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CONVENIENT ROUTES TO TRIFLUOROMETHYL-SUBSTITUTED PYRIDYL-ISOTHIOCYANATES AND ISOCYANATES STARTING FROM 2,3-DICHLORO-5-TRIFLUOROMETHYL PYRIDINE

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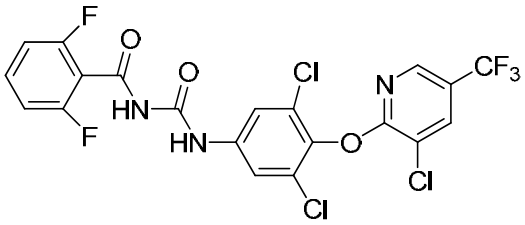
A convenient preparative route for the synthesis of 3-chloro-2-(isothiocyanatoethyl)-5-(trifluoromethyl)pyridine (1) and 3-chloro-2-(isocyanatoethyl)-5-(trifluoromethyl)pyridine (2) has been developed, involving 5 steps starting from 2,3-dichloro-5-(trifluoromethyl)pyridine (3). All intermediates and final products were obtained in good yields and purity. The structure of one intermediate, 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)malonate, was confirmed by X-ray crystallography.

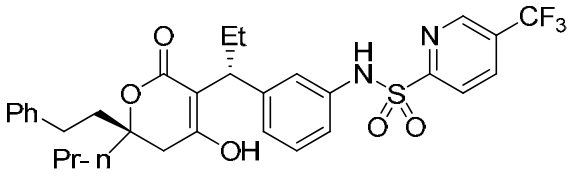
INTRODUCTION

Insecticides represent a major tool in pest management and thus play a very important role in modern agriculture, but their application has also led to an inevitable problem, the occurrence and the development of resistance of pest species to classic insecticides. Therefore, there is a critical need for the discovery of a new class of compounds that would affect different insect targets and exhibit a novel mode of action.

The pyridine nucleus is a major component of a variety of natural products and drugs. In this family, trifluoromethylated *N*-heterocycles are widely applied in the field of medicinal and agricultural chemistry. The presence of a trifluoromethyl moiety can dramatically modify the physical and chemical properties of a compound, thus making it a privileged motif in medicinal and materials chemistry when attempting to tailor a specific activity profile.[1] Trifluoromethylsubstituted heteroaryls, *e.g.* pyridines and pyrazoles, are found in several biologically active compounds.[2] For example, the insecticide Chlorfluazuron (4) is a chitin synthesis inhibitor[3] and Tipranavir (5) is a commercial HIV protease inhibitor.[4] (Fig. 1).



Chlorfluazuron(4)
Insecticide, chitin synthesis inhibitor



Tipranavir(5)
HIV protease inhibitor

Fig. 1 – Biologically active compounds with a pyridinic tail.

