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Diastereoselective vinylogous Mannich reaction of perfluoroalkylated cyclic imines with 2-trimethylsilyloxyfuran

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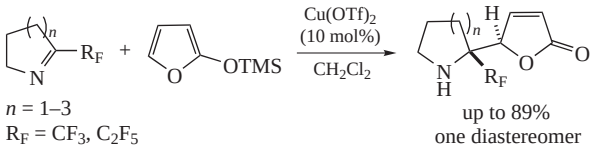
The reaction between 2-trimethylsilyloxyfuran and perfluoroalkylated cyclic ketimines with different ring sizes affords 5-(2-perfluoroalkyl-1-azacycloalk-2-yl)furan-2(5*H*)-ones in yields up to 89% and with excellent *rel*-(*R*,*R*)-diastereoselectivity.



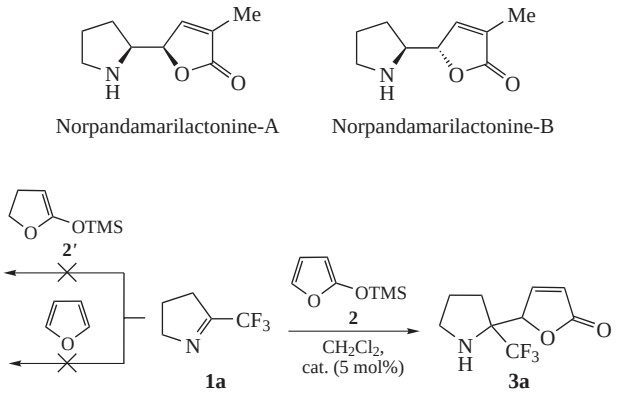
Organofluorine chemistry is an important branch of modern pharmaceutics and materials science,[1] while organofluorine compounds are rarely occurring in nature. There are two general approaches to their synthesis, namely, straightforward fluorination or application of fluorine-containing building blocks.[2] Recently we have obtained and studied perfluoroalkyl-substituted 5-, 6- and 7-membered cyclic ketimines **1a**–**d**.[3,4] Fluorinated cyclic ketimines appeared to be useful for the preparation of molecules bearing both fluorinated fragment and cyclic amine or aminoalkyl group.

In this work we have focused attention on the Mannich reaction of cyclic ketimines and 2-trimethylsilyloxyfuran **2** for obtaining analogues of alkaloids norpandamarilactonine-A and -B.[5] Some examples of reactions of imines with 2-trimethylsilyloxyfuran **2** can be found in the literature, mostly of aldimines or imines activated with electron-withdrawing group. These reactions were carried out in the presence of Lewis acids at room or lowered temperature in aprotic solvents,[6] and in some cases 1–2 equiv. of alcohols were added to accelerate the processes.

This study was started from screening of the reaction conditions for aminoalkylation of 2-trimethylsilyloxyfuran **2** with 2-trifluoromethylpyrroline **1a** (Scheme 1). First, the alkylation was carried out in CH_2Cl_2, a wide range of catalysts was tested. Application of $TiCl_4$ and TMSOTf led to complex mixtures of undefined byproducts, while the reaction did not proceed in the presence of $Ti(OPr^i)_4$ and $MgCl_2$. In the case of AgOAc, the desired product **3a** was obtained in only 15% yield. To our delight, the application of $ZnCl_2$, $Zn(OTf)_2$ or $Cu(OTf)_2$ as catalysts resulted in clean formation of the single target compound **3a** with the best result having been achieved with $Cu(OTf)_2$ (100% ^{19}F NMR yield, and 85% isolated yield). Screening of the solvents (THF, Et_2O, toluene) and varying the amount of Lewis acid did not improve the yield.

Previously[4(e)] we demonstrated that nucleophilicity of furan was not sufficient to react with imines **1a**–**d** in the presence of Lewis acids (see Scheme 1). We also attempted to alkylate [(4,5-dihydrofuran-2-yl)oxy]trimethylsilane **2′** with imine **1a**. However, no reaction occurred in the presence of different Lewis acids [$ZnCl_2$, $Cu(OTf)_2$, $BF_3{\cdot}Et_2O$]. Less reactive nonfluorinated cyclic ketimines also did not couple with 2-trimethylsilyloxyfuran **2**.

Other cyclic perfluoroalkyl substituted ketimines **1b**–**d** were also examined in the reaction with 2-trimethylsilyloxyfuran **2** under optimal conditions (Scheme 2).† The highest yields were achieved in the cases of 5- and 7-membered 2-trifluoromethylketimines **1a**,**d**, when the target products **3a**,**d** were isolated in

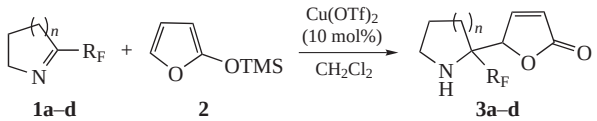


Catalyst	Yield of **3a** (%)	Catalyst	Yield of **3a** (%)
$ZnCl_2$	85	$MgCl_2$	no reaction
$Zn(OTf)_2$	75	TMSOTf	–
$BF_3{\cdot}Et_2O$	40	$Ti(OPr^i)_4$	no reaction
$Cu(OTf)_2$	100	$TiCl_4$	–
AgOAc	15		

Scheme 1 ^{19}F NMR yields are given.

