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SYNTHESIS
## Reviews and Full Papers in Chemical Synthesis

Thieme

2-Trifluoromethyl-1,3-diazabutadienes as Useful Intermediates for the Construction of 2-Trifluoromethylpyrimidine Derivatives

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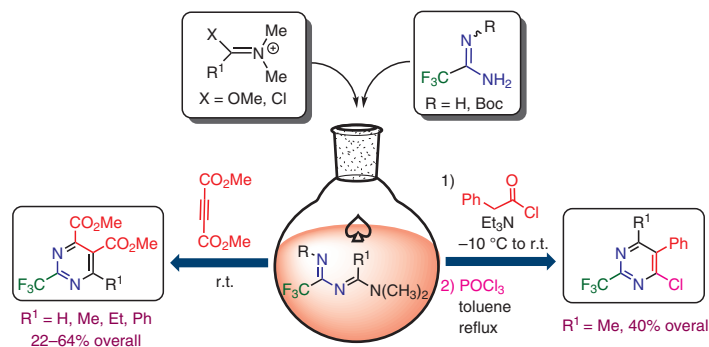
**Abstract** A methodology to prepare 2-trifluoromethylpyrimidines has been developed on the basis of a cyclization reaction of 2-trifluoromethyl-1,3-diazabutadienes. These 2-trifluoromethyl-1,3-diazabutadienes were prepared by the condensation of trifluoroacetamidine and amide acetals or with chloromethaniminium salt derived from N,N-dimethylbenzamide with phosphorus oxychloride. The cycloaddition reactions of these 2-trifluoromethyl-1,3-diazabutadienes with DMAD and phenylacetyl chloride provided 2-trifluoromethylpyrimidine derivatives in regular to moderate overall yield.

Key words trifluoroacetamidine, cycloaddition reaction, 1,3-diazabutadienes, 2-trifluoromethylpyrimidines, trifluoromethyl group
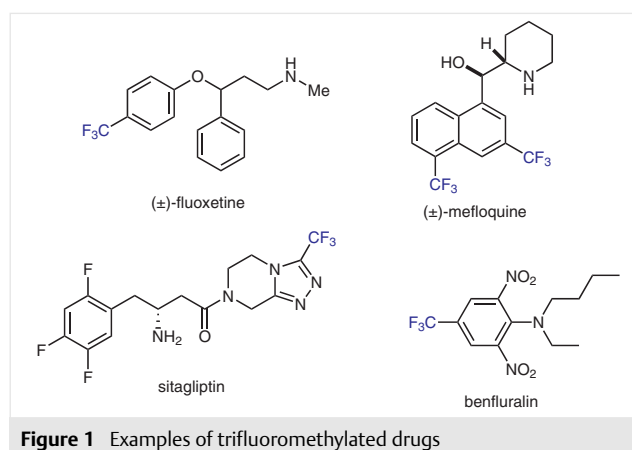
Figure 1 Examples of trifluoromethylated drugs

It is well known that fluorination or perfluorination of organic molecules causes a significant change in their physicochemical properties. For this reason it is important to devise efficient methods for the synthesis of organofluorine compounds to obtain derivatives with pharmaceutical properties.[1] In fact, about 25% of drugs and at least 30% of all agrochemicals that are in the market contain at least one fluorine atom, and several of them have important biological activities due to the presence of this element.[2]

In this context, a trifluoromethyl group attached to aromatic systems is one of the most important units used for the design of new molecules with specific biological activity.[3] Some examples of arenes and heterocyclic rings with biological properties that contain the trifluoromethyl group in the structure include the antidepressant fluoxetine (Prozac®), (±)-mefloquine (Larim®; used to treat malaria), antidiabetic sitagliptin (Januvia®), and a herbicide benfluralin (Balan®) (Figure 1). For this reason, the development of new synthetic routes for the introduction of trifluoromethyl groups in heterocyclic systems including aromatic rings has become a major challenge within the area of synthetic organic chemistry and medicinal chemistry.

