CF PLUS CHEMICALS
Fluoroalkylation and bioconjugation

Fluorinated azides: access to a new chemical space

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Introduction

Azide-containing molecules have become very popular thanks to the advent of click chemistry and its numerous applications in combinatorial chemistry and several new high-throughput drug discovery technologies, such as DEL. Small-molecule fluorinated azidoalkanes represent an emerging exotic subclass of these highly useful building blocks. However, the commercial availability of small fluorinated azides has so far been very limited.

Here we report several newly commercialized fluoroakyl azides as safe, easy to handle solutions, their basic chemistry as well as the Rh-catalyzed transformations of *N*-perfluoroalkyl triazoles to a plethora of novel fluorinated heterocycles, such as *N*-fluoroalkyl imidazoles, pyrroles, imidazolones or pyrrolones.

New fluorinated azides

$CF_3{-}N_3$	$C_2F_5{-}N_3$	$HCF_2{-}N_3$	$CF_3CH_2{-}N_3$	$HCF_2CF_2CH_2{-}N_3$	$HCF_2CH_2{-}N_3$	$BrCF_2CF_2{-}N_3$
0,5 M in THF	0,15 M in THF	0,5 M in DME	0,5 M in DME	0,5 M in DME	0,5 M in DME	0,5 M in THF
FAZ001	FAZ002	FAZ003	FAZ004	FAZ007	FAZ012	FAZ011

Physicochemical properties of fluoroalkyl azides

Pure low molecular fluoroalkyl azides are typicaly highly volatile colorless liquids or gases with boiling points in the range of -28 °C to 82 °C and they display good solubility in etheral solvents, such as THF or DME. Despite the general notion that low molecular azides are highly unstable explosive compounds, highly fluorinated low molecular azides have been shown to be suprisingly thermally stable compounds (150 °C in an NMR pressure tube).[1,2] Due to the high volatility of low molecular azides, well-defined solutions in THF or DME with significantly lower vapour pressure are more practical for routine synthesis work and can be easily stored in a freezer.

CF_3N_3
CAS: 3802-95-7
b.p.: -28 °C

$CF_3CF_2N_3$
CAS: 2055167-74-1
b.p.: est. 10 °C

HCF_2N_3
CAS: 41796-84-3
b.p.: 8 °C

$BrCF_2CF_2N_3$
CAS: 2476559-31-4
b.p.: 50-52 °C

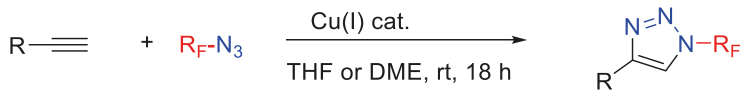
$CF_3CH_2N_3$
CAS: 846057-92-9
b.p.: 54-55 °C

$HCF_2CH_2N_3$
CAS: N/A
b.p.: est. 60-65 °C

$HCF_2CF_2CH_2N_3$
CAS 846057-93-0
b.p.: 81-82 °C

Cu-catalyzed azide-alkyne click reaction

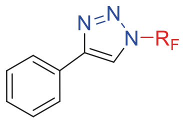
The fluoroalkyl azides undergo copper catalyzed alkyne-azide cycloaddition, forming 1,4-regioisomers in high selectivity.[1,2]



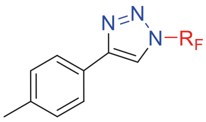
Method A: $CuSO_4.5H_2O$ (10 mol %)
Na L-ascorbate (10 mol %), H_2O

Method B: CuMeSal (1-5 mol %)

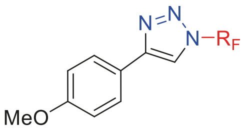
CuMeSal = copper(I)-3-methylsalicylate



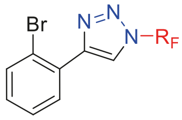
$R_F = CF_3$, 81 %, B
$R_F = C_2F_5$, 84 %, A
$R_F = C_2F_5$, 84 %, B
$R_F = CF_2H$, 82 %, B



