RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

One-pot four component domino strategy for the synthesis of novel spirooxindole pyrrolizine linked 1,2,3-triazoles *via* stereo- and regioselective [3+2] cycloaddition reaction in acidic Medium.

Rajeswari M., Sudesh Kumari and Jitender M. Khurana*

Department of Chemistry, University of Delhi, New Delhi - 110 007, India.
Corresponding author: Fax: +91 11 27666605; Tel: +91 11 27667725.
Email: jmkhurana1@yahoo.co.in

Abstract

An efficient, one-pot four component condensation procedure for the synthesis of selective spirooxindole pyrrolizine linked 1,2,3-triazole conjugates *via* [3+2] cycloaddition has been reported by coumarin-3-carboxylic acid (**1**), *N*-propargylated isatin (**2**), *L*-proline/ sarcosine (**3**) and aryl azides (**4**) using Cu(I) as a catalyst in the presence of glacial CH_3COOH at 60 ^oC. The structures of the compounds synthesized herein were confirmed by ^1H NMR, ^{13}C NMR, Mass spectra and X-ray crystallographic techniques.

Keywords: Spirooxindole pyrrolizine, 1,2,3-triazole, [3+2] cycloaddition, Azomethine Ylides.

Introduction

In biology-oriented synthesis, the underlying scaffold classes of natural products are useful starting points for the synthesis of compounds with focused structural diversity.[1] Oxindole or spirooxindole[2] core structures represent interesting synthetic challenge due to their biological activity in natural products such as spirotryprostatins A and B,[3] horsfiline,[4] rhynchophylline,[5] formosanine[6] and elacomine[7,8] (Fig.1). Also, coumarin containing natural products[9] as well as its synthetic hetero fused analogs are endowed with wide array of biological properties which

include antidiabetic,[10] anticoagulant,[11] anticancer,[12] antitubercular,[13] anti-HIV[14] and AChE inhibition.[15] 1,2,3-Triazole based heterocycles exhibit important biological activities such as antiviral, agonist, antibacterial, anti-HIV, DNA labeling, etc.[16] One of the most efficient approaches for the synthesis of 1,2,3-triazole framework is the 1,3-dipolar cycloaddition reaction of azides with alkynes.[17]

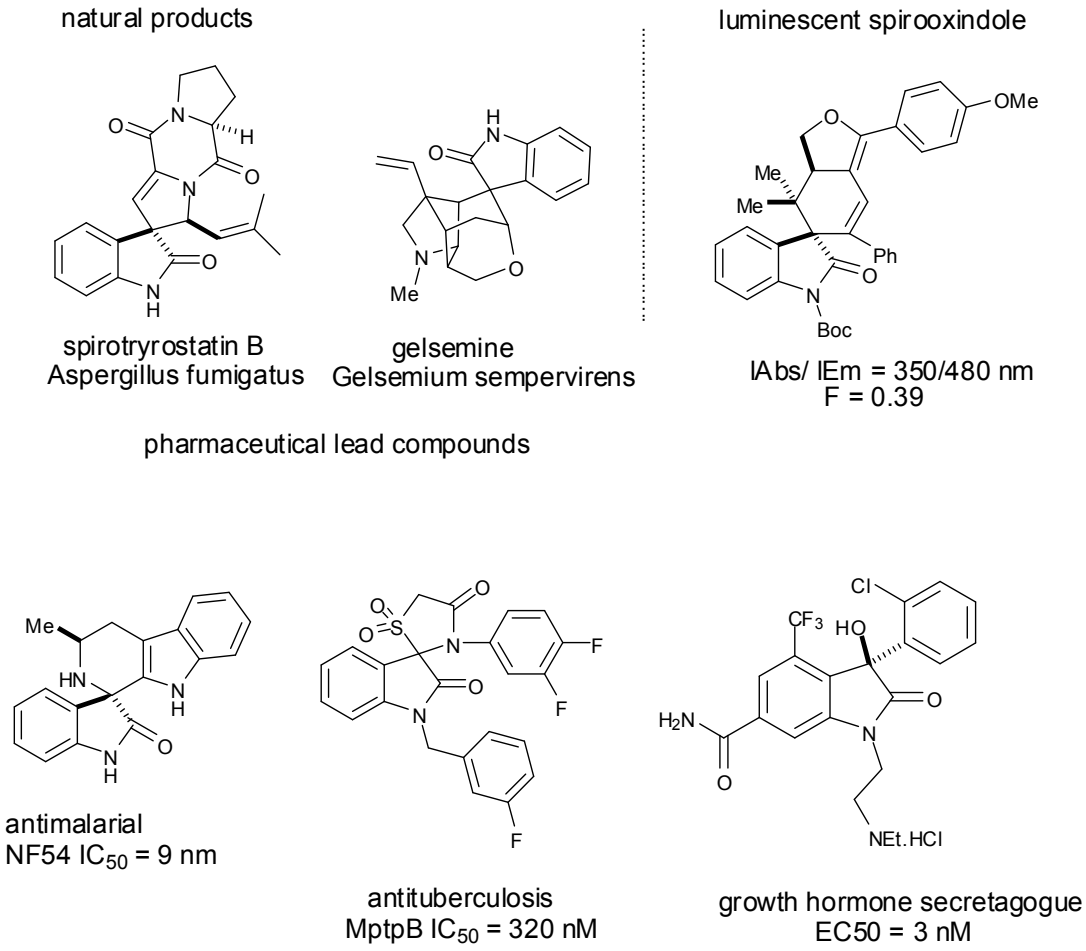


Figure 1: Examples of natural products, pharmaceutical leads, and luminescent molecules containing an oxindole or spirooxindole core structure.