There are several strategies for introducing the trifluoromethyl group in a range of heterocyclic systems, for example, from prefunctionalized organic substrates such as heteroaryl halides, heteroaryl amines or heteroaryl boronic acids using different trifluoromethylating agents.[4–7] However, few reports for the synthesis of trifluoromethylpyrimidine derivatives can be found in the literature. The majority of these synthetic methods involve condensation reactions with building blocks that contain the trifluoromethyl group in their chemical structure.[8–17]

Early studies on the [4+2]-cycloaddition reactions of azadienes with different dienophiles established the great potential of the approach for the synthesis of six-membered heterocycles that contain nitrogen.[18] Specifically, 1,3-diaza-1,3-butadienes have been used as key intermediates for the synthesis of various heterocyclic systems.[19] Unfortu-

nately, most of these 1,3-diazadienes are substituted with an alkyl or aryl group at position N-1, and it is thus not possible to obtain aromatic compounds.[20–24]

As part of an ongoing study on the cycloaddition reaction of 1,3-diazadienes, our group previously reported some strategies for the preparation of N*H*-2-trichloromethyl-1,3-diaza-1,3-butadienes and showed their utility for the construction of pyrimidine[25,26] and quinazoline[27] derivatives by cycloaddition reactions mainly with electron-deficient acetylenes or benzyne. Herein, we now describe the synthesis of trifluoroacetamidine **1** (Scheme 1) and its preliminary study as a suitable building block for the synthesis of 2-trifluoromethyl-1,3-diazabutadienes, and the use of the latter as intermediates, particularly in cycloaddition reactions for the construction of 2-trifluoromethylpyrimidines.
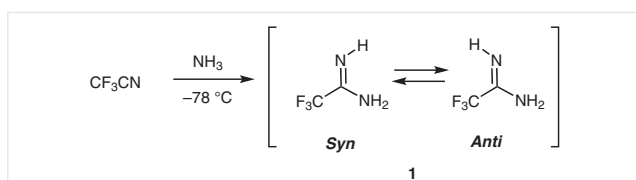

Scheme 1 Synthesis of trifluoroacetamidine **1**

Trifluoroacetamidine **1** was described first by Husted[28] in 1954 and it was synthesized in 87% yield from trifluoroacetonitrile and ammonia.[29] Unfortunately, it has not been characterized because it is typically used in its crude form for the synthesis of other types of compounds.[29–31] In this paper, we present its synthesis, spectroscopic characterization, and some of its uses in the preparation of 2-trifluoromethyl-1,3-diazadienes.

Our study began with the synthesis and characterization of **1**, which was prepared from trifluoroacetonitrile and ammonia at –78 °C (Scheme 1). The excess of ammonia was removed from the reaction mixture followed by further vaporization under vacuum of the volatile residues. Compound **1** does not survive silica gel column chromatography; therefore, no attempt was made to obtain pure trifluoroacetamidine and the usual yield in crude form was similar to that reported in the literature. Although the ^{1}H and ^{13}C NMR spectra correspond to the structure of **1**, the ^{19}F spectrum shows two signals at –74.56 and –75.31 ppm, which indicates the presence of *syn*- and *anti*-isomers of trifluoroacetamidine.

Trifluoroacetamidine **1** was obtained as an oil with ammonia odor and is relatively stable at low temperatures (–5 °C). In its solution form, in CH_2Cl_2 and $CHCl_3$ at room temperature for 24 hours, the decomposition to trifluoroacetonitrile and ammonia accelerates, and in the presence of a trace amount of water its hydrolysis to trifluoroacetamide occurs easily.

