Triphenylphosphine Catalyzed, One-Pot, Multicomponent Synthesis of Spirooxindoles

Syed Riyaz*, A. Naidu and Pramod K. Dubey

Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Kukatpally, Hyderabad (A.P), 500 085, India

Received July 22, 2011: Revised September 14, 2011: Accepted October 19, 2011

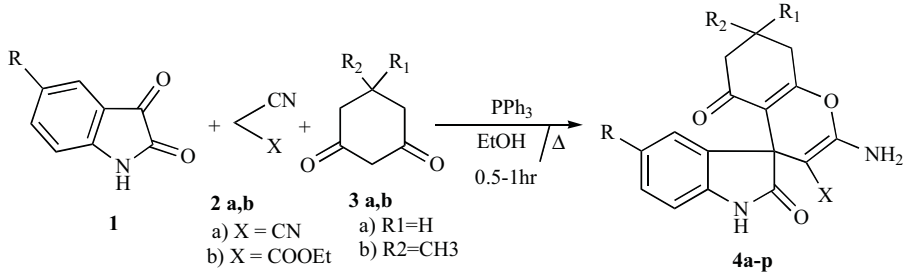
Abstract: Multicomponent reaction involving isatin (**1**), malononitrile (**2**), and dimedone (**3**), in the presence of triphenylphosphine as an efficient catalyst in the eco-friendly solvent ethanol, results in the formation of spirooxindole derivatives **4** i.e 2-Amino-5-oxo-7,7-dimethyl spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3-(3*H*)-indol]-(10*H*)-2-one-carbonitrile. The reaction proceeds smoothly under mild conditions and the products are obtained in good to excellent yields. This method is applicable to a variety of isatin derivatives.

Keywords: Cyclo addition, multicomponent reaction, spirooxindoles, triphenylphosphine.

INTRODUCTION

Spirocyclic compounds represent a prominent class of naturally occurring substances with highly pronounced biological properties [1]. The spirooxindole system is the core structure of many pharmaceutical agents and natural alkaloids. Thus, the development of new and simple synthetic methods for the preparation of spirooxindole derivatives has become an interesting synthetic challenge. Consequently, many synthetic methodologies have been developed for constructing these spirooxindole derivatives, most of which are based on cycloaddition or condensation reactions [2]. Particularly, domino multicomponent reactions have emerged as an efficient and powerful tool for the synthesis of complex molecules as a one-pot procedure [3]. Several reactions for the synthesis of spirooxindole through multicomponent reactions have been developed, by using indium(III) chloride [4] as a Lewis acid catalyst, triethylamine [5] as lewis base and electrocatalysis [6]. However, the above mentioned reported methods suffer from the usage of costly rare earth metals and toxic solvents such as acetonitrile [4]. Herein, we developed a new and simple methodology for the preparation of spirooxindoles *via* multicomponent reaction with triphenylphosphine [7, 8] as an efficient catalyst and ethanol as an eco-friendly solvent.

To realize the reaction shown in Scheme **1**, isatin **1**, malononitrile **2**, dimedone **3** and TPP (10mol%) were refluxed for 20-30 min to afford the corresponding spirooxindole product (Table **1**). The reaction was examined in different solvents including acetonitrile, methanol, ethyl acetate and ethanol. The best results were obtained in ethanol medium (Table **1**).