In continuation of our interest in the synthesis of novel heterocycles employing multicomponent reactions[18] we decided to explore a new protocol for the synthesis of novel spirooxindole pyrrolizine linked 1,2,3-triazole conjugates *via* [3+2] cycloaddition reaction by

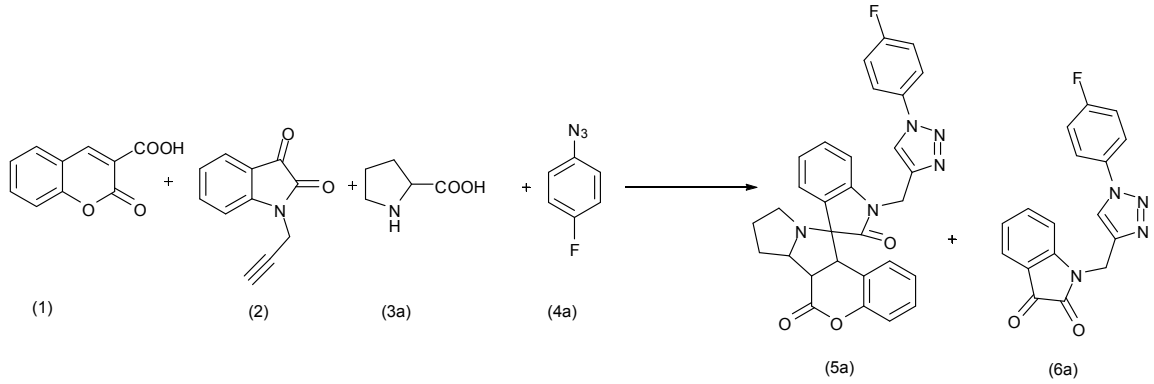
one-pot four component condensation of coumarin-3-carboxylic acid, *N*-propargylated isatin, *L*-proline/ sarcosine and aryl azides.

Results and discussion

The present manuscript describes a first protocol for the synthesis of novel coumarin fused spirooxindole pyrrolizine linked 1,2,3-triazole conjugates *via* one-pot, four component condensation of coumarin-3-carboxylic acid (**1**), *N*-propargylated isatin (**2**), *L*-proline (**3a**)/ sarcosine (**3b**) and aryl azides (**4**) using Cu(I) as catalyst in glacial CH_3COOH as reaction medium at 60 ^oC. The condensation involves two sequential [3+2] cycloaddition reactions of azide-alkyne and azomethine ylide-alkene, in one-pot to give the desired products.

The four component condensation of coumarin-3-carboxylic acid (1.0 mmol) (**1**), *N*-propargylated isatin (1.0 mmol) (**2**), *L*-proline (1.0 mmol) (**3a**) and 4-fluorophenyl azide (1.0 mmol) (**4a**) was examined in different solvents and also under solvent-less condition in presence of Cu(I) and acid catalyst. Initially, this four component reaction was attempted in MeOH: H_2O (1:1, v/v) at 80 ^oC in presence of aq. solution of $CuSO_4.5H_2O$ (10 mol%) and aq. solution of sodium ascorbate (20 mol%) in glacial CH_3COOH (10 mol%) as catalyst. The reaction was complete after 3 h, but yielded a mixture of products as evident by TLC using ethyl acetate: petroleum ether (30:70, v/v) as eluent. The reaction was quenched by water. The solid so obtained after filtration was subjected to flash column chromatography. Two different products were separated from column chromatography and characterized as 1-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione **(6a)** in 16% yield and 1'-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-

a]pyrrolizine-11,3'-indoline]-2',6(6*aH*,11*aH*)-dione (**5a)** in 52% yield (Scheme 1) by spectroscopic analysis (Table 1, entry 1).



Scheme 1: Synthesis 1'-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-*a*]pyrrolizine-11,3'-indoline]-2',6(6*aH*,11*aH*)-dione (5a)

The yield of our desired product **5a**, however, was only 52%. In order to achieve high reaction yield in less time the same model reaction was further explored with different acid catalysts like conc. HCl, conc. H_2SO_4 and *p*-TSA (10 mol%) in presence of Cu(I). All the reactions were incomplete even after 3 h and yielded 41, 35 and 38% of **5a** along with traces of **6a**, respectively (Table 1, entries 2-4). The above reaction was attempted in water at 100 ^oC using glacial CH_3COOH (10 mol%) as catalyst under otherwise identical conditions, was also incomplete after 3 h, but afforded 31% of **5a** after separation (Table 1, entry 5). The reaction was attempted using glacial CH_3COOH (10 mol%) as catalyst in the absence of any solvent at ambient temperature. The reaction was found to be complete in 90 min and afforded the desired product **5a** in 72% of yield (Table 1, entry 6). Subsequently, the same reaction was attempted at 60 ^oC. The reaction was complete in 35 min and yielded the desired product **5a** in 89% after a simple work-up (Table 1, entry 7). The above reaction was performed using 20 mol% of glacial CH_3COOH was complete in 60 min and gave 88% of **5a** (Table 1, Entry 8). The reaction was also attempted in [NMP]H_2PO_4 and [bmim]HSO_4 as catalyst in an analogous manner but

resulted in formation of mixture of products (Table 1, entries 9-10). All these results are compiled in Table 1.

