ICC
Iranian Chemical Communication
Short Communication
Payame Noor University http://icc.journals.pnu.ac.ir

A novel synthesis of diastereomerically pure spiro-oxindolopyrrolizidines and oxindolopyrrolidines *via* cycloaddition reactions of azomethine ylides

Mohammad Javad Taghizadeh[a,*], Khosrow Jadidi[b]

[a]*Department of Chemistry, Imam Hossein University, P.O. BOX 995-16765 Tehran, Iran*

[b]*Department of Chemistry, Shahid Beheshti University, P.O. BOX 1983963113 Tehran, Iran*

Received: 29 June 2014, Accepted: 25 July 2014, Published: 1 October 2014

Abstract

An efficient one-pot three-component procedure for the synthesis of new chiral spiro oxindolopyrrolidines/pyrrolizidines with highly regio- and diastereo-enantio selective from 1,3-dipolar cycloaddition of azomethine ylides and chiral menthol-drived *trans*-cinnamic are described. The mechanism of the reaction is discussed on the basis of the assignment of the absolute configuration of one of the cycloaddition products, which was obtained by single crystal X-ray analysis.

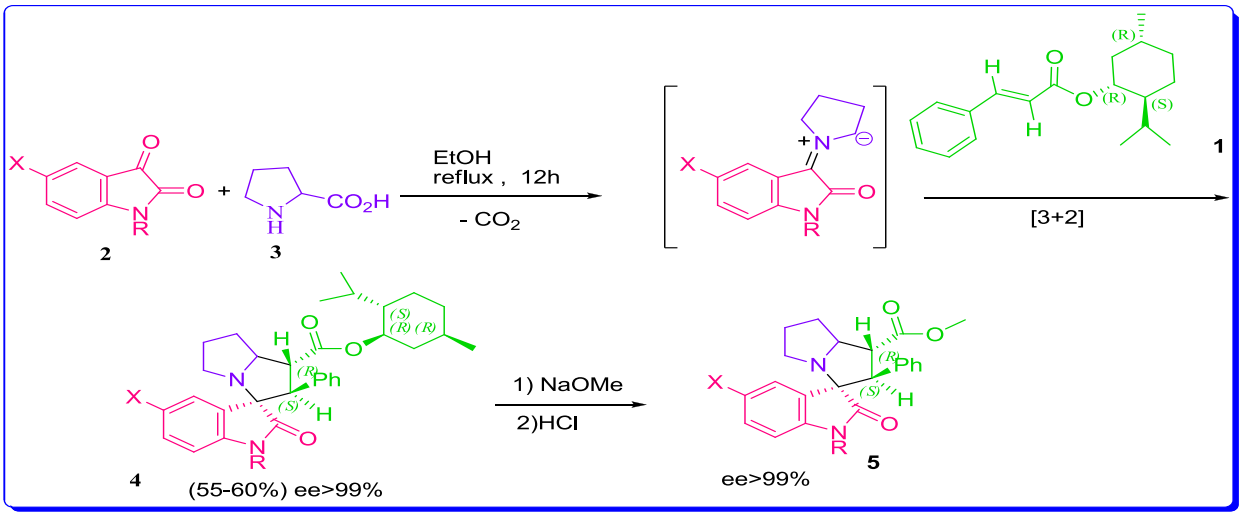
Keywords: Chiral spiro oxindolopyrrolidines; pyrrolizidines; azomethine ylides; chiral menthol-drived *trans*-cinnamic; isatin; sarcosine.

