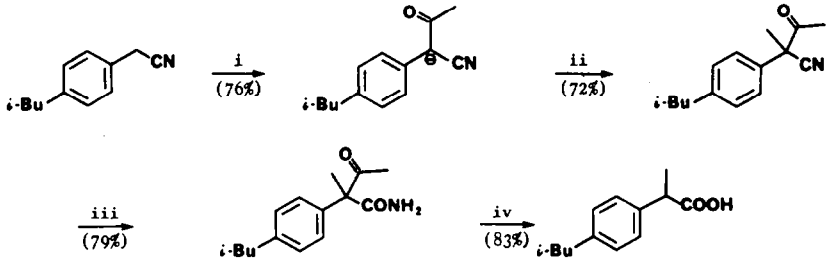
Nevertheless the reaction was improved for the synthesis of ibuprofen.[67]



Scheme 17. Reagents: (i) HCHO, KOH, EtOH, 75°, 1 h; (ii) xylene, Dean Stark, reflux 2.5 h; (iii) aq 9 N HCl, AcOH, reflux 16 h under N_2.

2.2.5. *From α-aryl acetylacetonitriles*

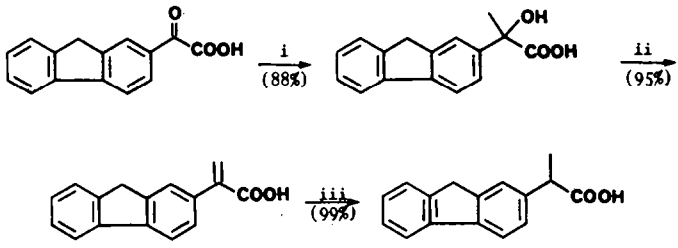
Hydratropic acids were formed from arylacetonitriles by acetylation according to Claisen's reaction. As in the preceding method the carbanion was formed *in situ* and then submitted to the action of methyl iodide. Hydration of the nitrile gave the corresponding amide which was then hydrolysed to the carboxylic acid. This process was applied to the manufacture of ibuprofen[68] (Scheme 18).



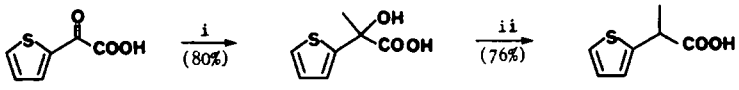
Scheme 18. Reagents: (i) EtOAc, Na, EtOH at 70°, 0.5 h; (ii) MeI, i-PrOH/DMF; (iii) 84% H_2SO_4 at 70°; (iv) conc HCl–AcOH at 100°.

2.3. *Grignard Compounds Condensation with Arylglyoxylic Acids or Esters*

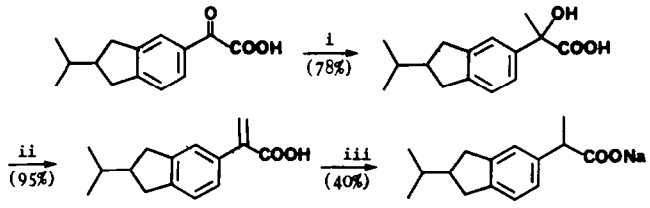
Ethyl chloroglyoxylate prepared from diethyl oxalate was easily condensed with aromatic substrates according to a Friedel–Crafts reaction,[69] to give after hydrolysis aryl glyoxylic acid in good yields. The acids obtained in this way were combined in an unequivocal manner with Grignard compounds to give the corresponding atrolactic acids. The expected hydratropic acids were prepared directly or indirectly (via α-aryl acrylic acid) by reduction of precedent acids as for example in the cicloprofen[70] (Scheme 19), thiaprofenic acid[71] (Scheme 20) and isoprofen[46] synthesis (Scheme 21).



Scheme 19. Reagents: (i) MeMgI, Et_2O, 20°, 2 h; (ii) H_2SO_4, dioxane, reflux 2 h; (iii) dioxane, H_2, Pd/C, 50 psi.



Scheme 20. Reagents: (i) MeMgI, Et_2O at −5°, 20°, 1 h, reflux 2 h; (ii) $SnCl_2$, AcOH, conc HCl, 20°, 5 h.



Scheme 21. Reagents: (i) MeMgI, Et_2O, 0°, 1 h, then 2 h at 25°; (ii) H_2SO_4, dioxane, reflux 2 h; (iii) H_2, Raney Ni, 50 atm, MeOH, 7 h at 80°, then EtONa/EtOH.

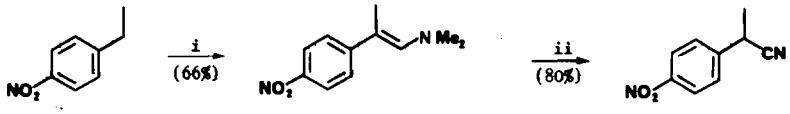
Application to the preparation of ibuprofen was claimed, the reduction was carried out either directly using stannous chloride;[72] with phosphorus and iodine[73] or indirectly via a substituted atrolactic acid.[74] The same was true for flurbiprofen and its derivatives.[43,75–77]

3. METHODS BY CARBOXYLIC FUNCTION INTRODUCTION

α-Aryl propionic acids were obtained from functionalization of the aromatic side chain by carboxylic group introduction. This principle required two carbon atoms in the lateral chain. The methods were classified according to the structural complexity of the side aliphatic chain.

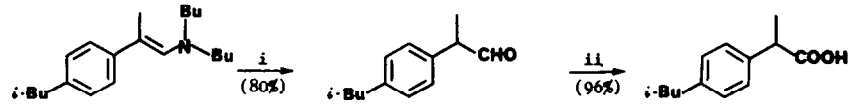
3.1. *From Ethyl Arenes*

The process of Biere and Russe[78] consisted of combining N,N-dimethylformamide dimethyl acetal with 4-ethylnitrobenzene. The intermediate enamine so obtained was treated with hydroxylamine-O-sulfonic acid which led to the hydratroponitrile precursor in good yield (Scheme 22).



Scheme 22. Reagents: (i) $(MeO)_2CH—NMe_2$; (ii) $NH_2O—SO_3H$, H_2O, 25°.

When the enamine intermediate was hydrolysed by hydrochloric acid, hydratropaldehyde was easily formed and its oxidation gave the corresponding acid as claimed for the ibuprofen synthesis[79] (Scheme 23) in improved yields.



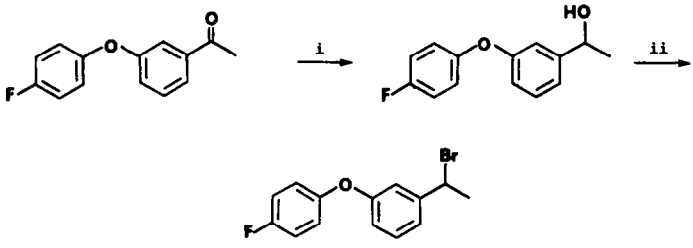
Scheme 23. Reagents: (i) 1 N HCl, reflux 5 h; (ii) $AgNO_3$, NaOH, $EtOH/H_2O$, reflux 4 h.

3.2. *From α-Halo Ethyl Arenes*

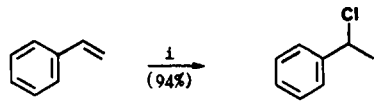
3.2.1. *Via the synthesis of nitrile precursors*

There are many ways to synthesize 2-aryl propionic acids from secondary α-aryl alkyl halide using classical organic methods. The preparation of these halides was also derived from standard procedures: acetophenone reduction into corresponding secondary alcohols and then halogenation with a halohydric acid[80,81] (Scheme 24).

Halogeno compounds were also obtained by the addition reaction of hydrochloric acid to styrene using a quaternary ammonium salt[82] as catalyst (Scheme 25) and then according to the bromination

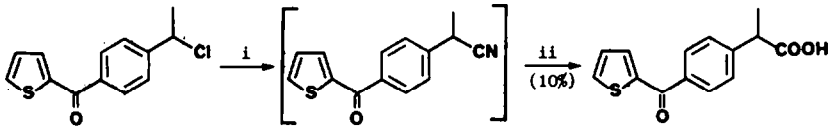


Scheme 24. Reagents: (i) $NaBH_4$, MeOH; (ii) 48% HBr.

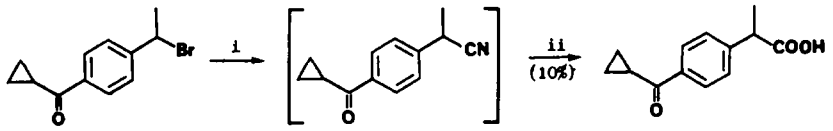


Scheme 25. Reagents: (i) aq HCl, $(C_8H_{17})_3N^+Me\ Cl^-$, reflux 0.5 h.

reaction of ethyl arenes promoted by UV light.[83] To attempt condensation of secondary benzylic halides with cyanides, polar atropic solvents are generally recommended. Yields are poor[84,85] (Scheme 26), or were increased when the process was applied to the synthesis of ibuprofen[86] (Scheme 27) and

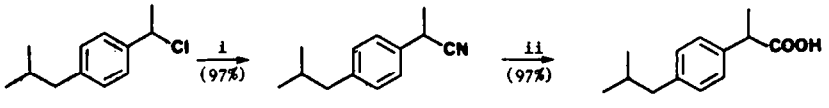


Reagents: (i) NaCN, DMSO, 50°, 2 h; (ii) H_2SO_4, $AcOH/H_2O$, reflux 2 h.

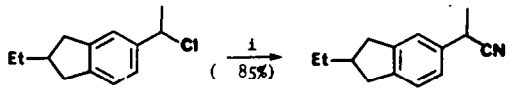


Scheme 26. Reagents: (i) NaCN, DMF, 25°, 24 h; (ii) KOH, $EtOH/H_2O$, reflux 3 h, then H^+.

its analogues[87,88] and in a lower extent to the manufacture of fenoprofen[80] and 3-nitrohydratroponitrile.[81] Yields were also improved by using a strong polar aprotic complexing solvent such as HMPT for the synthesis of analogues of ibuprofen[46] (Scheme 28). When cyanide ion was

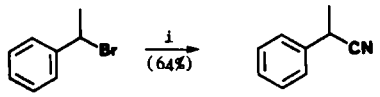


Scheme 27. Reagents: (i) NaCN, HMPT, 90°, 2 h; (ii) NaOH, $EtOH/H_2O$, reflux 2 h.

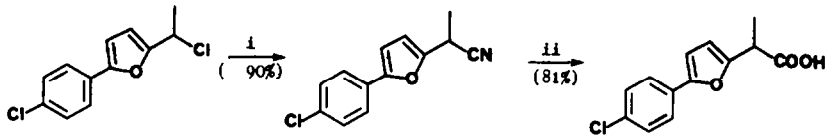


Scheme 28. Reagents: (i) NaCN, HMPT, 90°, 5 h.

complexed as a quaternary ammonium salt, the condensation reaction proceeded with good yield[82,89,90] (Scheme 29). This condensation could be monitored in a continuous process in improved yields using phase transfer catalysis[91] (Scheme 30).



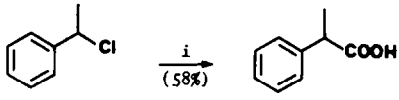
Scheme 29. Reagents: (i) $Et_4N^+CN^-$, MeCN, 50°, 18 h.



Scheme 30. Reagents: (i) NaCN, Me_3N, NaOH, $PhCH_2N^+Me_3\ OH^-$, 0–15°; (ii) KOH, $EtOH/H_2O$, reflux 16 h.

