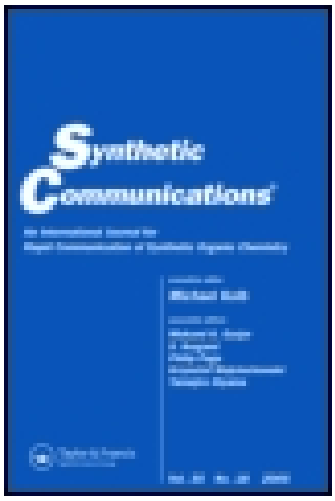

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Synthesis of Novel Spiro[indol-2,2′-pyrroles] Using Isocyanide-Based Multicomponent Reaction

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SYNTHESIS OF NOVEL SPIRO[INDOL-2,2'-PYRROLES] USING ISOCYANIDE-BASED MULTICOMPONENT REACTION

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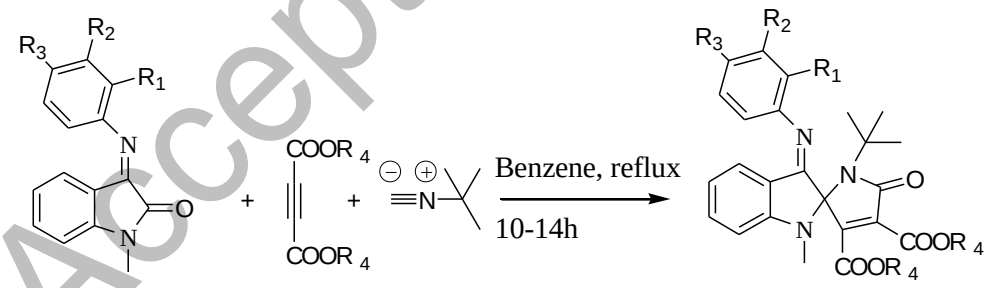
Abstract

An efficient and facile method for the synthesis of novel spiro[indole-2,2'-pyrroles] from N-methyl-3-isatin imines, t-butyl isocyanide and dialkyl acetylenedicarboxylate has been achieved by [3+2] cyclo addition reaction. All the products were purified by column chromatography as yellow solids and confirmed with ^{1}H NMR, ^{13}CNMR, FAB mass, IR. Compound 11 was further confirmed with X-ray analysis.



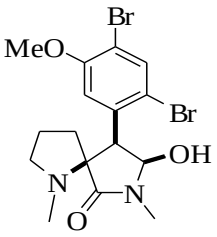
KEYWORDS: Spiro[indole-2,2'-pyrroles], N-methyl-3-isatin imine, [3+2] cyclo addition, Multicomponent reaction, X-ray crystallography

INTRODUCTION

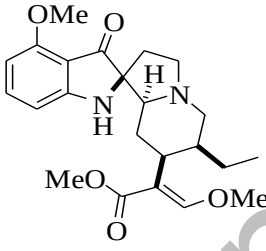
Isatin derivatives have several pharmacological and biological properties such as anti-HIV,[1] anticancer,[2] anti-mycobacterial,[3] anti-inflammatory,[4] and anticonvulsant activities.[5] Isatin found to be a prevalent motif in several alkaloids,[6] drugs,[7] dyes,[8] pesticides and analytical reagents. Spiro compounds having both indole and pyrrole nucleus is found to be the key structural unit in many natural products such as Spirotriprostrain A, Spirotriprostrain B and Horsfiline, which were proven to have anticancer activity. [9] Because of the versatile reactivity of the isatin various methods have been developed for the synthesis of spiro [indole-pyrroles] using multi component reactions.[10] However most of these methods were involved the C-3 carbon of isatin in the formation of spiro heterocycle. Spiro compounds having dipyrrole namely Amathaspiramide A, Mytraginine psuedoindoxyl as shown below was proven to have prominent antiviral and anticancer properties.[11] Very few reports were there in the literature for the synthesis of spiro [indole-2,2'-pyrroles] bearing spiro carbon at C-2 position.[12]

The reported method involved the multistep organic synthesis, used metal catalysts and tedious workup procedures. As a consequence and our passion towards the synthesis of novel heterocycles using multi component reactions, in this article we

investigated an efficient and simple route for the synthesis of novel spiro [indole-2,2'-pyrroles] bearing spiro carbon at C-2 position. Previously we have reported the novel heterocycles like benzazepine, chromeno [4, 3-b] quinolin-6-ones, chromeno-pyrimidine-N-oxides and chromeno [4, 3-b] pyridine-2, 5-diones. [13]



Amathaspiramide A



Mytraginine psuedoindoxyl

Herein we have demonstrated a novel three component [3+2] cyclo addition reaction for the synthesis of spiro [indole-2,2'-pyrroles] using C-2 carbon atom of isatin.