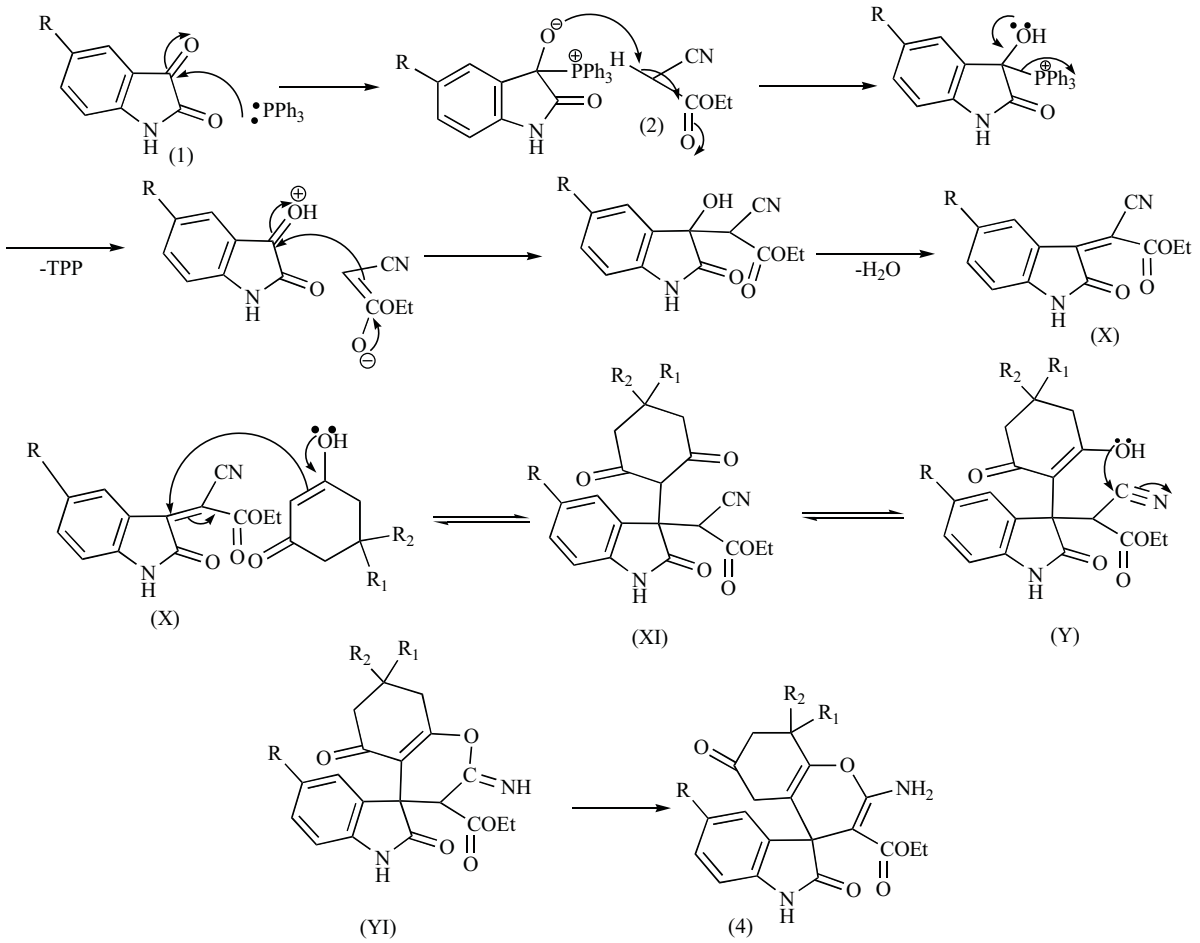


Scheme 1.

In order to investigate the scope of these conditions, several examples were studied and are summarized in Table **2**. In all cases, the three component reaction proceeded smoothly to give the corresponding spirooxindoles in good yields. As shown in Table **2**, it was found that this method works with wide scope of substrates. A variety of various halo substituted isatins and different 1,3-cyclohexanedione were subjected to this reaction. Additionally, the reaction with ethyl cyanoacetate or malononitrile also proceeded without any side products formation. However, we observed that the reaction time of ethyl cyanoacetate with isatins and cyclic 1,3-dicarbonyl compounds was longer than those with malononitrile, which is probably due to the lower reactivities of the cyanoacetates, when compared with malononitrile.

*Address correspondence to this author at the Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Kukatpally, Hyderabad (A.P), 500 085, India; Tel: +91-40-23158661 Fax: 040-23158661; E-mail: riyazsd@gmail.com

1875-6255/12 $58.00+.00



Scheme 2.

