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$Yb(OTf)_3$-catalyzed Mannich-type reaction of a chiral non-racemic silyloxypyrrole

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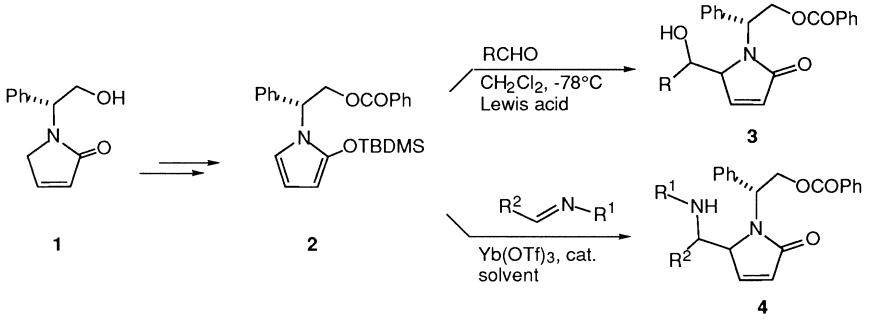
Abstract

A $Yb(OTf)_3$-catalyzed Mannich-type reaction of the chiral non-racemic silyloxypyrrole **2** is described. The three-component (silyloxypyrrole, aldehyde and amine) reaction allowed the use of aromatic as well as aliphatic enolisable aldehydes. The *erythro* selectivity was proved by chemical correlation and X-ray analysis.

We have already reported on the reactivity of lactam **1**[1] which was proved to be easily substituted at several positions of the five-membered ring.[2,3] Alkylations at C-3, 1,4-additions at C-4, as well as substitutions at C-5, were achieved with high diastereoselectivities.

Special attention was paid to the transformation of lactam **1** into the silyloxypyrrole **2** since the latter undergoes a Lewis acid-catalyzed aldol-type reaction with various carbonyl derivatives (Scheme 1).[3] This reaction allowed access to interesting derivatives in good yield and with good diastereoselectivity.



Scheme 1.

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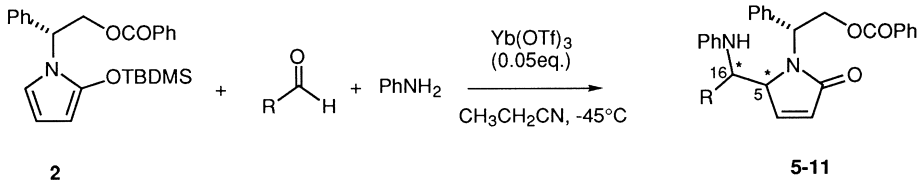
Lanthanide triflates, particularly $Sc(OTf)_3$ and $Yb(OTf)_3$, were recently described to be very efficient and highly selective catalysts for the addition of various nucleophiles to imines.[4] It has been reported by Kobayashi that $Yb(OTf)_3$-catalyzed addition of silyl enol ethers or ketene acetals to aldimines proceeded very efficiently and selectively while the reaction with aldehydes did not occur under the same reaction conditions.[4b] We recently reported[5] the reaction of **2** with imines catalyzed by $Yb(OTf)_3$. This reaction was found to be very efficient with aromatic imines but failed with aliphatic enolisable imines.

In order to extend the scope of reactivity of lactam **1**, we thus decided to investigate the $Yb(OTf)_3$-catalyzed Mannich-type reaction of silyloxypyrrole **2** in the one-pot three-component condensation depicted in Scheme 2.



Scheme 2.

In a typical experiment, 5% mol. of $Yb(OTf)_3$ was added to a solution of silyloxypyrrole **2** (1 equiv.) and aldehyde (1.5 equiv.) in CH_3CH_2CN containing molecular sieves at –45°C, followed by the dropwise addition of aniline (1.5 equiv.). A very rapid reaction occurred (the disappearence of starting materials was generally observed within 30 min) and the adducts **5–11** were easily obtained in high yields as mixtures of diastereomers as indicated in Table 1. Crude reaction mixtures were examined by NMR (^{13}C and ^{1}H) and HPLC in order to determine the diastereomeric ratios. As shown in Table 1, fair diastereoselectivities, very similar to those observed using preformed imines,[5] were obtained for aromatic aldehydes.