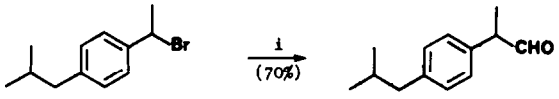
3.2.2. *Via organometallics*

This mode of synthesis was investigated by Bakshi and Turner[92] for the preparation of hydratropic acid in moderate yields (Scheme 31). This method was improved upon and permitted the

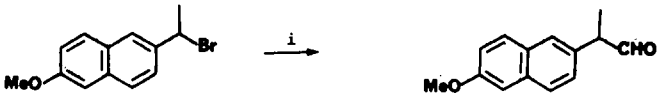


Scheme 31. Reagents: (i) Mg, Et_2O, CO_2, H^+.

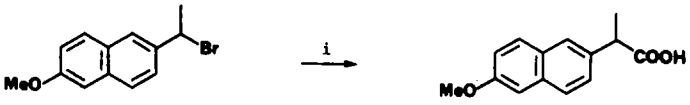
preparation of ibuprofen[93–95] in greater than 80% yield, and of naproxen from the bromo derivative.[96] Condensation of the Grignard reagent with ethyl orthoformate gave the hydratropaldehyde intermediate[97] (Scheme 32). The aldehyde could also be formed by substituting ethyl orthoformate for dimethylformamide with sodium[98] (Scheme 33). Secondary benzyl halides were combined with nickel carbonyl using a strong base to give the expected acids: naproxen[99] (Scheme 34) and hydra-



Scheme 32. Reagents: (i) Mg, Et_2O, $HC(OEt)_3$, 78% acid yield.

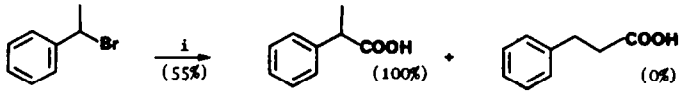


Scheme 33. Reagents: (i) DMF, Na, THF at $< 10°$, 65% overall acid yield.



Scheme 34. Reagent: (i) $Ni(CO)_4$, t-BuOH/t-BuONa.

tropic acid[100] or ketoprofen[101] with cobalt carbonyl as reagent. This reaction mode was achieved by phase transfer catalysis in the presence of cobalt carbonyl. The selectivity was improved using butanol as solvent and phenyl trimethylammonium bromide or iodide as catalyst. In this case the side product formed by the β-carboxylation of double bond was avoided. Moderate yields were obtained[102] (Scheme 35).

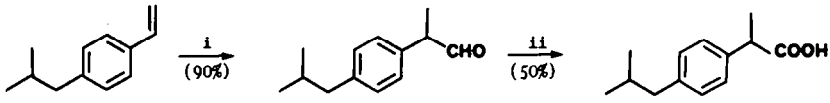


Scheme 35. Reagents: (i) 50% aq KOH, $PhNMe_3Br^-$, $Co_2(CO)_8$, BuOH, 35°, 4 h.

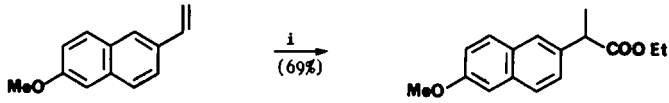
The reaction mechanism proceeded with inversion of configuration and was accompanied by extensive racemization.[103] Application to the synthesis of many antiinflammatory substituted hydratropic acids was claimed by the same authors.[104,105]

3.2.3. *Via the styrenes (oxo process)*

Generally catalytic condensation of styrene compounds with carbon monoxide and a labile hydrogen derivative (hydrogen, alcohol, water . . .) led selectively to the corresponding hydratropic aldehyde or acid. The expected product was usually obtained in greater than 90% grade. Using carbon monoxide and hydrogen, the aldehyde was obtained as in the preparation of ibuprofen[106] (Scheme 36). Replacement of hydrogen by ethyl alcohol furnished the expected ethyl ester. Thus the ethyl ester of naproxen was prepared in good yield[107,108] (Scheme 37).

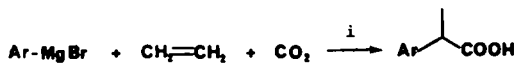


Scheme 36. Reagents: (i) $CO+H_2$, $Rh(CO)_2Cl_2$, PhH, 80°, 2 h/100 kg; (ii) $KMnO_4/H_2SO_4$, 15°, 2.5 h.



Scheme 37. Reagents: (i) CO + EtOH, $(Ph_3P)PdCl_2$, BF_3/Et_2O, pressure, 120°.

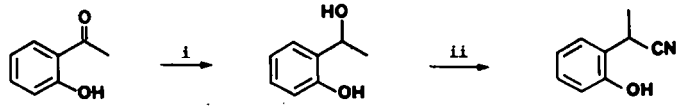
Similar methods were described when styrene was prepared *in situ* by secondary benzylic alcohol dehydration.[109,110] This reaction was successfully applied to the preparation of α-thiophene propionic acid.[111] Use of a chiral catalyst such as (+)-diphenyl neomenthylphosphine was an enantioselective method to synthesize chiral hydratropic acid.[108] At last, a trimolecular reaction between an aromatic Grignard reagent, ethylene and carbon dioxide gave rise to α-aryl propionic acid[112–114] (Scheme 38).



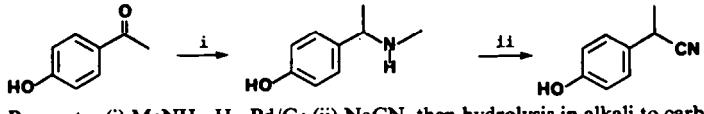
Scheme 38. Reagent: (i) $NiCl_2$, at −10°.

3.3. *From Acetophenones*

Acetophenones readily prepared by the Friedel–Crafts reaction were raw materials of choice for hydratropic acid synthesis. First they could be converted into the nitrile through either the secondary alcohol[115] (Scheme 39) or the substituted benzylamine according to a reductive amination[116] (Scheme 40) but most of the processes described needed a more complex synthesis course.



Scheme 39. Reagents: (i) EtOH, H_2, catalyst; (ii) NaCN, 100–150°, then hydrolysis in alkali at 75–125° to carboxylic acid.

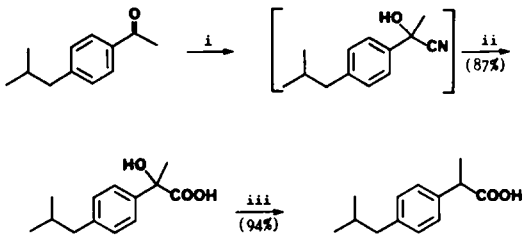


Scheme 40. Reagents: (i) $MeNH_2$, H_2, Pd/C; (ii) NaCN, then hydrolysis in alkali to carboxylic acid.

3.3.1. *Via cyanohydrin (Urech method)*

Cyanohydrins readily obtained by nucleophilic addition of a cyanide to an acetophenone were converted to α-aryl propionic in two different ways.

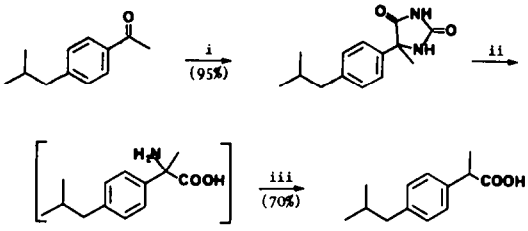
3.3.1.1. *Through atrolactic acids (2-aryl lactic acid).* In this conventional way, hydration of the nitrile function and hydrogenolysis of the alcoholic function were involved. This excellent process was applied to the synthesis of ibuprofen[117] (Scheme 41) and naproxen.[118]



Scheme 41. Reagents: (i) NaCN, DMF, HCl, 30°, 3 h; (ii) conc HCl, HCl gas, 3 h, 27°, then 45% NaOH, 80°, 3 h; (iii) H_2, Raney Ni, aq NaOH, 150–160°.

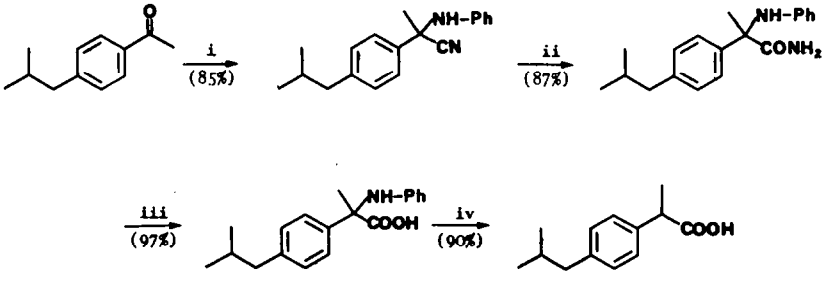
Terminal hydrogenolysis of the secondary functional alcohol was performed using either stannous chloride,[119] iodine with phosphorus,[120] hydroiodic acid with phosphorus,[121] or catalytic hydrogenation with palladium on charcoal.[122]

3.3.1.2. *Through amino acid intermediates.* The Bucherer–Bergs reaction was applied to substituted acetophenones to give hydantoin intermediates and these were decomposed into α-amino acids which were readily converted to the expected substituted hydratropic acid, as shown for instance in the ibuprofen[123,124] (Scheme 42) or naproxen[125] synthesis.



Scheme 42. Reagents: (i) $(NH_4)_2CO_3$, KCN, aq EtOH, reflux 24 h; (ii) aq NaOH, 160°, 6 h; (iii) 25% aq HCOOH, HCHO, 3 h, then H_2, Pd/C, 50°, 7 h.

Conversion of the α-amino acid to α-hydroxy acid was possible by nitrous deamination using a mixture of sodium nitrite with hydrogen chloride.[126] Modified Strecker's reaction with aniline gave rise to the α-phenyl amino hydratropic acid in excellent yield[127,128] passing through an α-amino nitrile intermediate (Scheme 43).

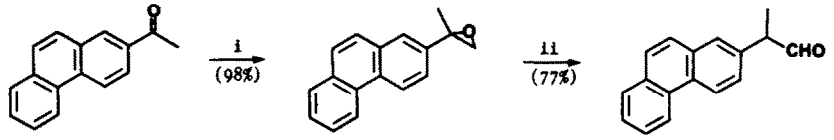


Scheme 43. Reagents: (i) $PhNH_2$, NaCN, AcOH, 45°, 8 h; (ii) H_2SO_4, 45°, 7 h; (iii) aq NaOH, reflux 7 h; (iv) HCl, H_2, Pd/C, P = 25 kg, 40–50°, 5 h.

3.3.2. *Via the epoxides*

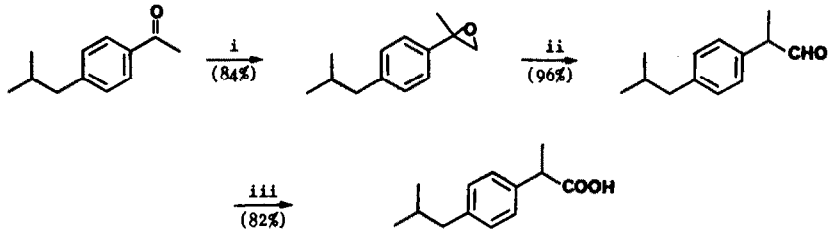
3.3.2.1. *Corey's procedure.* Trimethylsulfonium iodide was added to acetophenones in a basic medium to give 1-aryl, 1-methyl epoxy ethane[129] intermediates which were rearranged into hydra-

tropaldehydes[130] (Scheme 44). The oxidation of aldehydes to the corresponding acids was a new synthetic method to these compounds.



Scheme 44. Reagents: (i) $Me_3S^+I^-$, NaH, DMSO/THF, 0°, 0.25 h then 25°, 1.5 h; (ii) fluorisil PhH.