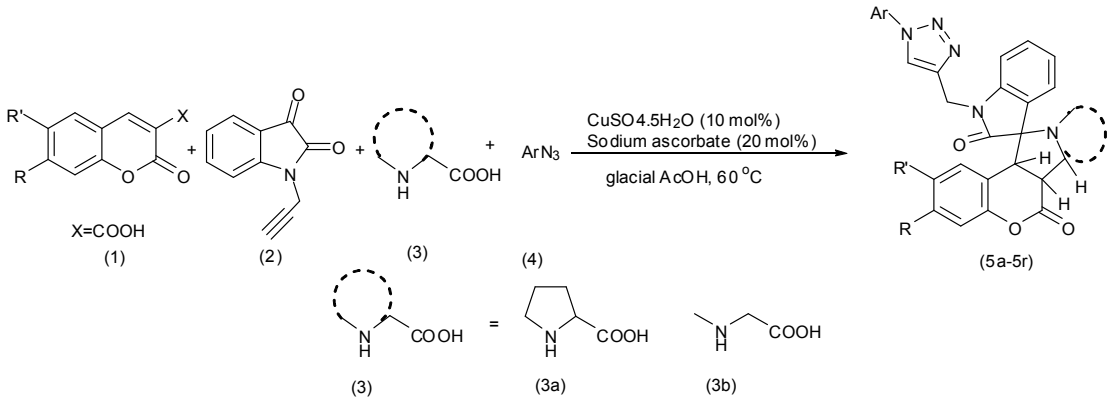
Table 1: Optimization of reaction conditions for the synthesis 1'-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-*a*]pyrrolizine-11,3'-indoline]-2',6(6*aH*,11*aH*)-dione **(5a)**

Entry	Solvent	Catalyst [a]	Catalyst (mol %)	Temp.(°C)	Time (min.)	Yield (%)
1	MeOH:H_2O	CH_3COOH	10	80	180	52[b]
2	MeOH:H_2O	HCl	10	80	180	41[b]
3	MeOH:H_2O	H_2SO_4	10	80	180	35[b]
4	MeOH:H_2O	*p*-TSA	10	80	180	38[b]
5	H_2O	CH_3COOH	10	100	120	31[b]
6	-	CH_3COOH	10	RT	90	67
7	-	CH_3COOH	10	60	35	89
8	-	CH_3COOH	20	60	35	88
9	-	$[NMP]H_2PO_4$	10	60	120	27[c]
10	-	$[BMIM]HSO_4$	10	60	120	23[c]

[a] aq. $CuSO_4$. $5H_2O$ (10 mol%) and aq. Sodium ascorbate (20 mol%) were added in all reactions.
[b] Incomplete.
[c] Mixture of products.

Thus, condensation of one-pot four components protocol using $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%) in 10 mol% of glacial CH_3COOH at 60 °C proved to be the optimum reaction condition. Subsequently, reactions were carried out with differently

substituted aryl azides. All the reactions were facile with both electron rich and electron deficient aryl azides and afforded the desired products **5a-5f** in high yields (Table 2, entries 1-6). Further, with a view to extend the scope of the above one-pot four component protocol, coumarin-3-carboxylic acid was replaced with 7-hydroxy coumarin-3-carboxylic acid and 6-bromocoumarin-3-carboxylic acid. The reactions were carried out under otherwise identical conditions. All the reactions proceeded smoothly and afforded corresponding triazoles containing spirooxindole pyrrolizines **5g-5k** and **5l-5p** in high yields (Table 2, entries 7-16). Subsequently, the scope of reaction was investigated with sarcosine (**3b**) also in place of *L*-proline (**3a**) under otherwise identical conditions. The reactions were complete and yielded corresponding triazole containing spirooxindole pyrrolidines **5q-5r** (Table 2, entries 17-18). Structural assignments have been made on the basis of IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.



