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A QUICK ONE-POT SYNTHESIS OF SPIROINDOLINE DERIVATIVES USING 1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN

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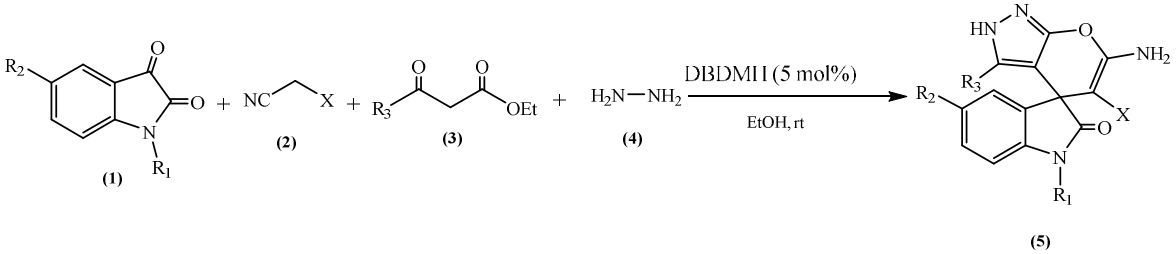
ABSTRACT
A novel multi-component reaction for synthesis of spiro[indoline3,4′-pyrano[2,3-c]pyrazole] derivatives is reported herein. 1,3-Dibromo-5,5-dimethylhydantoin is found to catalyze efficiently the four-component one-pot condensation of isatin, malononitrile, ethyl acetoacetate and hydrazine hydrate to afford a wide range of spiro[indoline3,4′-pyrano[2,3-c]pyrazole] derivativesin good yields. The use of a 1,3-Dibromo-5,5-dimethylhydantoin catalyst makes this method simple, convenient, and cost-effective.

KEYWORDS: Heterocycles, Multi-component reactions, Spiroindoline, One-pot synthesis.

INTRODUCTION
Multicomponent reactions have been attracted a great deal of intrest by chemists and biochemists because of their application for the formation of biologically active multi-functional heterocycles. Spiro indoline and pyranopyrazole moiettes are tow substantial categories of natural alkaloids that exhibit a wide range of biological activities such as anti-dysplasia, anti-allergic, hypoglycaemi[i], anti-microbial[ii], anti-fungal[iii],anti-inflammatory[iv], anti-bacterial[v]and anti-cancer[vi] effects and they have been studied in the development of insecticides, acaricides, herbicides[vii] and fungicides[viii]. therefore, the synthesis of spiro indoline pyrano pyrazole derivatives is have been recieved much attention by synthetic chemists. Among various reportedmethods for the synthesis of these heterocycles, multi-component condensation reaction in different conditions is the most common procedure. Recently, some catalysts such as $InCl_3$[ix], 4-(dimethylamino)pyridine (4-DMAP)[i], $NaHCO_3$[x], I_2[xi], Et_3N[xii],pipiridin[vi] and $C_{17}H_{35}COONa$[xiii] have been used to this propose. Some of these procedures take care from prolonged reaction times, moderate yields, the use of expensive or toxiccatalyst and harsh reaction condition. Therefore, the development of new methods for the synthesis of this compounds is still in demand. In continuation of our privious works on the development of new and efficient methods for the synthesis of biologically active heterocycles[xiv], herein, we describe a highly efficient

protocol for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*] pyrazole] *via* four-component condensation of isatins, malononitrile or ethyl cyanoacetate, ethylacetoacetate or ethyl benzoylacetate and hydrazinhydrate using DBDMH as catalyst (Scheme 1).



a) R_1 = H, R_2 = H, R_3 =Me, X = CN, **b**) R_1 = H, R_2 = Cl, R_3 = Me, X = CN
c) R_1 = H, R_2 = NO_2, R_3 = Me, X = CN, **d**) R_1 = H, R_2 = F, R_3 = Me, X = CN
e) R_1 = Me, R_2 = H, R_3 = Me, X = CN, **f**) R_1 = H, R_2 = Br, R_3 = Me, X = CN
g) R_1 = Bn, R_2 = H, R_3 = Me, X = CN, **h**)R_1 = H, R_2 = H, R_3 = Ph, X = CN
i) R_1 = H, R_2 = Cl, R_3 = Me, X = COOEt, **j**) R_1 = H, R_2 = NO_2, R_3 = Ph, X = CN
k) R_1 = H, R_2 = H, R_3 = Me, X = COOEt, **l**) R_1 = Me, R_2 = H, R_3 = Me, X = COOEt
m) R_1 = Me, R_2 = H, R_3 = Ph, X = COOEt, **n**) R_1 = Bn, R_2 = H, R_3 = Me, X = COOEt

Scheme 1.DBDMH catalyzed synthesis of pyranopyrazole derivatives

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) is a five-membered heterocycle that has been extensively used as a highlyefficient catalyst in organic syntheses. DBDMH is a useful, cheap, commercially availible reagent as the catalyst, nontoxic and environment-friendly, anti-bacterial agent[xv] and insensitive to air and moisture[xvi].

