1,3-Dipolar Cycloadditions of Ethyl 2-Diazo-3,3,3-trifluoropropanoate to Alkynes and [1,5] Sigmatropic Rearrangements of the Resulting 3*H*-Pyrazoles: Synthesis of Mono-, Bis- and Tris(trifluoromethyl)-Substituted Pyrazoles

by **Daniel Gladow**, **Sebastian Doniz-Kettenmann**, and **Hans-Ulrich Reissig***

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, DE-14195 Berlin (fax: +49(30)83855367; e-mail: hans.reissig@chemie.fu-berlin.de)

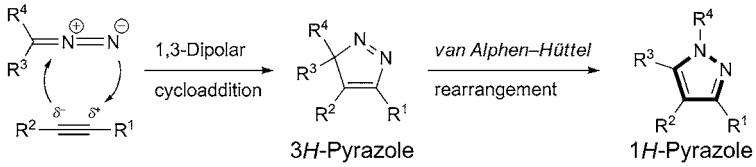
The 1,3-dipolar cycloadditions of ethyl 2-diazo-3,3,3-trifluoropropanoate with electron-rich and electron-deficient alkynes, as well as the *van Alphen–Hüttel* rearrangements of the resulting 3*H*-pyrazoles were investigated. These reactions led to a series of CF_3-substituted pyrazoles in good overall yields. Phenyl- and diphenylacetylene proved to be unreactive, but, at high temperature, the diazoalkane and phenylacetylene furnished a cyclopropene derivative. As expected, the 1,3-dipolar cycloaddition to the ynamine occurred much faster than those to electron-deficient alkynes. With one exception, all cycloadditions proceeded with excellent regioselectivities. The [1,5] sigmatropic rearrangement of the primary 3*H*-pyrazoles provided products with shifted acyl groups; products resulting from the migration of a CF_3 group were not detected. In agreement with literature reports, this rearrangement occurs faster with 3*H*-pyrazoles bearing electron-withdrawing substituents.

Introduction. – Although rare in nature, the intriguing pharmacological properties[1]) and importance in agriculture [2] of pyrazoles, five-membered heterocycles with two adjacent N-atoms, have raised great interest in such derivatives in the last decade [3]. A general approach to functionalized pyrazoles consists of the addition of hydrazine derivatives to 1,3-dicarbonyl compounds or other 1,3-bis-electrophiles [4]. For electronic reasons, this approach most often lacks satisfactory regioselectivity. On the contrary, the 1,3-dipolar cycloadditions of diazoalkanes to alkenes or alkynes are intrinsically more regioselective due to the increased electronegativity difference between the C- and the N-atom of the 1,3-dipole [5–8]. It is well-known that 3*H*-pyrazoles obtained by cycloadditions of disubstituted diazoalkanes undergo thermal [1,5] sigmatropic rearrangements to aromatic 1*H*-pyrazoles, as discovered by *van Alphen,* and later investigated systematically by *Hüttel et al.* (*Scheme 1*) [6][9][10].

Despite the high abundance of fluorine in the Earth's crust in form of inorganic fluorides, natural organofluorine compounds are extremely rare [11]. In contrast, the introduction of F into organic molecules, frequently as a CF_3 group (for selected reviews and recent original articles, see [12]) has most often a severe impact on their biological, pharmacological, and agricultural profile [13]. Not surprisingly, three out of five top-selling pharmaceuticals contain at least one F-atom, and the number of compounds is steadily increasing [14]. For example, the blockbuster drug *Celecoxib*

[1]) For a review, see [1a]. For recent original reports, see [1b–1d].

Scheme 1. *Construction of Pyrazole Derivatives by [3+2] Cycloadditions of Diazo Compounds to Alkynes and Subsequent [1,5] Sigmatropic Rearrangement*



(*Celebrex*®) contains a pyrazole ring with a CF_3 moiety which is essential for its pharmacological activity (*Fig.*) [15]. AS-136A [16] and SC-560 [17] are other successful drug candidates. Trifluoromethyl-substituted N*H*-pyrazoles and derivatives thereof were also studied as mono- and bidentate ligands in transition-metal complexes [18].

Remarkably, 1,3-dipolar cycloadditions of easily available ethyl 2-diazo-3,3,3-trifluoropropanoate (**1**; *cf. Scheme 2*) have so far not been reported, although they should provide interestingly functionalized heterocycles. In connection with our ongoing research on organofluorine compounds and our recent reports on the synthesis of perfluoro-substituted donor–acceptor cyclopropanes [18][19], we were interested in the reactivity of compound **1** as a 1,3-dipole for the preparation of selectively CF_3-substituted pyrazoles. We were also curious to learn how the strong inductive electron-withdrawing effect of the CF_3 group influences the reactivity pattern in comparison to the well-investigated dimethyl diazomalonate [6]. We also wanted to study how the subsequent [1,5] sigmatropic rearrangements of the resulting 3*H*-pyrazoles are effected by the presence of one or more CF_3 groups.

Results. – The reaction of neat ethyl 2-diazo-3,3,3-trifluoropropanoate (**1**) with the electron-rich 1-(diethylamino)prop-1-yne (**2**) in equimolar amounts furnished in 3 h at 40° 3*H*-pyrazole-3-carboxylate **3** in 50% yield as yellow oil (*Scheme 2*). The constitution of **3** was deduced from the observed coupling constant of 1.2 Hz for $(MeCH_2)_2N$ in the ^{13}C-NMR spectrum, which results from coupling to the adjacent CF_3 group. Under the applied conditions, the formation of unknown side-products was observed, and **1** was not fully consumed. The reaction proceeded more efficiently with a slight excess (1.5 equiv.) of **2** in refluxing Et_2O, cleanly affording product **3** as yellow oil in 81% yield.

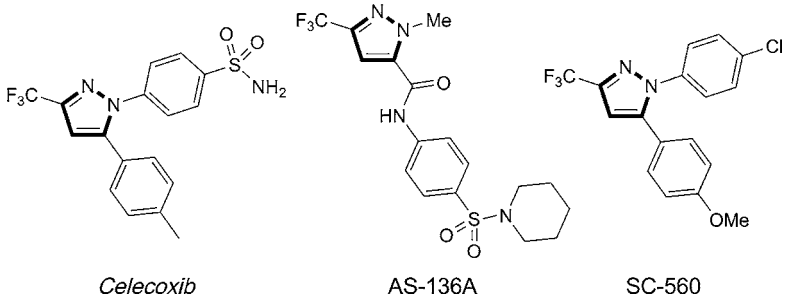
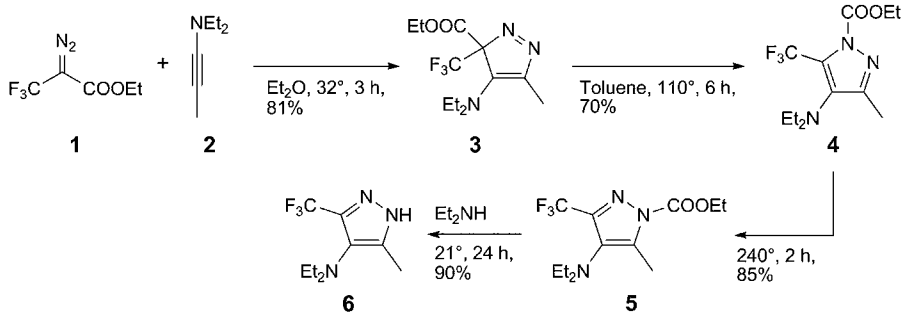


