# Improved Syntheses of Cyanuric Fluoride and Carboxylic Acid Fluorides

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*Dedicated to Prof. Dr. H. Vorbrüggen on the Occasion of his 70th Birthday*

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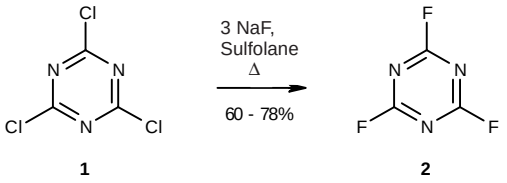
**Abstract.** Cyanuric fluoride (**2**) is one of the most popular fluorinating agents in organic chemistry. The title compound could be prepared in a 50 to 100 g scale by means of a chlorine fluorine exchange, the process was characterized by a simple preparation procedure, cheap reactants and a low time exposure. Carboxylic acids were converted into the corresponding acid fluorides **4a**–**g** using cyanuric fluoride. A non-aqueous work-up led to high yields on synthesizing a range of functionalized acid fluorides.

Carboxylic acid fluorides are widely used in organic syntheses. On the one hand they serve as efficient activated acyl compounds in peptide couplings, the amide bond is formed without any $\alpha$-epimerization of the reactant chiral aminoacid fragment [1]. Acceptor or *N*-trityl protected amino acids [2] can be involved as acid fluorides allowing a wide range of substitution patterns. On the other hand carboxylic acid fluorides are used in alkylations to generate ketones [3], to run one pot reductions of carboxylic acids to carbinols [4], to achieve the esterification of sensitive carboxylic acids [5] and to generate optically active $\gamma,\delta$ unsaturated amides and lactams in zwitterionic aza-Claisen rearrangements with *N*-allylamines [6].

Employing carboxylic acid fluorides in syntheses of complex target molecules or in solid phase processes demanding a complete conversion of the resin linked carboxylic acid an efficient introduction of the fluorine is mandatory. Originally, carboxylic acid fluorides had been built starting from the corresponding chlorides by means of a F–Cl exchange using KF or KF/HF [7] at high temperatures or related conditions preventing any reaction with acid sensitive functional groups. Paying attention to a increasing interest in a broader application of acid fluorides several mild fluorinating reagents had been extensively investigated. During the last decade predominantly cyanuric fluoride [8] and DAST (diethylamino sulfurtrifluoride) [9] and, furthermore, $SF_4$ [10], 2-fluoro pyridinium salts [11], fluoro formamidinium salts [12] and $XeF_2$ [13] had been used as versatile fluorine carriers.

Cyanuric fluoride **2** is by far the most popular reagent to convert carboxylic acids into acid fluorides with high yields under mild conditions. Though commercially available, the price is such high, that it might be a problem to use it as a "bulk chemical". Encouraged by an early publication of Tullock *et al*. [14] we developed a preparation procedure that allows the generation of the cyanuric fluoride **2** for less than tenth part of the charges using cheap reactants. Any handling of liquid HF was avoided [15]: Cyanuric chloride **1** and NaF (excess) were heated in sulfolane to about 150–200 °C, the cyanuric fluoride **2** was distilled off directly from the reaction mixture.




**1** **2**

**Scheme 1** Conversion of cyanuric chloride into cyanuric fluoride

All chemicals were used without further purification and drying. No unusual and dried apparatus was necessary (no teflon apparatus). For vigorous stirring, a mechanical stirrer was found to be much better than a magnetic stirring bar. Teflon sockets had been used in all (heated) glassware connections to prevent any sticking. The time exposure was low (about 4 to 6 hours including all operations) and the experimental technique was quite facile. Best yields (< 75%) were obtained running the reaction with 100–200 g cyanuric chloride.

For storing of the cyanuric fluoride a dry PE bottle was necessary. The alternative use of glassware should be avoided because of the destruction of the fluoride in presence of traces of acid and $SiO_2$. Cyanuric fluoride had been stored at 0 °C for several months. In some cases a white precipitate occurred. In such case, a further distillation was recommended before use.