EXPERIMENTAL SECTION

Chemicals and apparatus

All materials required were obtained from Merc and Aldrich. IR spectra were recorded using KBr pelletson a shimadzu 435-U-04 spectrophotometer and ^{1}H NMR spectra were obtained on a Bruker AVANCE spectrometer 300 MHZ in dimethylsulfoxide (d6) (DMSO) as solvent. Melting points were determined with an Electrothermal 9100 apparatus.

General experimental procedure

A mixture of ethyl acetoacetate (3; 1 mmol), hydrazinehydrate (4; 1.3 mmol) and DBDMH (5 mol%) in ethanol (1 ml) was prepared and stirred at room temperature for 10 min. Then isatin (1; 1 mmol) and malononitrile (2; 1 mmol) (or ethylcyanoacetate) were added to the reaction mixture and stirred at room temperature for the required time according to Table 2. TLC (2:1 *n*-hexane/ethylacetate) showed the completion of the reaction. Then reaction mixture was filtered and precipitate was purified by recrystallization in ethanolto afford correspondingSpiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivativesin excellent yields (*Table2*). All products were characterized by melting point, IR and ^{1}H NMR spectra (**5a-n**).

6′-Amino-3′-methyl-2-oxo-2′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5a**), IR (KBr): 3378, 3338, 3131, 2691, 1711, 1641 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.54 (3H, s, CH_3), 6.90-7.26 (4H, m, ArH), 7.23 (2H, s, NH_2), 10.59 (1H, s, NH), 12.28 (1H, s, NH).

6′-Amino-3′-methyl-2-oxo-2H′-spiro[5-choro-indoline-3,4′-pyrano-[2,3-c] pyrazole]-5′-carbonitrile (**5b**),IR (KBr): 3396, 3136, 2182, 1714, 1644 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.58 (3H, s, CH_3), 6.92–6.93 (1H, m, ArH), 7.23–7.24 (1H, m, ArH), 7.29–7.31 (3H, m, ArH, NH_2), 10.76 (1H, s, NH), 12.35 (1H, s, NH).

6′-Amino-3′-methyl-2-oxo-2H′-spiro[5-niroindoline-3,4′-pyrano[2,3-c] pyrazole]-5′-carbonitrile (**5c**), IR (KBr): 3450, 3322, 2193, 1731, 1644 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.58 (3H, s, CH_3), 7.13–7.15 (1H, m, ArH), 7.43 (2H, s, NH_2), 7.91–7.92 (1H, m, ArH), 8.23–8.25 (1H, m, ArH), 11.37 (1H, s, NH), 12.41 (1H, s, NH).

6′-Amino-3′-methyl-2-oxo-2H′-spiro[5-flouroindoline-3,4′′-pyrano-[2,3-c]pyrazole]-5′-carbonitrile (**5d**),IR (KBr): 3400, 3137, 2180, 1714, 1642 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.58 (3H, s, CH_3), 6.94–6.98 (1H, m, ArH), 7.23–7.24 (1H, m, ArH), 7.30- 7.32 (3H, m, ArH, NH_2), 10.75 (1H, s, NH), 12.35 (1H, s, NH).

6′-Amino-1,3′-dimethyl-2-oxo-2′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5e**),IR (KBr): 3196, 3136, 2682, 1714, 1644 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.45 (3H, s, CH_3), 3.20 (3H, s, CH_3), 7.06–7.14 (4H, m, ArH), 7.25 (2H, s, NH_2), 7.31–7.41 (1H, m, Ar), 12.29 (1H, s, NH).

6′-Amino-3′-methyl-2-oxo-2H′-spiro[5-bromoindoline-3,4′-pyrano-[2,3-c] pyrazole]-5′-carbonitrile (**5f**),IR (KBr): 3391, 3138, 2181, 1713, 1642 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.58 (3H, s, CH_3), 6.87–6.89 (1H, m, ArH), 7.23–7.24 (1H, m, ArH), 7.32 (2H, s, NH_2),7.42–7.44 (1H, m, ArH), 10.78 (1H, s, NH), 12.35 (1H, s, NH).

