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Sudesh Kumari, Harjinder Singh, Jitender M. Khurana

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Graphical Abstract

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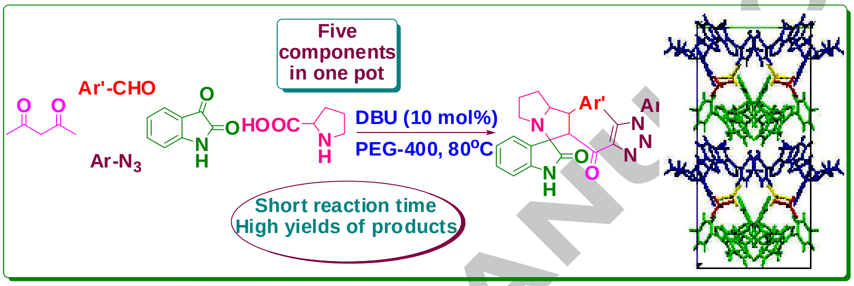

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Sudesh Kumari, Harjinder Singh and Jitender M. Khurana*

Department of Chemistry, University of Delhi, Delhi-110007
*Email:- jmkhurana1@yahoo.co.in, jmkhurana@chemistry.du.ac.in

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ABSTRACT

We have described an efficient one-pot five component reaction of acetylacetone, aryl azides, aromatic aldehydes, isatin and L-proline by using DBU as catalyst in PEG-400 at 80°C for the construction of novel heterocyclic triazolyl spirocyclic oxindole derivatives. Structures of all synthesized novel compounds have been confirmed by spectral and X-ray studies. Crystal packing of compound **6i** has also been reported. Green solvent, less reaction time, easy work up and high yields are the salient features of the present protocol. The same reaction has also been reported by stepwise reactions including a one-pot three component reaction.

Spirocyclic oxindoles[1] are important heterocycles with diverse biological activities including antibacterial, antifungal, anticonvulsant, antiviral and antiproliferative.[2] They acts as potent inhibitors of monoamine oxidase in human urine, rat tissues[3] and acetylcholinesterase,[4] They also act as antagonist of *in vitro* receptor binding by atrial natriuretic peptide[5] and possess a wide range of CNS activities.[6] Spiro oxindole ring system also occurs in nature as a part of some natural products with diverse biological activities such as paraherquamide A which possesses antiparasitic activity and antinematodal properties,[7] spirotryprostatins A and B[8] which possess anti-mitotic and anti-cancer properties etc. (Figure 1). 1,2,3-Triazoles are another privileged nitrogenous heterocycles with a plethora of biological activities including antiHIV,[9] antimicrobial,[10] antiviral,[11] antiproliferative,[12] antibiotics,[13] insecticides[14] and fungicidal.[15] Fluconazole[16] is a well-known antifungal drug consisting of 1,2,3-triazole ring, while Tazobactum[17] is a broad spectrum antibiotic for treatment of various infections (Figure 1).

