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Trifluoromethyl Ketones from Carboxylic Acids. Part II[1]. A Versatile Access to Trifluoromethylated Heterocycles.

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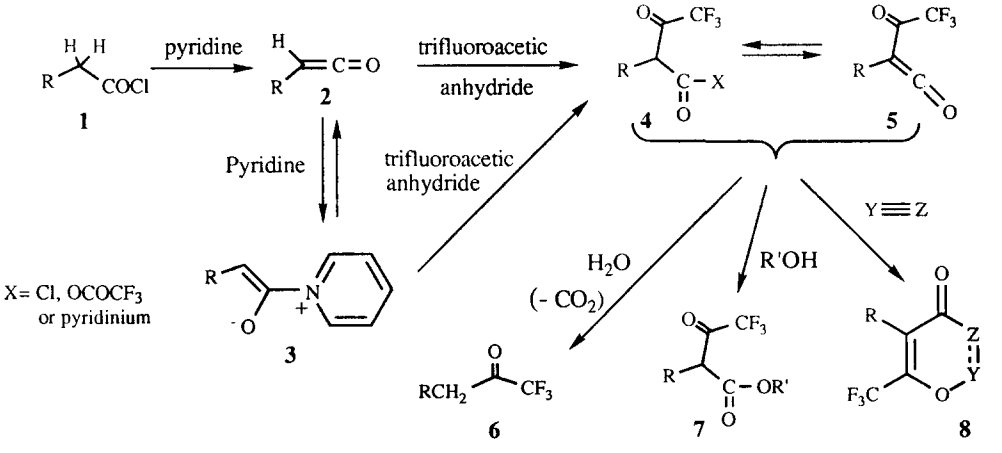
Abstract:: Various trifluoromethylated heterocycles can be prepared in good yield from carboxylic acid chlorides by reaction with pyridine and trifluoroacetic anhydride followed by capture of the intermediate trifluoroacyl ketene with suitable reagents..

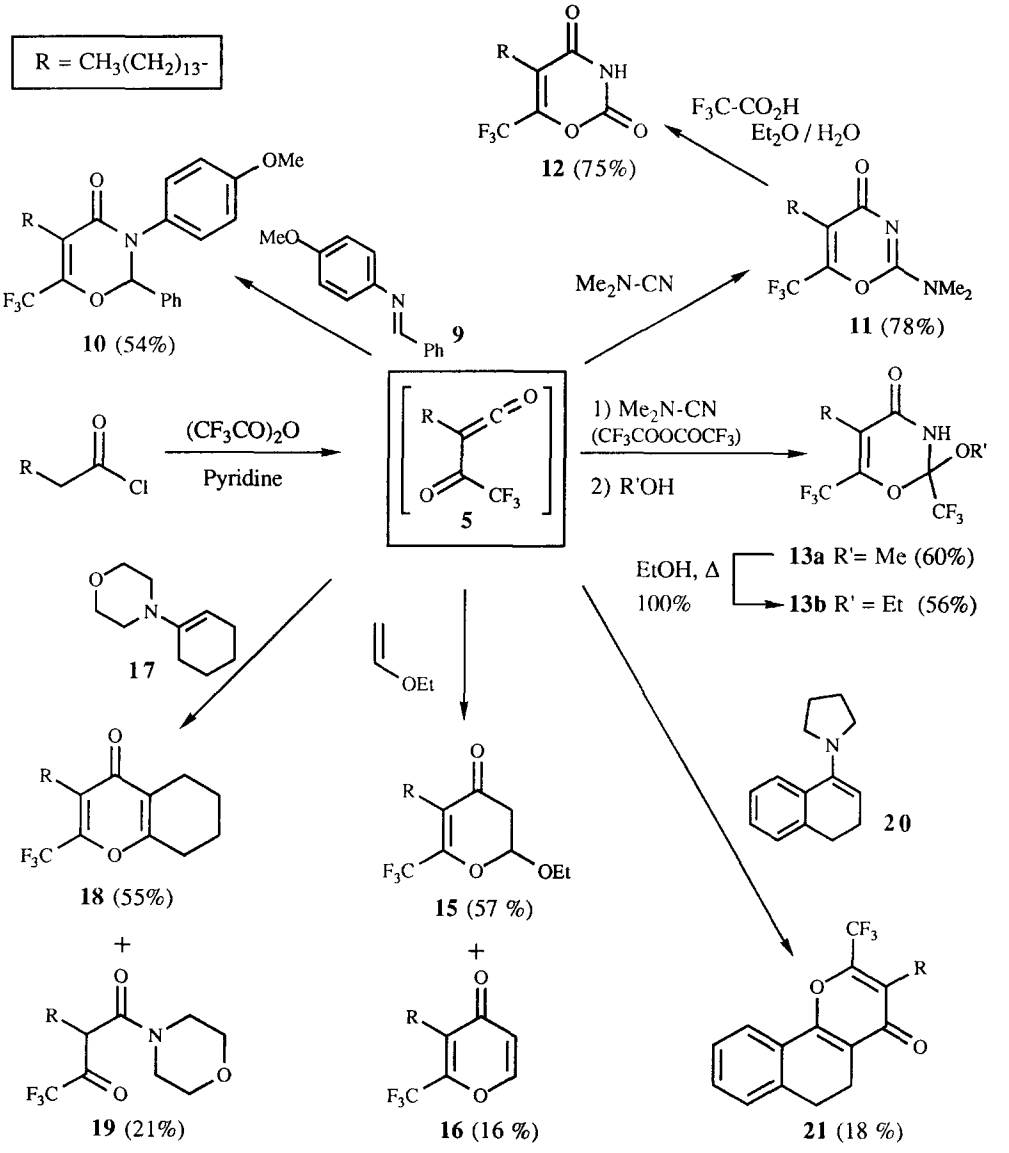
In the first part of this work,[1] we studied the synthesis of trifluoromethyl ketones and ketoesters starting from primary carboxylic acids by a novel method which relied on the acylation of the corresponding ketene derived from the acid chloride **1** by trifluoroacetic anhydride in the presence of pyridine. This reaction leads to an intermediate trifluoroacylketene **5** or its synthetic equivalent **4**, as outlined in scheme 1. Capture of this species by an alcohol provides a trifluoromethyl ketoester **7** whereas quenching with water leads to a keto acid which decarboxylates spontaneously to the trifluoromethyl ketone **6**. We now wish to report that various other reagents react with this key intermediate to give an array of trifluoromethylated heterocycles of general formula **8**. In view of the high demand for fluorine containing heterocyclic derivatives,[2] such compounds may prove interesting in their own right or act as springboards towards more elaborate substances.