Scheme 2: Synthesis of 1'-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-*a*]pyrrolizine-11,3'-indoline]-2',6(6a*H*,11a*H*)-diones **(5a-5r)**

Table 2: Synthesis of 1'-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-*a*]pyrrolizine-11,3'-indoline]-2',6(6a*H*,11a*H*)-diones [a]

Entry	R	R'	3	Ar	Time (min.)	Product	Yield (%)
1	H	H	**3a**	4-FC_6H_4	35	**5a**	89
2	H	H	**3a**	4-$(OCH_3)C_6H_4$	45	**5b**	85
3	H	H	**3a**	4-$(NO_2)C_6H_4$	35	**5c**	90
4	H	H	**3a**	4-$(CH_3)C_6H_4$	50	**5d**	86
5	H	H	**3a**	7-Chloroquinoline	40	**5e**	89
6	H	H	**3a**	4-BrC_6H_4	35	**5f**	85
7	OH	H	**3a**	4-FC_6H_4	35	**5g**	87
8	OH	H	**3a**	4-BrC_6H_4	35	**5h**	88
9	OH	H	**3a**	4-$(NO_2)C_6H_4$	30	**5i**	83
10	OH	H	**3a**	4-$(CH_3)C_6H_4$	45	**5j**	86
11	OH	H	**3a**	4-ClC_6H_4	35	**5k**	87
12	OH	H	**3a**	7-Chloroquinoline	35	**5l**	90
13	H	Br	**3a**	4-ClC_6H_4	30	**5m**	89
14	H	Br	**3a**	4-BrC_6H_4	35	**5n**	88
15	H	Br	**3a**	7-Chloroquinoline	35	**5o**	85
16	H	Br	**3a**	4-$(OCH_3)C_6H_4$	45	**5p**	84
17	H	H	**3b**	4-$(CH_3)C_6H_4$	65	**5q**	71
18	H	H	**3b**	4-$(NO_2)C_6H_4$	55	**5r**	78

[a] All the reactions carried out in glacial CH_3COOH at 60 ^oC in presence of $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%).

The two-dimensional NMR spectra of HMBC and COSY correlations are useful in the signal assignment of **5a**, and various characteristic signals are shown in Fig. 2. The ^{1}H NMR spectrum of **5a** revealed quartet at δ 4.67-4.55 for two protons of N-CH_2. A doublet at δ 4.14 (J = 11.45 Hz) can be readily assigned to 11-CH on the basis of its multiplicity. From the H,H-COSY of 11-CH, the doublet of doublet at δ 3.40 (J = 11.22, 2.75 Hz) is due to 6-CH. The coupling constant value of 11.45 and 11.22 Hz suggests that 11-H and 6-H are *cis* to each other (Fig. 2). Further, it is evident from the H,H-COSY of 6-CH that the triplet of doublet at δ 4.43 ppm ($^{3}J_{H\text{-}H}$ = 7.42, 3.66 Hz) accounting for one proton is due to 7-CH. Aromatic protons appeared as a multiplet in the region of δ 7.77-6.04. One proton at C-4' carbon of triazole appears at δ 7.48 which confirms the formation of triazole ring. Nine aliphatic protons of pyrrolizine protons appeared in the region of δ 4.42-1.57. Further, the off-resonance decoupled ^{13}C NMR of the product exhibited signal at δ 76.0 which corresponds to the spiro C_1 of the pyrrolizidine ring of **5a**. The downfield signals at δ 175.3 and δ 167.5 of the product **5a** are arising from the carbonyl carbon of oxindole and coumarin ring. The signal at δ 150.7 corresponds to the O-C of chromene ring of **5a**. The coupling between ^{13}C-F signals appeared at δ 161.7 (^{1}J = 245.3 Hz), δ 116.7 (^{2}J = 23.0 Hz), δ 122.8 (^{3}J = 8.6 Hz) and δ 132.9 (^{4}J = 2.8 Hz). From the C,H-HMBC, the correlation between the H of C-11 interacting with spiro carbon of C-13 at δ 76.4 suggests the formation of product **5a** proceeding *via* path a. In case of path b, the correlation must have appeared between the H of C-6 with spiro carbon of C-13 at 76.4. The mass spectrum of **5a** showed a molecular ion peak at m/z 522.1936 (M^{+}).