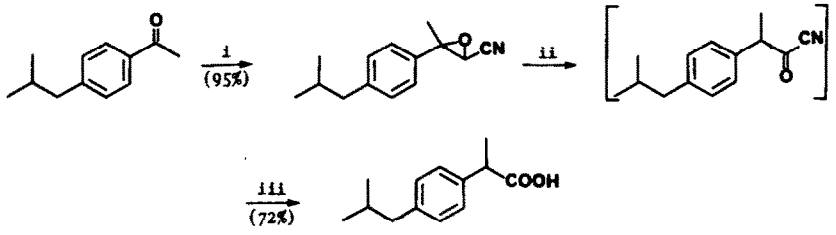
This process was applied to the synthesis of ibuprofen[131,132] in almost quantitative yield (Scheme 45), the epoxide was also prepared from the corresponding chlorohydrine.[133]



Scheme 45. Reagents: (i) $Me_3S^+ {}^-SO_4Me$, MeONa/MeCN, 25°, 0.15 h; (ii) Al_2SiO_5, PhMe, reflux; (iii) NaOCl–AcOH/Me_2CO.

Naproxen[134] and ketoprofen[135,136] were also prepared according to the same method. Other oxidative reagents were used such as: sodium hypochlorite,[137,138] silver nitrate,[139,140] the pair sodium chlorite–sulfonic acid[141] and then selenium oxide.[142]

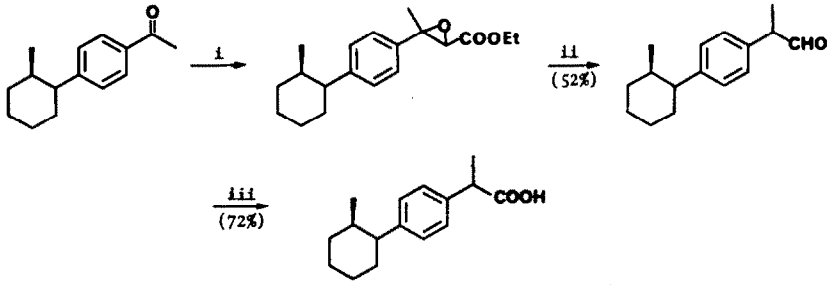
3.3.2.2. *Darzens' reaction.* Chloroacetonitrile was condensed with ketones and especially with acetophenones[145] according to Darzens' reaction.[143,144] Glycidic derivatives formed in basic medium were rearranged easily into aldehydes.[145] This process was improved using acetonitrile by sodation with sodium tertiomylate. This glycido nitrile was successfully rearranged into an α-keto nitrile in the presence of lithium perchlorate and then readily suffered an oxidation to hydratropic acid in basic medium[146] (Scheme 46).



Scheme 46. Reagents: (i) $ClCH_2CN$, t-AmONa/t-AmOH; (ii) $LiClO_4$, PhMe, reflux; (iii) aq NaOH, reflux.

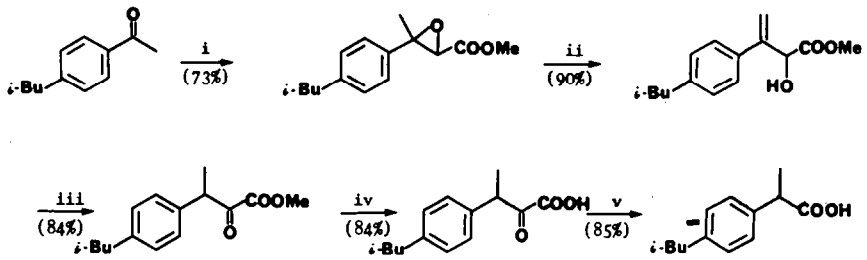
These authors have claimed the application to the synthesis of ibuprofen[147] and its derivatives.[148] Glycidyl nitriles were also readily prepared in excellent yield by phase transfer catalysis.[149]

Substitution of chloroacetonitrile by ethyl chloroacetate gave rise directly to ethyl aryl-glycidates[150] (Scheme 47).



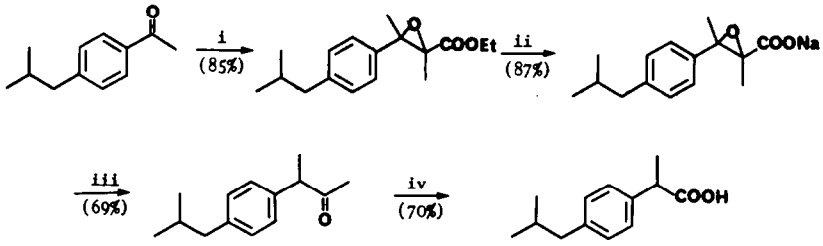
Scheme 47. Reagents: (i) $ClCH_2COOEt$, PhH, EtONa, 25°; (ii) EtONa/EtOH, H_2O, 0.5 h then AcOH/H_2O refluxed; (iii) Et_2O, $Na_2Cr_2O_7/H_2O$ < 3° then $H_2O + H_2SO_4$.

Application to the synthesis of flurbiprofen,[151] ibuprofen[142,152,153] or naproxen derivatives[138] was also claimed. A modification of the procedure consisted in rearranging alkyl arylglycidates using boron trifluoride etherate. The alkyl (3-aryl-2-hydroxy-3-butenoate) thus formed was easily isomerized to alkyl (3-aryl-2-oxobutyrate) whose oxidation furnished the expected 2-aryl propionic acids as in the case of the ibuprofen synthesis (Scheme 48) in improved yields.[154,155]



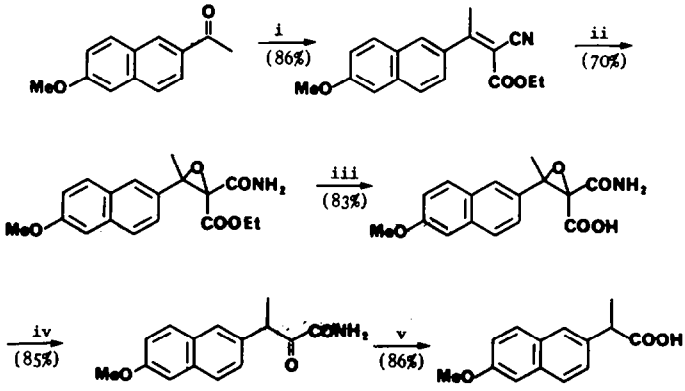
Scheme 48. Reagents: (i) $ClCH_2COOMe$, hexane, $MeONa/N_2$, 0° then 50°, 0.5 h; (ii) BF_3, H_2O/DMSO, 25°, 2 h; (iii) MeONa/MeOH reflux, 0.3 h; (iv) KOH/H_2O, 25°, 0.5 h; (v) 3% aq NaOH, 30% aq H_2O_2, 0° then 25°, 18 h.

This method was patented[156,157] by Nisshing Flour Co. investigators and adaptation to the naproxen[158] and ketoprofen[159,160] syntheses was also claimed by the same authors. Mercuric chloride[161] was also used to perform rearrangement of glycidic esters. The patent was got round using ethyl α-chloropropionate and the penultimate step gave a 3-aryl 2-butanone whose oxidation produced substituted hydratropic acid[162] (Scheme 49).



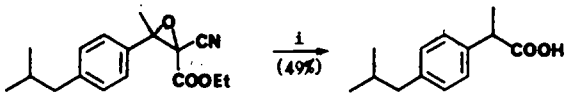
Scheme 49. Reagents: (i) ClCHMeCOOEt, t-BuOK/t-BuOH, 10°, 4.5 h, reflux 2h; (ii) EtOH/EtONa, H_2O, 0°; (iii) aq HCl then Cu, 80–140°, 2.5 h; (iv) Br_2, aq NaOH/dioxane, 0°, 3 h.

3.3.2.3. *Cope's procedure.* Knoevenagel's reaction was modified by Cope and applied to the condensation of ketones with ethyl cyanacetate.[163,164] This process involved analogous final intermediates as in Darzens' reaction. The process and intermediates were mainly claimed by Grelan Pharmaceuticals and applied to many antiinflammatory aryl 2-propionic acids such as naproxen[165] (Scheme 50) and ibuprofen[166] for example, in good yields.



Scheme 50. Reagents: (i) $CNCH_2COOEt$, AcONa, AcOH/PhH, reflux 43 h; (ii) Na_3PO_4, EtOH, H_2O_2, 75°, 4 h; (iii) KOH–EtOH, 85°, 1 h; (iv) dry, 100° several min; (v) 10% aq NaOH; 30% H_2O_2, 0°, then 25°, 16 h.

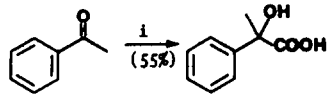
Epoxidation was also made with sodium tungstate as catalyst.[167] In an alternative method, ibuprofen was obtained directly from the epoxide in moderate yield[168] (Scheme 51).



Scheme 51. Reagents: (i) KOH/EtOH, 25°, then PhMe reflux, 0.25 h.

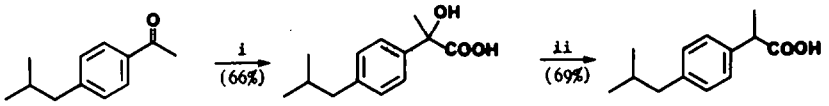
3.3.3. *Via tertiary α,α,α-trichloroalcohols*

Attempts to condense chloroform on acetophenones failed at first[169] but it succeeded using caustic soda and quaternary ammonium salt as catalyst (Scheme 52). This method gave rise to atrolactic[170] or atropic acid as intermediate according to reaction conditions and reduction or hydrogenolysis furnished the expected acid.



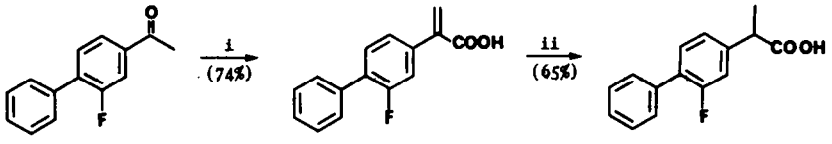
Scheme 52. Reagents: (i) PhH/50% NaOH, $CHCl_3$, $Et_3N^+CH_2PhCl^-$, 25°, 2.5 h.

This synthetic route with fewer stages was applied to the synthesis of many compounds in good yields such as: ibuprofen[171] substituting chloroform by bromoform[172] (Scheme 53) or naproxen.[173,174]



Scheme 53. Reagents: (i) 50% KOH, $CHBr_3$, LiCl, $PhCH_2N^+Et_3Cl^-$, 0°, 20 h then 20°, 18 h; (ii) H_2, Pd/C, EtOH, 60°/30 kg.

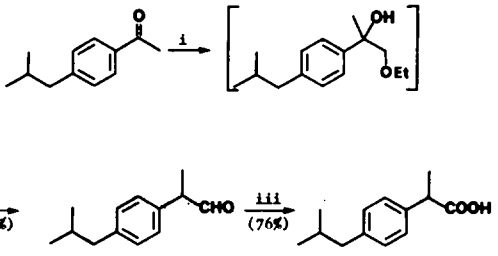
In other cases the reaction was further pushed beyond the atrolactic acid stage to give the corresponding dehydrated atrolactic acid as in the synthesis flurbiprofen[175] (Scheme 54) or ibuprofen.[176,177]



Scheme 54. Reagents: (i) 50% NaOH, $CHCl_3$, $PhCH_2OH$, CH_2Cl_2, $PhCH_2N^+Me_3Cl^-$, 20°, 12 h; (ii) 10% aq NaOH, H_2, Pd/C at 25°.

3.3.4. *Via 1-hydroxy ethers*

The Grignard reagent obtained from chloromethyl ethyl ether was condensed with substituted acetophenones to give β-hydroxy ether intermediates which were readily hydrolysed to hydratropaldehyde precursors of acids in good yields as in the preparation of ibuprofen[178,179] (Scheme 55).