Two possible mechanisms have been proposed to account for the formation of **4** from **1, 2** and **3.** In the first mechanism proposed (Scheme **2**), the reaction includes a fast Knoevenagel condensation catalyzed by TPP in ethanol between isatin and the active methylene group of the cyano derivative to yield an α, β- unsaturated nitrile intermediate **(X)**. The formed knoevenagel intermediate is then attacked by the enol form of cyclic 1,3-diketo compound (Michael addition) followed by a keto-enol tautomerization to furnish the enol intermediate **(X^I)**. Nucleophilic addition of the hydroxyl group of intermediate **(Y)** to the cyano moiety afforded imine intermediate **(Y^I)**, which finally underwent further reaction to give the desired product.

In the second probable mechanism (Scheme **3**), the lone pair on the TPP abstracts the proton from the active methylene group of the cyano derivative to afford carbanion species, which further attacks the carbonyl group of the isatin to result in a C-C bond intermediate. Loss of water molecule gives the α, β- unsaturated nitrile intermediate **(X).** The formation of the final product spirooxindole **4** from **X** is similar to that as shown in the Scheme **2**.

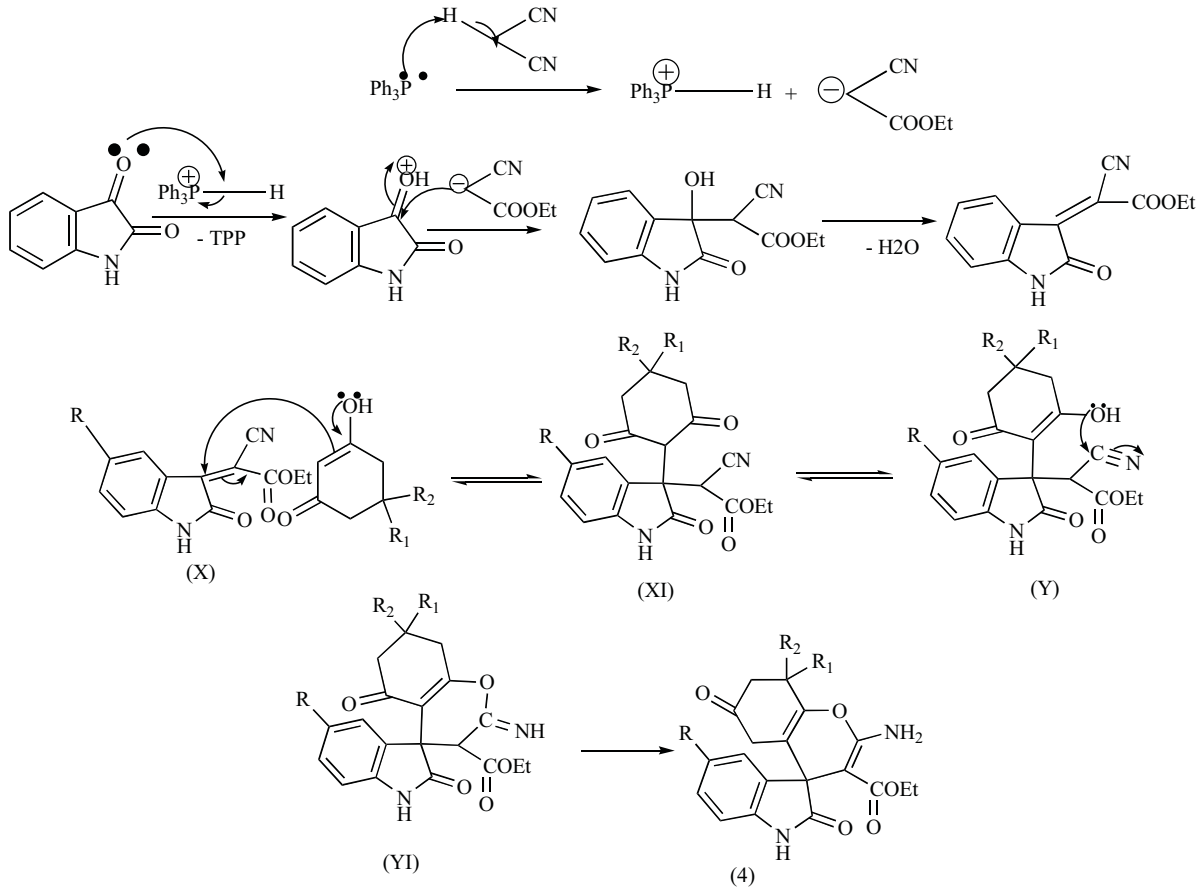
In substance, it can be said that the two mechanisms (shown in Scheme **2** and Scheme **3**) differ from one another in that the Scheme **2** involves a C-P bond formation between isatin and TPP to result in the intermediate **X** followed by Michael addition with cyclic-1,3-diketo compound, whereas in the Scheme **3**, TPP plays a typical base role by abstracting a proton from active methylene group to afford the intermediate **X** with the subsequent Michael addition to yield the final product. In this study, all the derivatives were characterized by melting point, IR, NMR and Mass spectral data, as well as by elemental analyses.

