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# A Short Synthesis of Rigid 2-Alkylthio-2,2-Diaryl Substituted Acetic Acids

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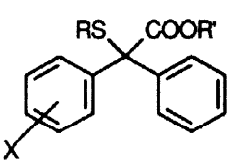
**Abstract:** The metalation of rigid diphenyl methane derivatives has been studied, aiming at the synthesis of 2-alkylthio-2,2-diaryl substituted acetic acids esters, a class of compounds with a potential antimuscarinic activity. Mixed metal bases have shown to be necessary in order to obtain the desired compounds with a good regiocontrol. 

The metalation of alkylarenes is a very useful synthetic tool often used to build important target molecules. [1] In order to produce a regioisomerically pure product, it is often required a careful choice of the organometallic base which is related to the structure of the substrate. Toluene [2] and ethyl benzene, [3] for instance, are easily deprotonated by the Schlosser's base [2] while the branched cumene requires trimethylsilylmethyl potassium [4] in order to be converted into the benzylmetallic derivative. 2- 3- and 4-Fluorotoluene undergo deprotonation on the benzylic position with the superbasic mixture butyllithium/ diisopropylamine/ potassium *tert*-butoxide (LIDAKOR[5-8]) whereas when treated the Schlosser's base they undergo ring metalation in the position *ortho* to fluorine. [9]

We have recently studied the metalation of fluoro- and methoxy-substituted diphenylmethane [10] finding that, in analogy to the Schlosser's report on the deprotonation of fluorotoluenes, [9] the superbasic mixture LIDAKOR is a very efficient reagent to effect the removal of the benzylic proton while the other organometallic reagents we have tested allow the ring deprotonation on the *ortho* position relative to the hetero substituent. The benzylic position has been also doubly deprotonated, thus allowing the preparation of a series of 2-ethylthio-2,2-diphenylacetic acids, the N,N-diethylaminoethyl esters of which are good muscarinic antagonists. [11,12]

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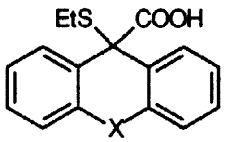
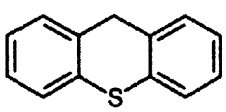
Both a chemical and a pharmacological interest induced us to study the behaviour of more rigid substrates towards the same reaction sequence. It is known in fact, that reduction of the conformational freedom of the phenyl rings of the diphenyl acetic acid esters with anticholinergic properties, usually affords potent muscarinic antagonists. [13] Therefore our attention was focused on target molecules of type **1**, having a rigid tricyclic structure with two phenyl ring fused to a five, six or seven membered ring.



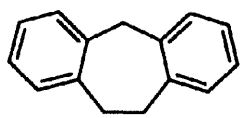

**1**

| | |
|---|---|
| X= none | a |
| O | b |
| S | c |
| $CH_2CH_2$ | d |
| CH=CH | e |

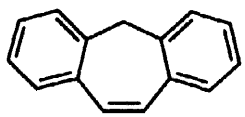
Thus thioxanthene **2c**, dibenzosuberane **2d** and dibenzosuberene **2e** were submitted to a double




**2c**

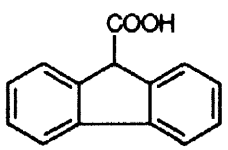


**2d**

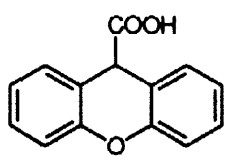


**2e**

metalation aiming at the sequential introduction on their benzylic position of a carboxyl and a thioethyl group. A monometalation approach was instead planned for the commercially available 9-fluorenecarboxylic acid **3a** and 9-xanthenecarboxylic acid **3b**.




