Fluorinated diazoalkanes: synthesis and application

Pavel Mykhailiuk
2016
World's largest producer of building blocks

~100,000 compounds on stock (gram-scale)
500 chemists
10 own buildings
private company
50 papers
Ethyl diazoacetate is extremely popular (> 100 reactions).

Until 2006 \( CF_3CHN_2 \) was rarely used in chemistry.


H. Gilman, R. G. Jones JACS, 1943, 1458.
19F-label for Proline

Synthesis of $^{19}$F-label for Proline

Advanced CF₃-amines for drug discovery

Synthesis of CF₃-amines

\[ \text{OH} \rightarrow 1. \text{TosCl} \rightarrow 2. \text{KOTBu} \rightarrow 55\% \]

\[ \begin{array}{c}
\text{N} \\
\text{Boc}
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\text{Boc}
\end{array} \]

\[ \text{CF₃CHN₂} \rightarrow \text{CuCl} \rightarrow 25\% \]

\[ \begin{array}{c}
\text{F₃C} \\
\text{H} \\
\text{N} \\
\text{Boc}
\end{array} \rightarrow \begin{array}{c}
\text{F₃C} \\
\text{H} \\
\text{N} \\
\text{Boc}
\end{array} \]

\[ \text{TFA} \rightarrow \text{CH₂Cl₂} \rightarrow \text{quant.} \]

\[ \begin{array}{c}
\text{F₃C} \\
\text{H} \\
\text{N} \\
\text{Boc}
\end{array} \rightarrow \begin{array}{c}
\text{F₃C} \\
\text{H} \\
\text{N}
\end{array} \]

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**CF₃-cyclopropanation of alkenes**

\[
\begin{align*}
\text{CF₃} & \quad \text{NH₂} \\
\xrightarrow[1) \text{NaNO}_2, \text{rt}\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}]{} & \quad \text{N}_2 \\
\xrightarrow[2) \text{Ar}/\text{MgSO}_4} & \quad \text{EDG} \\
\text{individual dry gas} & \quad \text{dry CuCl} \\
\rightarrow & \quad \text{EDG: electron-donation group}
\end{align*}
\]

- CF₃\(\text{C}_{\text{p}}\text{H}_{\text{p}}\) 61%
- CF₃\(\text{C}_{\text{p}}\text{H}_{\text{O}}\) 48%
- CF₃\(\text{C}_{\text{p}}\text{C}_\text{O}\) 51%
- CF₃\(\text{C}_{\text{p}}\text{C}_\text{N}\) 11%
- CF₃\(\text{Boc}_{\text{N}}\) 24%
- CF₃\(\text{Boc}_{\text{N}}\text{CO}_2\text{Me}\) 69%
- CF₃\(\text{Boc}_{\text{N}}\) 71%

Do we need dry CF₃CHN₂ here?
Do we need to isolate it then?

[3+2]-cycloaddition with alkenes
[3+2]-cycloaddition with alkenes

No purification

Scalable (500 g)

one-pot,
RT,
no inert atmosphere,
no catalysts,
common solvents,
no gaseous reagents,
no side products,
97% yield

CF₃-pyrazolines

Bioaktive $\text{CF}_3$-pyrazoles
**CF₃-pyrazoles**

\[
\begin{align*}
\text{CF}_3\text{-pyrazoles} & \quad \text{CF}_3\text{NH}_2 + \text{NaNO}_2 \rightarrow \text{CF}_3\text{N}_2 \quad \text{in situ-generated} \quad \text{CF}_3\text{EWG} \\
\text{CF}_3\text{HCl} & \quad \text{CH}_2\text{Cl}_2/\text{H}_2\text{O} \quad \text{RT} \quad \text{[3+2]} \quad \text{one-pot} \\
\text{EWG: electron-withdrawing group} & \\
\end{align*}
\]

- CF₃CO₂Me: 97%
- CF₃PO₃Ph: 92%
- CF₃CO₂Ph: 95%
- CF₃CH₁Ph: 98%
- CF₃NHCO₂Me: 80%
- CF₃NHCO₂Ph: 94%
- CF₃NHCO₂Ph: 96%
- CF₃NHCO₂Ph: 97%
- CF₃NHCO₂Ph: 97%
- CF₃NHCO₂Me: 75%
- CF₃HCO₂Et: 97%
- CF₃HCO₂Et: 94%

Japp-Klingemann reaction

\[
\text{CF}_3^*\text{HCl} \xrightarrow{\text{NaNO}_2} \xrightarrow{\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}} \text{RT} \quad \text{in situ-generated} \quad \xrightarrow{\text{EWG} \_\text{EWG}} \quad \text{Base} \quad \text{RT}
\]

