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Stereoselective Synthesis of Hydroxypyrrolidines and Hydroxypiperidines by Cyclization of γ-Oxygenated-α,β-unsaturated Sulfones

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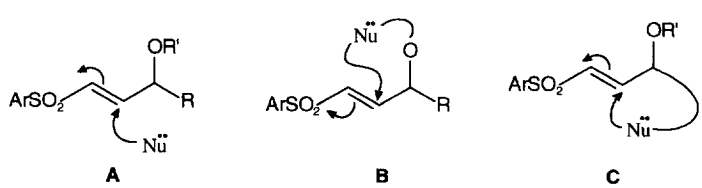
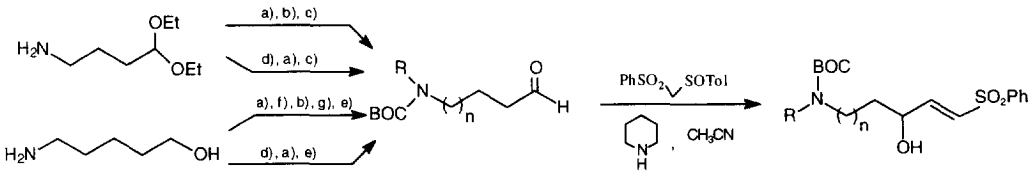
Abstract: *cis* and *trans* 2,3-disubstituted pyrrolidines and piperidines have been prepared stereoselectively by intramolecular conjugate addition of N-substituted γ-oxygenated-α,β-unsaturated phenyl sulfones. The best *cis*-selectivities were obtained from the alcohols and the best *trans*-selectivities from the OTIPS derivatives. Copyright © 1996 Published by Elsevier Science Ltd

Vinylsulfones are excellent substrates for the conjugate addition of nucleophiles and radicals.[1] For instance, the intermolecular conjugate addition of organometallics to γ-oxygenated-α,β-unsaturated sulfones has been widely applied in stereoselective synthesis and in natural product synthesis due to the high asymmetric control induced by the stereogenic center at γ position[2] (reactions **A**). On the contrary, the intramolecular version of this type of reaction has been less studied and most of the reported examples concern cyclizations from the oxygenated chain[3] (reactions **B**) and not from the carbon chain[4] (reactions **C**).

In particular, we are very interested in the development of stereoselective cyclizations of type **C**, where Nu=nitrogen, because the resulting nitrogenated heterocycles, specially hydroxypyrrolidines and hydroxypiperidines are frequently found in the structures of many natural products with interesting biological activities, like the indolizidine[5] and the pyrrolizidine[6] alkaloids.



The N-substituted γ-hydroxy-α,β-unsaturated sulfones **5a-8a** were prepared with complete E-stereoselectivity in excellent yields (90-94% after chromatography) by the usual procedure based on the condensation of phenylsulfonyl *p*-tolylsulfinyl methane with the corresponding aldehydes in the presence of piperidine.[7] The required N-protected aldehydes **1-4** were readily prepared in few steps from commercially available aminoalcohols or aminoketals by the straightforward sequences shown in Scheme 1.



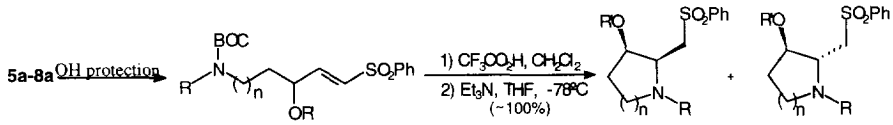
1	n = 1,	R = BOC	(95%)	**5a** (94%)
2	n = 1,	R = $CH_2CH_2CO_2Me$	(80%)	**6a** (93%)
3	n = 2,	R = BOC	(65%)	**7a** (90%)
4	n = 2,	R = $CH_2CH_2CO_2Me$	(60%)	**8a** (93%)

a) BOC_2O (1 eq), CH_2Cl_2, 0°C, 20 min; **b)** i. BuLi (1 eq), THF, 0°C, 15 min. ii BOC_2O (1 eq), 15 min; **c)** AcOH/H_2O 2:1; **d)** $CH_2{=}CHCO_2Me$ (1 eq), EtOH, 0°C, 5h; **e)** PCC (1.3 eq), CH_2Cl_2, 4h; **f)** TBDMSCl (1.3 eq), Imidazole (2 eq), CH_2Cl_2, 1.5 h; **g)** TBAF, (1.2 eq), THF, 0°C, 2h.

Scheme 1

In order to determine the influence of the oxygen substitution at γ-position in the *cis/trans* stereoselectivity of the intramolecular conjugate addition, the hydroxyl group of **5a-8a** was protected as ethoxymethoxy ketals (**5b-8b**, chloromethyl ethyl ether, diisopropyl ethyl amine, CH_2Cl_2, 85-91%) and as the silyl ethers OTBDMS (**5c-8c**, TBDMSCl, imidazole, CH_2Cl_2, 94-98%) and OTIPS (**5d-8d**, TIPSOTf, 2,6-lutidine, CH_2Cl_2, 88-97%). Complete N-BOC deprotection of compounds **5-8** by treatment with CF_3CO_2H (CH_2Cl_2, rt) afforded quantitatively the corresponding ammonium salts, which, after isolation, were redissolved in THF, cooled at -78°C and treated with Et_3N (10 equiv). Regardless of the substitution at γ position and the chain length, the cyclizations were complete in less than 30 min at -78°C, giving pyrrolidines **9** and **10** and piperidines **11** and **12** as mixtures of *cis/trans* isomers in almost quantitative yield (table 1).[8]

Table 1.-Intramolecular conjugate addition of γ-oxygenated-α,β-unsaturated sulfones **5-8**.