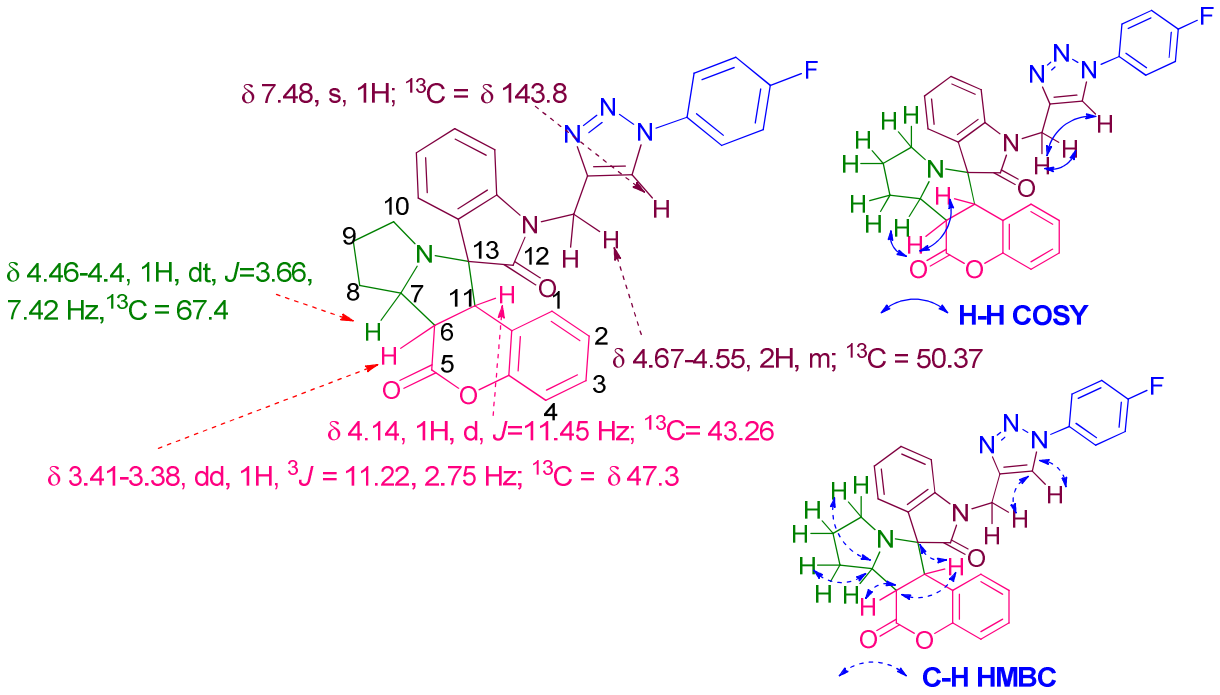


Figure 2: HMBC and COSY correlations useful in the signal assignments of **5a** and various characteristic ^{1}H and ^{13}C NMR peaks.

Additionally, the structures of the synthesized novel triazole containing spiro-oxindole pyrrolizine derivatives (**5**) have been confirmed by the single crystal X-ray diffraction analysis of compound **5e** (Fig. 3). All our attempts to obtain single crystal of compound **5a** were not successful. Single crystal of **5e** suitable for X-ray diffraction was obtained by layering method of CH_2Cl_2/hexane solutions at -4 ^{o}C. The crystal packing shows four molecules in a unit cell and the structural resolution of **5e** showed one disordered molecule of DCM solvent is located in the crystal (the crystal refinement data is listed in supplementary file table 1). The crystal structure shows that spiro carbon of propargyl isatin and pyrrolizine ring deviate by an angle 110.26^{o} (See supplementary file, Fig. 55a). The compounds also reveal two types of interactions, namely, intermolecular and intramolecular hydrogen bonding ((For details, See supplementary file Fig. 55b, 55c) (table 2).

