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Aza-Wolff rearrangement of *N*-fluoroalkyl triazoles to ketenimines†Anna Kubičková,^{a,b} Athanasios Markos,^a Svatava Voltrová,^a Anežka Marková,^a Josef Filgas,^b Blanka Klepetářová,^a Petr Slaviček^b and Petr Beier^{a*}

N-Fluoroalkylated 1,2,3-triazoles underwent a microwave-heating-assisted ring opening, nitrogen molecule elimination and concomitant group rearrangement to form isolable *N*-fluoroalkylketenimines. This reagent-free process is characterized by a wide scope and high efficiency and provides a new route to unexplored *N*-fluoroalkyl compounds. The reaction mechanism was investigated by a combination of mechanistic and computational studies. [2 + 2] cycloaddition of ketenimines with alkynes or alkenes afforded novel cyclobutenimines and cyclobutanimines, respectively. Addition of oxygen-, sulfur- and nitrogen nucleophiles to ketenimines gave new *N*-fluoroalkyl imidates, thioimidates and amidines.

Introduction

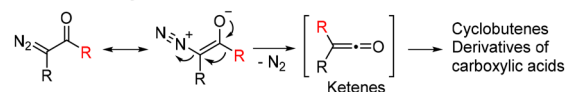
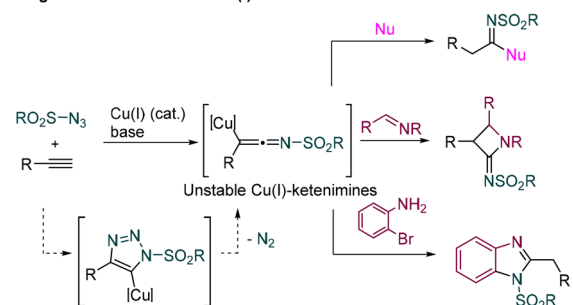
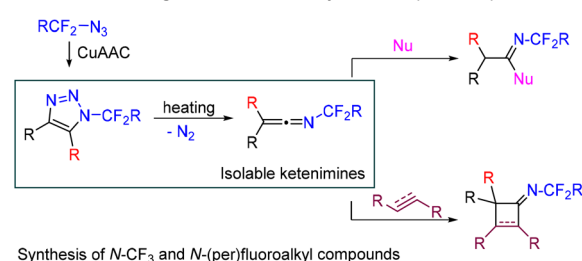
The Wolff rearrangement of α -diazo carbonyl compounds to ketenes is one of the most significant transformations that has contributed to the growth of chemical synthesis in the 20th century (Scheme 1A).¹ The ketenes generated in this way are highly useful substrates with a wide range of synthetic applications.²

Ketenimines, aza-analogues of ketenes, are a related class of compounds with cumulated double bonds and a broad range of applications in organic chemistry.³ Although they are generally more stable than ketenes, most ketenimines are not isolable materials and therefore need to be formed *in situ* as reactive intermediates. For example, highly reactive *N*-sulfonylketenimines are generated by copper-catalyzed azide alkyne cycloaddition (CuAAC) of *N*-sulfonyl azides and alkynes and subsequent spontaneous denitrogenative rearrangement of a copper-triazole intermediate (Scheme 1B, left). They can serve as three atom (C–C–N) synthons in the syntheses of amides,^{4–6} amidines,⁷ imidates,⁸ four-, five-, six- and seven-membered heterocycles, amino acids, and many other biologically and pharmaceutically valuable compounds (see Scheme 1B, right for selected examples).⁹

The formation of ketenimines by CuAAC is limited to electron-deficient sulfonyl/phosphoryl azides; alkyl or aryl azides pre-

ferably form triazole rings.¹⁰ Even *N*-fluoroalkyl azides with a strong electron-withdrawing *N*-CF₂R groups react with terminal alkynes in a CuAAC fashion to form *N*-fluoroalkyl triazoles,^{11–14}

A: Wolff rearrangement

B: Copper-catalyzed cycloaddition *N*-sulfonyl azides and alkynes and the generation of unstable Cu(I)-keteniminesC: Aza-Wolff rearrangement of *N*-fluoroalkyl triazoles (this work)

Scheme 1 A: Wolff rearrangement. B: Generation of *N*-sulfonyl ketenimines and their selected reactions. C: Aza-Wolff rearrangement of *N*-fluoroalkyl triazoles (this work).