Initially, the fluorination of carboxylic acids **3** had been carried out following Carpinos [8] or Olahs [15] procedures: The carboxylic acid **3**, cyanuric fluoride **2** and pyridine were stirred in MeCN for an appropriate time, a final aqueous work-up allowed to isolate the desired fluoride **4** with high yields. On synthesizing aryl, alkenyl or saturated carboxylic acid fluorides as **4a**–**c** we succeeded running the reactions in a scale > 3 g. Especially, small scale preparations and the fluorination of $\alpha$-acceptor substituted carboxylic acids **3d**–**f** suffered from a more or less efficient cleavage of the acyl fluorides

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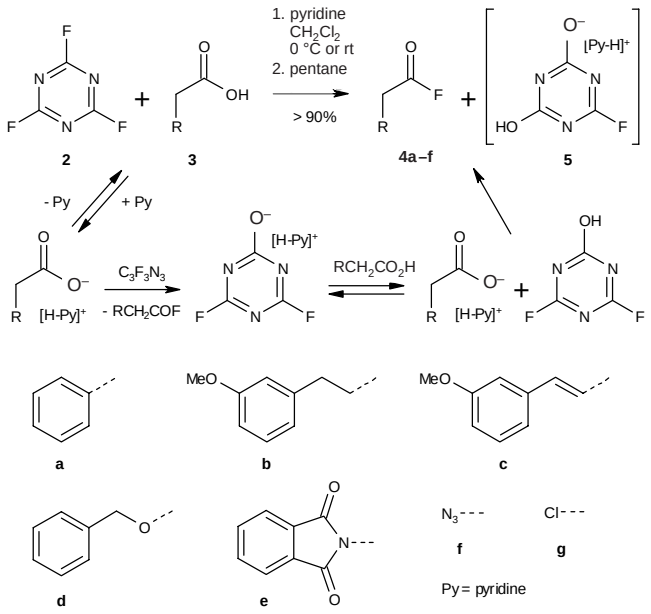
**4d**–**f** during the aqueous work-up. In our hands, two alterations gave increased yields: a non-aqueous work-up and the diminution of the base quantum (pyridine) used for deprotonation during the reaction.

Pyridine was found to promote the fluorination by an initial deprotonation of the carboxylic acid **3**. Thus, **3** and pyridine were used in a 1:1 ratio [15]. Because of the fact, that cyanuric fluoride **2** transferred more than one fluoride, **2** had been employed sub-stoichiometrically (ratio **3**:**2**: 1:1 to 2:1). Paying attention to the fact, that even halogenated cyanuric acids were weak acids [16], the pyridine should cause only a single deprotonation of a resulting derivative **5**. Consequentially, cyanuric fluoride **2** and pyridine could be employed in equal molar ratios (sub-stoichiometric with respect to **3**) to achieve a complete conversion of **3** into **4** presupposing proton transfers all over the reaction period. The solvent of choice was found to be $CH_2Cl_2$. The almost quantitative formation of the ammonium salt **5** from **2** and pyridine facili-tated the non-aqueous work-up.

On preparing non volatile acid fluorides **4b**–**e**, the amount of pyridine was less crucial. Work-up (method A) started by evaporating the $CH_2Cl_2$. The residue was suspended in dry toluene. Solid salt **5** was separated by filtration to result a clear solution. The final distillation of the solvent simultaneously removed residual pyridine to give the product **4** with high purity ($^{13}$C NMR).

On preparing volatile fluorides as **4a** and **4f** (*b.p.* < 150 °C), an exact dosage of pyridine was recommendable running the reaction to avoid the presence of any residual base in the product. The non-aqueous work-up (method B) started with the addition of dry pentane to the reaction mixture ($\rightarrow CH_2Cl_2$/pentane = 1:1) to cause the precipitation of all polar compounds **5**. After filtration, the solvent could be removed to give the desired carboxylic acid fluoride in a sufficient purity




**Scheme 2** Synthesis of functionalized carboxylic acid fluorides

and a high yield. The present procedure is restricted to compounds with a boiling point > 60 °C to avoid any distillation during the removal of the solvent (fluorides with *b.p.* < 60 °C → [15]). As a limitation, the synthesis of chloroacetyl fluoride **4g** (*b.p.* 77 °C) failed under the conditions described above (best method for preparation following Olahs procedure, teflon apparatus [7]).

All new compounds were analyzed by $^1$H and $^{13}$C NMR spectroscopy to exclude any residual acid **3** or pyridine, and, if operative, by GC. All compounds were used in syntheses without further purification. The preparation of carboxylic acid fluorides succeeded in a 100 to 200 mg scale as well as in a 1 to 15 g scale (Table 1).