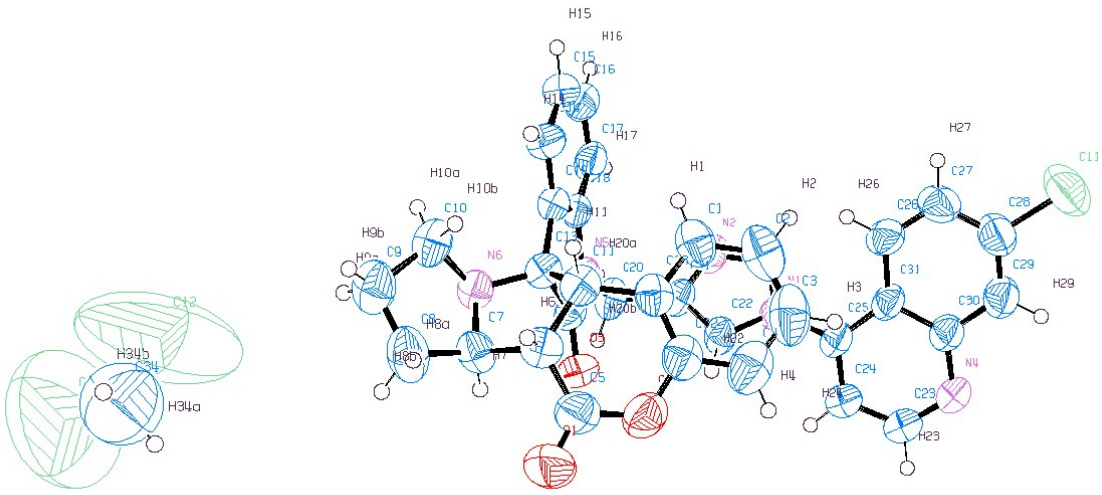
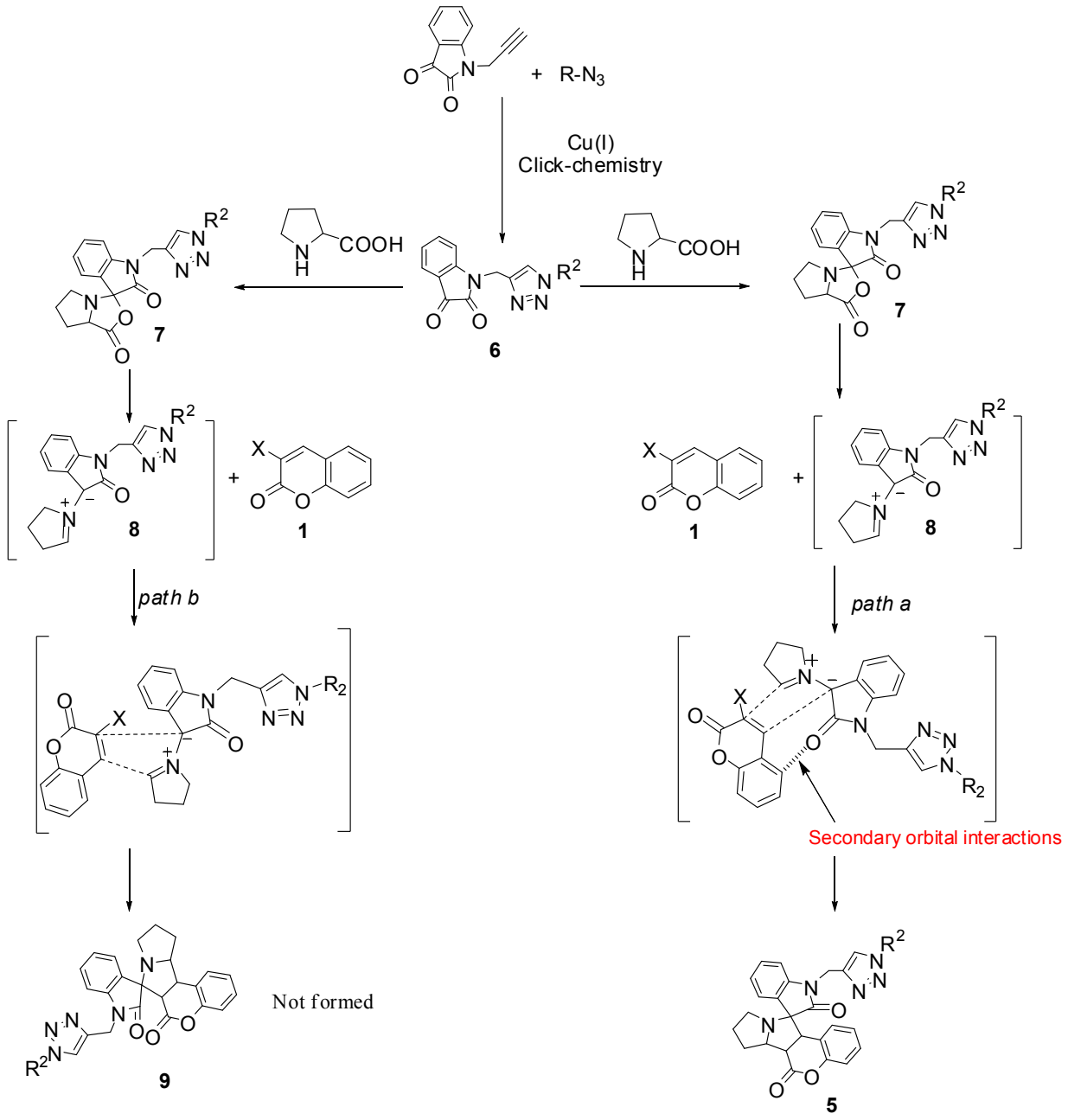


Figure 3: X-ray crystal structure of **5e** (CCDC- 1407486)

A plausible reaction mechanism for the formation of triazole containing spiro-oxindole pyrrolizine heterocycles **5** is depicted in Scheme 3. The triazoles **6**, formed by [3+2] cycloaddition of propargylated isatin azides in presence of Cu(I), undergo condensation with *L*-proline to give the spiro intermediate **7**. The decarboxylation of **7** gave the reactive ylide **8**,[19] which undergoes [3+2] cycloaddition with **1.** The ylide **8** can undergo [3+2] cycloaddition with **1** by two ways, *path a* and *path b* to give the products **5** and **9**, respectively. However, in the case of *path a*, the secondary orbital interactions[20] between the aromatic rings of coumarin-3-carboxylic acid and carbonyl group of isatin in the transition state stabilize the intermediate and result in the formation of **5** but in case of *path b* no such stabilization by secondary orbital interactions are observed as shown in Scheme 3. Therefore formation of **5** was observed exclusively. The formation of **5** was also confirmed by HMBC as discussed earlier besides spectral data and X-ray analysis.



Scheme 3: Plausible mechanism for the formation of **5**

The role of Cu(I)[21] in catalyzing only the first part of the pathway was also confirmed by an independent reaction of **6** with coumarin-3-carboxylic acid and *L*-proline. The reaction was attempted both in the presence and absence of $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate

(20 mol%). The reactions resulted in the formation in 89 and 90% yield of **5**, respectively, in 35 min, which suggests that Cu(I) was catalyzing only [3+2] azide-alkyne cycloaddition and has no effect on [3+2] cycloaddition reaction of azomethine ylide and alkene.