Table 1
$Yb(OTf)_3$-catalyzed Mannich-type reaction of silyloxypyrrole **2** with aniline and various aromatic and aliphatic aldehydes in CH_3CH_2CN at –45°C

R	adduct	Yield (%)	Diastereomeric ratio[a] *erythro* : *threo*[b]			
Ph	**5**	71	45	27	19	9
Furan	**6**	86	53	34	10	3
t-Bu	**7**	81	73	27	0	0
CH_3	**8**	82	74	16	8	2
$PhCH_2$	**9**	80	85	15	0	0
$CH_3(CH_2)_6$	**10**	85	81	13	6	0
$PhCH_2CH_2$	**11**	77	80	14	6	0

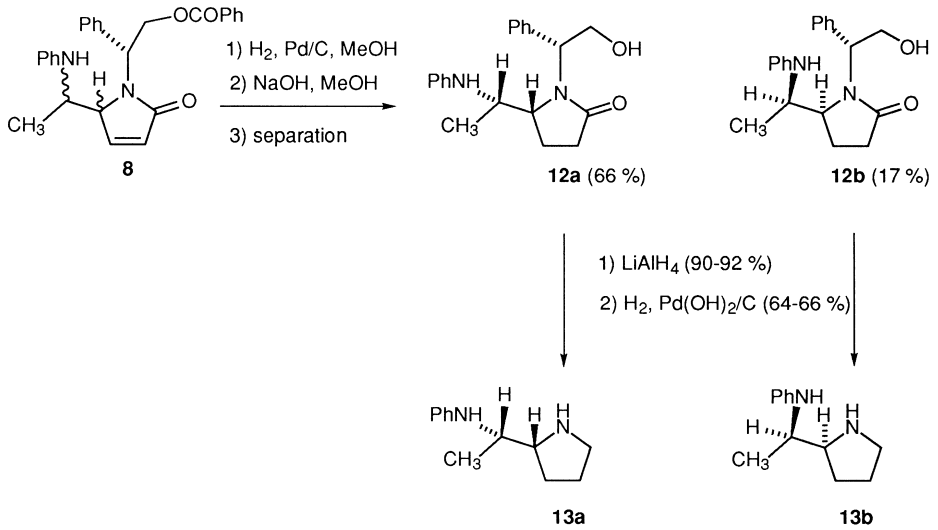
[a]ratio determined by ^{1}H NMR and HPLC on a Novapak Si column. [b] In these structures, *erytrhro* corresponds to *syn* and *threo* is equivalent to *anti*

To our knowledge, such a one-pot Mannich reaction, described for silyl enol ethers[4c,d] was not reported using silyloxydienes.[6] It is also noteworthy that this three-component reaction was also possible using aliphatic enolisable aldehydes giving rise to compounds **8**–**11** in good yields (77–85%). The diastereoselectivities were better than that of imines derived from aromatic aldehydes, the major isomer being formed in 73% (R = *t*-Bu) to 85% (R = CH_2Ph).

The choice of the above reaction conditions was the result of a preliminary study. The reaction was tested in various solvents and proved to be efficient at –70°C in CH_2Cl_2, THF or ether and at –23°C in CH_3CN. Under these conditions, the yields were in the range 65–80% and the diastereoselectivities a little bit lower than in propionitrile as judged by NMR analysis of the crude reaction mixture.

The determination of the relative configuration of the different diastereomers appeared to be a very difficult task. In the ^1H NMR spectra, the diagnostic protons H-5 and H-16 (see Scheme 2 for numbering) of the two major isomers, when visible, exhibited the same very small coupling constant. An *erythro* (*syn*) configuration for the two major isomers was then proposed, in agreement with the stereochemical outcome observed with preformed non-enolisable imines.[5] This has been proved unambiguously for adducts **8**, derived from an enolisable aldehyde, after chemical transformation and X-ray analysis of a derivative.

