Pergamon

Tetrahedron Letters 43 (2002) 967–971

TETRAHEDRON LETTERS

Asymmetric synthesis of diversely substituted *N*-hydroxypyrrolidines using cycloadditions with chiral nitrone enolate/ylids

Stephen Hanessian* and Malken Bayrakdarian

Department of Chemistry, Université de Montréal, C.P. 6128, Succ. Centre-Ville, Montréal, P.Q., Canada H3C 3J7

Received 28 August 2001; accepted 28 November 2001

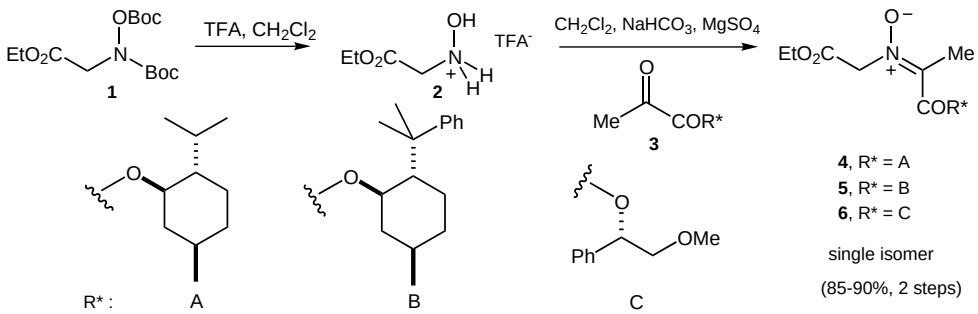
Abstract—A stereoselective synthesis of diversely substituted *N*-hydroxypyrrolidines is reported, based on the cycloaddition reaction of chiral non-racemic nitrone ylids with a variety of α,β-unsaturated esters.

The pyrrolidine nucleus is found as a common subunit of many naturally occurring alkaloids,[1,2] or an entity in itself as for example the antifungal antibiotic preussin.[3] Several polysubstituted pyrrolidines have shown very potent activities as enzyme inhibitors,[4] as agonists, or antagonists of receptors.[5] Polyhydroxy pyrrolidines, considered as 'azasugars' that mimic carbohydrates, are known to be inhibitors of glycosidases.[6] Beside their pharmacological activities, several substituted pyrrolidines and prolines are also used as chiral catalysts[7] and auxiliaries[8] in a variety of asymmetric reactions.

There are numerous methods for the stereocontrolled synthesis of substituted heterocycles including pyrrolidines and prolines using a 1,3-dipolar cycloaddition.[9] A lesser exploited reaction is the condensation of nitrone enolate/ylids derived from glycinate esters with electron deficient alkenes to give polysubstituted *N*-hydroxypyrrolidines.[10] In this communication, we report our results on the asymmetric synthesis, characterization and further functionalization of diversely substituted *N*-hydroxypyrrolidines resulting from the reaction of chiral nitrone ylids or their enolate equivalents with a variety of α,β-unsaturated esters.

Treatment of *N*,*O*-bis(*tert*-butoxycarbonyl) hydroxylamine ethyl glycinate **1** with TFA, followed by condensation[11] with chiral pyruvate esters **3**, afforded the intended nitrones **4**–**6** as single isomers based on NOE studies (Scheme 1).

Cycloadditions of cinnamate esters with nitrones **4**–**6** were carried out in THF at 0°C in the presence of lithium bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst.[12] The stereoselectivity of the cycloaddition reaction was studied by varying the



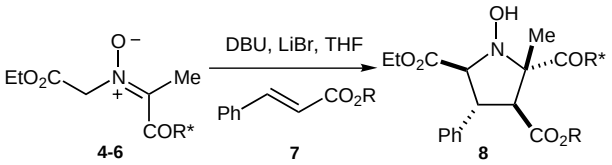
Scheme 1.

Keywords: 1,3-dipolar cycloaddition; pyrrolidine scaffold.

* Corresponding author. Tel.: (514) 343-6738; fax: (514) 343-5728; e-mail: stephen.hanessian@umontreal.ca

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02305-X

nature of the cinnamate ester **7** with each of the nitrones **4–6**. Little or only modest improvement was observed between methyl and benzyl esters as seen in Scheme 2 and Table 1. A definite improvement was observed with benzyl cinnamate and 8-phenylmenthyl ester nitrone **5** (Table 1, entry 4, 9:1 ratio). With benzhydryl cinnamate as the dipolarophile (Table 1, entry 5), cycloaddition led to a single isomer in 85% yield.[13] Similar enhancement in diastereoselectivity has been previously observed in intramolecular Michael additions of anions of menthyl and 8-phenylmenthyl esters of β-diketones to α,β-unsaturated esters.[14] Michael-type additions of phosphonamide anions to benzhydryl and *tert*-butyl cinnamates exhibit higher selectivity compared to methyl or benzyl esters.[15]

