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A Novel Synthesis of Enantiopure Octahydropyrrolo[3,4-b]pyrroles by Intramolecular [3 + 2] Dipolar Cycloaddition on Chiral Perhydro-1,3-benzoxazines

Rafael Pedrosa,* Celia Andrés,* Laura de las Heras, and Javier Nieto

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid,
Dr. Mergelina s/n, 47011-Valladolid, Spain

pedrosa@qo.uva.es

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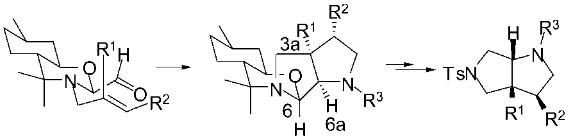
ABSTRACT



Condensation of N-substituted glycines with chiral 3-allyl-2-formyl perhydro-1,3-benzoxazines forms an azomethine ylide that cyclizes to give octahydropyrrolo[3,4-b]pyrrole derivatives. The [3 + 2] dipolar cycloadditions are stereoespecific leading to a single diastereoisomer. The chemical yields are dependent on the reaction temperature and the presence or absence of a base.

The 1,3-dipolar cycloaddition reaction is one of the most useful methods for the preparation of five-membered heterocycles, and consequently, it has been extensively studied.[1] In particular, the reaction of azomethine ylides[2] with alkenes provides pyrrolidine ring systems that are the central skeleton of numerous alkaloids[3] and the core of physiologically active compounds.[4] The intramolecular version of this reaction results in the formation of new fused or bridged nitrogen-containing bicyclic systems and generally occurs with high regio- and stereocontrol.[5] This intramolecular reaction takes place easily even with unactivated dipolarophiles such as terminal alkenes, which do not react intermolecularly.[6] Therefore, this powerful strategy has been extensively applied toward the synthesis of complex molecules,[7] including the preparation of enantiopure substituted actahydropyrrolo[3,4-b]pyrroles[8] after chiral chromatographic separation of the

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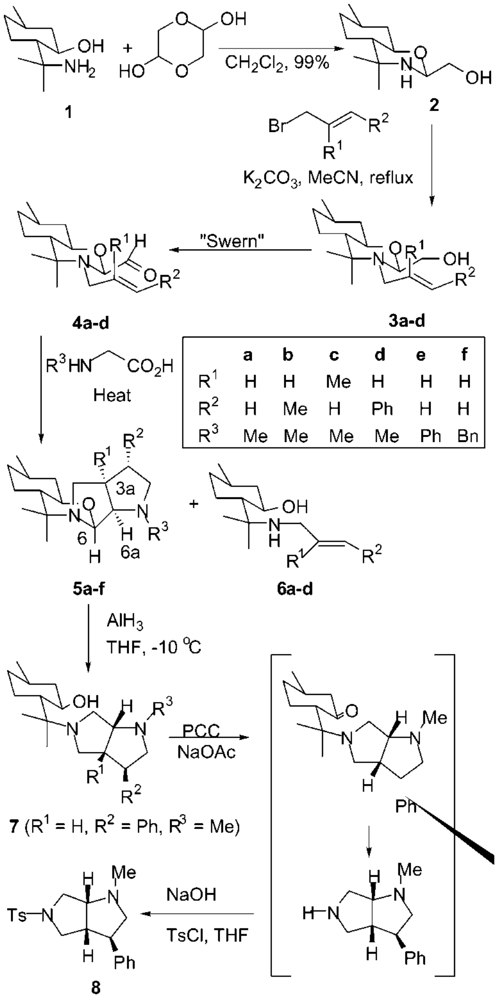
racemate. Enantiopure pyrrolidines have been also obtained in good de by cyclization of azomethine ylides, generated in situ by decarboxylation, with alkenes bearing oxazolidinones[9] or (*R*)-phenethylamine derivatives[10] as chiral auxiliaries. The intermolecular asymmetric cycloaddition is well known,[11,12] whereas the intramolecular version using a removable chiral auxiliary or catalyst has been less studied.[13]

Recently, we have exploited (−)-8-amino menthol,[14] prepared from the easily accessible natural (+)-pulegone, as a chiral environment and the source of the nitrogen atom in diastereoselective cyclization processes leading to nitrogen heterocycles.[15,16] We now report the stereospecific 1,3-dipolar cycloadditions of nonstabilized azomethine ylides with unactivated alkenes positioned on a chiral perhydro-1,3-benzoxazine moiety.