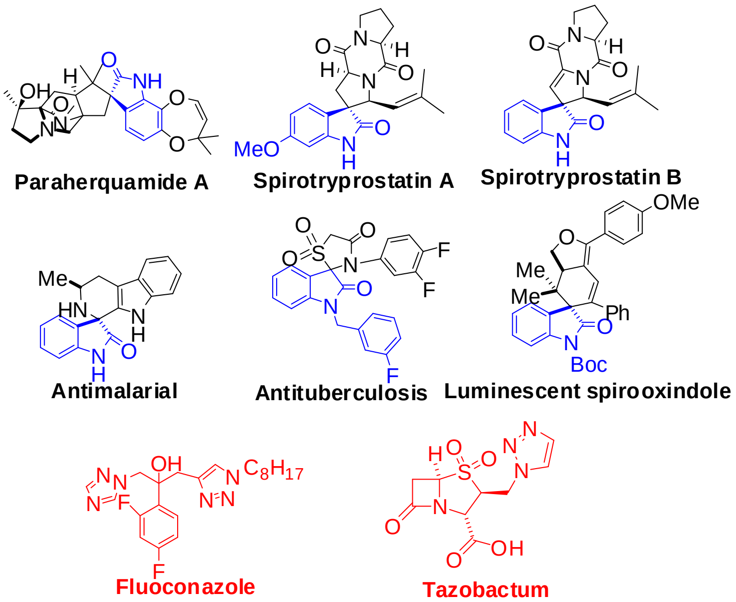


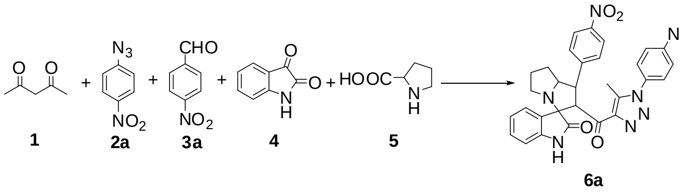
Figure 1: Some biologically active compounds containing spirooxindole and 1,2,3-triazole core structure.

Multicomponent reactions (MCRs) offer valuable strategies for the synthesis of complex molecules with several advantages *e.g.* elimination of intermediate steps, diversity, high efficiency, selectivity and minimal waste production.[18] Polyethylene glycol (PEG-400) and modified polyethylene glycol derivatives have become popular alternate reaction media due to their non-toxicity, bio-compatibility and bio-degradability compared to other ‘neoteric solvents’ such as ionic liquids, super-critical fluids and micellar systems.[19] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), regarded as a non-nucleophilic, strong tertiary amine base has been widely used as an effective corrosion free catalyst in many organic transformations in recent years.[20]

Therefore, in continuation of our research interest in the synthesis of potentially bioactive heterocyclic compounds with diverse applications,[21] we decided to investigate the synthesis of novel conjugates consisting of spirocyclic oxindole and 1,2,3-triazoles in a single matrix through MCR approach under green conditions.

The present manuscript reports a new, diversity oriented and highly efficient green protocol for the synthesis of novel 1,2,3-triazole tethered spirooxindole derivatives namely 2'-(5-methyl-1-aryl-1*H*-1,2,3-triazole-4-carbonyl)-1'-aryl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-ones *via* one-pot five component condensation of acetylacetone, aryl azides, aromatic aldehydes, isatin and L-proline using DBU as organocatalyst in PEG-400 at 80°C.

The optimized reaction conditions for this proposed five-component reaction were established by attempting model reaction for the synthesis of **6a** (Scheme 1) comprising acetylacetone (1) (1.0 mmol), 4-nitrophenyl azide (2a) (1.0 mmol), 4-nitrobenzaldehyde (3a) (1.0 mmol), isatin (4) (1.0 mmol) and L-proline (5) (1.0 mmol) under different reaction conditions as shown in Table 1. First, the model reaction of acetylacetone (1) (1.0 mmol), 4-nitrophenyl azide (2a) (1.0 mmol), 4-nitrobenzaldehyde (3a), isatin (4) and L-proline (5) was carried out using DBU (10 mol%) as base in H_2O and EtOH at 80°C. The progress of the reactions was monitored by TLC (eluent: ethyl acetate: petroleum ether, 40:60, v/v) and reactions were found to be incomplete even after 300 min. After work-up and separation by column chromatography, desired product 2'-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbonyl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**6a**) was obtained in 37% and 42% yield respectively (Table 1, entries 1 and 2).



