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Reactivity in [4+2] Cycloadditions of New 4-Trifluoromethyl-1,3-oxazin-6-ones: Access to Functionalized 2-Trifluoromethyl Pyridines

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Abstract. Recently discovered 4-trifluoromethyl-1,3-oxazin-6-ones react with electron-poor dienophiles as 2-aza-1,3-dienes in Diels-Alder cycloadditions to give new 2-trifluoromethyl pyridines (**3a – d, 4a – c**). Regioselectivity is excellent in the case of unsymmetrical dienophiles. These new pyridines permit further useful transformations.

In the previous publication [1], we described the synthesis of new 4-trifluoromethyl-1,3-oxazin-6-ones **1a – d** by cyclisation of ethyl 3-amino- and 3-acylamino-4,4,4-trifluorocrotonates with phosgeniminium chloride.

1,3-Oxazin-6-ones have a 2-aza-1,3-diene skeleton [2] useful for Diels-Alder cycloadditions [3]. 1,3-Oxazin-6-ones generally react easily with electron-rich dienophiles and when the electrophilic carbon C_2 carries a withdrawing group, e. g. CF_3, the reactivity is further increased. Conversely, more drastic conditions are necessary for cycloadditions with electron-poor dienophiles. These reactions with triple-bonds lead to pyridines after extrusion of carbon dioxide, but reactions with alkenes, imines and azirines are possible: dihydropyridines, dihydropyrimidines and 1,3-diazepines are then obtained [3].

In contrast to 4-methyl-2-trifluoromethyl-1,3-oxazin-6-one studied by W. Steglich et al. [3], 4-trifluormethyl-1,3-oxazin-6-ones **1a – d** react well with dimethyl acetylene dicarboxylate and ethyl propiolate, but no reaction was observed with other electron-poor dienophiles (1,4-naphthoquinone, N-phenylmaleimide, ethyl cyanoformate and 2-chloro acrylonitrile), or with neutral dienophiles (diphenyl acetylene) or electron-rich ones (1-morpholino cyclohexene, 1-tert butylthio-1-propyne).

The cycloadditions occur in refluxing o-xylene or chlorobenzene and lead to the corresponding pyridines **3a – d** and **4a – c**, via the not detected bicyclic intermediate **2**. Accordingly, carbon dioxide evolution is observed during the reaction (Scheme 1 and Table 1).

The regioselectivity of the reaction with ethyl propiolate can be easily rationalized by a polar mechanism, especially with 2-dialkylamino oxazinones **1a – c** according to Scheme 2.

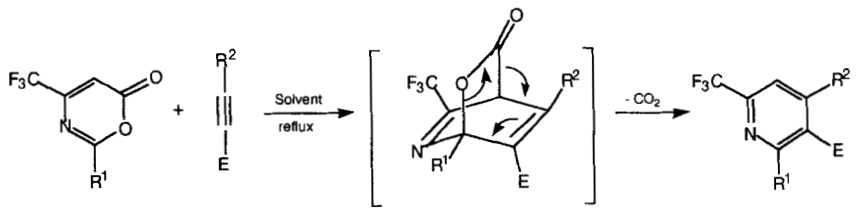
The ester function in these trifluoromethyl pyridines is useful for further reactions. Thus, we found that 3-carboethoxy-2-phenyl-6-trifluoromethyl pyridine **4c** leads almost quantitatively to the new 4-aza-3-trifluoromethyl fluorenone **7** via acid chloride **6** (Scheme 3).

Further, acid **5** permits the preparation of 3-amino-6-trifluoromethyl pyridine **10**, via the Curtius reaction in 81 % yield (Scheme 4).

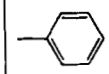
Pyridine diesters **3a – d** are interesting compounds because of their different chemoselectivity. When treated by only one equivalent of sodium hydroxide in refluxing aqueous methanol, pyridines **3a,c** lead selectively to monoacid esters **11a,c** in almost quantitative yield (Scheme 5).

The position of the acid function on the pyridine ring has been determined by the ^{13}C-NMR analysis of 3 bond carbon-proton coupling constants, by comparison with the values obtained in the case of pyridine diesters **3a,c**. The carbonyl in position 3 is not coupled with the pyridine 5-hydrogen (4 bonds), in contrast to the carbonyl in position 4 (3 bonds). In fact coupled ^{13}C-NMR spectra of **11a** and **c** for the carbonyl signal of the methyl ester present a quadruplet ($J = 4$ Hz), whereas that of the free acid present a doublet, splitted by the proton at C-5. The coupling constants of pyridines **11a,c**, and of pyridines **3a,c** are given in Table 2 for comparison. The quintet splitting of the C-1 signal of the last ones is due to the accidental equivalency of ^{3}J coupling constants.

The access to these selectively hydrolysed pyridine acid-esters **11a, c** allows their transformation into 4-



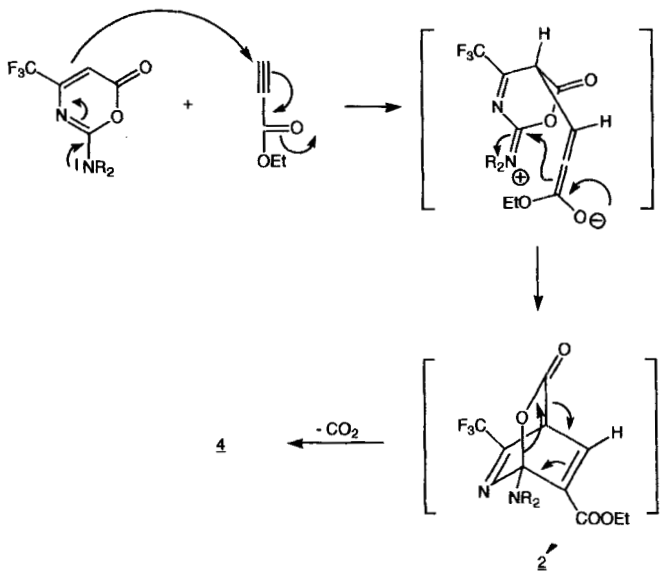
1a-d E = CO_2R^3 2 3a-d 4a-c

Entry	R^1	R^2	R^3	Solvent	Time (h)	Yield % a)	m.p.°C (hexane)	b.p.°C (Torr)
3a	—$N(CH_3)_2$	E	CH_3	xylene	5	85	72-73	-
4a		H	C_2H_5	chloro-benzene	3 days	48	-	120(0.1)
3b		E	CH_3	xylene	5	82	110-112	-
3c		E	CH_3	chloro-benzene	6	85	64-66	-
4b		H	C_2H_5	chloro-benzene	6 days	54	-	110(0.3)
3d		E	CH_3	chloro-benzene	7	51	110-112	-
4c		H	C_2H_5	xylene	2 days	68	-	200(0.3)
				chloro-benzene	7 days	96 b)	-	

