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Alum ($KAl(SO_4)_2 \cdot 12H_2O$) Catalyzed Multicomponent Transformation: Simple, Efficient, and Green Route to Synthesis of Functionalized Spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraones in Ionic Liquid Media

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The combination of isatin, barbituric acid, and cyclohexane-1,3-dione derivatives in the presence of alum ($KAl(SO_4)_2 \cdot 12H_2O$) as a catalyst for 15 min was found to be a suitable and efficient method for the synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraones.

Keywords isatin, spirooxindoles, dimedone, barbituric acid, ionic liquids

Introduction

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals is heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature.[1] Spirocyclic systems containing one carbon atom common to two rings are structurally interesting.[2] The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[3] Spiro compounds represent an important class of naturally occurring substances characteristic by their highly pronounced biological properties.[4,5] Similarly, Functionalized spiro cycloalkyloxindoles are found in a variety of natural products and bioactive molecules.[6,7] Consequently, many synthetic methodologies have been developed for constructing these spirocycles, most of which were based on cycloaddition or condensation reactions.[8-16] Compounds with an indole moiety exhibit antibacterial and antifungal activities. Furthermore, it has been reported that spiroindoline derivatives have highly enhanced biological activity.[17-19] Oxindoles derivatized at C_3 as spirocarbocycles, spiroheterocycles, spirolactones, and spirocyclic ethers are elegant targets in organic synthesis because of their significant biological activities.[20,21] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids. For example, cytostatic alkaloids as spirotryprostatins A, and B have been shown to modulate the function of muscarinic serotonin receptors (Figure 1).[22-26] On the basis of biological studies, the existence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal activity remarkably.[27-34]

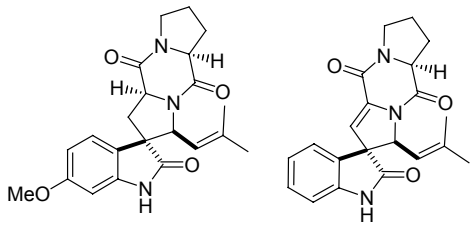

Figure 1 Spirooxindole-containing compounds.

Ionic liquids (ILs) have received vast research interests in recent years. They exhibited unique properties such as high ionic conductivity, wide electrochemical window, non-volatility, high thermal stability, non-flammability and miscibility with organic compounds, especially with the heterocyclic compounds as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion

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and the length of alkyl chain attached to the organic cation (Figure 2).[35-39] Because of these useful properties, ILs have been applied in several areas, including catalysis, electrochemistry, separation science for extraction of heavy metal ions, as solvents for green chemistry and materials for optoelectronic applications.[40-44]

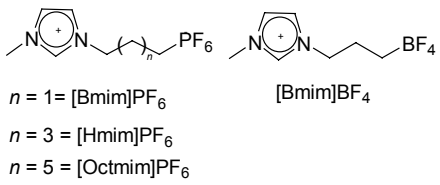

Figure 2 Chemical structure of the ionic liquids.

Room temperature ionic liquids are increasingly finding a range of laboratory, developmental and technical applications, for example, as media for organic and inorganic chemical synthesis, materials productions, and electrochemical devices.[36] In continuation of our investigations into the synthesis of novel heterocyclic compounds in the green media,[45-53] herein, we wish to report an efficient and green protocol for the three-component synthesis of some spirochromene derivatives in excellent yields at short reaction time.

Experimental

Melting points were measured on an Elecrtothermal 9100 apparatus. ^{1}H NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 MHz, respectively. The starting materials and TLC papers were prepared from Merck and Aldrich.

Typical procedure for preparation of 8,8-dimethyl-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4a)

A mixture of dimedone (0.14 g, 1 mmol), isatine (0.15 g, 1 mmol), barbituric acid (0.13 g, 1 mmol) and Alum (0.05 g 10 mol%) in [Bmim]PF_6 (0.5 mL) was stirred for 15 min at 100 ℃ (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was washed with water (10 mL×2) and the solid residue was crystallized from ethanol to give **4a** as white powder (98%), m.p.＞300 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.98 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.08, 2.10 (m, 2H, CH_2), 2.57—2.65 (m, 2H, CH_2), 6.72 (d, J=7.7 Hz, 1H, HAr), 6.79 (t, J=7.9 Hz, 1H, HAr), 6.95 (d, J=7.8 Hz, 1H, HAr), 6.10 (t, J=7.4 Hz, 1H, HAr), 10.38 (s, 1H, NH), 11.00 (s, 1H, NH), 12.21 (brs, 1H, NH).

