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A synthesis of licofelone using Fenton's reagent

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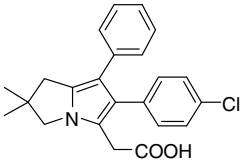
ABSTRACT

An efficient synthesis of licofelone, an anti-inflammatory drug currently undergoing phase-III clinical studies, based on Fenton-type radical alkylation of 2,3-dihydro-1*H*-pyrrolizine **3** with iodoacetonitrile or iodoacetates is reported. The iodoacetates can be replaced by NaI and by the corresponding bromoacetate.

Licofelone (ML3000),[1] a dual cyclooxygenase/5-lipoxygenase inhibitor developed by Merckle, is the first member of a new class of analgesic and anti-inflammatory drugs currently undergoing phase-III clinical studies for treatment of osteoarthritis.[2]



licofelone

There are several methods for construction of the parent moiety of the drug; it is usually formed by condensation of rather unstable 2-benzyl-4,4-dimethyl-1-pyrroline (**1**) with 4-chlorophenacyl bromide (**2**) providing 2,3-dihydro-1*H*-pyrrolizine **3**.[3–5] Though a different synthesis of **3** based on the Suzuki cross-coupling reaction has been published,[6–8] the original method using the intermediacy of **1** seems to be more efficient. Compound **3** when treated with ethyl diazoacetate gives ester **4a** and its hydrolysis gives licofelone. Alternatively, compound **3** on treatment with oxalyl chloride followed by hydrolysis gives acid **5**. Wolff–Kishner reduction then provides licofelone (Scheme 1).[3–5]

The only known methods for the transformation of **3** into licofelone avoiding the use of diazoacetate are based on reduction of the oxo group of **5** by classical Wolff–Kishner reduction[3–5] or by its modification using $NaBH_3CN$ reduction of the corresponding *p*-toluenesulfonyl hydrazide.[9] The latter methodology can also be used for the reduction of the corresponding ethyl ester leading to **4a**.[8] In order to circumvent using hydrazine derivatives, we decided to develop a new methodology for the transformation of **3** into licofelone which would be suitable for industrial application.

Our attempts at both electrophilic alkylation using Lewis acids ($BF_3{\cdot}Et_2O$, $MgBr_2$, $AlCl_3$) and nucleophilic alkylation (NaH, BuLi, LDA) of **3** with ethyl bromoacetate failed, as did initial attempts at radical alkylation with ethyl iodoacetate using AIBN and tributyltin hydride, tris(trimethylsilyl)silane or *N*-ethylpiperidine hypo-phosphite.

Surprisingly, we found that the reaction was successful using Fenton's reagent.[10,11] Fenton's reagent is a solution of hydrogen peroxide and a Fe^{2+} salt, typically ferrous sulfate. It is used as a powerful source of radicals and is often applied for hydroxylation of aromatic compounds,[12,13] including polycyclic aromatic compounds.[14] It can also be used for other reactions, for example, for the oxidation of barbituric acid to alloxane.[15]

Torssell et al.[16–20] discovered that Fenton's reagent in the presence of DMSO generates methyl radicals, which can, under suitable conditions, methylate reactive substrates, for example, quinones, nitroaromatic compounds, thiophene, furan, pyridine, and quinoline derivatives. Minisci et al.[21] and Baciocchi et al.[22–24] found that the methyl radicals formed from DMSO and Fenton's reagent in the presence of iodo derivatives generated the corresponding alkyl radicals, which alkylate effectively reactive pyrrole, indole, thiophene, or furan derivatives. This methodology was used for the

