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Synthesis of 9-(5-Pentyl-2-furyl)nonanoic Acid

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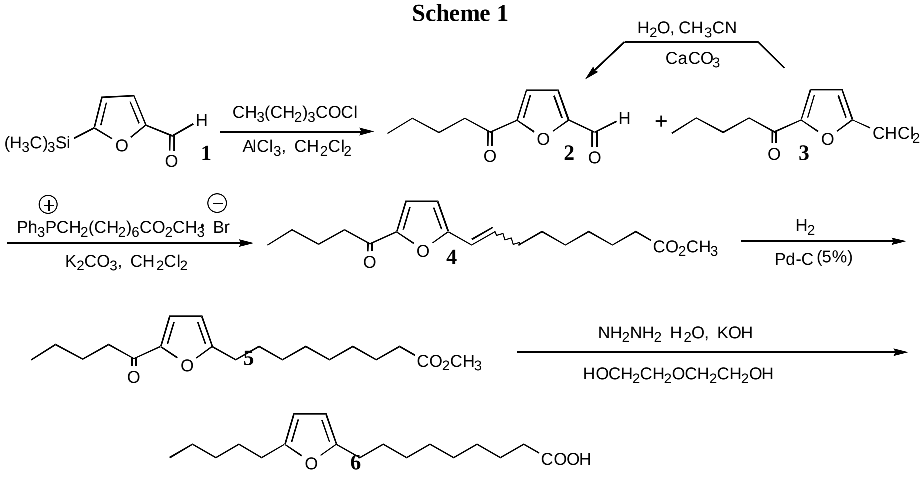
Abstract: Naturally occurring 9-(5-pentyl-2-furyl) nonanoic acid which was synthesized through five steps in about 20% overall yield by using 5-trimethylsilyl-2-furancarboxaldehyde as a starting material.

Keywords: 9-(5-pentyl-2-furyl) Nonanoic acid, furanoid fatty acid, acyldesilylation; synthesis.

Recently, several kinds of total synthetic methods for naturally occurring furanoid fatty acids (F-acids) which have many biological activities[1] have been developed[2]. In the present paper the authors wish to report a new simple route of synthesizing 9-(5-pentyl-2-furyl) nonanoic acid using 5-trimethylsilyl-2-furancarboxaldehyde **1** as a starting material which can be easily prepared from furfural by reported method[3]. The synthetic route having five steps includes acyldesilylation, hydrolysis, Wittg reaction, hydrogenation and Huang-Minlon reduction as shown in **scheme 1**.

Scheme 1



In the first step of acyldesilylation, **1** reacts with pentanoyl chloride in the presence of aluminum chloride in dichloromethane to give 5-pentanoyl-2-furancarboxaldehyde **2** and 5-dichloromethyl-2-pentanoylfuran **3** after chromatography in 8% and 83% yields, respectively[4]. Hydrolysis of **3** was carried out in a solution of acetonitrile-water (1:3) in the presence of calcium carbonate at 50℃ for 3 h. After usual work-up and recrystallization in petroleum ether, **2** was obtained as colorless needles (70% from **3**).

The intermediate methyl 9-(5-pentanoyl-2-furyl)-8-nonenoate **4** was obtained as a not evaluated mixture of E/Z stereoisomers by Wittig reaction between **2** and (7-carbomethoxyheptyl) triphenylphosphonium bromide in the presence of potassium carbonate and 1,2-butylene oxide in an unexpectedly low yield (34%), mainly due to the extremely unstable character of **2** in basic conditions, especially for strong base like sodium methoxide which gave rise to considerable resinification and other side reactions.

Selective hydrogenation of **4** in ethyl acetate at atmospheric pressure at 0℃ using 5% Pd-C as a catalyst afforded methyl 9-(5-pentanoyl-2-furyl) nonanoate **5** in high yield (91%), in which the further hydrogenated products were not found but they can be detected by GC-MS if the reaction was carried out at room temperature. ^{1}H-NMR spectrum of **5** shows clear two signals of the protons of furan ring (1H, d, δ=6.34 and 1H, d, δ=6.90) and no signals of olefin can be found comparing to the ^{1}H-NMR spectrum of **4**.

Finally, the desired target product **6** was obtained by Huang-Minlon reduction in excellent yield (95%), which structure has been confirmed by IR, ^{1}H-NMR and exact MS[4]. Thus, the 2,5-disubstituted F-acid **6** was successfully synthesized through five steps in about 20% overall yield. With this total synthetic method, we wish to synthesize a variety of disubstituted F-acids by using different acyl chlorides and (ω-alkoxycarbonylalkyl) triphenylphosphonium bromide. Further more, combined with the method reported by Lie Ken Jie *et al* [5] more recently this synthetic way can be applied to synthesizing various tetrasubstituted naturally occurring F-acids and their derivatives.

Referances and notes

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4. Spectral data for **6**: IR (KBr) 1715cm^{-1} (C=O); ^{1}H-NMR (CCl$_4$) δ 0.90 (3H, t, CH$_3$), 1.10～1. 82 (2H, m, CH$_2$), 2.18～2.62 (6H, m, CH$_2$), 5.68 (2H, s, F-3, F-4), 11.00 (1H, s, COOH); MS (m/z): 294 (M$^+$); Exact Mass Calcd. For $C_{18}H_{30}O_3$: 294.2185. Found: 294.2176.
5. M. S. F. Lie Ken Jie and K. P. Wong, *Lipids*, **1993**, *28*, 43.

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