The crude reaction mixture of compounds **8a**–**d** was submitted to hydrogenation (H_2/Pd/C, 95% yield) followed by basic hydrolytic cleavage of the benzoyl ester (Scheme 3). At this stage, the two major isomeric alcohols **12a**[7] and **12b**[8] were separated by flash-chromatography and were obtained in 66 and 17%, respectively. The minor isomer **12b** was isolated as nice crystals suitable for X-ray analysis.[9] The crystal structure is depicted in Fig. 1 showing the *erythro* configuration. Reduction of the lactam function ($LiAlH_4$ in THF, 91% yield) and hydrogenolysis of the chiral appendage (H_2, $Pd(OH)_2$/C, 65% yield) were performed separately on each alcohol **12a** and **12b** to furnish the diamines **13a** and **13b**.[10] These two diamines were found to be enantiomeric materials (**13a**.2HCl, $[\alpha]_D$ +47 (CH_3OH, *c* 0.4); **13b**.2HCl, $[\alpha]_D$ –46 (CH_3OH, *c* 0.3)). This clearly proved that the two major isomers of the initial mixture **8** possess the same relative *erythro* configuration at C-5, C-16.



Scheme 3.

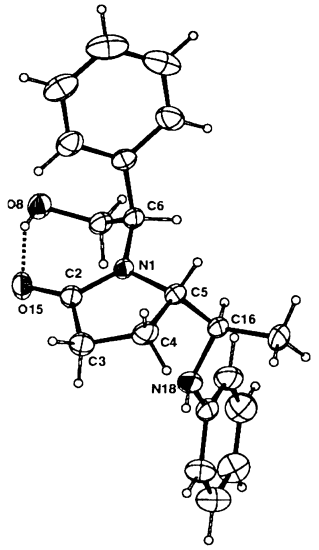


Figure 1. Crystal structure of **12b** showing the ellipsoids displacement (30%) and the intramolecular hydrogen bond: O8–H···O15 (O8···O15:2.690(2) Å, O8–H···O15 = 157°)

In conclusion, we have described a diastereoselective one-pot Mannich reaction of silyloxypyrrole **2**. The reaction is very efficient and particularly useful for enolisable aldehydes. The determination of the relative configuration, clearly established in the case of acetaldehyde and suggested in all cases by NMR data, showed a good *erythro*:*threo* selectivity ranging from 90:10 to 100:0 for enolisable aldehydes. This reaction could permit access to original diamines useful as chiral ligands or could constitute a key step in the asymmetric synthesis of alkaloids. These potential applications are under investigation in our laboratory.

