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N-Alkoxyl Templates for Diastereoselective Pyrrolidine Synthesis

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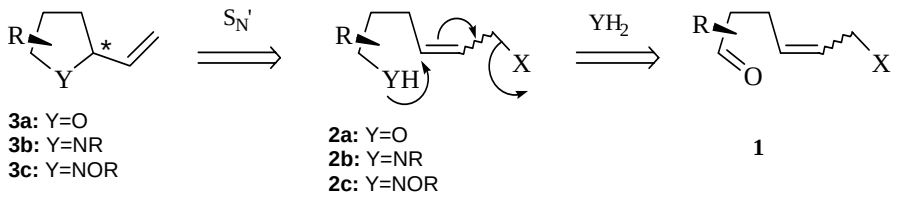
Abstract: Intramolecular cyclization of N-alkoxyl amines are studied for the stereoselective preparation of 2, 4-disubstituted pyrrolidine derivatives. Reduction of oximes under acidic conditions by $NaBH_3CN$ afforded the corresponding nucleophilic hydroxylamine derivatives, which subsequently cyclized *via* S_N2' mechanism to give the desired N-alkoxyl pyrrolidines.

Keywords: S_N' reaction, pyrrolidines, oxime, hydroxylamine.

Pyrrolidines are common structural subunits present in natural and unnatural products[1]. Depending upon the substituents, pyrrolidines have been reported to possess a variety of important biological activities[2], including antibacterial, neuromodulatory, glycosidase inhibitory, and fungicidal activities. Pyrrolidines are also widely employed as chiral auxiliaries in asymmetric organic synthesis[3]. Hence, the development of efficient methods for the construction of this motif remains an important chemical problem[4].

Pyrrolidines can be prepared *via* intramolecular S_N2' reactions (**Scheme 1**)[5] in a manner related to furan derivatives **3a** as previously reported (**1** to **3a**)[6]. Pyrrolidine **3b** can similarly be obtained from **2b**, however the latter contains allyl bromide and amine moieties, provides an efficient route to a variety of 2, 4-disubstituted pyrrolidines with good stereoselectivity. which are difficult to be prepared. Hydroxylamines **2c**, which are obatined through thecyanoborohydride-mediated reduction of oximes[7], may be ideal for

Scheme 1



3a: Y=O
3b: Y=NR
3c: Y=NOR

2a: Y=O
2b: Y=NR
2c: Y=NOR

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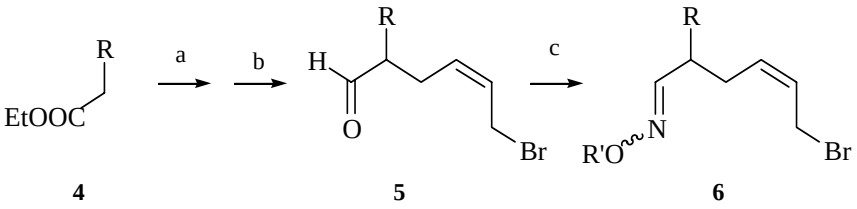
the intramolecular cyclization. Since hydroxylamines possess the requisite nucleophilicity for only intramolecular cyclizations, intermolecular reactions are completely avoided. By exploiting the intrinsically decreased nucleophilicity of hydroxylamine nitrogen on allyl bromide derivatives, we carried out the desired intramolecular cyclization for the stereoselective synthesis of corresponding vinyl pyrrolidine derivatives **3c**.

The preparation of 2,4-disubstituted pyrrolidines *via* intramolecular cyclization confirms this methodology can be applied to the preparation of pyrrolidine-containing products (**Scheme 2**). Aldehydes **5**, prepared from esters **4** in two steps, were treated with hydroxylamines in methanol at pH 6 to give oxime derivatives **6**. Different hydroxylamines $R'ONH_2$ (R' = H, Me, *n*-Pr, *n*-Bu, Bn) reacted with the carbonyl group of **5** to give oximes **6** in high yield with preservation of the allyl bromide electrophilic moiety in **5** and **6.**

Scheme 2



4 **5** **6**

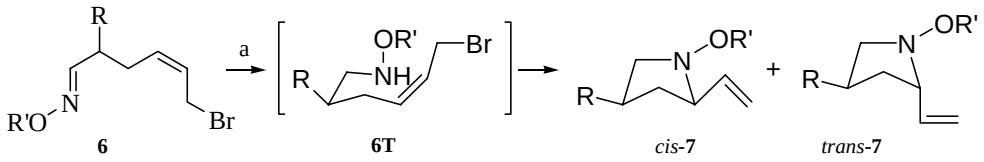
a) LDA, *Z*-1,4-dibromo-2-butene; b) DIBAL, CH_2Cl_2; c) $R'ONH_2$, MeOH.