a) all products are isolated and purified by chromatography on silicagel

b) this reaction was done in a sealed tube at 120°C during 7 days

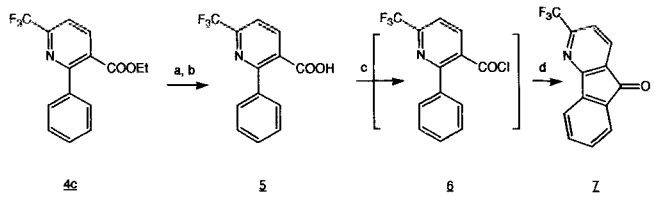
Schema 1



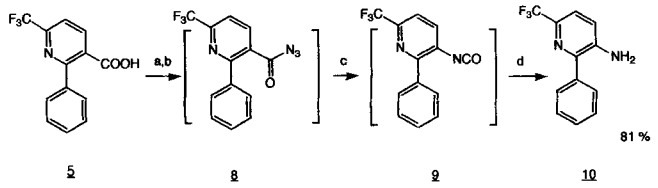
4 2

Schema 2

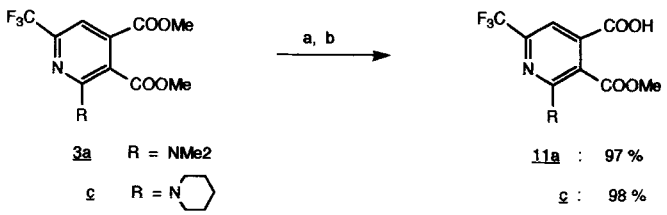
amino-3-esters via the Curtius rearrangement. Furthermore, acid **11a** has been transformed into 4-amino pyridine **12**, in an overall yield of 54%. The intermediate isocyanate **14** could also be reacted with N-methyl piperazine, giving the urea **15** in 79% yield. In this last case, the acylazide intermediate **13** has been isolated and purified by recrystallisation, which explains the increase in yields (Scheme 6).



Schema 3 Conditions and reagents: a) MeOH, H_2O, KOH, reflux 30 min; b) HCl, 2N, pH1 (yield of **5**: 98%); c) $SOCl_2$, benzene, reflux 15 min; d) $AlCl_3$ 1.3. eq., CH_2Cl_2, 20 °C, 1 h (94% from **5**)



Schema 4 Conditions and reagents: a) $SOCl_2$, benzene, reflux 15 min; b) NaN_3, acetone, H_2O, 0 °C, 1 h; c) benzene, reflux, 1 h; d) aqueous saturated Na_2CO_3, 20 °C, 1 h.



Schema 5 Conditions and reagents: a) NaOH 1 eq., MeOH, H_2O, reflux 30 min; b) HCl 6N, pH1, extraction with ether.

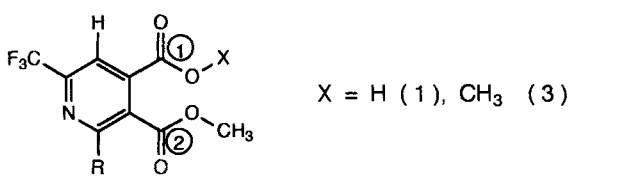
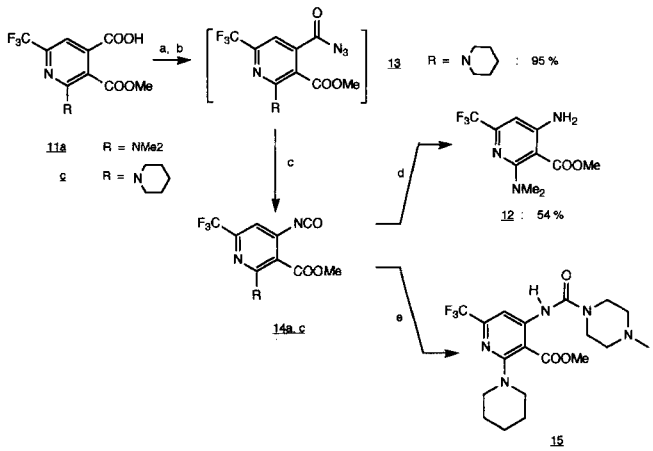


Table 1

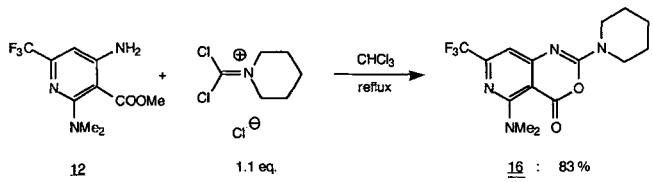
$^3J_{C-H}$ (Mult)	**3a**	**3c**	**11a**	**11c**
for C1	3.9 (quint)	4.0 (quint)	4.1 (d)	4.0 (d)
for C2	3.9 (q)	4.1 (q)	4.0 (q)	4.0 (q)

Pyridine amino-ester **12** undergoes a heterocyclisation with phosgeniminium chlorides [1] to form oxazinones. Thus, treatment of **12** with 1.1 equivalent of N-dichloromethylene piperidinium chloride in refluxing chloroform leads readily to 7-trifluoromethyl-[4,3 – d]-pyrido-3,1-oxazin-4-one **16** in excellent yield (83%), which is comparable to that obtained in an analogous reaction with ethyl 3-amino-4,4,4-trifluoro crotonate [1] (Scheme 7).