**3a**

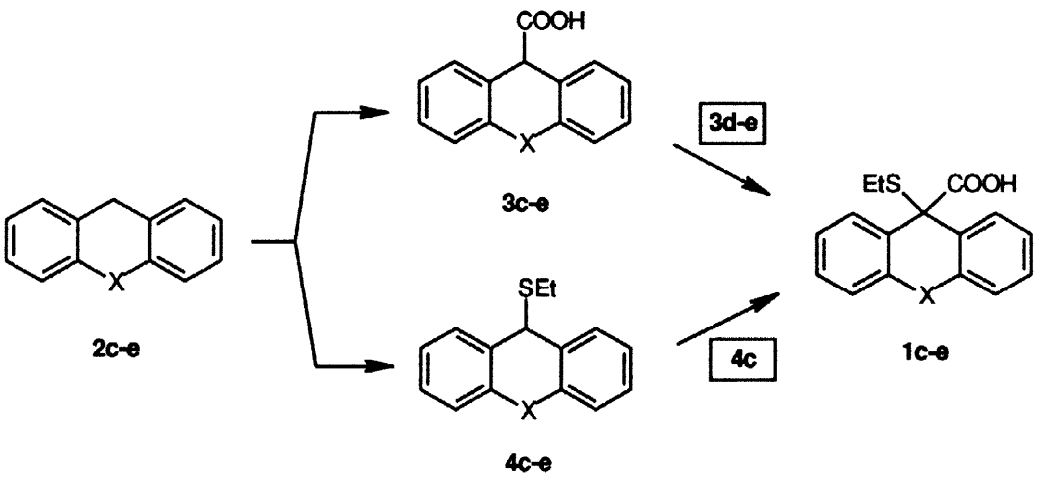



**3b**

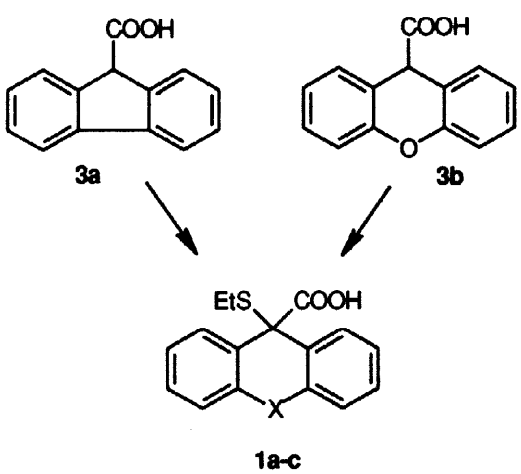
The best results in the deprotonation of both dibenzosuberane **2d** and its unsaturated analogue dibenzosuberene **2e** were obtained with the equimolar mixture lithium diisopropylamide/ potassium *tert*-butoxide (LIDAKOR), butyllithium alone [14] being less effective. The two carboxylic acids **3d** and **3e** were isolated after reaction with carbon dioxide in 84% and 80% yield resepctively. Reaction with diethyl disulfide or ethylthio phthalimmide afforded the two thioethyl derivatives **4d** and **4e** in 67% and 80% yield, respectively. Thioxanthene **2c** was easily monometalated even by butyllithium [15] alone in tetrahydrofuran at -78 °C affording both the carboxylic acid **3c** and the thioether **4c** in 64% and 98% yield, respectively, after reaction with carbon dioxide or diethyl disulfide.

Dimetalation of thioxanthene was easily accomplished by treating 9-thioethyl-thioxanthene **4c** with LIDAKOR in tetrahydrofuran at -50 °C, followed by quench with carbon dioxide. 9-Thioethyl-9-thioxanthenecarboxylic acid **1c** was thus obtained in a 74% overall yield. The reverse order double metalation approach did not work: 9-thioxanthenecarboxylic acid **3c** was not deprotonated under similar reaction

conditions. 5-Dibenzosuberane- and 5-dibenzosuberene-carboxylic acid (**3d** and **3e**) on the other hand, gave the difunctionalized products **1d** and **1e** in 57% and 86% yields respectively when treated with LIDAKOR in tetrahydrofuran at -50 °C followed by reaction with diethyl disulfide.




The commercially available compounds **3a** and **3b** were easily deprotonated by butyllithium alone and then thioalkylated in the benzylic position. The benzyllithium derivative of 9-xanthenecarboxylic acid, upon tretment with diethyl disulfide, gave 9-thioethyl-9-xanthenecarboxylic acid **1b** in a 54% yield, while, in order to obtain 9-thioethyl-9-fluorenylcarboxylic acid **1a**, ethylthio phthalimide had to be used as electrophile, leading to the desired product in 62% overall yield.




The thioethyl carboxylic acid esters thus obtained were tested for their antimuscarinic activity showing promising results. [16]

## EXPERIMENTAL SECTION

*General methods*

*Air and moisture sensitive compounds* were protected by and handled under an atmosphere of 99.99% pure nitrogen. *Ethereal extracts* were dried with sodium sulfate. Purifications by *flash column chromatography*[17] were performed using glass columns (10-50 mm wide); silica gel 230-400 mesh was chosen as the stationary phase (15 cm high), with an elution rate of 5 cm/min. *Nuclear magnetic resonance spectra* of hydrogen nuclei were recorded at 200 or 300 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Coupling constants (*J*) are measured in Hz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), m (multiplet), bs (broad singlet). *Nuclear magnetic resonance spectra* of carbon-13 nuclei were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). *Mass spectra* were obtained at a 70 eV ionization potential.

*Starting materials* were commercially available unless otherwise stated. All commercial reagents were used without further purification except *diisopropyl amine* which was distilled over calcium hydride. Anhydrous *tetrahydrofuran* was distilled from sodium diphenylketyl. *Petroleum ether*, unless specified, was the 40-70 °C boiling fraction.

*Metalation procedure with butyllithium*

The substrate (5.0 mmol) was dissolved in THF (3 mL) and cooled to -20 °C. Butyllithium in hexane (3.2 mL; 5.0 mmol) was then added and the mixture stirred for 30 min at -20 °C. The electrophile (6.0 mmol) was then added, the mixture warmed up to 25 °C and then treated with water (5 mL). The solution was then extracted with diethyl ether (3x5 mL) and the organic phase dried. The product was then purified by recristallization from hexane (carboxylic acids) or by column chromatography.

