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A highly stereoselective synthesis of α,β-unsaturated oxazolines

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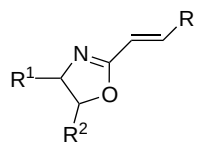
Abstract—Lithiated 2,4,4-trimethyl-2-oxazoline **2a** and 2-chloromethyl-4,4-dimethyl-2-oxazoline **2b** react smoothly with a number of nitrones **3** to produce α,β-unsaturated oxazolines **6** and **7** highly stereoselectively. © 2001 Elsevier Science Ltd. All rights reserved.

α,β-Unsaturated oxazolines of the kind (**S**) are quite interesting compounds either as such or as useful intermediates for the preparation of other substances by the elaboration of both the heterocyclic moiety and the C–C double bond functionality.[1] Moreover, they are possible Michael acceptors and potential activated dienophiles and heterodienes.[2,3] α,β-Unsaturated oxazolines are usually synthesized by an aldol-type condensation reaction of lithiated 2-alkyl-2-oxazolines[4] or via a Horner–Wadsworth–Emmons reaction from 2-alkyl-2-oxazolines and diethylchlorophosphate.[3] A synthesis of α,β-unsatured oxazolines by a two-step sequence from amino alcohols and acyl chloride has also been reported.[1c,5] A Pd-mediated cross-coupling of alkenylstannanes with chiral 2-bromo oxazoline has also been reported,[6] as well as an alkylation–oxidation–dehydrosulfinylation route from α-phenylthiooxazolines.[7] Concerning the stereochemistry, these procedures, however, lead mainly to the *E* isomers.



(*S*)

In this paper we report a useful and convenient stereoselective synthesis of *cis*- and *trans*-α,β-unsatured oxazolines based on the addition of lithiated 2-methyl-**2a** and 2-chloromethyl-2-oxazoline **2b** to a number of nitrones.[8]

In a first experiment we reacted 2-lithiomethyl-2-oxazoline **2a** (Table 1), generated by deprotonation of the commercially available 2,4,4-trimethyl-2-oxazoline, with *N*-*tert*-butyl-α-phenylnitrone **3a** in THF at −98°C. Quenching of the reaction mixture with satd aq. NH_4Cl after 18 h gave an excellent yield of *trans*-2-styryl-2-oxazoline **6a** (95% yield; *trans*/*cis* ratio >99/1, $^3J_{H,H(E)}$ = 15.8 Hz) (Table 1). Similarly, very good to excellent yields of aryl substituted *trans*-2-styryl-2-oxazolines **6b–f** were obtained when **2a** was reacted with aryl nitrones **3b–f**. Yet highly *trans* stereoselective was the reaction of **2a** with alkyl nitrones **3g–h** leading to oxazolinyl alkenes **6g–h** but yields were lower (Table 1). The alkene formation can be explained as illustrated in Scheme 1. According to such a scheme, hydroxylamino derivative **5**, which is in equilibrium with spirocyclic compound **4**, eliminates *N*-*tert*-butylhydroxylamine as proven by NMR and GC–MS.[9] The origin of the *trans* stereoselection of the conversion of **2a** to **6a–h** resides in the *tert*-butylhydroxylamine elimination step. Transition state **A** (Scheme 2) leading to the *trans*-2-alkenyl-2-oxazolines **6** and allowing the antiperiplanar arrangement of the groups to be eliminated is of lower energy with respect to transition state **B** leading to the *cis* isomers for steric reasons. Surprisingly, the reaction of **2a** with *N*-*tert*-butyl-α-(*p*-nitrophenyl)nitrone did not take place and starting materials were recovered unchanged. In contrast, the reaction of 2-lithiochloromethyl-2-oxazoline **2b**[10] (Table 2) with **3a** followed by quenching with NH_4Cl after 3 h afforded *cis*-2-styryl-2-oxazoline **7a** in 46% yield (*cis*/*trans* ratio: 97/3); $^3J_{H,H(Z)}$ = 12.6 Hz, together with oxazetidines **12** (7%) and **13** (22%). Similarly, treatment of **2b** with nitrones **3b–g** afforded *cis*-α,β-unsaturated oxazolines **7b–g** highly diastereoselectively with the *cis*/*trans* ratio ranging from 90/10 to 97/3.[11] There was no reaction when **2b** was added to