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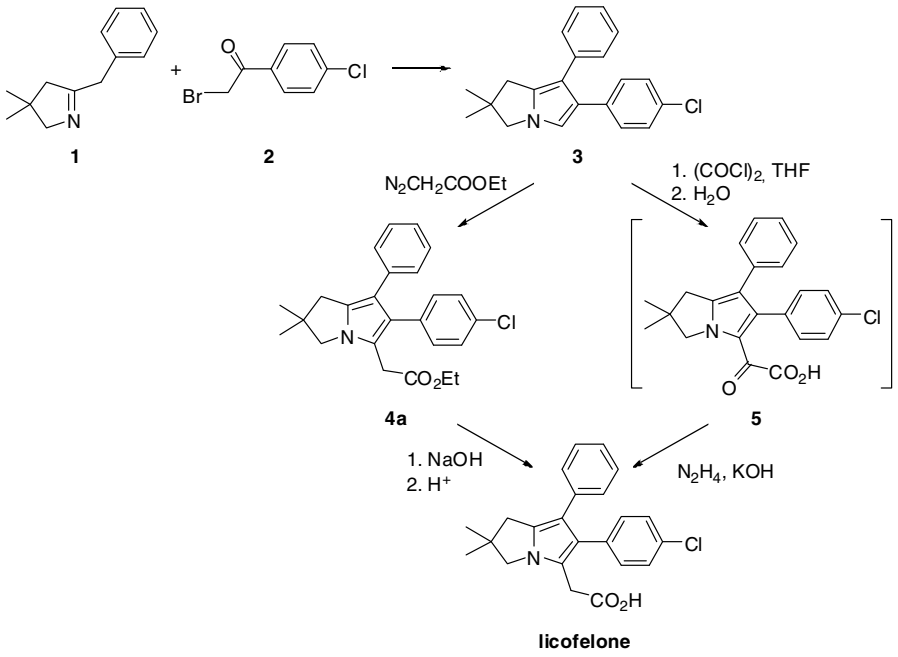
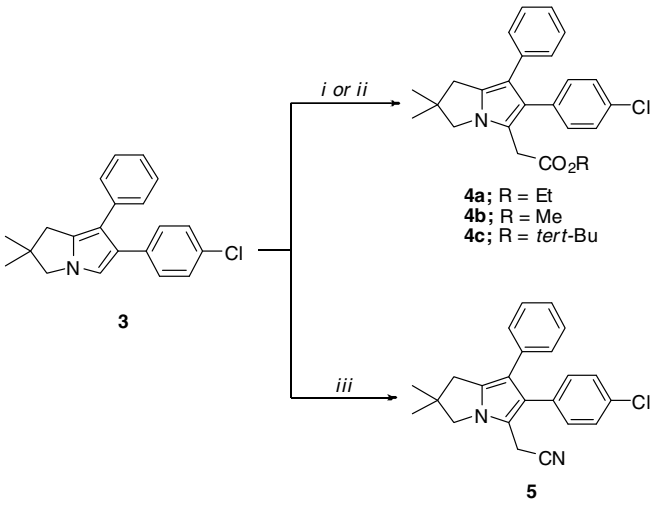


Scheme 1. Synthesis of licofelone.

alkylation of pyrrole, 1-methylpyrrole and, pyrrole-2-carboxylic acid with iodoacetonitrile, or methyl and ethyl iodoacetate.[22]

For our purposes, we reacted **3** with Fenton's reagent in combination with DMSO and ethyl iodoacetate to obtain a good yield of product **4a**. Though the best results were achieved with DMSO, the reaction also proceeded with other sulfoxides, for example, dibutyl sulfoxide, tetrahydrothiophene 1-oxide, methyldodecyl sulfoxide, and methylphenyl sulfoxide (thioanisole *S*-oxide). However, with these sulfoxides, the reaction rate was lower and incomplete conversion was often achieved. In the case of methylphenyl sulfoxide, its solution in acetonitrile or DMF was used and only low yields of **4a** were obtained both due to poor conversion and due to the formation of several minor by-products. We also tried to substitute DMSO with dimethyl sulfone and methylphenyl sulfone, but no reaction was observed. Therefore DMSO was used routinely for further optimization of the reaction.



Scheme 2. Radical alkylations of **3**. Reagents: (i) $FeSO_4/H_2O_2$, DMSO, ICH_2CO_2R; (ii) $FeSO_4/H_2O_2$, DMSO, NaI, $BrCH_2CO_2R$; (iii) $FeSO_4/H_2O_2$, DMSO, ICH_2CN.

Next we extended our study to the use of methyl and *tert*-butyl iodoacetate, as well as iodoacetonitrile with similar results obtained to those with ethyl iodoacetate (see Scheme 2 and Table 1).[25–27]

Esters **4a** and **4b** were saponified easily with aqueous NaOH or KOH at 60 °C within 1 h, while saponification of **4c** was slower requiring 10 h for complete conversion. However, good yields of licofelone were obtained from all esters **4**. Attempts to prepare licofelone by hydrolysis of nitrile **5** failed; even vigorous hydrolysis provided only moderate yields of the corresponding amide **6** instead. Its treatment with an ethanolic solution of hydrogen chloride provided a crude mixture containing mainly ester **4a** and hydrolysis of the mixture then gave licofelone (Scheme 3). Licofelone was found to be unstable and its quantitative decarboxylation was observed by NMR after 72 h in $CDCl_3$ at ambient temperature.