**Table 1** Synthesis of carboxylic acid fluorides **4**

| Entry | R | scale: acid **3** (g) | work-up: method | yield **4** (%) |
|---|---|---|---|---|
| **a** | Ph | 0.2–10 | B | > 95 |
| **b** | (3-MeOPh)–$CH_2CH_2$- | 0.1–0.5 | A or B | > 95 |
| **c** | (*E*)- (3-MeOPh)–CH=CH- | 0.1–0.5 | A or B | > 95 |
| **d** | BnO- | 0.2–12 | A | > 95 |
| **e** | PhtN- | 0.2–5 | A | > 95 |
| **f** | $N_3$- | 0.2–8 | B | > 80 [a]) |
| **g** | Cl | 0.2–3 | A | failure |

[a]) *b.p.* < 90 °C, yield varied between 60 and 95%

In conclusion, the facile preparation of cyanuric fluoride with low price materials provides the extensive use of the fluorinating reagent even as a "bulk material". Thus, the synthesis of a range of carboxylic acid fluorides succeeded with high yields treating the corresponding acids with a 1:1 mixture of cyanuric fluoride and pyridine. The non-aqueous work-up allowed an efficient generation of the activated carboxylic acids with excellent yields and with sufficient purity for further applications.

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## Experimental

All reactions involved water sensitive chemicals and were carried out in flame-dried glassware under Ar, in most cases with magnetic stirring. All solvents were dried before use following standard procedures. $^1$H NMR spectra were recorded on a Bruker AM 270 spectrometer (270 MHz), all spectra were obtained in $CDCl_3$ with TMS as internal standard, 23 °C. Coupling constants (*J* in Hz) were listed as $^3J$ ($^1$H, $^1$H) data unless noted otherwise for spectra judged to be first order. $^{13}$C NMR and DEPT spectra were obtained on the same instrument operating at 67 MHz. Mass spectrum: Varian MAT 711, HRMS with PFK as internal standard. GC: Perkin-Elmer 8420.

*Caution!*

All organo fluorine compounds are toxic! Cyanuric fluoride is highly toxic, corrosive, moisture sensitive, lachrymatory. Cyanuric chloride is corrosive and moisture sensitive. NaF is irritant, toxic, hygroscopic.

An efficient hood should be used for all operations! After finishing the experiments, the glassware should be stored in aqueous NaOH overnight to cleave all remaining impurities of cyanuric halides. Avoid any skin contact!

*Synthesis of Cyanuric Fluoride* (**2**) *(2,4,6-Trifluoro-1,3,5-triazine, 50 g scale)*

A 1000-mL three necked flask was equipped with an internal thermometer, a sealed mechanical stirrer, a small distillation apparatus (distillation head inc. thermometer, Liebigs condenser and distillate receiver) and a drying tube and was charged with cyanuric chloride **1** (100 g, 0.542 mol) and sodium fluoride (136.6 g, 3.253 mol, 6 eq.). Sulfolane (tetramethylene sulfone, 414 mL, 521 g, 4.338 mol, 8 eq.) was added with stirring. The mixture was heated by means of a heating hood (infinitely variable heat regulator), the temperature of was carefully monitored by the internal thermometer. As soon as the temperature reached 160 °C a clear liquid was distilled off, the overhead temperature observed was about 88 °C, after additional 30 min the distillate muddied. The internal temperature was continuously raised to 250 °C and the distillate was collected until the overhead temperature reached 100 °C (about 2.5 h). Vigorous stirring of the suspension was crucial to maximize the yield. The color of the reaction mixture changed from pale yellow to dark brown. Then, the reaction was terminated to avoid any distillation of chlorodifluoro triazine (*b.p.* = 113 °C), dichlorofluoro triazine (*b.p.* = 154 °C) or cyanuric chloride (*b.p.* = 190 °C).

*Purification*. The crude cyanuric fluoride **2** was immediately distilled a second time at normal pressure under argon to remove all impurities: Heating bath 100 °C, overhead temperature 72–73 °C. The clear liquid was directly collected in a PE-bottle and stored at 0 or –20 °C.

*Yield*. 56.69 g, 0.420 mol, 78% of **2**. NMR and GC analysis indicated a purity greater than 98%. (Scale 50g/290g **1**: yield 69%/71% **2**).