Scheme 1: Model reaction for synthesis of 2'-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbonyl)-1'-(4-nitrophenyl)-1',2',5',6',7',7*a*'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**6a**)

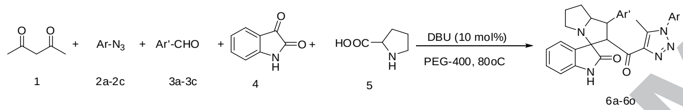
The above reaction was then repeated in glycerol, ethylene glycol and 1,4-dioxane as solvents under otherwise identical conditions. The reactions were complete in 120 min, 100 min and 90 min and gave 74%, 75% and 87% yield of product **6a**, respectively (Table 1, entries 3, 4 and 5). The same reaction was then explored in PEG-400 under otherwise identical conditions. The reaction was found to be complete in 40 min and gave 93% yield of the desired product **6a** (Table 1, entry 6). Thus, the best results were obtained when this five-component reaction was attempted in PEG-400, and hence PEG-400 was chosen as suitable solvent for further exploration of this reaction. To determine the effect of bases other than DBU over this model reaction, the five-component model reaction was attempted using K_2CO_3 (10 mol%), DABCO (10 mol%) and piperidine (10 mol%) as base catalyst in PEG-400 at 80°C. This gave desired product 6a in 70%, 72% and 45%, respectively (Table 1, entries 7-9). The effect of temperature and catalyst loading on the reaction time and yield of the product was also examined. The above reaction using DBU (10 mol%) in PEG-400 was therefore attempted at higher temperature (100°C), lower temperature (60°C), lower loading of catalyst (5%) and higher loading of catalyst (15%). There was no significant effect on the product yield and time of reaction under these conditions (entries 10-13).

Thus, condensation of five-components in one-pot using DBU (10 mol%) in PEG-400 at 80°C were chosen as optimum reaction conditions for further study of scope of this reaction. Subsequently, reactions were attempted with differently substituted azides and aromatic aldehydes under the optimized conditions. All the reactions were facile and complete in less than 60 min with both electron rich and electron deficient aryl azides and aldehydes affording the desired products **6a-6o** in high yields (Scheme 2).[24] All the results have been compiled in Table 2. Structural assignments have been made on the basis of ^{1}H NMR, ^{13}C NMR, IR and mass spectra.

Table 1: Optimization for the synthesis of 2'-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbonyl)-1'-(4-nitrophenyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (6a)[a]

S. No.	Solvent	Catalyst	Catalyst (mol %)	Temp. (^{o}C)	Time (min)	Yield (%)
1.	H_2O	DBU	10	80	300	37[b]
2.	EtOH	DBU	10	80	300	42[b]
3.	Glycerol	DBU	10	80	120	74
4.	Ethylene glycol	DBU	10	80	100	75
5.	1,4-Dioxane	DBU	10	80	90	87
6.	PEG-400	DBU	10	80	40	93
7.	PEG-400	K_2CO_3	10	80	90	70
8.	PEG-400	DABCO	10	80	90	72
9.	PEG-400	Piperidine	10	80	300	45[b]
10.	PEG-400	DBU	10	100	40	90
11.	PEG-400	DBU	10	60	70	85
12.	PEG-400	DBU	5	80	60	88
13.	PEG-400	DBU	15	80	40	91

[a]Reaction was carried out between acetylacetone (1) (1.0 mmol), 4-nitrophenyl azide (2a) (1.0 mmol), 4-nitrobenzaldehyde (3a) (1.0 mmol), isatin (4) (1.0 mmol) and L-proline (5) (1.0 mmol) [b]Incomplete reaction



Scheme 2: Synthesis of compounds **6a-6o**

Table 2: Synthesis of 2'-(5-methyl-1-aryl-1*H*-1,2,3-triazole-4-carbonyl)-1'-aryl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one derivatives (6a-6o) using multicompoenent approach[a]