Figure. *Drugs or drug candidates with CF_3-substituted pyrazole units*

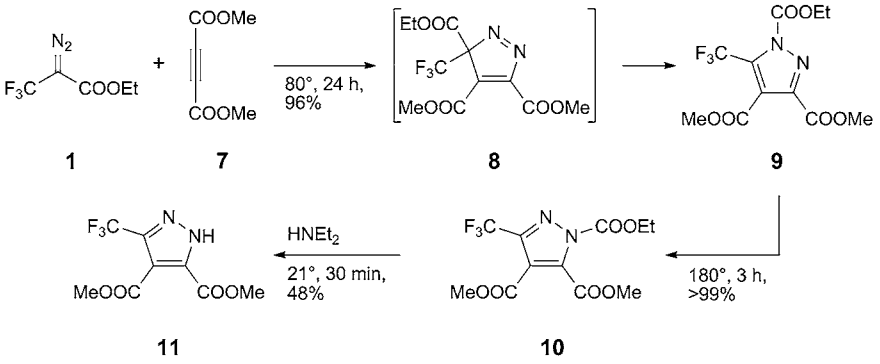
Scheme 2. *Cycloaddition of Ethyl 2-Diazo-3,3,3-trifluoropropanoate* (**1**) *with 1-(Diethylamino)prop-1-yne* (**2**) *and Subsequent [1,5] Sigmatropic Rearrangements*



Heating of 3*H*-pyrazole-3-carboxylate **3** in refluxing toluene provided the expected 1*H*-pyrazole-1-carboxylate **4** in 70% yield. The rearranged product **4** was clearly distinguished from its precursor **3** by comparison of the chemical shifts of the C=O C-atom in the ^{13}C-NMR spectra. Interestingly, **4** shows fluorescence with an emission at 451 nm. At this stage, the spectroscopic data do not rule out that **4** might have undergone a second [1,5] sigmatropic rearrangement to isomeric pyrazole **5**. To eliminate this possibility, **4** was heated to 240° to yield a colorless compound with small but significant differences in the NMR spectra and without photoluminescent activity. The obtained data are in agreement with structure **5**. Deacylation of **5** proceeded smoothly by treatment with Et_2NH at room temperature and afforded 1*H*-pyrazole **6** in 90% yield.

Next, we studied the cycloadditions of ethyl 2-diazo-3,3,3-trifluoropropanoate (**1**) with a series of electron-deficient alkynes. In detail, we investigated the influence of alkoxycarbonyl *vs.* CF_3 substitution at the alkyne regarding the reactivity, regioselectivity, and the stability of products. Heating of **1** and dimethyl acetylenedicarboxylate (**7**) to 80° in a sealed tube without solvent cleanly provided 1*H*-pyrazole-tricarboxylate **9** in 96% yield (*Scheme 3*). In this case, the *van Alphen–Hüttel* rearrangement was

Scheme 3. *Cycloaddition of Diazo Ester* **1** *to Dimethyl Acetylenedicarboxylate* (**7**) *and Subsequent Reactions*

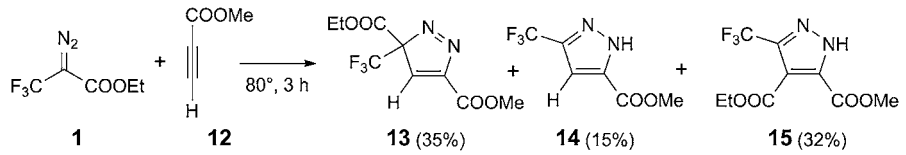


apparently faster than the preceding 1,3-dipolar cycloaddition; hence, the primary 3*H*-pyrazole **8** was not isolated. The rearrangement of **9** to 1*H*-pyrazole-tricarboxylate **10** proceeded quantitatively at 180°, and deacylation of **10** with Et_2NH at room temperature smoothly provided 1*H*-pyrazole-dicarboxylate **11**. After purification on silica gel, the pure compound was isolated in 48% yield.

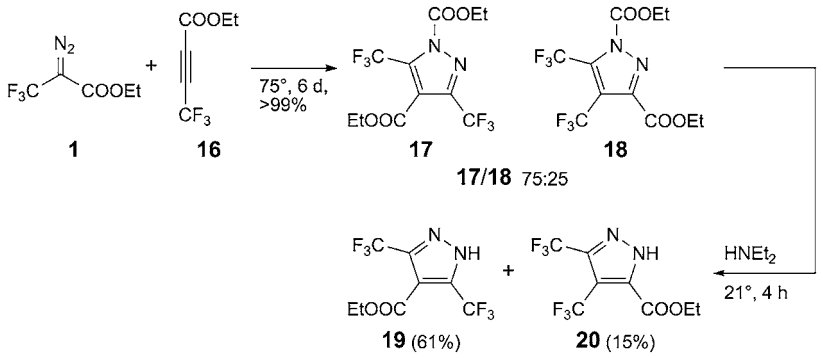
We next investigated the less electron-deficient methyl prop-2-ynoate (**12**) in order to test its reactivity and regioselectivity. Due to the higher volatility of **12**, diazo ester **1** was reacted with an excess of **12** (10 equiv.) under solvent-free conditions (*Scheme 4*). At ambient temperature, the reaction required 22 d to be completed, yet at 80° **1** was fully consumed within 3 h. In both cases an identical mixture of products was obtained, which was separated by column chromatography (CC). The initially formed 3*H*-pyrazole-dicarboxylate **13** was obtained in 35% yield. Under the reaction conditions employed, a minor amount of **13** underwent EtOCO-group transfer to the N-atom, and subsequent deacylation led to 15% of pyrazole **14**. Remarkably, a larger amount of **13** underwent [1,5] sigmatropic rearrangement of the EtOCO group to C(4), followed by H-atom shift, leading to pyrazole derivative **15** in 32% yield. As expected, the spectroscopic data of **15** were very similar to those of the almost identical compound **11**.