*Recycling*. About 50% of the sulfolane was recycled: Firstly, the dark brown reaction mixture (suspension of NaCl in sulfolane) was allowed to cool to temperatures below 100 °C. Then, the precipitate was filtered off with suction. The remaining crude liquid was distilled under reduced pressure to give pure sulfolane (147 mL, 233 g, 1.938 mol, 45 %), which could be used for a second chloride-fluoride-exchange without further purification.

*Spectral data*: $C_3N_3F_3$ (**2**): $^{13}$C NMR (67 MHz, $CDCl_3$): $\delta$/ppm = 173 (dt, $^1J[^{13}C,^{19}F]$ = 241, $^3J[^{13}C,^{19}F]$ = 18.7 Hz). – MS (70 eV, EI, 20 °C): *m/z* 135 ($M^{+\cdot}$, 100%), 116 (21%), 90 (50%), 71 (8%), 45 (4%), 28 (9%), 18 (17%); HRMS Calcd. for $C_3N_3F_3$: 135.00444. Found: 135.003910.

Potential side product (not found using the procedure as aforesaid) $C_3N_3ClF_2$: $^{13}$C NMR: $\delta$/ppm = 171.5 (dd, $^1J[^{13}C,^{19}F]$ = 241, $^3J[^{13}C,^{19}F]$ = 16.9 Hz), 179 (t, $^3J[^{13}C,^{19}F]$ = 15.3 Hz).

**Preparation of carboxylic acid fluorides 4a–f**

The carboxylic acid **3** (10 mmol) was dissolved in dry $CH_2Cl_2$ (17 mL) at 0 °C or r.t. Pyridine (0.4 g, 0.4 mL, 5 mmol) was added with stirring, then, cyanuric fluoride (**2**) (675 mg, 0.43 mL, 5 mmol) was added. A white precipitate occurred in several cases. The mixture was stirred for about 2 h at ambient temperature. In most attempts the reaction was found to be complete at that time detected by tlc or $^1$H NMR control. Work-up method A: The solids were filtered off and the solvent was removed by distillation. The crude acid fluoride was suspended in dry toluene (10 mL). After storing at –20 °C for 20 min, the remaining solid was filtered off, the solvent was removed to result the acid fluoride **4**, which was found to be pure enough for further transformations.

Work-up method B: dry pentane (17 mL) was added to complete the precipitation of polar compounds (pyridinium salts **5**). The solids were filtered off to result a clear solution. The solvents were carefully removed to give the carboxylic acid fluoride **4**, which was found to be pure enough for further transformations.

*Phenylacetyl fluoride* (**4a**) [17]

Reaction with phenylacetic acid (**3a**) (5 g, 36.7 mmol) following the standard procedure, 0 °C, work-up method B. Yield 4.96 g **4a** ( 36 mmol, 98 %) as a pale yellow oil. – $^1$H NMR: $\delta$/ppm = 7.50–7.20 (m, 5H), 3.84–3.80 (d, $^3J[^1H,^{19}F]$ = 2.4 Hz, 1H). – $^{13}$C NMR: $\delta$/ppm = 161.3 (CO, d, $^1J[^{13}C,^{19}F]$ = 361 Hz), 130.7 (C), 129.2 (CH), 128.8 (CH), 127.9 (CH), 38.8 ($CH_2$, $^2J[^{13}C,^{19}F]$ = 53.7 Hz).

*4-(3-Methoxyphenyl)-butanoyl fluoride* (**4b**) [18]

Reaction with 4-(3-methoxyphenyl)-butanoic acid (**3b**) (475 mg, 2.45 mmol) following the standard procedure, 0 °C, work-up method B. Yield 456 mg **4b** (2.33 mmol, 95%) as a yellow oil. – $^1$H NMR: $\delta$/ppm = 7.29–7.16 (m, 1H), 6.79–6.72 (m, 3H), 3.82 (s, 3H), 2.67 (dt, $^3J[^1H,^{19}F]$ = 6.9 Hz, $^3J$[H,H] = 7.4 Hz, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.01 (qi, 2H, *J* = 7.3 Hz, 2H). – $^{13}$C NMR: $\delta$/ppm = 159.8 (C), 155.2 (CO, d, $^1J[^{13}C^{19}F]$ = 310 Hz), 129.6 (C), 128.0 (CH), 120.8 (CH), 114.3 (CH), 111.5 (CH), 55.1 ($OCH_3$), 34.8 ($CH_2$, d, $^2J[^{13}C,^{19}F]$ = 55 Hz), 31.6 ($CH_2$), 25.3 ($CH_2$).