In previous reports we have described that trichloroacetamidine can be condensed either with amide acetals[25] or with chloromethaniminium salts, also known as Vilsmeier–Haack reagents.[26,27] It was thought that trifluoroacetamidine **1** might react with these electrophilic agents in an analogous manner. This supposition proved to be correct when **1** was treated with a slight excess of *N,N*-dimethylformamide dimethylacetal (1.2 equiv) in tetrahydrofuran solution at room temperature for 16 hours, which led to the formation of 2-trifluoromethyl-1,3-diazabutadiene **2a** in 95% yield in crude form (Scheme 2). Unfortunately, 2-trifluoromethyldiazadiene **2a** was obtained as a mixture together with the 4-dimethylaminotrifluoroacetamide **3** (possibly formed by the partial hydrolysis of **2a**) in ca. 1:1 ratio. The corresponding 2-trifluoromethyldiazapentadiene **2b** was prepared in the same manner from **1** using *N,N*-dimethylacetamide dimethylacetal in 96% yield as practically the only product. The 4-phenyl-2-trifluoromethyldiazabutadiene **2c** was prepared in 80% yield from the condensation of **1** with the respective chloromethaniminium salt (Vilsmeier–Haack reagent) derived from the reaction of *N,N*-dimethylbenzamide and phosphorus(V) oxychloride, according to our previously reported methodology.[26] Unfortunately, **2c** was isolated as a mixture with *N,N*-dimethylbenzamide.
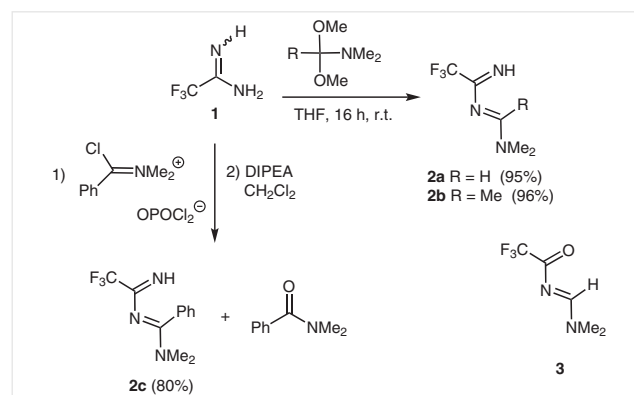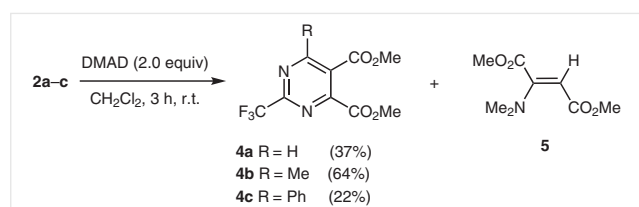

Scheme 2 Synthesis of 2-trifluoromethyl diazadienes **2a–c**

In our previous work, we observed that when the 1,3-diazabutadienes with the trichloromethyl group in position 2 are exposed to conditions of dilution at room temperature for long periods of time, they tend to degrade to trichloroacetonitrile and their respective *N,N*-dimethylamidine.[25] We found that the 2-trifluoromethyldiazabutadienes **2a** and **2b** were decomposed in CH_2Cl_2 solution at room temperature in less than 3 hours. An attempt to obtain the 2-trifluoromethyldiazadiene **2a** in pure form by silica gel column chromatography failed, and produced the 4-(dimethylamino)trifluoroacetamide **3** as the only isolable product in low yield together with very polar decomposition products, possibly as a consequence (amongst other things) of a fragmentation of **2a** to *N,N*-dimethylformamidine and trifluoroacetonitrile or hydrolysis by the presence of water.

In startling contrast to **2a** and **2b**, 4-phenyl-2-(trifluoromethyl)diazadiene **2c** exhibited good stability when it was purified by silica gel column chromatography and it could be isolated and characterized by NMR spectroscopy.

Focusing on the study to evaluate the cycloaddition process of 1,3-diazadienes to prepare heterocyclic systems, we decided to use the 2-trifluoromethyl-1,3-diazadienes **2a–c** without purification. Like 2-trichloromethyldiazabutadienes, which are well behaved in cycloaddition reactions towards DMAD, the 2-trifluoromethyldiazadiene **2a** reacted efficiently when it was treated with 2.0 equivalents of DMAD at room temperature in CH_2Cl_2 solution (Scheme 3). After 3 hours, the respective 2-trifluoromethylpyrimidine **4a** was obtained in 37% overall yield (from trifluoroacetamidine **1**) accompanied by the dimethylamine-acetylene adduct **5**. In an analogous manner, 2-trifluoromethyldiazapentadiene **2b** under the same conditions gave pyrimidine **4b** in 64% overall yield. In the same way, **4c** could be obtained from **2c** in 22% overall yield.

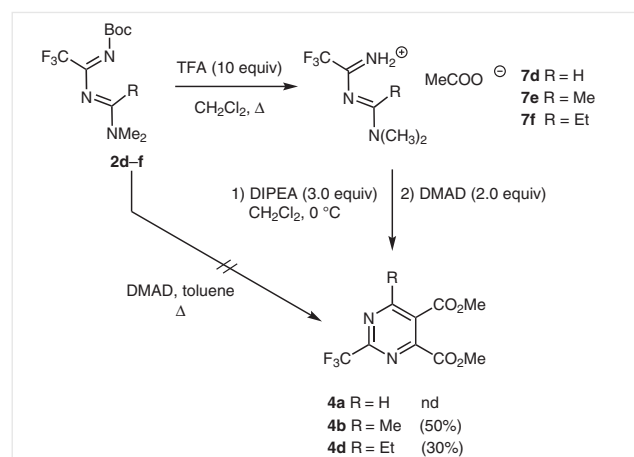**Scheme 3** Cycloaddition reaction of **2a–c** with DMAD