Now we directed our attention to CF_3-substituted alkynes. Under neat conditions, ethyl 4,4,4-trifluorobut-2-ynoate (**16**) reacted with diazo ester **1** within 6 d at 75° to quantitatively furnish a 75:25 mixture of the two regioisomeric *N*-EtOCO-substituted pyrazoles **17** and **18** (*Scheme 5*). The constitutional assignment of the two isomers was achieved by ^{19}F-NMR spectroscopy: The two CF_3 groups show two *singlet*s for **17**, but two *quadruplet*s with a coupling constant of 9.7 Hz for **18**, evidencing to the proximity

Scheme 4. *Cycloaddition of Diazo Ester* **1** *with Methyl Prop-2-ynoate* (**12**)



Scheme 5. *Reaction of Diazo Ester* **1** *with Ethyl 4,4,4-Trifluorobut-2-ynoate* (**16**) *and Subsequent Reactions*



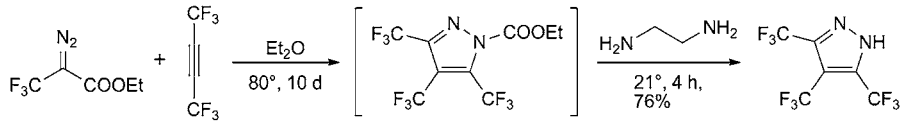
of these two moieties. As expected, the adduct of the 1,3-dipolar cycloaddition was not detected by NMR spectroscopy. An attempt to separate **17** and **18** by CC on silica gel led to partial deacylation and decomposition. Fortunately, deacylation of the crude product mixture **17**/**18** with Et_2NH proceeded smoothly and afforded a mixture of clean pyrazoles, **19**/**20**. This mixture was successfully separated by HPLC and afforded **19** and **20** in 61 and 15% yield, respectively, allowing a full characterization of the two isomers.

We then investigated the addition of diazo ester **1** to hexafluorobutyne **21**. For a better handling of **21**, the reaction was not performed under neat conditions, but in Et_2O as the solvent in a sealed tube. The cycloaddition was slow, even employing 2 equiv. of **21**, and complete consumption of **1** was detected by ^{19}F-NMR spectroscopy only after 10 d at 80° (*Scheme 6*). NMR Analysis of the crude material evidenced the formation of the *N*-EtOCO-substituted pyrazole **22**. The ^{1}H-NMR spectrum revealed the presence of an EtOCO group, the ^{13}C-NMR spectrum indicated the connection of the EtOCO group to a *N*-atom, and the ^{19}F-NMR spectrum exhibited signals for three different CF_3 groups. There was no indication that the primary cycloaddition product was still present. Attempts to purify the *N*-acylated pyrazole by CC or by distillation failed, whereas deacylation with Et_2NH led to an inseparable mixture of compound **23**, and the resulting carbamate by-product. Gratifyingly, immediate treatment of the crude product **22** with $NH_2CH_2CH_2NH_2$ at room temperature, followed by an acidic extraction and distillation, afforded the desired tris(trifluoromethyl)-substituted 1*H*-pyrazole **23** in 76% overall yield.

It should be mentioned that two procedures for the preparation of **23** have already been published. *Atherton* and *Fields* described a highly efficient 1,3-dipolar cycloaddition of diazotrifluoroethane with **21**; however, it has to be kept in mind that the mixture is potentially explosive if warmed too rapidly [20]. The alternative five-step sequence recently reported by *Gerus et al.* allows preparation on larger scale; however, in the crucial step toxic gases such as SF_4 and HF are required [21]. In view of the commercial availability of starting materials and the increased stability of diazo alkane **1** – compared to diazo compounds without electron-withdrawing groups – our approach is a viable alternative to the reported procedures.

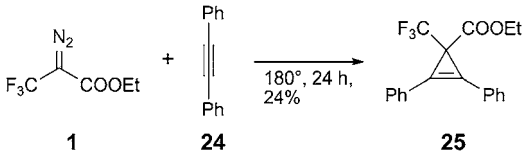
Alkyl diazoacetates were reported to react with phenylacetylene and diphenylacetylene (**24**) in high yields [6][22]. Surprisingly, all our attempts to isolate pyrazoles from the addition of **1** to phenylacetylene or **24** were unsuccessful. These alkynes apparently do not undergo smooth 1,3-dipolar cycloadditions as desired but afforded after 4 weeks at 80° complex mixtures. Ultrasonification, microwave irradiation, or heating to 110° did not alter the outcome. However, heating of **1** to 180° in the presence of 1 equiv. of **24** led to cyclopropene **25**, probably by N_2 extrusion of **1** and carbene addition to alkyne **24** (*Scheme 7*) [23].

Scheme 6. *Cycloaddition of Diazo Ester* **1** *with 1,1,1,4,4,4-Hexafluorobut-2-yne* (**21**) *and Subsequent Deacylation*



1 **21** **22** **23**

Scheme 7. *Cyclopropenation of 1,2-Diphenylacetylene* (**24**) *with Diazo Ester* **1**

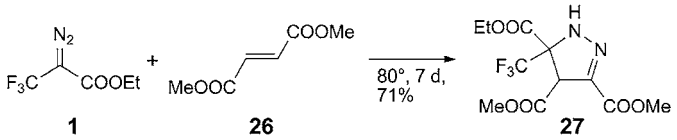


1 **24** **25**

For comparison, we briefly studied the reactions of diazo ester **1** with typical electron-deficient and electron-rich alkenes. Stoichiometric amounts of neat dimethyl fumarate (**26**) and **1** afforded after 7 d at 80° the 4,5-dihydro-1*H*-pyrazole-tricarboxylate **27** in 71% yield (*Scheme 8*). The initially formed 4,5-dihydro-3*H*-pyrazole tautomerizes to **27** that is formed as a single diastereoisomer. Under the conditions employed, the thermodynamically more stable diastereoisomer should dominate, presumably the compound with *trans*-configuration of the two alkoxycarbonyl groups. Dimethyl maleate did not react with diazo ester **1** under these conditions.

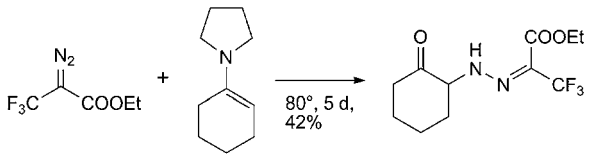
Heating of neat diazo ester **1** with an excess of 1-(pyrrolidin-1-yl)cyclohexene (**28**) at 80° for 5 d afforded hydrazone **29**. CC on silica gel and subsequent HPLC purification afforded the pure compound in 42% yield (*Scheme 9*). In principle, the obtained azo-coupling product could also be existent as a hydrazone isomer of **29** with the C=N moiety in conjugation with the cyclohexane CO group [24]. The constitution of **29** as depicted was evidenced by the downfield signal (δ 115.5 ppm) of the C=N moiety in the ^{13}C-NMR spectrum, which showed a typical ^{2}J coupling of 35.2 Hz with the adjacent CF_3 group. For the alternative hydrazone tautomer, a similar chemical shift for the C=N moiety is to be expected, however, no comparable coupling to F-atoms is possible. We assume the (*E*)-geometry for **29**, which should be favored due to a possible H-bond.

Scheme 8. *Cycloaddition of Diazo Ester* **1** *with Dimethyl Fumarate* (**26**)



1 **26** **27**

Scheme 9. *Azo Coupling of 1-(Pyrrolidin-1-yl)cyclohexene* (**28**) *and Diazo Ester* **1**



1 **28** **29**

Discussion. – The following aspects of our results should be discussed: *i*) the rate and the regioselectivity of the 1,3-dipolar cycloadditions and *ii*) the facility and selectivity of the [1,5] sigmatropic rearrangements of the resulting 3*H*-pyrazoles.