Introduction

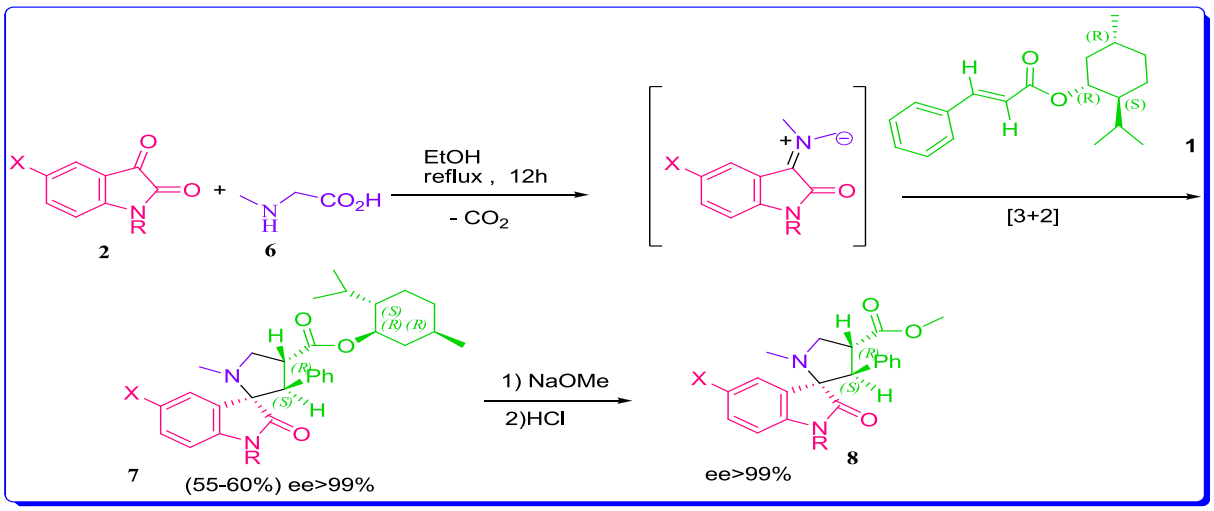
Functionalized pyrrolidines and pyrrolizidines with spirooxindole ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds [1]. Gelesmine, pseudotabersonine, formosanine, isoformosanine, morroniside and mitraphylline are some of the alkaloids containing spirooxindole ring systems [2]. Derivatives of spirooxindole find very wide biological applications as antimicrobials, anti-inflammatory, antitumourals, antibiotic agents and inhibitors of human NK-1 receptors [3]. 1,3-Dipolar cycloaddition reaction is an efficient method for the construction of heterocyclic units in a highly regio- and stereo- selective manner [4]. Chiral pyrrolidines are extensively found as significant skeleton of numerous biologically relevant alkaloids [5] and are of considerable interest in medicinal chemistry [6]. On the other hand, chiral pyrrolizidines have a long history for the interest of synthetic chemists because of wide distribution in nature and variegated biological activities. Hence, various derivatives of this important class of spiro compounds have been synthesized [7]. But, only a few derivatives of chiral spirooxindolopyrrolizidine have been prepared. The reported methods suffer from many limitations, such as using toxic solvents in reflux condition and absence of enantiomeric purity [8]. Based on the literature review [9], Grigg and co-workers synthesized a series of diastereomerically pure and new spiro oxindolopyrrolidines/pyrrolizidines using a 1,3-dipolar cycloaddition

*Corresponding author: Mohammad Javad Taghizadeh
Tel: +98 (021) 77103554; Fax: +98 (021) 73829506
E-mail: mohammadjavadtaghizadeh31@yahoo.com

reaction of the chiral menthyl acrylate with non-stabilized azomethine ylides generated *in situ* by the decarboxylative condensation of isatins with L-proline or sarcosine. We decided to synthesize a series of diastereomerically pure and new spiro oxindolopyrrolidines/pyrrolizidines using a three com ponent reaction involving 1,3-dipolar cycloaddition reactions. Since Padwa performed the first diastereofacial selective 1,3-dipolar cycloaddition reaction using a chiral azomethine ylide, asymmetric 1,3- dipolar cycloaddition reaction azomethine ylide in presence of chiral auxiliaries, it has received much attention. In this report, at first, we prepared chiral non-racemic dipolarophiles from the reaction of cinnamic acid with pure menthol as achiral auxiliary. Then, the reactions were carried out in a one-pot and proceeded through a 1,3-dipolar cycloaddition reaction of the chiral dipolarophiles with non-stabilized azomethine ylides which was generated *in situ* by the decarboxylative condensation of isatins with L-proline or sarcosine. Based on the literature review [10], the chiral auxiliary menthyl cinnamate 1 was easily prepared from reaction of cinnamic acid with thionyl chloride; and then reacted readily with chiral menthol to provide chiral non-racemic menthyl cinnamate 1. Three-component reactions between this chiral non-racemic dipolarophile 1, isatin derivatives 2 and L-proline 3 or sarcosine 6 were carried out in ethanol at reflux temperature with excellent yields. As shown in Scheme 1 and 2, condensation of compounds 2 and 3 (or 6) after decarboxylation leads to the non-stabilized azomethine ylides stereogenic centers in one step. Consequently, eight different stereoisomers could have been produced. But, by using this strategy, only diastereoisomer 4 (or 7) were obtained purely in high total yield and high optical purity as shown by TLC, GC–MS and NMR analysis **(**Schemes 1 and 2). After this, other derivatives of this new chiral spirooxindolo(pyrrolizidine/pyrrolizidin e) were synthesized. The results are summarized in Table 1.