Scheme 1

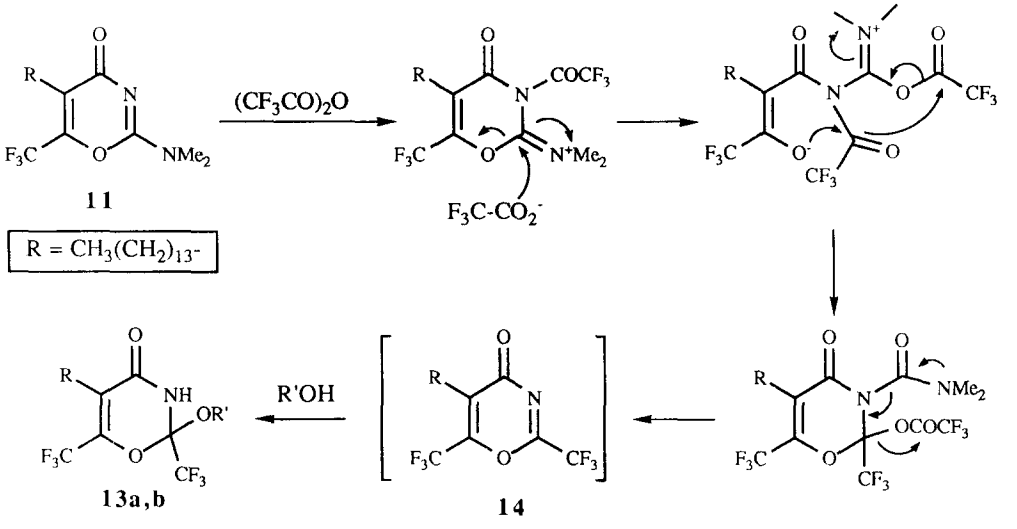
Acylketenes have previously been prepared by the Wolf rearrangement of α diazo-β-diketones,[3] by thermal decomposition of 2,2,6-trimethyl-4-H-1,3-dioxin-4-one,[4] or by dehydrohalogenation during

distillation of acyl chlorides derived from malonic acids.[5] In the absence of a suitable trap, acyl ketenes dimerise, but they can be intercepted in an inter or intramolecular manner, by alcohols, amines, etc.., and electron rich olefins.[6] In the latter case, the product can be viewed as resulting from a formal [4+2] cycloaddition,[7] in contrast to simple ketenes which usually yield products of a formal [2+2] cycloaddition.[8] The highly electrophilic chlorocarbonyl ketenes and perfluoroacyl ketenes also follow the same pattern of reactivity.[5,9]