CONCLUSION

In conclusion, we have described a simple one-pot three component reaction involving isatin, activated methylene compound and cyclic 1,3-diketo compound to yield a series of spirooxindoles derivatives using TPP as a novel and inexpensive catalyst. Furthermore, this methodology conveniently afforded the desired products in good yields under mild conditions with operational simplicity.

EXPERIMENTAL SECTION

Melting points were uncorrected and determined in open capillary tubes in sulphuric acid bath. Thin-layer chromatography (TLC) was performed on silica gel G, and spotting was done using iodine or UV light. IR spectra were recorded with Jasco FT-IR 5300, ^{1}H NMR on Varian 400-MHz instrument, and Mass spectra on an Agilent LC-MS instrument giving only $M^{+\cdot}$ values in Q+1 mode.



Scheme 3.

Table 1. Rate of Reaction in Different Solvent Mediums

Entry	Solvent	Time (hrs)	Yield(%)
1	Methanol	1.5	80-85
2	Ethylacetate	3.0	78-85
3	Acetonitrile	2.0	85-90
4	Ethanol	0.5	90-95

Table 2. TPP Catalyzed One-Pot Multi Component Synthesis of Spirooxindoles 4

Entry	(1) R	(2) X	(3)		Product (4)	Yield(%)	M.P (Lit) (^{o}C)
			R^1	R^2			
1	H	CN	H	H	4a	92	>300 (304-305)
2	H	COOEt	H	H	4b	85	265-267 (263-265)[6]
3	H	CN	CH_3	CH_3	4c	94	270-272 (268-270)[4]
4	H	COOEt	CH_3	CH_3	4d	89	260-262 (257-258)[6]
5	F	CN	H	H	4e	93	275-277

(Table 2). Contd…..

Entry	(1) R	(2) X	(3)		Product (4)	Yield(%)	M.P (Lit) (^oC)
			R^1	R^2			
6	F	COOEt	H	H	4f	88	270-272 (273-74)[6]
7	F	CN	CH_3	CH_3	4g	86	268-270 (270-272)[6]
8	F	COOEt	CH_3	CH_3	4h	83	238-240 (240-42)[6]
9	Cl	CN	H	H	4i	93	274-276
10	Cl	COOEt	H	H	4j	87	281-283
11	Cl	CN	CH_3	CH_3	4k	92	290-292 (289-291)[6]
12	Cl	COOEt	CH_3	CH_3	4l	85	275-278
13	I	CN	H	H	4m	91	277-279
14	I	COOEt	H	H	4n	86	280-282
15	I	CN	CH_3	CH_3	4o	93	>300
16	I	COOEt	CH_3	CH_3	4p	89	281-283

General Procedure

A mixture of appropriate isatin (**1**, 1.0mmol), malononitrile or ethyl cyanoacetate (**2**, 1.0mmol), appropriate 1,3-dicarbonyl (**3**, 1.0mmol) and catalytic amount of TPP in EtOH (15ml) were refluxed for 20-30 mins at 78^0C and then cooled to R.T. The separated solid was collected by filtration, washed with excess of EtOH (5ml), and dried in oven to obtain crude **4.** The latter, was recrystallized from MeOH to get pure **4**.