Acknowledgements

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7. Compound **12a**: white amorphous solid; $[\alpha]_D$ +44 ($CHCl_3$, *c* 1); I.R. (cm^{-1}): 3444, 1667; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm), J (Hz): 7.4–7.2 (m, 5H), 7.1 (dd, 2H, J = J′ = 7.9), 6.7 (t, 1H, J = 7.3), 6.35 (d, 2H, J = 7.9), 4.75 (dd, 1H, J = 4.1, J′ = 8.1), 4.15 (dd, 1H, J = 8.1, J′ = 11.7), 3.95 (dd, 1H, J = 4.1, J′ = 11.7), 3.8 (ddd, 1H, J = J′ = 3.4, J″ = 9.2), 3.6–3.45 (qd+broad s overlapped, 2H, J = 6.4, J′ = 2.4), 3.4–3.1 (broad s, 1H), 2.65 (ddd, 1H, J = 8.7, J′ = 9.9, J″ = 17.4), 2.6–2.4 (ddd, 1H, J = 4.6, J′ = 10.6, J″ = 17.4), 2.15–2.05 (m, 1H), 1.95–1.8 (m, 1H), 0.95 (d, 3H, J = 6.3); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 177.8, 146.2, 137.1, 129.0, 128.4, 127.7, 127.5, 117.6, 113.3, 63.9, 63.0, 62.0, 50.6, 30.9, 19.8, 15.7; HRMS (IC): calcd for $C_{20}H_{24}N_2O_2$: $[MH]^+$ 325.19155; found: 325.19206.
8. Compound **12b**: colourless crystals, mp 131°C (1,2-dimethoxyethan); $[\alpha]_D$ –53 (CH_3OH, *c* 1); I.R. (cm^{-1}): 3331, 1662; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm), J (Hz): 7.25–7.1 (m, 7H), 6.7 (t, 1H, J = J′ = 7.3), 6.55 (d, 2H, J = 7.9), 4.5 (dd, 1H, J = 3.4, J′ = 8.0), 4.3 (dd, 1H, J = 8.2, J′ = 12.2), 3.8 (dd, 2H, J = 3.4, J′ = 12.2), 3.75 (qd, 1H, J = 3, J′ = 6.4), 3.7–3.3 (broad s+ddd overlapped, 2H, J = 3, J′ = 4.5, J″ = 7.9), 2.7–2.55 (ddd, 1H, J = 7.6, J′ = 9.6, J″ = 17.3), 2.55–2.4 (ddd, 1H, J = 5.6, J′ = 10.2, J″ = 17.3), 2.2–2.05 (m, 1H), 1.95–1.85 (m, 1H), 1.15 (d, 3H, J = 6.3); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 177.7, 146.8, 137.4, 129.4, 128.7, 127.8, 127.3, 118.0, 113.5, 63.5, 62.4, 61.8, 50.0, 31.5, 20.3, 16.5; anal. calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64; found: C, 73.85; H, 7.37; N, 8.55.
9. Crystal data: $C_{20}H_{24}N_2O_2$, *Mw* = 324.41, colourless crystal of 0.36×0.33×0.26 mm, orthorhombic, space group *P* 21 21 21, *Z* = 4, *a* = 8.235(4), *b* = 12.401(5), *c* = 17.481(8) Å, *V* = 1785.2(14) $Å^3$, d_{calc} = 1.207 g cm^{-3}, *F*(000) = 696, λ = 1.54180 Å (Cu*K*α), μ 0.620, Nonius CAD4 diffractometer, theta range: 4.37–67.86, 3493 collected reflexions, 3247 unique (R_{int} = 0.0614), 2830 observed ($I > 2\sigma(I)$), Full-matrix least-squares (SHELXL93), *R* = 0.0474 for 2830 observed reflexions, wR_2 = 0.1331 for 3247 unique reflexions, goodness of fit = 1.034, residual electron density between: –0.123 and 0.135 eA^{-3}. In the crystal the amino group N18 is linked by hydrogen bond with the oxygen atom O8 of a neighbourhood molecule (X+1, Y, Z).
10. Compounds **13**: amorphous solid: I.R. (cm^{-1}): 3293, 1601, 1498; ^1H NMR (250 MHz, $CDCl_3$), δ (ppm), J (Hz): 7.15 (dd, 2H, J = 7.5, J′ = 8.5), 6.7 (t, 1H, J = 7.3), 6.65 (d, 2H, J = 8.7), 3.6–3.5 (qd, 1H, J = J′ = 6.2), 3.25–3.1 (m, 1H), 3.05–2.85 (m, 2H), 1.95–1.7 (m, 3H), 1.55–1.4 (m, 1H), 1.2 (d, 3H, J = 6.3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 147.8, 129.4, 117.3, 113.6, 63.3, 51.8, 47.3, 27.8, 26.0, 17.6; MS (ESI): $[MH]^{+\cdot}$ = 191. **13a**.2HCl: $[\alpha]_D$ +47 (CH_3OH, *c* 0.4); anal. calcd for $C_{12}H_{20}N_2Cl_2$: C, 54.76; H, 7.66, N, 10.61; found: C, 54.14, H, 7.51, N, 10.13. **13**.2HCl: $[\alpha]_D$ –46 (CH_3OH, *c* 0.3).