Products	Ar	Ar’	Time (min)	Yield (%)
6a	4-$(NO_2)C_6H_4$	4-$(NO_2)C_6H_4$	40	93
6b	4-$(NO_2)C_6H_4$	4-$(CH_3)C_6H_4$	55	87
6c	4-$(NO_2)C_6H_4$	4-BrC_6H_4	50	89
6d	4-$(CH_3)C_6H_4$	4-$(NO_2)C_6H_4$	45	91
6e	4-$(CH_3)C_6H_4$	4-$(CH_3)C_6H_4$	60	86
6f	4-$(CH_3)C_6H_4$	4-BrC_6H_4	55	88
6g	4-BrC_6H_4	4-$(NO_2)C_6H_4$	45	92
6h	4-BrC_6H_4	4-$(CH_3)C_6H_4$	55	88
6i	4-BrC_6H_4	4-BrC_6H_4	50	89
6j	3-Cl-4-FC_6H_3	4-$(NO_2)C_6H_4$	40	90
6k	3-Cl-4-FC_6H_3	4-$(CH_3)C_6H_4$	55	86
6l	3-Cl-4-FC_6H_3	4-BrC_6H_4	50	89
6m	7-Chloroquinoline	4-$(NO_2)C_6H_4$	40	91
6n	7-Chloroquinoline	4-$(CH_3)C_6H_4$	55	87
6o	7-Chloroquinoline	4-BrC_6H_4	50	88

[a]All the reactions were carried out by using DBU (10 mol%) as catalyst in PEG-400 at 80^{o}C

IR spectra of compound **6a** revealed peaks at 3306 cm^{-1} (N-H stretch), 1715 cm^{-1} (carbonyl stretch), 1660 cm^{-1} (amide C=O stretch), 1516 cm^{-1} (N-O asymmetric stretch) and 1347 cm^{-1} (N-O symmetric stretch). The ^{1}H NMR spectrum of **6a** showed a sharp singlet at δ 10.41 for NH proton, twelve aromatic protons in the range of δ 8.40-6.57, one methine proton appeared as doublet at δ 4.95 (^{3}J= 10.68 Hz, vicinal coupling) and two methine protons as multiplets at δ 4.16-4.11 and δ 4.01-3.96, three protons of methyl group appeared as a sharp singlet at δ 2.13, two CH_2 groups appeared as multiplets at δ 1.94-1.83 and δ 1.74-1.65 and third CH_2 group showed two multiplets at δ 2.90-2.84 and δ 2.41-2.38 for each proton. Three methylene carbons in the ^{13}C NMR appeared at δ 48.8, 28.2, 25.9 and three methine carbons appeared at δ 71.4, 66.2 and 51.1. One methyl carbon appeared at δ 9.70 and quaternary carbon at δ 72.5. Eighteen aromatic and two olefinic carbons appeared in the range of δ 109.9 to 149.2. Two carbonyl carbons appeared at δ 192.6 and 179.9. (Peak at δ 179.9 is due to oxindole carbonyl carbon). The position of peaks for methyl, methylene, methine and quaternary carbons were assigned by DEPT spectra of compound **6a**. The two- dimensional NMR spectra of HMBC and COSY correlations are useful in the signal assignment of **6a**, and various characteristic signals are shown in figure 2. The mass spectrum of **6a** showed a molecular ion peak at *m/z* 580.1932 [M+H]$^{+}$. From the C-H HMBC, the correlation between the H of C-3 interacting with spiro carbon C4 at δ 72.5 suggests the formation of product **6a** proceeding *via Path a* (See proposed pathway, Scheme 4). In case of *Path b*, the correlation should appear between the H of C-2 and spiro carbon C4 at δ 72.5, but no such interaction is observed in HMBC.

The structure of compound **6i** has been further confirmed by the single crystal X-ray diffraction analysis. Single crystal of compound **6i** suitable for X-ray diffraction was obtained by vapour diffusion of petroleum ether into chloroform solution of compound at room temperature. The crystal packing shows eight molecules in a single unit cell (Figure S1, Electronic supplementary information). The structural resolution of **6i** showed two disordered molecules of chloroform solvent located in the crystal. The crystal chemical unit of compound **6i** contains two molecules which are chemically identical but not related by crystallographic symmetry, each different molecule is coloured differently in crystal packing (Figure S2, Electronic supplementary information).