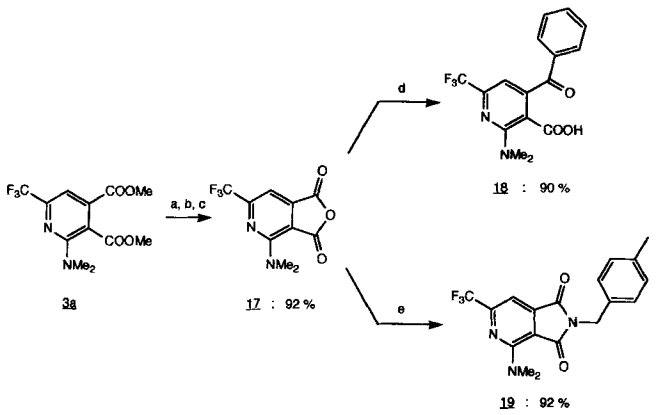
In analogy to the selective hydrolysis of diesters **3a**, the nucleophilic attack on anhydride **17** is also selective. Accordingly, the reaction of **17** with benzene and $AlCl_3$ leads to 4-benzoyl-3-carboxy pyridine **18**. However, when this anhydride **17** is heated with 4-methyl benzylamine, the imide **19** is isolated in 92% yield (Scheme 8).



Schema 6 Conditions and reagents: a) $SOCl_2$, 3 eq., benzene, reflux 2 – 3 h; b) NaN_3 1.3 eq., H_2O, acetone, 0 °C, 1.5 h; c) benzene, reflux 3 – 5 h (for **14a**) or toluene 100 °C, 1 – 5 h (for **14b**); d) aqueous saturated $NaHCO_3$, 20 °C, 1 h; e) methyl piperazine, toluene, 20 °C, 30 min.



Schema 7



Schema 8 Conditions and reagents: a) NaOH, 3 eq., MeOH, H_2O, reflux 30 min; b) HCl 6N, pH1; c) P_2O_5, benzene, reflux 1 h; d) benzene, $AlCl_3$ 2 eq., reflux 12 h; e) 4-methyl benzylamine, xylene, reflux 10 h

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Experimental

Melting points were taken in sealed tube using a Dr. Tottoli apparatus and are uncorrected. IR (ν_{max} in cm^{-1} and mass spectra were measured on a Perkin Elmer 1710 and a Finnigan Mat TSQ 70 apparatus, respectively. ^1H, ^{19}F and ^{13}C-NMR spectra were recorded in $CDCl_3$ solutions on a Varian VXR or Gemini 200 spectrometers using TMS as the internal reference for ^1H and ^{13}C spectra and $CFCl_3$ for ^{19}F spectra. Chemical shifts are expressed in ppm on the δ scale and coupling constants J are given in Hz. The following abbreviations are used s singlet, D,d doublet, T,t, triplet, Q,q quartet, quint quintet, sex sextet, sept septuplet and m multiplet, capitalized characters indicating one bond couplings.

Diels-Alder cycloadditions of 1,3-oxazin-6-ones (1 a – d) and (4 a – c)

General procedure
A few equivalents of the corresponding acetylene are added portionwise to a refluxing solution of 1,3-oxazin-6-one **1 a – d** in chlorobenzene or p-xylene, waiting every time for the end of the CO_2 evolution. After cooling and evaporation of the solvent (0.1 Torr), the residue is chromatographed on silicagel to give **3 a – d** or **4 a – c**.

3,4-Dicarbomethoxy-2-N,N-dimethylamino-6-trifluoromethyl pyridine **(3 a)**

5 Mmoles of oxazinone **1 a** (1.04 g) in 10 ml of xylene and 3 eq. of dimethyl acetylene dicarboxylate are refluxed for 5 h to give 1.3 g of a white solid (85 % yield). M.p. = 72 – 73 °C (Hex); IR: 2960, 1740, 1510, 1410, 1260, 1130, 1030; MS: 306 (M^+.), 291, 275, 259, 216, 188, 69; ^{19}F-NMR: – 69.7; ^1H-NMR: 3.10 (6H, s), 3.92 (6H, s), 7.25 (1H, s); ^{13}C-NMR: 39.8 (Q.q, 138.0/3.6), 52.7 (Q, 148.0), 107.6 (D.q, 174.0/^3J_F = 3.0), 116.8(S.d, 4.5), 122.2 (Q.d,^1J_F = 275.4/2.4), 141.7 (s), 147.7 (q,^2J_F = 35.0), 157.6 (sept, 2.4), 165.8 (quint, 3.9), 168.0 (q, 3.9); Anal. Calcd for $C_{12}H_{13}F_3N_2O_4$ (306.24): C 47.06; H 4.28; N 9.15; Found: C 47.09; H 4.31; N 9.20.

3-Carboethoxy-2-N,N-dimethylamino-6-trifluoromethyl pyridine **(4 a)**

6 Mmoles of oxazinone **1 a** (1.25 g) in 3 ml of chlorobenzene and 4 eq. of ethyl propiolate are refluxed for 3 days, to give 0.76 g of a colourless oil (48 % yield) and 0.6 g of unreacted oxazinone **1 a** (93 % corrected yield). B.p. = 120 °C (0.1 Torr); IR: 2960, 2920, 1710, 1580, 1500, 1400, 1340, 1300, 1250, 1170, 1100, 1050, 970; MS: 262 (M^+·), 233, 201, 174, 161, 146, 127, 69; ^{19}F-NMR: – 69.6 (s); ^1H-NMR: 1.36 (3H, t, 7.1), 3.04 (6H, s), 4.35 (2H, q, 7.1) 6.91 (1H, d, 7.7), 7.96 (1H, d.q. 7.7/^4J_F = 0.6); ^{13}C-NMR: (Q.t, 127.1/2.7), 39.8 (Q.q. 137.8/3.5), 60.9 (T. q, 147.8, 4.5), 107.0 (D.q.d, 170.8/^3J_F = 2.9/1.0), 114.0 (d.d, 6.2/1.2), 121.0 (Q.t, ^1J_F = 274.4/1.9), 141.0 (D.d, 165.0/1.6), 147.3 (q.d.d,^2J_F = 34.6/8.4/1.9), 157.4 (m), 166.2 (d.t, 5.0/3.1); Anal. Calcd for $C_{11}H_{13}F_3N_2O_2$ (262.23): C 50.38, H 5.00, N 10.68; Found: C 50.70, H 5.06, N 10.64.