Scheme 2

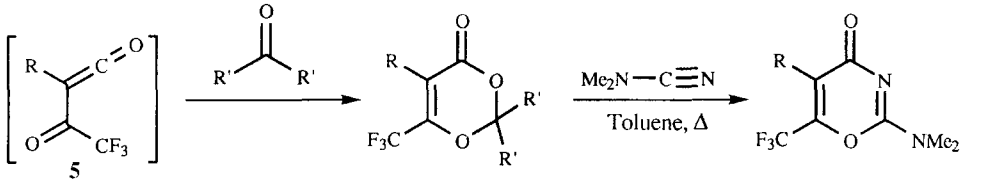
With a practical source of trifluoroacetyl ketenes **5** (or their betaine equivalents **4**) in hand, we set out to study their reactivity with various unsaturated molecules. In order to avoid unwanted side reactions with trifluoroacetic anhydride, we usually either used an excess of the trap, or eliminated the excess trifluoroacetic anhydride by dilution of the reaction mixture with anhydrous toluene followed by distillation of part of the solvent under reduced pressure, prior to addition of the trap (see experimental section). We first examined the reaction of imine **9**, prepared by condensation of benzaldehyde with p-anisidine. Addition to trifluoroacyl ketene **4a** derived from palmitoyl chloride **1a** occured readily affording compound **10** in 54% yield. Condensation with N,N-dimethylcyanamide[6d] was even more efficient, giving the corresponding **11** in 78% yield. The latter was converted easily into oxazinedione **12** by acidic hydrolysis. Interestingly, when the reaction with N,N-dimethylcyanamide was conducted *without* first eliminating the excess trifluoroacetic anhydride and quenched with methanol or ethanol, heterocycles **13a** and **13b**, incorporating two trifluoromethyl groups, were obtained respectively. This unexpected reaction may be rationalised by the mechanism depicted in Scheme 3. Compound **14** is a possible intermediate in this reaction, even though it could not be isolated, probably because of easy hydration. However, the fact that methoxy derivative **13a** can be converted into **13b** by simply heating it in ethanol for two days strongly supports this assumption.



Scheme 3

Ethyl vinyl ether reacted cleanly to yield a mixture of pyrones **15** (57%) and **16** (16%). The latter clearly arises from the former through β-elimination of ethanol. Enamines also produced pyrones. Thus, addition of enamine **17** to the intermediate from palmitoyl chloride gave pyrone **18** as the major product (55%), accompanied by amide **19** (21%). The latter arising from the reaction of the trifluoroacylketene intermediate with the morpholine released in the formation of **18**. Enamine **20**, derived from α-tetralone, underwent a sluggish reaction from which pyrone **21** could be isolated in poor yield (18%). A peri interaction between the pyrrolidine moiety and the aromatic hydrogen could result in a twisting of the former and, as a consequence of the poor overlap of the lone pair of the nitrogen with the π orbitals of the olefin, a decrease in the nucleophilicity of the olefin of the enamine[10].

In contrast to ethyl vinyl ether, reaction with 1-trimethysiloxycyclohexene in the presence of tributyl ammonium fluoride did not produce the expected pyrone but gave instead dioxinone **22** in 47% yield. A better way to such dioxinones is in fact to react the intermediate acylketene **5** with a ketone, a reaction that has been previously described with other acylketenes [6,7,9] (Scheme 4). Starting with palmitoyl chloride, treatment of reaction mixture the with acetone furnished **23** (72% yield), and **24** (66%) when the starting material was butanoyl chloride. In the case of acetyl chloride, the desired sequence was inefficient in our hands, and the rather unstable **25** was obtained in a poor 8% yield. As mentionned above, dioxinones decompose upon heating into acylketene and ketone, providing thus a convenient and relatively stable generator of the former, which can then be intercepted by various traps in the usual way. For example, simply boiling a mixture of dimethylcyanamide and **22** in toluene afforded **11** in 65% yield. Probably because of the higher volatility of acetone, the analogous reaction with dimethyldioxinone **24** was even more efficient since the expected compound **26** could now be isolated in essentially quantitative yield.



22, R=Me$(CH_2)_{13}$-; R'=-$(CH_2)_5$-
23, R=Me$(CH_2)_{13}$-; R'=Me
24, R=Et; R'=Me
25, R=H; R'=Me

11, R=Me$(CH_2)_{13}$-
26, R=Et

Scheme 4

In summary, the present procedure provides a simple and practical access to trifluoromethyl acyl ketenes which are useful precursors to a variety of heterocyclic derivatives containing a trifluoromethyl group. We have studied only a limited number of the possible partners against such reactive ketenes. Moreover, other perfluoro anhydrides which, like trifluoroacetic anhydride are highly electrophilic yet unable to produce a ketene in the presence of pyridine, could in principle be used to prepare heterocyles possessing longer perfluoroalkyl side chains.

