One pot four-component reaction for the efficient synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives

Suman Pal, Nasim Khan, Shaik Karamthulla, Sk Jahir Abbas, Lokman H. Choudhury

PII: S0040-4039(13)01285-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.07.117
Reference: TETL 43315

To appear in: *Tetrahedron Letters*

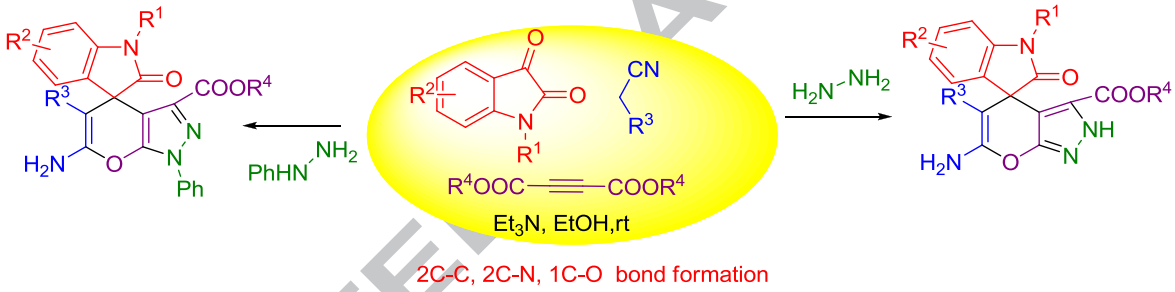
Please cite this article as: Pal, S., Khan, N., Karamthulla, S., Abbas, S.J., Choudhury, L.H., One pot four-component reaction for the efficient synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.07.117

Graphical abstract

One pot four-component reaction for the efficient synthesis of spiro[indoline-3,4'-pyrano[2,3 c]pyrazole]-3'-carboxylate derivatives

Leave this area blank for abstract info.

Suman Pal, Md. Nasim Khan, Shaik Karamthulla, Sk Jahir Abbas and Lokman H. Choudhury*



One pot four-component reaction for the efficient synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives

Suman Pal, Md. Nasim Khan, Shaik Karamthulla, Sk Jahir Abbas and Lokman H. Choudhury*

Department of Chemistry, Indian Institute of Technology Patna, Patna-800 013, INDIA

E-mail: lokman@iitp.ac.in ; Tel: +916122552038 ; Fax: +916122277383

Abstract: A novel one pot protocol has been developed to synthesize various spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives from the four-component reaction of isatin, malononitrile, hydrazine derivatives and dialkyl acetylenedicarboxylates. In this process two C-C bonds, two C-N bonds and one C-O bond have formed in one pot. The notable features of this protocol are simple and environmentally benign reaction condition, easy isolation of products, applicable to a wide range of readily available starting materials and good yields.

Keywords: Multicomponent reaction, Domino reaction, Isatin, Malononitrile, Hydrazine hydrate, Dialkyl acetylenedicarboxylate.

Spirocyclic compounds are considered as important building blocks for the easy access of a variety of cyclic products by rearrangement reaction due to their steric strain associated with the quaternary carbon.[1] Development of new methods for the construction of spirocyclic compounds is an interesting and challenging task in organic synthesis.[2] Isatin, a bioactive natural product having a benzylic ketone and a γ-lactam moiety attached with the arene ring is a widely used building block for the construction of spirooxindole derivatives.[3] Isatin based spiro compounds or spirooxindoles are important subunit found in many natural products as well as in synthetic pharmaceuticals such as spirotryprostatin B,[4] NITD609,[5] cyclopiamine B,[6] strychnofoline,[7] elacomine,[8] horsfiline[9] etc. (Fig. 1). Due to their significant and varied biological activities design and development of novel methods for the construction of

functionalized spirooxindoles have drawn remarkable interest from the synthetic organic as well as medicinal chemists.[10]