3,4-Dicarbomethoxy-2-pyrrolidino-6-trifluoromethyl pyridine **(3 b)**

5 Mmoles of oxazinone **1 b** (1.17 g) in 1 ml of xylene and 3 eq. of dimethyl acetylene dicarboxylate are refluxed for 5 h to give 1.36 g of a white solid (82 % yield). M.p.: 110 – 112 °C (Hex); IR: 2940, 2880, 1725, 1580, 1555, 1445, 1380, 1280, 1250, 1230, 1110, 850; MS: 332 (M^+.), 317, 301, 285, 272, 251, 242, 223, 214, 186, 127, 69; ^{19}F-NMR: – 69.7 (s); ^1H-NMR: 1.94 (4H, m), 3.52 (4H, m), 3.91 (6H, s), 7.26 (1H, s); ^{13}-NMR: 25.1 (T.quint, 133.0/3.5), 48.2 (T.m, 144.3), 52.4 (Q, 147.6), 52.6 (Q, 148.1), 105 (D.q, 173.7/^3J_F = 3.0), 114.9 (d, 5.2), 120.8 (Q.d, ^1J_F = 274.6/2.3), 139.2 (s), 147.0 (q,^2J_F = 34.8), 153.7 (m), 164.9 (q.d, 4.0), 167.6 (q, 4.0); Anal. Calcd. for $C_{14}H_{15}F_3N_2O_4$ (332.28): C 50.61, H 4.55, N 8.43; Found: C 50.77, H 4.65, N 8.39.

3,4-Dicarbomethoxy-2-piperidino-6-trifluoromethyl pyridine **(3 c)**

15 mmoles of oxazinone **1 c** (3.72 g) in 10 ml of chlorobenzene and 3 eq. of dimethyl acetylene dicarboxylate are refluxed for 6 h to give 4.4 g of a yellow solid (85 % yield). M.p.: 64 – 66 °C (Hex); IR: 2930, 2840, 1730, 1560, 1430, 1240, 1120, 1060, 990, 940; MS: 346 (M^+.), 331, 315, 299, 282, 248, 220, 219, 164, 151, 112, 84, 83, 69; ^{19}F-NMR: – 69.6 (s); ^1H-NMR: 1.6 – 1.7 (6H, m), 3.45 (4H, m), 3.91 (6H, s), 7.35 (1H, s); ^{13}C-NMR: 23.8 (T.m, 128.6) 25.2 (T.m, 129.4), 49.2 (T.m, 137.7), 52.4 (Q, 148.2), 52.6 (Q, 148.6), 108.4 (D.q, 174.0/^3J_F = 3.0), 118.7 (d.q, 5.4/1.1), 120.7 (Q.d, ^1J_F = 275.3/2.3), 140.7 (s), 147.0 (q.d, ^2J_F = 35.1/1.4), 158.1 (quint, 2.5), 165.1 (quint, 4.0), 167.3 (q, 4.1); Anal. Calcd for $C_{15}H_{17}F_3N_2O_4$ (346.30): C 52.03, H 4.95, N 8.09; Found: C 51.92, H 4.89, N 7.99.

3-Carboethoxy-2-piperidino-6-trifluoromethyl pyridine **(4 b)**

15 mmoles of oxazinone **1 c** (3.72 g) in 7 ml of chlorobenzene and 5 eq. of ethyl propiolate are refluxed for 6 days to give

2.44 g of a pale yellow oil (54 % yield). B.p. = 110 °C (0.3 Torr); IR: 2920, 2840, 1705, 1580, 1480, 1430, 1340, 1300, 1230, 1170, 1130, 1000, 950; MS: 302 (M^+.), 273, 257, 227, 201, 146, 84, 69; ^{19}F-NMR: −69.6 (s); ^{1}H-NMR: 1.39 (3H, t, 7.2), 1.6 − 1.7) (6H, m), 3.43 (4H, m), 4.37 (3H, q, 7.2), 6.96 (1H, d, 7.7), 7.98 (1H, d, 7.7); ^{13}C-NMR: 13.5 (Q.t, 127.4/2.6), 24.0 (T.m, 129.2), 25.2 (T.m, 128.6), 49,3 (T.m, 137.9), 60.9 (T.q, 148.2/4.5), 108.2 (D.q.d, 171.3/^3J_F = 2.9/0.8), 115.8 (d.d, 6.4/1.1), 121.1 (Q.t,^1J_F = 275.4/1.8), 141.5 (D.d, 165.4/1.6), 147.7 (q.d.d,^2J_F = 34.5/8.6/1.9), 158.2 (d.m, 8.0), 166.7 (d.t, 4.9/3.2); Anal. Calcd. for $C_{14}H_{17}F_3N_2O_2$ (302.29): C 55.63, H 5.67, N 9.27; Found: C 55.53, H 5.74, N 9.27.

3,4-Dicarbomethoxy-2-phenyl-6-trifluoromethyl pyridine (**3 d**)

5 Mmoles of 2-phenyl oxazinone **1 d** in 10 ml of chlorobenzene and 3 eq. of dimethyl acetylene dicarboxylate are refluxed for 7 h to give 0.86 g of a white solid (51 % yield). M.p.: 110 − 112 °C (Hex); IR: 3105, 2985, 1800, 1750, 1600, 1460, 1380, 1280, 1200, 1100, 960; MS: 339 (M^+.), 324, 308, 276, 248, 223, 202, 154, 127, 105, 77, 69; ^{19}F-NMR: −68.6 (s); +1H-NMR: 3.80 (3H, s), 4.00 (3H, s), 7.45 − 7.55 (5H, m), 8.15 (1H, s); ^{13}C-NMR: 51.9 (Q, 148.1), 52.4 (Q, 148.7), 117.1 (D.q, 173.1/^3J_F = 2.9), 119.9 (Q.d, ^1J_F = 274.7/2.1), 127.5 (D.m, 161.0), 128.8 (D.t, 161.7/7.0), 130.1 (m), 136.3 (m), 137.2 (s), 147.9 (q.d,^2J_F = 35.7/1.2), 157.2 (t,3.8), 162.7 (q.t, 4.0), 166.1 (q,4.0); Anal. Calcd. for $C_{16}H_{12}F_3NO_4$ (339.27): C 56.64, H 3.57, N 4.13; Found: C 56.68, H 3.57, N 3.96.

