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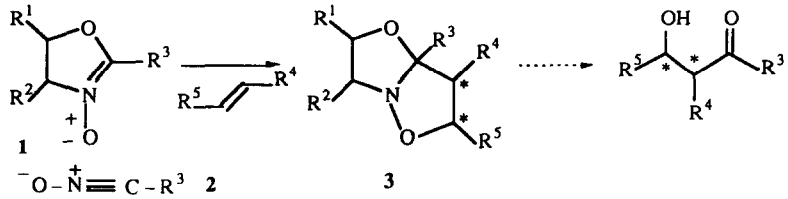
Oxazolines N-oxides as powerful dipoles in Asymmetric [2+3] Cycloadditions

T. Bérranger, C. André-Barrès, M. Kobayakawa and Y. Langlois*

Laboratoire de Synthèse des Substances Naturelles
Associé au CNRS, ICMO, Bâtiment 410, Université de Paris-Sud
91405 Orsay Cedex, France

Abstract : (+)-Norephedrine and (+)-camphor oxazolines N-oxides **9a**, **9b** and **13a**, **13b** underwent regio- and stereoselective [2+3] cycloadditions on various electron poor dipolarophiles .

In the last ten years, asymmetric 1,3 dipolar cycloaddition have become a potent method for the stereocontrol of acyclic, carbocyclic and heterocyclic systems[1]. Chiral oxazolines N-oxides of general formula **1**, which can be considered to be an equivalent of nitrile oxides **2**, have never been used in such asymmetric cycloadditions as far as we know. This is probably due to the fact that the achiral version of this reaction, described some years ago by Coates[2] was poorly regio- and stereoselective. More recently, and in order to overcome this disadvantage, the corresponding intramolecular cycloaddition have been studied in our laboratory[3]. In this paper, we present our preliminary results in the first asymmetric intermolecular cycloadditions of oxazolines-N-oxides with various electron poor dipolarophiles with the aim to develop a new alternative to the asymmetric aldol condensation (Scheme 1).

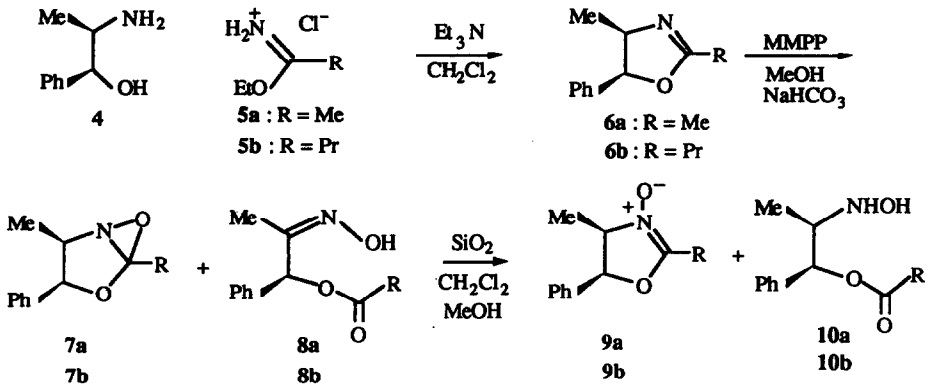


Scheme 1

– Preparation of oxazolines N-oxides 9a, 9b and 13a, 13b :

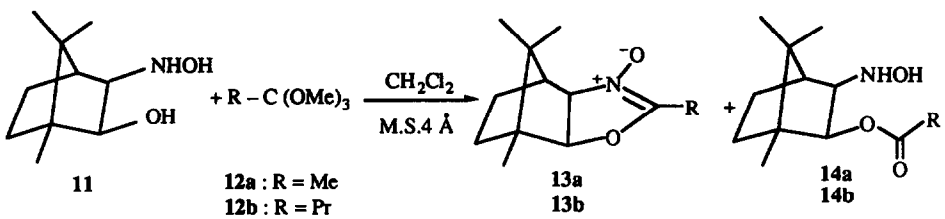
Oxazolines N-oxides used in this study have been prepared following two complementary methods. According to Keana[4], oxazolines **6a**, **6b** prepared by the classical condensation between (+)-norephedrine **4** and iminoethers hydrochlorides **5a**, **5b**, were oxidized with the magnesium salt of monoperphtalic acid in methanol. The side reaction affording oxime esters **8a**, **8b** has been minimized by the use of 2 equivalents of oxidant which increased the rate of formation and the yields of oxaziridines **7a**, **7b** (90-95%). In the following step however, the silica gel induced isomerisation gave rise to the expected oxazolines-N-oxides **9a**, **9b** with various amount of hydroxylamino esters **14a**, **14b** resulting from a subsequent hydrolysis [5]. The instability of oxazoline N-oxides **9a**, **9b** precluded further purification and the crude products were used directly in cycloadditions (Scheme 2).