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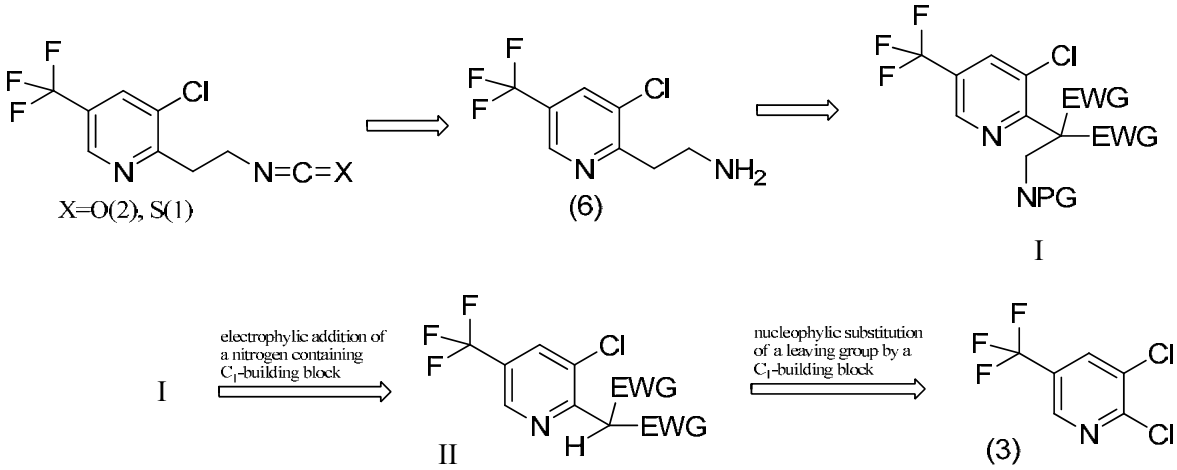
We therefore wished to investigate whether the trifluoromethyl moiety could be introduced in other molecules. One way might be to use the isocyanate and isothiocyanate groups. It is known that isocyanates and isothiocyanates can undergo a series of reactions to yield a variety of interesting products including heterocyclic derivatives. Heterocyclic isocyanates and isothiocyanates have however not been given the same attention as the corresponding aromatic compounds in synthesis and reactivity studies.[5,6] One reason for this is their instability and their high reactivity.[7] Here we report our studies of the preparation, stability and reactivity of 3-chloro-2-(isocyanatomethyl)-5-(trifluoromethyl)pyridine (2) and of 3-chloro-2-(isothiocyanatoethyl)-5-(trifluoromethyl)pyridine (1), which bear the same pyridyl groups as the biologically active compounds in Fig. 1.

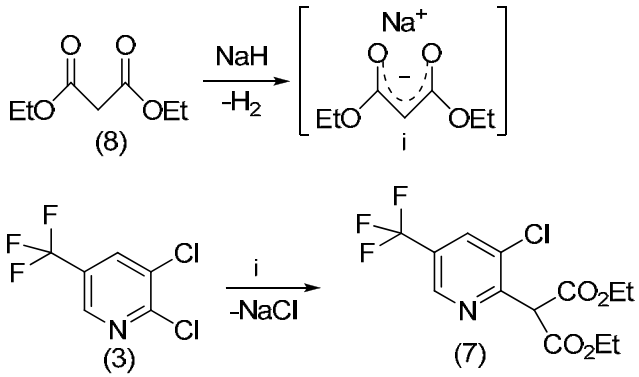
RESULTS AND DISCUSSION

Introduction of the first C1-building block

A suitable starting molecule is 2,3-dichloro-5-(trifluoromethyl)pyridine (3) (Scheme 1). The first step is the synthesis of the malonic ester of 3-chloro-5-(trifluoromethyl)pyridine (7) (Scheme 2).



Scheme 1. Retrosynthetic analysis of 3-chloro-2(isothiocyanatoethyl)-5-(trifluoromethyl)pyridine(1) and 3-chloro-2-(isocyanatomethyl)-5-(trifluoromethyl)pyridine(2).



Scheme 2. Synthesis of diethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)malonate(7)

The reaction started with the deprotonation of diethyl malonate (8). We used a slight excess of NaH as base and dried dimethylformamide (DMF) as solvent. The carbanion (i) can undergo nucleophilic substitution at the aryl halide to give the arylated compound (7). The reaction was stopped by adding acetic acid until the hydrogen evolution had ceased.

The molecular structure of compound (7) was determined by X-ray analysis (Fig 2). It crystallizes in the monoclinic space group $P2_1/n$ with one independent molecule in the asymmetric unit. The C8-O1 and C9-O3 bond lengths (1.202(2) and 1.205(2) Å) clearly indicate double bonds. These bonds are considerably shorter than the single bonds observed for C8-O2 1.337(2) and C9-O4 1.332(2) Å.