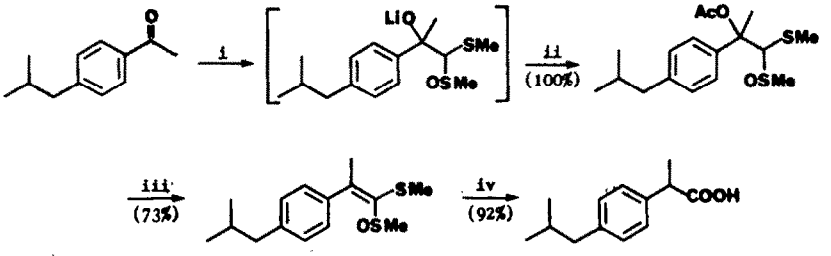


Scheme 55. Reagents: (i) $ClCH_2OEt$, Mg, $HgCl_2$, THF, EtI, 0–5°; (ii) aq NH_4Cl then HCOOH; (iii) H_2NSO_3H aq $NaClO_4$.

3.3.5. *With sulfur reagents*

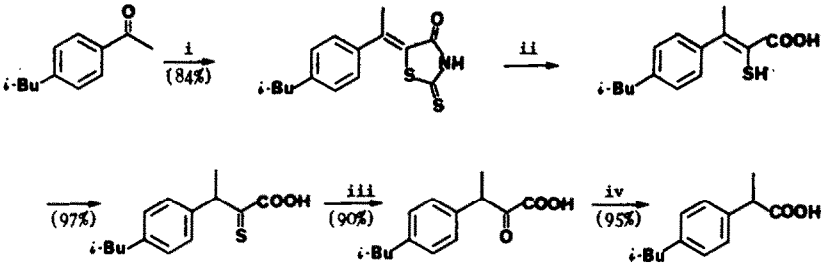
3.3.5.1. *Modified Knoevenagel's reaction.* The condensation of methyl methylthiomethyl sulfoxide (MMTS) was at first carried out with aldehydes leading to alkyl arylacetates. This reaction

was then extended to the alkyl α-aryl propionate synthesis, using acetophenones and the lithium derivative to promote carbanion formation.[180] The hydroxy intermediate was isolated as the acetate ester, then deacetoxylated to a sulfur olefin product whose ready hydrolysis gave the substituted hydratropic acid. Yields were generally improved as in the preparation of ibuprofen for example[181–183] (Scheme 56).



Scheme 56. Reagents: (i) MeSCH(Li)SOMe, THF, −75°, 0.33 h; (ii) Ac_2O, −75°, then 25°, 1 h; (iii) t-BuONa/t-BuOH, 25°, 0.15 h; (iv) HCl/MeOH, 25°, 15 h.

3.3.5.2. *Using rhodanine as reagent.* Acetophenones were successfully condensed with rhodanine leading after basic hydrolysis to thiocinnamic acid intermediates, then converted into the keto acid which suffered a degradative oxidation into the expected acid as in the preparation of ibuprofen[184] (Scheme 57), naproxen[185] and ketoprofen.[186,187]

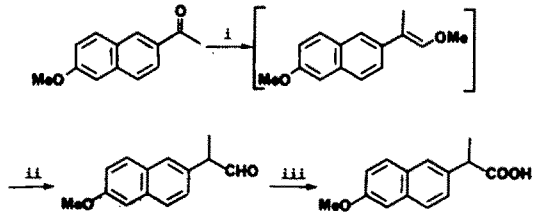


Scheme 57. Reagents: (i) rhodamine, NH_4OAc, AcOH/PhMe, reflux 8 h; (ii) 15%, NaOH, 95°, 0.5 h; (iii) 5 N NaOH, 75°, 0.5 h; (iv) 30% H_2O_2, aq 1 N NaOH at 0°, then 25°, 5 h.

3.3.6. *Using phosphine derivatives according to Wittig's reaction*

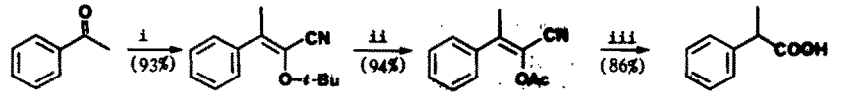
Functionalized phosphonium salts were combined to acetophenones leading either to enol ethers or to protected ketenes under thioketal or dichloroform.

From methoxymethylene triphenyl phosphorane. This reagent was condensed with 2-acetyl 6-methoxy naphthalene to give the unstable enol ether which was readily hydrolysed to the corresponding aldehyde whose oxidation gave naproxen (*dl*)[188] (Scheme 58). In a modified procedure,



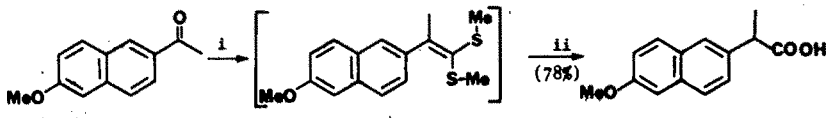
Scheme 58. Reagents: (i) $Ph_3P{=}CHOMe$; (ii) HCl; (iii) $Na_2Cr_2O_7$.

use of diethyl (t-butoxycyano) methyl phosphonate was preferred as the Wittig–Horner reagent. 1-t-Butoxy-1-cyano-2-aryl propene obtained as the intermediate[189] product was transformed into the acetate and then easily hydrolysed to hydratropic acid in almost quantitative yield[190] (Scheme 59).



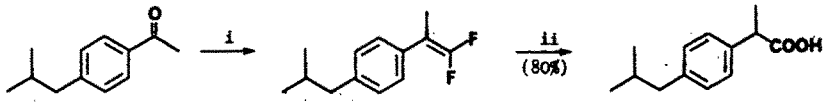
Scheme 59. Reagents: (i) $(EtO)_2P(O)CH(CN)O$—t-Bu, NaH; (ii) $ZnCl_2$, Ac_2O; (iii) 20% aq KOH.

From the dimethyl S,S-thioacetal of dimethyl formyl phosphonate. This versatile reagent was condensed to carbonyl compounds and more specifically with acetophenone to give readily the hydratropic acid through the ketene S,S-dimethyl ketal intermediate[191,192] in excellent yield, as in the naproxen synthesis[193] (Scheme 60).



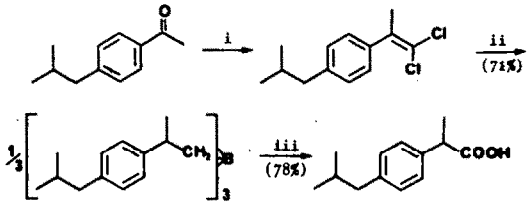
Scheme 60. Reagents: (i) $(MeO)_2P(O)CH(SMe)_2$, THF, BuLi, $-78°/N_2$, then 25°, 1 h; (ii) H_2O, H_3O^+.

From tributyl dihalomethylene phosphorane. Aryl methyl ketene halides were obtained by condensation of substituted acetophenones with the appropriate Wittig reagent.[194] For example, tributyl difluoro methylene phosphorane was condensed to *p*-isobutyl acetophenone to give the related α-methyl β,β-difluorostyrene according to a Wittig reaction. This unstable intermediate was readily hydrolysed to ibuprofen in good yield[195] as shown in Scheme 61. The dichloro derivative was



Scheme 61. Reagents: (i) $Bu_3P{=}CF_2$; (ii) H_2SO_4 at $-10°$, then 25°, 3 h.

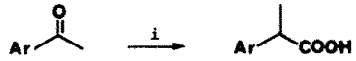
prepared in an analogous process.[196] Nevertheless an attempt to hydrolyse this halo intermediate failed. The preparation of hydratropic acid succeeded in oxidizing[197] the organo borane derivative obtained from the dichloro compound according to Scheme 62. This procedure was improved by oxidizing with hydrogen peroxide in a basic medium and applied to the manufacture of ibuprofen.[198]



Scheme 62. Reagents: (i) $Ph_3P{=}CCl_2$; (ii) B_2H_6, THF/N_2, 60°, 4 h; (iii) CrO_3/AcMe H_2SO_4, 25°, 20 h.

3.3.7. *Reaction with tosylmethylisocyanide* (TosMIC)

This versatile reagent was readily synthesized in two steps from sodium *p*-toluenesulfinate[199] and was condensed to acetophenones in a strong basic medium to the substituted hydratroponitrile as end products through a complex mechanism (Scheme 63). Yields were dependent on the organic base used as shown in Table 2.



Scheme 63. Reagents: (i) tosylmethylisocyanate, base, solvent, −60°, 0.25 h.

Table 2

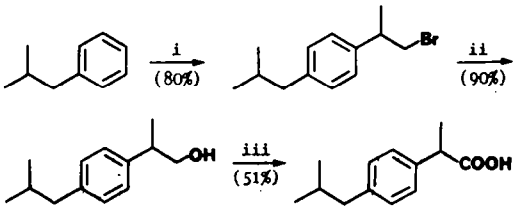
Ar	Base	Solvent	Temperature/ hours	Yield (%)	Reference
$C_{10}H_7$—	BuLi	THF	−65°; 0.25 h	50	200
C_6H_5—	BuLi	THF	−65°; 0.25 h	42	200
C_6H_5—	MeONa	MeOH	reflux; 0.25 h	69	201
C_6H_5—	t-BuOK	t-BuOH $MeO(CH_2)_2OMe$	0°–20°; 1 h	80	202
C_6H_5—	t-BuOK	EtOH $MeO(CH_2)_2OMe$	0°–35°; 0.5 h	68	203
4-BrC_6H_4—	t-BuOK	EtOH $MeO(CH_2)_2OMe$	0°–35°; 0.5 h	79	203

3.4. *Formation of Carboxylic Function by Oxidation*

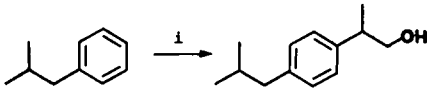
Oxidation is a usual method for the formation of carboxylic acid compounds. Many raw materials have been used, thus oxidation of aldehydes (see Sections 2.1, 2.2.3 and 2.3.2) and aryl propanones and butanones (see Sections 2.3.2.2 and 2.3.5.2) was already considered. Other compounds were recommended as intermediates to give hydratropic acids after oxidation.

3.4.1. 2-*Aryl propanol oxidation*

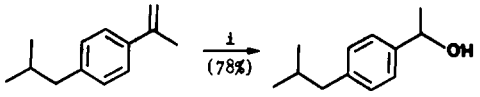
Firstly alcohols were prepared from a halide obtained according to a Friedel–Crafts reaction[204] (Scheme 64). This 2-aryl propanol was best obtained in a straight Friedel–Crafts alkylation reaction from propene oxide[205,206] (Scheme 65). In another method methyl styrenes underwent hydroboration



Scheme 64. Reagents: (i) F—$(CH_2)_3$—Br, BF_3 at 10°, 2 h; (ii) NaOAc, HMPT, 25° then aq NaOH; (iii) $Na_2Cr_2O_7$.



Scheme 65. Reagents: (i) propylene oxide, CS_2, $AlCl_3$ at −10° to 5° during 3 h, then 1.5 h.