Unpublished results
C$_2$F$_5$N$_2$

Lonaprisan
anticancer
(Bayer HC; Phase II)

Fulvestrant
anticancer
(AstraZeneca; launched)

KC-515
antimigraine
(Chugai; preclinical)

2014: unknown
**C$_2$F$_5$-pyrazolines**


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![Image of C$_2$F$_5$-pyrazolines](image-url)
C$_2$F$_4$H-pyrazoles

Unpublished results
C$_2$F$_5$-pyrazoles

**Chem. Eur. J.** 2014, 4942;  
**Beilstein J. Org. Chem.** 2015, 16;  

P. Mykhailiuk
DIAZOALKANE EXPANDS FLUORINE FOCUS ON ETHYL GROUPS

Developing new methods for introducing fluorine into complex organic molecules has been all the rage during the past few years. Researchers preparing drug candidates and crop protection chemicals typically seek to add a single fluorine atom or trifluoromethyl group and now have myriad ways to do so. But methods for adding longer, more lipophilic perfluoroalkyl groups such as pentafluoroethyl, $\text{C}_2\text{F}_5$, to complex molecules usually generates the fluorinated diazoalkane, $\text{C}_2\text{F}_5\text{CH}=$N$_2$, in situ from $\text{C}_2\text{F}_5\text{CHNHNH}_2\cdot\text{HCl}$ and NaNO$_2$. He demonstrated the utility of the reagent by using it in $[3+2]$ cycloadditions with alkynes to prepare perfluoroethylated pyrazolines (one example shown) with better than 95% conversion rates. Mykhailuk believes the diazofluoroalkane will also be as useful as other diazoalkanes for cyclopropanations, carbene insertions, and alkyne cycloadditions.—SR

A new fluorinated reagent 

Invented by Enamine, Enamine Ltd., that is, $\text{C}_2\text{F}_5\text{CHN}_2$ is generated in situ from $\text{C}_2\text{F}_5\text{CHNHNH}_2\cdot\text{HCl}$ and sodium nitrite. The stars correspond to the atoms in the molecule. For more details see the Full Paper by P.K. Mykhailuk on page 4864ff.
2015: not used properly

Ethiprole
*insecticide*  
BASF

Fipronil
*insecticide*  
BASF

Pyrazonil
*herbicide*  
Hoechst Schering

Pyrafluprole
*insecticide*  
BASF
CN-pyrazoles

P. Mykhailiuk *EurJOC* 2015, 7235.
Cover Picture
Pavel K. Mykhailiuk
New Life for Diazoacetamide (N$_2$CHCN)

Microreview
M. Manuel B. Marques et al.
Metal-Catalyzed Cross-Coupling Reactions of Aminopyridines

A Journal of
ChemPubSoc Europe

Supported by
ACER

WILEY-VCH
Scope

P. Mykhailiuk EurJOC 2015, 7235.
In-situ generation of CHF$_2$CHN$_2$

non-aqueous conditions?

CHF$_2$-pyrazoles

![Chemical reaction diagram]

New Reagent Brings Fresh Approach To Fluorination

Stephen K. Ritter

To test its reactivity, Mykhailiuk trapped the reagent in a one-pot [3+2] cycloaddition with disubstituted alkynes. Mykhailiuk selected the pyrazoles as a target because agrochemicals made by Syngenta, Bayer, and BASF.
EtO₂C\(\equiv\)N₂

popular (> 4000 reactions)

in situ-generated RCHN₂
Alekseenko A. Gryshuk S. Martirosov R. Radchenko D.
Artamonov O. Iminov R. Moroz U. Savich V.
Artemenko A. Komarov I. Mituk A. Scherbatiuk A.
Andrushko O. Kokhan S. Mikhalchuk V. Shyshlik O.
Arkhipov A. Arkhipov V. Slobodianuk E. Tkachenko A.
Bilenko V. Chalyk B. Tkachuk G. Tolmacheva N.
Datcenko O. Denisenko O. Tolmachev A. Tverdokhlebov A.
Dmitriv U. Druzhenko T. Trofimchuk S. Tymtsunik A.
Granat D. Gryshuk S. Ostapchuk E. Volochnyuk D.
Gorulia O. Kondratov V. Pasternak A. Yakovenko N.
Garbuz P. Kubyshkin V. Parhomenko L. Yarmolchuk V.
Gavrilenko K. Khutorianskii A. Pervak I. Yarmoluk D.
Logvinenko V. Pustovit U.
Thank you!

Enamine: world's largest supplier of building blocks

2016