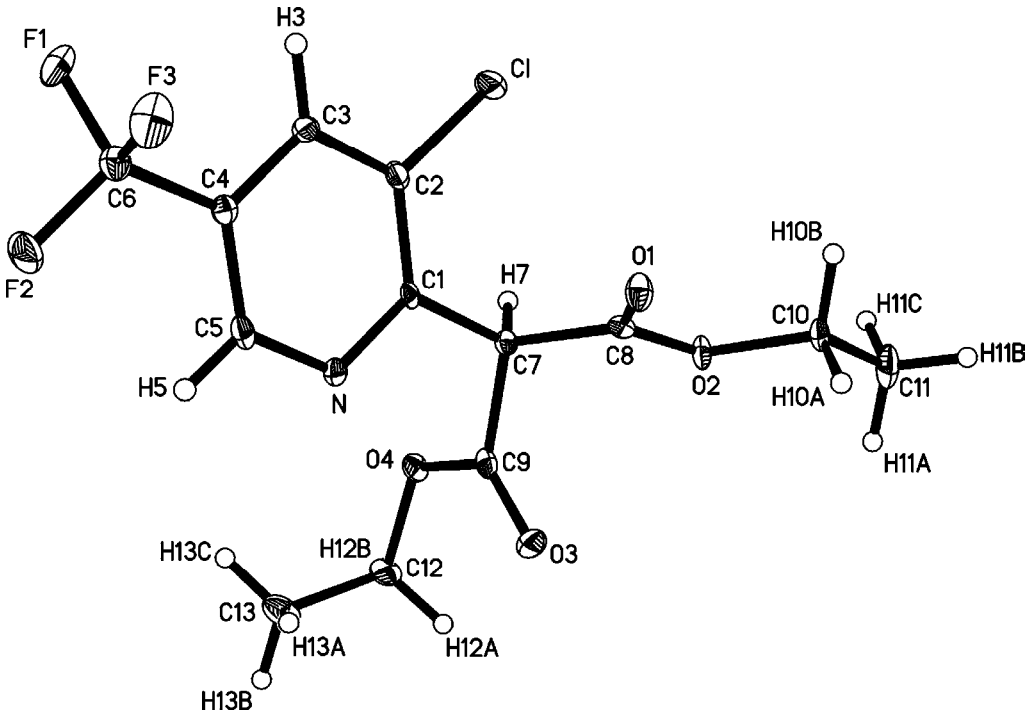
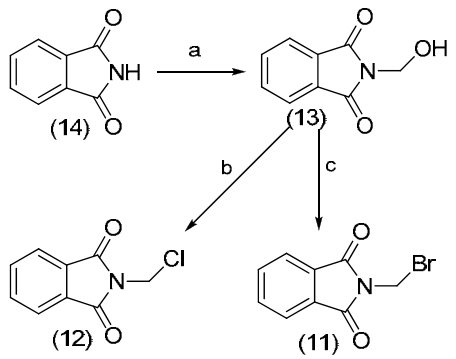


Fig. 2 – Molecular structure of diethyl-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)malonate (7). Atoms are drawn as 30% thermal ellipsoids. Selected bond lengths [Å] and angles [°]: C1-N 1.336(2), C5-N 1.339(2), C2-Cl 1.7330(19), C8-O1 1.202(2), C8-O2 1.337(2), C9-O3 1.205(2), C9-O4 1.332(2), C1-N-C5 118.26(16), O1-C8-O2 124.79(19), O3-C9-O4 126.10(19).

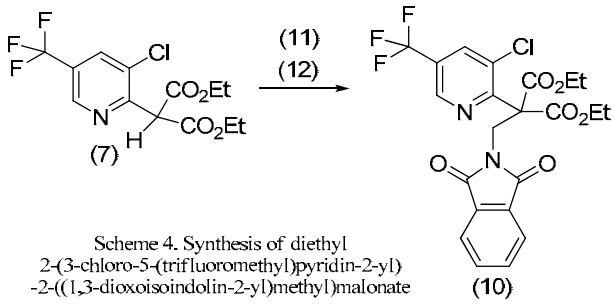
Introduction of the second C1-building block