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EXPERIMENTAL SECTION

All reactions were performed under an inert atmosphere (nitrogen or argon). Melting points were determined with a Köfler or a Reichert hot stage apparatus. ^1H and ^{13}C n.m.r.spectra are for deuteriochloroform solutions with tetramethylsilane as internal standard (δ ppm). Optical rotations are for chloroform solutions. I.R. spectra are of Nujol mulls unless otherwise stated. Mass spectra (electron impact) were recorded on MS 50 or VG ZAB spectrometers. MATREX 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

6-Trifluoromethyl-3-(4'-methoxyphenyl)-2-phenyl-5-tetradecyl-2H-1,3-oxazin-4-one (10). To a solution of trifluoroacetic anhydride (2.75 ml; 19.4 mmol) in anhydrous ether (25 ml) were added successively hexadecanoyl chloride (1 ml, 3.3 mmol.) and pyridine (2.1 ml; 25.8 mmol.). The reaction mixture was stirred at 20°C for 30 min. (formation of a white precipitate after ± 10 min.). Anhydrous

toluene (25 ml) was added. Ether and excess trifluoroacetic anhydride were removed by distillation under reduced pressure (20 mm Hg, 20°C). 4-Methoxy-N-benzylidene-aniline **9** [11] (0.70g, 3.3 mmol.) was then added to the reaction mixture which was then refluxed 2 hrs. The solvent was evaporated under reduced pressure and the residue taken-up in a mixture of ether-petroleum ether (50/50). The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (1.5 g) which was purified by silica gel chromatography [eluent dichloromethane/petroleum ether (25/75)] to give **10** (1.01 g; 54%) as a light yellow oil; IR (cm^{-1}), film: 2900, 2820, 1700, 1670, 1600, 1500, 1250, 1140, 730; n.m.r. ^1H : 7.5-7.35 (m, 5H); 7.25-7.15 (m, 2H); 6.78-6.88 (m, 2H); 6.60 (s, 1H); 3.75 (s, 3H); 2.65-2.48 (m, 2H); 2.35-2.19 (m, 2H); 1.26-1.14 (m, 22H); 0.87 (t, J = 6.1 Hz, 3H)); n.m.r. ^{13}C: 161.7; 158.2; 144.6 (q, J = 36 Hz); 135.6; 132.1; 129.9; 128.6; 127.4; 126.4; 119.8 (q, J = 275 Hz); 119.0; 114.3; 90.0; 77.8; 77.1; 76.5; 55.4; 32.0; 29.7; 29.5; 29.4; 29.3; 29.1; 23.8; 22.7; 14.1; M.S.: 545 (M^+); 265; 211; 196. (Calc. for $C_{32}H_{42}F_3NO_3$: C, 70.43 ; H, 7.76 %. Found: C: 70.42; H: 7.69 %).

6-Trifluoromethyl-2-dimethylamino-5-tetradecyl-1,3-oxazin-4-one (11). The same procedure as above was repeated except that dimethylcyanamide (0.40ml; 4.95 mmol) was used instead of the Schiff base. The reaction mixture was stirred for 10 hrs at room temperature. The solvent was evaporated under reduced pressure and the residue taken-up in pentane. The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (1.51 g) which was purified by silica gel chromatography [eluent dichloromethane/ ether (95/5)] to give **11** (1.05 g; 78%) as a white solid; m.p.: 57-58.5°C (petroleum ether); IR (cm^{-1}): 2900-2850, 1700, 1690, 1640-1560, 1390, 1310, 1150. (Nujol); n.m.r. ^1H: 3.19 (s, 3H); 3.13 (s, 3H); 2.56-2.45 (m, 2H),1.55-1.15 (m, 24H); 0.87 (t, J = 5.9 Hz, 3H); n.m.r. ^{13}C: 166.9; 156.6; 144,2 (q, J = 38 Hz); 121.7; 119.0 (q, J = 268 Hz); 37.4; 35.7; 31.7; 29.5; 29.2; 28.9; 23.8; 22.5; 13.9; M.S.: 404 (M^+); 335 (M^+ - CF_3); 249; 222. (Calc. for $C_{21}H_{35}F_3N_2O_2$: C, 62.34 ; H, 8.72 %. Found: C, 62.27; H, 8.77 %).

6-Trifluoromethyl-5-tetradecyl-1,3-oxazine-2,4-dione (12). Trifluoroacetic acid (1 ml) and water (10 ml) were added successively to a solution of 6-trifluoromethyl-2-dimethylamino-5-tetradecyl-1,3-oxazine-4-one **11** (200 mg.; 0.49 mmol) in ether (5 ml). The reaction mixture was stirred at 20°C for 4 days. Water (50 ml) was then added and the resulting mixture neutralized with sodium bicarbonate. Extraction with ether gave a crude residue (170 mg) which was purified by chromatography on silica gel [eluent ether/petroleum ether (10/90)] to give, besides some starting material (20 mg), oxazine dione **12** (140 mg; 75%, 84% based on consumed starting material) as a white solid; m.p.:60.5-62.5°C (ether/petroleum ether); IR (cm^{-1}): 3250, 2950, 2870, 1820, 1780, 1720, 1470, 1160. (Nujol); n.m.r. ^1H : 9,89 (s, 1H); 255-2,37 (m, 2H),1,55-1,105 (m, 24H); 0,83 (t, J = 5,9 Hz, 3H); n.m.r. ^{13}C: 162,4; 147,9(q, J = 38 Hz); 145,6; 118,8 (q, J = 275 Hz); 32,0; 29,8; 29,6; 29,2; 23,4; 22,8; 14,1; M.S.: 377 (M^+); 334 (M^+ - CNOH); 308 (M^+ - CF_3); 280; 265; 180. (Calc. for $C_{19}H_{30}F_3NO_3$: C, 60,46; H, 8,01 %. Found: C, 60,41; H, 7,97 %).