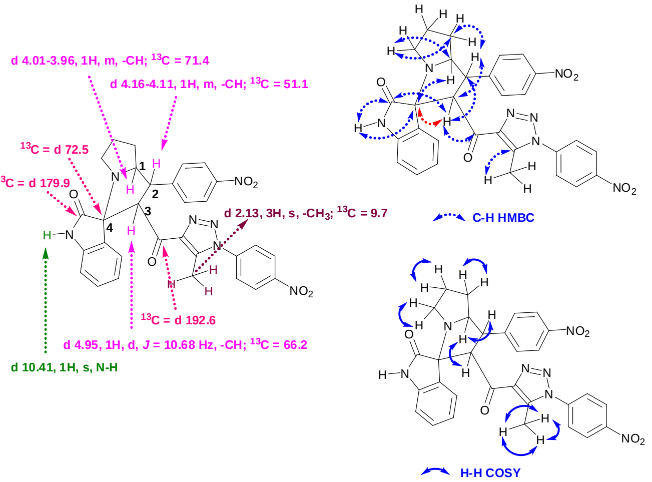


Figure 2: HMBC and COSY correlations of **6a** and various characteristic ^{1}H and ^{13}C NMR peaks

Compound **6i** shows four chiral centres, with ‘R’ configuration at C2 position, ‘S’ configuration at C23 position, ‘R’ configuration at C24 position and ‘R’ configuration at C25 position as observed from the crystal structure (Figure S3, Electronic supplementary information). The crystal data including the structure refinement are listed in Table S1 (Electronic supplementary information).

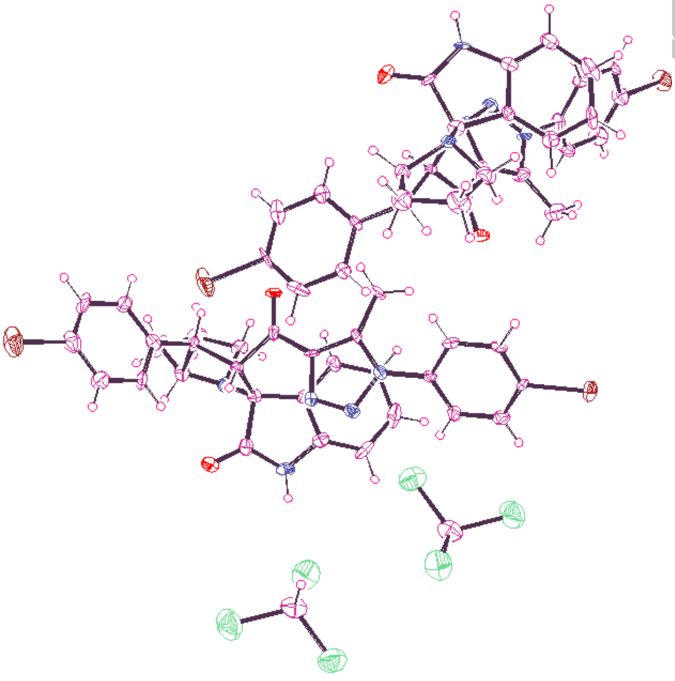
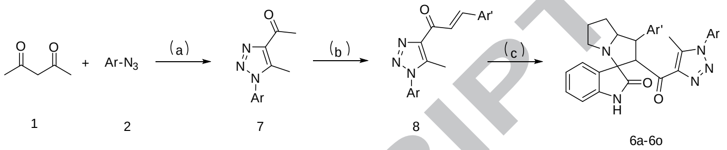


Figure 3: ORTEP diagram of compound **6i** (CCDC 1455726)

We have also carried out the sequential synthesis of **6a-6o** in three steps including one-pot three component reaction as depicted in Scheme 3 to demonstrate the advantages of multicomponent reaction for the synthesis of target molecules over sequential process. The reaction of acetylacetone (1) and aryl azides (2) in presence of DBU (10 mol%) in PEG-400 at 80°C gave 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)ethanone (7) in 95% yield, which on condensation with aromatic aldehydes (3) in PEG-400 in presence of DBU gave 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-3-(4-nitrophenyl)prop-2-en-1-one (8) in 92 % yield. The reaction of **8** (1.0 mmol) with isatin (4) (1.0 mmol) and L-proline (5) (1.0 mmol) in PEG-400 at 80°C gave the desired products 6a-6o (Table S2, Electronic supplementary information).