The second C1-building block had to contain a nitrogen atom, so we chose the halogenated methylphthalimides, Br-methylphthalimide (11) and 2-(chloromethyl) phtalimide (12). The halogenated methylphthalimides were made starting with the phthalimide (14).[18] This was treated with formalin to give the hydroxymethylphthalimide (13). The brommethylphthalimide (11) was then obtained from the direct reaction (without solvent) between hydroxymethylphthalimide (13) and phosphorus tribromide. For the chlormethylphthalimide (12)[13,14] we also started from (13), but used thionyl chloride in DCM, DMF. The two reagents were synthesized according to Scheme 3. For larger-scale reactions we chose the Cl-methylphthalimide (12) route because of the lower price of thionyl chloride compared with phosphorus tribromide, mild conditions and higher yield.[8-10]

We introduced methylphthalimide in the activated position of the malonate compound 7) (Scheme 4). The reaction was carried out using DMF as solvent, and NaH (slight excess) as a base.



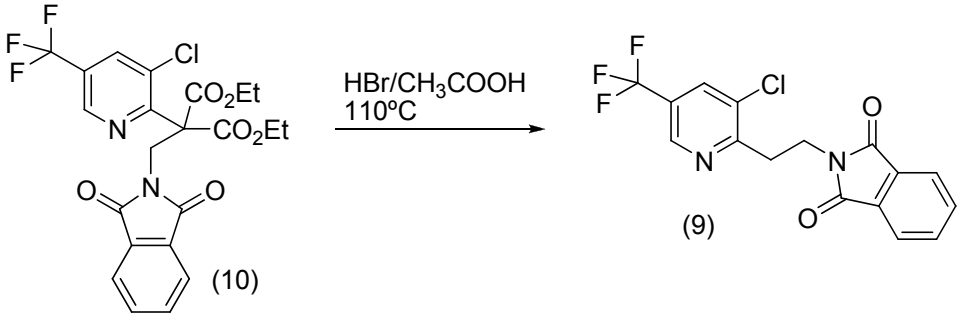
Scheme 3. Synthesis of halogenated C1-building block
a: H_2CO, H_2O; b: $SOCl_2$, DCM, DMF; c: PBr_3



Scheme 4. Synthesis of diethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl) -2-((1,3-dioxoisoindolin-2-yl)methyl)malonate

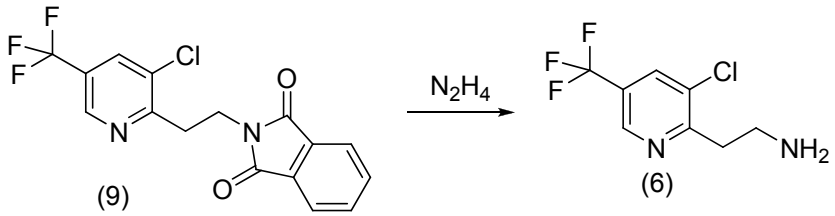
After all the reagents were added, the reaction mixture is stirred at room temperature. With the compound (10) we had acquired the desired basic molecular framework.

The next step requires the cleavage of the two ethylformate groups. In order to do this a mixture of hydrobromic acid and acetic acid was used. The ethylformate group hydrolyzes under the acid conditions with the formation of carbon dioxide and ethanol.



Scheme 5. Synthesis of 2-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)isoindoline-1,3-dione

After the synthesis of 2-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)isoindoline-1,3-dione(9), the N-protecting group had to be removed. Hydrazine monohydrate was used to obtain the amine (6).[11,12] The cleavage of the phthaloyl leaving group was performed in ethanol at 80ºC (Scheme 6).