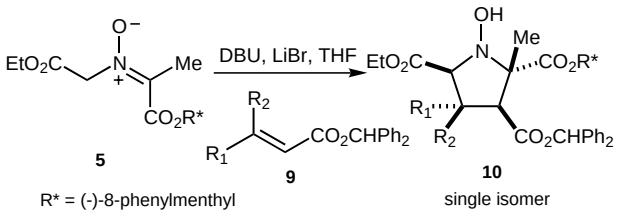


Scheme 2.

Table 1.

Entry	R	R*[a]	Yield[b]/ratio[c]
1	Me	A	78% (1.6:1)
2	Bn	A	85% (1.6:1)
3	Me	B	70% (3:1)
4	Bn	B	75% (9:1)
5	$CHPh_2$	B	85%, 1 isomer
6	$CHPh_2$	C	60% (1:1)

[a] Scheme 1.
[b] Isolated yield after silica gel purification.
[c] Determined by ^1H and ^{13}C spectroscopy of the crude product.



Scheme 3.

Scheme 3 and Table 2 show the generality of the cycloadditions for benzhydryl acrylate, and for a series of substituted cinnamates which afforded a single diastereomer in each case. With the exception of the *cis*-cinnamate ester (50%), yields for each *N*-hydroxypyrrolidine **10** synthesized were excellent. The absolute configuration of the cycloadducts was proven by detailed NOE studies of the crude products, and by an X-ray crystal structure of a derivative.

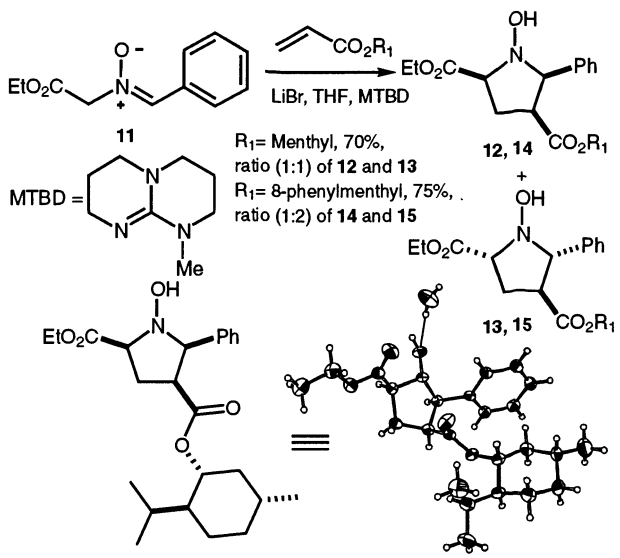
The reactions were also successful in the case of benzylidene nitrone analog **11**, which underwent cycloaddition with menthyl acrylate and 8-phenylmenthyl acrylate in the presence of LiBr and MTBD[16] to give 1:1 and 2:1 mixtures of separable diastereomeric pyrrolidines **12**, **13** and **14**, **15**, respectively (Scheme 4).

Contrary to cyclizations of azomethine ylids which can be carried out in the presence of several additives,[12] the reactions of nitrones **4–6** were only successful in the presence of lithium bromide and a base such as DBU, regardless of the nature of the solvent used (MeCN, CH_2Cl_2, THF, toluene). With LiHMDS in THF at −78°C, the same diastereoselectivity was observed. No reaction took place in the presence of additives such as AgOAc, $MgBr_2$, or $CoCl_2$.[12e,f]

Table 2.

R_1	R_2	Yield[a/b]
H	H	90%
Me	H	75%
F_3C	H	85%
F	H	80%
MeO	H	85%
H		50%[c]

[a] Isolated yield after silica gel purification. [b] For details see ref. 13. [c] 30% of **5** was isolated.



Scheme 4.

It is of interest to comment on the stereochemical outcome of these cycloadditions in which only carbon–carbon bond formation was observed. In contrast, there are numerous examples of isoxazolidine formation in the cycloaddition of nitrones with unsaturated compounds.[9] In the absence of a chiral auxiliary, nitrone ethyl ester and methyl cinnamate afforded the racemic *endo*-adduct corresponding to **8** as the major if not exclusive product. The results in Scheme 2 and Table 1 show that the size of the cinnamate ester and the nature of the chiral auxiliary have an influence on the diastereoselectivity. Thus, with methyl or benzyl cinnamates and menthyl nitrone lithium enolate **4**, virtually no selectivity was observed. An enrichment of the product **8** was observed in going to the 8-phenylmenthyl nitrone lithium enolate **5** eventually leading to a single isomer with benzhydryl cinnamate. Thus, bulky esters on the dipole and dipolarophile appear to have a cooperative effect in enhancing the diastereoselectivity of the cycloaddition reaction.