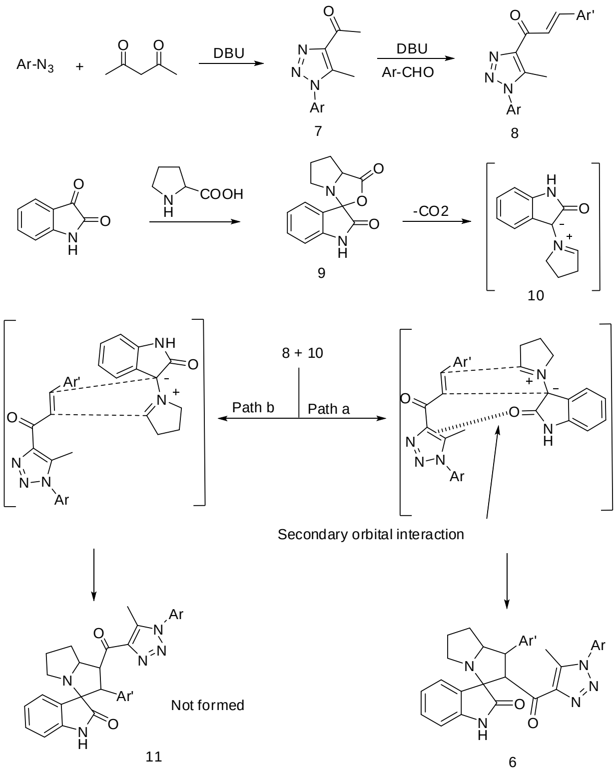


Scheme 3: Sequential synthesis of **6a-6o** (a) PEG-400, DBU (10 mol%), 80°C; (b) aromatic aldehydes (3), PEG-400, DBU (10 mol %), 0°C to rt; (c) Isatin (4), L-Proline (5), PEG-400, 80°C.

The above sequential reactions required longer reaction time and gave poorer overall yields compared to the above five component process as obvious from Table 2 and S2. It is also clear that DBU is required only for the synthesis of chalcones and has no further role in the synthesis of spiroheterocycles.

A plausible reaction mechanism for the formation of triazole containing spiro-oxindole derivatives **6** is depicted in Scheme 3. The triazole **7**, formed by [3+2] cycloaddition of acetylacetone and azide in presence of DBU undergoes aldol condensation with aromatic aldehydes to give the chalcone derivative **8**. Condensation of isatin and L-proline to give **9** followed by decarboxylation of spiro compound[22] gives the ylide **10**. The chalcone **8** can undergo [3+2] cycloaddition with ylide **10** by two ways, *path a* and *path b* to give either the product **6** or **11** respectively. In case of *path a*, the secondary orbital interaction[23] between the double bond of triazole ring and carbonyl group of isatin in the transition state stabilize the intermediate and results in the formation of **6** but in case of *path b* no such stabilization by secondary orbital interaction is observed as shown in scheme 3. Therefore formation of only **6** was observed instead of **11**. The formation of **6** was confirmed by HMBC and X-ray analysis as discussed earlier. The reaction of preformed chalcone **8a** with isatin and L-proline in PEG-400 at 80°C further confirms the proposed pathway.

We also examined the recyclability of the catalyst and solvent by using reactions for the synthesis of **6a**, **6e** and **6i**. The recyclability of DBU-(PEG-400) system was tested by six run recycling experiment by changing substrates from one cycle to another cycle. The product was separated from the reaction mixture by simple filtration.



