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Vinylogous Mannich reactions. Additions of trimethylsilyloxyfuran to fluorinated aldimines

Maria Vittoria Spanedda, Michèle Ourévitch, Benoit Crousse,* Jean-Pierre Bégué and Danièle Bonnet-Delpon*

Faculté de Pharmacie, J. B. Clément, F-92296 Châtenay-Malabry, France

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Abstract—Trifluoromethyl aldimines reacted with trimethylsilyloxyfuran in presence of Lewis acids to provide butenolides in high yields with total diastereoselectivity (>98%). The configuration of these products is *anti*. The butyrolactone **4a**, substituted with a 2-trifluoromethyl ethyl amine, could be converted into a *trans* α-trifluoromethyl piperidine derivative.

Trialkylsilyloxyfurans are interesting substrates in the vinylogous Mannich reaction,[1,2] which is an important process, involving an iminium or an acyl iminium salt, for the synthesis of alkaloids and other nitrogen-containing biologically active compounds.[2] This synthetic approach allows to obtain α,β-unsaturated γ-lactone via a regio- and diastereoselective four-carbon elongation of suitable imines with trimethyl silyloxyfuran (TMSOF). These unsaturated lactones can be envisaged as flexible substrates to elaborate a variety of advanced intermediates such as butyrolactones, piperidones, piperidine derivatives, which are often structural elements of biologically active compounds.[2,8]

Only few examples of (2′,2′,2′-trifluoroethyl)-2-buten-4-olides are reported in literature.[3] Conversely, due to their great interest, various routes (e.g., cycloaddition reactions or ring closure metathesis) to trifluoromethyl piperidines and piperidones have been reported.[4] However, the vinylogous Mannich reaction has not been studied so far with trifluoromethyl aldimines to give access to these compounds. Competitive features are expected in trifluoromethyl aldimine reactivity towards nucleophiles: on one hand, the trifluoromethyl group, due to its electron-withdrawing character, enhances the electrophilic character of the imine carbon; on the other hand, it significantly reduces the basicity of imine groups and hence the strength of complexation with a Lewis acid; moreover it could lower the reactivity through a steric effect. Our previous studies on aza-Diels–Alder reactions showed that the trifluoromethyl aldimines are very reactive towards dienophiles.[4d]

We report our results on the vinylogous Mannich reaction between CF_3-aldimines **1** and TMSOF **2** under Lewis acid conditions, and the further easy route to CF_3-substituted piperidine derivatives.

The reaction has been first explored with the aldimine **1a** (R = benzyl),[5] TMSOF **2** (1.1 equiv) in dichloromethane at −78 °C in the presence of three different Lewis acids: ($Yb(OTf)_3$, $BF_3{\cdot}Et_2O$ and *tert*-butyl dimethyl silyloxytriflate (TBSOTf)) (Table 1).

With $Yb(OTf)_3$ (20 mol%) as catalyst at −78 °C, the reaction time was very long (24 h) and led to the butenolides **3a** in 72% yield with a 88% de. Raising up temperature did not shorten reaction times but resulted in a loss of diastereoselectivity. In the presence of $BF_3{\cdot}Et_2O$ or TBSOTf (0.5 equiv) at −78 °C, the aldimine **1a** led to **3a** in short reaction times (0.5 h), in excellent yield and diastereoselectivity (>98% de). In ^1H and ^{19}F NMR spectra, only one diastereoisomer was detected.[6] The X-ray crystal structure of **3a** revealed the configuration *anti* between carbons 5 and 6 (Fig. 1).[7] The *anti* isomers are also the most frequently observed in

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* Corresponding authors. Tel.: +33-(0)146835744; fax: +33-(0)14683-5740; e-mail: benoit.crousse@cep.u-psud.fr

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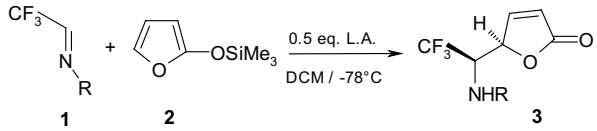
Table 1. Vinylogous Mannich reaction with CF_3-aldimines **1**



Entry	Imine **1**	LA	Time (h)	De (%)	Yield (%)
1	R = Bn **1a**	$Yb(OTf)_3$	24[a]	88	72
2	R = Bn **1a**	$BF_3{\cdot}Et_2O$	0.5	>98	90
3	R = Bn **1a**	TBSOTf	0.5	>98	97
4	R = allyl **1b**	$BF_3{\cdot}Et_2O$	0.5	>98	92
5	R = allyl **1b**	TBSOTf	0.5	>98	95
6	R = PMP **1c**	$BF_3{\cdot}Et_2O$	0.5	80	87
7	R = PMP **1c**	TBSOTf	0.5	36	80

[a] Reaction was allowed to warm up to rt.

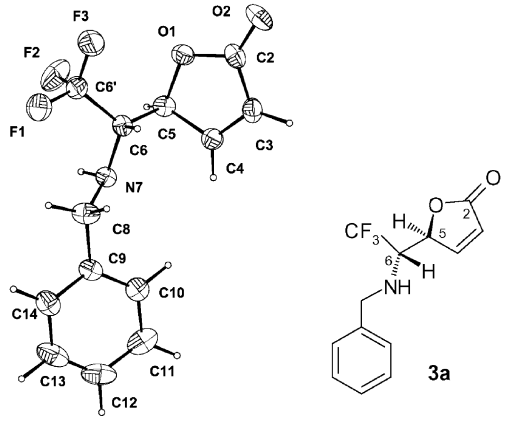


Figure 1. ORTEP view of **3a**.