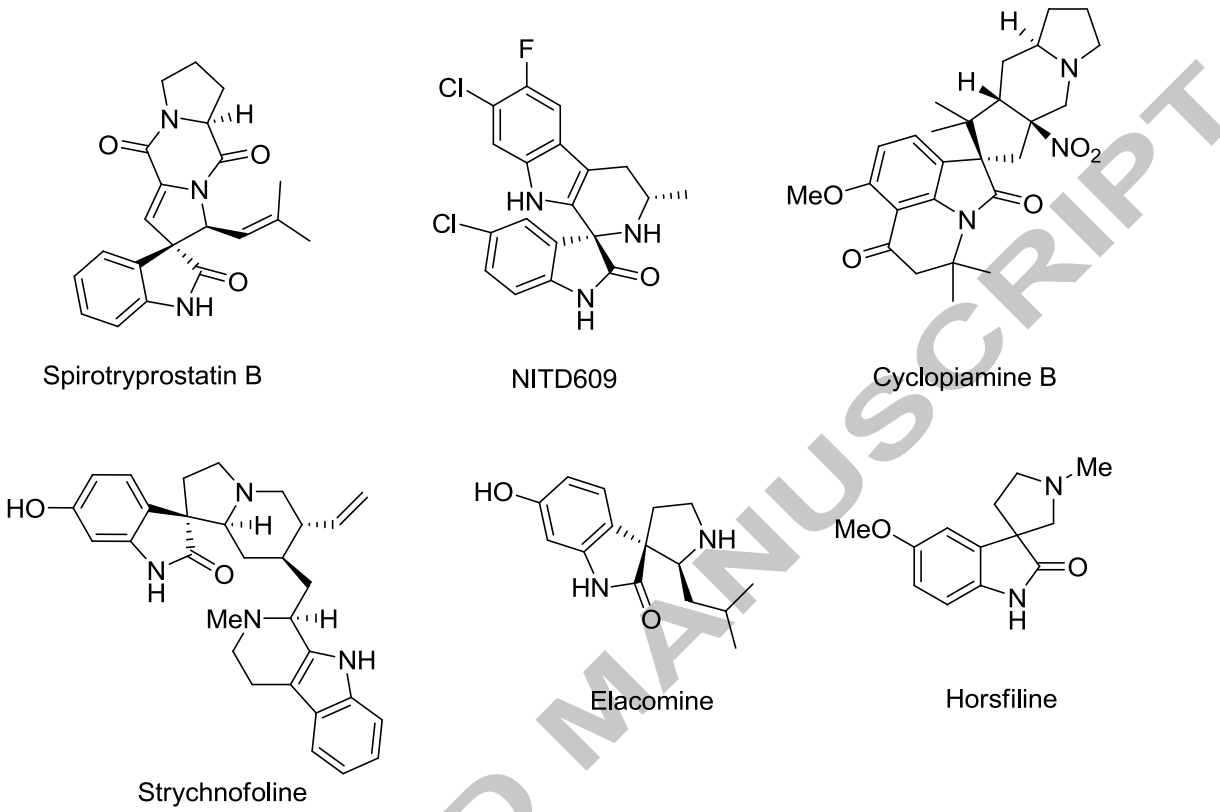
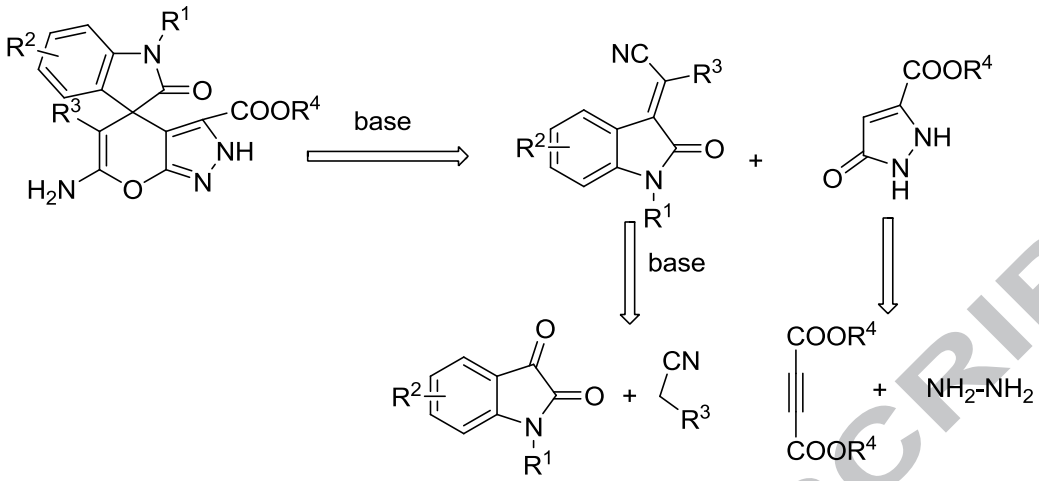


Figure 1. Some biologically important molecules containing spirooxindole motif

From the literature we realized that dihydropyrano[2,3-c]pyrazole scaffolds exhibit a wide range of biological activities such as antimicrobial[11], anticancer[12], anti-inflammatory[13] and molluscicidal activities.[14,15]Considering their clinical significance, development of efficient methods for the synthesis of dihydropyrano[2,3-c]pyrazole scaffolds have gained considerable attention from the synthetic community.[16] Although a number of methods are known for the construction of dihydropyrano[2,3-c]pyrazole and spirooxindole derivatives, however to our best of knowledge there is no method reported for the one-pot synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives from the multicomponent reaction of isatin, malononitrile, hydrazine hydrate and dialkyl acetylenedicarboxylates. In continuation of our efforts towards the development of functionalized heterocycles using multicomponent domino reactions[17] we envisioned that spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives could be synthesized by four-component reaction of isatin, malononitrile and hydrazine hydrate and dialkyl acetylenedicarboxylate in presence of a base (Scheme 1).