† *General procedure*. Starting cyclic ketimine **1a**–**d** (1 mmol) and 2-trimethylsilyloxyfuran **2** (0.2 g, 1.28 mmol) were dissolved in dry dichloromethane (2 ml), and copper(II) trifluoromethanesulfonate (0.018 g, 0.05 mmol) was added. The mixture was kept at room temperature from 1 to 5 days (TLC control). The solvent was evaporated and the product was purified by column chromatography (eluent: hexane–ethyl acetate).

5-[2-(Trifluoromethyl)pyrrolidin-2-yl]furan-2(5H)-one **3a**. ^{19}F NMR yield 100%, after purification 85%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.67–1.86 (m, 3H), 1.88–1.95 (m, 1H), 1.98–2.05 (m, 1H), 2.97 (t, 2H, *J* 6.4 Hz), 5.15 (t, 1H, *J* 1.7 Hz), 6.20 (dd, 1H, *J* 5.7 Hz, *J* 1.7 Hz), 7.47 (d, 1H, *J* 5.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 29.0 (CH_2–C_q), 47.4 (CH_2–N), 68.3 (q, *C*–CF_3, J_{CF} 25.8 Hz), 83.1 (CH), 123.6 (C=), 126.7 (q, CF_3, J_{CF} 284.9 Hz), 152.7 (C=), 171.9 (CO). ^{19}F NMR (376.50 MHz, $CDCl_3$) δ: –76.4 (s, 3F, CF_3). IR (ATR, ZnSe, ν/cm^{-1}): 3372 (br.s, NH), 3336 (br.s, NH), 1796 (CO), 1755 (CO), 1159, 1091. HRMS (ESI), *m*/*z*: 222.0739 $[M+H]^+$ (calc. for $C_9H_{11}F_3NO_2^+$, *m*/*z*: 222.0737).



1a–d **2** **3a–d**

	R_F	*n*	Yield of **3** (%)
a	CF_3	1	85
b	C_2F_5	1	66
c	CF_3	2	51
d	CF_3	3	89

Scheme 2

85 and 89% yields, respectively. The reaction between pentafluoroethyl homologue **1b** and 2-trimethylsilyloxyfuran **2** was not complete (yield of **3b** was 66%), and some amounts of starting imine **1b** remained. The application of additional amounts of trimethylsilyloxyfuran **2** or catalyst [$Cu(OTf)_2$] did not improve the result. In the case of 2-trifluoromethylpiperideine **1c**, the desired product **3c** was unstable under reaction conditions and its yield was moderate (51%). Thus, yield and stability of the products **3a–d** depend on the ring size of the starting ketimine and the nature of its substituents (CF_3 or C_2F_5). The lower yield in the case of C_2F_5-derivative **1b** compared to CF_3-one **1a** can be explained by a greater size of pentafluoroethyl group.[4]

Importantly, in all cases the formation of only one diastereomer **3a**,**d** was detected. To explain excellent diastereoselectivity of the reaction, DFT calculations were performed to compare energy of two diastereomers of **3a**. Computations (Gaussian 09, DFT B3LYP/6-311G*)[7] revealed that diastereomer having *rel*-(*R*,*R*)-configuration is approximately 3 kcal mol^{-1} more favorable than *rel*-(*R*,*S*) one (Figure 1). Therefore, the more thermodynamically stable product is formed. We believe that the similar situation is valid for other products **3**.

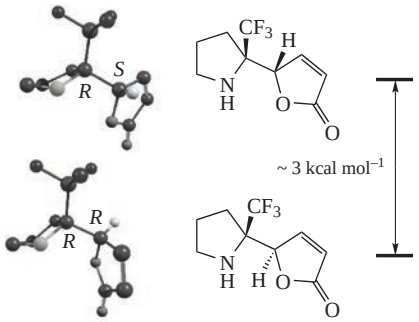


Figure 1 Calculated geometries for two diastereomers of **3a** (only one CH-bond is given for clarity).

In summary, the Mannich reaction of 2-perfluoroalkylated cyclic ketimines with 2-trimethylsilyloxyfuran affords furanone derivatives bearing fragment of cyclic amine with fluorinated group in good to high yields.

*5-[2-(Pentafluoroethyl)pyrrolidin-2-yl]furan-2(5*H*)-one* **3b**. Yield 66%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.74–1.87 [m, 3H, incl. 1.74 (br.s, 1H, NH)], 1.96–2.02 (m, 1H), 2.14–2.22 (m, 1H), 3.03 (t, 2H, *J* 6.6 Hz), 5.20 (s, 1H), 6.27 (dd, 1H, *J* 5.8 Hz, *J* 1.9 Hz), 7.44–7.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 29.2 (CH_2–C_q), 47.3 (CH_2–N), 68.9 (t, *C*–CF_3, J_{CF} 20.3 Hz), 83.3, 115.2–120.9 (m, C_2F_5), 123.9 (C=), 152.6 (C=), 172.0 (CO). ^{19}F NMR (376.50 MHz, $CDCl_3$) δ: –79.0 (s, 3F, CF_3), –117.9 (d, 1F, *J* 277.6 Hz), –120.3 (d, 1F, *J* 277.6 Hz). IR (ATR, ZnSe, ν/cm^{-1}): 3370 (br.s, NH), 1796 (CO), 1762 (CO), 1210, 1163, 1116. HRMS (ESI), *m*/*z*: 272.0698 $[M+H]^+$ (calc. for $C_{10}H_{11}F_5NO_2^+$, *m*/*z*: 272.0704).

For characteristics of products **3c**,**d**, see Online Supplementary Materials.

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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.2019.01.018.

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