Синтез спірооксиндопірролізидинів шляхом 1, 3-біполярного циклоприєднання азометан-іліду з арил-вініл-ефірами та вініл-сульфідами

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1,3-біполярне циклоприєднання азометан-іліду широко використовується для утворення складних гетероциклічних систем з відносно простих попередників. Азометин-іліди – це клас потужних реактивів, які використовуються в реакціях [1,3]-біполярного циклоприєднання і є готовими до реагування з різними біполярофілами для утворення пірролідинів та пірролізидинів.

Пірролідини та пірролізидини функціоналізовані з системами спірооксиндолевих кілець являються центральними скелетами для численних алкалоїдів і фармакологічно-важливих сполук. Ці сполуки є також присутніми у багатьох натуральних продуктах.

У цій роботі також представлено частину нашої існуючої дослідницької програми з синтезу різних спірогетероциклів[13], показано процес синтезу нових спірооксиндопірролізидинів через одно-складову трикомпонентну конденсацію азометан-іліду, створеного на місці з ізатину і проліну з похідними арил-вініл-ефіру або вініл-сульфіду.

Сім'я арил-вінил-ефірів і вінил-сульфідів була виготовлена шляхом прямого сполучення різних заміnених фенолів/тіолів з активізованими алкінами у воді в кімнатній температурі. Ці сполуки можна отримати виключно як (Z)-ізомери згідно з процедурою, яка описується в літературі.

Ми помітили, що коли біполярофіли 1a-k піддавалися 1,3-двополюсному циклоприєднанню з азометин ілідом, виготовленим шляхом декарбоксиляційної конденсації ізатину 3 і проліну 4 в етанолі, отримано високий до дуже високого виходу суміші циклоаддуктів 5a-k і 6a-k. Молярне співвідношення регіоізоерів визначено методом ^{1}H ЯМР спектроскопії. Виявилося, що дана реакція є відносно регіоселективною і високостереохімічною в центрі спіралі. Відмічено, що регіоізомери 5a-k були отримані як головні продукти в усіх випадках

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Synthesis of spirooxindolopyrrolizidines through1,3-dipolar cycloaddition of azomethine ylide with aryl vinyl ethers and vinyl sulfides

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The one-pot three-component 1,3-dipolar cycloaddition of the azomethine ylide, which were generated in situ from isatin and proline, with aryl vinyl ethers/vinyl sulfides were afforded spirooxindolopyrrolizidines in excellent yields. The regiochemistry and structures of the cycloadducts were determined with spectroscopic data and by X-ray crystal structure analysis.

Keywords – Aryl vinyl ether; vinyl sulfide; 1,3-dipolar cycloaddition; azomethine ylide; spiro compound; pyrrolizidine.

I. Introduction

The 1,3-Dipolar cycloaddition of azomethine ylides has been used widely to construct complex heterocyclic systems from relatively simple precursors.[1] The 1,3-dipolar cycloaddition reaction of azomethine ylide with olefinic dipolarophiles constitutes a versatile protocol for the synthesis of poly functionalized spiro-heterocycles alkaloids.[2] This mode of cycloaddition simultaneously constructs two carbon-carbon bonds and forms complex ring systems with regio- and stereocontrol.In general, spiro compounds such as pyridines, pyrroles, and pyrazolines display significant biological activities. In particular, spirooxindolopyrrolizidine derivatives have served as potential synthetic intermediates and also act as antiviral, antitumoral and antibiotic agents. Azomethine ylides are a class of powerful reagents used in [1,3]-dipolar cycloaddition reactions, react readily with various dipolarophiles to afford pyrrolidines and pyrrolizidines.[3] Functionalized pyrrolidines and pyrrolizidines with spirooxindole ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds.[4] These compounds are also present in a wide variety of natural products .[5–11]

Due to the above reasons, the synthesis of pyrrolidine and pyrrolizidine-based heterocycles has been the center of attraction for the past several decades.[12]

As a part of our ongoing research program on the synthesis of various spiro heterocycles,[13] herein we report a facile protocol for the synthesis of novel spirooxindolopyrrolizidines via a one-pot, three-component condensation of an azomethine ylide, generated in situ from isatin and proline, with prepared aryl vinyl ether or vinyl sulfid derivatives. (Scheme 1)

II. Results and Discussion

To the best of our knowledge, there has been a little report on the using vinyl ethers as dipolarophiles in [3+2] cycloaddition of azomethine ylide.[14] In this paper, we report the 1,3-dipolar cycloaddition of azomethine ylides with aryl vinyl ethers and vinyl sulfides.

