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Friedel–Crafts alkylation of natural amino acid-derived pyrroles with CF_3-substituted cyclic imines

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Natural amino acid-derived ethyl 2-(1-pyrrolyl)alkanoates react with 2-trifluoromethyl-1-azacycloalkenes selectivity at the β-position of the pyrrole moiety to afford ethyl 2-[3-(1-trifluoromethyl-2-azacycloalkyl)pyrrol-1-yl]alkanoates.

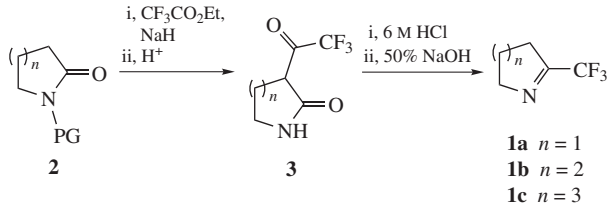
Recently we have elaborated the synthesis of perfluoroalkylated (CF_3- and C_2F_5-substituted) cyclic imines[1,2] and started investigation of their use as promising fluorine-containing building blocks.[3] It worth noting that both nitrogen heterocyclic core and fluorine-contaning fragment are very important structural units of many biological active compounds comprising modern pharmaceutical and crop protection products.[4]

Having these considerations in mind, we decided to investigate the α-CF_3 substituted cyclic imines in Friedel–Crafts type aminoalkylation of (hetero)aromatics. This study is focused on the reaction of such imines with easy accessible chiral pyrroles derived from natural amino acids. Pyrrole moiety is presented in many natural compounds[5] and chiral fragment may affect stereo outcome of the reaction. Investigation of diastereoselectivity in these reactions seemed of special interest.

In literature, only several examples of the aromatic substitution with fluorine-containing imines have been reported to date.[6] Highly active fluorinated imines bearing additional electron-withdrawing groups both on nitrogen and imine carbon atoms are able to react with electron-rich aromatics without any activators or in the presence of Brønsted acids. Other fluorinated imines require promoting by stronger Lewis acid, *e.g.* $BF_3{\cdot}Et_2O$. In addition, reaction of cyclic imines with heteroaromatics is known only for non-fluorinated aldimines (pyrroline and tetrahydropyridine).[7]

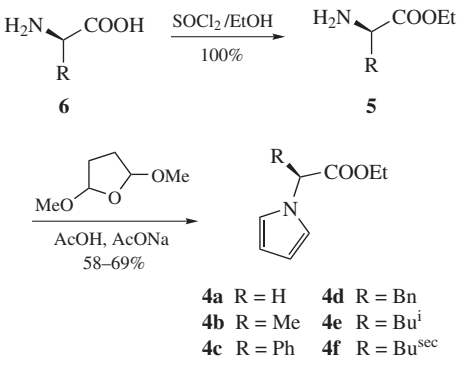
The starting CF_3-cyclic imines **1a–c** were prepared from N-protected lactams **2** using our previously published two-step method (Scheme 1).[1] First step of the synthetic sequence is Claisen condensation of N-protected lactams **2** with ethyl trifluoroacetate followed by deprotection. Subsequent decarboxylation of perfluoroacyl lactams **3** in acidic media afforded CF_3-cyclic imines after treatment with sodium hydroxyde.

Starting chiral pyrroles **4** were synthesized in good yields by condensation of 1,4-dimethoxytetrahydrofurane with ethyl esters of amino acids **5** (Scheme 2), which were prepared from natural amino acids **6**: glycine, alanine, phenylglycine, phenylalanine, leucine and isoleucine.[8] Early diastereoselective aminoalkylation of indoles and pyrroles with chiral imines was studied.[6(e),(d)] Pyrroles with a chiral moiety derived from the natural amino acids have never been studied in such kind of reactions. This situation motivated us to investigate the aminoalkylation of various CF_3-cyclic imines **1** with chiral pyrroles **4** and its diastereoselectivity.



2 **3**

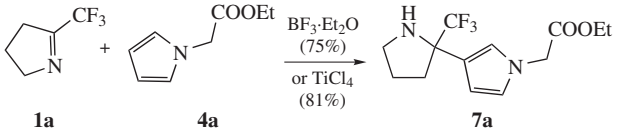
Scheme 1



6 **5**

Scheme 2

Using glycine derived pyrrole **4a** and 2-trifluoromethylpyrroline **1a**, we performed optimization of the reaction conditions and screening of the Lewis and Brønsted acids as activators. We examined equimolar amounts of TfOH, $BF_3{\cdot}Et_2O$ and $TiCl_4$ as imine activators. In a typical experiment, imine **1a** was mixed with 1 equiv. of the catalyst in dichloromethane at 0 °C. Then, pyrrole **4a** was added at the same temperature and progress of the reaction was monitored by ^{19}F NMR. No reaction was observed at all for TfOH. In the case of $TiCl_4$ reaction was complete within 2 h giving the product **7a** in 81% yield (Scheme 3). The reaction promoted by $BF_3{\cdot}Et_2O$ required longer but reasonable reaction time (5 days) and provided the slightly lower yield (75%). Nevertheless, there were no side products in the latter case, so the isolation of product **7a** was easier. The structure of product **7a**