Entry	Substrate	Product	n	R	OR'	*cis/trans*-ratio[a]
1	**5a**	**9a**	1	H	OH	80/20
2	**5b**	**9b**	1	H	OCH_2OEt	44/56
3	**5c**	**9c**	1	H	OTBDMS	40/60
4	**5d**	**9d**	1	H	OTIPS	22/78
5[b]	**6a**	**10a**	1	$CH_2CH_2CO_2Me$	OH	81/19
6	**6b**	**10b**	1	$CH_2CH_2CO_2Me$	OCH_2OEt	36/64
7	**6c**	**10c**	1	$CH_2CH_2CO_2Me$	OTBDMS	19/81
8	**6d**	**10d**	1	$CH_2CH_2CO_2Me$	OTIPS	10/90
9[c]	**7a**	**11a**	2	H	OH	50/50
10	**7b**	**11b**	2	H	OCH_2OEt	45/55
11	**7c**	**11c**	2	H	OTBDMS	33/67
12	**7d**	**11d**	2	H	OTIPS	20/80[d]
13	**8a**	**12a**	2	$CH_2CH_2CO_2Me$	OH	34/66
14	**8b**	**12b**	2	$CH_2CH_2CO_2Me$	OCH_2OEt	30/70
15	**8c**	**12c**	2	$CH_2CH_2CO_2Me$	OTBDMS	4/96
16	**8d**	**12d**	2	$CH_2CH_2CO_2Me$	OTIPS	<2/>98

a) Determined by ^{1}H-NMR on the crude mixtures. b) Reaction run in toluene (in THF the *cis/trans* ratio is a little lower: 72/28). c) Reaction run in DMSO (in THF the *cis/trans* ratio is 38/62). d) This isomer ratio increases to 5/95 when the reaction is performed in MeOH.

Some significant stereochemical effects are deduced from the data of Table 1[9]:

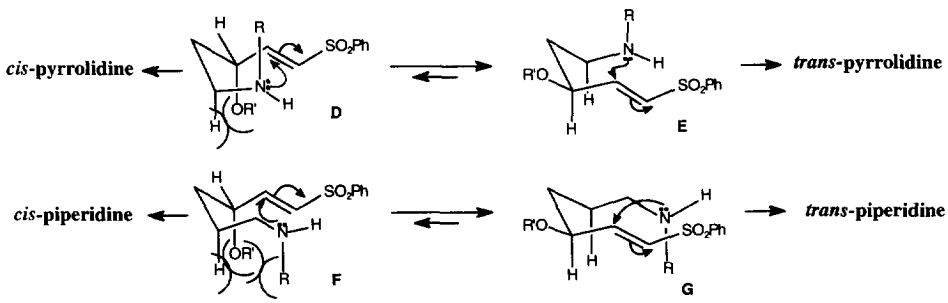
a) The stereoselectivity strongly depends on the oxygenated function: in the four series –vinyl sulfones **5**, **6**, **7** and **8**– the *trans* stereoselectivity increases in the order OH< OCH_2OEt< OTBDMS < OTIPS. Thus, the highest *trans*-stereoselectity was always obtained from the OTIPS derivatives.

b) In the synthesis of pyrrolidines (entries 1-8), the cyclization of alcohols (substrates **5a** and **6a**) and O-protected derivatives (substrates **5b-d** and **6b-d**) occurred with the opposite stereoselectivity. The cyclization of **5a** and **6a** was *cis*-stereoselective (entries 1 and 5) whereas that of **5b-d** and **6b-d** was *trans*-stereoselective (specially from the silyl ethers **5d**, **6c** and **6d**, entries 4, 7 and 8). A smaller dependence on the OR' group was observed in the synthesis of piperidines (entries 9-16). Regardless the OR' group, the cyclization of substrates **7** (entries 9-12) and **8** (entries 13-16) was *trans*-stereoselective.

c) Concerning the results of the NH and $NCH_2CH_2CO_2Me$ series (pairs of substrates **5-6** and **7-8**). Comparing the same OR' groups, in all cases the cyclization of the N-alkylated substrates was more *trans*-stereoselective than from the NH series. This difference is scarce in the case of the hydroxy and ketal derivatives and more important for the silyl ethers (entries 3/7, 4/8, 11/15 and 12/16).

From a synthetic point of view, it is noteworthy that three of the four possible products can be prepared stereoselectively and in high yield: *cis*-pyrrolidines are obtained from the hydroxyvinyl sulfones **5a** and **6a** (entries 1 and 5), *trans*-pyrrolidines from **6d** (entry 8) and *trans*-piperidines from **8c** and **8d** (entries 15 and 16).