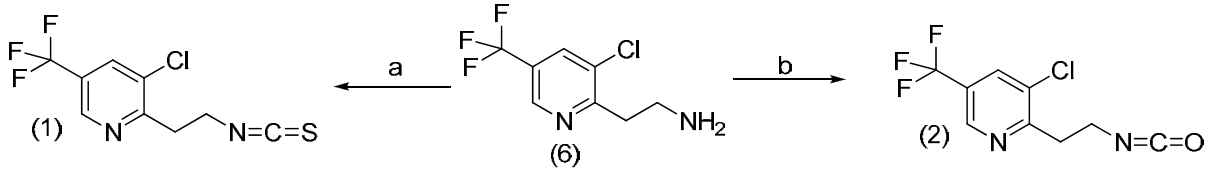


Scheme 6. Synthesis of 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine

Synthesis of the isocyanate and isothiocyanate

2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl) ethanamine (6) was converted to the corresponding isothiocyanate (3-chloro-2-(2-isothiocyanatoethyl)-5-(trifluoromethyl)pyridine (1)) using thiophosgene as a reagent. A heterogeneous mixture of aqueous sodium hydrogen carbonate solution and dichloromethane was stirred and cooled down at 0°C, when the thiophosgene was added dropwise. Next, the amine compound, dissolved in DCM, was added and the reaction was brought to room temperature.

The isocyanate (3-chloro-2-(2-isocyanatoethyl)-5-(trifluoromethyl)pyridine(2)) was synthesized using the same aqueous/organic reaction conditions. Triphosgene could also be successfully employed as a phosgene equivalent. The reaction time is short (2h) and the yields are very good.[15-17]



a: X=S, $CSCl_2$, DCM/$NaHCO_3$, 0ºC; b: X=O, $OC(OCCl_3)_2$, DCM/$NaHCO_3$, 0ºC

Scheme 7. Synthesis of isothiocyanate(1) and isocyanate(2)

EXPERIMENTAL

Synthesis of diethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)malonate (7)

To a suspension of 60% sodium hydride in mineral oil (1,5 eq.) in dry dimethylformamide at 0ºC was added a solution of diethyl malonate(8) (1 eq.) in dry dimethylformamide and the mixture was stirred for 10 minutes. A solution of 2,3-dichloro-5-(trifluoromethyl)pyridine(3) (500g, 1 eq.) in dry dimethylformamide was added dropwise and the mixture was stirred for another 10 minutes at 0ºC. The reaction mixture was warmed to room temperature and stirred for 24 hours. After the reaction was complete, acetic acid was added

dropwise and stirred until no further hydrogen was formed. The mixture was diluted with diethyl ether and then washed with water (3 times). The organic extract was dried over Na_2SO_4 and then evaporated. The residue oil was allowed to crystallize at low temperature and then filtered. Yield: 70%; MS: m/z = 339 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.80 – 8.71 (m, 1H), 8.00 – 7.93 (m, 1H), 5.25 (s, 1H), 4.31 (q, J = 7.1 Hz, 4H), 1.30 (t, J = 7.1 Hz, 6H).

Synthesis of diethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-((1,3-dioxoisoindolin-2-yl)methyl)malonate (10)

1 equivalent of 60% sodium hydride was washed 3 times with pentane to remove the mineral oil, decanted and then suspended in dry dimethylformamide. The suspension was cooled at 0ºC and the solution of diethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)malonate(7) (140g, 1eq.) in dry dimethylformamide was added dropwise, and the mixture was stirred for 10 minutes. A solution of *N*-chloro methylphthalimide(12) (1 eq.) in dry dimethyl formamide was added dropwise and the mixture was stirred for another 10 minutes at 0ºC. The mixture was warmed to room temperature and stirred for 4 hours. Glacial acetic acid was added and the mixture was poured into cold water and stirred until precipitation occured. The solid was filtered off, washed with water and dried. Yield: 75%;
MS: m/z = 498 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.73 (d, J = 0.9 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 3.0 Hz, 2H), 7.76 – 7.68 (m, 2H), 4.90 (s, 2H), 4.32 – 4.12 (m, 4H), 1.18 (t, J = 7.2 Hz, 6H).

Synthesis of 2-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)isoindoline-1,3-dione (9)

To a solution of (10) diethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-((1,3-dioxoisoindolin-2-yl)methyl)malonate (300g, 1 eq.) in glacial acetic acid (77 eq.) was added a solution of hydrobromic acid 62% (9 eq.) and the mixture was heated at 110ºC for 3.5 hours. When the reaction was complete, the mixture was cooled to room temperature and the pH adjusted to value 8 with a saturated aqueous solution of sodium hydrogen carbonate. The resulting solid was filtered off, washed with water and dried. Yield: 60,9%; MS: m/z = 354 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.64 (d, J = 1.0 Hz, 1H), 7.87 (d, J = 1.7 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.77 – 7.68 (m, 2H), 4.19 (t, J = 7.0 Hz, 2H), 3.40 (t, J = 7.0 Hz, 2H).

