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EFFECTIVE SYNTHESIS OF A CARBON-LINKED DIAZIRINYL FATTY ACID DERIVATIVE *VIA* REDUCTION OF THE CARBONYL GROUP TO METHYLENE WITH TRIETHYLSILANE AND TRIFLUOROACETIC ACID

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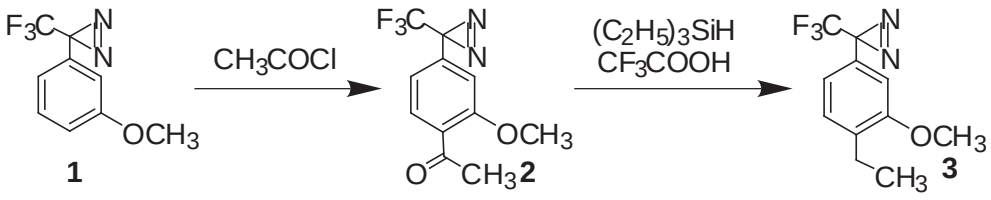
Abstract – Friedel-Crafts acylation of the aryldiazirine with ω-ester-α-acyl halide and successive reduction of the carbonyl group to methylene with triethylsilane and trifluoroacetic acid gave diazirinylated fatty acids.

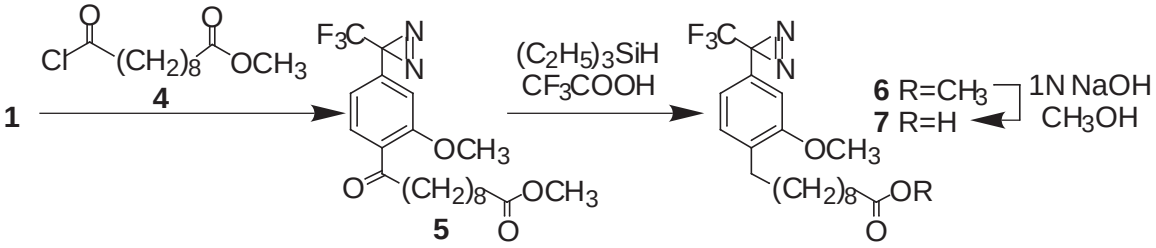
Photoaffinity labeling with the carbene generating precursor, 3-phenyl-3-trifluoromethyldiazirine, has become increasingly important as a photophor.[1] However, the complicated synthesis of the diazirinyl ring has resulted in fewer applications of the diazirines in biomolecular studies than other photophors. To resolve the problem, we have previously reported on the post-functional synthesis of a family of 3-phenyl-3-trifluoromethyldiazirines using the Friedel-Crafts reaction as a key step.[2] Synthesis of photoreactive fatty acid analogues presents a similar problem. Carbon-linked diazirinylated fatty acids are synthesized by introducing the fatty acid equivalents before the construction of the diazirinyl ring.[3] To avoid this complication, Friedel-Crafts acylation and successive reduction of carbonyl group to methylene are preferred. However, there is no report on the reduction of carbonyl group to hydrocarbon for diazirinyl compounds. In this paper we describe reduction of carbonyl group in a diazirinylaryl system to methylene with triethylsilane-trifluoroacetic acid and subsequent conversion to the diazirinylated fatty acids.



RESULTS AND DISCUSSION

Acylation of 3-(3-methoxyphenyl)-3-trifluoromethyl-3*H*-diazirine (**1**)[4] with acetyl chloride and $AlCl_3$ yielded the compound (**2**), NOE was observed between methoxy proton and methyl proton of the acetyl group. The result confirmed that the acetyl group was introduced at the 4-position of the compound. The acetophenone derivative (**2**) was subjected to several reduction methods, $LiAlH_4$-$AlCl_3$,[5] tosylhydrazine-$NaBH_3CN$[6] and Wolff-Kishner reduction.[7] However, all these reactions promoted decomposition of the diazirinyl ring. Triethylsilane in trifluoroacetic acid can reduce carbonyl group to methylene.[8] We used this reduction procedure to reduce compound (**2**) without the decomposition of diazirinyl ring.