2,6-Di(trifluoromethyl)-6-methoxy-5-tetradecyl-2H-1,3-oxazin-4-one (13a). To a solution of trifluoroacetic anhydride (2.75 ml; 19.4 mmol) in anhydrous ether (30 ml) were added successively hexadecanoyl chloride (1 ml, 3.3 mmol.) and pyridine (2.1 ml; 25.8 mmol.). The reaction mixture was stirred at 20°C for 30 min. (formation of a white precipitate after about 10 min.). N,N-dimethylcyanamide (0.53 ml; 6.6 mmol) was added and stirring was continued for 12 hrs. The reaction mixture was cooled to 0°C and methanol (10 ml) was added. Extraction with ether, and chromatography of the crude residue over silica gel (eluent dichloromethane) gave oxazine **13a** (900 mg; 60%) as a colourless oil; IR (cm^{-1}), film: 3190, 3080, 2900, 2840, 1690, 1660, 1460, 1290,1200; n.m.r. ^1H : 8.19 (s, 1H); 3.54 (s, 3H); 2.50-2.35 (m, 2H); 1.26 (s, 24H); 0.88 (t, J = 6.7 Hz, 3H); n.m.r. ^{13}C: 163.3; 146.0 (q, J = 37 Hz); 120.1 (q, J = 289 Hz); 119.4 (q, J = 275 Hz); 113.9; 102.2 (q, J = 37 Hz); 51.0; 32.1; 29.8; 29.6; 29.5; 29.4; 23.0; 22.8; 14.2; M.S.: 461 (MH^+); 430 (M^+ - MeO); 492 (M^+ - CF_3); 360 (M^+- MeOH - CF_3); 334. (Calc. for $C_{21}H_{33}F_6NO_3$: C, 54.65; H, 7.21 %. Found: C, 54.82 ; H, 7.23 %).

2,6-Di(trifluoromethyl)-6-ethoxy-5-tetradecyl-2H-1,3-oxazin-4-one (13b). Replacement of methanol by ethanol in the above procedure gave compound **13b** (880 mg; 56%) as a colourless oil; IR (cm^{-1}), film: 3220, 3210, 2950, 2870, 1710, 1680, 1480, 1310,1200; n.m.r. ^1H : 8.39 (s, 1H); 3.93-3.80 (m, 2H); 2.50-2.35 (m, 2H); 1.45-1.20 (m, 24H); 0.89 (t, J = 6.7 Hz, 3H); n.m.r. ^{13}C: 163.3; 145.9 (q, J = 37 Hz); 120.1 (q, J = 289 Hz); 119.3 (q, J = 275 Hz); 113.7; 101.8 (q, J = 36 Hz); 60.2; 32.0; 29.7; 29.5; 29.4; 29.3; 29.2; 22.9; 22.7; 14.6; 14.0; M.S.: 476 (MH^+); 430 (M^+- EtO); 406 (M^+ - CF_3); 360 (M^+ - EtOH - CF_3); 334. (Calc. for $C_{22}H_{35}F_6NO_3$: C, 55.57; H, 7.42 %. Found C, 55.30; H, 7.63 %).

1,2-Dihydro-2-ethoxy-5-tetradecyl-6-trifluoromethyl-γ-pyrone (15) and 6-trifluoromethyl-5-tetradecyl-γ-pyrone (16) . The same procedure as above was repeated using ethyl vinyl ether (5ml; 52 mmol) instead of the Schiff base. The reaction mixture was stirred for 10 hrs. The solvent was evaporated under reduced pressure and the residue taken-up in a mixture of ether-pentane (50/50). The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (1.7 g) which was purified by silica gel chromatography [eluent ether/petroleum ether (90/10)] to give the major compound **15** (760 mg; 57%) as a colourless oil, followed by the more polar unsaturated pyrone **16** (190 mg; 16%) also as a colourless oil.