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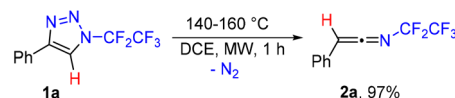
substrates which have been showcased as being useful for the synthesis of *N*-fluoroalkyl azoles (e.g. imidazoles, pyrroles)^{15–18} and other fluoroalkyl-containing compounds.^{19–22}

The incorporation of fluorinated groups into small molecules is a widely used approach to the modification of their pharmacological as well as pharmacokinetic properties.²³ Whereas *C*-, and *O*-fluoroalkyl compounds have been studied extensively, *N*-fluoroalkyl substrates have received more attention only recently.²⁴ That their potential is unexplored is caused mainly by the lack of efficient methods to synthesize these compounds using readily available starting materials. Introducing a CF₃ group directly into nitrogen functionalities is a greatly challenging and substrate-specific process.²⁵ However, an approach based on *N*-CF₃ synthons has recently emerged as an alternative and atom-economical route. The Schoenebeck group introduced versatile *N*-CF₃ carbamoyl fluorides as building blocks for the synthesis of highly attractive tertiary *N*-CF₃ amides,²⁶ hydrazines,²⁷ ureas,^{28,29} formamides³⁰ and other compounds.³¹ Synthesis of tertiary *N*-CF₃ amides was also recently reported by Toste and Wilson from carboxylic acid derivatives and isothiocyanates in the presence of AgF.³² Another synthon, the *N*-CF₃ nitrilium ion, was introduced by Xu and Wang for the synthesis of *N*-CF₃ azoles and imido derivatives.^{33,34} Despite the great progress in recent years, most of the strategies for this are limited to *N*-CF₃ compounds and methods for the synthesis of a wide range of *N*-fluoroalkyl compounds remain underdeveloped.

Here, we report a highly efficient, atom-economical, waste- and reagent-free way to synthesize isolable *N*-fluoroalkylketenimines by thermal aza-Wolff rearrangement of *N*-fluoroalkyl-1,2,3-triazoles (Scheme 1C). The synthetic utility of *N*-fluoroalkyl ketenimines has been shown on examples of [2 + 2] cycloadditions affording novel *N*-fluoroalkyl cyclobutenimines and cyclobutanimines as well as a variety of imido compounds in reactions of ketenimines with nucleophiles.

Results and discussion

While exploring the thermal stability of *N*-pentafluoroethyl-4-phenyl-1,2,3-triazole (**1a**) by differential scanning calorimetry (DSC), thermogravimetric analysis (TG) and gas chromatography with mass detection (GC/MS), we noticed decomposition at temperatures of around 140–160 °C in solution or without solvent and also decomposition in the gas phase (GC inlet temp.: 250 °C) with a mass loss of *m/z* 28. Detailed NMR and IR analyses of preparative reactions revealed the quantitative formation of *N*-(pentafluoroethyl)-2-phenylethen-1-imine (**2a**), which was fully characterized (Scheme 2, see the ESI†). RFA analysis ruled out any possible participation of the copper catalyst carried over from the synthesis of **1a** with CuAAC. Various solvents were tested including chloroform, toluene, THF, acetone and polar protic solvents, but the best results were obtained using DCE (see the ESI† for details).



Scheme 2 Synthesis of ketenimine **2a** by the thermal decomposition of triazole **1a**.

Conventional heating is also possible but leads to **2a** in a longer reaction time and unidentified side products.