Spectral Data of the Selected Compounds

4a: IR (KBr): 3390, 3310 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2208 (-CN group, sharp), 1720 (-C=O of chromene moiety, sharp), 1645cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 1.96 -2.95 (m, 6H –$(CH_2)_3$), 6.72-7.15 (m, 4H aromatic), 7.25 (S, 2H, -NH_2, D_2O exchangeable), 10.44 (s, 1H, -NH, D_2O exchangeable) M, /Z (M^++1): 308.

4e: IR (KBr): 3395, 3306 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2205 (-CN group, sharp), 1720 (-C=O of chromene moiety, sharp), 1645cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 1.91 -2.91 (m, 6H –(CH_2), 6.62-7.18 (m, 3H aromatic), 7.24 (S, 2H, -NH_2, D_2O exchangeable), 10.45 (s, 1H, -NH, D_2O exchangeable) m/z: (M^++1): 326.

4i: IR (KBr): 3405, 3316 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2201 (-CN group, sharp), 1720 (-C=O of chromene moiety, sharp), 1645cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 1.89 -2.81 (m, 6H –$(CH_2)_3$, 6.52-7.28 (m, 3H aromatic), 7.19 (S, 2H, -NH_2, D_2O exchangeable), 10.55 (s, 1H, -NH, D_2O exchangeable) m/z: (M^++1): 342.

4j: IR (KBr): 3395, 3303 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2208 (-CN group, sharp), 1742 (-C=O of ester group), 1710 (-C=O of chromene moiety, sharp), 1655cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 0.94 (t, 3H, -$COOCH_2CH_3$), 1.86 -2.85 (m, 6H –$(CH_2)_3$), 3.62(m, 2H, , -$COOCH_2CH_3$) 6.61-7.33 (m, 3H aromatic), 7.15 (S, 2H, -NH_2, D_2O exchangeable), 10.52 (s, 1H, -NH, D_2O exchangeable). m/z: (M^++1): 389.

4k: IR (KBr): 3435, 3328 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2191 (-CN group, sharp), 1715 (-C=O of chromene moiety, sharp), 1640cm-1 (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 1.02 (s, 3H, -CH_3) 1.08 (s, 3H, -CH_3), 1.95-2.13 (m, 2H), 2.35-2.63 (m, 2H), 6.76-7.29 (m, 3H aromatic), 7.32 (S, 2H, -NH_2, D_2O exchangeable), . m/z: (M^++1): 370.

4l: IR (KBr): 3408, 3327 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2203 (-CN group, sharp), 1720 (-C=O of chromene moiety, sharp), 1645cm^{-1} (-C=O of

isatin amide group, broad), ^{1}H-NMR (400MHz, DMSO-d6/TMS): δ 0.94 (t, 3H, -$COOCH_2CH_3$), 1.02 (s, 3H, -CH_3) 1.08 (s, 3H, -CH_3), 1.86 -2.85 (m, 6H –$(CH_2)_3$), 3.66(m, 2H, -$COOCH_2CH_3$), 6.61-7.33 (m, 3H aromatic), 7.15 (S, 2H, -NH_2, D_2O exchangeable), 10.52 (s, 1H, -NH, D_2O exchangeable). m/z: (M++1): 417.

4m: IR (KBr): 3401, 3310 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2210 (-CN group, sharp), 1719 (-C=O of chromene moiety, sharp), 1642cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 1.85 -2.79 (m, 6H –$(CH_2)_3$, 6.49-7.18 (m, 3H aromatic), 7.15 (S, 2H, -NH_2, D_2O exchangeable), 10.49 (s, 1H, -NH, D_2O exchangeable) m/z: (M^++1): 434.