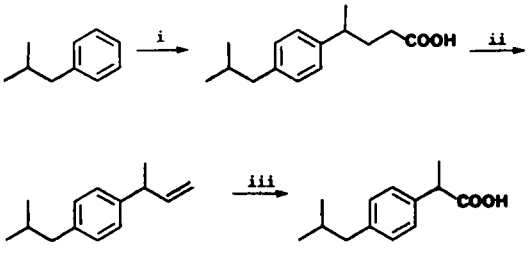
Scheme 66. Reagents: (i) $NaBH_4/BF_3$, diglyme, 20°.

to give the expected alcohol[207] (Scheme 66) in good yield. Oxidation was carried out with classical reagents:

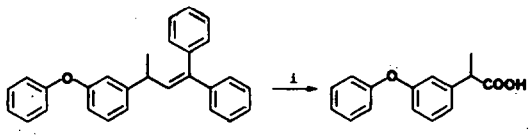
(a) chromium trioxide;[208,209]
(b) potassium dichromate or potassium permanganate;[210]
(c) oxygen of air using palladium as catalyst.[211]

3.4.2. 3-*Aryl* 1-*butene oxidation*

These unsaturated derivatives were obtained from 4-aryl valeric acids, themselves prepared from lactones and aromatic compounds by a Friedel–Crafts reaction. Generally alkylations were poorly selective, nevertheless the process was patented by Yoshimura *et al.*[212] and applied to the synthesis of ibuprofen (Scheme 67). A modified procedure was recommended using 3-aryl 1,1-disubstituted butenes as illustrated in Scheme 68 for the preparation of fenoprofen.[213]



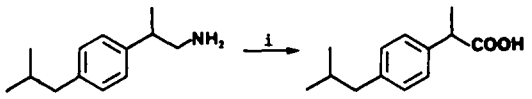
Scheme 67. Reagents: (i) γ-valerolactone, $AlCl_3$, 130°, 3 h; (ii) $Cu(OAc)_2$, C_5H_5N, PhH, 1.5 h/N_2, then $Pb(OAc)_4$, PhH, 6–8 h at 50°; (iii) t-BuOH, $NaIO_4$ + trace $KMnO_4$ aq H_2O at pH 8, 5.5 h.



Scheme 68. Reagents: (i) O_3/O_2, CH_2Cl_2, $-78°$, then 30% H_2O_2 in aq H_2SO_4.

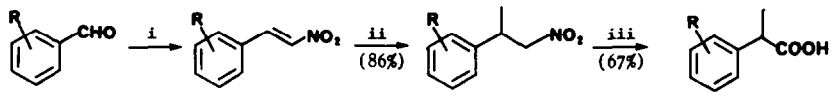
3.4.3. *Oxidation of nitrogen compounds*

Oxidation of 2-arylpropylamines[214] was carried out using a mixture of hydrogen peroxide and ferrous sulfate as oxidizing agent in basic medium as in the ibuprofen synthesis (Scheme 69).



Scheme 69. Reagents: (i) KOH, Fe_2SO_4, $7H_2O$; MeOH, 30% H_2O_2, 25°, 4 h.

Substituted nitrostyrenes were easily obtained from aldehydes and nitromethane according to a Claisen–Schmidt modified reaction. This product was condensed with methylmagnesium iodide to give 2-aryl nitropropane, whose hydrolysis was performed with concentrated hydrochloric acid to give hydratropic[215] acid in excellent yield (Scheme 70).



Scheme 70. Reagents: (i) $EtNO_2$, $NH_4OAc/AcOH$; (ii) MeMgI, Et_2O, 0°, 1 h then 25°, 1 h and reflux 0.66 h; (iii) 12 N HCl reflux 3 days.

4. METHODS BY INTRODUCTION OF THE PROPANOIC GROUP

In this synthesis mode a tricarbon chain was used which permitted the introduction of the whole chain directly on the aromatic nucleus. This was obtained using either an electrophilic (Friedel–Crafts type) or nucleophilic substitution from halo aryl compounds under activated form or by reaction in a Grignard reagent form.

4.1. *Arndt–Eistert Reaction*

This method was an exception because it only permitted the introduction of two additional carbons thanks to the condensation of diazoethane with benzoyl chloride.

This method should be classified in a special section but the anomaly is small because it was only used at the laboratory stage for sample synthesis in moderate yield (Scheme 71 and Table 3).

Scheme 71. Reagents: (i) CH_3CHN_2, Et_2O, $-20°$, 0.5 h; (ii) R—OH–Ag_2O, then hydrolysis.

4.2. *Electrophilic Substitution According to Friedel–Crafts Reaction*

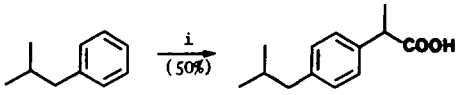
4.2.1. *From lactic acid derivatives*

These types of alkylation reactions were generally poorly selective, nevertheless two alkylating compounds were recommended.

Table 3

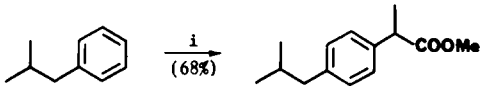
Ar	β-$C_{10}H_7$—	p-ClC_6H_4—	m-$NO_2C_6H_4$—	p-$NO_2C_6H_4$—	1-Fluorenyl—	4-Fluorenyl—
Yield (%)	58	85	48	36	41	62
Reference	216	216	217	217	70	70

(1) Lactide was condensed with isobutylbenzene to give ibuprofen directly in moderate yield (Scheme 72) using polyphosphoric acid as reagent.[218]



Scheme 72. Reagents: (i) 2,5-dioxo-3,6-dimethyl-1,4-dioxane, PPA, 70°, 12 h.

(2) Tosyl esters of lactic acid esters were better leaving groups than hydroxyls. Improved yields were obtained using the tosyl ester of methyl lactate when it was condensed with isobutyl benzene to give ibuprofen (Scheme 73) for example.[219–221]

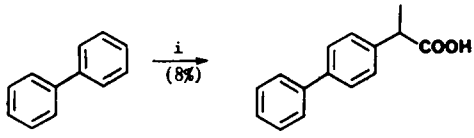


Scheme 73. Reagents: (i) 4-$MeC_6H_4SO_3CH(Me)COOMe$, $AlCl_3$, 0–3°, 6 h.

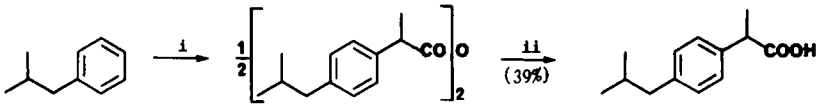
When tosylates of lactic acid were used as alkylating reagents, hydratropic acid was directly prepared but in smaller yields.[222–224] Similar results were obtained using the benzene sulfonate ester[225] whereas alkylation with the mesylate derivative gave poor yields.[226] Nevertheless recently, adaptation of this reaction to (*S*)-CH_3—$CH(OSO_2Me)COOMe$ with benzene gave (*S*)-methyl hydratropate in 80% yield and with high stereospecificity.[226a]

4.2.2. *From 2-halopropionic acids*

This alkylation reaction was not very selective[227] (Scheme 74), but the condensation with isobutyl benzene using 2-bromopropionic anhydride as reagent and ferric bromide as catalyst, was claimed to give a 39% yield[228] (Scheme 75). α-Chloropropionic acid also reacted similarly.[229] Nevertheless,

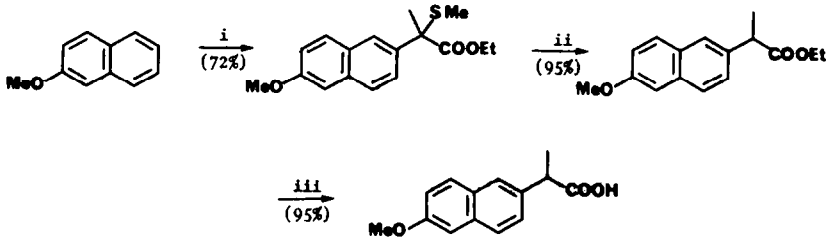


Scheme 74. Reagents: (i) $CH_3CHClCOOH$, $FeCl_3$, KBr, 200°, 16 h.



Scheme 75. Reagents: (i) 2-bromopropionic anhydride, $FeBr_3$, KBr, 170–200°, 2 h; (ii) 10% aq NaOH reflux 2 h.

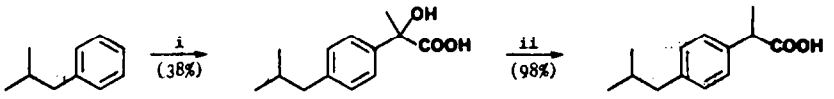
Arai *et al.* have recommended ethyl α-alkylthio α-chloropropionate as a selective alkylating reagent, using stannic chloride as catalyst (Scheme 76). Improved yields of ethyl 2-methylthio-2-(6-methoxy-2-naphthyl)propionate were obtained and successive desulfurization and saponification reactions were almost quantitative.[230]



Scheme 76. Reagents: (i) ethyl-2-chloro-2-methylthiopropionate, $SnCl_4$, CH_2Cl_2/CCl_4, 45°, 0.5 h; (ii) H_2, Raney Ni, EtOH; (iii) KOH, EtOH, H_2O.

4.2.3. *From pyruvic acid*

Pyruvic acid was condensed with isobutylbenzene, for example, according to the Friedel–Crafts reaction to leave an atrolactic acid which on hydrogenolysis gave the expected hydratropic acid[231] (Scheme 77). Red phosphorus in hydroiodic acid medium was a good substituting reagent for hydrogenolysis.[233] The latest step was also conducted via the dehydrated tropic acid intermediate which was then hydrogenated.[232]



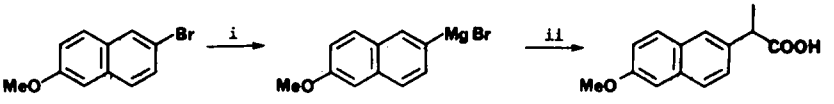
Scheme 77. Reagents: (i) $CH_3COCOOH$, CH_2Cl_2, $AlCl_3$, 0°, 4 h; (ii) 50% AcOH, Raney Ni, H_2, 170°, 16 h, 16 kg cm^{-2}.

4.3. *Reactions with Nucleophilic Character*

4.3.1. *From aromatic Grignard reagents*

An aryl Grignard reagent was directly coupled with the reactive α-halopropionic salt according to a substitution reaction or indirectly with a pyruvic acid derivative by an addition reaction mechanism.

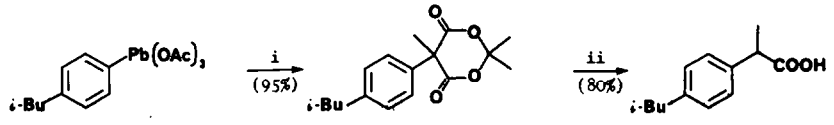
4.3.1.1. *Condensation with α-bromopropionic acid.* An aryl Grignard reagent was coupled to a bromomagnesium or a sodium salt of α-bromopropionic acid to give naproxen[234] (Scheme 78) or



Scheme 78. Reagents: (i) Mg, THF; (ii) $CH_3CHBrCOOH$, PhMe, MeMgBr THF/PhMe.

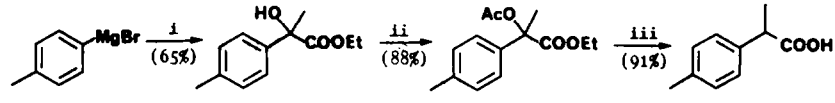
flurbiprofen.[235,236] The carboxylic acid function was also protected by converting it to an oxazolin.[237] Many types of organometallics were used as organozinc,[238,239] organocopper,[240] organocadmium[241] and organoboron compounds[242] to synthesize naproxen for example.

α-Methylated Meldrum's acid was easily coupled with an aryl lead triacetate to give ibuprofen in good yield[243] (Scheme 79). Condensation of an α-halopropionic acid compound was also performed with an aryl halide using a chiral transition metal derivative to an enantioselective reaction,[244] resolution of the racemic mixture was thus avoided.



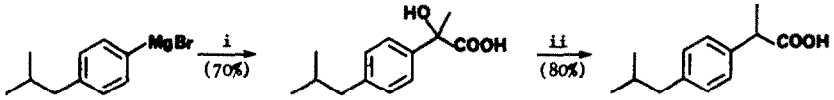
Scheme 79. Reagents: (i) methyl Meldrum's acid, $CHCl_3$, C_5H_5N, 40°, 1 h; (ii) hydrolysis.