6′-Amino-1-benzyl-3′-methyl-2-oxo-2′H-spiro[indoline-3,4′-pyrano[2,3-c] pyrazole]-5′-carbonitrile (**5g**),IR (KBr): 3187, 3140, 2182, 1714, 1644 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.35 (3H, s, CH_3), 4.91 (1H, d, *J*= 15.6 Hz, CH_2Ph), 5.00 (1H, d, *J*= 15.6 Hz, CH_2Ph), 7.00–7.14 (3H, m, ArH), 7.23–7.36 (6H, m, ArH, NH_2), 7.37–7.44 (2H, m, ArH), 12.30 (1H, s, NH).

6′-Amino-2-oxo-3′-phenyl-2′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5h**),IR(KBr): 3768, 3308, 3238, 2186, 1705, 1583 cm^{-1}; ^1H NMR (DMSO-d_6, 300MHz): δ 6.74-6.93 (4H, m, ArH), 7.03-7.27 (5H, m, ArH), 7.25 (2H, s, NH_2), 10.49 (1H, s, NH), 12.88 (1H, s, NH).

6′-Amino-5-chloro-3′methyl-2-oxo-2′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5i**); IR (KBr): 3390, 3346, 3136, 2967, 2179, 1713, 1642, 1580, 1497, 1414, 1298, 1157, 1055, 823, 697 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.06 (s, 3H, CH3), 6.92 (d, J = 8.4 Hz, 1H, Ar), 7.12 (s, 1H, Ar), 7.27 (s, 2H, NH2), 7.29–7.31 (m, 1H, Ar), 10.73 (s,1H,), 12.32 (s, 1H,).

6′-Amino-2-oxo-3′-phenyl-2′H-spiro[5-niroindoline-3,4′-pyrano[2,3-c] pyrazole]-5′-carbonitrile (**5j**),IR(KBr): 3396, 3225, 2194, 1726, 1631 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 6.84–6.85(2H, m, ArH), 6.90–6.92 (1H, m, ArH), 7.18–7.21 (2H, m, ArH), 7.26–7.29 (1H, m, ArH), 7.27–7.29 (1H, m, ArH), 7.46 (2H, s, NH_2), 7.90 (1H, s, 1H, ArH), 8.10 (1H, s, NH), 13.00 (1H, s, NH).

Ethyl-6′-amino-3′-methyl-2-oxo-2′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] -5′-carboxylate(**5k**),IR(KBr): 3385, 3281, 3188, 2578, 1715, 1666 cm^{-1}; ^1H NMR(DMSO-d_6, 300 MHz): δ 0.70-0.73 (3H, t, CH_3), 1.58 (3H, s, CH_3), 3.65-3.75 (2H, m, CH_2), 6.81-7.15 (4H, m, ArH), 8.02 (2H, s, NH_2), 10.37 (1H, s, NH), 12.15 (1H, s, NH).

4,3′-Spiro[(6-amino-5-carbethoxy-3-methyl-2H,4H-pyrano[2,3-c]pyrazolo)-N′-methyl-2′-oxindole] (**5l**); IR (KBr):3514, 3368, 3252, 2980, 2904, 2361, 1695, 1609, 1543, 1492, 1477, 1399, 1372, 1354 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz):δ0.61 (3H, t, J 6.7 Hz), 1.52 (s, 3H), 3.12 (s, 3H), 3.75 (2H, q, J 6.8 Hz), 6.8–7.10 (m, 3H), 7.22 (1H, t, J 7.6 Hz), 8.10 (s, 2H, NH2), 12.27 (s, 1H, NH).*Ethyl-6′-amino-1-methyl-2-oxo-3′-phenyl-2′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] -5′-carboxylate* (**5m**),IR (KBr): 3514, 3185, 2908, 1721, 1677, 1630 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 0.66-0.70 (3H, t, CH_3), 3.20 (3H, s,

CH_3), 3.64-3.72 (2H, m, CH_2), 6.85-7.06 (4H, m, ArH), 7.06-7.32 (5H, m, ArH), 8.07 (2H, s, NH_2), 12.59 (1H, s, NH).

4,3′-Spiro[(6-amino-5-carbethoxy-3-methyl-2H,4H-pyrano[2,3-c]pyrazolo)-N′-benzyl-2′-oxindole](**5n**), IR (KBr): 3276, 2978, 1676, 1612, 1546, 1485, 1466, 1397 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz):δ 0.55 (3H, t,J 6.7 Hz,), 1.00 (s, 3H), 3.28 (2H, q, J 7.1 Hz), 4.50 (s,2H), 6.9–7.2 (m, 3H), 7.22–7.48 (m, 6H), 7.85 (s, 2H, NH2), 11.85 (s, 1H, NH).