RESULTS AND DISCUSSIONS

It was already reported in the literature N-methyl isatin reacts with zwitterionic intermediates generated by the addition of isocyanides to electron withdrawing alkynes, such as dialkyl acetylenedicarboxylate to form spirooxindoles.[14] We wanted to attempt the similar reaction using C-2 carbon of isatin. For this purpose we have protected the C2 carbon of isatin by means of ketal formation using ethylene glycol. Now, we have attempted a three component reaction using the protected N-methyl isatin, dimethyl

acetylenedicarboxylate and t-butyl isocyanide in benzene solvent. We have observed many products in TLC. Hence, we have changed the protecting group to imine using different anilines. We have attempted a three component reaction by blocking the reactive C-3 carbonyl carbon atom of isatin by means of forming imine with 4-chloroanilines. To establish three component protocol, we have carried out a three component reaction using N-methyl isatin-3-(4-chlorophenyl) imine, dimethyl acetylenedicarboxylate and t-Butyl isocyanide in toluene solvent under refluxing conditions for 24h (Table 1, Entry. 6). After column chromatography we have obtained the final product as a yellow solid with 60% yield.

To optimize the reaction conditions we have screened the same reaction in different solvents and different conditions (Table 1). The choice of the solvent played profound effect on the reaction yields. No product formation was observed in polar solvents like MeOH, EtOH (Table 1, Entrys. 1, 2). Halogenated solvents like $CHCl_3$, DCM (Table 1, Entrys. 3, 4) less yields were observed. Among all the solvents screened benzene (Table 1, Entry. 7) was found to be the best solvent with 70% yield with less reaction time.

With the optimized reaction conditions in hand, we have demonstrated the reaction with different substituted N-methyl isatin imines and dialkyl acetylene dicarboxylates as shown in Table 2. We have attempted the reaction with various substituted N-methyl isatin imines, reaction went smoothly yielded 40-71%.

Substrates like N-methyl isatin-3-(4-bromophenyl) imine, N-methyl isatin-3-(4-chlorophenyl) imine, N-methyl isatin-3-(3-chlorophenyl) imine, N-methyl isatin-3-(phenyl) imine were reacted smoothly yielded the products as yellow solids (Table 2, Entrys. 1, 2, 4, 6, 7, 8, 9, 11) with 60-71%. Substrates like N-methyl isatin-3-(2-chlorophenyl) imine, N-methyl isatin-3-(2,4-dichlorophenyl) imine were less reactive yielded the products as yellow solids (Table 2**,** Entrys. 3, 5, 10, 12) with 40-45%. The reason for low yields of the reaction with substrates isatin-3-(2-chlorophenyl) imine, N-methyl isatin-3-(2, 4-dichlorophenyl) imine could be steric hindrance of ortho substitution with t-butyl group. The reaction was also successful with pentyl isocyanide (Table 2**,** Entry 13). We had successfully regenerated the isatin carbonyl of final product 13(Scheme 1) using 2M aq. HCl in THF at room temperature. The detailed procedure was provided in supporting information. However when we had attempted to hydrolyze the final product 11 possessing t-butyl group using 2M aq.HCl and 4M aq.HCl in THF at room

temperature for 24 h, we did not observe any reaction. When the reaction mixture was heated to 45^0C, we had observed multiple spots in TLC with very close R_f value.

All the products are novel characterized with ^{1}H NMR, ^{13}CNMR, FAB mass and IR. Structure of the product **11** was further confirmed by X-ray analysis of as shown in Figure 1. Good crystals were obtained for compound **11** in DCM solvent suitable for XRD. The molecule does not contain any hydrogen bonding from the X-ray analysis. The molecule was crystallized in a racemic form with two molecules in the unit cell and it has triclinic system with space group p-1.

On the basis of well-established chemistry of isocyanides II reactivity with dialkyl acetylenedicarboxylate I, initial step was the formation of zwitter ionic species as shown in scheme 1. This was reacted with activated N-methyl isatin imine amide carbonyl III expected to form a spiro Oxindole IV. This undergoes iminolactones-lactam rearrangement formed the final product spiro[indole-2,2'-pyrroles].

