

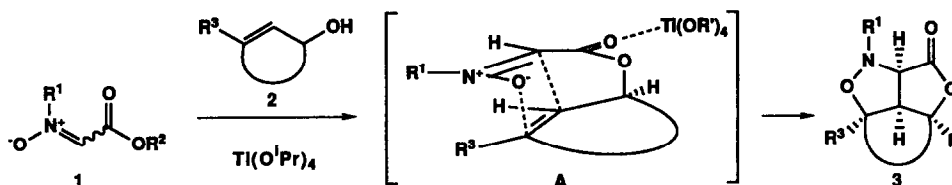
One Step Bicyclization by Way of Tandem Transesterification, Intramolecular 1,3-Dipolar Cycloaddition of α -Methoxycarbonylnitrones with Allyl Alcohols in the Presence of Titanium Isopropoxide

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Abstract: Treatment of α -methoxycarbonylnitrones with allyl alcohols in the presence of titanium isopropoxide caused tandem transesterification, *E,Z*-isomerization and intramolecular cycloaddition to provide stereocontrolled polycyclic compounds in one step.

Intramolecular cycloaddition of nitrones is recognized as a powerful method for construction of various nitrogen containing carbon frameworks, since it makes possible regio- and stereoselective polycyclization in one step.¹ In this category, α -allyloxycarbonylnitrones are also quite attractive substrates for the intramolecular cycloadditions.² However, the preparation of the nitrones from allyl alcohols requires multi steps,³ and this becomes a significant drawback for the synthetic applications of the cycloaddition of the nitrones. We have now found that α -methoxycarbonylnitrones (**1a,b**) cause tandem transesterification with allyl alcohols (**2**), *E, Z*-isomerization, and intramolecular cycloadditions in the presence of titanium isopropoxide to give stereocontrolled polycyclic products (**3**) under mild conditions in one step.⁴



As shown in Table 1, the cycloaddition of **1a** (1.6:1 *E, Z*-equilibrating mixture in $CDCl_3$)⁵ with allyl alcohol (**2a**) was first examined. The reaction of **1a** with **2a** in the presence of titanium isopropoxide smoothly proceeded at room temperature to afford **3a** (entry 1). The reaction of the nitrone having a bulky substituent on the nitrogen atom (**1b**, 1.1:1 *E, Z*-equilibrating mixture in $CDCl_3$)⁵ gave **3b** in even better yield (entry 2). In the present cycloaddition, the geometry of olefins is reflected in the products. Thus, the use of *trans*-allyl alcohol (**2b**) exclusively afforded 4,5-*trans*-stereochemistry on the isoxazolidine ring (entries 3,4) and the use of *cis*-allyl alcohols (**2c** and **2d**) gave 4,5-*cis*-stereochemistry on the isoxazolidine ring of the products (entries 5,6 and entries 7,8). In this series, it should be noted that the reactions of **1a,b** with **2c** and **2d** could generate four relative stereogenic centers in one step (entries 5-8).

In sharp contrast to these reactions, the reaction **1b** with **2a** in the absence of titanium isopropoxide took place quite slowly (at least two weeks) at room temperature to give cycloadduct (**4**) having the opposite

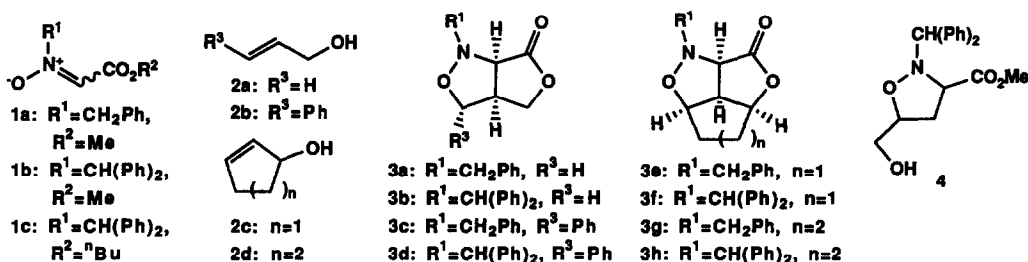


Table 1. Reactions of 1a,b with 2a-d in the Presence of Titanium Isopropoxide.^a

Entry	Nitrones	Allyl Alcohols	Conditions	Yield (%) ^b	Products
1	1a	2a	rt, 20 h	59	3a
2	1b	2a	rt, 5 h	74	3b
3	1a	2b	50°C, 11 h	85	3c
4	1b	2b	45°C, 14 h	78	3d
5	1a	2c	50°C, 11 h	70	3e
6	1b	2c	45°C, 14 h	99	3f
7	1a	2d	rt, 9 h	45	3g
8	1b	2d	rt, 34 h	77	3h

a. The all reactions were carried out using 1 eq. of 1, 5 eq. of 2, and 1 eq. of $\text{Ti}(\text{O}^i\text{Pr})_4$ in 1,2-dichloroethane.

b. Isolated yields by column chromatography on silica gel are given.

regiochemistry as a 1:1 mixture of diastereomers in 70 % yield (compare with entry 2). Furthermore, treatment of 1b with *n*-butanol in the presence of titanium isopropoxide gave α -*n*-butyloxycarbonylnitronone (1c).⁶ These facts clearly suggest that the present cycloaddition should occur by way of tandem transesterification, *E,Z*-isomerization, and intramolecular cycloaddition instead of intermolecular cycloaddition and lactonization. Titanium alkoxide may accelerate the cycloaddition step (A) by coordination with carbonyl oxygen atom, since even intramolecular cycloaddition of nitrones usually requires a higher temperature and a longer reaction period.^{1,2}

Asymmetric version of this reaction and its synthetic application are under current investigations.

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2. a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1990**, *55*, 1901-1908. For related cycloaddition of an α -homoallyloxycarbonylnitronone, see b) Tschäen, D. M.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 2604-2605.
3. α -Allyloxycarbonylnitronones have been prepared by bromoacetylation of allyl alcohols, substitution of the allyl bromoacetates with silver nitrate, treatment of the resulting nitronate esters with dimethylsulfoxide and sodium acetate, and condensation of the resulting glyoxylate with *N*-alkylhydroxylamine.²
4. After completion of this work, highly regio- and stereocontrolled cycloaddition of α -benzoyl-*N*-phenylnitronone with allyl alcohols appeared. Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87-90.
5. Inouye, Y.; Hara, J.; Kakisawa, H. *Chem. Lett.* **1980**, 1407-1410. This equilibrium was also observed by two dimensional TLC analysis (silica gel, CH_2Cl_2).
6. It was reported that titanium isopropoxide catalyzes transesterification of an ester in an alcohol as a solvent. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis*, **1982**, 138-141.