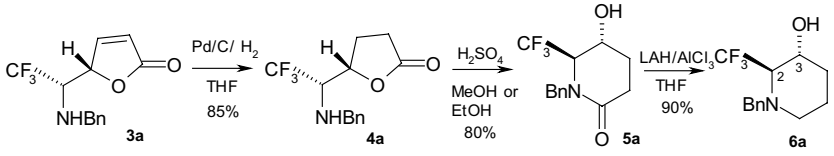
nonfluorinated series,[1,8] although reaction times are longer (3 h with TBSOTf, 6 h with $BF_3{\cdot}Et_2O$) and the reaction is slightly less stereoselective (80% de).[9] Due to its electronic effect, the trifluoromethyl group increases the reactivity, shortening reaction times, while its steric hindrance increases the stereoselectivity, facilitating the approach leading to the *anti* isomer.

The reaction has been extended to other aldimines, using $BF_3{\cdot}Et_2O$ and TBSOTf as Lewis acids. With **1b** (R = allyl), the same excellent yields (92–95%) and selectivities (>98%) were obtained.

When reactions were performed with the imine **1c** (R = *p*-methoxy phenyl), in the presence of $BF_3{\cdot}Et_2O$, the lactone **3c** was also obtained in good yield, but the level of diastereoselectivity was lower (80% de). When TBSOTf was used as catalyst, both yield (80%) and selectivity decreased (36% de).

From the butenolide **3a**, we attempted to prepare new trifluoromethyl-substituted piperidine derivatives. Exposure of **3a** to catalytic hydrogenation (H_2/Pd/C 10%) resulted in a clean saturation of the double bond leading to the butyrolactone **4a** without removal of the *N*-benzyl protective group. With the aim to obtain the δ-lactam **5a**, the 6-amino-butyrolactone **4a** so formed was then treated with DBU used as solvent at reflux, as described with nonfluorinated compounds.[1b] After 30 h, the expected-lactam **5a** was obtained in a very low yield (20%). When the compound **4a** was dissolved in ethanol or methanol and heated at reflux overnight in the presence of a catalytic amount of sulfuric acid, the δ-hydroxylactam **5a** was obtained in very good yield and only one diastereoisomer was observed in NMR. However, at this stage NMR data of **5a** did not allow an unambiguous determination of configuration. A further treatment of **5a** with $LiAlH_4/AlCl_3$[10] allowed the complete reduction of the carbonyl group and afforded the CF_3-substituted piperidine **6a** in 90% yield (Scheme 1).

For **6a** a complete assignment of protons and carbons by NMR has been made, showing a small coupling constant between H-2 and H-3 ($J_{2/3} = 2.2$ Hz in $CDCl_3$), which could fit with a *trans* diaxial configuration of CF_3 and OH (expected), but also with a *cis* configuration of the two substituents if an epimerization occurs in the reaction sequence from **3a**. Finally NOESY and HOESY experiments allowed to assert unambiguously that CF_3 and OH are *trans* diaxial in all solvents, protic (CH_3OD, D_2O) or aprotic ($CDCl_3$, C_6D_6, DMSO-d_6) and at all temperatures (−30 °C up to 187 °C). This phenomenon could be attributed to various factors, such as a hydrogen bond between OH and N, forcing the hydroxyl to be in an axial position.[11] This hypothesis has been rejected since the *trans* diaxial conformation



Scheme 1.

remains in the O–Me derivative and in the piperidine hydrochloride salt. The most likely explanation is that the equatorial benzyl group forces the two other substituents to be axial, to minimize steric and electronic interactions.

In conclusion, the Lewis acid-promoted vinylogous Mannich reaction involving a silyloxyfuran was investigated for the first time with trifluoromethyl aldimines. The butenolides could be obtained in excellent yields and diastereoselectivity. This approach allows the stereoselective access to *trans* functionalized 2-trifluoromethylated piperidine derivatives.

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6. Compound **3a**: white solid, mp: 78 °C (AcOEt/petroleum ether). ^{1}H NMR ($CDCl_3$): 7.43 (d, $J = 5.5$ Hz, 1H), 7.3 (5H, Ar), 6.25 (dd, $J = 5.5$ Hz, $J = 2$ Hz, 1H), 5.29 (dt, $J = 4$ Hz, $J = 2$ Hz, 1H), 4.02 (d, $J = 13$ Hz), 3.89 (d, $J = 13$ Hz), 3.64 (dq, $J = 4$ Hz, $J = 8$ Hz, 1H). ^{19}F NMR ($CDCl_3$): −72.13 (d, $J = 7.5$ Hz). ^{13}C NMR: 171.6, 151.6, 138.4, 128.3, 128.1, 127.4, 125.2 (q, $J = 285$ Hz), 123.9, 80.1 (q, $J = 2$ Hz), 59.7 (q, $J = 27.5$ Hz), 52.3. IR (neat): 3334, 2903, 1751, 1300, 1125 cm^{-1}. Anal. Calcd for $C_{13}H_{12}F_3NO_2$: C, 57.57; H, 4.46; N, 5.16. Found: C, 57.08; H, 4.62; N, 4.80.
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