Scheme 1. Proposed strategy for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives

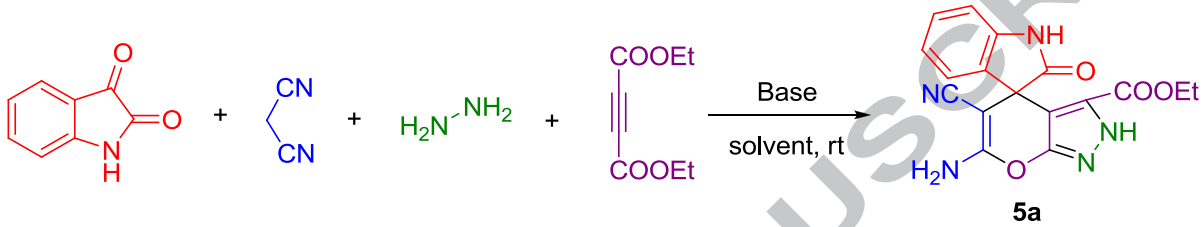
Recently we have demonstrated that the four-component reaction of amine, aromatic aldehyde, dimethyl acetylenedicarboxylate (DMAD) and malononitrile in presence of PEG as medium provides highly functionalized dihydropyridines and exhibit DNA cleavage properties.[18] Similarly, we have reported multicomponent reaction of malononitrile, aldehyde and thiols to provide highly functionalized amino pyridines with interesting photophysical properties.[19] In continuation of our work on multicomponent reactions, and considering the significant biological activities of spirooxindoles, we turned our attention towards isatin based MCRs.

For our initial investigation the reaction of isatin, malononitrile, hydrazine hydrate and diethyl acetylenedicarboxylate in ethanol was chosen as a model reaction. At room temperature and in the absence of any base or catalyst we could not isolate our desired four-component product even after 12 h stirring. After 24 h of stirring very trace amount of corresponding product was obtained. Next, the same set of reaction was performed in presence of one equivalent of mild base K_2CO_3. Within 8 h the corresponding four-component product **5a** was isolated in 52% yield. Product **5a** was characterized by usual spectroscopic techniques and elemental analysis. Encouraged by this result we attempted to optimize the yield of the reaction by screening the same set of reaction with various widely explored organic bases such as DBU, DABCO, DMAP and Et_3N and the results are summarized in Table 1. Among all the screened bases Et_3N was found superior with respect to reaction time and yield obtained. The same reaction was also tested using varying the

amount of Et_3N and one equivalent was found to be the optimum amount required for this reaction. Then we investigated the influence of different organic solvents in this reaction. Among the various solvents such as EtOH, CH_2Cl_2, CH_3CN, THF and DMF, EtOH was found the best solvent for this multicomponent reaction.

Table 1

Optimization of reaction condition[a]



5a

Entry	Base	Solvent	Time (h)	Yield(%)[b]
1	No catalyst	EtOH	24	trace
2	K_2CO_3	EtOH	8	52
3	DBU	EtOH	8	36
4	DABCO	EtOH	8	48
5	DMAP	EtOH	8	44
6	**Et_3N**	**EtOH**	**6**	**79**
7	Et_3N	CH_2Cl_2	6	trace
8	Et_3N	THF	6	56
9	Et_3N	CH_3CN	6	58
10	Et_3N	DMF	6	51

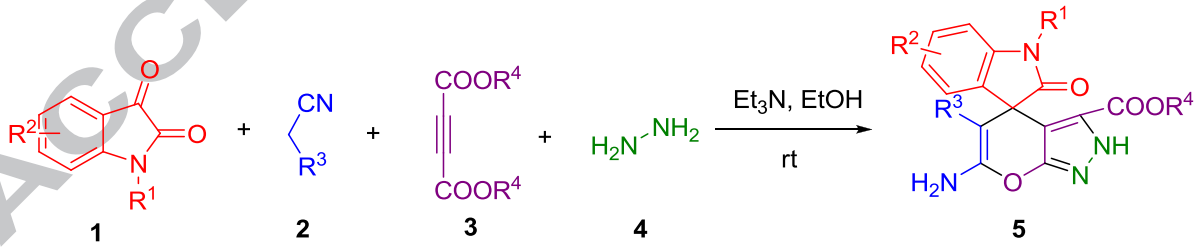
[a]Reaction conditions: Isatin (1.0 mmol), malononitrile (1.0 mmol), hydrazine hydrate (1.1 mmol), diethyl acetylenedicarboxylate (1.1 mmol), and base (1.0 mmol) at rt. [b] Isolated yield

With the optimized reaction condition in hand, the substrate scope, generality and versatility of this multicomponent reaction was investigated. A series of substituted isatin derivatives such as 5-Cl, 5-Br, 1-Me, 1-Ph, 7-Cl were found applicable for the synthesis of corresponding spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylates in good yields. Similar to malononitrile, ethyl cyanoacetate also participated in this multicomponent reaction to afford the corresponding spirooxindole derivatives in good yields. We also tested the variability of