1',8,8-Trimethyl-8,9-dihydrospiro[chromeno[2,3-*d*]-pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4b)

Colorless crystals (yield 95%); m.p.＞300 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.98 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.07—2.15 (m, 2H, CH_2), 2.57—2.65 (m, 2H, CH_2), 3.14 (s, 3H, NCH_3), 6.85—6.90 (m, 2H, HAr), 7.07 (d, J=7.5 Hz, 1H, HAr), 7. 21 (d, J=7.8 Hz, 1H, HAr), 11.01 (s, 1H, NH), 12.27 (brs, 1H, NH).

1'-Ethyl-8,8-dimethyl-8,9-dihydrospiro[chromeno-[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4c)

Colorless crystals, yield 92%; m.p. 253—255 ℃ dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.24 (t, J=7.2 Hz, 3H, CH_3), 2.11—2.22 (2H, CH_2), 2.54—2.67 (m, 2H, CH_2), 3.64—3.68 (m, 2H, NCH_2), 6.84—6.94 (m, 2H, HAr), 7.05 (d, 1H, HAr), 7.22 (t, 1H, HAr), 11.02 (s, 1H, NH), 12.20 (brs, 1H, NH).

1'-Benzoyl-8,8-dimethyl-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4d)

Colorless crystals, yield 92%; m.p. 258—259 ℃ dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.96 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.03—2.21 (m, 2H, CH_2), 2.57—2.74 (m, 2H, CH_2), 4.81—4.90 (m, 2H, NCH_2), 6.53 (d, J=7.6 Hz, 1H, HAr), 6.83—6.89 (m, 1H, HAr), 7.06—7.12 (m, 2H, HAr), 7.31—7.35 (m, 3H, HAr), 7.61—7.64 (m, 2H, HAr), 11.11 (s, 1H, NH), 12.4 (brs, 1H, NH).

5'-Bromo-8,8-dimethyl-8,9-dihydrospiro[chromeno-[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4e)

Colorless crystals (yield 95%); m.p.＞300 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.11—2.20 (m, 2H, CH_2), 2.62 (brs, 2H, CH_2), 6.69 (d, J=8.2 Hz, 1H, HAr), 7.20—7.25 (m, 2H, HAr), 10.53 (s, 1H, NH), 11.08 (s, 1H, NH), 12.22 (brs, 1H, NH).

8,8-Dimethyl-5'-nitro-8,9-dihydrospiro[chromeno-[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4f)

Colorless crystals (yield 98%); m.p. 292 ℃ dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.00 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.18 (brs, 2H, CH_2), 2.62 (brs, 2H, CH_2), 6.90 (d, J=8.1 Hz, 1H, HAr), 8.07 (s, 1H, HAr), 8.06—8.10 (m, 1H, HAr), 11.14 (s, 1H, NH), 11.17 (s, 1H, NH), 12.30 (brs, 1H, NH).

8,9-Dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4o)

Colorless crystals, yield 90%, m.p.＞300 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.92 (brs, 2H, CH_2), 2.21 (brs, 2H, CH_2), 2.72 (brs, 2H, CH_2), 6.68—6.76 (m, 2H, HAr), 6.95—7.08 (m, 2H, HAr), 10.34 (s, 1H, NH), 11.02 (s, 1H, NH), 12.21 (s, 1H, NH).

1'-Methyl-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4p)

Colorless crystals, yield 89%, m.p.＞300 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.92 (m, 2H, CH_2),

2.12—2.29 (m, 2H, CH_2), 2.72 (brs, 2H, CH_2), 3.14 (s, 3H, NCH_3), 6.86—6.91 (m, 2H, HAr), 7.07 (d, J=7.8 Hz, 1H, HAr), 7.17 (t, J=8.1 Hz, 1H, HAr), 11.05 (s, 1H, NH), 12.06 (brs, 1H, NH).

5'-Bromo-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4q)

Colorless crystals, yield 90%, m.p. 242—245 ℃ dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.90 (brs, 2H, CH_2), 2.25 (brs, 2H, CH_2), 2.67 (brs, 2H, CH_2), 6.66 (brs, 1H, HAr), 7.23 (brs, 2H, HAr), 10.49 (s, 1H, NH), 11.07 (s, 1H, NH), 12.22 (s, 1H, NH).

5'-Nitro-8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraone (4r)

Colorless crystals, yield 92%; m.p. 280—281 ℃ dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.93 (brs, 2H, CH_2), 2.26 (2H, brs, CH_2), 2.70 (brs, 2H, CH_2), 6.90 (d, 1H, Hz, HAr), 8.07 (s, 1H, HAr), 8.11 (d, J=8.8 Hz, 1H, HAr), 11.13 (s, 1H, NH), 11.17 (s, 1H, NH), 12.34 (brs, 1H, 3NH).

