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**Research Article**

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# Synthesis of Spiro[4H-pyran-3,3-oxindole] by 1,3-Dibromo-5,5-Dimethyl Hydantoin (DBDMH) as a Catalyst Using Eco-Friendly Medias

**Yasamin Saadati[1*], F Seyedeh Hojati[1], Maan Al Naddaf[2] and Mohammad Keshe[3]**

[1]*Department of Chemistry, Hakim Sabzevari University*
[2]*Gambrinusstraße*
[3]*Department of Chemistry, Faculty of Sciences, Al-Baath University, Homs, Syria*

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**ABSTRACT**

*A highly efficient method for the synthesis of unsymmetrical spiro[4H-pyran-3,3-oxindole] is reported by three-component condensation of isatin, malonitrile and dimedone in the presence of catalytic amount of 1,3-dibromo-5,5-dimethyl hydantoin (DBDMH); High yields of products, short reaction times the use of non-toxic solvent and easy work-up in combination with commercial availability, low cost and non-toxicity of the catalyst make this work eco-friendly and commercially acceptable.*

**Keywords**: Multicomponent synthesis; Isatin; Spiro [4H-pyran-oxindole]; 1,3-Dibromo-5,5-dimethylhydantoin

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## INTRODUCTION

Water is the most abundant compound in the earth and the human body. In fact, almost all of animates vital reactions are done in this revitalizing solvent. More than one century, the formation of carbon-carbon bonding in watery medium was restricted to electrochemical process and Aldoli condensation reactions. The Dilz-Alder reaction was first performed in watery medium in 1930 [1]. Also, the other reactions such as Fridel-crafts reactions and benzofuran derivatives synthesis were done in aqueous solution [2,3]. There are some reasons why water is appropriate medium for chemical reaction such as abundance, easily available, low cost, non-flammable and the most important factor is that it is non-poisonous [4-6].

Multi-component reactions (MCRs) were discovered by Esterker in 1850. The most important criteria for efficiency and applicability of a chemical process is to minimize the number of synthesis and purification steps. In this process, one-pot reactions of two or more substrates are performed simultaneously and then two or more bonds are formed. Therefore, valuable and useful complex structures can be efficiently achieved by a quick and commercially acceptable method. Multi-component reactions allow easy synthesizing of some interesting hetrocycles such as spiro oxindole. Spiroxindol are attractive target for organic synthesis because they are the main core of many pharmaceutical structures and natural alkaloids such as spyrotryprostatin A, B which are inhibitor of microtubule association [7-10].

Among the heterocyclic spiro-oxindole ring system, functionally substituted 4*H*-chromenes and pyrano [2,3-c]pyrazoles have received considerable attention due to their wide range of useful biological properties, which include antiviral, [11] herbicidal, [12,13] anticonvulsant and analgesic, [14] antitumor, [15-17] anti-cancer [18] and anti-malaria [19] and central nervous system activities. [10] Therefore, the development of an efficient method for the preparation of these biologically active heterocycles has been attracted a special attention of organic chemists and several protocol for multi-component synthesis of them have been reported. But, there is a strong demand for offering a mild, clean and efficient procedure for the synthesis of this worthy compound because most of the reported methods have some drawbacks such as long reaction times, low yields of product, the use of expensive reagent or toxic solvent and by-product formation.

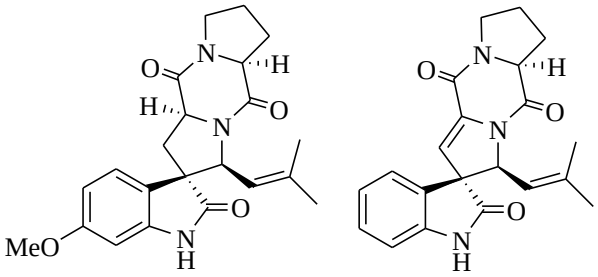



**Figure 1: Structure of Spirotryprostatins**

DBDMH (1,3-Dibromo-5,5-dimethylhydantoin) is a N-halo which has been applied in industrial process on the basis of its economical profits. [20] DBDMH has been known as a good oxidative and brominating agent and Recently, has been taken in to account as a homogeneous catalyst in organic transformation because of its commercial availability, low cost and high catalytic activity [21-24] (Figure 1).

## MATERIALS AND METHODS

### Experimental

All materials are commercial reagent grade and were obtained from Merck Co. IR spectra were recorded on a Shimadzu FT-IR 8440S spectrophotometer. $^1$H NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer and DMSO was used as NMR solvent. Melting Points were taken on a Bamstead Electrothermal apparatus.

**General Procedure for the synthesis of 2-amino-7,7-dialkyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile derivatives (4).** A mixture of isatin (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) and DBDMH (10 mol%) in $H_2O$ (2.5 ml) was stirred at 80°C for appropriate time according to Table 2. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/EtOAc=2:1). The reaction mixture was allowed to cool to room temperature and crude product was obtained by simple filtration. Further purification was performed by recrystallization in ethanol to afford pure products in good to excellent yields (Table 2).