A family of aryl vinyl ethers and vinyl sulfides has been prepared through the direct coupling of various substituted phenols/ thiols with activated alkynes in water at room temperature. (Fig 1).[15] These compounds are obtained exclusively as (*Z*)-isomers according to literature procedure.[15]

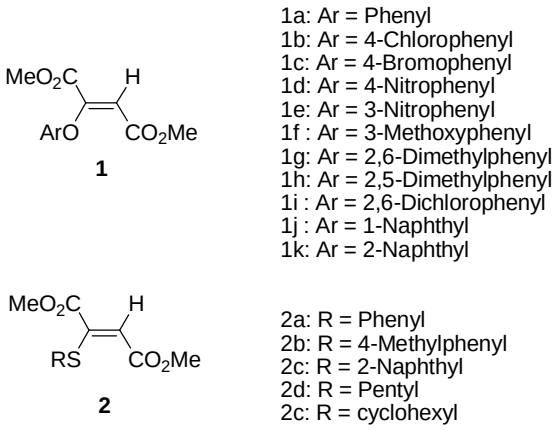
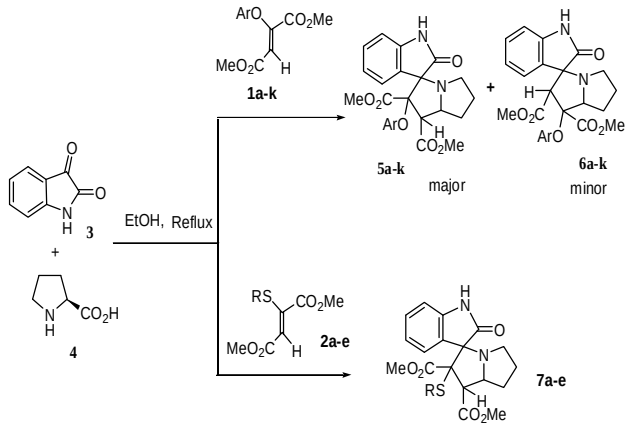


*Fig 1. Structure of substrates **1** and **2***

In this reaction we used (*Z*)-aryl vinyl ethers and (*Z*)-vinyl sulfides as dipolarophiles for spirooxindoles. We observed that when the dipolarophiles **1a–k**, were subjected to 1,3-dipolar cycloaddition with the azomethine ylide generated by decarboxylation condensation of isatin **3** and proline **4** in ethanol, a mixture of cycloadducts **5a–k** and **6a–k** was obtained in good to excellent yields (Scheme 1). A neat reaction carried out by refluxing the dipolarophiles **1a–k** with 1 mmol of isatin **3** and 1 mmol of L-proline **4** in ethanol, led to cycloadducts **5a–k** as the major products and **6a–k** as the minor products.



Scheme 1. Regioselective Synthesis of spirooxindolo pyrrolizidines 6a-n and 7a-n

The molar ratio of regioisomers was determined by ^{1}H NMR spectroscopy. The reaction was found to be relative regioselective and highly stereochemistry at the spiro centre. It is noted that regioisomers **5a–k** were obtained as major products in all cases (Table 1).

Table 1

1,3-Dipolar cycloaddition reaction of aryl vinyl ether 1a-k with isatin 3 and L-proline 4

Entry	substrate	Products	Yiled[a]%	Regioisomer ratio[b] (5:6)
1	**1a**	**5a + 6a**	94	65:34
2	**1b**	**5b + 6b**	89	54:46
3	**1c**	**5c + 6c**	85	74:26
4	**1d**	**5d + 6d**	88	54:46
5	**1e**	**5e + 6e**	87	56:44
6	**1f**	**5f + 6f**	89	58:42
7	**1g**	**5g + 6g**	86	57:43
8	**1h**	**5h + 6h**	90	59: 41
9	**1i**	**5i + 6i**	89	63:37
10	**1j**	**5j + 6j**	95	67:32
11	**1k**	**5k + 6k**	90	64:36

[a] Combind yield of isolated cycloadducts.
[b] Determind by ^{1}H NMR spectroscopy.