The rates of 1,3-dipolar cycloadditions are strongly influenced by electronic and steric effects, and the balance between these two basic effects is often subtle [25]. The reactions reported above demonstrate that ethyl 2-diazo-3,3,3-trifluoropropanoate (**1**) reacts rapidly with the electron-rich 1-(diethylamino)prop-1-yne (**2**), but slower with the strongly electron-deficient alkynes dimethyl acetylenedicarboxylate (**7**) and methyl prop-2-ynoate (**12**). Although monoester **12** is less electron-deficient than diester **7**, it is also less hindered, and hence the cycloaddition is slightly faster. The reactions with ethyl 4,4,4-trifluorobut-2-ynoate (**16**) and 1,1,1,4,4,4-hexafluorobut-2-yne (**21**) proceed considerably slower, since these compounds are disubstituted, and only in **16** the alkoxycarbonyl group acts as a strong acceptor. Compared to the alkoxycarbonyl group, a CF_3 group has apparently only a closely sufficient inductive electron-withdrawing effect. Phenylacetylene and diphenylacetylene (**24**) did not participate in a 1,3-dipolar cycloaddition with diazo ester **1** due to the lack of electronic activation. From these qualitative observations, the order of reactivity of alkynes for the cycloaddition with diazo ester **1** can be estimated as: $\mathbf{2} > \mathbf{12} > \mathbf{7} > \mathbf{16} \approx \mathbf{21} >> \mathbf{24}$. The reactivity of dimethyl fumarate (**26**) towards **1** is comparable to that of alkyne **16** and **21**.

Within the framework of the frontier-orbital model, diazo alkane **1** can be assigned as *Sustmann* type-III dipole [26] being related to dimethyl diazomalonate [6]. For an electron-rich alkyne such as **2**, the HOMO(alkyne)–LUMO(diazoalkane) interaction is very dominant, whereas, for strongly electron-deficient alkynes, the LUMO(alkyne)–HOMO(diazoalkane) interaction is more important. Dipolarophiles without electronic activation react sluggish or not at all. Since **1** is slightly less electron-deficient than dimethyl diazomalonate, its reactions with electron-deficient dipolarophiles merely occur with moderate rate.

The cycloadditions of diazo ester **1** to alkynes **2** and **12** are perfectly regioselective with the directions of addition being the same as reported in [6] for dimethyl diazomalonate, which may again be explained by the frontier-orbital model considering the orbital coefficients of the components in the dominant HOMO–LUMO interaction. However, this simple model cannot correctly predict the ratio of regioisomers formed in the cycloaddition of diazo ester **1** and alkyne **16** (*Scheme 5*). A ratio of 3:1 at 75° implies an energy difference of only 3.2 kJ/mol of the transition states, leading to the two isomers. This small difference is beyond the scope of frontier-orbital considerations and requires more sophisticated calculations including steric interactions. Although a different diazoalkane was used, *Shen* and co-workers reported a similar ratio of regioisomers in the addition of ethyl diazoacetate to methyl 4,4,4-trifluorobut-2-ynoate providing a 5:1 mixture of the two isomeric pyrazoles (*Scheme 10*) [27].

The facility of 3*H*-pyrazoles to undergo a thermal *van Alphen–Hüttel* rearrangement strongly depends on the ability of the pyrazole core to stabilize a partial negative charge and the ability of the migrating group to stabilize a partial positive charge[2]).

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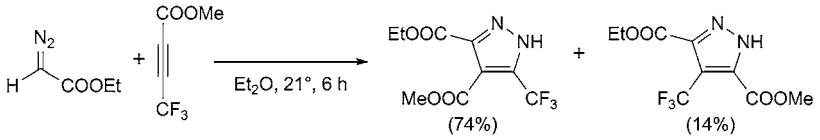
[2]) Calculations mentioned in [10] and refs. cit. therein.

Scheme 10. *Cycloaddition of Ethyl 2-Diazoacetate with Methyl 4,4,4-Trifluorobut-2-ynoate* [27]



The most important observation with our compounds was the fact that a migration of the CF_3 group was never detected. Based on the literature reports and our results, we can propose the following migratory tendency for thermal *van Alphen–Hüttel* rearrangements: CF_3 < alkyl < Ph < COR << H [6][9][10].

The electron-donating effect of the Et_2N group of 3*H*-pyrazole **3** clearly hampers the migration of the EtOCO group, and hence the first [1,5] sigmatropic rearrangement to give pyrazole **4** proceeded only at 110° (*Scheme 2*). The second rearrangement to pyrazole **5** starts from an aromatic compound, and, therefore, a higher activation barrier has to be overcome requiring heating to 240°. In contrast, the [1,5] sigmatropic rearrangement of electron-deficient 3*H*-pyrazole **8** was even faster than the cycloaddition (occurring at 80°; see *Scheme 3*). The rearrangement of 4-unsubstituted 3*H*-pyrazole **13** (*Scheme 4*) was in between these two cases, whereby the competitive migration of the alkoxycarbonyl group to C(4) was preferred over the migration to the N-atom.

Conclusions. – The 1,3-dipolar reactivity of 2-diazo-3,3,3-trifluoropropanoate (**1**) towards alkynes and alkenes was studied and compared with that reported for related electron-deficient diazoalkanes. With the exception of 1-(diethylamino)prop-1-yne (**2**) and hexafluorobutyne (**21**), all additions proceeded efficiently without solvents. The primary products were successfully isomerized and/or deacylated to provide the target pyrazoles containing one, two, or three CF_3 groups in good overall yields. Electronically unactivated alkynes did not afford the desired pyrazoles. At high temperature, decomposition of **1** to the free carbene led to the cyclopropenation of diphenylacetylene (**24**) in moderate yield. Addition of neat **1** to dimethyl fumarate (**26**) afforded the expected dihydropyrazole in good yield, whereas with 1-(pyrrolidin-1-yl)cyclohexene (**28**) only azo coupling was observed. Overall, our experiments reveal that 2-diazo-3,3,3-trifluoropropanoate (**1**) is an excellent 1,3-dipole providing a range of interesting pyrazoles with CF_3 groups. In addition, interesting mechanistic observations were made concerning the cycloaddition step and the subsequent [1,5] sigmatropic rearrangements to 1*H*-pyrazoles.

Experimental Part

General. Reactions were generally performed under Ar in flame-dried flasks. Solvents and reagents were added by syringes. Solvents were dried by standard procedures. *Ethyl 2-diazo-3,3,3-trifluoropropanoate* (**1**) [28] and N,N-*diethylprop-1-yn-1-amine* (**2**) [29] were prepared according to literature procedures. Reagents were purchased and were used as received without further purification. Bulb-to-bulb distillations were performed with a *Büchi* glass oven (*B-585*). Column chromatography (CC): SiO_2 (230–400 mesh; *Merck* or *Fluka*). Prep. HPLC: *Nucleosil 50-5* column, *Macherey-Nagel*; 96 ml/min; UV

detection at 254 nm. Yields refer to anal. pure samples. M.p.: *Reichert* apparatus *Thermovar*; uncorrected. UV/VIS Spectra: *Scinco S-3150 PDA* spectrophotometer; quartz cuvettes (1 cm); maxima (max.) in nm; molar extinction coefficients ε [dm^3/mol·cm] as log ε; sh, shoulder. Photoluminescence spectra (PL): *JASCO FP-6500*; quartz cuvettes (1 cm). IR Spectra: *JASCO FT/IR-4100* spectrometer. NMR Spectra: *Bruker* (*AVIII 700*) and *JEOL* (*ECS 500*, *ECX 400*, and *Eclipse 500*) instruments; chemical shifts relative to Me_4Si (δ(H) 0.00), $CDCl_3$ (δ(H) 7.26; δ(C) 77.2; δ(F), frequency calibrated lock with $\pm$1 ppm deviation); all ^{13}C-NMR spectra ^{1}H- or ^{19}F-decoupled; m_c, centered *multiplet*; coupling constants in Hz. HR-MS: *Agilent 6210* (ESI-TOF) instrument. Elemental analyses: *PerkinElmer CHN-Analyzer 2400* and *Vario EL Elemental Analyzer*.