4.3.1.2. *Reaction with ethyl pyruvate or its derivatives.* Substituted aryl magnesium bromides were condensed with ethyl pyruvate and lead to atrolactic acid intermediates; this reaction was performed in ether at low temperature[54] or in tetrahydrofuran in an ice bath.[245] Substituted atrolactic acid was either acetylated and reduced with lithium amidure[54] (Scheme 80) or directly hydrogenolysed using phosphorus with hydroiodic acid as in the preparation of flurbiprofen.[245]



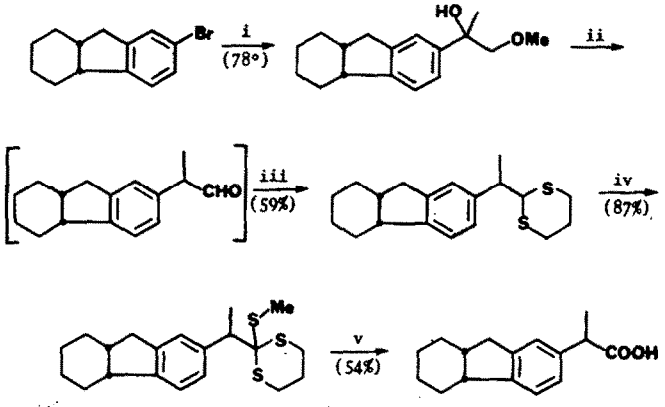
Scheme 80. Reagents: (i) $CH_3COCOOEt$, Et_2O, −78° then 20°, 16 h; (ii) Ac_2O, C_5H_5N, 4-Me_2N–C_5H_4N; (iii) Li, liq NH_3, Et_2O, then NH_4Cl and aq HCl at 0°.

In another route, sodium[246] or lithium salts[247] of pyruvic acid, successfully gave the substituted hydratropic acids (Scheme 81) in fewer steps and good yields.



Scheme 81. Reagents: (i) MeCOCOOLi, THF/HMPT, 0° then 45°, 2 h; (ii) KI/red P, H_3PO_4 heated 5 h.

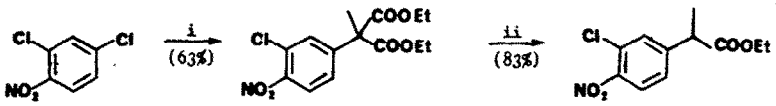
4.3.1.3. *Reaction with methoxy propanone.* When less vigorous procedures were required, methoxy propanone was reacted according to Ellison's process to give 2-aryl 2-hydroxy propyl methyl ether in a first step; the latter was readily hydrolysed to an aldehyde whose protected cyclic thio ketal was thio alkylated and then hydrolysed as shown to give the substituted acid[248] in Scheme 82.



Scheme 82. Reagents: (i) BuLi, hexane/Et_2O, 0°, $MeOCH_2Ac$, reflux 1.5 h, then H^+; (ii) 48% aq HBr reflux/N_2, 0.33 h; (iii) $HS(CH_2)_2SH$, $CHCl_3$, HCl gas, 0.5 h; (iv) BuLi, hexane/THF, −78°/Ar, 0.15 h, then MeS—SMe, 25°, 0.5 h; (v) $HgCl_2$, Hg_2O, 95% EtOH, reflux/N_2, 53 h then 10% aq NaOH, EtOH, reflux 1.2 h and finally H_2, Pd/C, dioxane.

4.3.2. *From activated halogeno arenes*

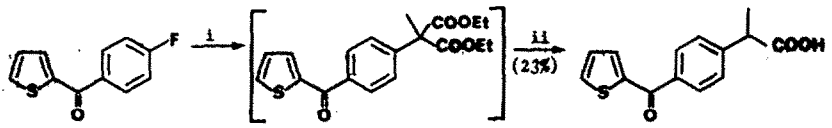
The presence of an electron-withdrawing group (such as —NO_2, $\rangle$CO, —COOR) in *o*- or *p*-halo arene permitted the removal of the halogen and the alkylation with an active hydrogen compound such as a dialkyl sodiomethyl malonate according to a nucleophilic reaction. The *p*-substitution was easier than *o*-substitution. Nitro compounds were used as activating reagents and permitted the preparation after reduction of amino hydratropic acids as in the synthesis of pirprofen[249,250] (Scheme 83), alminoprofen[60] or pyridyl derivatives.[251] Fluorine was the better leaving



Scheme 83. Reagents: (i) $MeCH(COOEt)_2$, NaH, DMF, 100°, 15 h; (ii) NaOH aq EtOH, HCl then EtOH/HCl reflux.

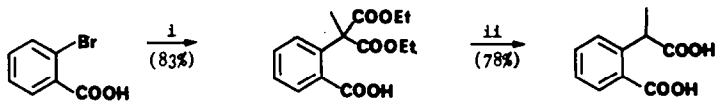
group and condensation with 2,4-difluoro nitrobenzene was easily carried out in aqueous sodium hydroxide[250,251,253] to give a flurbiprofen intermediate.

Aromatic ketones—a lower electron-withdrawing group—were also used as raw materials as in the suprofen synthesis[84] (Scheme 84) and in the preparation of a keto derivative of ibuprofen.[254]



Scheme 84. Reagents: (i) NaH, HMPT, $MeCH(COOEt)_2$, 100°, 10 h; (ii) 5% aq NaOH, reflux 6 h.

Activation with a carboxylic group in the *o*-position led to α-methyl homophthalic[255] acid in good yields (Scheme 85).

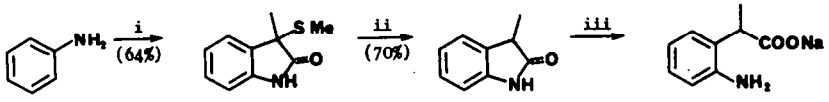


Scheme 85. Reagents: (i) NaH, PhH, $MeCH(COOEt)_2$, CuBr, 70°, 5 h; (ii) 2 N aq NaOH, EtOH, 60°, 12 h, then H_3O^+.

4.4. *Miscellaneous Substitution Reactions*

4.4.1. *Gassman's procedure*

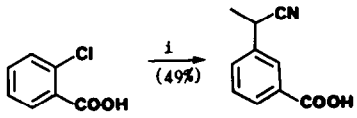
Orthoamino hydratropic acids were readily prepared from aniline and ethyl α-thiomethyl propionate using t-butyl hypochlorite through a 3-methyl oxindole intermediate[256,257] (Scheme 86). This reaction was applied to the synthesis of 2-(2-amino 3-benzoyl)propionic acid[258] a methyl derivative of amfenac, using an *o*-aminobenzophenone as starting material.



Scheme 86. Reagents: (i) $CH_3SCH(Me)COOEt$, t-BuOCl, Et_3N, Et_2O, −65°, 1 h, then aq HCl; (ii) Raney Ni, H_2, EtOH; (iii) 1 N NaOH, EtOH, reflux.

4.4.2. *Cine substitution*

When propionitrile was condensed with 2-chlorobenzoic acid, 2-(3-carboxyphenyl)propionitrile was formed in 49% yield when sodium amide was used as coupling reagent[259] (Scheme 87). Migration to the *m*-position was probably due to a cine type mechanism (Scheme 87). The procedure was

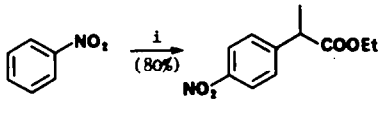


Scheme 87. Reagents: (i) Na, liq NH_3, $Fe(NO_3)_3$, Et—CN, 1 h, then NH_4Cl and H_3O^+.

extended to an electron-donating group in the aromatic such as 2,5-dimethoxy bromobenzene to give the expected nitrile in good yield.[259a] This method was successfully applied to the ketoprofen synthesis[260] by shortening the number of steps.

4.4.3. *"Vicarious" nucleophilic substitution*

Condensation of the carbanion prepared *in situ* from ethyl α-chloropropionate[261] or α-chloropropionitrile[262] with a strong base permitted the nucleophilic attack principally in the electron depleted *p*-position of a nitro aromatic compound. The mechanism probably proceeded through a Meisenheimer salt intermediate. With the most suitable base, i.e. sodium hydride and potassium or sodium t-butoxide, high yields were obtained using an aprotic polar solvent such as DMF[261] (Scheme 88). Many *o*-substituted nitrobenzenes were used as substrates in good yields. When



Scheme 88. Reagents: (i) $CH_3CH(Cl)COOEt$, t-BuOK, DMF, −5 to 0°, then H_3O^+.

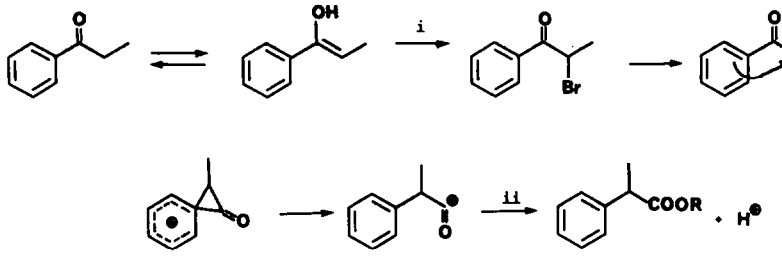
orthofluoronitrobenzene was coupled with α-chloropropionitrile, 2-(3-fluoro-4-nitrophenyl) propionitrile was prepared in 44% yield. Reduction of the nitro group into the amino group gave rise to a key intermediate in the synthesis of flurbiprofen[262] which was synthesized according to the Gomberg–Bachmann reaction.

5. REARRANGEMENT OF PROPIOPHENONES AND THEIR DERIVATIVES

Rearrangement of propiophenones and their derivatives to substituted 2-aryl propionic acids was a recent and very attractive method to readily accede to these compounds. Improvement and development of this technique already justified a review.[263]

5.1. *Principles*

α-Thallio, halo or diazopropiophenones were submitted to a rearrangement which proceeded through a carbocation intermediate and then through a cyclic transient state. The new rearranged carbocation was finally submitted to the solvent attack to directly give 2-aryl propionic acid with water or the corresponding ester when the reaction occurred in an alcohol (Scheme 89). This



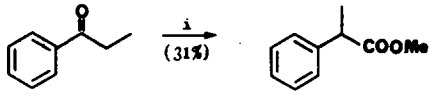
Scheme 89. Reagents: (i) Br_2; (ii) ROH.

rearrangement was applied either to propiophenones or to their α-functionalized substituted derivatives; often specificity was improved when the carbonyl group was protected as the ketal, enol ether or enamine form.

5.2. *Rearrangement of Propiophenones*

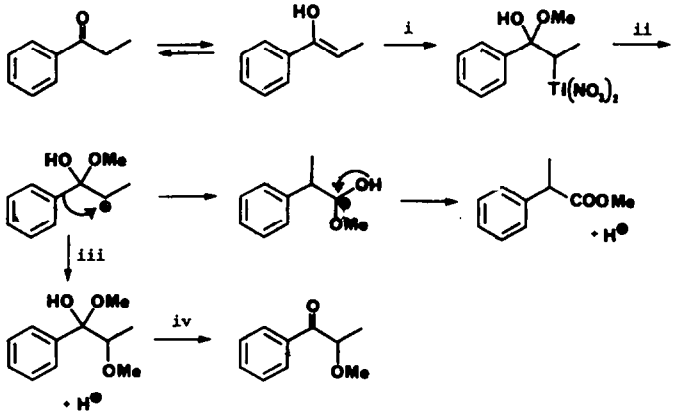
5.2.1. *Via α-metallo or metalloido propiophenones*

The preparation of aryl acetic acids from acetophenones and thallium(III) nitrate according to MacKillop *et al.*'s process[264] was extrapolated by them to propiophenones giving rise to esters of hydratropic acid[264] according to Scheme 90 in 31% yield. According to these authors after enolization



Scheme 90. Reagents: (i) $Tl(NO_3)_3$, MeOH, 70% aq $HClO_4$, 25°, 24 h.

of propiophenone and oxythallation of the double bond, oxidative rearrangement proceeded through aryl migration with simultaneous reduction of thallium(III) into thallium(I). A competing reaction was direct substitution (without rearrangement) where the enol ether was generated as a side product in low yield (Scheme 91).