Scheme 1. Synthesis of chiral spirooxindolopyrrolidines 4



Scheme 2. Synthesis of chiral spirooxindolo pyrrolizidines 7

Table 1. Synthesis of chiral spirooxindolopyrrolizidines 4 and 7

Entry	R	X	Product	4[a]		7	
				Yield (%)[b]	$[\alpha]_D^{25c}$	Yield (%)[b]	$[\alpha]_D^{25c}$
1	H	H	A	70	-5.4	65	-4.2
2	H	Br	B	75	-6.2	72	-4.3
3	H	NO_2	C	72	-5.8	65	-4.7
4	Me	H	D	65	-5.4	60	-4.4
5	Me	Br	E	70	-5.2	65	-4.5
6	Me	NO_2	F	67	-5.7	60	-4.4
7	Et	H	G	65	-5.2	60	-4.2
8	Et	Br	H	65	-5.7	62	-4.7
9	Et	NO_2	I	72	-5.1	65	-4.3

[a]The reaction was carried out in the ratio of **1**/**2**/**3**/ 1:1: 1.
[b]Isolated yield based on substituted isatins.
[c]$[\alpha]_D^{25}$ (c 1, CH_2Cl_2).

Experimental

General procedure for the synthesis of spirooxindolopyrrolizidines

A magnetically stirred solution of isatin derivatives (**2**) (1 mmol), proline (**3**) or sarcosine (**6**) (1 mmol) and *trans*-cinnamic acid derived from the menthol (**1**) (1 mmol), as chiral auxiliaries, was dissolved in EtOH (10 mL) and stirred at reflux temperature for about 12 h. The solvent was then removed under reduced pressure and the residue was separated by column chromatography (silica gel, Merck 230–400 mesh) using

n-hexane:ethyl acetate (90:10) as eluent.

Results and discussion

The structures of cycloaddition products were assigned by their elemental analysis including, IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data, HMQC, and COSY NMR. Observation of tree characteristic singlet at about (47.6, 53.0 and 61.3) in the ^{13}C NMR spectra of **4** is consistent with the formation of new pyrrolidine cyclic. The stereochemistry and the correct structure of its isomer and other derivatives were determined by ^{1}H NMR, ^{13}C NMR, IR, Mass, HMQC, and (H, H)-COSY. For example, the ^{1}H NMR spectrum of **4a** exhibits a triplet signal at δ=2.60 ppm, a multiplet at δ=3.58 and a multiplet at δ=4.07-4.22 ppm which are related to H*b*, H*c* and H*a* protons respectively. Also DEPT 135^{o} showed signals, corresponding to three (CH) carbons that were directly bonded to H*b*, H*c* and H*a* in the region 47.6, 53.1 and 61.3 respectively. In HMQC spectrum of cycloadduct 4a, the positions of three protons (H*a*, H*b*, and H*c*) that were directly bonded to these carbon atoms (CH) were assigned. Accordingly, the exact chemical shifts of these protons (δH*a*=4.02-4.22, δH*b*=2.60, δH*c*=3.58) were assigned by means of (H-H)-COSY spectrum. Stereochemistry of the **4a** has been assigned from ROESY spectrum. Absence of any correlation between H*a* and H*b* in the ROESY spectrum shows that the H*b* hydrogen could be *trans* to H*a*. But an intense contour between H*c* and H*a* shows these two hydrogen are *trans* to each other. This is also confirmed from the NOE between them. Therefore, the correct stereochemistry could be as shown in scheme 1. The ^{1}H NMR spectrum of 7g exhibits a triplet signal at δ=3.64 ppm and a doblet at δ=4.14 ppm which are related to H*b* and H*a* protons respectively. Also, DEPT 135^{o} of 7g showed signals corresponding to three (CH) carbons that were directly bonded to H*b*, H*c* and H*a* in the region 52.5, 66.5 and 72.6 respectively. Stereochemistry of the 7g has been assigned from ROESY NMR spectrum. Absence of any correlation between H*a* and H*b* in the ROESY spectrum shows that the H*b* hydrogen could be *trans* to H*a*. This is also confirmed from the NOE between them. Therefore, the correct stereochemistry could be as shown in scheame 2. The absolute configuration of spirooxindole 7g was determined by single crystal X-ray analysis (Figure 1).