*Ethyl 4-(Diethylamino)-5-methyl-3-(trifluoromethyl)-3*H*-pyrazole-3-carboxylate* (**3**). Compound **1** (500 mg, 2.75 mmol) was added to a soln. of **2** (458 mg, 4.12 mmol) in Et_2O (5 ml), and the resulting mixture was stirred at reflux for 3 h. Et_2O was removed under reduced pressure, and CC (SiO_2; 15% AcOEt in hexane) of the residue afforded **3** (650 mg, 81%). Yellow oil. UV/VIS (MeCN): max. 393 (3.89), 330 (sh, 3.39). IR (ATR): 3065–2750 (C–H), 1745 (C=O), 1580 (C=C), 1245, 1200, 1160, 1120, 1035 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.25 (*q*, *J* = 7.2, MeC*H*$_2$O); 3.42, 3.28 (2*dq*, *J* = 14.2, 7.1, 2 MeC*H*$_2$N); 2.48 (*s*, Me); 1.27 (*t*, *J* = 7.2, *Me*CH$_2$O); 1.14 (*t*, *J* = 7.1, 2 *Me*CH$_2$N). ^{13}C-NMR (101 MHz, $CDCl_3$): 161.0 (*q*, *J*(C,F) = 1.3, EtOCO); 152.9 (C(5)); 134.3 (*q*, *J*(C,F) = 1.6, C(4)); 121.0 (*q*, *J*(C,F) = 283, CF_3); 94.9 (*q*, *J*(C,F) = 25.5, C(3)); 63.1, 13.8 (EtOCO); 46.6 (*q*, *J*(C,F) = 1.2, Et_2N); 13.6 (Et_2N); 13.5 (Me). ^{19}F-NMR (470 MHz, $CDCl_3$): −67.7 (*s*, CF_3). HR-ESI-TOF-MS: 332.0998 ([*M* + K]$^+$, $C_{12}H_{18}F_3KN_3O_2^+$; calc. 332.0983). Anal. calc. for $C_{12}H_{18}F_3N_3O_2$ (293.29): C 49.14, H 6.19, N 14.33; found: C 49.45, H 6.17, N 14.29.

*Ethyl 4-(Diethylamino)-3-methyl-5-(trifluoromethyl)-1*H*-pyrazole-1-carboxylate* (**4**). Compound **3** (284 mg, 0.968 mmol) was dissolved in toluene (8 ml) and stirred at 110° for 6 h. Toluene was removed under reduced pressure, and CC (SiO_2; 15% AcOEt in hexane) of the residue afforded **4** (200 mg, 70%). Pale-yellow liquid. UV/VIS (MeCN): max. 307 (sh, 3.52), 239 (3.87). PL (MeCN): max. 451. IR (ATR): 3085–2745 (C–H), 1765 (C=O), 1505, 1475, 1440, 1370, 1340 (C=C), 1295, 1245, 1190, 1130, 1030 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.50 (*q*, *J* = 7.1, MeC*H*$_2$O); 3.03 (*q*, *J* = 7.2, 2 MeC*H*$_2$N); 2.26 (*s*, Me); 1.44 (*t*, *J* = 7.1, *Me*CH$_2$O); 0.99 (*t*, *J* = 7.2, 2 *Me*CH$_2$N)). ^{13}C-NMR (101 MHz, $CDCl_3$): 152.3 (C(3)); 148.6 (EtOCO); 137.2 (*q*, *J*(C,F) = 1.6, C(4)); 126.9 (*q*, *J*(C,F) = 39.5, C(5)); 119.9 (*q*, *J*(C,F) = 269, CF_3); 64.9, 13.6 (EtOCO); 47.5 (*q*, *J*(C,F) = 1.5, Et_2N); 14.0 (Et_2N); 12.7 (Me). ^{19}F-NMR (471 MHz, $CDCl_3$): −57.9 (*s*, CF_3). HR-ESI-TOF-MS: 316.1264 ([*M* + Na]$^+$, $C_{12}H_{18}F_3N_3NaO_2^+$; calc. 316.1243). Anal. calc. for $C_{12}H_{18}F_3N_3O_2$ (293.29): C 49.14, H 6.19, N 14.33; found: C 49.26, H 6.37, N 14.27.

*Ethyl 4-(Diethylamino)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-carboxylate* (**5**). Neat **4** (134 mg, 0.457 mmol) was heated in a *Büchi* apparatus to 240° for 2 h. CC (SiO_2; 10% AcOEt in hexane) of the crude product afforded **5** (114 mg, 85%). Colorless oil. IR (ATR): 3075–2720 (C–H), 1765 (C=O), 1290, 1170, 1135, 1110, 1090 (C–F). ^{1}H-NMR (500 MHz, $CDCl_3$): 4.52 (*q*, *J* = 7.1, MeC*H*$_2$O); 2.93 (*q*, *J* = 7.2, 2 MeC*H*$_2$N); 2.49 (*s*, Me–C(5)); 1.47 (*t*, *J* = 7.1, *Me*CH$_2$O); 0.93 (*t*, *J* = 7.2, 2 *Me*CH$_2$N). ^{13}C-NMR (101 MHz, $CDCl_3$): 149.8 (C(5)); 144.3 (EtOCO); 143.6 (*q*, *J*(C,F) = 37.6, C(3)); 130.1 (C(4)); 120.9 (*q*, *J*(C,F) = 270, CF_3); 65.0, 14.0 (EtOCO); 49.0 (*q*, *J*(C,F) = 0.9, Et_2N); 14.3 (Et_2N); 12.2 (Me). ^{19}F-NMR (471 MHz, $CDCl_3$): −61.9 (*s*, CF_3). HR-ESI-TOF-MS: 316.1266 ([*M* + Na]$^+$, $C_{12}H_{18}F_3N_3NaO_2^+$; calc. 316.1243). Anal. calc. for $C_{12}H_{18}F_3N_3O_2$ (293.29): C 49.14, H 6.19, N 14.33; found: C 49.43, H 6.14, N 14.11.