Scheme 91. Reagents: (i) $Tl(NO_3)_3$; (ii) $-\downarrow TlNO_3$; (iii) MeOH; (iv) H_3O^+.

The process was improved by the same authors using thallium(III) nitrate supported on montmorillonite clay in a mixture of methanol and trimethyl orthoformate followed by evaporation to dryness. The reaction was performed in methylene chloride at room temperature in almost quantitative yield.[265]

This procedure was claimed and adapted to the synthesis of:

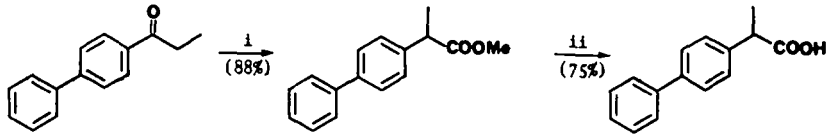
(a) ibuprofen or flurbiprofen using perchloric acid,[266] sodium perchlorate[267] as reagent or with the preparation of the thallium(III) salt *in situ*;[268]

(b) ketoprofen;[269,270]

(c) naproxen.[271]

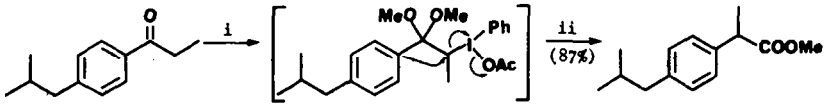
The reaction mechanism was reviewed by Higgins and Thomas.[272] According to these authors rearrangement proceeded through α-thallio ketals, while a side reaction was induced from α-thallioketones. As pointed out by Giordano *et al.*,[263] the price and toxicity of thallium salts induced limited industrial application of this process; therefore other polyvalent reagents were considered.

Thus lead tetraacetate was investigated for the rearrangement of propiophenone. Equimolar quantities of ketone and anhydrous lead tetraacetate were used in a mixture of trimethyl orthoformate and perchloric acid. The reaction was performed at room temperature in excellent yield[273] (Scheme 92). The process was claimed by these authors and applied to the synthesis of the usual



Scheme 92. Reagents: (i) $Pb(OAc)_4$, 70% $HClO_4$, $HC(OMe)_3$, 25°, 20 h; (ii) 2 N aq NaOH reflux 3 h, then H_3O^+.

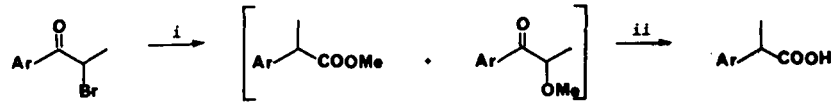
antiinflammatory hydratropic acids.[274,275] An improved procedure was perfected by Japanese[277] authors who recommended the use of a polyvalent iodide derivative devoid of toxicity. Diacetoxyphenyl iodide, a versatile oxidizing agent, was used for this rearrangement. This compound was readily prepared from iodobenzene and peracetic acid.[276] Transposition proceeded through an iodoketal intermediate according to a similar mechanism with a thallium salt. Yields were generally higher than 80% whatever the substituting group at the aromatic level (H, Me, MeO)[277] could be. Application to *p*-isobutylacetophenone led to the methyl ester of ibuprofen in 81% yield (Scheme 93).



Scheme 93. Reagents: (i) $PhI(OAc)_2$, $HC(OMe)_3$, H_2SO_4, 60°, 0.15 h; (ii) H_2O; then hydrolysis refluxing in 2 N NaOH for 3.5 h gave the pure acid in 87% yield.

5.2.2. *From α-halopropiophenones*

At first, rearrangement of α-halopropiophenones was carried out in the presence of a silver salt in methanol to give a mixture of methyl 2-aryl propionate and 2-methoxy propiophenone.[278] Yields and selectivity were raised by replacement of the silver salt by a trivalent thallium salt[279] or better still with anhydrous zinc bromide[280a,b,281] using methanol as solvent (Scheme 94). Good yields were obtained with electron-donating groups in the substrate[280a] (Table 4). As in the previous case probably the hemiketal or ketal intermediate formed *in situ* controls the transposition reaction.[278] This assumption was widely confirmed by the use of ketals as raw materials.



Scheme 94. Reagents: (i) $ZnBr_2$, MeOH, 115°, 4 h; (ii) NaOH, aq EtOH, 25°, 7 h.

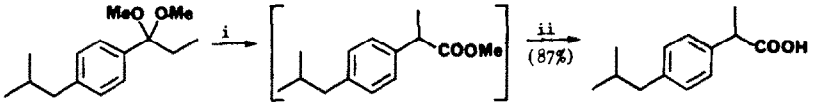
Table 4

Ar	6-MeO—2-$C_{10}H_6$—	4-MeO—C_6H_4—	4-MeC_6H_4—	C_6H_5—
Yield (%)	86	80	58	48

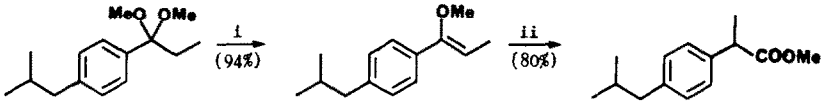
5.3. *Ketal Rearrangement*

5.3.1. *Ketals of propiophenones*

As with propiophenones, oxidative rearrangement of their ketals was carried out with thallium(III) nitrate under the same conditions but with improved yield[282,283] (Scheme 95). Enol ether obtained from the ketal was also rearranged under similar conditions to give substituted methyl 2-arylpropionate[284] (Scheme 96).



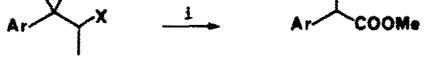
Scheme 95. Reagents: (i) $HC(OMe)_3$/MeOH, $Tl(NO_3)_3$, $3H_2O$, 55°, 1.5 h; (ii) NaOH, aq EtOH.



Scheme 96. Reagents: (i) NH_4Cl, 130–135° under vacuum; (ii) $Tl_2(SO_4)_3$, MeOH, 0° then 25°, 3 h at pH 3–5 (MeONa).

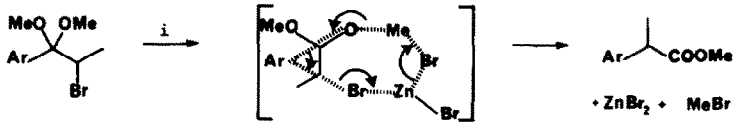
5.3.2. *Ketal of α-halopropiophenones*

This easy transposition was achieved in high yield using silver salts and in particular the fluoborate[285] according to Scheme 97 and Table 5. As in the case of propiophenone salts were looked



Scheme 97. Reagents: (i) AgY (see Table 5), $HC(OMe)_3$/MeOH, 40°.

for with low toxicity and not too high a price. This process was improved by using the zinc salt (chloride or bromide) as catalyst and generally α-bromoketone was often more advisable.[286] Enhancement of the rearrangement (Scheme 98) rate was favoured with an electron-donating group



Scheme 98. Reagents: (i) $ZnBr_2$, PhMe; 115°, reaction time see Table 6.

Table 5

Ar	X	Ag—Y	Reaction time (h)	Yield (%)
6-MeO—2-$C_{10}H_6$—	Br	$AgBF_4$	1	96
4-i-Bu—C_6H_4—	Cl	$AgBF_4$	16	82
4-MeO—C_6H_4—	Br	$AgBF_4$	1.5	97
4-MeO—C_6H_4—	Br	$AgNO_3$	4	89
6-MeO—2-$C_{10}H_6$—	Br	$AgNO_3$	3	95

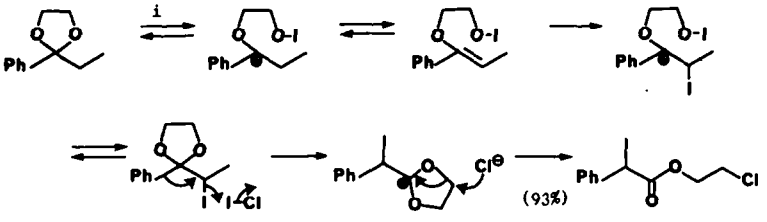
Table 6

Ar	6-MeO—2-$C_{10}H_6$—	4-MeO—C_6H_4—	4-Me—C_6H_4—	C_6H_5—	4-Cl—C_6H_4—
Reaction time (h)	0.5	0.5	1.5	5	24
Yield (%)[a]	98	98	96	80	78

[a] Overall yield from α-haloketals of α-arylpropionic acids obtained after hydrolysis of the crude methyl ester intermediates.

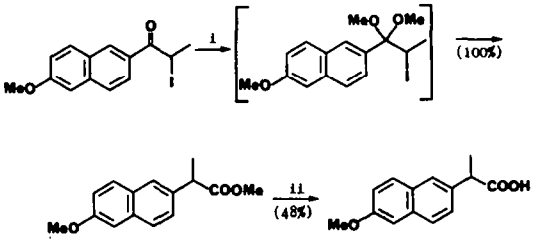
at the level of aromatic substrate. The rate of reaction was around 50 times lower with the chloro-derivative than with the methoxy compound (Table 6). Generally yields were higher than 80%. Application procedure was claimed for ibuprofen, naproxen[287] and their derivatives.[288] This process was improved by use of cyclic ketals and particularly 1,3-dioxane prepared from inexpensive neopentyl glycol. When the reaction was applied to *p*-isobutyl α-chloropropiophenone, the 3-chloro 2,2-dimethyl propyl ester of ibuprofen was formed as intermediate. Rearrangement was carried out in dry conditions at 140° using a zinc organic soluble salt as catalyst. The expected acid was prepared in 82% yield from the substituted propiophenone.[289]

Halogenation could be achieved *in situ* using iodine monochloride,[290] this permitted the simultaneous rearrangement. The presumed mechanism is shown in Scheme 99. When an α-iodoketone



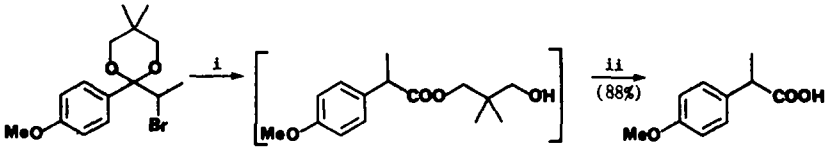
Scheme 99. Reagents: I—Cl (excess), CH_2Cl_2 at reflux.

was used as starting material, the ketal intermediate was spontaneously rearranged in the presence of the acid catalyst used in the preparation such as *p*-toluenesulfonic acid in the naproxen synthesis[291] (Scheme 100). These authors have investigated rearrangement of α-haloketals in weak basic media



Scheme 100. Reagents: (i) $HC(OMe)_3$, MeOH, APTS, reflux 24 h; (ii) 30% aq NaOH reflux 4 h.

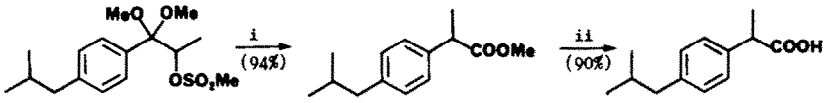
using protic solvents such as alcohols. Best results were obtained using potassium acetate and glycol as solvent, the crude acid was prepared in almost quantitative yield[292b] (Scheme 101). This process was applied successfully to the synthesis of ibuprofen and naproxen.[292a,b]



Scheme 101. Reagents: (i) KOAc, $HOCH_2CH_2OH$, 125°, 8 h; (ii) 30% aq NaOH, MeOH, reflux 4 h.