The methylene derivative of the diazirinyl compound was then used to synthesize carbon-linked photoreactive fatty acids, with the photophor at the end, because the reduction is selective to arylcarbonyl groups.[8] The diazirine (**1**) was treated with fatty acid equivalent (methyl 10-chloro-10-oxodecanoate, (**4**) and titanium tetrachloride to produce the acylated product (**5**). The regioisomer, acylation at 6-position, was observed as less than 3% from NMR spectral studies. The carbonyl group of compound (**5**) was



reduced to methylene with triethylsilane in trifluoroacetic acid in 95% yield. The methyl ester (**6**) was hydrolyzed to produce a photoreactive fatty acid (**7**). In the synthetic route, w-ester-a-acyl halides[9], which have a various carbon chain length, can be converted to photoreactive fatty acid, without repetition of the diazirinyl ring constructions. We have already reported on the synthesis of phenoxydiazrine based fatty acid derivatives *via* alkylation of diazirinylated phenol and its biological properties.[10] Both of our synthetic routes for photoreactive fatty acids was based on post-functionalization of 3-phenyl-3-trifluoromethyldiazirine. The described procedure should promote the elucidation of the biofunctions of fatty acids and related biomolecules based on diazirinyl photoaffinity labeling.

EXPERIMENTALS

All ^1H NMR spectra was taken on a JEOL JNM-FX270 spectrometer. MS spectra were obtained on a Hitach M-80B spectrometer. All solvents were reagent grade and distilled from the appropriate methods.

3-(3-Methoxy-4-oxoethylphenyl)-3-trifluoromethyl-3*H*-diazirine (2).

3-(3-Methoxyphenyl)-3-trifluoromethyl-3*H*-diazirine (**1**) (1.13 g, 5.2 mmol) was dissolved in $CHCl_3$ (30 mL). $AlCl_3$ (0.788 g, 5.91 mmol) and acetyl chloride (0.8 mL, 11.3 mmol) were added successively. The reaction mixture was stirred at rt for 2 h, and quenched with cold water. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was subjected to chromatography on silica gel (ethyl acetate : hexane = 1 : 5) to obtain a pale yellow oil (1.26 g, 93%). EI-

MS *m/z*: 258 (M^+), 230 (M^+-N_2), ^{1}H-NMR ($CDCl_3$) 7.73 (1H, d, *J* = 7.8 Hz), 6.82 (1H, d, *J* = 7.8 Hz), 6.67 (1H, s), 3.91 (3H, s), 2.60 (3H, s). *Anal*. Calcd for $C_{11}H_9N_2O_2F_3$: C, 51.17; H, 3.51; N, 10.85. Found: C, 51.17; H, 3.53; N, 10.73.

3-(4-Ethyl-3-methoxyphenyl)-3-trifluoromethyl-3*H*-diazirine (3).

To a stirred solution of 3-(3-methoxy-4-oxoethylphenyl)-3-trifluoromethyl-3*H*-diazirine (**2**) (20.9 mg, 80.9 μ mol) in trifluoroacetic acid (0.07 mL) at rt was added triethylsilane (0.03 mL, 187.8 μ mol). After 1 h at rt, the reaction mixture was neutralized with saturated $NaHCO_3$. The reaction mixture was extracted three times with ether. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was subjected to chromatography on silica gel (CH_2Cl_2 : hexane = 1 : 5) to obtain a reduced compound as a colorless oil (18.9 mg, 96%). EI-MS *m/z*: 244 (M^+), 216 (M^+-N_2), ^{1}H-NMR ($CDCl_3$) 7.16 (1H, d, *J* = 7.9 Hz), 6.74 (1H, d, *J* = 7.9 Hz), 6.58 (1H, s), 3.82 (3H, s), 2.62 (2H, q, *J* = 7.6 Hz), 1.17 (3H, t, *J* = 7.6 Hz). *Anal*. Calcd for $C_{11}H_{11}N_2OF_3$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.13; H, 4.50; N, 11.40.

