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Aza-Henry reaction with perfluoroalkylated cyclic ketimines

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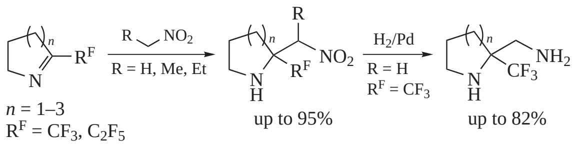
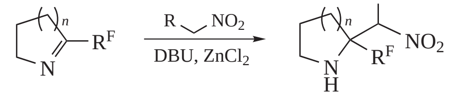
Aza-Henry reaction of 5-, 6- and 7-membered cyclic imines bearing perfluorinated group with nitroalkanes affords the corresponding nitro amines in up to 95% yield. Subsequent reduction of nitro group gives perfluoroalkyl-equipped vicinal diamines.



Organofluorine compounds are widely used in modern pharmaceuticals and materials science.[1] Incorporation of fluorine atom or perfluoroalkyl group (usually CF_3) into a molecule can significantly improve metabolic stability and modify the physico-chemical properties of obtained compounds.[2] Fluorine-containing compounds rarely occur in nature, and methods for direct introduction of fluorine are limited. Therefore, the use of building blocks is the most convenient tool for the synthesis of fluorinated molecules.[3] On the other hand, many drugs and natural compounds (alkaloids) contain structural motif of cyclic amine. For example, such modern drugs as Altace, OxyContin and Trandolaprile showed high efficiency in the treatment of nervous diseases, hypertension and heart diseases, and also as analgesics.[4]

Recently we have elaborated synthesis of perfluoroalkylated cyclic imines **1a**–**e** and started investigation of synthetic application of these new building blocks.[5] This article is devoted to the study of aza-Henry reaction with perfluoroalkylated cyclic imines.

First, the search for optimal conditions for the model reaction of 5-(trifluoromethyl)pyrroline **1a** with nitromethane was performed (Scheme 1, Table 1). Some organic bases were screened for the reaction. Previously we have shown that strong bases such as DBU and DBN are preferable catalysts/activators for the aza-Henry reaction with simple trifluoromethylated imines.[6] Considering lower reactivity of cyclic perfluoroalkyl substituted ketimines compared to hexafluoroacetone, trifluoroacetone and trifluoroacetophenone based ketimines, we suggested that it is necessary to activate imine with Lewis acid ($ZnCl_2$) along with activation of nitroalkane with base. However, low yields were observed for addition of nitromethane at room temperature with or without $ZnCl_2$ as an additive (entries 1–7). Reasonably high yields were achieved for DBU and Pr^i_2NEt (entries 8, 9) when this reaction was performed at elevated temperature. The combination of DBU with $ZnCl_2$ and heating at 95 °C were found most favorable to convert imine **1a** to target product **2a**. We managed to use this activator system (DBU/$ZnCl_2$) in lower amount (30%) to reach very high yield (95%) in reasonable reaction time (entry 13).[†]



1a $n = 1$, $R^F = CF_3$
1b $n = 2$, $R^F = CF_3$
1c $n = 3$, $R^F = CF_3$
1d $n = 1$, $R^F = C_2F_5$
1e $n = 2$, $R^F = C_2F_5$

2a $n = 1$, $R^F = CF_3$, R = H
2b $n = 2$, $R^F = CF_3$, R = H
2c $n = 3$, $R^F = CF_3$, R = H
2d $n = 1$, $R^F = C_2F_5$, R = H
2e $n = 2$, $R^F = C_2F_5$, R = H
2f $n = 1$, $R^F = CF_3$, R = Me
2g $n = 2$, $R^F = CF_3$, R = Me
2h $n = 1$, $R^F = CF_3$, R = Et

Scheme 1

Table 1 Aza-Henry reaction between **1a** and nitromethane with 0.5 equiv. of activator.

Entry	Activator	T/°C	t/h	Yield of **2a** (%)
1	DBU	20	56	20
2	Pr^i_2NEt	20	60	–
3	DBN	20	40	–
4	TBD	20	60	–
5	$ZnCl_2$/DBU	20	32	21
6	$ZnCl_2$/Pr^i_2NEt	20	64	–
7	$ZnCl_2$/DBN	20	40	–
8	DBU	95	52	73
9	Pr^i_2NEt	95	64	82
10	DBN	95	44	16
11	$ZnCl_2$/DBU	95	16	71
12	$ZnCl_2$/DBN	95	42	67
13	$ZnCl_2$/DBU[a]	95	48	95
14	$ZnCl_2$/DBU[b]	95	104	67
15	$ZnCl_2$/Pr^i_2NEt	95	64	90

[a] With 0.3 equiv. of activator. [b] With 0.1 equiv. of activator.

[†] *General procedure for the aza-Henry reaction*. Anhydrous $ZnCl_2$ (68 mg, 0.5 mmol) and DBU (75 μl, 0.5 mmol) were added to a solution of cyclic imine (1 mmol) in nitroalkane (1 ml). The mixture was heated at 95 °C (for **1a**) or kept at room temperature (for **1b**–**e**). The reaction was monitored by ^{19}F NMR. The mixture was cooled to room temperature, $ZnCl_2$ was filtered off, the filtrate was concentrated under reduced pressure, and the product was isolated by column chromatography (eluent: dichloromethane).