N,N-*Diethyl-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine* (**6**). At 0°, Et_2NH (40 mg, 0.55 mmol) was added to **5** (37 mg, 0.13 mmol), and the resulting mixture was stirred for 24 h at 21°. CC (SiO_2; 10% AcOEt in hexane) of the crude product afforded **6** (25 mg, 90%). Colorless oil. IR (ATR): 3600–2560 (N–H, C–H), 1470 (C=C), 1275, 1120, 995 (C–F). ^{1}H-NMR (500 MHz, $CDCl_3$): 12.09 (*s*, NH); 2.94 (*q*, *J* = 7.2, 2 MeC*H*$_2$N); 2.24 (*s*, Me); 0.93 (*t*, *J* = 7.2, 2 *Me*CH$_2$N). ^{13}C-NMR (126 MHz, $CDCl_3$): 139.6 (C(5)); 139.4 (*q*, *J*(C,F) = 36.3, C(3)); 127.3 (C(4)); 122.0 (*q*, *J*(C,F) = 269, CF_3); 49.4, 14.0 (Et_2N); 9.6 (Me). ^{19}F-NMR (471 MHz, $CDCl_3$): −60.4 (*s*, CF_3). HR-ESI-TOF-MS: 222.1213 ([*M* + H]$^+$, $C_9H_{15}F_3N_3^+$; calc. 222.1213). Anal. calc. for $C_9H_{14}F_3N_3$ (221.22): C 48.86, H 6.38, N 18.99; found: C 48.74, H 6.43, N 18.88.

*1-Ethyl 3,4-Dimethyl 5-(Trifluoromethyl)-1*H*-pyrazole-1,3,4-tricarboxylate* (**9**). In a one-dram vial were added **1** (1.00 g, 5.49 mmol) and **7** (0.717 g, 4.99 mmol). The vial was sealed with a *Teflon*-coated

cap, and the mixture was stirred at 80° for 24 h. The excess of **1** was removed from the resulting dark-yellow oil under reduced pressure (90°/15 mbar) to afford **9** (1.56 g, 96%). Yellow solid. M.p. 78–80°. IR (ATR): 3110–2775 (C–H), 1790, 1750 (C=O), 1270, 1210, 1160, 1030 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.61 (*q*, *J* = 7.1, MeC*H*$_2$O); 3.96, 3.95 (2*s*, 2 *Me*O); 1.49 (*t*, *J* = 7.1, *Me*CH$_2$O). ^{13}C-NMR (101 MHz, $CDCl_3$): 161.4, 159.8 (MeOCO); 147.0 (EtOCO); 142.6 (C(3)); 132.8 (*q*, *J*(C,F) = 42.3, C(5)); 122.3 (*q*, *J*(C,F) = 2.7, C(4)); 118.3 (*q*, *J*(C,F) = 271, CF_3); 67.1, 13.9 (EtOCO); 53.6, 53.2 (MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −58.7 (*s*, CF_3). HR-ESI-TOF-MS: 347.0465 ([*M* + Na]$^+$, $C_{11}H_{11}F_3N_2NaO_6^+$; calc. 347.0461). Anal. calc. for $C_{11}H_{11}F_3N_2O_6$ (324.21): C 40.75, H 3.42, N 8.64; found: C 41.21, H 3.51, N 8.65.

*1-Ethyl 4,5-Dimethyl 3-(Trifluoromethyl)-1*H*-pyrazole-1,4,5-tricarboxylate* (**10**). In a round-bottom flask with a condenser neat **7** (1.54 g, 4.75 mmol) was heated at 180° for 3 h to afford **10** (1.54 g, > 99%). Brown solid. Melting range: 60–70°. IR (ATR): 3145–2785 (C–H), 1780, 1745 (C=O), 1285, 1225, 1150, 1045 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.58 (*q*, *J* = 7.1, MeC*H*$_2$); 4.03, 3.89 (2*s*, 2 MeO); 1.48 (*t*, *J* = 7.1, *Me*CH$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): 159.6, 159.4 (MeOCO); 147.3 (EtOCO); 143.8 (*q*, *J*(C,F) = 39.8, C(3)); 142.2 (C(5)); 119.3 (*q*, *J*(C,F) = 271, CF_3); 113.8 (C(4)); 67.1, 14.0 (EtOCO); 54.0, 52.9 (MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −63.0 (*s*, CF_3). Anal. calc. for $C_{11}H_{11}F_3N_2O_6$ (324.21): C 40.75, H 3.42, N 8.64; found: C 40.45, H 3.46, N 8.43.

*Dimethyl 5-(Trifluoromethyl)-1*H*-pyrazole-3,4-dicarboxylate* (**11**). At 0°, Et_2NH (730 mg, 9.98 mmol) was added to **10** (1.54 g, 4.75 mmol), and the resulting mixture was stirred for 30 min at 21°. CC (SiO_2; 50% AcOEt in hexane) of the crude product afforded **11** (572 mg, 48%). Orange oil. IR (ATR): 3700–2580 (N–H, C–H), 1725 (C=O), 1315, 1225, 1135, 1000 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 12.39 (*s*, NH); 3.95, 3.93 (2*s*, 2 MeO). ^{13}C-NMR (101 MHz, $CDCl_3$): 161.7, 158.3 (MeOCO); 142.5 (*q*, *J*(C,F) = 40.0, C(5)); 135.0 (m_c, C(3)); 120.0 (*q*, *J*(C,F) = 270, CF_3); 115.1 (*q*, *J*(C,F) = 1.4, C(4)); 53.5, 53.2 (MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −61.7 (*s*, CF_3). HR-ESI-TOF-MS: 275.0266 ([*M* + Na]$^+$, $C_8H_7F_3N_2NaO_4^+$; calc. 275.0250). Anal. calc. for $C_8H_7F_3N_2O_4$ (252.15): C 38.11, H 2.80, N 11.11; found: C 38.35, H 2.80, N 11.28.

*3-Ethyl 5-Methyl 3-(Trifluoromethyl)-3*H*-pyrazole-3,5-dicarboxylate* (**13**), *Methyl 3-(Trifluoromethyl)-1*H*-pyrazole-5-carboxylate* (**14**), *and 4-Ethyl 5-Methyl 3-(Trifluoromethyl)-1*H*-pyrazole-4,5-dicarboxylate* (**15**). In a one-dram vial were added **1** (101 mg, 0.555 mmol) and **12** (468 mg, 5.57 mmol). The vial was sealed with a *Teflon*-coated cap, and the mixture was stirred at 80° for 3 h. After cooling to r.t., CC (SiO_2; 15% AcOEt in hexane) of the crude product afforded **13** (52 mg, 35%), **14** (16 mg, 15%), and **15** (47 mg, 32%).

Data of **13**. Colorless oil. IR (ATR): 3160–2775 (C–H), 1710 (C=O), 1300, 1245, 1210, 1130, 1030 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.28 (*q*, *J*(H,F) = 1.2, H–C(4)); 4.28 (*q*, *J* = 7.1, MeC*H*$_2$); 3.89 (*s*, MeO); 1.32 (*t*, *J* = 7.1, *Me*CH$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): 163.8, 162.9 (EtOCO, MeOCO); 133.2 (C(5)); 132.3 (*q*, *J*(C,F) = 6.5, C(4)); 122.8 (*q*, *J*(C,F) = 272, CF_3); 110.2 (*q*, *J*(C,F) = 31.1, C(3)); 61.6, 14.1 (EtOCO); 53.4 (MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −61.8 (*d*, *J*(F,H) = 1.2, CF_3). HR-ESI-TOF-MS: 289.0392 ([*M* + Na]$^+$, $C_9H_9F_3N_2NaO_4^+$; calc. 289.0407).