The structures and the regiochemistry of the cycloadducts were confirmed by spectroscopic data. The ^{1}H NMR spectrum of the cycloadduct **5a** showed a doublet at σ 3.94 ppm (J=10.0 Hz) for the -CH proton of the pyrrolizine ring system. The -NCH proton of the pyrrolizine ring appeared as multiplet at σ 4.83ppm. The structure of product **5a** was further confirmed by mass spectrometry which showed a molecular ion peak at m/z 436.

The ^{1}H NMR spectrum of pyrrolizidinoxindole derivative **6a** demonstrated a singlet at σ 4.66 ppm due to -CH proton of the pyrrolidine ring system and a multiplet at σ 4.61ppm for the -NCH proton.

The stereochemical outcome of the cycloaddition was determined by a single X-ray crystal structure of cycloadduct 5d (Fig. 2). The stereochemistry of cycloadducts is consistent with a *S*-shaped ylide and subsequent cycloaddition by an *endo*-transition state. However, the cycloadduct corresponding to exo-TS was not observed.

Attempts were also made to carry the reaction using dimethyl (*Z*)-2-(phenylthio)-2-butenedioate as dipolarophile and we found that cycloadduct **7a** was obtained in excellent yield in shorter time. No trace of the other regioisomer was obtained.(Table II, entry 1) A similar

trend was observed for all the derivatives when we replaced aryl vinyl ethers **1** with vinyl sulfides **2** as 2π component.(Scheme 1, Table 2) The reaction was very rapid and completed in 1-2 min, as indicated by TLC. The formation of the cycloadducts was confirmed by spectroscopic techniques.

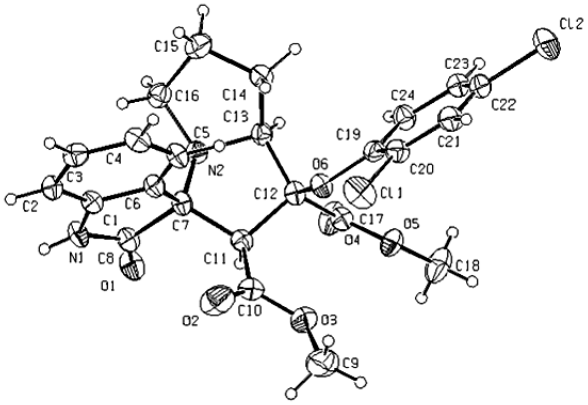


Fig. 2. ORTEP diagram of ***5d***

Table 2

1,3-Dipolar cycloaddition reaction of vinyl sulfide 2a-e with isatin 3 and L-proline 4

Entry	substrate	Products	Yiled[a]%
1	**2a**	**7a**	94
2	**2b**	**7b**	89
3	**2c**	**7c**	85
4	**2d**	**7d**	88
5	**2e**	**7e**	87

[a] Isolated yield.

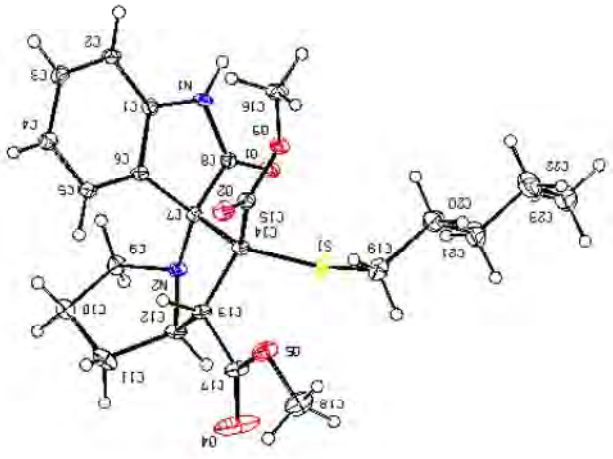


Fig. 3. ORTEP diagram of ***7d.***

The ^{1}H NMR spectrum of compound **7a** exhibited a doublet at σ 3.95ppm (J = 10 Hz) for the -CH proton of the pyrrolidine ring system and a multiplet at σ 4.77ppm for -NCH proton. The structure of product **7a** was further confirmed by mass spectrometry which showed a molecular ion peak at m/z 452. The regio- and stereochemical outcome of the cycloaddition was confirmed by X-ray crystallography of the cycloadduct **7d**. (Fig. 3) The stereochemistry of cycloadducts is consistent with a *S*-shaped ylide and subsequent cycloaddition by an *exo*-transition state. However, the cycloadduct corresponding to exo-TS was not observed.