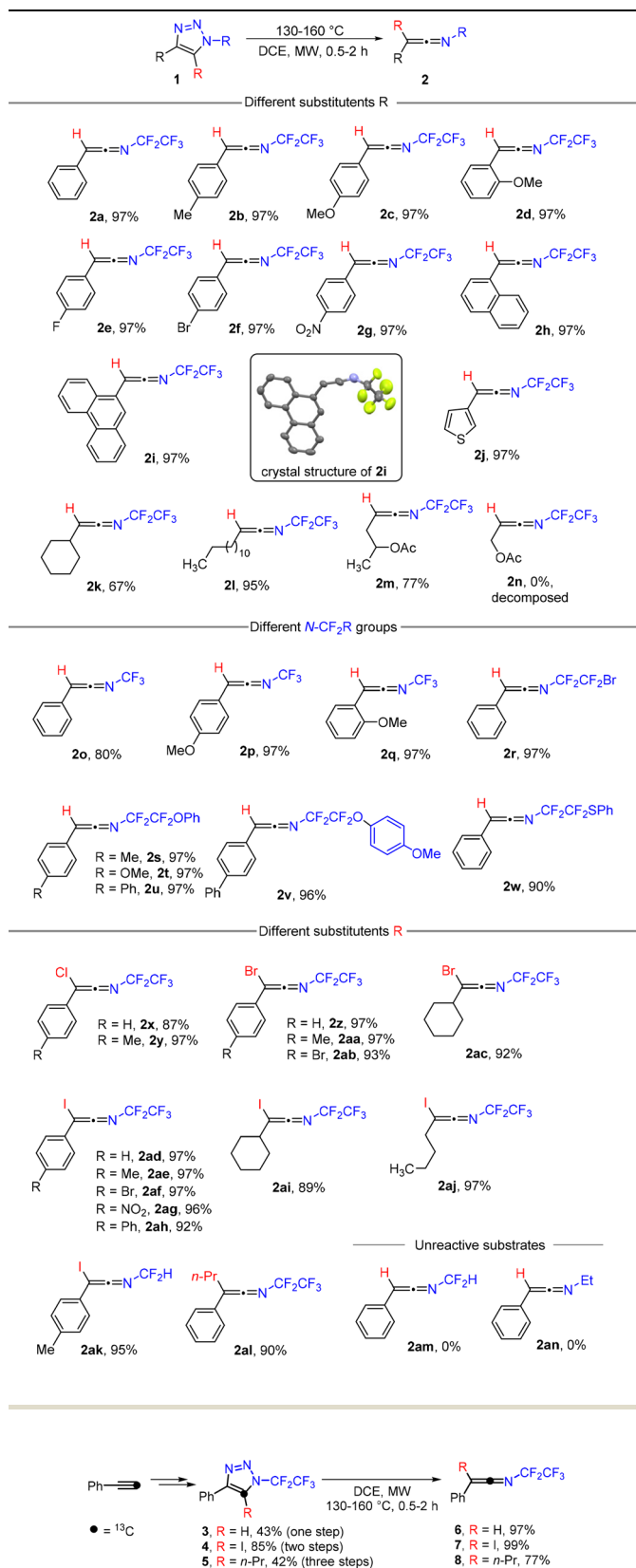
Subsequent investigation revealed that the denitrogenative rearrangement of *N*-fluoroalkyl-1,2,3-triazoles **1** to *N*-fluoroalkylketenimines **2** is of a wide scope and, in a vast majority of cases, highly efficient (Table 1).