1,2-Dihydro-2-ethoxy-5-tetradecyl-6-trifluoromethyl-γ-pyrone (15) : IR (cm^{-1}), film: 3000-2860, 1710, 1650, 1470; n.m.r. ^1H : 5.42 (t, J = 3.8 Hz, 1H); 3.9-3.5 (m, 2H); 2.73 (q, J = 16.0 Hz), 2.71 (q, J = 16.3 Hz) (2H); 2.35-2.20 (m, 2H); 1.30-1.10 (m, 24H); 0.81 (t, J = 5.4 Hz, 3H); n.m.r. ^{13}C: 190.7; 149.9 (q, J = 35 Hz); 120.4 (q, J = 276); 101.4; 65.3; 42.5; 32.0; 29.7; 29.6; 29.4; 22.8; 22.7; 14.8; 14.1; M.S.: 406 (M^+); 361 (M^+ - EtO); 337 (M^+ - CF_3); 322; 279; 223. (Calc. for $C_{22}H_{37}F_3NO_3$: C, 65.00; H, 9.17%. Found: C, 64.85 ; H, 9.05 %).

6-trifluoromethyl-5-tetradecyl-γ-pyrone (16) : IR (cm^{-1}), film: 3000-2980, 1730, 1670, 1480, 1300, 1210, 1160; n.m.r. ^1H : 7.71 (d, J = 5.8 Hz, 1H); 6.36 (d, J = 5.8 Hz); 2.55-2.40 (m, 2H); 1.45-1.10 (m, 24H); 0.81 (t, J = 6.0 Hz, 3H); n.m.r. ^{13}C: 177.7; 148.8 (q, J = 37 Hz); 131.5; 119.6 (q, J = 275); 32.0; 29.7; 29.6; 29.4; 29.3; 28.9; 23.6; 22.7; 14.1; M.S.: 361 (MH^+); 291 (M^+ - CF_3); 205; 176. (Calc. for C, 66.64 ; H, 8.67%. Found: C, 66.82; H, 8.42 %).

4-Oxo-3-tetradecyl-5,6,7,8-tetrahydro-2-trifluoromethylchromene (18) and N-2-(2,2,2-trifluoro-1,1-dihydroxyethyl)hexadecanoyl morpholine (19). The same procedure as above was repeated using 1-morpholino-1-cyclohexene **17** (0.65 ml; 3.87 mmol) instead of the Schiff base. The reaction mixture was stirred for 2 hrs at 20°C, then refluxed for an additional hour. The solvent was evaporated under reduced pressure and the residue taken-up in pentane. The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (1.5 g) which was purified by silica gel chromatography [eluent dichloromethane/ ether (80/20)] to give **18** (750 mg.; 1.8 55%) as a colourless oil, followed by amide **19** (290 mg.; 21%) which was a white solid.

4-Oxo-3-tetradecyl-5,6,7,8-tetrahydro-2-trifluoromethylchromene (18): IR (cm^{-1}), film: 2950, 2880, 1680, 1650, 1640, 1300, 1210, 1160; n.m.r. ^1H : 2.65-2.42 (m, 5H); 1.9-1.65 (m, 3H); 1.5-1.15 (m, 26H); 0.88 (t, J = 5,9 Hz, 3H); n.m.r. ^{13}C: 178.0; 162.9; 147.4 (q, J = 37 Hz); 128.0; 122.5. 119.8 (q, J = 269 Hz); 32.0; 29.9; 29.7; 29.4; 29.3; 29.1; 27.3; 23.6; 22.7; 21.6; 21.3; 21.0; 14.1; M.S.: 414 (M^+); 445 (M^+ - CF_3); 260; 245; 232. (Calc. for $C_{24}H_{37}F_3O_2$: C, 69.53 ; H, 9.00 %. Found : C, 69.74 ; H, 8.89 %).

N-2-(2,2,2-trifluoro-1,1-dihydroxyethyl)hexadecanoyl morpholine (19): m.p.: 65-75°C; IR (cm^{-1}): 3450-3150, 3000-2960, 1625, 1475, 1390. (Nujol); n.m.r. ^1H : 4.1-3.1 (m, 8H); 2.4-1.5 (ms, 2.5H); 1.26 (s, 24H); 0.88 (t, J = 6.0 Hz, 3H); n.m.r. ^{13}C: 186.5 (q); 173.1; 166.1; 122.8 (q); 94.2 (q); 66.7; 66.5; 50.4; 46.6; 42.6; 41.6; 32.0; 29.7; 29.4; 27.7; 27.2; 22.7; 14.1; M.S. 422 (MH^+), 421 (M^+), 352 (M^+ - CF_3); 324 (M^+ - $COCF_3$); 294; 267; 238; 225; 114; H.R.M.S.: peak: $C_{20}H_{38}NO_2^+$, Calc.: 324.2902, Found: 324.2900.