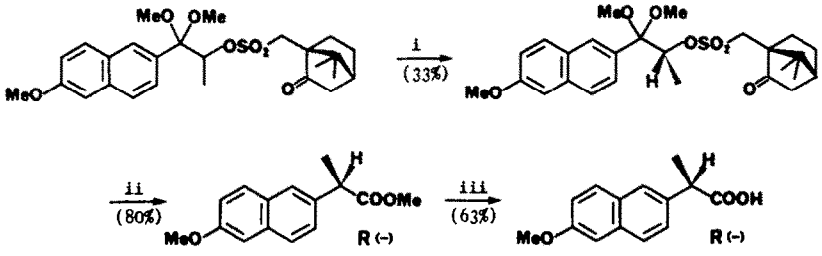
5.3.3. *Ketals of α-sulfonyloxy propiophenones*

Rearrangement of ketals using a weak base was first described by Tsuchihashi *et al.*[293] for the synthesis of ibuprofen and naproxen. Good yields of hydratropic acids were thus obtained (Scheme



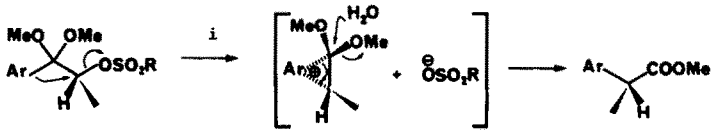
Scheme 102. Reagents: (i) $CaCO_3$, aq MeOH, reflux 72 h; (ii) KOH, aq MeOH, reflux 3 h.

102). This process was applied to many marketed hydratropic acids.[292a,294,295] When *d*-10-camphorsulfonyl chloride was used as leaving group, the diastereoisomeric camphosulfonyloxy ketone was obtained, the *R*-(+)-isomer of which was isolated by recrystallization. This intermediate was submitted to rearrangement to give the *R*-(−)-derivative of naproxen[296] according to Scheme 103. The enantiomeric *l*-sulfonyl chloride was used to obtain the marketed *S*-(+)-naproxen[296] isomer.



Scheme 103. Reagents: (i) recrystallization from MeOH; (ii) $CaCO_3$, DMF/H_2O, reflux 14 h; (iii) HCl, $MeOCH_2CH_2OMe$, 50°, 23 h.

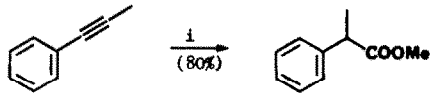
It was pointed out that rearrangement proceeded with 100% inversion of configuration[296] of the carbon atom at the 2-position, according to an intramolecular S_N2 type substitution as represented in Scheme 104.



Scheme 104. Reagents: (i) $CaCO_3$, aq DMF, reflux.

5.4. 1-*Aryl Propynes Rearrangement*

Oxidative rearrangement of 1-aryl propynes was also investigated by McKillop *et al.*[297] and then behaved like the reaction with ketals which also occurred with thallium(III) nitrate as shown in Scheme 105. Yields were excellent,[297] therefore this reaction was claimed for the preparation of fenoprofen[298] and ketoprofen[299] for example.

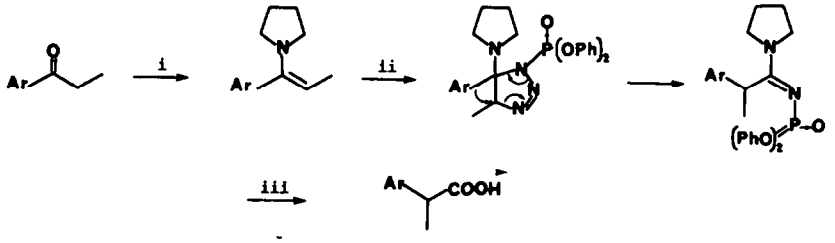


Scheme 105. Reagents: (i) $Tl(NO_3)_3$, MeOH, reflux 2 h.

5.5. *Enamine Rearrangement*

Diphenyl phosphorazidate (DPPA) easily prepared from phenol[300,301] was combined with enamines obtained from propiophenones and pyrrolidine to give after rearrangement the corres-

ponding hydratropic acid[302] according to Scheme 106. When 1-isobutyl 4-propionyl benzene and 6-methoxy-2-propionyl naphthalene were used as starting materials the expected ibuprofen and naproxen were prepared in 63 and 70% overall yields.[302] The process[303,304] and the intermediate enamines[305] were claimed.



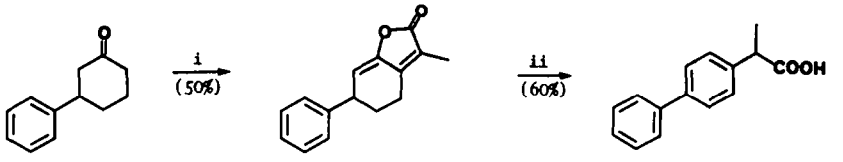
Scheme 106. Reagents: (i) pyrrolidine, BF_3/Et_2O, refluxing toluene; (ii) diphenyl phosphorazidate (DPPA or $(PhO)_2P(O)N_3$), THF, 25°, 1 h, 40°, 1 h, then reflux 2 h; (iii) aq KOH in refluxing ethylene glycol, H^+.

6. MISCELLANEOUS METHODS

6.1. *Terminal Aromatization*

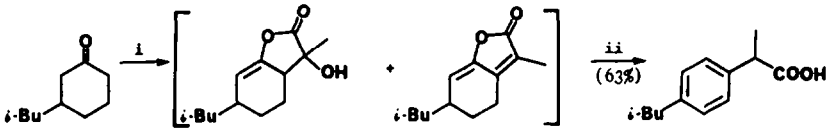
6.1.1. *From cyclanones*

When 3-phenyl cyclohexanone was condensed at reflux with ethyl pyruvate in acetic hydrochloric acid 3-methyl-6-phenyl-5,6-dihydro-2(4H)-benzofuranone was prepared in 50% yield. Aromatization[306] of this intermediate was performed in pyridine at reflux for 6 h according to Scheme 107.



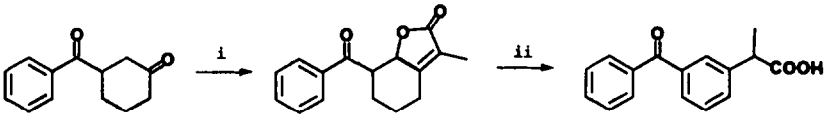
Scheme 107. Reagents: (i) MeCOCOOEt, 12 N HCl, AcOH, reflux 12 h; (ii) C_5H_5N–HCl, 230°, 6 h.

When 3-isobutylcyclohexanone was used as starting material the dehydrated intermediate was mixed with the hydrated side product, but the crude mixture was satisfactorily aromatized to hydratropic acid[307] (Scheme 108). When the reaction was performed with 3-benzoylcyclohexanone and pyruvic



Scheme 108. Reagents: (i) MeCOCOOEt, 150°, 14 h; (ii) C_5H_5N–HCl, reflux 4.5 h.

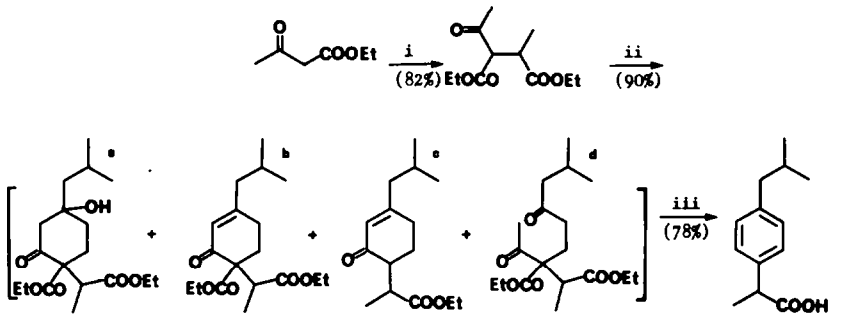
acid a key intermediate[308] was obtained whose aromatization led to ketoprofen (Scheme 109). Preparation of the preceding open intermediate was also claimed.[309–311] Naproxen was also synthesized by a similar process using 6-methoxy-1-tetralones as starting material.[312]



Scheme 109. Reagents: (i) MeCOCOOH; (ii) C_5H_5N–HCl, 200–230°.

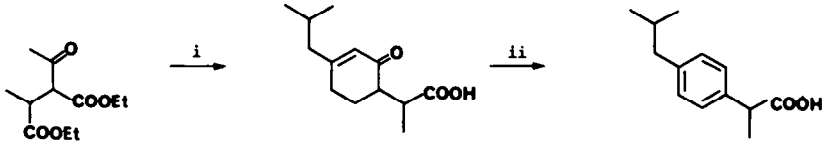
6.1.2. *From diethyl α-acetyl β-methyl succinate*

Diethyl α-acetyl β-methyl succinate readily produced from ethyl acetoacetate and ethyl α-chloropropionate undergoes a Michael reaction with vinyl isobutylketone to give a mixture of products in variable dehydrated stages (Scheme 110).



Scheme 110. Reagents: (i) MeCH(Cl)COOEt, NaH, EtOH; (ii) CH_2=$CHCOCH_2CHMe_2$, DMSO; (iii) APTS, PhMe, reflux 6 h.

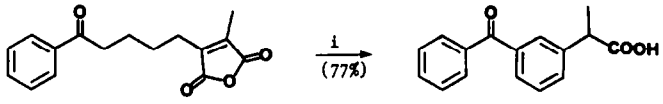
Crude product was involved for aromatization into ibuprofen in 78% overall yield[313,314] using APTS as catalyst. Acid intermediates were also claimed,[315] whereas in other cases Michael's reaction seemed more selective,[316] since only the expected undehydrated product was formed. (2-Diethylaminoethyl) isobutyl ketone, a precursor of vinyl isobutyl ketone, was selectively condensed with diethyl α-methyl β-acetyl succinate using potassium carbonate to give 2-(4-isobutyl, 2-oxo 3-cyclohexenyl)propionic acid whose aromatization with succinic anhydride produced ibuprofen[317] (Scheme 111).



Scheme 111. Reagents: (i) $Et_2NCH_2CH_2COCH_2CHMe_2$, EtOH, K_2CO_3, Me_2SO_4; (ii) succinic anhydride, 205–240°.

6.1.3. *From maleic derivatives*

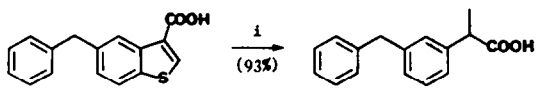
When α-(4-benzoylbutyl) β-methyl maleic anhydride was heated in pyridine hydrochloride at reflux for 6 h, aromatization proceeded in good yield[318] according to Scheme 112.



Scheme 112. Reagents: (i) C_5H_5N–HCl, 200–230°, 6 h.

6.2. *Dethiation of Substituted 3-Benzothiophene Carboxylic Acid*

Hannoun *et al.*[319] performed the dethiation of 5-benzyl 3-benzothiophene carboxylic acid to 2-(3-benzyl phenyl)propionic acid using nascent hydrogen produced from Raney nickel in sodium hydroxide with excellent yield (Scheme 113).



Scheme 113. Reagents: (i) Raney Ni, 5% aq NaOH, EtOH, 70–80°, 3–4 h, then H^+.

7. CONCLUSION

The number of methods proposed to prepare 2-aryl propionic acids demonstrates the importance of these derivatives used in therapeutics as NSAIs.

Many of the described processes expressed the imagination capacities necessary to get round the protection scope of the previous patents. This step has created methods which have extended the field of knowledge in organic chemistry. It also showed that the chemist's interest was gradually transferred from conventional step-by-step synthesis by introduction of methyl or carboxyl groups to suitable precursors, to more global sometimes more specific methods. It was the reason why recent rearrangement methods of propiophenones seemed attractive due to their improved yield, specificity and easy working. In the same way procedures using acetophenones as raw materials or the use of Grignard reagents were well controlled and widely used.

There is no versatile method available for the chemist in "first intention". The selection will always be dependent on the aromatic substrate and the structural character of the lateral chains in the cycle; the approach to the raw materials, the price and the possible harm these reagents may cause humans and the surroundings. But they are the old parameters controlling the decisions of any industrial chemist.

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