Condensation of hydroxylamino alcohol **11**[6] with trimethyl orthoester **12a** and **12b**[7] using the method reported by Coates[2a], afforded directly camphor derivatives oxazolines N-oxides **13a**, **13b**. The easy hydrolysis of these compounds has been supressed by adding 4Å molecular sieves to the reaction medium. Nevertheless, as above, the unstable N-oxides **13a**, **13b** were used without further purification (Scheme 3).



4 — 5a : R = Me; 5b : R = Pr — 6a : R = Me; 6b : R = Pr — 7a; 7b — 8a; 8b — 9a; 9b — 10a; 10b

Scheme 2

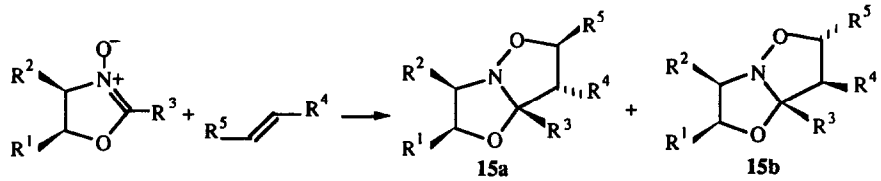


11 — 12a : R = Me; 12b : R = Pr — 13a; 13b — 14a; 14b

Scheme 3

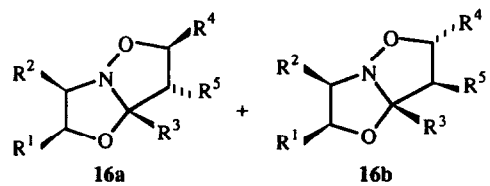
– Cycloadditions of oxazolines N-oxides 9a, 9b and 13a, 13b :

Oxazolines N-oxides **9a, 9b** and **13a, 13b** in the presence of alkenes conjugated with an electron withdrawing group afforded smoothly the corresponding adducts **15a, 15b, 16a** and **16b** (Scheme 4)[8].



15a **15b**

9a : R^1 = Ph, R^2 = Me, R^3 = Me
9b : R^1 = Ph, R^2 = Me, R^3 = Pr
13a : $R^1 + R^2$ =  R^3 = Me
13b : $R^1 + R^2$ = R^3 = Pr

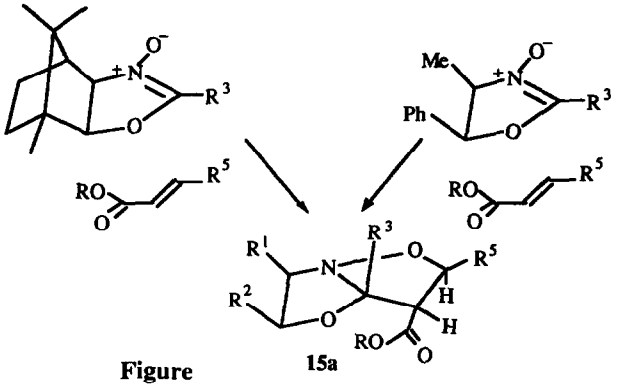


16a **16b**

Scheme 4

The results of these reactions are summarized in the table. With disubstituted dipolarophiles (entries 3-5 and 8-11) cycloadditions are highly regio and stereoselective : adducts **15a**[9] were the only products of these reactions. As already pointed out by Coates[2a] the regioselectivity of these cycloadditions can be rationalized in term of orbital frontier theory by a preferential orientation homo dipole-lumo dipolarophile. However the better regio- and stereoselectivity observed in our case is not completely understood. The same regioselectivity has been observed previously with nitrones[10] but cycloadditions with nitrile oxides are generally less selective[11]. The absolute configurations of adducts **15a** (entries 1, 2, 6-8) have been determined after ^{1}H NMR NOE experiments[12].

From a stereochemical point of view, formation of adducts **15a** could be rationnalized in both series as resulting from an endo approach of the less hindred α-face of the dipoles **9a**, **9b** and **13a**, **13b** (Figure). The regio and stereoselectivity of these cycloadditions are not dependent on the temperature which influenced only the rate of the reaction. The hydrolysis, hydrogenolysis and decarboxylation reactions of adducts **15a** are under study.