Benz[h]-5,6-dihydro-4-oxo-3-tetradecyl-2-trifluoromethyl-4H-chromene (21). The same procedure as above was repeated using 1-(3,4-dihydro-2-naphtyl) pyrrolidine **20** (550mg; 2.76 mmol) instead of the Schiff base. The reaction mixture was stirred for 2 hrs at 20°C. Toluene (25 ml) was added to the mixture, and the solvents were evaporated under reduced pressure. The residue, taken-up in a mixture of pentane and ether (50/50), was filtered and the filtrate evaporated to dryness, affording a crude residue (1.9 g) which was purified by silica gel chromatography [eluent ether/petroleum ether: 5/95] to give **21** (270 mg; 18%) as a light yellow oil; IR (cm^{-1}), film: 2925, 2854, 1637, 1252, 2000, 1148; n.m.r. ^1H : 8.69 (d, J = 7.1 Hz, 1H); 7.31-7.12 (m, 3H); 3.12-2.92 (m, 2H); 2.88-2.79 (m, 2H); 2.70-2.55 (m, 2H); 1.60-1.15 (m, 24H); 0.88 (t, J = 5.1 Hz, 3H); n.m.r. ^{13}C: 175.8; 165.5; 146.4 (q, J = 37 Hz); 133.8; 130.7; 129.1; 128.1; 127.4; 126.9; 119.8 (q, J = 276); 118.9; 32.0; 30.0; 29.7; 29.4; 29.2; 27.6; 27.2; 23.9; 22.8; 14.2; M.S.: 462 (M^+); 393 (M^+ - CF_3); 280. (Calc. for $C_{28}H_{37}F_3O_2$: C, 72.70 ; H, 8.06%. Found: C, 72.22 ; H, 7.88%).

4-Oxo-2-spirocyclohexane-5-tetradecyl-6-trifluoromethyl-1,3-dioxine (22). The same procedure as above was repeated using 1-trimethylsilyloxy-1-cyclohexene (0.77ml; 3.95 mmol) instead of the Schiff base. The reaction mixture was stirred for 2 hrs. Tetrabutylammonium fluoride (1.15 ml, 1M solution in THF) was added to the reaction mixture. The solvent was evaporated under reduced pressure and the residue taken-up in pentane. The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (1.6 g) which was purified by silica gel chromatography [eluent dichloromethane/petroleum ether (30/70)] to give **22** (670 mg.; 47%) as a colourless oil; IR (cm^{-1}), film: 2950, 2880, 1760, 1670, 1410, 1210, 1160; n.m.r. ^1H : 2.47-2.32 (m, 2H); 2.15-2.02 (m, 2H); 2.95-1.80 (m, 2H); 1.80-1.20 (m, 26H); 0.85 (t, J = 5.9 Hz, 3H); n.m.r. ^{13}C: 160.9; 148.0 (q, J = 36 Hz); 119.5; 119.0 (q, J = 276 Hz); 113.1; 107.6; 33.5; 32.04; 29.8; 29.6; 29.5; 29.3; 24.5; 24.3; 22.8; 22.1; 14.2; M.S.: 432 (M^+); 413 (M^+ - F); 334 (M^+ - $C_6H_{10}O$); 239 ($CH_3(CH_2)_{13}CO^+$). (Calc. for $C_{24}H_{39}F_3O_3$: C, 66.64 ; H, 9.09%. Found: C, 66.89 ; H, 8.77 %).

2,2-Dimethyl-4-oxo-5-tetradecyl-6-trifluoromethyl-1,3-dioxin-4-one (23). To a solution of trifluoroacetic anhydride (2.75 ml; 19.5 mmol) in anhydrous ether (25 ml) were added successively hexadecanoyl chloride (1 ml, 3.3 mmol.) and pyridine (2.1 ml; 25.8 mmol.). The reaction mixture was stirred at 20°C for 30 min. Anhydrous acetone (10 ml) was added and the stirring maintained for 60 hrs. Toluene (50 ml) was added and the solvents were removed by distillation under reduced pressure. The residue was taken-up in a mixture of pentane and ether (80/20). The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (1.6 g) which was purified by silica gel chromatography [eluent ether/petroleum ether (20/80)] to give compound **23** (925 mg.; 72%) as a colourless oil; IR (cm^{-1}), film: 2950, 2880, 1760, 1670, 1410, 1210, 1160; n.m.r. ^1H : 2.47-2.36 (m, 2H); 1.71 (s, 6H); 1.55-1.20 (m, 26H); 0.88 (t, J = 6.7 Hz, 3H); n.m.r. ^{13}C: 160.8; 148.3 (q, J = 37 Hz); 119.3 (q, J = 276 Hz); 112.7; 106.9; 32.0; 29.7; 29.6; 29.4; 29.3; 24.6; 24.3; 22.7; 14.1; M.S.: 393 (MH^+); 334 (M^+ - CH_3COCH_3); 265; 208; 180. (Calc. for $C_{21}H_{35}F_3O_3$ C, 64.26 ; H, 8.99 %. Found : C, 64.49; H, 9.08 %).