4n: IR (KBr): 3397, 3307 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2215 (-CN group, sharp), 1745 (-C=O of ester group), 1715 (-C=O of chromene moiety, sharp), 1649cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 0.96 (t, 3H, -$COOCH_2CH_3$), 1.84 -2.84 (m, 6H –$(CH_2)_3$), 3.59(m, 2H, , -$COOCH_2CH_3$) 6.51-7.29 (m, 3H aromatic), 7.19 (S, 2H, -NH_2, D2O exchangeable), 10.51 (s, 1H, -NH, D_2O exchangeable). m/z: (M^++1): 481.

4o: IR (KBr): 3415, 3325 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2195 (-CN group, sharp), 1710 (-C=O of chromene moiety, sharp), 1635cm^{-1} (-C=O of isatin amide group, broad), ^{1}H- NMR (400MHz, DMSO-d6/TMS): δ 1.04 (s, 3H, -CH_3) 1.09 (s, 3H, -CH_3), 1.99-2.17 (m, 2H), 2.35-2.73 (m, 2H), 6.76-7.39 (m, 3H aromatic), 7.40 (S, 2H, -NH_2), . m/z: (M^++1): 462.

4p: IR (KBr): 3409, 3321 (unequal doublet, asymmetric and symmetric stretching of -NH_2), 2201 (-CN group, sharp), 1710 (-C=O of chromene moiety, sharp), 1634cm^{-1} (-C=O of isatin amide group, broad), ^{1}H-NMR (400MHz, DMSO-d6/TMS): δ 0.99 (t, 3H, -$COOCH_2H_3$), 1.05 (s, 3H, -CH_3) 1.11 (s, 3H, -CH3), 1.91 -2.95 (m, 6H –$(CH_2)_3$), 3.69(m, 2H, -$COOCH_2H_3$), 6.71-7.39 (m, 3H aromatic), 7.19 (S, 2H, -NH_2, D_2O exchangeable), 10.72 (s, 1H, -NH, D_2O exchangeable). m/z: (M^++1): 509.

ACKNOWLEDGEMENTS

The authors are thankful to the authorities of Jawaharlal Nehru Technological University Hyderabad, for providing laboratory facilities. They are also indebted to University Grants Commission, Government of India, New Delhi, for providing financial support.

REFERENCES

[1] (a) James, D. M.; Kunze, H. B.; Faulkner, D. J. Two New Brominated Tyrosine Derivatives from the Sponge Druinella (=Psammaplysilla) purpurea *J. Nat. Prod.***1991**, *54,* 1137. (b) Kobayashi, J.; Tsuda, M.; Agemi, K.;Shigemiri, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. Purealidins B and C, new bromotyrosine alkaloids from the okinawan marine sponge *psammaplysilla purea Tetrahedron* **1991**, *47,* 6617. (c) Sannigrahi, M. Stereocontrolled synthesis of spirocyclics *Tetrahedron* **1999**, *55,* 9007. (d) Heathcock, C. H.; Graham,S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *SpirocyclicSystems, In The Total Synthesis of Natural Products, Vol. 5; Simon, J., Ed.; John Wiley & Sons: New York*, **1983**, 264

