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Regioselective Three Component Domino Synthesis of Polyhydrospiro[indoline-3,3'-pyrrolizine]-2-one *via* [3+2] Cycloaddition Reaction

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In present work, we have reported the synthesis and characterisation of novel hexahydrospiro[indoline-3,3′-pyrrolizine]-2-one derivatives in good to excellent yields *via* [3+2] cycloaddtion reaction in regioselective manner. These compounds were synthesized *via* multicomponent reaction of substituted 3-cinnamoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, isatin, L-proline at room temperature. All the synthesized hexahydrospiro molecules were characterized by ^{1}H and ^{13}C NMR, IR spectra, mass spectra and elemental analysis. Regioselectivity in synthesized molecules were also explained on the basis of secondary orbital interactions. A simple and facile methodology is developed which has great importance in synthetic chemistry.

Keywords: Spiropyrrolidine, Dehydroacetic acid, Isatin, Multicomponent reaction, Cycloaddition.

INTRODUCTION

In the past several years, significant advances have been achieved on the development of new synthetic methods to access spiroindole derivatives. Spiro compounds with attached indole moiety having all-carbon quaternary stereogenic center has attracted synthetic organic chemists due to its fascinating structure and biological importance [1-3]. These polyhydro heterocyclic compounds are important targets among synthetic as well as medicinal chemist due to its wide range of pharmacological properties. Spiroindoles and their derivatives have facile structural similarity the core unit of many naturally occurring molecules that possess significant biological activities, which include spasmolitic, diuretic, anticoagulant, anticancer, and antianaphylactic activities [4].

Therefore, a number of protocols have been developed to synthesize these structural frameworks *via* cycloaddition reaction [5]. The [3+2] cycloadditions have special place in synthetic chemistry as well for theoretical chemist because it constitutes one of the most fundamental reactions for regioselective construction of 5-membered heterocyclic compounds [6-8]. The reaction of azomethine ylides with various dipolarophils forms highly substituted pyrrolidines derivatives [9,10]. Enhancing the efficiency and manoeuvrability of reaction is a challenge in organic synthesis. For a molecule with fascinating structure and excellent pharmacological properties always promotes synthetic chemists to develop easy and ecofriendly synthesis [11]. Spirocyclic systems containing one carbon atom common to two rings are structurally interesting and asymmetric characteristic of the molecule due to the chiral spiro carbon which is one of the important criteria of the biological activities [12,13]. The presence of sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [14]. The spirooxindole ring system forms the core structure of many pharmacological agents and alkaloids [15]. For example, spirotryprostatin (Fig. 1), a natural product isolated from the fermentation of *Aspergillus funigatus*, has been identified as a novel inhibitor of microtubule assembly [16]. Natural product isopteropodine [17] (Fig. 1) has been shown to modulate the function of muscarinic and serotonin receptors. It has been observed that incorporation of more than one bioactive heterocyclic moiety into a single framework may result into the production of novel heterocycles with enhanced bioactivity [18-20]. Spirooxindoles have been reported to behave as aldose reductase,

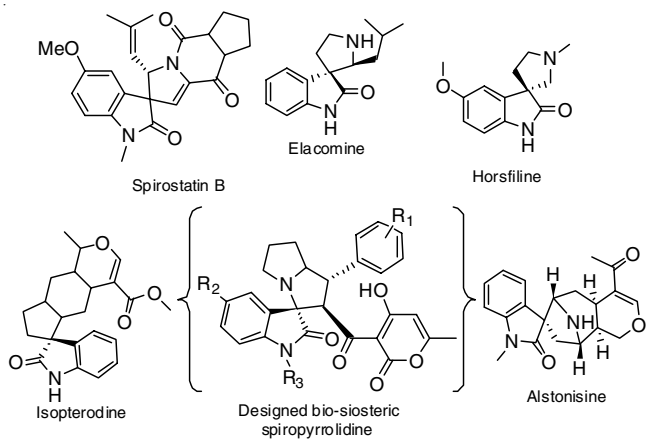


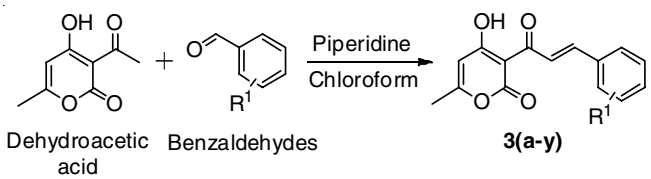
Fig. 1. Representatives of spiroindole containing compounds