III. Conclusion

In summary, we report a simple one-pot three-component protocol for a facile transformation of the aryl vinyl ethers and vinyl sulfides into spirooxindolopyrro-lizidines moiety through the1,3-dipolar cycloaddition reaction of the azomethine ylide generated from isatin and secondary amino acid, proline, in good to excellent yields

IV. Acknowledgments

We are grateful for the financial support of University of Mazandaran, Islamic Republic of Iran.

V. Experimental

General Considerations

All melting points are uncorrected. Infrared spectra were recorded on a Shimadzu IR-8300 series FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recordrd on a Bruker 500 and 300-MHz instrument in CDCl3 and DMSO solvent with TMS as a standard. Mass spectra were recorded by a Jeol DX303 HF mass spectrometer. Elemental analyses were carried out by Perkin-Elmer CHNS 2400 instrument. An Endraf-Nonius CHD4 diffractometer and Smart CCD Area diffractometer were used to perform X-ray diffraction data collection. Column chromatography was performed on silica gel (Acme, 100–200 mesh). Routine monitoring of the reaction was made using thin-layer chromatography (TLC) developed on glass plates coated with silica gel-G (Acme) 25 mm thick and visualized with iodine.

Typical procedure for the synthesis of spirooxindolopyrrolizidines:

A mixture of isatin (0.147 g, 1 mmol), proline (0.115 g, 1 mmol), and dimethyl 2-phenoxymaleate (0.236 g, 1 mmol) in ethanol (10 mL) was stirred at reflux for 2-3 min. After completion of the reaction, as indicated by TLC, and cooling the reaction mixture, the precipitated solid was separated by filtration, which contained mixture of two regioisomers **5a** and **6a**. The molar ratio of **5a/6a** was determined by ^{1}H NMR spectroscopy. However, the pure cycloadducts **5a** was obtained by recrystallization from ethanol and the products **6a** were purified on a silica-gel plate or column chromatography(eluent hexa-ne/ethyl acetate 1:1). The structures and the regioche-mistry of the cycloadducts were confirmed by spectrosco-pic data.

Spiro-[2.3']oxindole-3-methoxycarbonyl-3-pheno-xy-4-methoxycarbonyl-hexahydro-1H-pyrrolizine(5a). White solid, ^{1}H NMR (400 MHz, $CDCl_3$): σ = 9.17 (s, 1H, NH), 6.85 -7.30 (m, 9H, Ar-H), 4.82 (q, 1H, J= 8 Hz, N-CH), 3.85(d, 1H, J= 10.4 Hz, H pyrrolizine), 3.42 (s, 3H,

OMe), 3.01(s, 3H, OMe), 1.67-2.84 (m, 6H, pyrrolizine). ^{13}C NMR (75 MHz, $CDCl_3$): σ =176.52, 169.23, 167.72, 156.09, 141.96, 130.23, 128.92, 126.80, 123.80, 122.09, 121.72, 117.96, 117.47, 110.46, 97.91, 79.04, 66.95, 54.84, 52.09, 47.51, 31.31, 28.24. IR (KBr, cm^{-1}) ν =3195, 2983, 1746, 1617, 1494, 1290, 1210. Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.89; H, 5.48; N, 6.39; MS *m/z* = 436.1 (M+)

Spiro-[2.3']oxindole-3-methoxycarbonyl-4-methoxycarbonyl-4-phenoxy-hexahydro-1H-pyrrolizine(6a) White solid, ^{1}H NMR (400 MHz, CDCl3): σ= 8.79 (s, 1H, NH), 6.93- 7.63 (m, 9H, Ar-H), 4.56 (t, 1H, J= 7.6 Hz, N-CH), 4.55(s, 1H, H pyrrolizine), 3.68 (s, 3H, OMe), 3.32(s, 3H, OMe), 1.91-2.74 (m, 6H, pyrrolizine). ^{13}C NMR (75 MHz, $CDCl_3$): σ =177.37, 168.83, 167.57, 141.70, 135.72, 131.31, 130.25, 128.77, 128.50, 126.61, 125.32, 121.99, 110.66, 78.45, 72.75, 65.66, 55.26, 51.96, 51.56, 47.47, 32.01, 28.99. IR (KBr, cm^{-1}) ν =3187,2951, 1747, 1610, 1490, 1240. Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.89; H, 5.48; N, 6.39; MS *m/z* = 436.1 (M+)

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