These results can be accommodated by a concerted pathway,[17] in which the *re* face of the planar nitrone lithium enolate is masked by the dimethyl benzyl group[18] of the auxiliary as illustrated in Fig. 1. This conformation also allows for a preferred *syn* planar arrangement of the methine hydrogen on the menthyl ring with the ester carbonyl.[14,19] An *endo-si* face approach of the cinnamate ester in an *s-cis* conformation exposing its *re* face would lead to the observed major isomer A. Such a transition state model could also benefit from a pre-coordination of the cinnamate ester carbonyl group with the lithium cation. As the size of the cinnamate ester group decreases from benzhydryl to benzyl to methyl, and especially when a menthyl auxiliary is used, the alternative *endo-re* face approach is also possible. We tentatively suggest that the other minor product in the cycloadditions is the diastereomer corresponding to the enantiomeric pyrrolidine B (Fig. 1).

The cycloaddition of the benzylidene nitrone **11** with methyl acrylate afforded a 1:1 mixture of two cycloadducts which could be separated. Cycloaddition with menthyl and 8-phenylmenthyl acrylates afforded compounds **12**/**13** and **14**/**15** as separable diastereomers in each case. It follows that these are products arising from *endo*- and *exo*-transition states, respectively, approaching the *si*- and *re*-faces of the nitrone enolate (Fig. 1 C,D).

We chose to study a number of chemoselective transformations that would differentiate the functional appendages and offer opportunities for further modification in the context of a program aimed at generating diversity in a proline type scaffold. Hydrogenolysis of the benzhydryl ester **16** as a prototype, and intramolecular coupling afforded the novel bicyclic lactone **17** whose X-ray crystal structure confirmed the configurational assignment of the cycloaddition products (Scheme 5). Reduction of the N–O bond using molybdenum hexacarbonyl[20] afforded **18**, which was trans-