**Procedure for the Synthesis 2′-amino-3′-methyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano [2,3-*c*]pyrazole]-5′-carbonitrile derivatives (6).** To a mixture of isatin (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) and malononitrile (1 mmol) in $H_2O$ (2.5 ml), was added the catalyst (0.1 mmol) and stirred at 80°C for appropriate time according to Table 3. After completion of the reaction as indicated by TLC (eluent: *n*-hexane/EtOAc=2:1), the reaction mixture was cooled to room temperature and participated residue purified by recrystallization in EtOH.

**2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydro spiro[chromene-4,3'-indoline]-3-carbonitrile (4a).** mp 290-292°C; IR (KBr): 3412, 3280, 3114, 2200, 1692, 1650, 1526, 1132; $^1$H NMR (DMSO-$d_6$) δ 0.97 (s, 3H, $CH_3$), 1.00 (s, 3H, $CH_3$), 2.08 (d, *J*=16.2 Hz, 1H, CH) 2.17 (d, *J*=16.2 Hz, 1H, CH) 2.47 (d, *J*=6.2 Hz, 2H, $CH_2$) 6.75 (d, *J*=7.5 Hz, 1H, ArH), 6.84 (t, *J*=7.5 Hz, 1H, ArH), 6.94 (d, *J*=6.9 Hz, 1H, ArH), 7.09 (t, *J*=7.5 Hz, 1H, ArH), 7.22 (s, 2H, $NH_2$), 10.39 (s, 1H, NH).

**6′-amino-3′-methyl-2-oxo-1′-phenyl-1,2-dihydro-1′H-spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (6a).** mp 236–237°C; IR (KBr): $^1$H NMR (DMSO-$d_6$) δ 1.54 (s, 3H, $CH_3$), 6.94 (d, *J*=7.7Hz, 1H, ArH), 7.03 (t, *J*=7.4Hz, 1H, ArH), 7.18 (d, *J*=7.3Hz, 1H, Ar), 7.28 (t, *J* =7.6Hz, 1H, ArH), 7.35 (t, *J*=7.9Hz, 1H, Ph), 7.52 (t, *J*=7.9Hz, 2H, Ph), 7.57 (s, 2H, $NH_2$), 7.78 (d, *J*=7.9Hz, 2H, Ph), 10.74 (s, 1H, NH).

## RESULTS AND DISCUSSION

With regard to use of reagent, non-poisonous solvent, devotee of the environment, high efficacy of multicomponent reaction and biological property of various oxindol compound, we decide to offer simple and efficient method for synthesizing hetrocycle of oxindole multi factor with the use of three-component reaction, in watery medium and in the presence of DBDMH as a catalyst, in fact, we want to offer them in an economical and chemical profit. So, first we choose

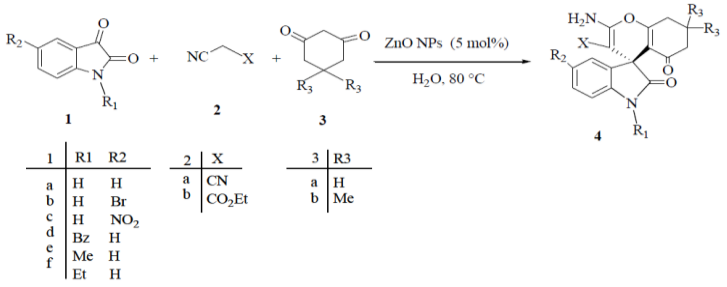
Isatin, Dimedon and Malononitril as a model reaction in an optimum circustance (condition) with various tests in order to obtain the best temperature, solvent and the rate of catalyst mol. The best results from value reaction have been shown both mol in the presence of DBDMH 10 mol% in watery medium and in the 10°C. Under this circumstance Spiroxindole with yield of 90% is separated after 10 minutes. In order to indicate the importance of DBDMH presence, smilar reaction are done in the absence of catalyst and in the presence of base and acid catalyst. The results have been summarized in Table 1.

**Table 1: The effect of different reagents on the model reaction**

| Entry | Catalyst | Amount (mol%) | Temperature (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $ZrCl_4$ | 5 | 80 | 150 | 80 |
| 2 | $K_2CO_3$ | 5 | 80 | 60 | 86 |
| 3 | $Na_2CO_3$ | 5 | 80 | 70 | 83 |
| 4 | Morpholine | 20 | 80 | 50 | 74 |
| 5 | Pyridine | 5 | 80 | 54 | 86 |
| 6 | DBDMH | 10 | 80 | 10 | 90 |
| 7 | --- | --- | 80 | 60 | Trace |

## Synthesis of Spiro [4H-oyran-oxindole] Using Various Temperatures and Catalysts

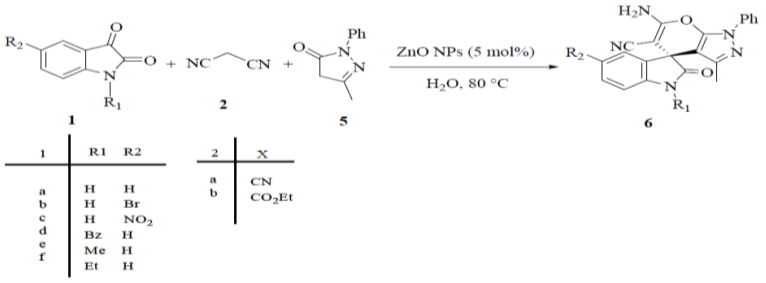
The table shows the presence of DBDMH is really essential for synthesizing of spiroxindole. Indeed, this compound is the best selection for preparing the compounds. In order to generalize the present method various derivations have reacted at the optimization Isatin, malononitril or Ethyl cyano asetet (Scheme 1). The results are shown in Tables 1-3. As you see in the table, products are appropriate in a short time with high yields.