Scheme 4: Plausible mechanism for the synthesis of **6**

This allows quick recovery of catalyst and solvent for reuse in the next run. The results of recycling experiment are shown in Table S3 (in supplementary information). All reactions were complete in 40-65 min and afforded the products in 93-81% yield. The catalyst showed no substantial reduction in activity. Therefore this system can act as an excellent recyclable reaction medium cum catalyst for synthesis of triazole tethered spirooxindoles in high yields.

In conclusion, we have developed an efficient, clean approach for the synthesis of novel structurally diverse triazolyl spirocyclic oxindole derivatives by one-pot five component condensation of acetylacetone, aryl azides, aromatic aldehydes, isatin and L-proline using DBU as catalyst in PEG-400 at 80^{o}C. All the reactions were facile and gave high yields by simple work-up. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and Mass spectra.

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Supplementary data

Supplementary data associated with this article can be found, in the online version**,** of this article

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24. *General procedure for the synthesis of 2'-(5-methyl-1-aryl-1H-1,2,3-triazole-4-carbonyl)-1'-aryl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one derivatives (6a-6o):*

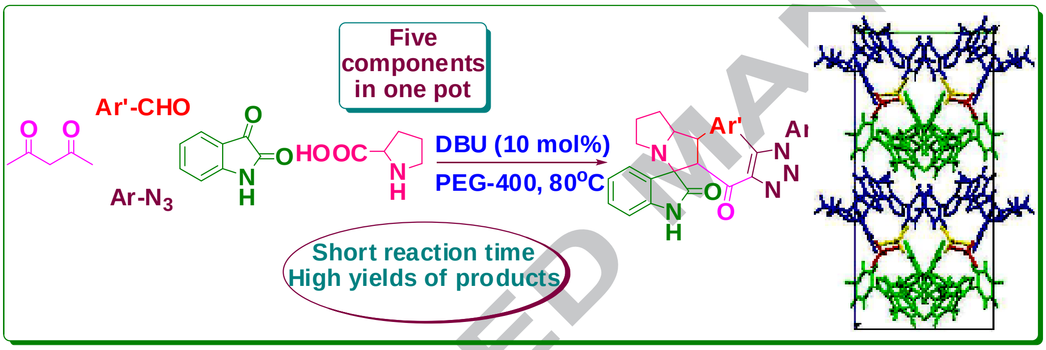
An equimolar mixture of acetylacetone (1) (1.0 mmol), aryl azides (2) (1.0 mmol), aromatic aldehydes (3), isatin (4) (1.0 mmol) and L-proline (5) (1.0 mmol) was dissolved in PEG-400 (10 ml) in a 50 mL round-bottomed flask and 10 mol% of DBU catalyst was added to this reaction mixture. The reaction contents were stirred magnetically in a pre-heated oil-bath maintained at 80^{o}C. The progress of the reaction was monitored by TLC (Ethyl acetate: Petroleum ether, 40:60, *v/v*). After completion of the reaction, the reaction mixture was allowed to cool at room temperature and quenched with water (~10 mL). The solid formed was filtered 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 ^{1}H NMR, ^{13}C NMR, IR and Mass spectra. Product **6i** was also analyzed by X-ray diffraction studies.

An efficient green approach for the synthesis of novel triazolyl spirocyclic oxindole derivatives *via* one-pot five component protocol using DBU as catalyst in PEG-400

Sudesh Kumari, Harjinder Singh and Jitender M. Khurana[*]

Department of Chemistry, University of Delhi, Delhi-110007
**Email:- jmkhurana1@yahoo.co.in, jmkhurana@chemistry.du.ac.in*

Graphical abstract



Highlights:

- DBU catalysed synthesis of fused heterocyclic triazolyl spirocyclic oxindoles
- High yield of products and short reaction time
- Structure has been characterized by X-ray crystallography
- Recyclability of DBU-PEG-400 system