Data of **14**. Colorless oil. IR (ATR): 3500–2690 (N–H, C–H), 1715 (C=O), 1310, 1290, 1250, 1145, 1125, 1020 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 11.75 (*s*, NH); 7.09 (*s*, H–C(4)); 3.97 (*s*, MeO). ^{13}C-NMR (176 MHz, $CDCl_3$): 159.2 (MeOCO); 144.2 (*q*, *J*(C,F) = 39.6, C(3)); 135.3 (C(5)); 120.7 (*q*, *J*(C,F) = 269, CF_3); 107.5 (*q*, *J*(C,F) = 2.3, C(4)); 52.9 (MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −62.3 (*s*, CF_3). HR-ESI-TOF-MS: 193.0219 ([*M* − H]$^-$, $C_6H_4F_3N_2O_2^-$; calc. 193.0230).

Data of **15**. Colorless wax. Melting range: 28–40°. IR (ATR): 3740–2700 (N–H, C–H), 1730 (C=O), 1310, 1230, 1140, 1080 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.97 (*s*, NH); 4.39 (*q*, *J* = 7.1, MeC*H*$_2$); 3.94 (*s*, MeO); 1.36 (*t*, *J* = 7.1, *Me*CH$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): 161.3 (MeOCO); 158.5 (EtOCO); 141.9 (*q*, *J*(C,F) = 38.9, C(5)); 135.0 (C(3)); 120.1 (*q*, *J*(C,F) = 270, CF_3); 115.5 (*q*, *J*(C,F) = 1.2, C(4)); 62.5, 14.0 (EtOCO); 53.3 (MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −61.5 (*s*, CF_3). HR-ESI-TOF-MS: 305.0159 ([*M* + K]$^+$, $C_9H_9F_3KN_2O_4^+$; calc. 305.0146). Anal. calc. for $C_9H_9F_3N_2O_4$ (266.17): C 40.61, H 3.41, N 10.52; found: C 40.62, H 3.38, N 10.49.

*Diethyl 3,5-Bis(trifluoromethyl)-1*H*-pyrazole-1,4-dicarboxylate* (**17**) *and Diethyl 4,5-Bis(trifluoromethyl)-1*H*-pyrazole-1,3-dicarboxylate* (**18**). In a one-dram vial were added **1** (219 mg, 1.20 mmol) and **16** (200 mg, 1.20 mmol). The vial was sealed with a *Teflon*-coated cap, and stirring at 75° for 6 d afforded a

mixture **17**/**18** (419 mg, >99%, **17**/**18** 75:25). Pale-yellow oil. IR (ATR): 3170–2790 (C–H), 1800, 1745 (C=O), 1270, 1225, 1145, 1030 (C–F). HR-ESI-TOF-MS: 371.0460 ($[M+Na]^+$, $C_{11}H_{10}F_6N_2NaO_4^+$; calc. 371.0437). Anal. calc. for $C_{11}H_{10}F_6N_2O_4$ (348.20): C 37.94, H 2.89, N 8.05; found: C 37.70, H 2.92, N 8.09.

Data of **17**. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.61, 4.40 (2*q*, *J* = 7.2, 2 MeC*H*$_2$); 1.49, 1.36 (2*t*, *J* = 7.2, 2 *Me*CH$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): 159.4, 146.7 (2 EtOCO); 142.3 (*q*, *J*(C,F) = 40.1, C(3)); 133.9 (*q*, *J*(C,F) = 42.6, C(5)); 119.2 (*q*, *J*(C,F) = 271, CF_3); 119.1 (m_c, C(4)); 118.1 (*q*, *J*(C,F) = 272, CF_3); 67.3, 63.2, 13.86, 13.76 (2 EtOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −58.3, −62.4 (2*s*, 2 CF_3).

Data of **18**. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.61, 4.44 (2*q*, *J* = 7.2, 2 MeC*H*$_2$); 1.48, 1.39 (2*t*, *J* = 7.2, 2 *Me*CH$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): 159.7, 146.9 (2 EtOCO); 144.4 (*q*, *J*(C,F) = 2.2, C(3)); 119.9 (*q*, *J*(C,F) = 270, CF_3); 117.8 (*q*, *J*(C,F) = 272, CF_3); 67.6, 63.1, 13.92, 13.81 (2 EtOCO); C(4) and C(5) were not detected, probably due to low signal intensity or overlap with signals of the major isomer. ^{19}F-NMR (376 MHz, $CDCl_3$): −55.4, −57.4 (2*q*, *J* = 9.7, 2 CF_3).

*Ethyl 3,5-Bis(trifluoromethyl)-1*H*-pyrazole-4-carboxylate* (**19**) *and Ethyl 3,4-Bis(trifluoromethyl)-1*H*-pyrazole-5-carboxylate* (**20**). The mixture of **17**/**18** (419 mg, 1.20 mmol, **17**/**18** 75:25) was treated at 0° with Et_2NH (88 mg, 1.20 mmol), and the mixture was stirred for 4 h at 21°. CC (SiO_2; 15% AcOEt in hexane) of the resulting mixture and subsequent HPLC (10% AcOEt in hexane) afforded **19** (202 mg, 61%) and **20** (50 mg, 15%). Traces of AcOEt were removed from **19** at 95°/10 mbar.

Data of **19**. Colorless crystals. M.p. 90–92°. IR (ATR): 3500–2750 (N–H, C–H), 1710 (C=O), 1510, 1235, 1210, 1140, 1060 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.40 (*q*, *J* = 7.2, MeC*H*$_2$); 1.38 (*t*, *J* = 7.2, *Me*CH$_2$); the NH signal was not detected. ^{13}C-NMR (101 MHz, $CDCl_3$): 159.9 (EtOCO); 140.9–139.8 (*m*, C(3), C(5)); 119.2 (*q*, *J*(C,F) = 271, CF_3); 112.3 (m_c, C(4)); 62.7, 13.6 (EtOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −61.6 (*s*, CF_3). HR-ESI-TOF-MS: 299.0239 ($[M+Na]^+$, $C_8H_6F_6N_2NaO_2^+$; calc. 299.0226).

Data of **20**. Colorless liquid. IR (ATR): 3490–2810 (N–H, C–H), 1730 (C=O), 1235, 1135, 1050 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.49 (*q*, *J* = 7.2, MeC*H*$_2$); 1.42 (*t*, *J* = 7.2, *Me*CH$_2$); the NH signal was not detected. ^{13}C-NMR (101 MHz, $CDCl_3$): 157.5 (EtOCO); 141.5 (*q*, *J*(C,F) = 39.6, C(3)); 135.4 (C(5)); 120.5, 119.7 (2*q*, *J*(C,F) = 269, 270, CF_3); 112.6 (*q*, *J*(C,F) = 41.7, C(4)); 63.6, 13.9 (EtOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −55.3 (*q*, *J* = 7.6, CF_3); −61.7 (*q*, *J* = 7.4, CF_3). HR-ESI-TOF-MS: 299.0239 ($[M+Na]^+$, $C_8H_6F_6N_2NaO_2^+$; calc. 299.0226).