EXPERIMENTAL

All reagents were purchased from TCI and Sigma Aldrich and used without further purification. N-methyl isatin imines were synthesized according to the procedure reported in the literature. All the products were characterized by ^{1}H NMR, C^{13} NMR, IR, and Fab-Mass analysis. The NMR spectra were recorded on a Bruker AMX-500 MHz instrument at room temperature in $CDCl_3$ using TMS as an internal reference. Melting points were determined by AS ONE instrument. X-ray data for the compound were collected at room temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Crystallographic data of **11** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1037350 contains the supplementary crystallographic data for this paper

General Procedure For The Synthesis Of Spiro[Indole-2,2'-Pyrroles] (1-12):

A solution of substituted N-methyl isatin imine (1 mmol), t-Butyl isocyanide (1 mmol) and dimethyl (or) diethyl acetylenedicarboxylate (1 mmol) in 10ml benzene were refluxed for 10-14h. After completion of the reaction monitored by TLC, volatiles were removed under reduced pressure. The crude reaction mixture was subjected to column

chromatography using (SiO2, 15% EtOAc/n-Hexane) yielded 40-71% as yellow color solids in most reactions and some cases as yellow color semi solids were obtained.

Procedure For The Hydrolysis Of Product 13:

Compound 13 (1 mmol) was taken in 10 ml of 2M aq. HCl in THF and stirred at room temperature for 5h. The reaction mixture was basified with 20% $NaHCO_3$ and extracted with EtOAC, product was isolated as yellow color solid using column chromatography using 20% EtOAC/Hexane.

CONCLUSION

An efficient method for the synthesis of novel spiro[indole-2,2'-pyrroles] using readily available starting materials is reported. The notable advantages of this protocol are operational simplicity, easily available starting materials, available diversity of each component, catalyst free and easy work procedure employed. We believed in this protocol will help in developing novel spiro heterocyclic compounds using C-2 carbon atom of isatin.

ACKNOWLEDGMENTS

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SUPPLEMENTARY DATA

General experimental section, analytical data for compounds 1-12 and the X-ray analysis of 11 can be accessed on the publisher's website.

Crystallographic data of **11** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1037350 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

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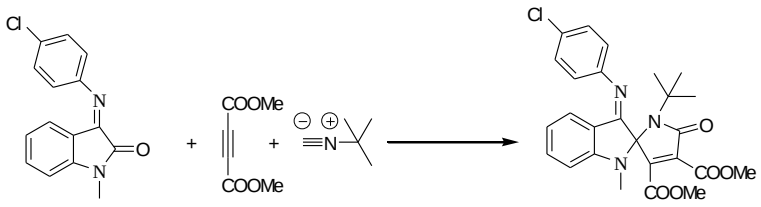
Table 1. Effect of solvents for the synthesis of spiro[indole-2,2'-pyrroles] with N-methyl-3-(4-chloro phenyl) isatin imine, dimethyl acetylenedicarboxylate and t-butyl isocyanide



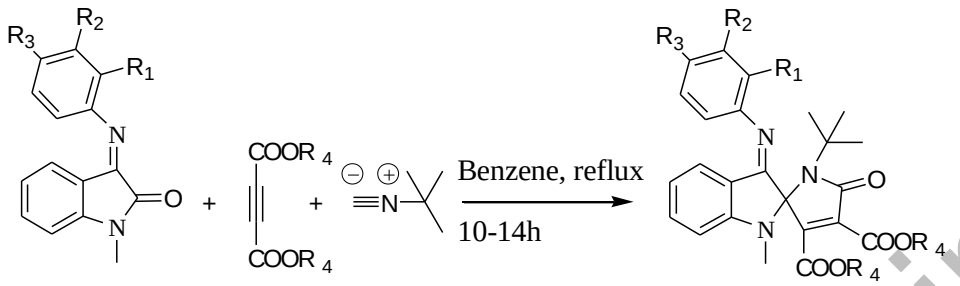
Entry	Solvent	T (^{0}C)	Time (h)	Yield (%)
1	EtOH	80	24	NR[c]
2	MeOH	80	24	NR
3	DCM	60	24	20[b]
4	CHCl3	60	24	20
5	THF	80	24	50
6	Toluene	80	24	60
7	Benzene	80	12	70