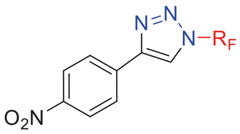
$R_F = CF_3$, 79 %, B
$R_F = C_2F_5$, 88 %, B
$R_F = CF_2H$, 91 %, B



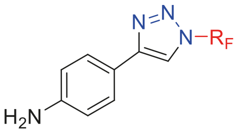
$R_F = CF_3$, 79 %, B
$R_F = C_2F_5$, 63 %, A



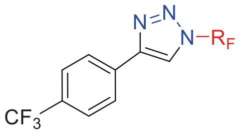
$R_F = CF_3$, 84 %, B
$R_F = C_2F_5$, 37 %, A



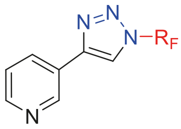
$R_F = CF_3$, 82 %, B
$R_F = CF_2H$, 83 %, B



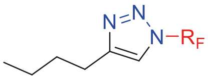
$R_F = CF_3$, 76 %, B
$R_F = C_2F_5$, 97 %, B
RF = CF_2H, 96 %, B



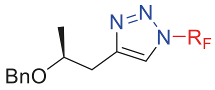
$R_F = C_2F_5$, 91 %, B
$R_F = CF_2H$, 45 %, B



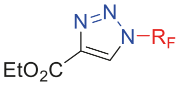
$R_F = C_2F_5$, 37 %, A (60 °C)
$R_F = CF_2H$, 62 %, B



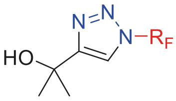
$R_F = CF_3$, 24 %, B
$R_F = CF_2H$, 69 %, B



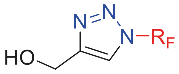
$R_F = CF_3$, 90 %, B



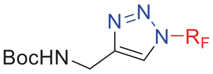
$R_F = CF_3$, 48 %, B
$R_F = CF_2H$, 92 %, B



$R_F = CF_3$, 74 % (83:17), B
$R_F = CF_2H$, 66 %, B



$R_F = CF_2H$, 75 %, A
$R_F = CH_2CF_3$, 79 %, B
RF = CH_2CF_2H, 75 %, B
RF = $CH_2CF_2CF_2H$, 81 %, B

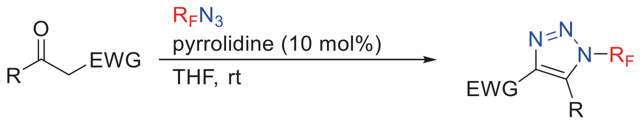


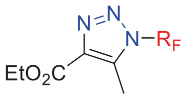
$R_F = CF_3$, 74 %, B
$R_F = CF_2H$, 91 %, A
$R_F = C_2F_5$, 86 %, B
$R_F = CH_2CF_3$, 81 %, B
$R_F = CH_2CF_2H$, 84 %, B
$R_F = CH_2CF_2CF_2H$, 80 %, B

[3+2] azide-ketone cycloaddition

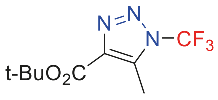
Fluorinated azidoalkanes undergo metal-free, enamine-mediated [3+2] cycloaddition, forming 4,5-disubstituted-1,2,3-triazoles.

The reaction works well with easily enolisable ketones possessing electron-withdrawing groups.[2,3]

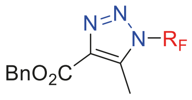




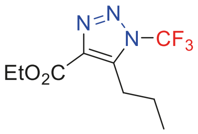
$R_F = CF_3$, 78 %
$R_F = CF_2H$, 74 %
$R_F = C_2F_5$, 78 %*