*E-4-(3-Methoxyphenyl)-3-butenoyl fluoride* (**4c**) [19]

Reaction with *E*-4-(3-Methoxyphenyl)-3-butenoic acid (**3c**) (220 mg, 1.15 mmol) following the standard procedure, 0 °C, work-up method B. Yield 213 mg **4c** (1.13 mmol, 99 %) as a yellow oil. – $^1$H NMR: $\delta$/ppm = 7.28–7.22 (m, 1H), 6.99–6.81 (m, 3H), 6.55 (d, br, *J* = 15.6 Hz, 1H), 6.2 (td, *J* = 6.8, 15.6 Hz, 1H), 3.82 (s, 3H), 3.44 (dd, br, $^3J[^1H,^{19}F]$ = 6.9 Hz, $^3J$[H,H] = 7.4 Hz, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.01 (qi, *J* = 7.3 Hz, 2H). – $^{13}$C NMR: $\delta$/ppm = 159.0 (C), 155.7 (CO, d, $^1J[^{13}C^{19}F]$ = 406 Hz), 137.4 (C), 135.3 (CH), 129.6 (CH), 119.0 (CH), 118.2 (CH), 113.7 (CH), 111.7 (CH), 55.2 (OCH3), 35.8 (CH2, d, $^2J[^{13}C,^{19}F]$ = 55 Hz).

*Benzyloxyacetyl fluoride* (**4d**) [6]

Reaction with benzyloxyacetic acid (**3d**) (3 g, 18 mmol) following the standard procedure, 23 °C, work-up method A. Yield 3 g **3d** (1.13 mmol, 99%) as a colorless oil. – $^1$H NMR: $\delta$/ppm = 7.40–7.20 (m, 5H), 4.65 (s, 2H), 4.25 (d, $^3J[^1H,^{19}F]$ = 3.4 Hz, 2H). – $^{13}$C NMR $\delta$/ppm = 160.4 (CO, d, $^1J[^{13}C,^{19}F]$ = 366 Hz), 136.1 (C), 128.6 (CH), 128.4 (CH), 128.1 (CH), 73.4 ($ArOCH_2$), 64.4 ($OCH_2$, d, $^2J[^{13}C,^{19}F]$ = 71 Hz).

*N-Phthaloylglycinyl fluoride* (**4e**) [20]

Reaction with *N*-phthaloylglycine (**3e**) (2 g, 9.75 mmol) following the standard procedure, 23 °C, work-up method A. Yield 1.95 g **4e** (9.75 mmol, 99%) as a colorless oil. –

$^1$H NMR: $\delta$/ppm = 7.86 (dd, $J$ = 3.0, 5.4 Hz, 2H), 7.73 (dd, $J$ = 3.0, 5.4 Hz, 2H), 4.55 (d, $^3J$ [$^1$H,$^{19}$F] = 4.4 Hz, 2H). – $^{13}$C NMR: $\delta$/ppm = 157.9 (CO, d, $^1J$[$^{13}$C,$^{19}$F] = 363 Hz), 134.6 (CH), 131.4 (C), 123.8 (CH), 36.8 ($CH_2$, d, $^2J$[$^{13}$C,$^{19}$F] = 76 Hz).

*Azidoacetyl fluoride* (**4f**) [21]

Reaction with azidoacetic acid (**3f**) (3.1 g, 31 mmol) following the standard procedure using 0.7 eq. of **2** and pyridine, 23 °C, work-up method B. Volatile product, *b.p.* < 90 °C! Yield 3 g **4f** (29 mmol, 94%) as a yellow oil, which darkens after a short time. – $^1$H NMR: $\delta$/ppm = 4.08 (s, br, 2H). – $^{13}$C NMR: $\delta$/ppm = 158.9 (CO, d, $^1J$[$^{13}$C,$^{19}$F] = 364 Hz), 48.2 ($CH_2$, d, $^2J$[$^{13}$C,$^{19}$F] = 70 Hz).

*Caution*

Azidoacetyl fluoride contains more than 40% N and might be explosive. Avoid heating and contact with metal ions.

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