One-pot reduction-cyclization chemistry was investigated using oximes **6a-j** (**Table 1**). Reduction of oximes **6** with $NaBH_3CN$ in acetic acid (HOAc)[7] provided the corresponding intermediates, which were cyclized upon workup with ethylenediamine to produce pyrrolidines **7** diastereoselectively[8-9]. The results for the synthesis of 2, 4-disubstituted N-substituted pyrrolidines *via* intramolecular *N*-cyclization are listed in **Table 1**. The R' group on the nitrogen had less effect upon the diastereoselectivity. In case R'=*n*-Bu *cis/trans* ratio was 4:1. When R' = H, (entry a), the *cis/trans* ratio was 3.5/1, which was quite similar to that observed in entry b. Notably, the *cis*-2, 4-selectivity observed for pyrrolidine derivatives[10] parallels results obtained from the construction of 2, 4-disubstituted tetrahydrofurans[6]. A comparable trend was also observed when the substituent group R was a bulky alkyl group (entries e-h and i-j). This *cis*/*trans* ratio was significantly increased to 10-12:1 when a bulky R group, such as cyclohexyl, was substituted (entries i-j). It is probably due to the fact that cyclization reaction went through the pseudo-chair transition state **6T**, in which the bulky R group preferred to occupy the equitorial position to lead the formation of *cis*-**7** as the major products.

In conclusion, the strategy of intramolecular S_N2' cyclization has been successfully applied to the synthesis of N-substituted pyrrolidine derivatives. The obtained results indicated that hydroxylamines are useful nitrogen-equivalent nucleophiles. This

method provides an efficient route to a variety of 2, 4-disubstituted pyrrolidines with good stereoselectivity.

Table 1 Diastereoselective synthesis of *N*-alkoxy pyrrolidines *via* S_N' cyclization



6 **6T** *cis*-**7** *trans*-**7**

(a) $NaNH_3CN$/HOAc; then $(NH_2CH_2)_2$.

entry	oxime	R	R'	products	*cis* / *trans*[b]	yield (%)
a	**6a**	Ph	H	**7a**	4 / 1	71
b	**6b**	Ph	*n*-Bu	**7b**	3.5 / 1	85
c	**6c**	Ph	$PhCH_2$	**7c**	6 / 1	65
d	**6d**	*n*-Pr	$PhCH_2$	**7d**	7 / 1	66
e	**6e**	*n*-C_6H_{13}	$PhCH_2$	**7e**	5 / 1	72
f	**6f**	*n*-C_6H_{13}	*n*-Pr	**7f**	5.2 / 1	83
g	**6g**	*n*-C_6H_{13}	*n*-Bu	**7g**	4.6 / 1	65
h	**6h**	*n*-C_6H_{13}	Me	**7h**	6.5 / 1	65
i	**6i**	Cyclohexyl	Me	**7i**	10 / 1	62
j	**6j**	Cyclohexyl	$PhCH_2$	**7j**	12 / 1	65

(b) Determined by GC/MS and ^{1}H-NMR on the crude reaction mixtures.

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8. General procedure and selected spectroscopic data: To the solution of **6a** (600 mg, 2.34 mmol) in acetic acid was added $NaBH_3CN$ (250 mg, 3.97 mmol) at room temperature. The mixture was stirred for 3 h, quenched by addition of ethylene diamine (10 mL), and stirred for another 3 h. The reaction mixture was dissolved in $NaHCO_3$ (25 mL) solution, and extracted with ethyl acetate (3x30 mL). The combined organic layers were dried over $MgSO_4$. Removal of solvent under reduced pressure gave a pair of products, which was a mixture of *cis* and *trans* isomers with the ratio 4/1 determined by ^{1}H-NMR. The mixture was then subjected to flash silica gel chromatography to separate the *cis* and *trans* isomers and gave pure *cis*-*N*-hydroxy-4-phenyl-2-vinyl pyrrolidine (total 314 mg, 1.66 mmol, 71%) as a colorless oil. *cis*-**7a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70 (ddd, 1H, J = 7.6, 10.5, 12.7, one of the 3-CH_2), 2.5 (ddd, 1H, J = 6.8, 9.0, 13.2, another one of the 3-CH_2), 3.35-3.65 (m, 4H, -NCH-, -NCH_2-, -CHAr), 5.18-5.38 (m, 2H, -CH=CH_2), 5.97 (ddd, 1H, J = 7.4, 10.3, 17.5, -CH=CH_2), 7.28 (m, 5H, -C_6H_5); *trans*-**7a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13 (dt, 2H, J = 1.7, 9.1, 3-CH_2), 2.97 (t, 1H, J = 10.1, -CHAr), 3.28-3.50 (m, 2H, -NCH_2-), 3.69 (dd, 1H, J = 7.4, 9.4, -NCHCH=), 5.18-5.38 (m, 2H, -CH=CH_2), 5.95 (ddd, 1H, J = 7.3, 10.1, 17.3, -CH=CH_2), 7.29 (m, 5H, -C_6H_5).
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10. The relative stereochemistry was determined by ^{1}H-NMR by comparing the chemical shift of allylic proton. The C-2 allylic proton usually appears more upfield for the *cis*-isomer than that for the *trans*-isomer[6a]. For example, *cis*-**7a**: ^{1}H NMR (200 MHz, $CDCl_3$) 3.55 (m, 1H); *trans*-**7a**: ^{1}H NMR (200 MHz, $CDCl_3$) 3.70 (m, 1H).

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