N-tert-Butoxycarbonylamidines are synthetic equivalents of N-unsubstituted amidines. In an effort to improve yields of the 2-trifluoromethyldiazabutadienes **2**, we proposed the protection of position 1 with the *tert*-butoxycarbonyl group (Boc). To this end, *N*-Boc-trifluoroacetamidine **6** was prepared by the reaction of **1** with di-*tert*-butylpyrocarbonate in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) and was obtained in 62% yield after flash column chromatography purification (Scheme 4). This *N*-Boc-amidine **6** shows greater stability than its predecessor **1** and reacts efficiently with amide dimethylacetals in refluxing THF solution, to give *N*-Boc-2-trifluoromethyl diazadienes **2d–f** in good yields. However, heating in refluxing toluene solution of diazadienes **2d–f** with an excess of DMAD, did not lead to the formation of the respective 2-trifluoromethylpyrimidines and only the starting materials were observed after 16 hours, possibly because of the electron-withdrawing effect of the Boc group.

Given that the Boc group deactivates diazadienes **2e–d** in the cycloaddition process with DMAD, we explored removal of the Boc group with trifluoroacetic acid (TFA) in refluxing CH_2Cl_2 solution before the cycloaddition reaction (Scheme 5). The 2-trifluoromethyldiazadienium trifluoroacetates **7d–f** were obtained as oils. The salts **7d–f** were
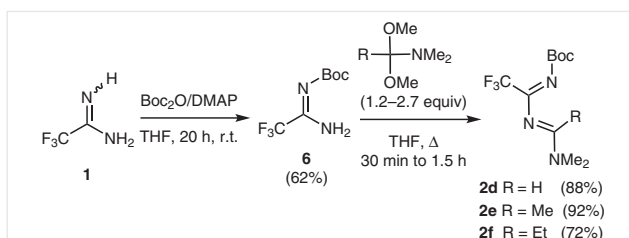

Scheme 4 Synthesis of *N*-Boc-2-trifluoromethyl-1,3-diazadienes **2d–f**

treated with DIPEA (3.0 equiv) at 0 °C in CH_2Cl_2 solution, followed by subsequent addition of DMAD (2.0 equiv) at room temperature. Under these conditions only the 2-trifluoromethylpyrimidines **4b** and **4d** could be obtained from **7e** and **7f** in 50% and 30% yield, respectively. In startling contrast, when the same reaction was carried out using **7d**, no cyclization product could be obtained and only the *N,N*-dimethylaminotrifluoroacetamide **3** was obtained. This result is consistent with the rapid hydrolysis reaction that 2-trifluoromethyldiazadiene **2** suffers when the substituent at C-4 is hydrogen.

Scheme 5 Cycloaddition reaction of 1,3-diaza-1,3-butadienes with DMAD

Recently, we reported that trichloromethyl analogues 1,3-diazadienes, react with different acyl chlorides, followed by chlorination reaction with an excess of $POCl_3$ to produce 2-trichloromethylchloropyrimidines. We decided to exemplify this type of strategy using phenylacetyl chloride and diazadiene **2e**. Once the Boc group in **2e** was removed with TFA, Et_3N was added to generate the free diazadiene **2b** followed by addition of phenylacetyl chloride, giving a mixture of the 2-trifluoromethyl-4-pyrimidone **8** and *O*-acylpyrimidine **9** (Scheme 6). Finally, treatment of this mixture of **8** and **9** with $POCl_3$ in refluxing toluene solution, afforded only 2-trifluoromethyl-4-chloropyrimidine **10** in 40% overall yield from **6**.
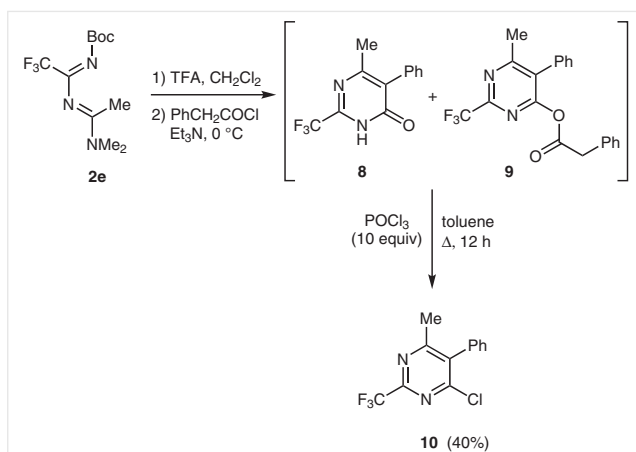
Scheme 6 Cycloaddition reaction of **2e** with phenylacetyl chloride