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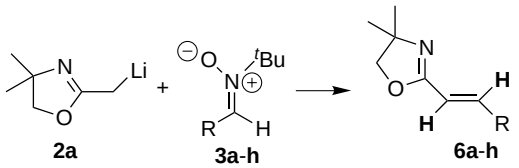
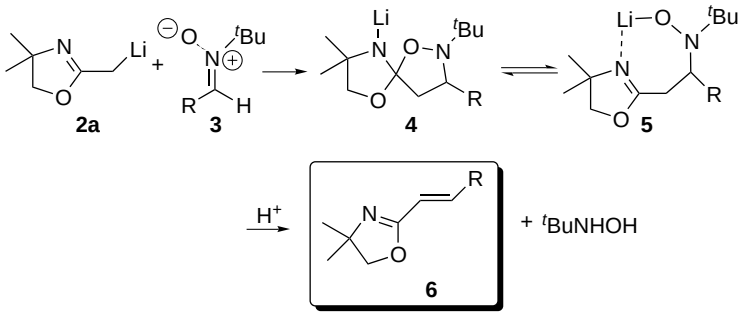
Table 1. Synthesis of *trans*-α,β-unsaturated oxazolines **6**

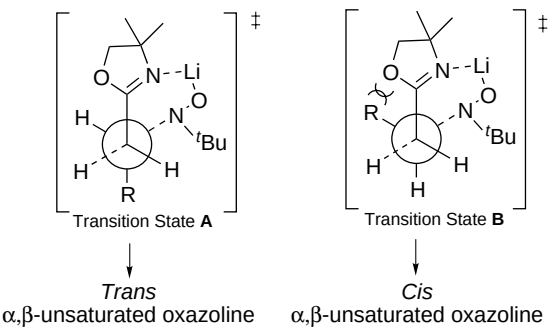


R	Compound (yield %)[a,b]	Conversion (%)	*trans*/*cis*[c]	Selected ^{1}H NMR data[d] ($CDCl_3$) δ (ppm) J
Ph-	**6a** (95)	>95	>99/1	6.58 (d, J=15.8 Hz, 1H), 7.31 (d, J=15.8 Hz, 1H)
p-MeC_6H_4-	**6b** (95)	>95	>99/1	6.55 (d, J=16.2 Hz, 1H), 7.31 (d, J=16.2 Hz, 1H)
p-ClC_6H_4-	**6c** (70)	>95	>99/1	6.54 (d, J=16.3 Hz, 1H), 7.26 (d, J=16.3 Hz, 1H)
p-$CH_3OC_6H_4$-	**6d** (85)	90	>99/1	6.47 (d, J=16.2 Hz, 1H), 7.30 (d, J=16.2 Hz, 1H)
2,4,6-$(CH_3O)_3C_6H_2$-	**6e** (95)	70	>99/1	7.0 (d, J=16.2 Hz, 1H), 7.63 (d, J=16.2 Hz, 1H)
Piperonyl	**6f** (70)	>95	>99/1	6.43 (d, J=16.2 Hz, 1H), 7.26 (d, J=16.2 Hz, 1H)
Cyclohexyl	**6g** (60)	>95	>99/1	5.86 (dd, J=15.9 Hz, J=1.3 Hz, 1H), 6.47 (dd, J=15.9 Hz, J=6.8 Hz, 1H)
$CH_3(CH_2)_6$-	**6h** (52)	>95	>99/1	5.91 (d, J=15.9 Hz, 1H), 6.54 (dt, J=15.9 Hz, J=6.8 Hz, 1H)
p-$NO_2C_6H_4$-	N.r.	–	–	–

[a] Based on the converted nitrone.
[b] Yields were not optimized.
[c] Determined by ^{1}H NMR analysis.
[d] Chemical shifts, multiplicity and coupling constants of the two vinylic protons of each compound are reported.