*3,4,5-Tris(trifluoromethyl)-1*H*-pyrazole* (**23**). In a flask equipped with a *J. Young PTFE* valve, **1** (500 mg, 2.75 mmol) was dissolved in dry Et_2O (30 ml). Compound **21** (890 mg, 5.49 mmol) was condensed into the soln. at −196°. After warming to 21° the soln. was stirred at 80° for 10 d. At 21°, excess of **21** was evaporated, $NH_2CH_2CH_2NH_2$ (165 mg, 2.75 mmol) was added at 0°, and the soln. was stirred for 4 h at 21°. The mixture was diluted with Et_2O (200 ml) and washed with 1M HCl soln. (2 × 100 ml). After separation, the org. layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product (780 mg, >99%) was pure according to NMR spectroscopy. Bulb-to-bulb distillation (140–150°/0.1 mbar) afforded **23** (568 mg, 76%). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 11.63 (br. *s*, NH). ^{13}C-NMR (101 MHz, $CDCl_3$): 138.1 (m_c, C(3), C(5)); 119.9 (*q*, *J*(C,F) = 269, F_3C–C(4)); 118.7 (*q*, *J*(C,F) = 271, F_3C–C(3), F_3C–C(5)); 111.1 (m_c, C(4)). ^{19}F-NMR (376 MHz, $CDCl_3$): −55.7 (m_c, F_3C–C(4)); −61.0 (br. *s*, F_3C–C(3), F_3C–C(4)). The data agreed with those reported in [21].

Ethyl 2,3-Diphenyl-1-(trifluoromethyl)cycloprop-2-ene-1-carboxylate (**25**). Compound **1** (1.00 g, 5.49 mmol) and **24** (0.980 g, 5.50 mmol) were heated to reflux for 24 h at an oil-bath temp. of 180°. After cooling to r.t., CC (SiO_2; 15% AcOEt in hexane) of the mixture afforded **25** (445 mg, 24%). Yellow wax. Melting range: 60–79°. IR (ATR): 3195–2780 (C–H), 1730 (C=O), 1310, 1265, 1145, 1040 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.50–7.43 (*m*, 10 arom. H); 4.22 (*q*, *J* = 7.1, MeC*H*$_2$) 1.20 (*t*, *J* = 7.1, *Me*CH$_2$OCO). ^{13}C-NMR (101 MHz, $CDCl_3$): 168.8 (COOEt); 130.4, 130.0, 129.2, 124.7 (Ph); 125.1 (*q*, *J*(C,F) = 277, CF_3); 104.6 (*q*, *J*(C,F) = 1.5, C(2), C(3)); 61.4, 14.0 (COOEt); 33.6 (*q*, *J*(C,F) = 35.7, C(1)). ^{19}F-NMR (376 MHz, $CDCl_3$): −63.0 (*s*, CF_3). HR-ESI-TOF-MS: 355.0876 ($[M+Na]^+$, $C_{19}H_{15}F_3NaO_2^+$; calc. 355.0916).

*5-Ethyl 3,4-Dimethyl 4,5-Dihydro-5-(trifluoromethyl)-1*H*-pyrazole-3,4,5-tricarboxylate* (**27**). In a one-dram vial were added **1** (200 mg, 1.10 mmol) and **26** (158 mg, 1.10 mmol). The vial was sealed with a *Teflon*-coated cap, and the mixture was stirred at 80° for 7 d. The reaction was stopped despite of the

incomplete consumption of **1**; *ca.* 85% conversion according to ^{19}F-NMR spectroscopy. Filtration (SiO_2; 15% AcOEt in hexane, then 100% AcOEt) of the crude product afforded **27** (255 mg, 71%) as a single diastereoisomer. Yellow viscous oil. IR (ATR): 3720–2700 (N–H, C–H), 1745, 1730, 1720 (C=O), 1270, 1215, 1080 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.05 (*s*, NH); 4.42–4.39 (*m*, H–C(4)); 4.34, 4.24 (*AB* of *ABX*$_3$, $J_{AX} = J_{BX} = 7.1$, $J_{AB} = 11.0$, MeCH_2); 3.84, 3.78 (2*s*, 2 MeOCO); 1.31 (*X* of *ABX*$_3$, $J_{AX} = J_{BX} = 7.1$, *Me*CH$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): 167.3, 164.1, 160.9 (2 MeOCO, EtOCO); 139.6 (C(5)); 122.9 (*q*, *J*(C,F) = 283, CF_3); 76.7 (*q*, *J*(C,F) = 29.4, C(3)); 64.3, 13.7 (COOEt); 55.1 (*q*, *J*(C,F) = 1.1, C(4)); 53.2, 52.8 (2 MeOCO). ^{19}F-NMR (376 MHz, $CDCl_3$): −76.0 (*s*, CF_3). HR-ESI-TOF-MS: 349.0629 ([*M* + Na]$^+$, $C_{11}H_{13}F_3N_2NaO_6^+$; calc. 349.0618).

Ethyl 3,3,3-Trifluoro-2-[2-(2-oxocyclohexyl)hydrazinylidene]propanoate (**29**). In a one-dram vial were added **1** (500 mg, 2.75 mmol) and **28** (1.25 g, 8.24 mmol). The vial was sealed with a *Teflon*-coated cap, and the mixture was stirred at 80° for 5 d. After cooling to r.t., CC (SiO_2; 15% AcOEt in hexane) of the crude product and subsequent HPLC (12% AcOEt in hexane) afforded **29** (325 mg, 42%). Yellow oil. IR (ATR): 3360–2800 (N–H, C–H), 1720, 1680 (C=O), 1200, 1115, 1035 (C–F). ^{1}H-NMR (400 MHz, $CDCl_3$): 11.30 (*s*, NH); 4.30 (*q*, *J* = 7.1, MeCH_2); 4.27–4.20 (*m*, CH); 2.57, 2.14, 1.98, 1.66 (4*m*, 3 CH_2); 2.39 (*tdd*, *J* = 13.7, 6.2, 0.9, 1 H of CH_2); 1.78 (*qt*, *J* = 13.2, 3.3, 1 H of CH_2); 1.33 (*t*, *J* = 7.1, *Me*CH$_2$)). ^{13}C-NMR (101 MHz, $CDCl_3$): 206.3 (C=O); 161.2 (EtOCO); 121.7 (*q*, *J*(C,F) = 270, CF_3); 115.5 (*q*, *J*(C,F) = 35.2, C=N); 67.5, 14.0 (EtOCO); 61.1 (CH); 41.0, 34.8, 27.4, 23.8 (4 CH_2). ^{19}F-NMR (376 MHz, $CDCl_3$): −64.5 (*s*, CF_3). HR-ESI-TOF-MS: 279.0962 ([*M* − H]$^-$, $C_{11}H_{14}F_3N_2O_3^-$; calc. 279.0962).

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