polio virus and rhino virus 3C-proteinase inhibitors [21]. Inspired from these excellent pharmacological properties and structurally complex nature of these spiro compounds, here we wish to report some new bioisosetric analogues of natural spiropyrrolidines *via* [3+2] cycloaddition reaction.

EXPERIMENTAL

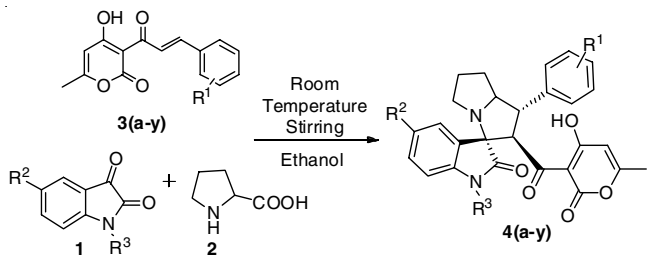
All the reactions were carried out at room temperature, under ultrasound and microwave condition. Unless otherwise specified, all the reagents were purchased from Sigma-Aldrich Chemical Co, Lancaster and used directly without further any purification. NMR spectra were obtained using Brucker DRX 300MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were taken on VARIAN FT-IR spectrometer as KBr pellets (when solid). Elemental analysis was preformed using a Perkin Elmer Autosystem XL Analyzer. Melting points were measured using a COMPLAB melting-point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

General procedure for synthesis of chalcone analogues (3): Chalcone analogues were synthesized *via* aldol condensation of substituted benzaldehyde and dehydro acetic acid. In dry chloroform substituted benzaldehyde (1.0 mmol), dehydroacetic acid (1.0 mmol) in the presence of catalytic pyrrolidine (20 mol %) was taken. Reaction was stirred at room temperature for 2 h leading to generation of chalcone. Progress of reaction was monitored by TLC. After completion of reaction solvent was evaporated under the reduced pressure and residue was extracted with ethyl acetate and water. The organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum on a rotary evaporator (**Scheme-I**).



Scheme-I: Synthesis of substituted 3-cinnamoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one

General procrdure for synthesis of compounds (4a-y) (method A): Isatin (147 mg, 1.0 mmol), L-proline (115 mg, 1 mmol) and chalcone derivatives (1 mmol) was taken in 50 mL round bottom flask follwed by the addition of 10 mL of ethanol. Reaction mixture was allowed to stir at room temperature. The progress of reaction was monitored by TLC. After completion of rection, solvent was evaporated under vaccum and poured in ice-water. Solid residue was filtered off and recrystallized in ethanol (**Scheme-II**).