Methyl 10-[2-methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]-10-oxodecanoate (5).

Methyl 10-chloro-10-oxodecanoate (**4**) (0.7237 g, 3.08 mmol) and titanium chloride (0.5 mL, 4.56 mmol) were mixed at 0 °C. 3-(3-Methoxyphenyl)-3-trifluoromethyl-3*H*-diazirine (**1**) (0.430 g, 1.99 mmol) was added to the yellow reaction mixture. The reaction mixture was stirred at rt for 8 h, then poured into cold water and AcOEt. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered and concd. The residue was purified by chromatography on silica gel (AcOEt : hexane = 1 :4) to obtain a pale yellow oil (0.3574 g, 43%). EI-MS *m/z*: 414 (M^+), 386 (M^+-N_2), ^{1}H-NMR ($CDCl_3$) 7.62 (1H, d, *J* = 7.9 Hz), 6.80 (1H, d, *J*= 7.9 Hz), 6.64 (1H, s), 3.88 (3H, s), 3.64 (3H, s), 2.89 (2H, t, *J* = 7.3 Hz), 2.27 (2H, t, *J* = 7.3 Hz), 1.65-1.55 (m, 4H), 1.27 (m, 8H). *Anal*. Calcd for $C_{20}H_{25}N_2O_4F_3$: C, 57.96; H, 6.08; N, 6.76. Found: C, 57.80; H, 6.11; N, 6.62.

Methyl 10-[2-methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]decanoate (6).

To a stirred solution of **5** (0.1283 g, 0.31 mmol) in trifluoroacetic acid (0.25 mL, 3.25 mmol) at rt was added triethylsilane (0.12 mL, 0.75 mmol). The reaction mixture was stirred at rt for 10 min, then quenched with saturated $NaHCO_3$. The product was extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was applied to chromatography on silica gel (AcOEt : hexane = 1 : 6) to obtain a pale yellow oil (0.1178 g, 95%). EI-MS *m/z*: 400 (M^+), 372 (M^+-N_2), ^{1}H-NMR ($CDCl_3$) 7.12 (1H, d, *J* = 7.9 Hz), 6.72 (1H, d, *J* = 7.9 Hz), 6.57 (1H, s), 3.81 (3H, s), 3.66 (3H, s), 2.57 (2H, t, *J* = 7.6 Hz), 2.29 (2H, t, *J* = 7.6 Hz), 1.65-1.50 (m, 4H), 1.27 (m, 10H). *Anal*. Calcd for $C_{20}H_{27}N_2O_3F_3$: C, 59.99; H, 6.80; N, 7.00. Found: C, 59.91; H, 6.71; N, 6.96.

10-[2-Methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]decanoic acid (7).

Methyl ester (**6**, 12.8 mg, 32.0 mmol) was dissolved in methanol (1 mL), and sodium hydroxide solution

(1N, 0.2 mL) was added. The reaction mixture was stirred at rt for 2 h and concd *in vacuo*. The residue was made acid with 1N HCl and extracted twice with AcOEt. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered and concd. The residue was purified with chromatography on silica gel (AcOEt) to obtain a pale yellow oil (11.0 mg, 89%). EI-MS *m/z*: 386 (M^+), 358 (M^+-N_2), ^{1}H-NMR ($CDCl_3$) 7.12 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J*= 7.6 Hz), 6.56 (1H, s), 3.81 (3H, s), 2.57 (2H, t, *J* = 7.6 Hz), 2.34 (2H, t, *J* = 7.6 Hz), 1.65-1.55 (m, 4H), 1.27 (m, 10H). *Anal.* Calcd for $C_{19}H_{25}N_2O_3F_3$: C, 59.06; H, 6.52; N, 7.25. Found: C, 59.09; H, 6.55; N, 6.95.

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