2,2-Dimethyl-5-ethyl-6-trifluoromethyl-1,3-dioxin-4-one (24). To a solution of trifluoroacetic anhydride (7.5 ml; 53 mmol) in anhydrous ether (60 ml) were added successively butanoyl chloride (1 ml, 9.6 mmol.) and pyridine (6.26 ml; 77 mmol.). The reaction mixture was stirred at 20°C for 30 min. (meanwhile, a precipitate was formed). Anhydrous acetone (30 ml) was added, the precipitate went rapidly in solution and another precipitate was formed within one hour. The stirring maintained for 24 hrs. Ether and excess trifluoroacetic anhydride were removed by distillation under reduced pressure. The insoluble material was removed by filtration (3.7 g), washed with anhydrous ether. The filtrate was poured into an aqueous solution of citric acid (10 g in 200 ml). Extraction with dichloromethane afforded a crude residue (4 g) which was purified by silica gel chromatography [eluent dichloromethane/petroleum ether (40/60)]. to give dioxinone **25** (1.42 g.; 66%) as a colourless oil; IR (cm^{-1}), film: 3000, 2950, 2900, 1760, 1670, 1410, 1210, 1160, 890; n.m.r. ^1H : 2.55-2.40 (m, 2H); 1.73 (s, 6H); 1.12 (t, J = 7.4 Hz, 3H); n.m.r. ^{13}C: 160.5; 148.2 (q, J = 37 Hz); 119.2 (q, J = 275 Hz); 113.6; 106.9; 24.4; 17.6; 13.7. (Calc. for $C_9H_{11}F_3O_3$: C, 48.21; H, 4.95%. Found : C, 48:06 ; H, 4.87 %).

2,2-Dimethyl-6-trifluoromethyl-1,3-dioxin-4-one (25). To a solution of trifluoroacetic anhydride (5 ml; 35.4 mmol) in anhydrous acetone (40 ml) were added successively acetyl chloride (0.5 ml, 7.0 mmol.) and pyridine (4.6 ml; 56.6 mmol.). The reaction mixture heated violently upon addition of pyridine and turned to an orange colour. Stirring was maintained for 3 hrs. Toluene (50 ml) was added and the major part of the solvents was removed by distillation under reduced pressure. The reamining of the solution was taken-up in a mixture of ether/ petroleum ether (10/90). The insoluble material was removed by filtration and the filtrate evaporated to dryness, affording a crude residue (0.29 g) which was purified by silica gel chromatography [eluent ether/petroleum ether (20/80)] to give compound **25** (0.100 g, 8%) as a colourless oil, which proved to be unstable at room temperature and completely decomposed after 24 hrs; n.m.r. ^1H : 5.9 (s, 1H); 1.78 (s, 6H); n.m.r. ^{13}C: 158.7; 154.6 (q, J = 38 Hz); 118.2 (q, J = 301 Hz); 115.2; 96.9; 24.6.

6-Trifluoromethyl-2-dimethylamino-5-tetradecyl-1,3-oxazin-4-one (11). N,N-Dimethyl-cyanamide (0.075 ml; 0.93 mmol) was added to a solution of 4-oxo-2-spiro-cyclohexane-5-tetradecyl-6-trifluoromethyl-1,3-dioxine **23** (200 mg.; 0.46 mmol) in anhydrous toluene (10 ml). The reaction mixture was refluxed for 8 hrs. Evaporation of the solvent left a residue which was chromatographed over silica gel [eluent dichloromethane/ether (95/5)], thus yielding compound **11**(120 mg.; 65%), identical to the sample prepared above, and some starting material **23** (60 mg.).

6-Trifluoromethyl-2-dimethylamino-5-ethyl-1,3-oxazin-4-one (26). N,N-dimethylcyanamide (0.15 ml, 1.85 mmol.) was added to a solution of 2,2-dimethyl-4-oxo-5-ethyl-6-trifluoromethyl-1,3-dioxine **46**

(400 mg.; 1.78 mmol) in anhydrous (10 ml). The reaction mixture was refluxed for 3 hrs under inert atmosphere. N,N-dimethylcyanamide (0.05 ml, 0.62 mmol.) was added and reflux maintained for 2 additional hours.Toluene was removed by distillation under reduced pressure and excess dimethylcyanamide was eliminated by passing a stream of nitrogen. Compound **26** (423 mg; 100%) crystallised in the flask; m.p.: 48-50°C (petroleum ether); IR (cm^{-1}): 3000-2870, 1710, 1690, 1640-1560, 1390, 1310, 1150. (Nujol); n.m.r. ^{1}H : 3.20 (s, 3H); 3.16 (s, 3H); 2.56 (qd, J = 7.4Hz, J = 1.6Hz, 2H); 1.12 (t, J = 7.4 Hz, 3H); n.m.r. ^{13}C: 166.6; 156.4; 144.0 (q, J = 38 Hz); 122.4; 118.9 (q, J = 268 Hz); 37.1; 35.5; 17.1; 13.0; M.S.: 236 (M^+); 189; 167 (M^+ - CF_3); 114. (Calc. for $C_9H_{11}F_3N_2O_2$: C: 45.76 ; H: 4.70 ; N: 11.86, Found : C, 45.97; H, 4.68; N, 11.75%).

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