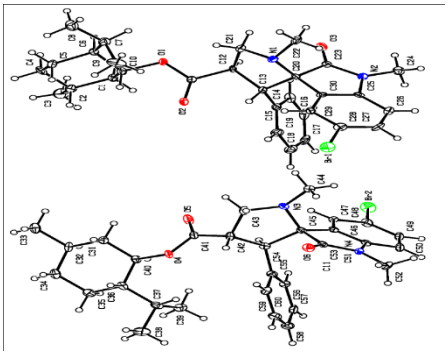


Figure 1. The ORTEP diagram of one of the two crystallographic independent molecules in the asymmetric unit of 7g is shown.Thermal ellipsoids are at 30% probability level

Conclusion

Because of wide distribution in nature and variegated biological activities, chiral pyrrolizidines alkaloids are very attractive synthetic targets. Since a pyrrolizidine can be viewed as a fused

pyrrolidine, the method employed for the formation of pyrrolidine rings can be used to construct the pyrrolizidine ring system. So, the asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides, including pyrrolidine derivatives with olefins, can be the useful method for the synthesis of chiral pyrrolizidines. On the other hand, oxindoles are also structural key moieties in many bioactive substances and it is interesting that systematic investigation has shown that if this moiety is joined to the pyrrolizidine or pyrrolidine ring through a spiro atom at C-3, the resulting compounds show an increased spectrum of biological activity. As a result, we have found a tri- component synthetic method for the prepration of some oxindoles derivatives of potential synthetic interest. The present method carries the advantage that not only the reaction is performed under neutral conditions, but also the starting materials and the reagents can be mixed without any activation or modification.

Acknowledgments

We gratefully acknowledge financial support from the Research Council of Shahid Beheshti and Immam Hossein University.

References

[1] J.W. Daly, T.W. Spande, N. Whittaker, R.J. Highet, D. Feigl, N. Noshimori, T. Tokuyama, C.W. Meyers, *J. Nat. Prod*., **1986**, *46*, 210-214.

[2] W.A. Carroll, P. Grieco, *J. Am. Chem. Soc*., **1993**, *115*, 1164-1165.

[3] T. Okita, M. Isobe, *Tetrahedron*., **1994**, *50*, 11143-11152.

[4] R. Huisgen, in: A. Padwa (Ed.), 1,3-Dipolar Cycloaddition Chemistry, vols. 1 and 2, Wiley, NewYork, **1984**.

[5] N. Asano, *J. Enzyme Inhib*., **2000**, *15*, 215-234.

[6] N. Li, Q. Xia, J. Ruan, P.P. Fu, G. Lin, *Curr. Drug Metab.*, **2011**, *12*, 823-834.

[7] A.R. Suresh Babu, R. Raghunathan, S. Baskaran, *Tetrahedron.*, **2009**, *65*, 2239-2243.

[8] T. Coulter, R. Grigg, J.F. Malone, V. Sridharan, *Tetrahedron Lett.*, **1991**, *32*, 5417-5420.

[9] A.K. Ganguly, N. Seah, V. Popov, C.H. Wang, R. Kuang, A.K. Saksena, B.N. Pramanik, T.M. Chan, A.T. McPhail, *Tetrahedron Lett.*, **2002**, *43*, 8981-9883.

[10] B. Ennis, J. Womack, *Organic Syntheses.*, **1955**, *3*, 714-715.