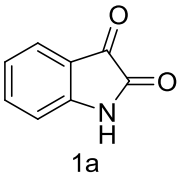
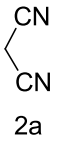
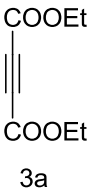
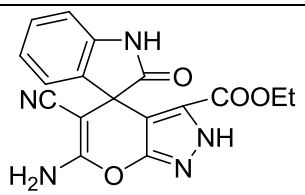
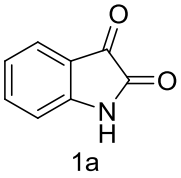
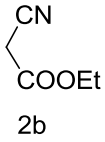
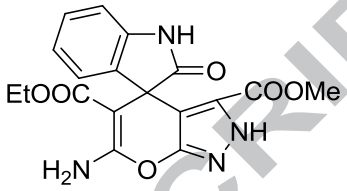
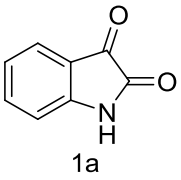
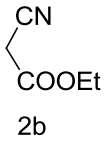
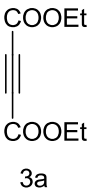
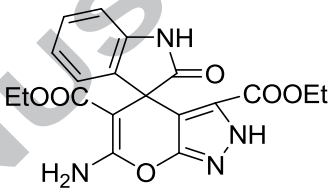
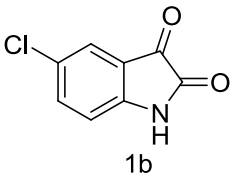
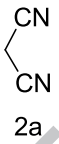
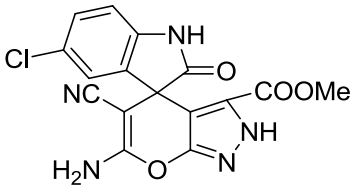
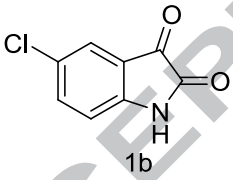
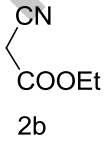
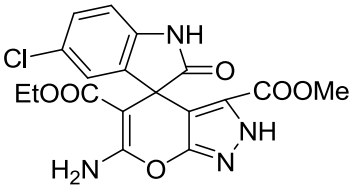
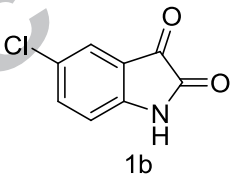
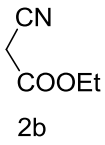
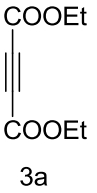
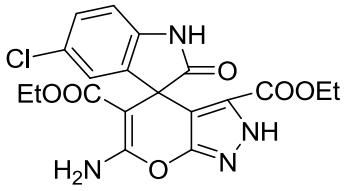
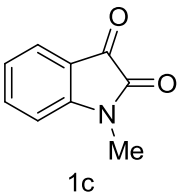
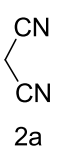
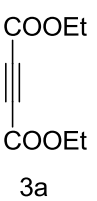
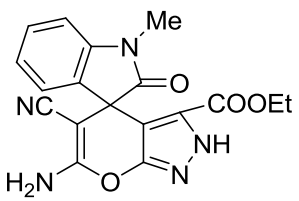
diethyl acetylenedicarboxylate by replacing it with dimethyl acetylenedicarboxylate under the similar reaction condition and the results are summarized in Table 2. Next, applicability of phenyl hydrazine in place of hydrazine hydrate was examined under the optimized reaction condition. The compounds **5r** and **5s** were obtained in good yields using phenyl hydrazine in place of hydrazine hydrate. It is evident from these results that the present protocol is highly versatile as all the four starting materials can be varied independently and bond-forming efficiency, i.e., total number of new bonds formed in one pot is five for this multicomponent reaction. All the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. The molecular structure of a representative compound **5i** was established unambiguously by single crystal X-ray diffraction (Fig. 2). The compound **5i** was recrystallized from the mixture of MeOH and MeCN and the crystal belongs to Triclinic, P-1 space group with Z = 2. In this molecule intra molecular hydrogen bonding has been observed between the CO of ethyl ester moiety and the NH_2 of the pyran ring due to their close proximity. Similarly intermolecular hydrogen bonding also exists between the NH_2 present in the pyran ring and the amide carbonyl (CONH) of oxindole moiety. The crystal structure (**5i**) also shows the inclusion of solvent molecule (MeOH) and showing hydrogen bonding with the **5i** (Fig. 3). It is noteworthy to mention that in all the cases the reactions were found remarkably clean except a few cases all the products were purified by recrystallization.[20]