In summary, 2-trifluoromethyl-1,3-diazabutadienes were prepared from trifluoroacetamidine using amide acetals or by Vilsmeier–Haack reagent. 2-Trifluoromethyl-1,3-diazabutadienes in free from reacted with electron-deficient acetylenes or with acyl chlorides to form 2-trifluoromethylpyrimidine derivatives in moderate global yields. Further investigations, including the extension of this methodology to other substrates are continuing in our laboratory.

Reagents were purchased from Aldrich and used without further purification. Solvents such as THF and CH$_2$Cl$_2$ were previously dried according to standard laboratory methods. *N,N*-Dimethylpropionamide dimethylacetal[32] was prepared according to a published procedure.

The reactions were followed by thin-layer chromatography (TLC) using silica gel 60 aluminum plates, coated with fluorescent indicator F-254 from Merck, which were visualized under UV light (254 nm). Compounds were purified by column chromatography using silica gel 60 Merck 0.04 to 0.063 (230–400 mesh ASTM). Melting points reported were obtained with a Mel-Temp II apparatus, and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with Bruker Avance 300 and Varian 500 NMR Systems, in CDCl$_3$ with TMS as the internal standard; chemical shifts are reported in ppm. Mass spectra were recorded with a Shimadzu GCMS-QP2010 plus (EI, 70 eV).

Trifluoroacetamidine (1)

In a 100 mL round flask equipped with a dry-ice/acetone cooled condenser and immersed in a dry-ice/acetone bath, ammonia and trifluoroacetonitrile were condensed. The reaction was stirred at –78 °C for 1 h and the cold bath was removed. The excess of ammonia was evaporated at r.t. and the remains of ammonia were removed under vacuum to give the product as a colorless oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.98 (br s).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 154.67 (dd, *J* = 69.6, 34.8 Hz), 117.12 (q, *J* = 281.0 Hz).

^{19}F NMR (282 MHz, CDCl$_3$): δ = –74.56, –75.31.

2-Trifluoromethyl-1,3-diazabutadienes 2a,b; General Procedure

Under nitrogen atmosphere, the amide acetal (1.2 equiv) was added to a solution of trifluoroacetamidine **1** (1.0 equiv) in anhydrous THF (5.0 mL). The reaction mixture was stirred at r.t. for 16 h, then the remains of solvent and the amide acetal were evaporated under vacuum to obtain the product as an oil. These 1,3-diazadienes were used in crude form for the following reactions.

2-Trifluoromethyl-4-*N,N*-dimethylamino-1,3-diazabutadiene (2a)

According to the general procedure using **1** (0.2655 g, 2.3 mmol) and *N,N*-dimethylformamide dimethylacetal (0.36 mL, 2.7 mmol), **2a** (191 mg, 95% yield) was obtained as a yellow oil.

2-Trifluoromethyl-4-*N,N*-dimethylamino-1,3-diazapentadiene (2b)

According to the general procedure using **1** (143 mg, 1.23 mmol) and *N,N*-dimethylacetamide dimethylacetal (0.25 mL, 1.53 mmol), **2b** (0.2241 g, 96% yield) was obtained as a red oil.

N-((Dimethylamino)methylene)-2,2,2-trifluoroacetamide (3)

This product was obtained after flash column chromatography (silica gel, hexanes–EtOAc 1:1) from crude **2a** as a colorless oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.59 (s, 1 H), 3.25 (s, 3 H), 3.21 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.43 (q, *J* = 35.7 Hz), 162.49, 116.87 (q, *J* = 287.0 Hz), 41.99, 35.96.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –76.52.

MS: *m/z* (%) = 169 (23) [M$^+$ + H], 121 (18), 101 (100), 68 (48), 50 (60).