Scheme 1.

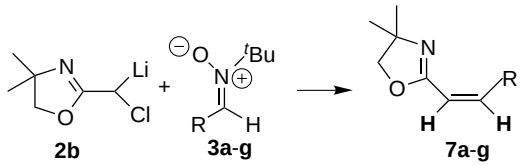


Scheme 2.

N-*tert*-butyl-α-(2,4,6-trimethoxyphenyl)- and (*p*-nitrophenyl)nitrones (Table 2).

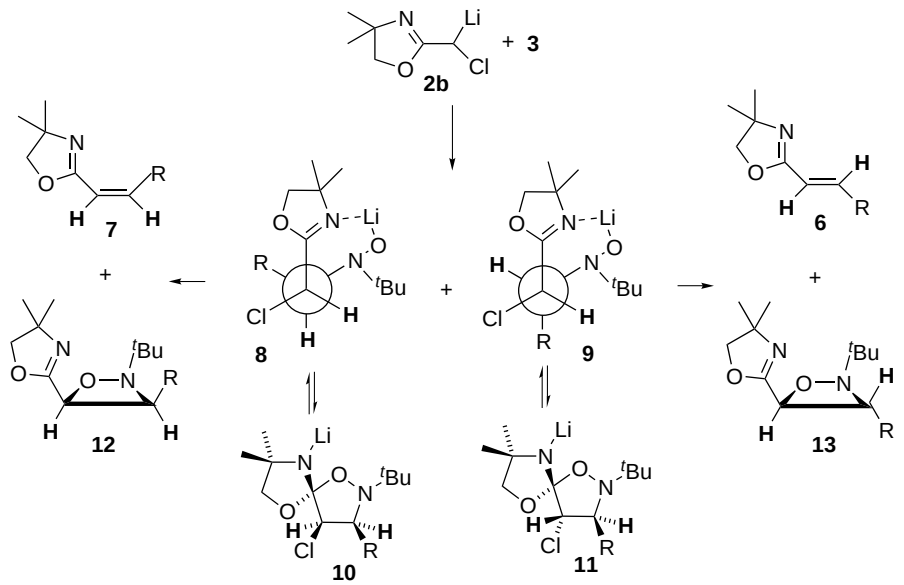
The explanation for the observed *cis* diastereoselectivity of the reaction of **2b** with nitrones **3** is that probably the stereoselective determining step is the addition of **2b** to the nitrone, which occurs in a stereoselective manner producing the lithiated hydroxylamino derivatives **8** and **9** (**8**/**9** ratio=4.1/1, when R=Ph)[12] (Scheme 3), which are in equilibrium with lithiated spirocyclic compounds **10** (*cis* arrangement of the Cl and R groups) and **11** (Cl and R *trans*).[13] The main route of evolution of **8** (which equilibrates with **10**) is the elimination of ^{t}BuN=O and LiCl to give *cis*-alkenyloxazoline **7**. In contrast, compound **9** (which equilibrates with **11**) undergoes an intramolecular S_N2 substitution affording oxazetidine **13** (22% yield) together with a very small amount of alkenyloxazoline **6** (<2% yield). Following a secondary reaction path the equilibrating derivatives **8**–**10** undergo an intramolecular S_N2 substitution leading to *cis*-oxazetidine **12** (7% yield).[12] Oxazetidines **12** and **13** could be isolated and characterized by NMR, GC–MS and IR spectroscopy. Moreover, it is worth pointing out that *trans*-oxazetidine **13** (R=Ph) is less stable than **12** and in $CDCl_3$ tends to undergo cycloreversion to give 2-formyl-4,4-dimethyl-2-oxazoline and *N*-*tert*-Butyl-benzylidenimine.[14] *cis*-Oxazetidine **12** is