3-Carboethoxy-2-phenyl-6-trifluoromethyl pyridine (**4 c**)

2.5 eq. of ethyl propiolate (2.5 ml) are added to a solution of 10 mmoles of 2-phenyl oxazinone **1 d** (2.4 g) in 6 ml of chlorobenzene placed in a 100 ml tube which is sealed under vacuum and warmed at 120 °C for 7 days. The resulting mixture is diluted with ether, filtered an evaporated. The residue is distilled at 200 °C (0.3 Torr) to give 2.85 g of a colourless oil (96 % yield). IR: 3000, 1760, 1580, 1460, 1340, 1280, 1180, 1120, 1050; MS: 295 (M^+.), 276, 266, 250, 246, 223, 202, 152, 127, 69; ^{19}F-NMR: −68.7 (s); ^{1}H-NMR: 1.06 (3H, t, 7.2), 4.19 (2H, q, 7.2), 7.4 (3H, m), 7.6 (2H, m), 7.71 (1H, d, 8.0), 8.23 (1H, d. q, 8.0/^4J_F = 0.7); ^{13}C-NMR: 12.9 (Q.t, 126.6/2.7), 61.4 (T.q, 148.6/4.5), 117.8 (D.q.d, 170.2/^3J_F = 2.3/2.4), 120.9 (Q.d.d, ^1J_F = 274.6/2.0/1.8), 127.8 (D.m, 161.0), 128.4 (D.m, 158.6), 128.9 (D.t, 161.5/7.4), 129.9 (m), 138.3 (d.d, 8.5/5.0), 139.0 (D.d, 168.3/1.5), 158.4 (t.d, 4.5/6.0), 166.7 (S.t.d, 3.2/4.4); Anal. Calcd for $C_{15}H_{12}F_3NO_2$ (295.26): C 61.02, H 4.10, N 4.74; Found: C 61.03, H 4.20, N 4.60.

Transformation of 3-Carboethoxy-2-phenyl-6-trifluoromethyl pyridine (**4 c**) *into 3-Carboxy-2-phenyl-6-trifluoromethyl pyridine* (**5**)

5 ml of aqueous potassium hydroxide (2N − 10 mmoles) are added to a solution of 3.1 mmoles of ester **4 c**, and the resulting mixture is refluxed for 30 min. After cooling, the aqueous solution is acidified to pH 1 and extracted with ether. After drying and evaporation of the organic layer, 0.8 g of a white solid is obtained (98 % yield). M.p.: 166 °C; MS: 267 (M^+.), 250, 246, 223, 202, 154, 127, 99, 69; ^{19}F-NMR: −68.6 (s); ^{1}H-NMR: 7.43 (3H, m), 7.65 (2H, m), 7.73 (1H, d, 8.0), 8.32 (1H, d.q, 8.0/^4J_F = 0.8), 10.2 (1H, s); Anal. Calcd for $C_{13}H_8F_3NO_2$ (267.20): C 58.44, H 3.02, N 5.24; Found: C 58.55, H 3.20, N 5.28.

4-Aza-3-trifluoromethyl fluorenone (**7**)

2 Eq. of thionyl chloride (0.22 ml) are added to a suspension of 1.5 mmoles of carboxylic acid **5** (0.4 g) in 5 ml of anhydrous benzene. The mixture is refluxed for 15 min (cessation of SO_2 and HCl evolution) and evaporated. The residue is diluted with 5 ml of anhydrous methylene chloride, and 1.3 eq. of aluminium chloride (260 mg) are added in three portions, under argon, at room temperature. The resulting dark red solution is stirred for 1 h and then hydrolysed with an aqueous saturated sodium bicarbonate solution. The crude solid, obtained after extraction with ether, drying and evaporation of the solvents, is recrystallized from hexane to give 0.35 g of white needles (94 % yield). M.p.: 103 °C (Hex); IR: 3060, 1720, 1605, 1405, 1320, 1270, 1130, 1110, 910, 860; MS: 249 (M^+.), 221, 180, 152, 125, 99, 75, 69; ^{19}F-NMR: −68.8 (s), ^{1}H-NMR: 7.52 (1H, m), 7.62 (1H, d, 7.6), 7.68 (1H, m), 7.79 (1H, m), 7.98 (1H, m) 8.04 (1H, d.q, 7.6/^4J_F = 0.6); ^{13}C-NMR: 120.1 (D.q.d, 172.4/^3J_F = 3.2/1.6), 121.2 (Q.d.d,^1J_F = 275.2/3.7/1.3), 121.7 (D.d.t, 166.5/7.7/1.3), 124.3 (D.d.t, 165.7/8.2/1.4), 130.3 (S), 131.8 (D.d, 164.2/7.1), 132.2 (D.d, 171.4/1.3), 134.8 (t.d.d, 6.6/3.8/1.5), 135.8 (D.d, 163.5/7.0), 142.4 (d.d, 8.0/1.5), 151.7 (q.d.d, ^2J_F = 34.3/6.8/1.8), 165.2 (t.m, 4.3), 190.0 (t.m, 3.0); Anal. Calcd for $C_{13}H_6F_3NO$ (249.19): C 62.66, H 2.43, N 5.62; Found: C 62.75, H 2.32, N 5.71.