RESULTS AND DISCUSSION

Evaluation of catalytic activity of DBDMH in the synthesis of pyranopyrazole derivatives

the reaction of isatin, malononitrile, ethyl acetoacetate and hydrazinhydrate was chosen as model reaction. The model reaction was performed by different molar ratios of starting materials and catalyst, and in various solvents and temperatures (Table 1, entries 1-10). The best result was obtained by 1:1:1:1.3 molar ratios of isatin:malononitrile:ethyl acetoacetate:hydrazine hydrate. The results exhibit that different solvents have different effects on the activity of DBDMH in the reaction as in ethanol 96% yield was obtained after 6 min whereas, in the other solvents such as water and acetone medium yields were obtaind (Table 1, entries 5-6).

Furthermore, the effect of catalyst amount has been investigated and shown in figure 1 and Table 1 (entries 1-4).The best yield was obtained with 5 mol% of catalyst after 6 min.In the model reaction, the temperature was increased from 25 to 100 °C to studythe effect of temperature. The best result was obtained at room temperature (Table 1, entry 2). Therefore, 1:1:1:1.3 molar ratios of isatin:malononitrile:ethyl acetoacetate:hydrazine hydrate in the presence of 5 mol% of catalyst in ethanol at room temperature was selected as optimized reaction conditions which led to 96% yield after 6 min.

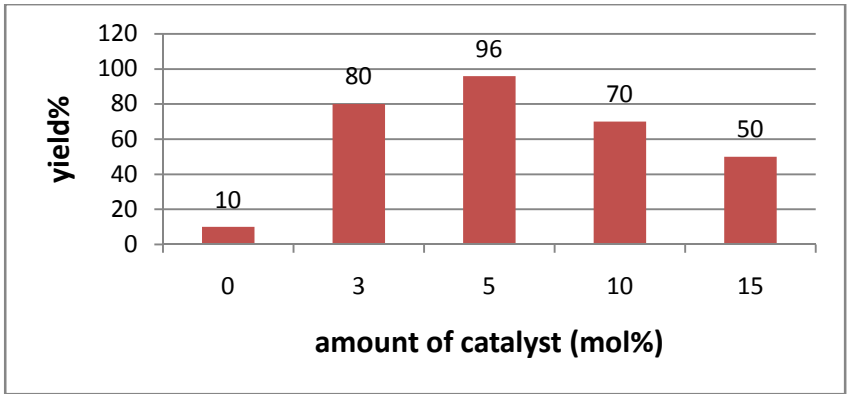


Figure 1. The effect of the amounts of catalyst on the reaction yields

Table1
Optimization of the reaction conditions.

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield [1,2] (%)
1	DBDMH (3)	EtOH	Rt	6	80
2	DBDMH (5)	EtOH	Rt	6	96
3	DBDMH (10)	EtOH	Rt	6	70

4	DBDMH (15)	EtOH	Rt	6	50
5	DBDMH (5)	Water	Rt	20	60
6	DBDMH (5)	Acetone	Rt	60	40
7	DBDMH (5)	EtOH	50	20	80
8	DBDMH (5)	EtOH	80	35	73
9	DBDMH (5)	EtOH	100	45	65
10	-----	EtOH	Rt	6	trace