Experimental

Silica gel 60 F_{254} (Precoated aluminium plates) from Merck were used to monitor reaction progress. Melting points were determined on Buchi melting point 545 apparatus and are uncorrected. IR ($CHCl_3$) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer, and the values are expressed as ν_{max} (cm^{-1}). The ^1H and ^{13}C spectra were recorded on Jeol JNM ECX-400P at 400 MHz and 100 MHz, respectively. Chemical shift values are recorded on δ scale, and the coupling constants (*J*) are in Hertz. Mass spectra were recorded at Bruker Micro TOF Q – II. The aryl azides and *N*-propargylated isatin were prepared from aromatic amines and isatin by reported procedure.[22]

Data Collection and Refinement

The intensity data for compound **5e** was collected on an Oxford Xcalibur CCD diffractometer equipped with graphite monochromatic MoK_α radiation (λ 0.71073 Å) at 293(2) K. The multiscan absorption correction was applied. The crystal structure of **5e** was solved by direct methods and refined by full-matrix least squares refinement techniques on *F*2 using *SHELXL-97*.[23] The coordinates of non-hydrogen atoms were refined anisotropically using *SHELXL-97*. The positions of hydrogen atoms were obtained from difference Fourier maps and were included in the final cycles of refinement. All calculations were done using the *Wingx* software package.[23] Complete crystallographic data (excluding factors) of **5e** has been deposited at the Cambridge Crystallographic Data Centre under number CCDC 1407486.

General procedure for the synthesis of 1'-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-*a*]pyrrolizine-11,3'-indoline]-2',6(6*aH*,11*aH*)-diones (5a-5r)

An equimolar mixture of coumarin-3-carboxylic acid **(1)** (1.0 mmol), *N*-propargylated isatin **(2)** (1.0 mmol), *L*-proline **(3a)**/ sarcosine **(3b)** (1.0 mmol) and aryl azides **(4)** (1.0 mmol) was dissolved in glacial CH_3COOH (10 mol%) in a 50 mL round-bottomed flask. The reaction contents were stirred magnetically in a pre-heated oil-bath maintained at 60 ^oC. Aqueous solution of $CuSO_4.5H_2O$ (10 mol%) followed by an aqueous solution of sodium ascorbate (20 mol%) were then added to the reaction mixture and the heating was continued. All the reactions were complete in 35-50 min (Table 2). The progress of the reaction was monitored by TLC (Ethyl acetate: Petroleum ether, 30:70, *v/v*). After completion of the reaction, the reaction mixture was allowed to cool at room temperature and was quenched with water (~5 mL). The precipitate formed was collected by filtration at the pump and washed with water. The crude material was purified by flash chromatography over silica gel (230–400 mesh) to afford pure products. The products were characterized by IR, ^1H NMR, ^{13}C NMR and Mass spectra. Product **5e** was also analyzed by X-ray diffraction studies.

Conclusion

In conclusion, we have developed a facile synthesis of novel structurally diverse triazole containing spiro-oxindole pyrrolizine heterocycles by condensation of substituted coumarin-3-carboxylic acid **(1)**, *N*-propargylated isatin **(2)**, *L*-proline (**3a**)/ sarcosine **(3b)** and aryl azides **(4)** using Cu(I) as catalyst in glacial CH_3COOH at 60 ^oC. All the reactions were facile and gave high yields by simple work-up. All the compounds were characterized by IR, ^1H NMR, ^{13}C NMR and Mass analysis.

Acknowledgements

RM thanks C.S.I.R., New Delhi, India for the grant of Senior Research Fellowship. SK thanks C.S.I.R., New Delhi, India for the grant of Junior Research Fellowship.

Reference

1. E. Ruijter, R. Scheffelaar, and R.V.A. Orru, *Angew. Chem. Int. Ed*., 2011, **50**, 6234-6246.
2. B. Yu, D. -Q. Yu and H. -M. Liu, *Eur. J. Med. Chem*., 2015, **97**, 673-698.
3. (a) C. -B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **52**, 12651-12666. (b) H. Wang and A. Ganesan, *J. Org. Chem*., 2000, **65**, 4685-4693.
4. (a) A. Jossang, P. Jossang, H. A. Hadi, T. Sbvenet and B. Bodo, *J. Org. Chem*., 1991, **56**, 6527-6529. (b) M. G. Kulkani, A. P. Dhondge, S. W. Chavhan, A. S. Borhade, Y. B. Shaikh, D. R. Birhade, M. P. Desai and N. R. Dhatrak, *Beilstein J. Org. Chem*., 2010, **6**, 876-879.
5. J. Zhou, S. Zhou, *J. Ethnopharmacol*., 2010, **132**, 15-27.
6. Y. Ban, N. Taga and T. Oishi, *Tetrahedron Lett*., 1974, **130**, 187-190.
7. C. Pellegrini, M. Weher, and H. -J. Borschberg, *Helv. Chim. Acta*, 1996, **79**, 151-168.
8. N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem*., 2012, **10**, 5165-5181.
9. A. Cervi, P. Aillard, N. Hazeri, L. Petit, C. L. L. Chai, A. C. Willis, and M. G. Banwell, *J. Org. Chem*., 2013, **78**, 9876-9882.
10. X. -H. Zhang, J. -F. Yan, L. Fan, G. -B. Wang, D. -C. Yang, *Acta Pharm. Sin B*, 2011, **1**, 100-105.