**Scheme 1: Synthesis route of the main reaction**

## DBDMH-Catalyzed Multi-Component of Isatin, Active Methylene Compounds and Dimedon

Thus The efficacy of obtained method is estimated in preparing 6-Amino-3-methyl-2-oxo-1-phenyl-1H-spiro[indoline-3,4 pyrano[2,3-c]pyrazole-5-carbonitrile from Isatin, Malononitrile, prazol 5 one (Scheme 2). With regard to this scheme, the products are available in a short time and appropriate yield. So, DBDMH is a good and effective regent for preparing both of categorization of compounds.




**Scheme 2: Spirooxindoles from 3-methyl-1-phenyl-2-pyrazolin-5-one**

Infact, the mechanics of derivation synthesis of 2-Amino-5-oxo-spiro(4H)-5,6,7,8-tetrahydrochromene-4,30-(30H)-indole-(10H)-20-one-3-carbonitrile is not clearly evident, but reasonable mechanism is offered for synthesizing these hytrocycles in the presence of DBDMH.

**Table 2: Synthesis of spiro oxindole derivatives catalyzed by DBDMH**

| Entry | R1 | R2 | X | R3 | Product | Time (min) | Yield (%)[a] | Mp°C |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | CN | Me | 4a | 10 | 97 | 290-292 |
| 2 | H | Br | CN | Me | 4b | 9 | 85 | 307-309 |
| 3 | H | Cl | CN | Me | 4c | 9 | 90 | |
| 4 | H | $NO_2$ | CN | Me | 4d | 14 | 94 | >300 |
| 5 | Bz | H | CN | Me | 4e | 20 | 93 | 285-287 |
| 6 | Me | H | CN | Me | 4f | 10 | 90 | 267-268 |
| 7 | Et | H | CN | Me | 4g | 9 | 95 | >300 |
| 8 | H | H | $CO_2Et$ | Me | 4h | 25 | 94 | 279-281 |
| 9 | H | Cl | $CO_2Et$ | Me | 4i | 30 | 80 | |
| 10 | H | $NO_2$ | $CO_2Et$ | Me | 4j | 9 | 95 | |
| 11 | Me | H | $CO_2Et$ | Me | 4k | 20 | 89 | >300 |
| 12 | Et | H | $CO_2Et$ | Me | 4l | 15 | 83 | 244-245 |
| 13 | H | H | CN | H | 4m | 25 | 94 | 239-240 |
| 14 | H | Br | CN | H | 4n | 15 | 83 | 274-276 |
| 15 | H | Cl | CN | H | 4o | 20 | 83 | |
| 16 | Bz | H | CN | H | 4p | 35 | 91 | |
| 17 | Me | H | CN | H | 4q | 15 | 82 | 243-244 |
| 18 | H | H | $CO_2Et$ | H | 4r | 12 | 97 | 294-296 |
| 19 | H | H | CN | --- | 6a | 30 | 97 | 217 |
| 20 | H | Br | CN | --- | 6b | 6 | 94 | 218-220 |
| 21 | H | Cl | CN | --- | 6c | 15 | 90 | |
| 22 | H | $NO_2$ | CN | --- | 6d | 10 | 90 | |
| 23 | Me | H | CN | --- | 6e | 10 | 96 | 279-281 |
| 24 | H | H | $CO_2Et$ | --- | 6f | 20 | 85 | 280-282 |
| 25 | H | Cl | $CO_2Et$ | --- | 6g | 20 | 92 | 234-236 |
| 26 | H | $NO_2$ | $CO_2Et$ | --- | 6h | 52 | 83 | 248-250 |
| 27 | Me | H | $CO_2Et$ | --- | 6i | 20 | 87 | |
| [a] Isolated yield | | | | | | | | |

## CONCLUSION

Simple and efficient method for preparing derivation 2-(30H)-inddol –(10H)-20-one-3-carbonitrile are offered in the watery medium from condensation of Isatin with Malononitrile in the compounds ß-3carbonitrile in the presence of DBDMH. There are some qualities that turn this method into devotee of environment with high profit economic, applicability in industrial scale. Indeed, these qualities are in a short time of the reaction, high yields of products, The use of water as a solvent, easy separation of products, simple method with being available, high efficiency good and the high thermal stability. The present method can also be used to prepare 6-Amino-3-methyl-2-oxo-1-phenyl-1H-spiro[indoline-3,4-pyrano[2,3-c]pyrazole-5-carbonitrile derivations easily.

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