The starting 3-allyl-2-formyl perhydro-1,3-benzoxazines **4a−d** were prepared as single diastereoisomers in good chemical yields from (−)-8-amino menthol in three steps as summarized in Scheme 1. Condensation of the amino alcohol with glycolaldehyde dimer at room temperature afforded nearly quantitative 2-hydroxymethyl perhydro-1,3-benzoxazine **2**, which was transformed into *N*-allyl derivatives **3a−d** by alkylation with allyl-, crotyl-, methallyl-, and cinnamyl bromides, respectively, in refluxing acetonitrile and potassium carbonate.[17] Swern oxidation[18] of **3a−d** yielded the starting compounds **4a−d**, respectively, in good yields (70−74% from **1**) as single diastereoisomers.

Scheme 1. Synthesis of Octahydropyrrolo[3,4-b]pyrroles by Intramolecular [3 + 2] Dipolar Cycloaddition



The formation of the unstabilized azomethine ylides was carried out by decarboxylative condensation of aldehydes **4a−d** with N-substituted α-amino acids.[19,20] Different reaction conditions were initially tested on compound **4a** (Table 1).

Condensation of **4a** with *N*-benzyl glycine hydrochloride in the presence of potassium carbonate provides, after decarboxylation, the azomethine ylide, which cyclizes to yield the cis adduct **5f** as a single diastereomer but in low yield. The change to triethylamine as a base only slightly increases the yield of the desired adduct. In both reactions

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Table 1. Dipolar Cycloadditions of Compounds **4a**−**d**

entry	compd	amino acid	base	solvent (T (°C))	time (min)	products[a]
1	**4a**	N-Bn-Gly	K_2CO_3	DMF (90)	60	**5f** (26), **6a** (60)
2	**4a**	N-Bn-Gly	Et_3N	DMF (90)	60	**5f** (38), **6a** (46)
3	**4a**	N-Ph-Gly	Et_3N	DMF (153)	300	**5e** (16), **6a** (30)
4	**4a**	N-Ph-Gly	none	DMF (90)	120	**5e** (34), **6a** (30)
5	**4a**	N-Ph-Gly	none	$PhCH_3$ (110)	120	**5e** (70)
6	**4a**	N-Me-Gly	Et_3N	DMF (90)	60	**5a** (61), **6a** (25)
7	**4a**	N-Me-Gly	Et_3N	DMF (153)	60	**5a** (52), **6a** (22)
8	**4a**	M-Me-Gly	none	DMF (153)	45	**5a** (76), **6a** (16)
9	**4a**	N-Me-Gly	none	DMF (90)	60	**5a** (94)
10	**4b**	N-Me-Gly	none	DMF (90)	45	**5b** (78)
11	**4c**	N-Me-Gly	none	DMF (90)	45	**5c** (90)
12	**4d**	N-Me-Gly	none	DMF (90)	120	**5d** (56), **6d** (18)
13	**4d**	N-Me-Gly	Et_3N	DMF (153)	360	**5d** (76)

[a] Yields in parentheses refer to isolated and pure compounds.

the major product isolated was the 8-allylaminomenthol **6a**, resulting from the hydrolysis of **4a** (entries 1 and 2 in Table 1).

The reaction of **4a** with *N*-phenyl glycine in boiling DMF for 5 h, in the presence of Et_3N, yielded a complex reaction mixture from which **5e** and **6a** were only isolated in 16 and 30%, respectively. When the reaction was carried out in DMF at 90 °C for 2 h, in the absence of the base, the adduct **5e** was only isolated in 34%; however, the yield of the desired cyclization product was improved to 70% when a mixture of *N*-phenyl glycine and **4a** was boiled in toluene for 2 h under Dean−Stark conditions (entries 3−5).

The best results were obtained when *N*-methyl glycine was used as a condensation amino acid for the formation of the azomethine ylide. In this way, aldehyde **4a** was condensed with sarcosine (1.5 equiv), in the presence of Et_3N (1.5 equiv), in DMF at 90° C for 1 h leading to **5a** as a single diastereoisomer in 61%. When the reaction was carried out at reflux of the solvent, compound **5a** was isolated in only 52% yield. In the absence of Et_3N, cycloadduct **5a** was isolated in 76% yield after refluxing a mixture of **4a** and sarcosine for 45 min (entries 6−8). In all these reactions, 16−60% yields of 8-*N*-allylamino menthol **6a**, resulting from the hydrolysis of **4a**, were isolated.