[2] (a) Fuchs, J. R.; Funk, R. L Indol-2-one Intermediates: Mechanistic Evidence and Synthetic Utility. Total Syntheses of (±)-Flustramines A and C. *Org. Lett*. **2005**, 7, 677. (b) Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. Syntheses of spiro[cyclopropane-1,3′-oxindole]-2-carboxylic acid and cyclopropa[*c*]quinoline-7b-carboxylic acid and their derivatives *Tetrahedron* **2007**, *63*, 1191. (c) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. Design, synthesis and biological evaluations of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors. Part I *Bioorg. Med. Chem.Lett*. **2006**, *16,* 2105. (d) Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A.H.;Turner, P. Synthesis of 2-azaspiro[4.4]nonan-1-ones *via* phosphine-catalysed [3+2]-cycloadditions *Tetrahedron* **2005**, *61,* 8120. (e) Feldman, K. S.;Vidulova, D. B.; Karatjas, A. G. Extending Pummerer Reaction Chemistry. Development of a Strategy for the Regio- and Stereoselective Oxidative Cyclization of 3-(ω-Nucleophile)-Tethered Indoles *J.Org. Chem*. **2005**, 70, 6429. (f) Osman, F. H.; Samahy, F. A. On the Reaction of Isatin with Cyanomethylene(triphenyl)-phosphorane. A Nucleophilic Attack of Alkyl Phosphites on the Carbon–Carbon Double Bond of (*E*)-Oxindolylideneacetonitrile*Tetrahedron* **2000**, *56,* 1863. (g) Mao, Z.; Baldwin, S. W. New Spirocyclic Oxindole Synthesis Based on a Hetero Claisen Rearrangement. *Org. Lett*. **2004**, *6,* 2425. (h) Feldman, K. S.; Karatjas, A. G. Extending Pummerer Reaction Chemistry. Asymmetric Synthesis of Spirocyclic Oxindoles *via* Chiral Indole-2-sulfoxides. *Org. Lett*. **2006**, *8,* 4137. (i) Marti, C.; Carreira, E. M. Total Synthesis of (−)-Spirotryprostatin B: Synthesis and Related Studies. *J. Am. Chem. Soc*. **2005**, *127,* 11505. (j) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. Dihydropyridazinone cardiotonics: synthesis and inotropic activity of 5'-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-spiro[cycloalkane-1,3'-[3H]indol]-2'(1'H)-ones. *J. Med.Chem*. **1987**, *30,* 824. (k) Lo, M.M.-C.; Neumann, C. S.; agayama, S.; Perlstein, E. O.; Schreiber, S. L. A Library of Spirooxindoles Based on a Stereoselective Three-Component Coupling Reaction. *J. Am. Chem. Soc*. **2004**, *126,* 16077.

[3] (a) Dömling, A.; Ugi, I. Multicomponent Reactions Isocyanides. *Angew. Chem. Int. Ed.* **2000**, *39,* 3168. (b) Dömling, A. *Chem. Rev*. **2006**, 106, 1. (c) Zhu, J. Recent Developments in the Isonitrile-Based Multicomponent Synthesis of Heterocycles . *Eur. J. Org. Chem*. **2003**, *7,* 1133.

[4] Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. A new $InCl_3$-catalyzed, facile and efficient method for the synthesis of spirooxindoles under conventional and solvent-free microwave conditions *Tetrahedron* **2007**, *63,* 2057.

[5] Litvinov,M.Y.; Mortikov.V; and Shestopalov, A.M; Versatile Three-Component Procedure for Combinatorial Synthesis of 2-Aminospiro[(3′*H*)-indol-3′,4-(4*H*)-pyrans]. *J. Comb. Chem.* **2008**, *10,* 741.

[6] Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov,F. M.; Ogibin, Y. N.; Nikishin, G. I. Electrocatalytic multicomponent transformation of cyclic 1,3-diketones, isatins, and malononitrile: facile and convenient way to functionalized spirocyclic (5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole system *Tetrahedron* **2007**, *63,* 10543 .b) Dabiri.M, baharamnejad. M, Baghbanzadeh. M; Ammonium salt catalyzed multicomponent transformation: simple route to functionalized spirochromenes and spiroacridines *Tetrahedron* **2009**, *65,* 9443.

[7] Yadav, J.S; Subba Reddy, B.V; Basak, A.K ; Visali, B; Venkata Narsaiah, A; Nagaiah, K; Phosphane-Catalyzed Knoevenagel Condensation: A Facile Synthesis of α-cyanoacrylates and α-Cyanoacrylonitriles, *Eur. J.Org. Chem*. **2004**, 546.

[8] Debache, A; Mouna. A.; Ali Belfaitah.; Rhouati, S; Carboni,B; A one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones catalyzed by triphenylphosphine as Lewis base. *Tetrahedron Lett*. **2008**, 49, 6119.