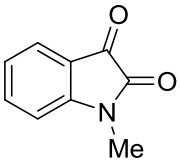
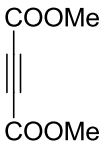
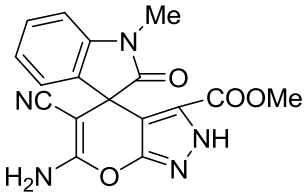
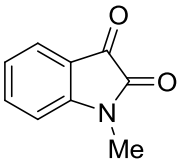
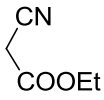
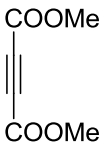
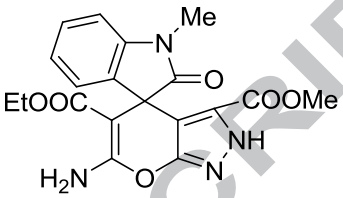
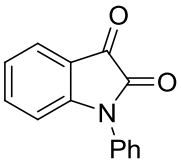
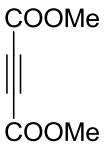
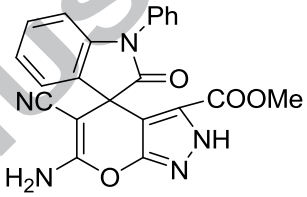
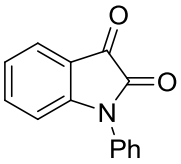
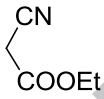
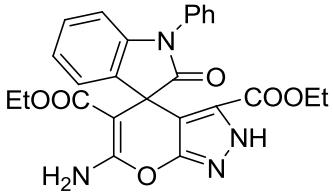
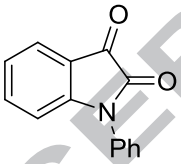
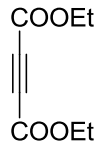
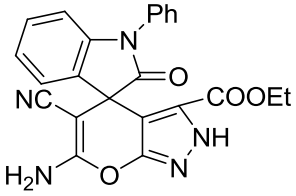
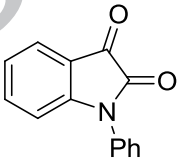
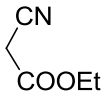
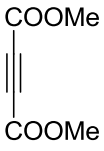
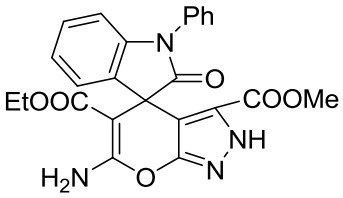
Table 2

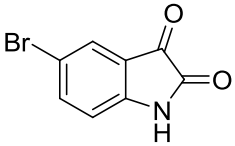
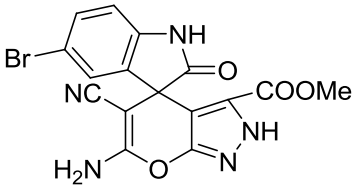
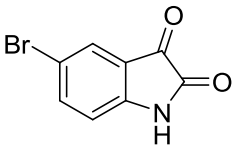
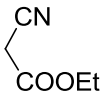
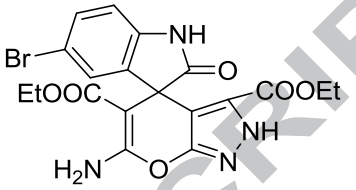
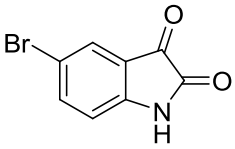
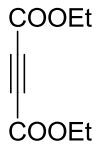
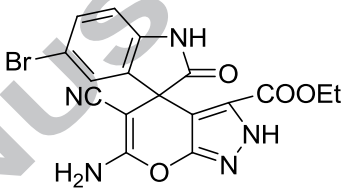
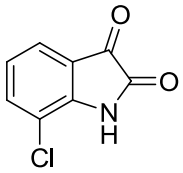
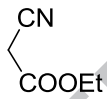
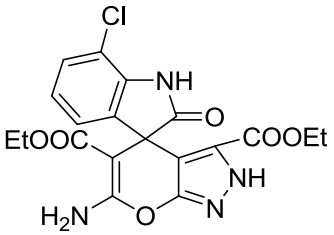
Synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives[a]



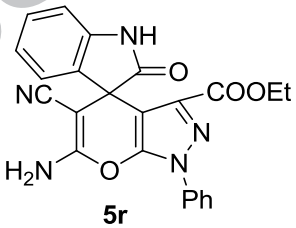
Entry	**1**	**2**	**3**	Time(hr)	Product	Yield[b] (%)

1	 1a	 2a	 3a	6	 **5a**	79
2	 1a	 2b	 3b	10	 **5b**	70
3	 1a	 2b	 3a	10	 **5c**	68
4	 1b	 2a	 3b	8	 **5d**	71
5	 1b	 2b	 3b	10	 **5e**	68
6	 1b	 2b	 3a	10	 **5f**	66
7	 1c	 2a	 3a	6	 **5g**	84

8	 1c	 2a	 3b	6	 **5h**	83
9	 1c	 2b	 3b	6	 **5i**	80
10	 1d	 2a	 3b	8	 **5j**	79
11	 1d	 2b	 3a	8	 **5k**	76
12	 1d	 2a	 3a	8	 **5l**	78
13	 1d	 2b	 3b	8	 **5m**	74