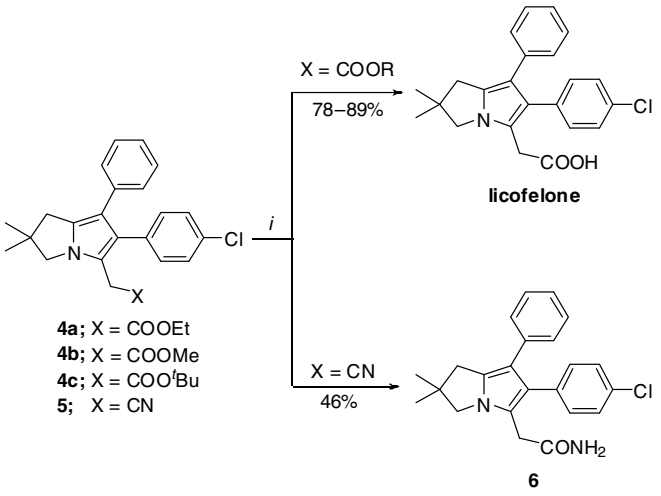
The starting iodo esters were either commercially available or prepared from the corresponding bromo derivative and NaI in acetone or acetonitrile. We found that though the bromoacetates were not effective in the radical reaction, it was possible to use them in the presence of NaI under similar conditions as the iodo analogs. This fact is interesting since the reaction is performed in the presence of relatively high amounts of water. Selected examples are given in Table 1.

All compounds were identified on the basis of analytical and spectral data (IR, UV, ^1H NMR, ^{13}C NMR, MS, HRMS).[28–33] For compounds **4a** and **5**, HMBC and HSQC NMR spectra were also studied.

Table 1
Radical alkylation of **3** using Fenton's reagent

Product	Reagent	Conditions[a]	Yield (%)
4a	ICH_2CO_2Et	DMSO	78
4a	$BrCH_2CO_2Et$	DMSO, NaI	75
4a	ICH_2CO_2Et	THTO,[b] MeCN	43
4a	ICH_2CO_2Et	PhS(O)Me, DMF	28
4b	$BrCH_2CO_2Me$	DMSO, NaI	57
4c	$BrCH_2CO_2Bu^t$	DMSO, MeCN, NaI	62
5	ICH_2CN	DMSO	65

[a] In all cases, Fe(II)SO_4 and 30% H_2O_2 were used.
[b] THTO—tetrahydrothiophene 1-oxide.



Scheme 3. Saponification of esters **4** and nitrile **5**. Reagents and conditions: (i) aqueous NaOH or KOH, MeOH or EtOH, 60–70 °C.

In summary, we have developed an efficient synthesis of licofelone, an anti-inflammatory drug currently undergoing phase-III clinical studies, based on Fenton-type radical alkylation of compound **3** with iodoacetonitrile or iodoacetates. The iodoacetates can be replaced by NaI and the corresponding bromoacetate.