A plausible mechanistic explanation for the dependence of the stereoselectivity on the OR' group, the substitution at nitrogen and the length of the carbon chain is shown in Scheme 2.



Scheme 2

First, as it is usual in intramolecular conjugate additions,[10] we consider as the most favourable transition states the chair-like cyclizations (**D**, **E**, **F** and **G**). As a second hypothesis, we assume that the alkyl substituent at nitrogen (R= $CH_2CH_2CO_2Me$ in substrates **6** and **8**) should be in axial position in the transition states in order to avoid a highly destabilizing non-bonded interaction with the bulky phenylsulfonyl group. Moreover, at this disposition a favourable intramolecular hydrogen bond between the equatorial NH and an oxygen atom of the sulfonyl group could be involved.

In the formation of *cis* and *trans*-pyrrolidines (transition states **D** and **E**, respectively) the axial position of R group should not introduce a significant energetic difference between transition states **D** and **E**, the steric interaction $(OR'/H)_{1,3}$ being the main factor destabilizing conformation **D**. This interaction would increase with the size of R' group, justifying the observed increase of the *trans*-stereoselectivity in the order: OH < OCH_2OEt < OTBDMS < OTIPS (compare entries 1-4 and 5-8).

By contrast, in the case of the proposed transition states corresponding to the cyclizations to the piperidines (**F** and **G**), there should be a significant stability difference between **F** and **G** because transition state **F**, besides the $(OR'/H)_{1,3}$ interaction, would have an additional destabilizing 1,3-diaxial repulsion between OR' and R. This hypothesis could explain that, the cyclization of substrates **7** and **8** was always *trans*-stereoselective regardless the OR' group, cyclization of substrates **8** (R=$CH_2CH_2CO_2Me$) occurs with a higher *trans*-stereoselectivity than from compounds **7** (R=H), and the best stereoselectivities were observed from the bulkiest OR' groups, R'=TBDMS and TIPS (entries 15 and 16).

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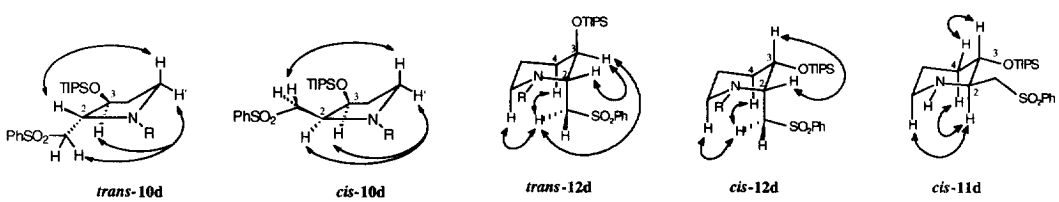
7. Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197.
8. In the case of **10b**, **10c**, **10d**, **12b**, **12c** and **12d** the *cis/trans* mixture could be readily separated by flash chromatography.
9. Stereochemical assignment.
   The stereochemical assignment of *cis/trans* **9-12** was firmly established by a combination of chemical correlations and NMR studies. The *cis/trans* mixtures of the hydroxy derivatives (compounds **a**) were correlated with the ketal or silyl derivatives (compounds **b**, **c**, and **d**) by straightforward protection or deprotection reactions. Also the NH series (compounds **9** and **11**) were transformed into the $NCH_2CH_2CO_2Me$ series (compounds **10** and **12**, respectively) by reaction with methyl acrylate. Spectroscopically, the value of $J_{2,3}$ is very significant for the *cis/trans* assignment in the pyrrolidines. Thus, in agreement with the reported data of related products (see for instance, Gallina, C,; Paci, M.; Viglino, P. *Org. Magn. Reson.* **1972**, *4*, 31), for all pairs of stereoisomers **9** and **10**, $J_{2,3}$-*cis* (~ 6.5 Hz) > $J_{2,3}$-*trans* (~ 2.5 Hz). This assignment has been confirmed by NOESY experiments (see figures below). On the other hand the coupling constants and NOESY spectra of *cis* and *trans*-piperidines **12** ($R=CH_2CH_2CO_2Me$) show that in both isomers the sulfonylmethyl group is in axial position. This determines that H_2 and H_3 are in a gauche relationship in both isomers ($J_{2,3}$-*cis* ≈ 4.8 Hz and $J_{2,3}$-*trans* ≈3.2 Hz), but whereas H_3 is in equatorial position in the *trans* isomers ($J_{3,4}$~ $J_{3,4'}$≈ 3.2 Hz), in the *cis* isomers it is in axial position ($J_{3,4}$ ≈ 11.3 Hz ; $J_{3,4'}$ ≈ 4.8 Hz). By contrast, the high value of $J_{2,3}$ (≈ 9.5 Hz) and NOESY spectra of *trans*-**11** (R=H) show that both substituents at C-2 and C-3 are in equatorial positions.



trans-**10d** *cis*-**10d** *trans*-**12d** *cis*-**12d** *cis*-**11d**

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