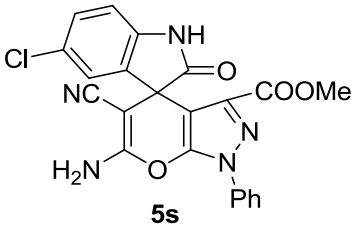
14	 1e	 2a	 3b	10	 **5n**	64
15	 1e	 2b	 3a	10	 **5o**	62
16	 1e	 2a	 3a	10	 **5p**	65
17	 1f	 2b	 3a	10	 **5q**	66

[a]Reaction conditions: Isatin (1.0 mmol), malononitrile or its derivative (1.0 mmol), hydrazine hydrate (1.1 mmol), dialkyl acetylenedicarboxylate (1.1 mmol), and Et_3N (1.0 mmol) in ethanol at rt. [b]isolated yield.



5r

10h, 74%



5s

10h, 72%

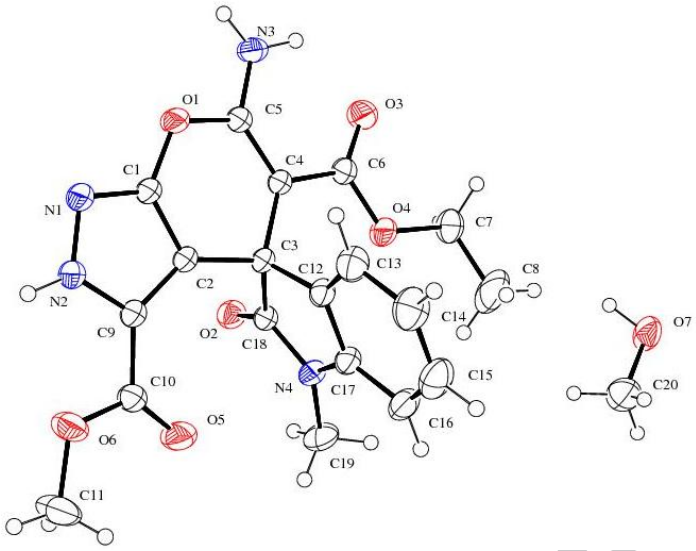


Figure 2. ORTEP diagram of compound **5i.**MeOH (CCDC 950299)

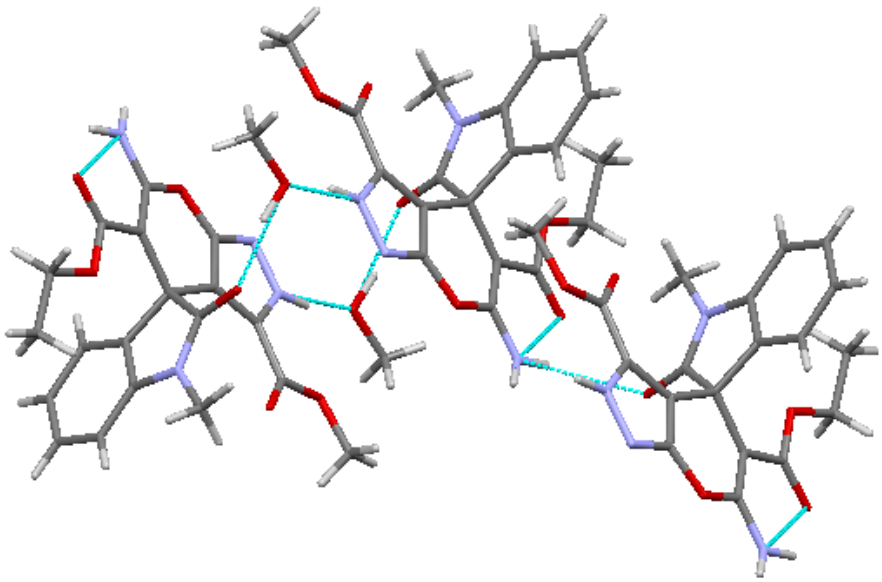
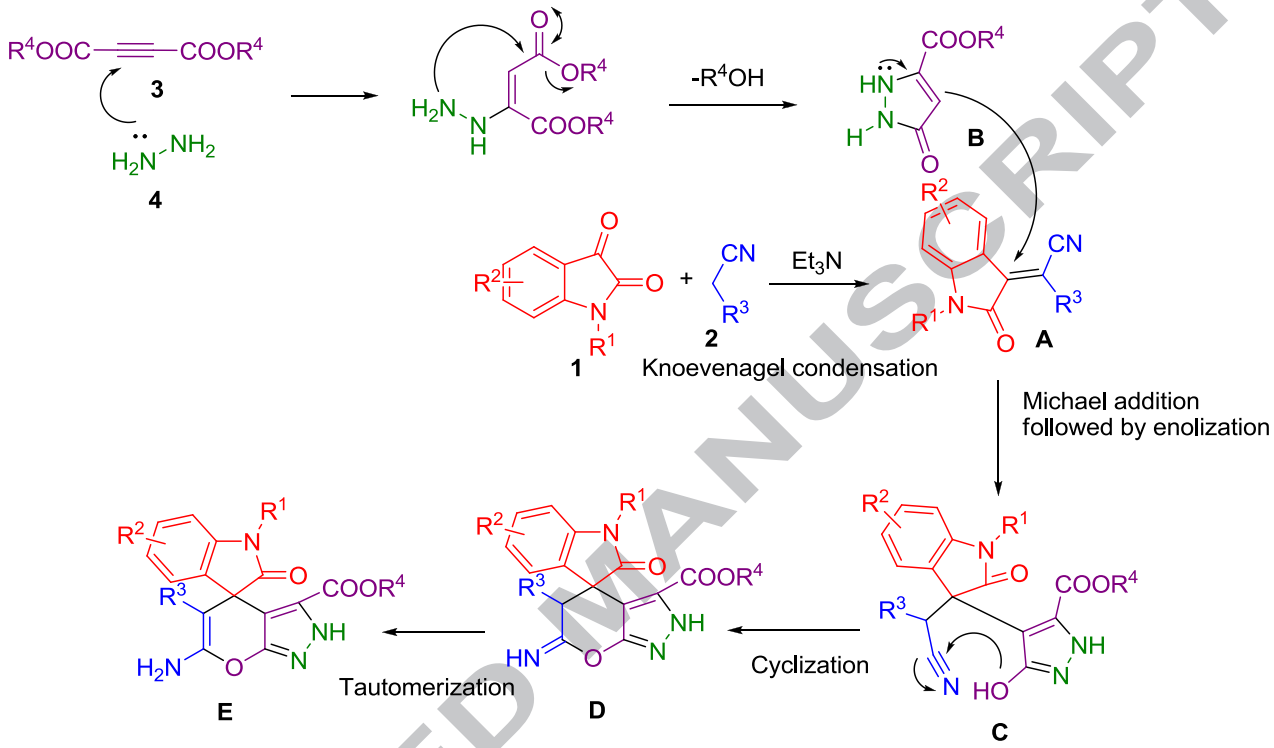