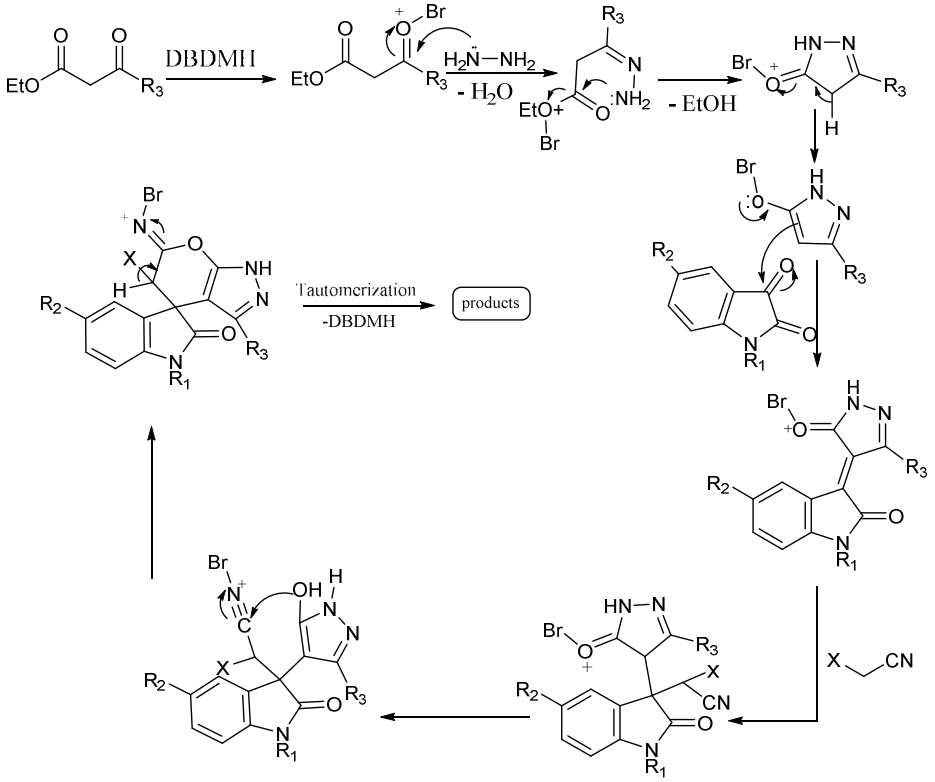
[1]Molar ratios of isatin:malononitrile:ethylacetoacetate:hydrazine hydrate were 1:1:1:1.3 in all experiments.
[2]Isolated yield

To scope the generality of this method, various isatins were reacted with hydrazinehydrate, malononitrile or ethyl cyanoacetate and ethyl acetoacetate or ethyl benzoylacetate under the optimized conditions. The corresponding spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazoles] were generated in good to excellent yields in short times by the current method (Table 2). a plausible mechanism has been shown in Scheme 2.

Table 2
Synthesis of Spiro[indoline-3, 4'-pyrano[2,3-*c*]pyrazoles] using DBDMH

Entry	Cmpd	Time (min)	Yield (%)	mp (^{o}C)	Lit. mp (^{o}C)
1	**5a**	6	96	279-280	278-280[vii]
2	**5b**	9	93	296-298	296-298[vii]
3	**5c**	8	92	269-271	268-270[vii]
4	**5d**	10	88	276-279	274-275[iii]
5	**5e**	9	90	270	268-270[vii]
6	**5f**	10	95	283-285	282-283[iii]
7	**5g**	12	92	266-268	263-265[xvii]
8	**5h**	8	94	219-221	220-222[vii]
9	**5i**	10	93	296-297	295-297[xviii]
10	**5j**	9	96	211-213	210-212[vii]
11	**5k**	10	94	285-287	285-287[vii]
12	**5l**	9	92	193-134	193-195[xix]
13	**5m**	6	92	220-222	224-226[iii]
14	**5n**	12	95	125-128	125-128[xix]

[1]Isolated yield.



Scheme 2

Finally, the efficiency of the present method has been compared with reported methods for the synthesis of 6'-amino-3'-methyl-2-oxo-2'H-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile in Table 3. The results clearly demonstrate that DBDMH is more efficient than the other reagents for this reaction.

Table 3
Comparison of some other procedure with the present method for the synthesis of 6'-amino-3'-methyl-2-oxo-2'H-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (**5a**).

Entry	Catalyst (mol%)	Solvent	Reaction condition	Time (min)	Yield[ref.] (%)
1	Piperidine	H_2O	Rt	300	89[vi]
2	4-DMAP	EtOH	60 °C	60	80[i]
3	Pipyridine	EtOH	rt, us irradiation	60	92[iii]
4	Et_3N	EtOH	Reflux	15	65[xii]
5	-----	EtOH/H_2O	60 °C	12 h	85[xx]
6	DBDMH	EtOH	Rt	6	96

[1]4-DMAP = 4-dimethylaminopyridine.

In summary, we have described a convenient method for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives via multi-component reaction of various isatins, malononitrile or ethyl cyanoacetate, ethyl acetoacetate or ethyl benzoylacetate and hydrazinhydrate using DBDMHas a homogeneous, highly efficient, safe and commercially available inexpensive

catalyst inethanol[xxi]. High yields of products, short reaction times, mild reaction condition and easy work-up procedure are other advantages of this procedure.

CONCLUSION

In summary, we have described a convenient method for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives via multi-component reaction of various isatins, malononitrile or ethyl cyanoacetate, ethyl acetoacetate or ethyl benzoylacetate and hydrazinhydrate using DBDMHas a homogeneous, highly efficient, safe and commercially available inexpensive catalyst inethanol. High yields of products, short reaction times, mild reaction condition and easy work-up procedure are other advantages of this procedure.

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