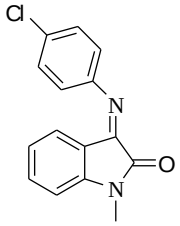
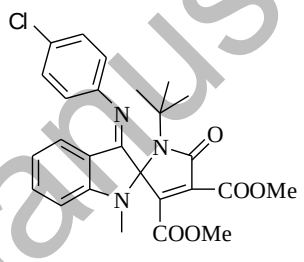
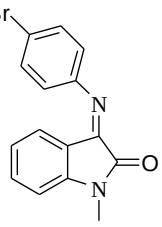
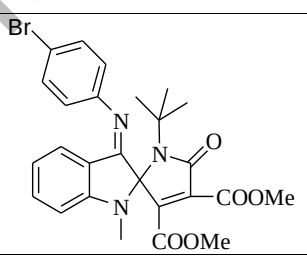
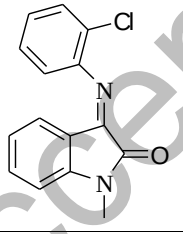
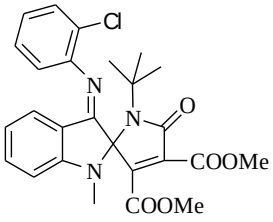
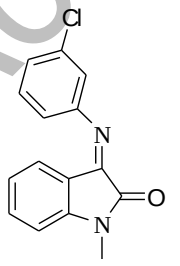
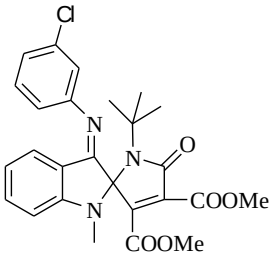
[a] All the reactions were performed with 1 mmol of each reactant and 10ml of solvent

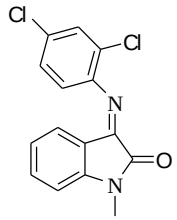
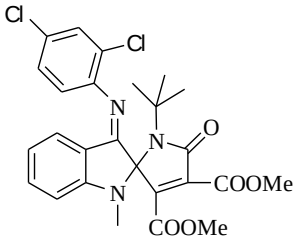
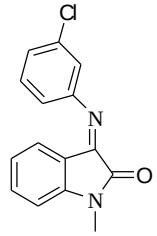
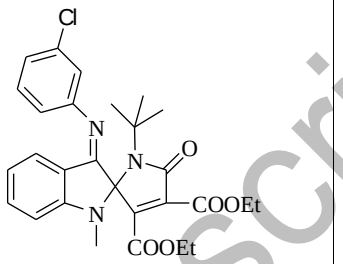
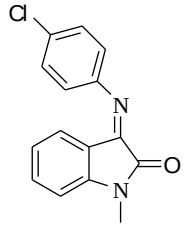
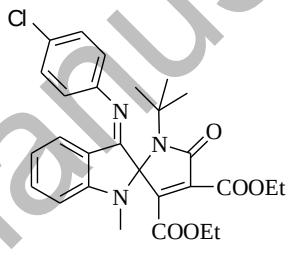
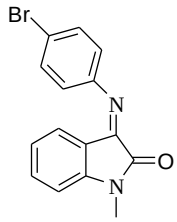
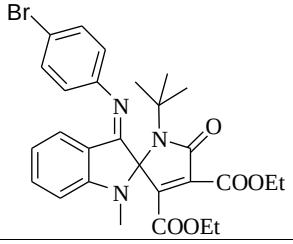
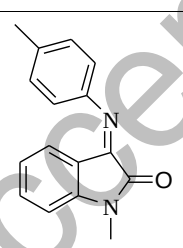
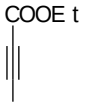
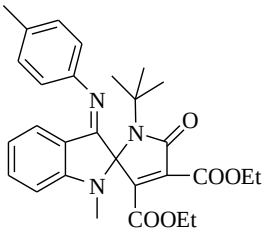
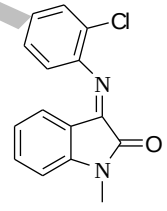
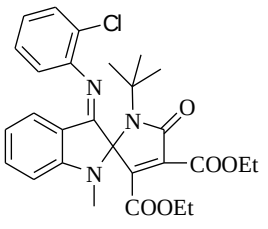
[b] Isolated yields