Triazoles with various combinations of aryl, substituted aryl, heteroaryl, alkyl, substituted alkyl or cycloalkyl groups in position four, hydrogen, Cl, Br, I or an alkyl group in position five and trifluoromethyl (–CF₃), pentafluoroethyl (–CF₂CF₃), bromotetrafluoroethyl (–CF₂CF₂Br), substituted tetrafluoroethyl (–CF₂CF₂R) and even difluoromethyl groups (–CF₂H) on the nitrogen atom all underwent the reaction and provided products **2** in high to excellent yields. Despite the robustness of the method, certain limitations were observed. Triazole **1n** underwent rearrangement; however, the product was not stable (see the ESI† for details). The presence of a 5-halo substituent (iodo in particular) in triazoles **1** improved isolated yields for difficult substrates (4-alkyl, 4-cycloalkyl) compared to unsubstituted examples. This effect is strikingly strong in the case of *N*-difluoromethyl substrates, where the iodo product formed in high yield (**2ak**) and the unsubstituted one did not form at all (**2am**). *N*-Alkyl triazole (**1an**) was not a competent substrate in this reaction. Generally, ketenimines **2** did not require any purification; solvent removal was sufficient to obtain suitably pure samples. Their purification using silica gel column chromatography is also possible. Keteneimines **2** are mostly liquids (**2i** and **2v** are solids; see the crystal structure in Table 1) with limited air and moisture stability as pure substances; in solution (DCE, pentane) they were stable for weeks at room temperature in an inert atmosphere.

Having demonstrated the broad scope of the reaction, we investigated the mechanism of this unprecedented transformation. First, we synthesized isotopically labelled triazoles **3–5** from ¹³C-phenylacetylene.³⁵ All three triazoles underwent ring opening and rearrangement to form ketenimines **6–8**, which contained the label exclusively in the central sp-hybridized carbon atom, proving that the reaction proceeds *via* a [1,2]-shift of the R group, similarly to the Wolff rearrangement (Scheme 3).

As the Wolff rearrangement can proceed *via* a concerted or step-wise mechanism involving carbenes,³⁶ we performed *ab initio* calculations. We optimized the structures with the multi-reference CASSCF(4,4)/6-31+g* method, as it was able to localize open-shell systems such as carbene and nitrene (unlike, e.g., density functional approaches). Single point energies were calculated using the coupled cluster CCSD(T) method with the aug-cc-pVDZ basis set. The differences in



Table 1 Substrate scope of thermal transformation of triazoles **1** to ketenimines **2**

thermal corrections were found to be on the order of 10^{-4} eV (at the DFT/BMK/6-31+g* level), so entropic effects do not play any role here. The effect of the solvent was also found to be negligible. The lowest energy pathway involved the expected diazo intermediate and final ketenimine product (Fig. 1A, blue box). This result is consistent with a concerted Wolff rearrangement, which also requires an *s-cis* configuration of the diazo and heteroatom groups.

Carbene and its hypothetical rearrangement products such as 1*H*-azirine, and nitrene species were found to be very unstable (see the ESI† for more details), too high in energy and are not involved in the reaction mechanism (Fig. 1B).

Next, the synthetic utility of the prepared ketenimines in [2 + 2] cycloadditions and in additions of nucleophiles was explored. Thermal cycloaddition of phenylacetylene proceeded with expected regioselectivity and produced cyclobutenimines **9** in good yields as *E/Z* mixtures with moderate to high stereoselectivities towards *E*-isomers (Scheme 4). Keteneimines with halogen substituents (R = Cl, Br, I) were unreactive, but the alkyl group (R = *n*-Pr) was tolerated well. Internal alkyne diphenylacetylene proved to be a competent substrate in cycloaddition under microwave heating affording cyclobutenimines **10** in good yields and exclusively as *E*-isomers. The crystal structure of cyclobutenimine (*E*)-**10b** is presented in Scheme 4. On the other hand, the electron acceptor terminal or internal alkynes (ethyl propiolate, diethyl acetylenedicarboxylate) exhibited no reactivity even under heating.