Figure 3. The hydrogen bonding pattern in molecule **5i**

On the basis of the above results a plausible reaction mechanism is shown in Scheme 2.

We believe that the initial step is formation of intermediate **A** by Knoevenagel condensation of **1** and **2**. Next step is the formation of pyrazolone **B** from the reaction of dialkyl acetylenedicarboxylate (**3**) and hydrazine hydrate (**4**). Then the intermediate **B** undergoes

Michael addition to **A** in the presence of a base followed by enolization affording intermediate **C** which undergoes intramolecular cyclization to form **D**. In the final step **D** undergoes tautomerization and transforms into the desired product **E**.



Scheme 2. Proposed mechanism for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives.

In conclusion, we have developed a simple and efficient four-component domino reaction mediated by Et_3N for the easy access of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives under mild reaction condition from the readily available starting materials. Considering the presence of spirooxindole and pyranopyrazole moiety in the products, this type of molecule may become useful in medicinal chemistry. Further efforts to see the scope and diversity of this multicomponent domino is currently underway and will be reported in due course.

Acknowledgements

L.H.C. is grateful to DST, New Delhi for financial assistance under the fastrack scheme with sanction No. SR/FT/CS-042/2009. S.P. is thankful to UGC for his research fellowship.

M.N.K. and S.K. are grateful to CSIR for their research fellowships. The authors are also grateful to SAIF, Panjab University, SAIF, IIT Madras and IIT Kanpur for providing analytical facilities for characterization of compounds.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:xxxxxxxxxxxxxx

References and notes

1. (a) Rousseau, G.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2008**, *10*, 4441-4444; (b) Zhao, F.; Wang, C.; Liu, L.; Zhanga, W.-X.; Xi, Z. *Chem. Commun.* **2009**, 6569-6571; (c) Murai, K.; Komatsu, H.; Nagao, R.; Fujioka, H. *Org. Lett.* **2012**, *14*, 772-775; (d) Bogdanowicz-Szwed, K.; Budzowski, A.; Gil, R.; Serda, P. *Monatsh Chem* **2010**, *141*, 63-74.
2. (a) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060-1074; (b) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Shu, X.-Z.; Liang, Y.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 7068-7071; (c) Jin, T.; Himuro, M.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 5893-5896; (d) Pigge, F. C.; Coniglio, J. J.; Dalvi, R. *J. Am. Chem. Soc.* **2006**, *128*, 3498-3499; (e) Huang, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 8060-8061.
3. (a) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104-6155; (b) Lashgari, N.; Ziarani, G. M. *Arkivoc* **2012**, *i*, 277-320.
4. (a) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651-12666; (b) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832-835.
5. Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175-1180.
6. Bond, R. F., Boeyens, J. C. A., Holzapfel, C. W.; Steyn, P. S. *J. Chem. Soc. Perkin Trans.* **1979**, *1*, 1751-1761.
7. Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758.

8. Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711-713.
9. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527-6530.
10. (a) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schu¨rmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nature Chemistry* **2010**, *2*, 735-740; (b) Tan, B.; Candeias, N. R.; Barbas III, C. F. *Nature Chemistry* **2011**, *3*, 473-477; (c) Wu, H.; Zhang, L.-L.; Tian, Z.-Q.; Huang Y.-D.; Wang Y.-M. *Chem Eur. J.* **2013**, *19*, 1747-1753; (d) Ghahremanzadeh, R.; Shakibaei, G. I.; Ahadi, S.; Bazgir, A. *J. Comb. Chem.* **2010**, *12*, 191-194; (e) Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 393-396; (f) Liang, B.; Kalidindi, S.; Porco, J. A.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 572-575.
11. El-Tamany, E. H.; El-Shahed, F. A.; Mohamed, B. H. *J. Serb. Chem. Soc.* **1999**, *64*, 9-18.
12. Wang, J. L.; Liu, D.; Zhang, Z. J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124-7129.
13. Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. *Z. Naturforsch.* **2006**, *61*, 1-5.
14. Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. *Arch. Pharm.* **2006**, *339*, 456-460.
15. Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. *Arch. Pharm.* **2007**, *340*, 543-548.
16. (a) Zou, Y.; Hu, Y.; Liu, H.; Shi, D. *ACS Comb. Sci.* **2012**, *14*, 38-43; (b) Litvinov, Y. M.; Shestopalov, A. A.; Rodinovskaya, L.A.; Shestopalov, A. M. *J. Comb. Chem.* **2009**, *11*, 914-919; (c) Zonouz, A. M.; Eskandari, I.; Khavasi, H. R. *Tetrahedron Lett.* **2012**, *53*, 5519-5522; (d) Bihani, M.; Bora, P. P.; Bez, G.; Askari, H. *ACS Sustainable Chem. Eng.* **2013**, *1*, 440-447.
17. (a) Pal, S.; Choudhury, L. H.; Parvin, T. *Mol Divers* **2012**, *16*, 129-143; (b) Choudhury, L. H.; Parvin, T. *Tetrahedron* **2011**, *67*, 8213-8228.
18. Pal, S.; Singh, V.; Das, P.; Choudhury, L. H. *Bioorganic Chemistry* **2013**, *48*, 8-15.
19. Khan, M. N.; Pal, S.; Parvin, T.; Choudhury, L. H. *RSC Adv.* **2012**, *2*, 12305-12314.

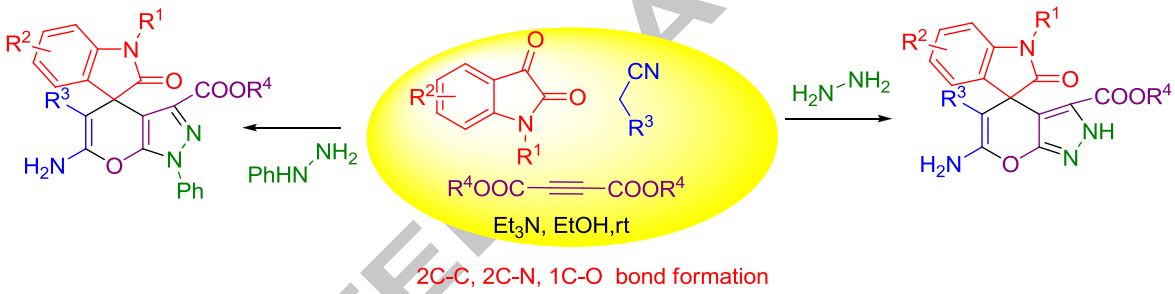
20. **General procedure for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate derivatives:** A mixture of isatin (1.0 mmol), malononitrile or its derivative (1.0 mmol) and Et_3N (1.0 mmol) in 3.0 mL ethanol were stirred at room temperature for 0.5h. Then a solution of hydrazine hydrate (1.1 mmol) and dialkyl acetylenedicarboxylate (1.1 mmol) in 2.0 mL ethanol was added to it. The whole solution was stirred at room temperature for stipulated time as indicated in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting precipitates were collected by filtration and the crude product was recrystallized from the mixture of methanol and acetonitrile (7:3). In some cases the crude product were purified by column chromatography using silica gel (60-120 mesh) and 50% ethyl acetate in hexane as eluent.

Graphical abstract

One pot four-component reaction for the efficient synthesis of spiro[indoline-3,4'-pyrano[2,3 c]pyrazole]-3'-carboxylate derivatives

Leave this area blank for abstract info.

Suman Pal, Md. Nasim Khan, Shaik Karamthulla, Sk Jahir Abbas and Lokman H. Choudhury*



2C-C, 2C-N, 1C-O bond formation