*Metalation procedure with LIDAKOR*

The solvent was stripped off from a solution of butyllithium in hexane (3.2 mL; 5.0 mmol). Precooled THF (5 mL) was added at -78 °C followed by diisopropylamine (0.5g, 5.0 mmol) and potassium *tert*-butoxide (5.0 mmol). The mixture was stirred for 30 min and the substrate (5.0 mmol) was added. After 3h at -78 °C, the electrophile (6.0 mmol) was added and the mixture warmed up to 25 °C and then treated with water (5 mL). The solution was then extracted with diethyl ether (3x5 mL) and the organic phase dried. The product was then purified by recristallization from hexane (carboxylic acids) or by column chromatography.

*Products*

9-Thioxanthenecarboxylic acid [15] **3c**: 64%; mp 225-226 °C; $^1$H-NMR: 7.4 (4H, m); 7.2 (4H, m); 5.02 (1H, s). 5-Dibenzosuberanecarboxylic acid [14] **3d**: 84%; mp 226-227 °C (lit. [14] 218-220 °C); $^1$H-NMR: 7.2 (8H, m); 4.80 (1H, s); 3.35 (2H, m); 2.88 (2H, m). 5-Dibenzosuberenecarboxylic acid [14] **3e**: 80%; mp 238-240 °C (lit. [14] 232-238 °C); $^1$H-NMR: 7.3 (8H, m); 6.96 (2H, s); 4.90 (1H, s). MS (*m/z* %): 236 ($M^+$, 27); 192 (36); 191 (100); 189 (87); 187 (14); 165 (34); 163 (17); 96 (17); 94 (12); 83 (20). 9-Thioethylthioxanthene **4c**: 98%; mp 127-129 °C; $^1$H-NMR: 7.4 (2H, m); 7.3 (6H, m); 5.29 (1H, s); 2.38 (2H, q, *J* 7.2); 1.21 (3H, t, *J* 7.2). 5-Thioethyldibenzosuberane **4d**: 67%; $^1$H-NMR: 7.2 (8H, m); 5.06 (1H, s); 3.81 (2H, m); 2.93 (2H, m); 2.40 (2H, q, J 7.2); 1.21 (3H, t, J 7.2). 5-Thioethyldibenzosuberene **4e**: 80%; $^1$H-NMR: 7.3 (8H, m); 7.00 (2H, s); 5.20 (1H, s); 2.26 (2H, q, *J* 7.4); 1.13 (3H, t, *J* 7.4). 9-Thioethyl-9-fluorenecarboxylic acid **1a**: 62%; mp 110-112 °C; $^1$H-NMR: 7.7 (4H, m); 7.4 (4H, m); 2.16 (2H, q, *J* 7.4); 0.93 (3H, t, *J* 7.4). MS (*m/z* %): 270 ($M^+$, 6); 226 (59); 209 (15); 197 (18); 181 (21); 180 (11); 166 (53); 165 (100); 163 (62); 152 (35). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.09; H, 5.22. Found: C, 71.03; H, 5.24. 9-Thioethyl-9-xanthenecarboxylic acid **1b**: 54%; mp 153-155 °C; $^1$H-NMR: 7.7 (2H, m); 7.3 (2H, m); 7.1 (4H, m); 2.03 (2H, q, *J* 7.4); 0.92 (3H, t, *J* 7.4). MS (*m/z* %): 241 (30); 225 (84); 212 (27); 197 (36); 182 (18); 181 (100); 168 (18); 152 (41); 151 (16); 139 (15); 91 (27); 57 (13). Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 67.03; H, 4.91. 9-Thioethyl-9-thioxanthenecarboxylic acid **1c**: 74%; mp 163-165 °C; $^1$H-NMR: 7.5 (2H, m); 7.4 (2H, m); 7.3 (4H, m); 2.29 (2H, q, *J* 7.1); 1.00 (3H, t, *J* 7.1). Anal. Calcd for $C_{16}H_{14}O_2S_2$: C, 63.55; H, 4.67. Found: C, 63.53; H, 4.715-Thioethyl-5-dibenzosuberane carboxylic acid **1d**: 57%; mp 168-169 °C; $^1$H-NMR: 7.53 (2H, d, *J* 7.3); 7.2 (6H, m); 3.24 (2H, m); 2.90 (2H, m); 2.33 (2H, q, *J* 7.4); 1.06 (3H, t, J 7.4). MS (*m/z* %): 296 ($M^+$, 5); 251 (7); 236 (17); 235 (100); 221 (26); 207 (23); 191 (55); 190 (18); 189 (54); 187 (16); 179 (15); 178 (64); 165 (15). Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08. Found: C, 72.43; H, 5.91. 5-Thioethyl-5-dibenzosuberene carboxylic acid **1e**: 86%; mp 175-177 °C; $^1$H-NMR: 7.85 (2H, d, *J* 7.3); 7.3 (6H, m); 7.07 (2H, s); 2.53 (2H, q, *J* 7.6); 1.32 (3H, t, *J* 7.6). MS (*m/z* %): 253 (4); 237 (48); 235 (27); 193 (57); 192 (39), 191 (100); 189 (47); 178 (45); 165 (22); 115 (17); 86 (19); 84 (27). Anal. Calcd for $C_{18}H_{16}O_2S$: C, 72.95; H, 5.44. Found: C, 72.98; H, 5.41

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