2-Trifluoromethyl-4-*N,N*-dimethylamino-4-phenyl-1,3-diazabutadiene (2c)

Under a nitrogen atmosphere, phosphorus oxychloride (0.13 mL, 1.39 mmol, 1.0 equiv) was added dropwise at r.t. to a solution of *N,N*-dimethylbenzamide (210 mg, 1.41 mmol, 1.0 equiv) in anhydrous CH$_2$Cl$_2$ (4.0 mL) and the solution was heated at 40 °C for 5 h. After this time the mixture was diluted with anhydrous CH$_2$Cl$_2$ (5.0 mL) and a solution of trifluoroacetamidine **1** (166 mg, 1.49 mmol, 1.05 equiv) in anhydrous THF (2.0 mL) was added dropwise at 0 °C and the mixture was stirred overnight at r.t. Finally, DIPEA (0.54 mL, 3.1 mmol, 2.2 equiv) was added dropwise at 0 °C and the reaction mixture was washed with saturated NaCl solution (20.0 mL), the product was extracted with CH$_2$Cl$_2$ (3 × 15.0 mL), and the organic phase was dried over Na$_2$SO$_4$ and concentrated under vacuum. Compound **2c** was purified by flash column chromatography (silica gel, hexanes–EtOAc 1:1).

Yield: 274 mg (80%); brown oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.39–7.34 (m, 3 H), 7.25–7.19 (m, 2 H), 3.24 (s, 3 H), 2.94 (s, 3 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 170.52, 164.36 (q, *J* = 35.6 Hz), 132.56, 130.54, 128.78, 127.42, 116.83 (q, *J* = 288.3 Hz), 40.50, 38.99.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –75.82.

N-*tert*-Butoxycarbonyltrifluoroacetamidine (6)

Under a nitrogen atmosphere, a solution of di-*tert*-butylpyrocarbonate (4.88 g, 22.36 mmol, 1.02 equiv) in anhydrous THF (10.0 mL) was added dropwise at r.t. to a solution of trifluoroacetamidine **1** (2.46 g, 22 mmol, 1.0 equiv) and DMAP (5 mol%, catalytic amount) in anhydrous THF (10.0 mL). The reaction mixture was stirred for 20 h. After this time, the reaction mixture was washed with saturated NH$_4$Cl

solution (30.0 mL) and extracted with EtOAc (3 × 20.0 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash column chromatography (silica gel, hexanes–EtOAc 8:2) to give **6**.

Yield: 2.9 g (62%); colorless oil.

1-*tert*-Butoxycarbonyl-2-trifluoromethyl-1,3-diazabutadienes 2d–f; General Procedure

Under a nitrogen atmosphere, the amide acetal (1.2–2.7 equiv) was added to a solution of *N*-*tert*-butoxycarbonyltrifluoroacetamidine **6** (1.0 equiv) in anhydrous THF (5.0 mL). The solution was heated at reflux (30–90 min), then the remains of solvent and the amide acetal were evaporated under vacuum to obtain the product as an oil. These compounds were used in crude form for the following reactions.

1-*tert*-Butoxycarbonyl-2-trifluoromethyl-4-*N,N*-dimethylamino-1,3-diazabutadiene (2d)

By following the general procedure using **6** (210 mg, 1.01 mmol), *N,N*-dimethylformamide dimethylacetal (0.17 mL, 1.2 mmol, 1.2 equiv) in 30 min, **2d** was obtained.

Yield: 203 mg (88%); yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.12 (s, 1 H), 3.13 (s, 3 H), 3.09 (s, 3 H), 1.51 (s, 9 H).

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.32.

1-*tert*-Butoxycabonyl-2-trifluoromethyl-4-*N,N*-dimethylamino-1,3-diazapentadiene (2e)

By following the general procedure using **6** (240 mg, 1.17 mmol), *N,N*-dimethylacetamide dimethylacetal (0.28 mL, 1.72 mmol, 1.5 equiv) in 1 h, **2e** was obtained.

Yield: 300 mg (92%); yellow oil.

1-*tert*-Butoxycabonyl-2-trifluoromethyl-4-*N,N*-dimethylamino-1,3-diazahexadiene (2f)

By following the general procedure using **6** (134 mg, 0.634 mmol), *N,N*-dimethylpropionamide dimethylacetal (253 mg. 1.72 mmol, 2.7 equiv) in 1.5 h, **2f** was obtained.