Scheme-II: Synthesis of novel hexahydrobenzo[*b*][1,8]naphthyridines

2′-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-carbonyl)-1′-(3-methoxyphenyl)-1-propyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (4a): White solid; m.p. 180 ºC; IR (KBr, ν_{max}, cm^{-1}): 3621, 3020, 2971, 1720, 1604, 1216, 1043. ^1H (300 MHz, $CDCl_3$): δ 10.97 (s, 1H,), 7.21 (s, 1H), 7.20-7.04 (m, 4H), 6.80-6.72 (m 3H,), 5.68 (s, 1H), 4.91 (d, 1H, *J* = 9.4 Hz), 4.57 (t, 1H, *J* = 8.14 Hz), 4.48 (t, 1H, *J* = 9.9 Hz), 3.79 (s, 3H), 3.64 (t, 2H, *J* = 7.5 Hz), 2.58 (t, 1H, *J* = 7.62 Hz,), 2.28 (s, 3H), 2.14-1.73 (m, 5H), 1.22-1.15 (m, 2H), 1.00 (t, 3H, *J* = 4.3 Hz). ^{13}C NMR (75MHz, $CDCl_3$): δ 13.7, 22.5, 23.2, 33.4, 38.9, 41.6, 49.7, 51.2, 55.8, 63.4, 65.8, 72.3, 101.5, 103.1, 111.5, 114.8, 116.1, 117.2, 118.4, 119.4, 122.5, 126.6, 129.2, 131.9, 134.4, 140.9, 144.3, 157.8, 163.2, 184.7, 204.4; MS (ES): *m/z* (%) 529.1(100) $[M+1]^+$. Anal. calcd. (found) % for $C_{31}H_{32}N_2O_6$: C, 70.44 (70.39); H, 6.10 (6.05); N, 5.30 (5.20).

RESULTS AND DISCUSSION

Our synthetic journey begins by synthesizing a series of different substituted 3-cinnamoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3a-y**) as substrate for cycloaddition reaction by condensation of dehydroacteic acid and substituted benzaldehydes *via* Claisen-Schmidt condensation reaction. Further, efforts were made for synthesis of spiroindoles. Our first objective was to find optimum reaction condition. We started study in search of best solvent for synthesis of spiropyrrolidines (**4a-y**). To achieve this goal the reaction of (*E*)-4-hydroxy-3-(3-(2-methoxyphenyl)acryloyl)-6-methyl-2*H*-pyran-2-one (**3a**), isatin (**1**) and L-proline (**2**) was taken as the model reaction. Various solvents such as methanol, dichloromethane, ethanol, acetonitrile, chloroform, benzene and DMSO were explored to check the feasibility of reaction. To our delight, product **4a** was formed in excellent yield. Whereas yield of product was not satisfactory with other solvents, even at refluxing condition and prolonged reaction time. Hence ethanol was chosen as the solvent for reaction. The results are summarized in Table-1.

After optimizing appropriate solvent for reaction, to verify general procedure for synthesis of spirooxindole we carried out reaction with different 3-cinnamoyl-4-hydroxy-6-methyl-

TABLE-1
SYNTHESIS OF HEXAHYDROSPIRO[INDOLINE-3,3'-PYRROLIZIN]-2-ONE DERIVATIVES

S. No.	Compound	R^1	R^2	R^3	Method A (room temperature)		m.p. (°C)
					Time (h)[c]	Yield (%)[b]	
1	**4a**	3-OMe	H	$(CH_2)_2CH_3$	5.0	89	180
2	**4b**	2-Cl	H	CH_2Ph	4.5	90	191
3	**4c**	4-F	H	H	4.0	90	184
4	**4d**	4-F	H	$(CH_2)_2CH_3$	4.0	90	181
5	**4e**	4-OMe	H	H	4.0	90	186
6	**4f**	3-OH	H	$(CH_2)_3CH_3$	4.0	82	167
7	**4g**	2-OMe	H	$(CH_2)_2CH_3$	4.0	86	182
8	**4h**	4-NO_2	H	$(CH_2)_2CH_3$	3.0	86	163
9	**4i**	3,4-$(OCH_3)_2$	H	$(CH_2)_2CH_3$	4.5	87	174
10	**4j**	3-OMe	H	CH_2Ph	4.0	89	169
11	**4k**	4-F	H	CH_2CH_3	3.0	94	182
12	**4l**	4-F	H	$(CH_2)_3CH_3$	3.0	94	186
13	**4m**	3-OH,4-OCH_3	H	H	4.5	90	206
14	**4n**	3-OH,4-OCH_3	H	CH_2CH_3	4.5	89	201
15	**4o**	4-Cl	H	H	3.5	91	176
16	**4p**	3-OH	H	H	4.0	87	181
17	**4q**	4-F	H	CH_3	3.0	93	186
18	**4r**	4-NO_2	H	CH_2Ph	3.5	90	197
19	**4s**	2-Cl	H	CH_3	3.5	91	188
20	**4t**	2-OMe	H	H	5.0	91	159
21	**4u**	4-Me	NO_2	$(CH_2)_3CH_3$	5.0	88	186
22	**4v**	4-OH	H	$(CH_2)_2CH_3$	5.5	89	159
23	**4w**	3-Cl	H	H	5.0	92	184
24	**4x**	4-NO_2	H	CH_3	3.0	88	181
25	**4y**	H	H	H	4.5	83	147