Synthesis of 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine (6)

To a solution of (3) 2-(2-(3-chloro-5-(trifluoromethyl) pyridin-2-yl)ethyl)isoindoline-1,3-dione(9) (50g, 1 eq.) in ethanol was added hydrazine hydrate (3.5 eq.) and the mixture was heated under reflux for 3 hours. Hydrochloric acid (1N) was added to give a pH of 2 and then the mixture was stirred for 1 hour. The precipitate was filtered off and to the filtrate a solution of NaOH was added until the pH value was >10. This aqueous solution was extracted 3 times with diethyl ether and the combined extracts were washed with brine, dried over Na_2SO_4 and evaporated. The resulting product was used without purification in the next step. Yield: 88%; MS: m/z = 224 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.89 (s, 1H), 4.16 (bs, 2H), 1.86 (bs, 2H).

Synthesis of 3-chloro-2-(isothiocyanatoethyl)-5-(trifluoromethyl)pyridine (1)

2.5 eq. of sodium carbonate was dissolved in water and cooled to 0ºC. A solution of thiophosgene (1,08 eq.) in dichloromethane was added and the mixture was stirred for 5 minutes at 0ºC. 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine (6) (49g, 1eq.) dissolved in dichloromethane was added dropwise and then the cooling was removed. The resulting mixture was stirred for 3 hours at room temperature. When the reaction was finished, the two phases were separated. The aqueous phase was washed 3 times with dichloromethane and then all organic phases were combined and washed 3 times with water, dried over Na_2SO_4 and evaporated. Yield: 94%; MS: m/z = 266 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.74 (m, J = 0.8 Hz, 1H), 7.93 (m, J = 3.8 Hz, 1H), 4.07 (t, J = 6.8 Hz, 2H), 3.40 (t, J = 6.7 Hz, 2H).

Synthesis of 3-chloro-2-(isocyanatoethyl)-5-(trifluoromethyl)pyridine (2)

2.5 eq. of sodium carbonate was dissolved in water and cooled to 0ºC. A solution of triphosgene (1,08 eq.) in dichloromethane was added and the mixture was stirred for 5 minutes at 0ºC. 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine (6)(50g, 1eq) dissolved in dichloromethane was added dropwise and then the cooling was removed. The resulting mixture was stirred for 3 hours at room temperature. When the reaction was finished, the two phases were separated. The aqueous phase was washed 3 times with dichloromethane and then all organic phases were combined and washed 3 times with water, dried on Na_2SO_4 and evaporated. Yield: 90%; MS: m/z = 250 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.68 (m, 1H), 7.84 (m, J = 4.0 Hz, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.23 (t, J = 6.5 Hz, 2H).

X-ray Crystal Structure Determination

Data were recorded on an Oxford Diffraction Xcalibur area detector at low temperature using Mo-$K\alpha$ radiation (λ = 0.71073 Å). An absorption correction was performed on the basis of multi-scans. The structure was refined anisotropically using the program SHELXL-97.[19] Hydrogen atoms were included using rigid methyl groups or a riding model.

Crystal data for 7*:* $C_{13}H_{13}ClF_3NO_4$*;* M_r = 339.69, monoclinic, space group $P2_1/n$, a = 12.1287(8), b = 9.0918(6), c = 13.5472(10) Å; β= 97.354(6)°; V = 1481.58(18) Å^3; Z = 4; T = 100(2) K; μ = 0.308 mm^{-1}. Of 30459 reflections measured to 2θ 54°, 3264 were independent (R_{int} = 0.101). Final $R1$ ($I > 4\sigma(I)$) = 0.0331, $wR2$ = 0.0504 (all data).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication no. CCDC- (7). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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