These results indicate that both an increase in the reaction temperature and the presence of Et_3N as a base decreased the yield of the cyclized product. Then, a mixture of **4a** and sarcosine (1.5 equiv) was heated in DMF for 1 h at 90° C leading to **5a** in excellent yield (94%) as a single diastereoisomer. Under the same experimental conditions, 3-crotyl-2-formyl derivative **4b** yielded a single cycloadduct **5b** in 78% after heating with sarcosine in DMF for 45 min, and 2-formyl-3-methallyl perhydro-1,3-benzoxazine **4c** was transformed into **5c** in 90% yield. Nevertheless, under these conditions the cinnamyl derivative **4d** yielded **5d** in only 56% yield, and it was necessary to increase the reaction temperature to reflux and the reaction time to 6 h, using Et_3N as a base to achieve **5d** in 76% yield (entries 12 and 13).

It is noteworthy that the reaction for all the compounds **4a**−**d** was stereospecific, leading to cis,syn-adducts **5a**−**f** as single diastereoisomers, and other diastereoisomers were not detected on the ^{1}H NMR of the reaction mixtures. The relative stereochemistry of the tetracyclic compounds was determined on the basis of NOESY and COSY experiments. The values of the coupling constants between H_{3a} and H_{6a} (8.4−8.9 Hz) point to a cis,syn relationship for the cycloadducts.[20e]

Interestingly, the signal for H_6 appears as a singlet in the ^{1}H NMR spectra for all the cyclization compounds, indicating that it does not couple with the vicinal H_{6a}. These data show that the fusion of the oxazinine ring and the pyrrolidine was established in a "cis" axial−equatorial fashion, and consequently, the dihedral angle between H_6 and H_{6a} is near 90°.

The absolute stereochemistry was determined by transformation of **5d** into 1-methyl-3-phenyl-5-tosyl octahydropyrrolo[3,4-b]pyrrole **8**. Cycloadduct **5d** was reduced in 97% yield with aluminum hydride in THF at −10 °C for 10 min to 8-aminomenthol derivative **7**. The elimination of the menthol appendage was effected by oxidation of **7** with PCC in the presence of sodium acetate at room temperature to the 8-amino menthone derivative, which spontaneously decomposed to give (+)-pulegone and the diazabicyclic derivative. This compound was isolated as tosyl derivative **8** in 34% yield by treatment of the reaction mixture with 10% NaOH solution and tosyl chloride. The absolute configuration of **8** was established as (3*R*,3a*S*,6a*S*) by X-ray diffraction analysis (Figure 1), corroborating the absolute configuration of **5d** and the stereochemical outcome of the [3 + 2] dipolar cycloaddition.

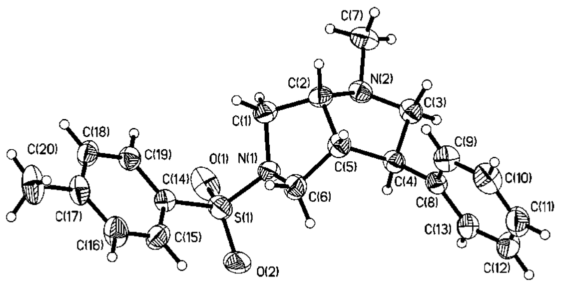
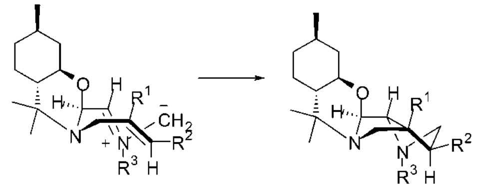


Figure 1. ORTEP diagram for compound **8**.

The cis,syn stereochemistry of the cyclization products can be only explained by accepting that the [3 + 2] dipolar cycloaddition occurs with total diastereofacial selectivity from the conformation shown in Scheme 2. In this conformation, the allyl substituent attached to the nitrogen atom is

Scheme 2. Proposed Stereochemistry of the Intermediate Ylide in the Formation of **5a−f**



5a-f

in an "axial" arrangement, and the reaction occurs only in an endo mode.

In summary, we have shown that the intramolecular [3 + 2] dipolar cycloaddition of nonstabilized azomethine ylides with unactivated alkenes performed on a chiral perhydro-1,3-benzoxazine template occurs with total regio- and stereoselectivity and provides an efficient synthesis of enantiopure nitrogen heterocycles. Efforts are currently underway to optimize the reaction yield in both the cycloaddition and elimination of the chiral template.

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Supporting Information Available: Copies of COSY and NOESY experiments for **5d**, full experimental procedures and physical and spectroscopic data for all the compounds, and X-ray crystal data, including atomic coordinates, isotropic and anisotropic displacement parameters, and a listing of bond angles and bond lengths. This material is available free of charge via the Internet at http://pubs.acs.org.

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