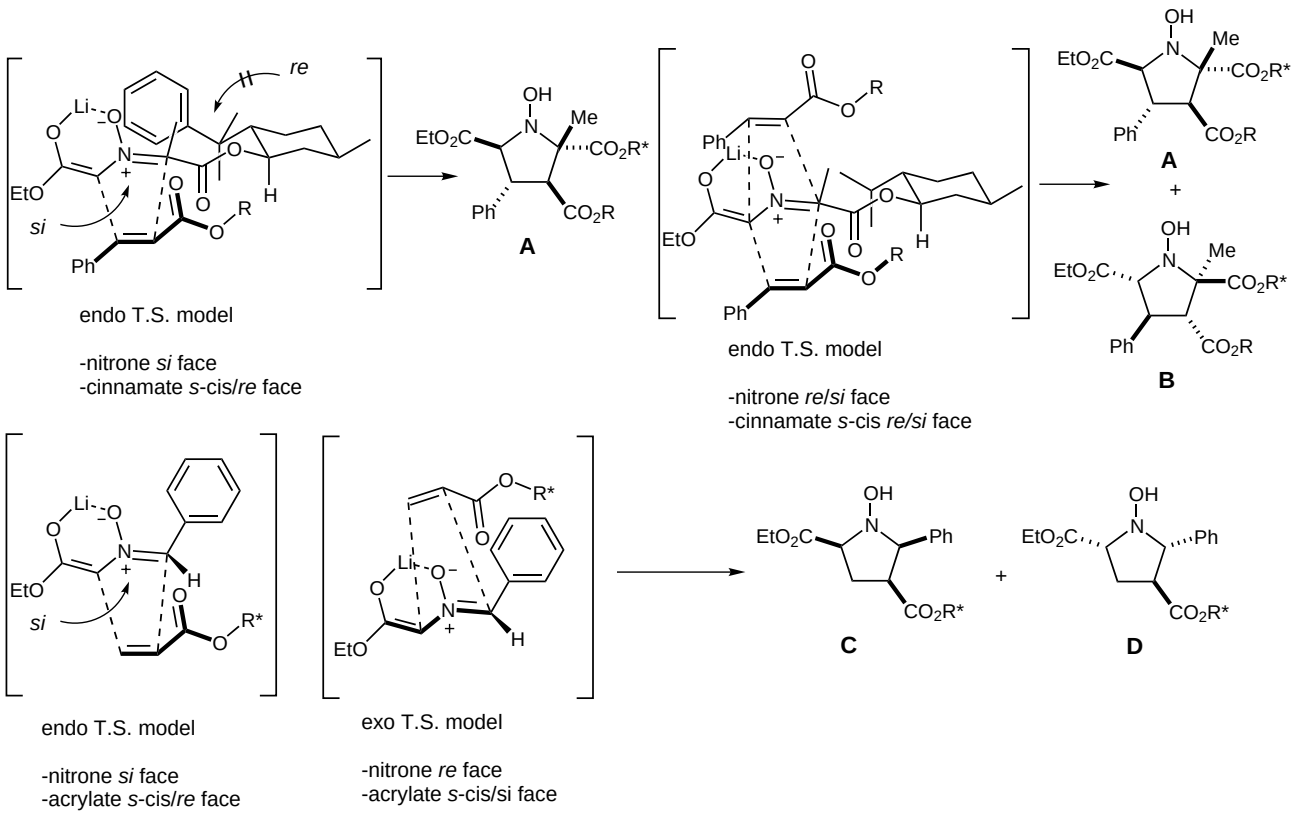
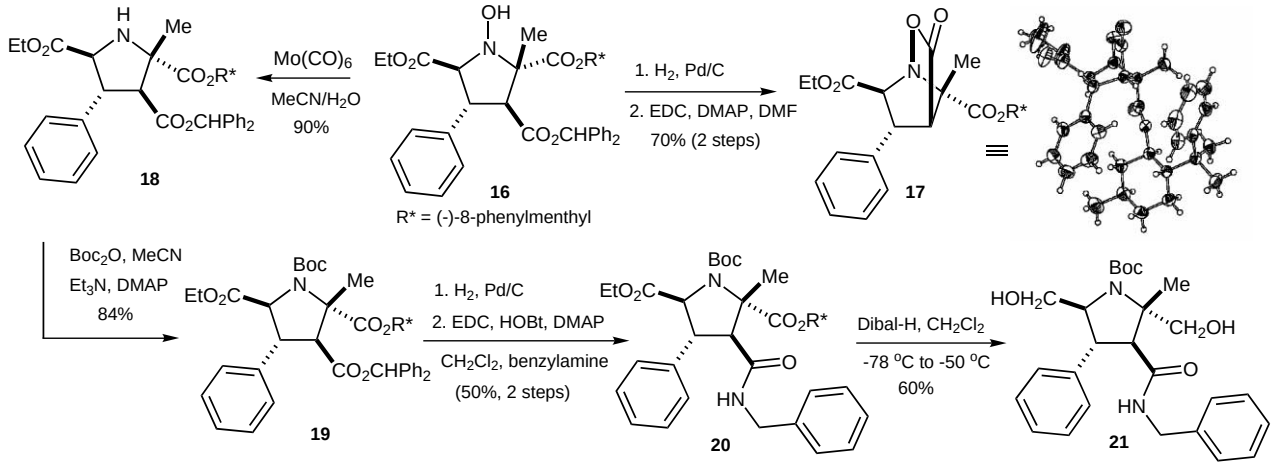


Figure 1.



Scheme 5.

formed into the *N*-Boc derivative **19**. Hydrogenolysis and coupling under standard conditions with a prototypical amine gave benzylamide **20** (Scheme 5). Treatment of **20** with Dibal-H[21] resulted in the cleavage of the ethyl and 8-phenylmenthyl esters affording the amide prototype **21**. A focussed library of diversely aryl substituted amides related to **21** can be easily assembled, since the cycloaddition reaction is possible with a variety of cinnamate esters.

The synthesis of polyfunctional, enantiopure *N*-hydroxypyrrolidines and pyrrolidines reported in this paper complements our previous results[22] utilizing azomethine ylid chemistry.[9,23] The nitrone methodology is versatile and affords a different set of diastereomers, in addition to maintaining the *N*-hydroxy functionality intact.

The polyfunctional pyrrolidine motifs available through nitrone cycloaddition methodology represent core scaffolds with functionally diverse appendages which can find utility in displaying desirable pharmacophores to biological targets. The successful implementation of the method with a variety of aryl substituted cinnamates shows its potential in parallel array synthesis.

Acknowledgements

We thank NSERC for financial assistance through the Medicinal Chemistry Chair Program.

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13. For a typical procedure: DBU (61 μL, 62 mg, 0.41 mmol) is added to a solution of nitrone (150 mg, 0.37 mmol), LiBr (63 mg, 0.74 mmol) and cinnamate ester (0.56 mmol) in THF (3 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min, a saturated solution of NH_4Cl (5 mL) was added and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The resulting residue was purified by flash chromatography (EtOAc/hexane, 1:9 to 2:8) to give the desired *N*-hydroxypyrrolidine as a colorless oil.
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