3-Amino-2-phenyl-6-trifluoromethyl pyridine (**10**)

2 Eq. of thionyl chloride (0.22 ml) are added to a suspension of 1.5 mmoles of carboxylic acid **5** (0.4 g) in 5 ml of anhydrous benzene. The mixture is refluxed for 15 min and evaporated. The oily residue is diluted with 6 ml of acetone, and a solution of 1.7 eq. of sodium azide (170 mg) in 1 ml of water is added at 0° C. The resulting mixture is stirred for 1 h at 0° C, then diluted with cold water (10 ml) and extracted two times with ether. The organic layer is dried and evaporated to give 0.41 g of a white solid (yield of crude acyl azide **8**: 94 %). This acyl azide is dissolved in **5** ml of dry benzene and is refluxed for 30 min (cessation of N_2 evolution), cooled to room temperature and hydrolysed with 5 ml of aqueous saturated sodium carbonate. After 1 h stirring, the mixture is extracted with ether. The residue is chromatographed on silicagel to give 0.29 g of **10** as a white solid (81 % yield from acid **5**). This amine is stable in form of hydrochloride. M.p. (HCl salt): 170 − 175 °C (dec.); IR (HCl): 3200 − 2650, 2560, 1610, 1470, 1410, 1350, 1180, 1140, 850; MS (free amine): 274 (M^+.), 237, 217, 197, 167, 140, 109, 77,69; ^{19}F-NMR (HCl): −65.4 (s); ^{1}H-NMR (HCl): 762 (3 H, m), 7.71 (2 H, m), 7.91 (1 H, d, 8.6), 8.04 (1 H, d.q, 8.6/^4J_F = 0.6); $_{13}$C-NMR (HCl): 122.0 (Q.d.d,^1J_F = 272.7/2.0/1.0), 123.0 (D.q, 172.5/^3J_F = 3.1), 130.0 (2C, D.t.m, 163.0/8.0), 130.3 (2C, D.d.m, 162.6/5.1), 131.2 (D, 168.9), 131.7 (D.t.t, 161.8/7.1/1.4), 133.7 (t.t, 6.8/1.6), 138.6 (q.t, ^2J_F = 36.7/2.2), 139.8 (d, 7.5), 148.6 (m); Anal. Calcd for $C_{12}H_{10}ClF_3N_2$ (274.67): C 52.47, H 3.67, N 10.20; Found: C 52.32, H 3.75, N 10.15.

Transformations of pyridines 3a, c. Hydrolysis with only one equivalent of sodium hydroxide

General procedure
An aqueous solution of 1 eq. of sodium hydroxide is added to a methanolic solution of pyridine **3a, c**. The resulting mixture is refluxed for 30 min, and after cooling and acidification to pH 1 (HCl 6N), is extracted with ether: pure monoacid **11a, c** is obtained after evaporation of the ether solution as a pale yellow (for **11a**) or white (for **11c**) solid.

3-Carbomethoxy-4-carboxy-2-N,N-dimethylamino-6-trifluoromethyl pyridine (**11a**)
For 4 mmoles of **3a** (1.22 g) 2 ml of methanol, 8 ml of water and 4 mmoles of NaOH (0.16 g) are used to give 1.13 g of acid **11a** (97 % yield). M.p.: 162 °C; IR: 3200 – 25000, 1730, 1710, 1590, 1570, 1510, 1450, 1400, 1280, 1260, 1170, 1120, 1010, 860; MS: 292(M^+.), 261, 231, 187, 149, 97, 69; ^{19}F-NMR (CD_3OD): −68.8 (s); ^{1}H-NMR CD_3OD): 3.08 (6H, s), 3.88 (3H, s), 7.25 (1H, s); ^{13}C-NMR (CD_3OD): 40.5 (2C, Q.q, 138.0/3.6), 53.7 (Q, 146.0), 108.3 (D.q, 174.0/^3J_F = 3.0), 117.3 (d, 6.0), 122.7 (Q.d, ^1J_F = 275.0/2.3), 143.9 (s), 148.4 (q, ^2J_F = 35.0), 158.6 (s), 168.3 (d, 4.1), 171.5 (q, 4.1); Anal. Calcd for $C_{11}H_{11}F_3N_2O_4$ (292.21): C 45.22, H 3.78, N 9.59; Found C 45.13, H 3.57, N 9.53.

3-Carbomethoxy-4-carboxy-2-piperidino-6-trifluoromethyl pyridine (**11c**)
For 10.6 mmoles of **3c** (3.52 g) 5 ml of methanol, 20 ml of water and 11 mmoles of NaOH (0.45 g) are used to give 3.46 g of acid **11c** (98 % yield). M.p.: 131 °C; IR: 3400 – 2400, 1720, 1705, 1580, 1560, 1480, 1440, 1280, 1210, 1160, 1110; MS: 332 (M^+.), 300, 272, 257, 245, 231, 199, 173, 146, 84, 69; ^{19}F-NMR (CD_3OD): −69.0 (s); ^{1}H-NMR (CD_3OD): 25.2 (T.m, 131.0), 26.6 (2C, T.m, 128.1), 50.7 (2C, T.m, 137.3), 53.5 (Q, 148.2), 110.2 (D.q, 173.8/^3J_F = 3.0), 120.8 (d.q, 5.3/1.2), 122.5 (Q.d, ^1J_F = 274.6/2.3), 143.5 (s), 148.4 (q.d, ^2J_F = 35.1/1.5), 159.8 (quint, 2.1), 167.7 (d, 4.0), 169.5 (q, 4.0); Anal. Calcd for $C_{14}H_{15}F_3N_2O_4$ (332.28): C 50.61, H 4.55, N 8.43; Found: C 50.63, H 4.49, N 8.27.