Yield: 130 mg (72%); yellow oil.

2-Trifluoromethylpyrimidines 4a–c; General Procedure

Under a nitrogen atmosphere, DMAD (2.0 equiv) was added dropwise to a solution of 1,3-diazabutadiene **2** in anhydrous CH$_2$Cl$_2$ (5.0 mL) at r.t., then the reaction was stirred for 3 h. After this time, the mixture was washed with saturated NH$_4$Cl solution (20.0 mL) and extracted with CH$_2$Cl$_2$ (3 × 15.0 mL). The organic phase was dried over Na$_2$SO$_4$ and the solvent was evaporated under vacuum. The product was purified by column chromatography.

Dimethyl 2-Trifluoromethylpyrimidine-4,5-dicarboxylate (4a)

By following the general procedure using **2a** (190 mg, 1.14 mmol) and DMAD (0.28 mL, 2.29 mmol), **4a** was obtained and purified by column chromatography (silica gel, hexanes–EtOAc 9:1).

Yield: 110 mg (37%); white solid; mp 79–80 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.43 (s, 1 H), 4.06 (s, 3 H), 4.03 (s, 3 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 163.90, 162.34, 160.10, 159.58, 158.42 (q, *J* = 38.3 Hz), 123.61, 118.83 (q, *J* = 276.2 Hz), 53.73, 53.65.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.34.

MS: *m/z* (%) = 264 (5) [M$^+$], 233 (92), 206 (39), 175 (86), 148 (90), 51 (100).

Dimethyl 6-Methyl-2-trifluoromethylpyrimidine-4,5-dicarboxylate (4b)

By following the general procedure using **2b** (220 mg, 1.24 mmol) and DMAD (0.3 mL, 2.44 mmol), **4b** was obtained and purified by column chromatography (silica gel, hexanes–EtOAc 9:1).

Yield: 280 mg (64%); white solid; mp 69–70 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.04 (s, 3 H), 4.02 (s, 3 H), 2.76 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 169.23, 165.29, 163.48, 156.34 (q, *J* = 37.8 Hz), 153.92, 128.19, 118.92 (q, *J* = 276.1 Hz), 53.89, 53.52, 22.74.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.42.

MS: *m/z* (%) = 278 (4) [M$^+$], 219 (35), 190 (100), 161 (36), 110 (33).

Dimethyl 6-Phenyl-2-trifluoromethylpyrimidine-4,5-dicarboxylate (4c)

By following the general procedure using **2c** and DMAD (0.34 mL, 2.76 mmol), **4c** was obtained and purified by column chromatography (silica gel, hexanes–EtOAc 9:1).

Yield: 100 mg (22%); white solid; mp 120–122 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.80–7.77 (m, 2 H), 7.61–7.50 (m, 3 H), 4.06 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.39, 165.46, 162.99, 156.07 (q, *J* = 37.9 Hz), 154.44, 134.68, 131.29, 128.57, 128.41, 126.96, 118.57 (q, *J* = 276.2 Hz), 53.55, 53.02.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.28.

MS: *m/z* (%) = 340 (86) [M$^+$], 325 (100), 309 (85), 224 (91), 127 (88).

Dimethyl 6-Ethyl-2-trifluoromethylpyrimidine-4,5-dicarboxylate (4d)

Under a nitrogen atmosphere, a solution of 1,3-diazabutadiene **2f** (130 mg, 0.44 mmol) and TFA (0.35 mL, 4.54 mmol, 10.0 equiv) in anhydrous CH$_2$Cl$_2$ (4.0 mL) was heated at reflux for 3 h and stirred for 15 h at r.t. After this time, the excess of TFA and solvent were removed under vacuum to obtain the 1,3-diazadienium trifluoroacetate as a brown oil. Subsequently, the oil was dissolved in anhydrous CH$_2$Cl$_2$ (1.0 mL), DIPEA (0.24 mL, 1.37 mmol, 3.0 equiv) and DMAD (0.11 mL, 0.89 mmol, 2.0 equiv) were added dropwise at 0 °C and the mixture reaction was stirred at r.t. for 3 h. After this time, the mixture was washed with saturated NH$_4$Cl solution (20.0 mL) and extracted with CH$_2$Cl$_2$ (3 × 15.0 mL). The organic phase was dried over Na$_2$SO$_4$ and the solvent was evaporated under vacuum. The product was purified by column chromatography (silica gel, hexanes–EtOAc 8:2) to give **4d**.