11. N. M. Pecheniuk, H. Deguchi and J. H. Griffin, *J. Thromb. Haemost*., 2005, **3**, 340-345.

12. D. Kaminskyy, D. Khyluk, O. Vasylenko, L. Zaprutko and R. Lesyk, *Sci. Pharm*., 2011, **79**, 763-777.

13. K. A. Badiola, D. H. Quan, J. A. Triccas and M. H. Todd, *PLoS ONE*, 2014, **9**, 1-20.

14. Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett*., 2014, **24**, 3673-3682.

15. (a) Y. A. Al-Soud, H. H. Al-Sa'doni, H. A. S. Amajaour, K. S. M. Salih, M. S. Mubarak, N. A. Al-Masoudic, and I. H. Jaber, *Z. Naturforsch*., 2008, **63b**, 83-89. (b) S. S. Sahoo1, S. Shukla, S. Nandy and H. B. Sahoo, *Eur. J. Exp. Biol*., 2012, **2**, 899-908.

16. S. Haider, M. S. Alam and H. Hamid, *Inflamm. Cell Signal*., 2014, **1**, 95-107.

17. (a) R. Huisgen, *Angew. Chem. Int. Ed*., 1963, **2**, 633-696. (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem. Int. Ed*., 2002, **41**, 2596-2599. (c) D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, E. Zunino, and L. Vaccaro, *J. Org. Chem*., 2005, **70**, 6526-6529.

18. (a) M. Rajeswari, J. Sindhu, H. Singh and J. M. Khurana, *RSC Advan*., 2015, **5**, 39686-39691. (b) J. Sindhu, H. Singh and J. M. Khurana, *Mol. Divers*., 2014, **18**, 345-355. (c) J. Sindhu, H. Singh, J. M. Khurana, C. Sharma and K. R. Aneja, *Chin. Chem. Lett*., 2015, **26**, 50-54.

19. (a) S. Kanchithalaivan, R.V. Sumesh, and R. R. Kumar, *ACS Comb. Sci*., 2014, **16**, 566-572. (b) G. P. Rizzi, *J. Org. Chem*., 1970, **35**, 2069-2072. (c) A. M. D'Souza, N. Spiccia, J. Basutto, P. Jokisz, L. S. –M. Wong, A. G. Meyer, A. B. Holmes, J. M. White and J. H. Ryan, *Org. Lett*., 2011, **13**, 486-489. (d) M. F. Aly, G. M. El-Nagger, T. I. El-Emary, R. Grigg, S. A. M. Metwally and S. Sivagnanam, *Tetrahedron*, 1994, **50**, 895-906. (e) I. Coldham and R. Hufton, *Chem. Rev*., 2005, **105**, 2765-2809.

20. (a) L. Srinu, S. Thennarasu, P. T. Perumal, *Tetrahedron Lett*., 2012, **53**, 7052-7055. (b) Y. Apeloig and E. Matzner, *J. Am. Chem. Soc*., 1995, **117**, 5375-5376. (c) A. Arrieta and F. P. Cossio, *J. Org. Chem*., 2001, **66**, 6178-6180. (d) J. I. Garcia, J. A. Mayoral and L. Salvatella, *Eur. J. Org. Chem*., 2005, 85-90.

21. F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc*., 2004, **127**, 210-216.

22. (a) N. D. Obushak, N. T. Pokhodylo, N. I. Pidlypnyi and V. S. Matiichuk, *Russ. J. Org Chem*., 2008, **44**, 1522-1527. (b) H. Singh, J. Sindhu, J. M. Khurana, C. Sharma and K. R. Aneja, *Eur. J. Med. Chem*., 2014, **77**, 145-154.

23. (a) L. J. Farrugia, *WinGX Version 1.80.05: An Integrated System of Windows Programs for the solution, Refinement and Analysis of Single Crystal X-Ray Diffraction Data* 1997-2009 (Department of Chemistry, University of Glasgow: Glasgow). (b) G. M. Sheldrick, *Acta Crystallogr*., 2008, **64**, 112-122.

One-pot four component domino strategy for the synthesis of novel spirooxindole pyrrolizine linked 1,2,3-triazoles *via* stereo- and regioselective [3+2] cycloaddition reaction in acidic Medium.

Rajeswari M., Sudesh Kumari and Jitender M. Khurana*

Department of Chemistry, University of Delhi, New Delhi - 110 007, India.

Corresponding author: Fax: +91 11 27666605; Tel: +91 11 27667725.

Email: jmkhurana1@yahoo.co.in

Abstract

An efficient, one-pot four component condensation procedure for the synthesis of selective spirooxindole pyrrolizine linked 1,2,3-triazole conjugates *via* [3+2] cycloaddition has been reported by coumarin-3-carboxylic acid (**1**), *N*-propargylated isatin (**2**), *L*-proline/sarcosine (**3**) and aryl azides (**4**) using Cu(I) as a catalyst in the presence of glacial CH_3COOH at 60 ^oC. The structures of the compounds synthesized herein were confirmed by ^1H NMR, ^{13}C NMR, Mass spectra and X-ray crystallographic techniques.