Formations of amino or urea derivatives **12** *and* **15**.
4-Amino-3-carbomethoxy-2-N,N-dimethylamino-6-trifluoromethyl pyridine (**12**)
Thionyl chloride (1.7 ml) are added to a suspension of 7.5 mmoles of acid **11a** (2.19 g) in 15 ml of dry benzene. The mixture is refluxed for 2 h (cessation of gas evolution) and evaporated. The oily yellow residue is dissolved in 20 ml of acetone, and a solution of 1.3 eq. of sodium azide (0.6 g) in 2.5 ml of water is added with stirring at 0 °C. After 1 h at 0 °C, the mixture is diluted with 40 ml of cold water and extracted with ether. The organic layer is dried and evaporated to give 2.2 g of a yellow solid. This acyl azide is dissolved in 30 ml of dry benzene and is refluxed for 3.5 h (cessation of N_2 evolution), cooled to room temperature and hydrolysed with saturated aqueous sodium bicarbonate. After 1 h stirring, the mixture is extracted with ether, and the organic layer is washed with brine, dried and evaporated. The oily residue is quickly chromatographed on silicagel to give finally 1.07 g of a thick yellow oil (54 % yield). The free amine **12** is transformed into its hydrochloride. B.p.: 130 °C (0.3 Torr); M.p. (HCl salt): 165 °C (dec.); IR: 3450, 3350, 2930, 1680, 1600, 1550, 1510, 1400, 1270, 1170, 1120, 1060, 930; MS: 260 (M^+.), 248, 234, 232, 216, 189, 176, 162, 160, 141, 102, 69; ^{19}F-NMR: −70.5 (s); ^{1}H-NMR: 3.00 (6H, s), 3.88 (3 H, s), 5.8 (2H, broad s), 6.25 (1H, s); ^{13}C-NMR: 39.8 (Q.q, 137.8/3.7), 51.0 (Q, 147.8), 93.8 (q, 4.0), 97.5 (D. sex, 167.0/3.1/^3J_F = 3.1), 121.4 (Q.d, ^1J_F = 275.2/2.7), 146.8 (q, ^2J_F = 33.7), 156.7 (s), 160.9 (sept, 3.0), 168.6 (q, 4.0); Anal. Calcd for 40.08, H 4.37, N 14.02; Found: C 40.08, H 4.28, N 13.77.

3-Carbomethoxy-4-(N-methylpiperazin)carboxamido-2-piperidino-6-trifluoromethyl pyridine (**15**)
The previous procedure is applied to prepare the acyl azide **13** from acid **11c** (12.2 mmoles): the crude yellow solid obtained is recrystallized from hexane to give the pure acyl azide **13** in 95 % yield. M.p.: 80 °C (dec.); IR: 2990, 2820, 2130, 1730, 1695, 1560, 1440, 1230, 1185, 1130, 1025, 965, 940; MS: 357 (M^+.), 312, 268, 242, 215, 188, 84, 69; Anal. Calcd for $C_{14}H_{14}F_3N_5O_3$ (357.29): C 47.06, H 3.95, N 19.60; Found: C 47.12, H 4.09, N 19.75.

3.9 mmoles of acyl azide **13** (1.4 g) are dissolved in 20 ml of dry toluene and the solution is refluxed for 1.5 h; after cooling at room temperature, 1.1 eq. of N-methyl piperazine (0.38 ml) are added and the solution is stirred for 30 min. The solvent is evaporated to dryness to give a white solid which is recrystallized in hexane: 1.39 g of urea **15** are finally obtained (79 % yield from **11c**). M.p.: 133 – 134 °C; IR: 3300, 2930, 2840, 1680, 1585, 1430, 1250, 1020, 840; MS: 429 (M^+.), 414, 370, 314, 270, 242, 188, 162, 101, 84, 70; ^{19}F-NMR (CD_3OD): −70.0 (s); ^{1}H-NMR (CD_3OD): 1.64 (6H, m), 2.36 (3H, s), 2.52 (4H, t, 4.8), 3.43 (4H, m), 3.60 (4H, t, 4.8), 3.93 (3H, s), 6.54 (1H, s) 8.05 (1H, broad s); ^{13}C-NMR (CD_3OD): 24.9 (T.m, 129.5), 26.3 (2C, T.m, 128.4), 44.0 (2C, T.m, 139.7) 46.0 (Q.m, 134.6), 50.5 (2C, T.m, 136.9), 52.8 (Q, 148.4), 54.9 (2C, T.m, 133.0), 98.4 (d, 4.6), 100.2 (D.q, 176.5/^3J_F = 3.5), 122.0 (Q.d, ^1J_F = 275.3/2.6), 148.9 (q.d, ^2J_F = 34.2/1.1), 151.7 (d, 1.8), 154.3 (quint, 2.2), 161.1 (quint, 2.9), 170.8 (q, 4.0); Anal. Calcd for $C_{19}H_{26}F_3N_5O_3$ (429.44): C 53.15, H 6.10, N 16.31; Found: C 53.92, H 6.06, N 16.31.

4H-5-N,N-Dimethylamino-2-piperidino-7-trifluoromethyl-[4,3 – d]-pyrido-3,1-oxazin-4-one (**16**)
A solution of 2.4 mmoles of the 4-amino pyridine **12** (obtained from 0.73 g of hydrochloride) in 3 ml of dry chloroform is added dropwise at room temperature to a stirred suspension of 1.1 eq. of N-dichloromethylene piperidinium chloride (0.51 g) in 3 ml of the same solvent. The mixture is refluxed until the end of HCl evolution and, after cooling, it is washed with aqueous sodium bicarbonate, then with brine. The crude yellow solid obtained after drying and evaporation of the solution is recrystallized from hexane to give 0.68 g of **16** as a white solid (83 % yield). M.p.: 164 – 165 °C; IR: 2940, 2830, 1740, 1615, 1550, 1390, 1270, 1240, 1160, 1085, 940; Ms: 342 (M^+.), 327, 313, 258, 242, 202, 187, 84, 69, 58; ^{19}F-NMR: −70.5 (s); ^{1}H-NMR: 1.7 (6H, m), 3.12 (6H, s), 3.72 (4H, m), 6.70 (1H, s); ^{13}C-NMR: 23.7 (T.m, 129.6), 25.3 (2C, T.m, 127.7), 41.1 (Q.q, 138.7/3.6), 45.0 (2C, T.m, 142.3), 93.9 (d, 4.3), 104.5 (D.q, 171.5/^3J_F = 3.0), 121.1 (Q.d, ^1J_F = 275.8/2.6), 150.5 (q.d, ^2J_F = 34.2/1.5), 155.7 (m), 155.8 (d, 2.9), 160.9 (quint, 3.0), 162.6 (s); Anal. Calcd for $C_{15}H_{17}F_3N_4O_2$ (342.32): C 52.63, H 5.01, N 16.37; Found: C 52.70, H 5.01, N 16.40.