Yield: 55.6 mg (30%); white solid; mp 48–49 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.03 (s, 3 H), 4.01 (s, 3 H), 2.99 (q, 2 H, *J* = 7.5 Hz), 1.37 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.52, 165.47, 163.55, 156.59 (q, *J* = 37.8 Hz), 153.68, 128.05, 119.04 (q, *J* = 276.1 Hz), 53.91, 53.51, 29.19, 12.42.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.37.

MS: *m/z* (%) = 292 (35) [M$^+$], 260 (73), 232 (25), 202 (56), 174 (100), 59 (57).

Cycloaddition Reaction of 1,3-Diazabutadienium Trifluoroacetate 7e with Phenylacetyl Chloride

Under a nitrogen atmosphere, Et$_3$N (0.68 mL, 4.87 mmol, 6.0 equiv) and phenylacetyl chloride (0.21 mL, 1.59 mmol, 2.0 equiv) were added dropwise at 0 °C to a solution of 1,3-diazabutadienium trifluoroacetate (generated from 220 mg of **2e**) in anhydrous CH$_2$Cl$_2$ (5.0 mL). The reaction was stirred at r.t. for 2 h. After this time, two products were observed by TLC analysis (**8** and **9**) and the mixture reaction was washed with saturated NH$_4$Cl solution (10.0 mL) and the product was extracted with CH$_2$Cl$_2$ (3 × 15.0 mL). The organic phase was dried over Na$_2$SO$_4$ and the solvent was evaporated under vacuum. The product was purified by column chromatography (silica gel, using hexanes–EtOAc 9:1).

6-Methyl-5-phenyl-2-trifluoromethylpyrimidin-4(3*H*)-one (8)

Yield: 55.6 mg (28%); white solid; mp 177–179 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.47–7.41 (m, 3 H), 7.32–7.26 (m, 2 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 164.34, 163.83, 147.83 (q, *J* = 38.3 Hz), 131.88, 129.55, 128.59, 128.53, 126.21, 117.94 (q, *J* = 276.4 Hz), 22.74.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.75.

MS: *m/z* (%) = 254 (97) [M⁺], 253 (100), 233 (45), 89 (45).

6-Methyl-5-phenyl-2-trifluoromethylpyrimidin-4-yl-2-phenylacetate (9)

Yield: 46 mg (20%); white solid; mp 137–140 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.40–7.35 (m, 3 H), 7.23–7.21 (m, 3 H), 7.14–7.11 (m, 2 H), 6.94–6.93 (m, 2 H), 3.60 (s, 2 H), 2.47 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.12, 167.16, 162.58, 154.21 (q, *J* = 37.5 Hz), 131.08, 130.26, 128.64, 128.43, 128.22, 128.07, 127.97, 127.86, 126.58, 118.35 (q, *J* = 275.7 Hz), 39.90, 22.10.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.27.

MS: *m/z* (%) = 254 (56), 253 (57), 136 (100), 92 (69), 65 (65).

4-Chloro-6-methyl-5-phenyl-2-trifluoromethylpyrimidine (10)

POCl$_3$ (2.0 mL, 21.8 mmol, 10.0 equiv) was added to the crude mixture of **8** and **9** in toluene (5.0 mL) and the mixture was heated at reflux for 12 h. After this time, the solvent and residual POCl$_3$ were evaporated under vacuum and the residue was washed with saturated NaHCO$_3$ solution (30.0 mL), and the product was extracted with CH$_2$Cl$_2$ (5 × 10 mL). The organic phase was dried over Na$_2$SO$_4$ and the solvent was removed under vacuum. The product was purified by column chromatography (silica gel, hexanes–EtOAc 9:1) to give **10**.

Yield: 0.1196 g (40% from **6**); white solid; mp 73–74 °C (CH$_2$Cl$_2$–hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.54–7.52 (m, 3 H), 7.26–7.24 (m, 2 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.86, 160.94, 154.38 (q, *J* = 37.9 Hz), 135.60, 133.08, 128.95, 128.82, 128.25, 118.65 (q, *J* = 275.9 Hz), 23.29.

^{19}F NMR (282 MHz, CDCl$_3$): δ = –70.35.

MS: *m/z* (%) = 274 (32) [M⁺+2], 272 (100) [M⁺], 140 (54), 115 (52), 69 (66).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610444.

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