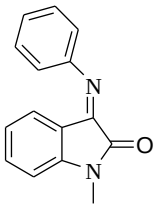
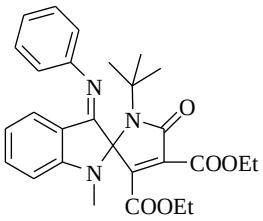
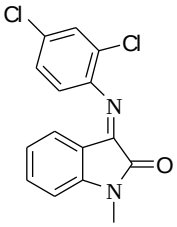
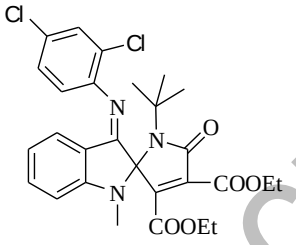
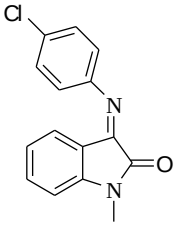
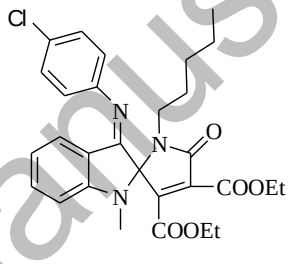
[c] NR no reaction

Table 2.Synthesis of novel spiro [indole-2,2'-pyrroles] scaffolds.



Entrys	N-methyl isatin imine	Dialkyl acetylenedicarboxylate	Spiro [indole-2,2'-pyroles] (1-12)	Yield (%)[a]
1				70
2				70
3				40
4				60

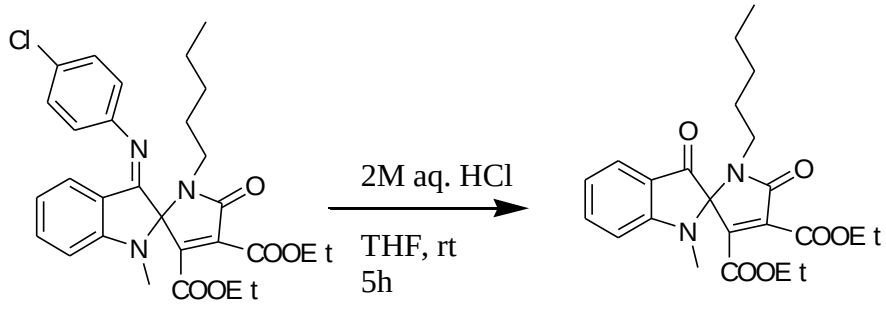
5				40
6				60
7				71
8				71
9				60
10				45

11				60
12				45
13[c]				70

[a]Isolated yield after column chromatography

[c]Reaction was performed using pentyl isocyanide

Scheme 1. Hydrolysis of product 13 to retain isatin carbonyl



Scheme 2. Plausible reaction mechanism for the formation of spiro[indole-2,2'-pyrroles].

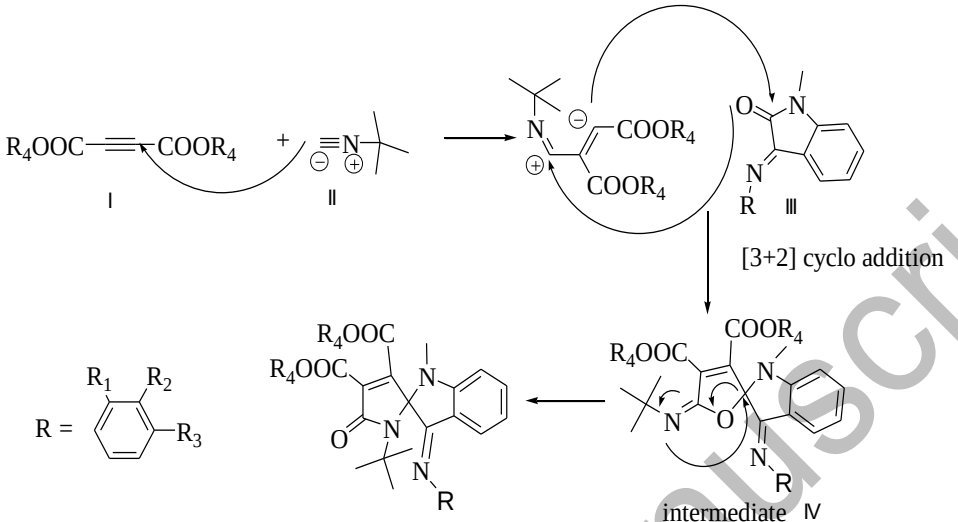


Figure 1. ORTEP plot for the X-ray crystal structure of 11 at 30% probability