Cycloaddition of ketenimines with terminal alkenes, such as styrene (60 °C) or electron-rich ethyl vinyl ether (room temperature) proceeded well; however, the products (cyclobutenimines) were unstable. With disubstituted alkene (2-ethylbut-1-ene) cyclobutenimines **11** formed with high efficiency, regio- and stereoselectivity (Scheme 4). Internal alkenes (*cis*- or *trans*-

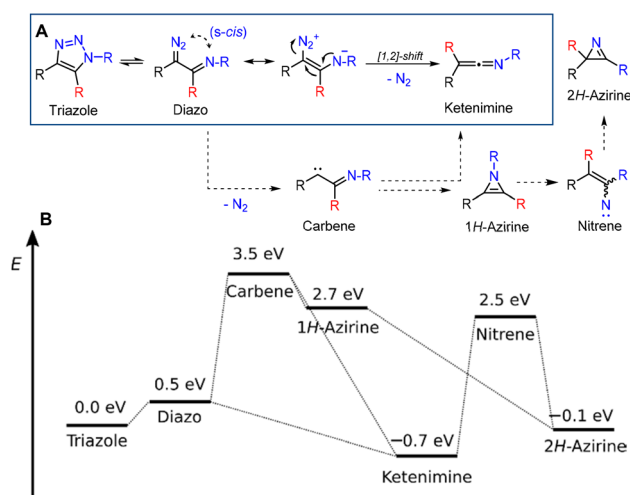
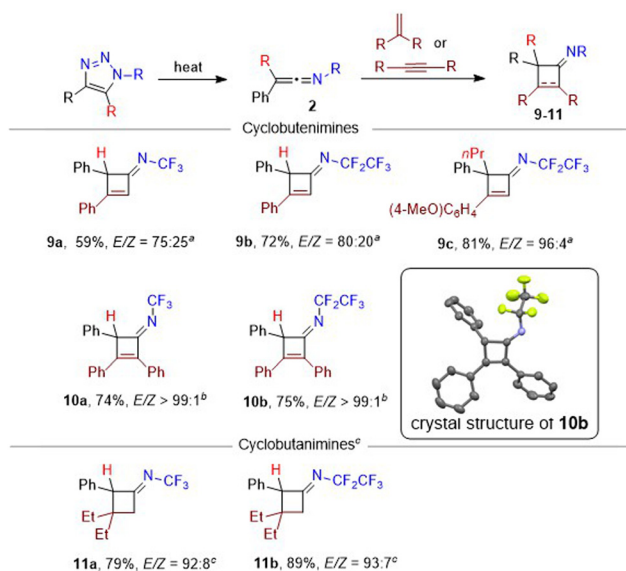
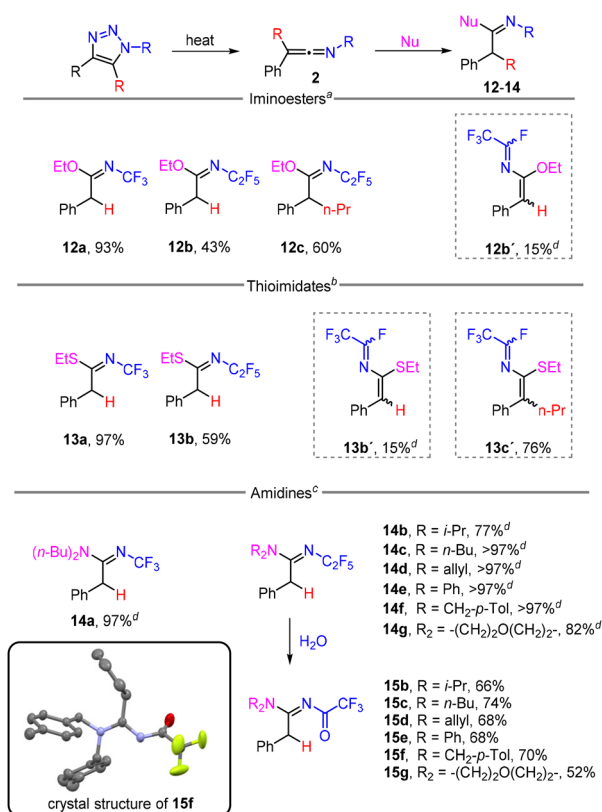


Fig. 1 A: Reactive species considered in the *ab initio* calculation of the reaction mechanism (R = Me, R = H, R = CF₃). B: Calculated energies of the structures (related to the starting triazole). The geometries were optimized at the CASSCF(4,4)/6-31+g* level and the energies were calculated using the CCSD(T)/aug-cc-pVDZ method.