Figure

Entry	Dipole	Dipolarophile	Solvant Temp. °C (Time h)	Adducts Yield %	ratio % 15a	15b	16a + 16b
1	**9a**	R^4 = CN R^5 = H	CH_2Cl_2 20 (18)	75[a]	**15a1** : 86	12	2
2	**9a**	R^4 = CO_2Me R^5 = H	CH_2Cl_2 40 (18)	80[a]	**15a2** : 87	7	6
3	**9a**	R^4 = CO_2Me R^5 = Me	CH_2Cl_2 40 (48)	76[a]	**15a3** :100	0	0
4	**9a**	R^4 = CO_2Bn R^5 = Me	Toluene 80 (18)	48[a]	**15a4** : 100	0	0
5	**9b**	R^4 = CO_2tBu R^5 = Pr	Toluene 80 (18)	52[a]	**15a5** :100	0	0
6	**13a**	R^4 = CN R^5 = H	CH_2Cl_2 40 (3)	49[b]	**15a6** : 70	25	5
7	**13a**	R^4 = CO_2 Me R^5 = H	CH_2Cl_2 40 (18)	50[b]	**15a7** : 60	25	15
8	**13a**	R^4 = CO_2Me R^5 = Me	Toluene 80 (5)	53[b]	**15a8** : 100	0	0
9	**13b**	R^4 = CO_2Bn R^5 = Me	CH_2Cl_2 40 (24)	52[b]	**15a9** : 100	0	0
10	**13b**	R^4 = CO_2 Bn R^5 = Me	Toluene 80 (1.30)	50[b]	**15a10** :100	0	0
11	**13b**	R^4 = CO_2tBu R^5 = Pr	Toluene 80 (18)	63[b]	**15a11** :100	0	0

Table *a) Yields are calculated from N-oxides* **9a**, **9b** *b) Yields are calculated from hydroxylamine alcohol* **11**.

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References and notes

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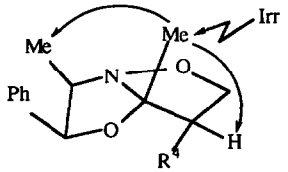
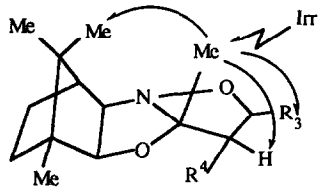
2. a- Ashburn S.P., Coates R.M., *J. Org. Chem.*, **1984**, *49*, 3127-3133. b- Ashburn S.P., Coates R.M., *J. Org. Chem.*, **1985**, *50*, 3076-3081.
3. Kobayakawa M., Langlois Y., *Tetrahedron Lett.*, **1992**, *33*, 2353.
4. Keana J.F.W., Lee, T.D., *J. Am. Chem. Soc.*, **1975**, *97*, 1273-1274.
5. The purity of oxazolines N-oxides **9a**, **9b** was estimated to be c.a : 50 % by ^1H NMR. The same instability of oxazolines N-oxides has been met by Coates with achiral oxazolines, see Ref. 2a.
6. Baldwin S.W., Mac Fayden R.B., Aubé J., Wilson J.D., *Tetrahedron Lett.* **1991**, *32*, 4431-4434.
7. Orthoester **12b** has been prepared according to : Casy G., Patterson J.W., Taylor R.J.K., *Organic Synthesis*, **1989**, *67*, 193-198.
8. Typical Experiment: Preparation of Adduct **15a11**: Triethylamine (0.38mL; 2.75mmol), trimethylorthobutyrate (740mg; 5mmol) and E-terbutyl-2-hexenoate (850mg; 5mmol) was added sucessively to a stirred suspension of hydroxylaminoalcohol **11** hydrochloride (550 mg;2.5 mmol) and 4Å molecular sieves (500mg) in toluene (10mL). After beeing stirred at 20°C under argon for 3 hours, the reaction medium was heated at 80°C for 24 hours. After filtration and evaporation, the crude residue was dissolved in dichloromethane, washed with water, dried over magnesium sulfate and evaporated under vacuum. The crude product was purified by flash chromatography (silice Merck 60, 230-400 mesh; pentane-ether 90:10) affording cycloadduct **15a11** (640mg; 63%).
9. **15a4** : $[\alpha]_D$ = - 41 (20°C, c= 1.82, $CHCl_3$). **15a5** : $[\alpha]_D$ = +2.3 (20°C, c= 2.18, $CHCl_3$). **15a9** : $[\alpha]_D$ = -112 (20°C, c= 1.025, $CHCl_3$). **15a11** : $[\alpha]_D$ = -53 (20°C, c=1.31, $CHCl_3$).
10. a- Huisgen R., Hauck H., Grashey R., Seidl H., *Chem. Ber.*, **1969**, *102*, 736-745 and references there in.

    b- Joucla M., Grée D., Hamelin J., *Tetrahedron*, **1973**, *29*, 2315-2322.
11. Christl M., Huisgen R., *Chem. Ber.*, **1973**, *106*, 3345-3367.
12. The main NOE modifications in both series are indicated below (400MHz, NOE ~ 6%):



R^4 = CN, CO_2 Me



$R^4 = CO_2Me$; R^3 = Me

R^4 = CN ; R^3 = H

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