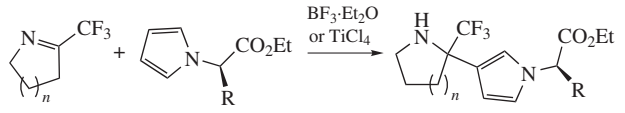


1a **4a** **7a**

Scheme 3

was quite unusual. We expected to obtain α-substituted pyrrole,[7] however, in fact β-substitution product was formed regardless BF_3 or $TiCl_4$ were used as a catalyst. Apparently, such a regioselectivity could occur due to steric hindrance of bulky intermediate iminium species. The structure of compound **7a** was undoubtedly proved using HMBC experiment (for details of HMBC correlations, see Online Supplementary Materials).

The transformations were carried out in the similar manner for other N-substituted pyrroles **4**† with $BF_3{\cdot}Et_2O$ and/or $TiCl_4$ as activators (Scheme 4). No restrictions on the structure of pyrroles **4** or trifluoromethylated imines **1** were found. β-Substituted pyrroles **7a–j** bearing both pyrrolidine moiety and its homologues were synthesized in good yields (Table 1). However, according to NMR data, no diastereoinduction was observed and 1:1 mixture of diastereomers was formed in cases of chiral substrates **4b–f** since newly formed stereocentres are too distant from starting chirality.



1a–c **4a–f** **7a–j**

R = H, Me, Ph, Bn, Bu^i, Bu^{sec}
n = 1, 2, 3

Scheme 4

In summary, substituted pyrroles **4**, including chiral ones, were successfully involved in the Friedel–Crafts aminoalkylation with the cyclic trifluoromethylated imines **1**. This aminoalkylation opens a straightforward route to the pyrrole-substituted pyrrolidines, piperidines and azepanes bearing CF_3 group. In all reactions studied the unexpected β-regioselective substitution at the pyrrole ring took place.

† *General procedure for preparation of* **7**. Freshly distilled $BF_3{\cdot}Et_2O$ (0.126 ml, 1 mmol) or $TiCl_4$ (0.11 ml, 1 mmol) was added slowly under vigorous stirring and cooling to a solution of imine **1** (1 mmol) in dry dichloromethane (10 ml). After 5 min a solution of the corresponding pyrrole (1 mmol) in dichloromethane (3–4 ml) was added dropwise. The mixture was stirred for 2 h at 0 °C in the case of $TiCl_4$ and 5 days at room temperature for $BF_3{\cdot}Et_2O$. After that the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (15 ml), extracted with dichloromethane (2×10 ml), the combined organic extracts were dried over Na_2SO_4, concentrated under reduce pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane affording target amine to give after solvent evaporation products **7**.

*Ethyl {3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrol-1-yl}acetate* **7a**: 71%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, 3H, CH_2Me, *J* 7.13 Hz), 1.81–1.99 (m, 3H), 2.12–2.19 (m, 1H), 2.32–2.39 (m, 1H), 3.04–3.17 (m, 2H, CH_2N), 4.23 (q, 2H, CO_2CH_2Me, *J* 7.13 Hz), 4.58 (s, 2H, CH_2CO_2Et), 6.19–6.22 (m, 1H, H_{Ar}), 6.62–6.63 (t, 1H, H_{Ar}, *J* 2.52 Hz), 6.68–6.69 (m, 1H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9 (Me), 26.0, 34.0 (CH_2C_q), 47.3 (CH_2N), 50.8 (CH_2CO_2Et), 61.6 (CO_2CH_2Me), 66.3 (q, CCF_3, J_{CF} 27.3 Hz), 107.8 (Ar), 119.7 (Ar), 122.1 (Ar), 124.4 (C_q, Ar), 127.5 (q, CF_3, J_{CF} 282.7 Hz), 168.4 (CO). ^{19}F NMR (280 MHz, $CDCl_3$) δ: –78.6 (CF_3). IR (KBr, ν/cm^{-1}): 3367, 1753, 1155. Found (%): C, 53.85; H, 5.99; N, 9.58. Calc. for $C_{13}H_{17}F_3N_2O_2$ (%): C, 53.79; H, 5.90; N, 9.65.

For characteristics of compounds **7b–j**, see Online Supplementary Materials.

Table 1 Aminoalkylation reaction of pyrroles **4a–f** with imines **1a–c**.

R	*n*	Product	Yield (%)
H	1	**7a**	75 (81)[a]
Me	1	**7b**	69 (73)
Ph	1	**7c**	(81)
Bn	1	**7d**	74
Bu^i	1	**7e**	87
Bu^{sec}	1	**7f**	(68)
H	2	**7g**	62
Me	2	**7h**	75
H	3	**7i**	65
Me	3	**7j**	60

[a]Yields with $TiCl_4$ are given in parentheses.

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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.2013.03.013.

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