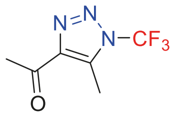
79 %



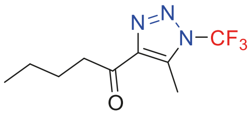
$R_F = CF_3$, 81 %
$R_F = CF_2H$, 65 %



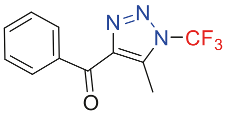
65 %*



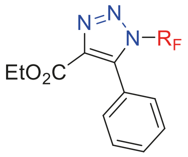
49 %
68 %*



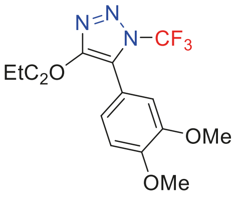
74 %



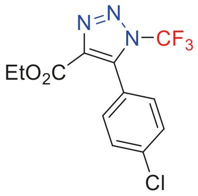
60 %



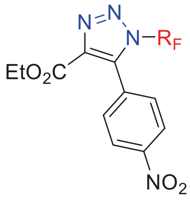
$R_F = CF_3$, 70 %
$R_F = CF_2H$, 89 %



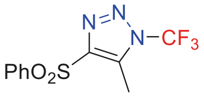
59 %



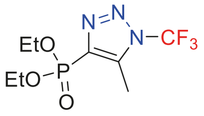
45 %



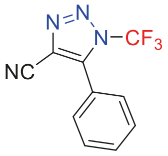
$R_F = CF_3$, 38 %*
$R_F = CF_2H$, 81 %



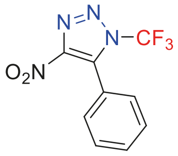
84 %**



88 %**



35 %**

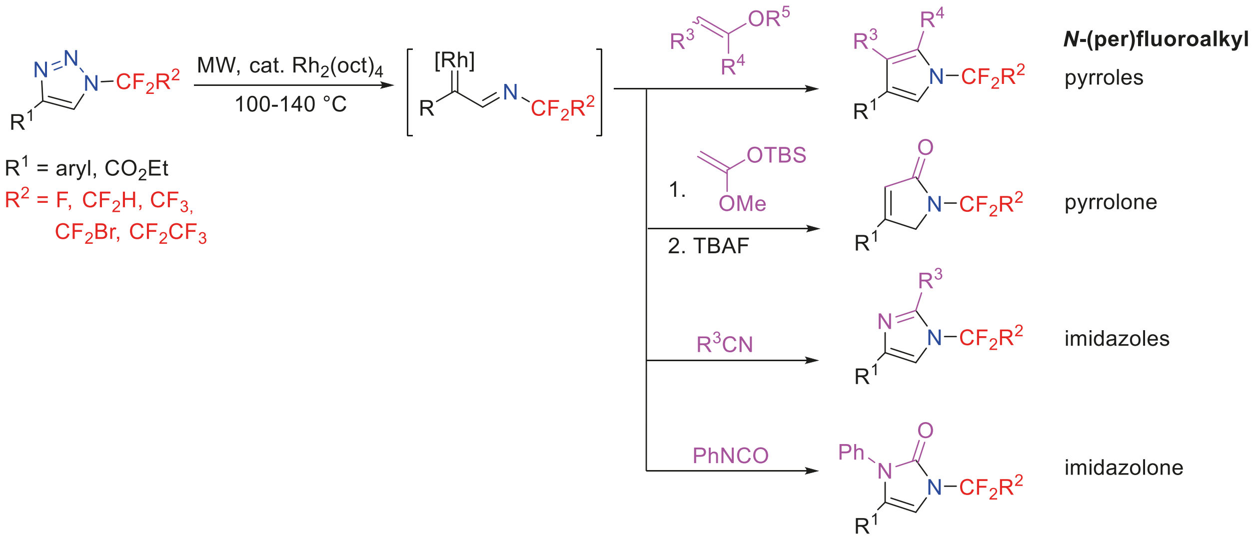


40 %**

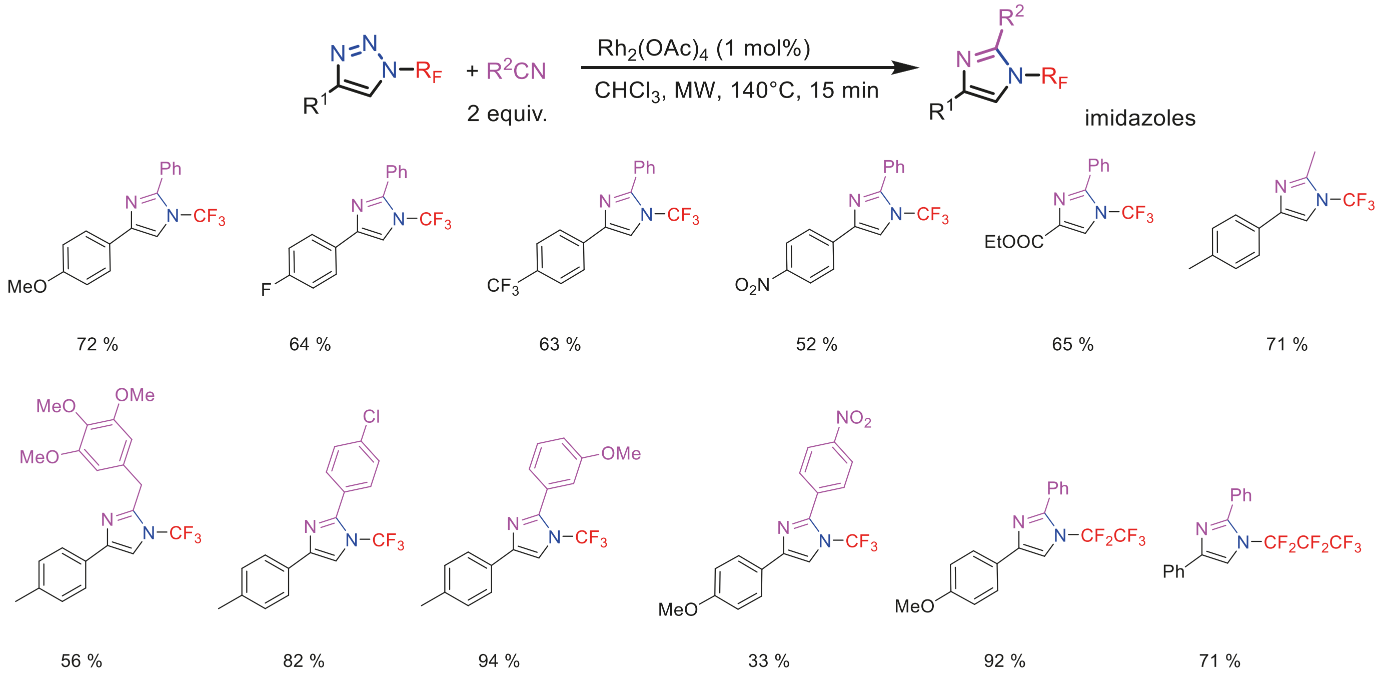
* using 20 mol% of pyrrolidine
** using 50 mol% of pyrrolidine

Transformations of *N*-(per)fluoroalkyl triazoles: access to new fluorinated heterocycles

N-fluoroalkyl-1,2,3-triazoles undergo various denitrogenative transformations when heated in a microwave in the presence of a Rh(II)-catalyst. The reaction proceeds through via Rh-carbenoid reactive intermediates. This way, previously unknown *N*-fluoroalkyl pyrroles, pyrrolones, imidazoles and imidazolones were efficiently prepared.[4]



N-Trifluoromethyl nitrogen heterocycles, such as pyrazoles or benzimidazoles are stable towards hydrolysis unlike *N*-trifluoromethyl secondary or tertiary amines. These azoles display favorable medicinal chemistry properties, such as increased lipophilicity and Caco2 permeability, no reactivity with glutathione and decreased pKa, which makes them interesting building blocks in drug design.[6] Although *N*-trifluoromethyl azoles are rare compounds,[7,8] this moiety is starting to appear in potential drug candidates. For example, replacing the methyl substituent on nitrogen in the checkpoint kinase 1 (CHK1) inhibitor for the trifluoromethyl group resulted in suppressed *N*-dealkylation while keeping comparable inhibitory activity.[9]



References

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3) Blastik, Z. E.; Klepetářová, B.; Beier, P., *ChemSelect* **2018**, 3, 7045.

4) Motornov, V.; Markos, A.; Beier, P., *Chem. Commun.* **2018**, 54, 3258

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8) Sokolenko, T. M.; Petko, K. I.; Yagupolskii, L. M., *Chem. Heterocycl. Comp.* **2009**, 45, 430.

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