2-Nitromethyl-2-(trifluoromethyl)pyrrolidine **2a**: Yield 95%, yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.73–1.81 (m, 1H, CH_2), 1.84–1.94 (m, 1H, CH_2), 2.00–2.07 (m, 1H, CH_2), 2.14–2.21 (m, 1H, CH_2), 2.39 (br. s, 1H, NH), 3.05 (t, 2H, CH_2, $^3J_{HH}$ 6.4 Hz), 4.52 (d, 1H, CH_2NO_2, $^2J_{HH}$ 11.5 Hz), 4.59 (d, 1H, CH_2NO_2, $^2J_{HH}$ 11.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8 (CH_2), 30.3 (CH_2), 46.9 (CH_2), 66.7 (q, CCF_3, $^2J_{CF}$ 27.9 Hz), 77.4 (CH_2NO_2), 126.1 (q, CF_3, $^1J_{CF}$ 284.3 Hz). ^{19}F NMR (280 MHz, $CDCl_3$) δ: –71.14 (CF_3). IR (KBr, ν/cm^{-1}): 1230 (CF). MS (ESI), m/z: 199.0686 $[M+H]^+$ (calc. for $C_6H_{10}F_3N_2O_2$, m/z: 199.0650).

Table 2 Aza-Henry reaction of perfluoroalkylated cyclic ketimines.[a]

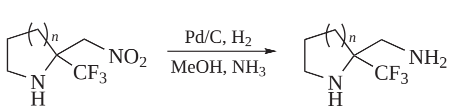
Entry	Imine	R^F	Product	R	Reaction time/days	Yield (%)
1	**1a**	CF_3	**2a**	H	2	95
2	**1b**	CF_3	**2b**	H	4	88
3	**1c**	CF_3	**2c**	H	7	78
4	**1d**	C_2F_5	**2d**	H	90	27
5	**1e**	C_2F_5	**2e**	H	150	16
6	**1a**	CF_3	**2f**	Me	30	60
7	**1b**	CF_3	**2g**	Me	30	28
8	**1a**	CF_3	**2h**	Et	90	38

[a] Conditions: 0.5 equiv. $ZnCl_2$, 0.5 equiv. DBU, 20 °C except for **1a** (95 °C).

However, the use of 10% of the activator demanded much longer time to make the reaction complete (entry 14). Slightly lower yield was observed for $ZnCl_2/Pr^i_2NEt$ system (entry 15).

Under the optimal conditions, addition of nitromethane to some other cyclic imines **1b–e** bearing either CF_3 or C_2F_5 group was carried out (Table 2, Scheme 1, ^{19}F NMR monitoring). The reaction with these imines was revealed to proceed at room temperature, however, it was extremely sensitive to the structure of both components. In the case of pentafluoroethylated imines **1d**,**e** (entries 4, 5) much longer time was necessary (up to 5 months at ~20 °C) to obtain the target products in low yields. These data can be due to higher steric hindrance of C_2F_5 group. Attempted acceleration of this reaction by refluxing led to complex mixture of products. In contrast, the reaction between nitromethane and trifluoromethylated imines **1b**,**c** proceeded smoothly at ~20 °C to give the corresponding nitro amines **2b**,**c** (entries 2, 3) in high yields (up to 88%) and in reasonable time (up to 7 days). These results revealed significant dependence of reactivity of cyclic imines **1a–c** on their ring size, which can be explained by conformation effects. The possibility of using nitroethane and nitropropane was demonstrated for trifluoromethylated imines **1a**,**b** (entries 6–8), however, these reactions demanded longer time to be complete and products **2f–h** (two diastereomers) were obtained in moderate yields.

Many natural compounds, drugs and catalysts contain a fragment of cyclic diamine in their structures. Reduction of prepared nitro amines **2a–c** can be applied to access such diamines. In fact, Pd/C-catalized hydrogenation (1 atm) of nitro amines **2a–c** in methanol furnished vicinal diamines **3a–c** in up to 82% yields (Scheme 2).‡



2a *n* = 1
2b *n* = 2
2c *n* = 3

3a *n* = 1, 48%
3b *n* = 2, 82%
3c *n* = 3, 78%

Scheme 2

In conclusion, aza-Henry reaction between C_{sp^2}-perfluoroalkylated cyclic ketimines and nitroalkanes using $ZnCl_2/DBU$ system as the activator affords the nitro amines. They can be readily reduced to the promising 1,2-diamines suitable for selective modification due to different nucleophilicity of their amino groups caused by the effect of perfluoroalkyl substituent.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.027.

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‡ *General procedure for the reduction of nitro amines*. Nitro amine **2a–c** (0.2 mmol) was dissolved in methanol (15 ml) and saturated aqueous ammonia (2 ml), and 10% palladium on carbon (50 mg) as catalyst was added. The suspension was stirred under hydrogen atmosphere (1 atm) for 28 h and then filtered through a Celite plug. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane–methanol, 10 : 1).

[2-(Trifluoromethyl)pyrrolidin-2-yl]methanamine **3a**. Yield 48%, yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.62–2.01 (m, 7H, CH_2CH_2, NH, NH_2), 2.68 (d, 1H, CH_2NH_2, *J* 13.4 Hz), 2.94 (d, 1H, CH_2NH_2, *J* 13.4 Hz), 2.98–3.08 (m, 2H, CH_2NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0 (CH_2), 30.1 (CH_2), 45.0 (CH_2), 47.4 (CH_2), 67.4 (q, CCF_3, $^2J_{CF}$ 24.7 Hz), 128.4 (q, CF_3, $^1J_{CF}$ 284.6 Hz). ^{19}F NMR (280 MHz, $CDCl_3$) δ: –78.20 (s, 3F, CF_3). IR (KBr, ν/cm^{-1}): 3300 (br., NH), 1169 (CF), 1147 (CF). HRMS (ESI), *m*/*z*: 169.0944 $[M+H]^+$ (calc. for $C_6H_{12}F_3N_2$, *m*/*z*: 169.0948).