Scheme 4 [2 + 2] cycloadditions of ketenimines **2** with alkynes and alkenes. All yields were calculated from triazoles **1**. Only (*E*)-**9-11** are shown. Conditions: ^a phenylacetylene (2 equiv.), DCE, 100 °C (for R = H) or 170 °C (for R = *n*-Pr), 1 h; ^b diphenylacetylene (2 equiv.), DCE, MW, 165–170 °C, 1–2 h; ^c 2-ethylbut-1-ene (3 equiv.), DCE, 40 °C, 12 h.



Scheme 5 Addition of heteroatom nucleophiles to ketenimines **2**. All yields were calculated from triazoles **1**. Conditions: ^a alcohol (3 equiv.), DCE, 25 °C, 30 min (14 h for **12c**); ^b thiol (3 equiv.), DCE, 25 °C, 30 min (14 h for **13c'**); ^c amine (1 equiv.), DCE, 25 °C, 30 min. ^d ¹⁹F NMR yield.

stilbene), were unlike internal alkynes unreactive, even upon prolonged heating. The *E/Z* selectivity is governed by the sterical factors. Cyclobutane and cyclobutene imines are rare compounds and their *N*-fluoroalkyl derivatives were never synthesized before.

Finally, the reactivity of ketenimines **2** with *N*-, *O*- and *S*-centred nucleophiles was investigated (Scheme 5). Fast reactions were observed with an excess of ethanol and ethanethiol at room temperature to afford iminoesters **12** and thioimidates **13**. In the cases of **12b** and **13b**, dehydrofluorinated side-product **12b'** and **13b'** formed in a small amount, and instead of thioimide **13c**, imidoyl fluoride **13c'** was isolated. All imino products formed in *E*-configuration. With primary amines, the addition took place, but the products decomposed and a complex reaction mixture was formed; however, quantitative formation of amidines **14** was observed using secondary amines as nucleophiles. Stable products of hydrolysis *N*-trifluoroacetylamidines **15** were obtained from *N*-pentafluoroethyl derivatives, using column chromatography. The crystal structure of amidine **15f** was determined (Scheme 5). Very recently, related *N*-CF₃ amidines, imidates and thioimidates were prepared by the reaction of PhI(CF₃)Cl with nitriles, followed by the addition of nucleophiles to the intermediate *N*-CF₃ nitriliums.³³

Conclusions

Structurally diverse *N*-(per)fluoroalkyl-1,2,3-triazoles rearranged under microwave heating to novel and surprisingly stable *N*-(per)fluoroalkyl ketenimines, which were isolated and fully characterized by spectroscopic methods and in one case also by X-ray diffraction. The mechanism, supported by control experiments, an isotopic labelling study and *ab initio* calculations, proceeds *via* triazole ring opening, nitrogen elimination and group rearrangement (1,2-shift). Keteneimines reacted with alkynes or alkenes in [2 + 2] cycloaddition reactions under mild conditions to yield novel cyclobutenimines or cyclobutanimines, respectively. The addition of alcohols, thiols, or secondary amine nucleophiles to ketenimines afforded imidates, thioimidates, or amidines, respectively. Thus, *N*-fluoroalkyl-1,2,3-triazoles have been demonstrated to be useful precursors of *N*-fluoroalkylated ketenimines, which served as valuable building blocks in the expansion of the chemical space of accessible *N*-fluoroalkyl compounds. Further transformations of these new *N*-fluoroalkyl building blocks are currently being investigated in our laboratory.

Author contributions

A. Kubičková, A. Markos, S. Voltrová, A. Marková conceived the idea, performed the experiments and partially wrote the manuscript. J. Filgas and P. Slaviček performed calculations and partially wrote the manuscript. B. Klepetářová measured



X-ray diffraction and solved crystal structures. P. Beier conceived the idea and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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