Table 2. Synthesis of *cis*-α,β-unsaturated oxazolines **7**



R	Compound (yield %)[a,b]	Conversion (%)	*cis*/*trans*[c]	Selected ^{1}H NMR data[d] ($CDCl_3$) δ (ppm) J
Ph-	**7a** (46)	75	97/3	6.01 (d, J=12.6 Hz, 1H), 6.83 (d, J=12.6 Hz, 1H)
p-MeC_6H_4-	**7b** (67)	57	97/3	6.0 (d, J=12.6 Hz, 1H), 6.82 (d, J=12.6 Hz, 1H)
p-ClC_6H_4-	**7c** (66)	77	97/3	6.04 (d, J=12.8 Hz, 1H), 6.80 (d, J=12.8 Hz, 1H)
p-$CH_3OC_6H_4$-	**7d** (57)	50	97/3	5.91 (d, J=12.0 Hz, 1H), 6.77 (d, J=12.0 Hz, 1H)
Piperonyl	**7e** (38)	86	94/6	5.88 (d, J=12.9 Hz, 1H), 6.72 (d, J=12.9 Hz, 1H)
Cyclohexyl	**7f** (55)	>95	90/10	5.71 (d, J=12.0 Hz, 1H), 5.78 (dd, J=12.0 Hz, J=9.4 Hz, 1H)
$CH_3(CH_2)_6$-	**7g** (49)	45	90/10	5.81 (d, J=11.8 Hz, 1H), 6.80 (dt, J=11.8 Hz, J=7.5 Hz, 1H)
p-$NO_2C_6H_4$-	N.r.	–	–	–
2,4,6-$(CH_3O)_3C_6H_2$-	N.r.	–	–	–

[a] Based on the converted nitrone.
[b] Yields were not optimized.
[c] Determined by ^{1}H NMR analysis.
[d] Chemical shifts, multiplicity and coupling constants of the two vinylic protons of each compound are reported.



Scheme 3.

much more stable than **13**. However, upon warming to high temperature (GC–MS conditions), oxazetidine **12** also cycloreverts as **13**.

This paper, therefore, reports a simple and useful route to both *cis*- and *trans*-α,β-unsaturated oxazolines, which appear to have an interesting synthetic potential.

Acknowledgements

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9. Protonated spirocyclic compound **4** could be isolated upon quenching the reaction after 1 min. Intermediate **4** converts into *trans*-2-styryloxazoline **6a** in an NMR tube in a solution of $CDCl_3$ keeping it at room temperature for 48 h. In the NMR spectrum we observe, after 48 h, only the signals of **6a** and a singlet at 1.09 ppm to be ascribed to the *tert*-butyl group of the *tert*-butylhydroxylamine. Moreover, protonated spirocyclic compound **4** undergoes thermal degradation and GC–MS analysis shows two signals related to the *trans*-2-styryl-2-oxazoline and *tert*-BuNHOH.
10. Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781–4784.
11. *cis*-α,β-Unsaturated oxazolines isomerize to the *trans* isomers in solution at room temperature. In order to prevent such isomerization, low temperature (–20°C) storage is needed.
12. The small ($^3J_{H,H}=4.3$ Hz) and the large ($^3J_{H,H}=10.3$ Hz) coupling constant values found for the protonated derivatives of **8** and **9** (when R = Ph), respectively, with the absence of NOEs for the latter, are indicative of a *gauche* and *anti* arrangement of the two vicinal protons in the two staggered rotamers (see: Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876), also favoured by a possible intramolecular hydrogen bonding between the OH group and the oxazolinyl nitrogen atom. The relative *cis* and *trans* configuration of oxazetidine **12** (R = Ph) was assigned on the basis of the NOESY phase-sensitive spectrum (see Gaudemar, A. In *Stereochemistry: Fundamentals and Methods*; Kagan, H. B., Ed. Determination of configurations by spectrometric methods. Georg Thieme Publishers: Stuttgart, 1977; Vol. 1., pp. 83–89).
13. The relative configuration of the protonated derivatives of **10** and **11** (when R = Ph) was assigned on the basis of their NOESY phase-sensitive spectra.
14. Both *cis*- and *trans*-oxazetidines **12** and **13** have been isolated (when R = Ph) by quenching the reaction after 3 h. Both **12** and **13** cyclorevert under GC–MS conditions showing two signals with $m/z=127$ and $m/z=161$ ascribable to 2-formyl oxazoline and *N*-*tert*-butyl-benzylidenimine, respectively. Leaving **13** in the NMR tube cycloreversion occurred and two singlets could be detected at 9.56 and 8.27 ppm for the 2-formyl oxazoline and *N*-*tert*-butyl-benzylidenimine, respectively.