Acknowledgments

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25. *General procedure for the preparation of compounds* **4** *using iodoacetates*: A solution of 30% aqueous hydrogen peroxide (15 mL) in DMSO (75 mL) was added dropwise over 20 min with cooling in a cold water bath (17–19 °C) to a stirred solution of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizine (**3**; 15.0 g, 46.6 mmol), the appropriate iodoacetate (56.1 mmol), and Fe(II)SO_4 heptahydrate (3.0 g) in DMSO (220 mL). After 1 h, the reaction mixture was diluted with brine (240 mL) and extracted with ethyl acetate (200 mL, 70 mL). The combined extracts were washed with aqueous 20% $Na_2S_2O_3$ (2 × 30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue was crystallized from ethanol to afford the desired product **4**.
26. *General procedure for the preparation of compounds* **4** *using bromoacetates*: To a stirred solution of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizine (**3**; 15 g, 46.6 mmol), the appropriate bromoacetate (55.7 mmol), NaI (9.45 g, 63.1 mmol), and Fe(II)SO_4 heptahydrate (3.0 g) in DMSO (375 mL) was added dropwise a solution of 30% aqueous hydrogen peroxide (15 mL) and DMSO (75 mL) over 20 min with cooling in a cold water bath (17–19 °C). After 1 h, the reaction mixture was diluted with brine (240 mL) and extracted with ethyl acetate (200 mL, 70 mL). The combined extracts were washed with aqueous 20% $Na_2S_2O_3$ (2 × 30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was crystallized from ethanol to give the desired product **4**.
27. *Preparation of 2-[6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl]acetonitrile* (**5**): To a stirred solution of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizine (**3**; 2.0 g, 6.21 mmol), iodoacetonitrile (1.5 g, 8.98 mmol), and Fe(II)SO_4 heptahydrate (0.8 g) in DMSO (50 mL) was added dropwise aqueous 30% hydrogen peroxide (4 mL) over 30 min with cooling in a cold water bath. After 4.5 h, the reaction mixture was diluted with brine (200 mL) and extracted with ether. The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from ethanol to afford 1.46 g (65%) of the desired product **5**.
28. *Data for compound* **4a**: mp 77–79 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.28 (t, *J* = 7.1, 2H, CH_2), 1.29 (s, 6H, 2 × CH_3), 2.85 (s, 2H, CH_2), 3.51 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 4.18 (q, *J* = 7.1, 2H, CH_2), 7.02–7.27 (m, 9H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.2, 28.0, 31.6, 40.5, 43.3, 58.4, 61.0, 114.8, 117.7, 123.6, 124.6, 128.0, 128.2, 128.2, 131.5, 131.6, 134.1, 134.7, 136.0, 170.8. IR (KBr): 1733 cm^{-1} (COO). UV (EtOH), λ_{max} (logε): 210 (4.45), 248 (4.34), 274 (4.10). HRMS *m*/*z* calcd for $C_{25}H_{27}ClNO_2$ (M+H) 408.17303, found 408.17255.
29. *Data for compound* **4b**: mp 166–168 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.29 (s, 6H, 2 × CH_3), 2.84 (s, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.72 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 7.02–7.27 (m, 9H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): 28.0, 31.3, 40.5, 43.3, 52.1, 58.8, 114.8, 117.5, 123.7, 124.7, 128.0, 128.2, 128.3, 131.6, 131.7, 134.2, 134.6, 135.9, 171.2. IR (KBr): 1734 cm^{-1} (COO). UV (EtOH), λ_{max} (logε): 208 (4.48), 246 (4.32). HRMS *m*/*z* calcd for $C_{24}H_{25}ClNO_2$ (M+H) 394.15738, found 394.15671.
30. *Data for compound* **4c**: mp 165–167 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.29 (s, 6H, 2 × CH_3), 1.46 (s, 9H, *t*-Bu), 2.84 (s, 2H, CH_2), 3.41 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 7.03–7.26 (m, 9H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): 28.1, 28.2, 33.0, 40.7, 43.5, 58.5, 81.3, 114.8, 118.5, 123.6, 124.7, 128.1, 128.3, 128.4, 131.7, 131.8, 134.1, 135.0, 136.3, 170.3. IR (KBr): 1726 cm^{-1} (COO). UV (EtOH), λ_{max} (logε): 206 (4.52), 248 (4.35), 276 (4.18). HRMS *m*/*z* calcd for $C_{27}H_{31}ClNO_2$ (M+H) 436.19651, found 436.20374.
31. *Data for compound* **5**: mp 144–146 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.33 (s, 6H, 2 × CH_3), 2.85 (s, 2H, CH_2), 3.62 (s, 2H, CH_2), 3.84 (s, 2H, CH_2), 7.00–7.31 (m, 9H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.5, 28.0, 40.4, 43.6, 58.3, 112.5, 115.4, 116.7, 124.2, 125.1, 128.1 (2 × CH_{Ar}), 128.7, 131.4, 132.3, 133.7, 135.2, 135.3. IR (KBr): 2245 cm^{-1} (CN). UV (EtOH), λ_{max} (logε): 208 (4.47), 246 (4.33). HRMS *m*/*z* calcd for $C_{23}H_{22}ClN_2$ (M+H) 361.14715, found 361.14664.
32. *Data for compound* **6**: mp 230–232 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.29 (s, 6H, 2 × CH_3), 2.85 (s, 2H, CH_2), 3.49 (s, 2H, CH_2), 3.71 (s, 2H, CH_2), 5.64 (br d, *J* = 61.5 Hz, 2H, $CONH_2$), 7.02–7.28 (m, 9H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): 27.9, 33.1, 40.6, 43.4, 58.1, 115.2, 118.5, 123.7, 124.9, 128.1 (2 × CH_{Ar}), 128.6, 131.3, 132.0, 134.4, 134.6, 135.6, 172.6. IR (KBr): 1654 cm^{-1} ($CONH_2$). UV (EtOH), λ_{max} (logε): 208 (4.50), 248 (4.33), 276 (4.17). HRMS *m*/*z* calcd for $C_{23}H_{24}ClN_2O$ (M+H) 379.15771, found 379.15744.
33. *Data for licofelone*: mp 156–157 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.29 (s, 6H, 2 × CH_3), 2.86 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 7.00–7.30 (m, 9H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): 28.0, 31.3, 40.5, 43.3, 58.4, 115.0, 116.7, 124.1, 124.8, 128.0, 128.1, 128.2, 128.4, 131.6, 131.8, 134.4, 135.8, 177.2. IR (KBr): 1721 cm^{-1} (COOH). UV (EtOH), λ_{max} (logε): 208 (4.49), 248 (4.33), 278 (4.17). HRMS *m*/*z* calcd for $C_{23}H_{23}ClNO_2$ (M+H) 380.14173, found 380.14117.