Method A = Reaction at room temperature

2*H*-pyran-2-one derivatives (**3a-y**), isatin (**1**) and L-proline (**2**) by stirring at room temperature (method A) to afford a series of novel spiroindoles (**4a-y**) in excellent yields. The results are summarized in Table-2.

TABLE-2
OPTIMIZATION OF SOLVENTS

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	Methanol	RT	4	78
2	Dichloromethane	Reflux	14	18
3	Ethanol	RT	2	94
4	THF	Reflux	10	32
5	Acetonitrile	Reflux	14	30
6	Chloroform	Reflux	14	10
7	Benzene	Reflux	14	28
8	DMSO[b]	60	40 min	73

[a]Isolated yields of purified fractions; [b]Reaction under microwave condition.

The structures of products were confirmed by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and elemental analysis). All the spectral data were in good support with the illustrated structure of spiroindole derivatives. This cycloaddition reaction proceeds *via* intermediate formation of azomathine ylide (Fig. 2). The regioselectivity of synthesized spiroindole derivatives were explained on the basis of secondary orbital interaction. It is evident from Fig. 2 that the approach of ylide to dipolarophile can lead to formation of transition state **5a** and **5b** leading to product **4a-y**, but predominantly forms transition state **5a**. This can be attributed to considering regioselective approach of HOMO of dipole to the LUMO of dipolarophile in path-A with secondary orbital interaction

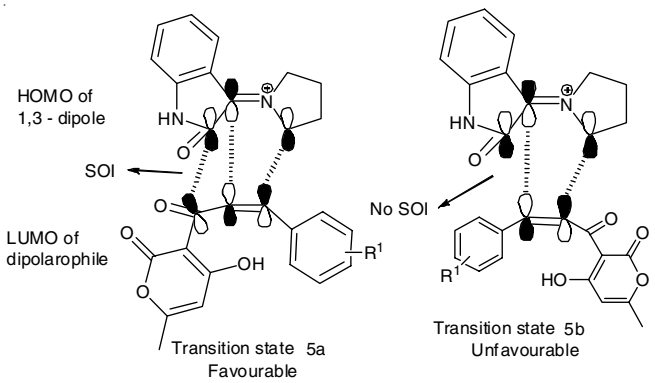


Fig. 2. Plausible transition states for 1,3-dipolar cycloaddition reaction

(SOI) between orbital of carbonyl group in dipolarophile with those of dipole. Hence formation of product **5a** is more favourable in comparison to **5b**.

After characterizing the synthesized spiroindole derivatives, to explore the effect of substituent on the reactivity of cycloaddition we used different groups at R^1 position. It was found that substituent with negative inductive effect tends to facilitate the reaction. As with N,N-dimethyl group at R^1 position decrease the reaction rate to such a extent that reaction does not complete even after heating at 80 ºC and product formed in low yield. Whereas with nitro and halogens at that positions activates the reaction and reaction complete within 3 h at room temperature and in 20 min under ultrasonic condition.

Conclusion

In conclusion, a facile synthesis of 22 membered library of hexahydrospiro[indoline-3,3′-pyrrolizine]-2-one derivatives

via [3+2] cycloaddition using isatin and L-proline and a pyran-2-one moiety in regioselective manner at room temperature is demonstrated. This method provides an easy access to novel five membered heterocyclic frameworks in regioselective manner, which are major building blocks of many natural products and may become a potential pharmacologically active nucleus in near future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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