Typical procedure for the synthesis of *trans*-2-(*p*-tolylvinyl)-2-oxazoline 6b. To a precooled (–98°C with a methanol/liquid nitrogen bath) solution of LDA (0.66 mmol) in dry THF (5 mL) and under N_2, a solution of 2,4,4-trimethyl-2-oxazoline (75 mg, 0.66 mmol) in 1.3 mL of THF was added dropwise and the resulting mixture stirred at this temperature for 20 min. After this time, a solution of nitrone **3b** (126 mg, 0.60 mmol) in 1.3 mL of THF was added dropwise at –98°C. The mixture was allowed to warm to room temperature, stirred overnight, quenched with satd aq. NH_4Cl, extracted with Et_2O (3×10 mL) and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/Et_2O: 3/2) afforded the ***trans* 2-(*p*-tolylvinyl)-2-oxazoline 6b** as a colorless oil (135 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 6H), 2.35 (s, 3H), 4.02 (s, 2H), 6.55 (d, $J=16.2$ Hz, 1H), 7.31 (d, $J=16.2$ Hz, 1H), 7.15–7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 67.4, 79.0, 114.6, 127.6, 129.8, 132.7, 139.8, 162.2. GC–MS (70 eV) m/z (%) 215 (39.0) [M^+], 214 (100.0) [M^+-1], 200 (97.7), 129 (27.8), 115 (26.4). FT-IR (film, cm^{-1}) 1658, 1605, 1356, 1004, 975, 808.

Typical procedure for the synthesis of *cis*-2-(*p*-tolylvinyl)-2-oxazoline 7b. To a precooled (–98°C with a methanol/liquid nitrogen bath) solution of LDA (0.66 mmol) in dry THF (5 mL) and under N_2, a solution of 2-chloromethyl-4,4-dimethyl-2-oxazoline (97 mg, 0.66 mmol) and nitrone **3b** (126 mg, 0.60 mmol) in 3 mL of THF was added dropwise and the resulting mixture was stirred overnight, quenched with satd aq. NH_4Cl, extracted with Et_2O (3×10 mL) and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/Et_2O: 3/2) afforded the ***cis*-2-(*p*-tolylvinyl)-2-oxazoline 7b** as a colorless oil (54 mg, 67% yield, based on 57% conversion) and the nitrone **3b** (54 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 6H), 2.34 (s, 3H), 3.92 (s, 2H), 6.0 (d, $J=12.6$ Hz, 1H), 6.82 (d, $J=12.6$ Hz, 1H), 7.15–7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 67.1, 79.1, 115.9, 128.7, 129.7, 132.9, 139.4, 161.5. GC–MS (70 eV) m/z (%) 215 (23.1) [M^+], 214 (100.0) [M^+-1], 200 (11.7), 160 (18.6), 115 (18.5). FT-IR (film, cm^{-1}) 1656, 1606, 1363, 1000, 977.