4-N,N-Dimethylamino-1,3-dioxo-6-trifluoromethyl-furano-[3,4-c]-pyridine (**17**)

A mixture of 7 mmoles of pyridine **3a** (2.14 g) and 3 eq. of sodium hydroxide (0.84 g) in 10 ml of water and 7 ml of methanol is refluxed for 30 min. After cooling, the alkaline solution is acidified to pH 1 (HCl 6 N) and extracted with ether. The pale yellow solid obtained after drying and evaporation of the organic solution (1.96 g) is suspended in 10 ml of dry benzene and 4 eq. of phosphorus hemipentoxide (2 g) are added. The mixture is refluxed for 1 h and, after cooling, decanted. The solid is washed several times with ether, and the organic layers are added and evaporated. The orange solid obtained is recrystallized from hexane to give 1.67 g of the anhydride **17** (92 % yield) as orange needles. M.p.: 92 °C; IR: 2950, 1850, 1790, 1625, 1590, 1430, 1280, 1225, 1140, 930, 760; MS: 260 (M^+.), 216, 187, 141, 119, 92, 69; ^{19}F-NMR: −69.9 (s); ^{1}H-NMR: 3.44 (6H, s), 7.33 (1H, s); ^{13}C-NMR: 40.6 (Q.m, 138.0), 102.5 (D.q, 179.0/^3J_F = 2.5), 107.1 (d, 4.5), 12.01 (Q.d, ^1J_F = 276.0/2.2), 145.1 (s), 153.6 (q.d, ^2J_F = 36.0/1.8), 155.7 (m), 161.1 (s), 161.4 (d, 3.9); Anal. Calcd for $C_{10}H_7F_3N_2O_3$ (260.17): C 46.17, H 2.71, N 10.77; Found: C 46.14, H 2.78, N 10.75.

4-Benzoyl-3-carboxy-2-N,N-dimethylamino-6-trifluoromethyl pyridine (**18**)

A mixture of 2 mmoles of anhydride **17** (0.52 g) and 2 eq. of aluminium trichloride in 4 ml of dry benzene is refluxed for 12 h. After cooling and dilution with 5 ml of ether, it is extracted three times with 2N sodium hydroxide. The alkaline aqueous layer is acidified and extracted with ether to give a brown amorphous solid (0.61 g; 90 % yield). M.p.: 120 °C; IR: 3350, 2950, 1775, 1610, 1505, 1415, 1290, 1170, 1120, 1060, 960, 880, 770; MS: 338 (M^+.), 321, 294, 293, 277, 249, 244, 217, 172, 144, 77, 75, 69; ^{19}F-NMR: −69.6 (s); ^{1}H-NMR: 3.22 (6H, s), 5.60 (1H, broad s), 6.90 (1H, s), 7.3 − 7.4 (3H, m), 7.49 (2H, m); ^{13}C-NMR: 40.4 (Q.q, 138.7/2.8), 102.1 (D.q, 174.0/^3J_F = 2.0), 104.2 (m), 104.8 (S.d, 3.7), 120.7 (Q.d, ^1J_F = 286.2/2.0), 125.4 (2C, D.m. 160.0), 128.8 (2C, D.m, 161.0), 129.6 (D.t, 162.0/7.0), 137.3 (m), 151.5 (q.d, ^2J_F = 35.1/1.6), 156.5 (m), 165.7 (t, 1.5), 167.8 (s); Anal. Calcd for $C_{16}H_{13}F_3N_2O_3$ (338.28): C 56.81, H 3.87, N 8.28; Found: C 56.92, H 3.96, N 8.19.

4-N,N-Dimethylamino(-1,3-dioxo-2N'-p-methylbenzyl-6-trifluoromethyl-pyrrolo)[3,4-c]-pyridine (**19**)

A solution of 2 mmoles of anhydride **17** (0.52 g) and 2.5 mmoles of p-methyl benzylamine in 5 ml of xylene is refluxed for 10 h. After evaporation in vacuum, the residue is recrystallized from hexane to give 0.64 g of the imide **19** as yellow needles (92 % yield). M.p.: 137 °C; IR: 3090, 2950, 1710, 1620, 1590, 1440, 1280, 1130, 770; MS: 363 (M^+.), 348, 334, 258, 230, 216, 190, 161, 105, 77, 69; ^{19}F-NMR: −69.7 (s); ^{1}H-NMR: 2.31 (3H, s), 3.34 (6H, s), 4.77 (2H, s), 7.13 (2H, d, 8.0), 7.28 (1H, s), 7.29 (2H, d, 8.0); ^{13}C-NMR: 21.1 (Q.t, 126.4/3.1), 40.8 Q.q, 139.9/4.1), 41.7 (T.t, 140.9/4.6), 101.9 (D.q, 176.0/^3J_F = 2.4), 108.7 (d, 4.7), 120.6 (Q, ^1J_F = 275.6), 128.6 (2C, D.q, 158.6/5.2), 129.4 (2C, D. qt, 158.6/5.2), 133.2 (m), 137.7 (m), 146.1 (s), 152.1 (q, ^2J_F = 35.3), 155.1 (m), 165.9 (d, 5.2), 167.1 (m); Anal. Calcd for $C_{18}H_{16}F_3N_3O_2$ (363.33) C 59.50, H 4.44, N 11.56; Found: C 59.47, H 4.32, N 11.49.

References

[1] M.-A. Decock-Plancquaert, F. Evariste, N. Guillot, Z. Janousek, C. Maliverney, R. Merényi, H.G. Viehe, Bull. Soc. Chim. Belg. **101** (1992) 313

[2] D.L. Boger, Tetrahedron **39** (1983) 2869

[3] a) W. Steglich, R. Jeschke, E. Buschbaum, Gazz. Chim. Ital. **116** (1986) 361; b) W. Steglich, E. Buschbaum, O. Hollitzer, Angew. Chem. Int. Ed. **13** (1974) 533; c) E. Buschbaum, W. Steglich, Angew. Chem., Int. Ed. **13** (1974) 484; d) G. Höfle, O. Hollitzer, W. Steglich, Angew. Chem., Int. Ed. **11** (1972) 720; e) O. Hollitzer, W. Steglich, Angew. Chem., Int. Ed. **12** (1973) 197

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