Results and Discussion

In the course of our research and evaluation of different catalysts and various conditions, and in order to evaluate the efficiency of this methodology, dimedone **1a**, isatin **2a**, and barbituric acid **3a** were further subjected to reaction using 10 mol% of a diverse type of Lewis and Bronsted acids such as Alum [Hydrated potassium aluminium sulfate ($KAl(SO_4)_2$•$12H_2O$)], SSA (silica sulfuric acid), $SnCl_4$, *p*-TSA (*para*-toluenesulfunic acid), and CAN (ceric ammonium nitrate) under identical conditions (Figure 3). We also evaluated the amount of catalyst required for this transformation. It was found that using 10 mol% Alum as an inexpensive and available catalyst in ionic liquid is sufficient to push the reaction forward. More amount of the catalyst did not increase the yield. We have found that use of amount 10 mol% Alum has a unique capability and best promoter to enhance the reaction rate in [Bmim]PF_6 medium. However, use of amount 10 mol% of SSA and *p*-TSA

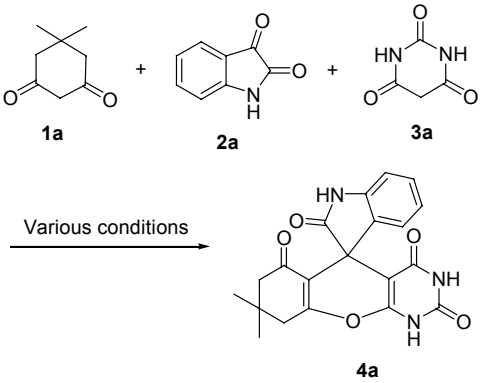

Figure 3 Synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraone.

led to lower yields (50%—60%) after 60 min reaction time. At first we examined this reaction in the ultrasonic irradiation in EtOH and THF as solvent and presence of various Bronsted and Lewis acids at 60 ℃. It was observed that the reaction did not occur in this condition with any catalyst. The various examined conditions are summarized in Table 1.

Table 1 Model reaction, conditions and yield[a]

Entry	Condition	Cat.	Time/h	Yield/%
1	Ethanol (U.S. Irradiation)	Alum	4	0
2	Ethanol (U.S. Irradiation)	*p*-TSA	4	0
3	Ethanol (U.S. Irradiation)	SSA	4	0
4	Ethanol (U.S. Irradiation)	$SnCl_4$	4	0
5	Ethanol (U.S. Irradiation)	CAN	4	0
6	THF (U.S. Irradiation)	Alum	4	0
7	THF (U.S. Irradiation)	*p*-TSA	4	0
8	THF (U.S. Irradiation)	SSA	4	0
9	THF (U.S. Irradiation)	$SnCl_4$	4	0
10	THF (U.S. Irradiation)	CAN	4	0

[a] Barbituric acid (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol), isatin (1 mmol) and catalyst (10% mol).

Then we examined this reaction under the solvent free condition and in presence of various Bronsted and Lewis acids at different temperatures. The best results with Alum as a catalyst were seen in the case of solvent free condition. The results are summarized in Table 2.

Table 2 Model reaction, conditions, and yield[a]

Entry	Condition	Cat.	Time/h	Temp./℃	Yield/%
1	Solvent free	CAN	2	100	＜50
2	Solvent free	*p*-TSA	2	100	60
3	Solvent free	SSA	2	100	62
4	Solvent free	$SnCl_4$	2	100	＜50
5	Solvent free	Alum	2	60	＜50
6	Solvent free	Alum	2	80	55
7	Solvent free	Alum	2	100	65
8	Solvent free	Alum	2	120	68

[a] Barbituric acid (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol), isatin (1 mmol) and catalyst (10% mol).

After that we examined this reaction in the ionic liquid media and presence of various Bronsted and Lewis acids at different temperatures. It was observed that the best results were seen with Alum as a catalyst and [Bmim]PF_6 as media at 100 ℃. The results are summarized in Table 3.

As shown in Table 4 it was found that this procedure works with a wide variety of substrates. Eight types of substituted isatins, two types of 1,3-cyclohexanediones and three types of barbituric acids were used in this reaction for the library validation (Figure 4). Correspondingly, 9-dihydrospiro[chromeno[2,3-*d*]pyrimi-

Table 3 Model reaction, conditions and yield[a]

Entry	Condition	Cat.	Time/min	Temp./℃	Yield/%
1	[BMIM] Br	CAN	120	100	＜50
2	[BMIM] Br	*p*-TSA	60	100	65
3	[BMIM] Br	$SnCl_4$	60	100	60
4	[BMIM] Br	SSA	60	100	68
5	[BMIM] Br	Alum	60	100	70
6	[BMIM] Cl	Alum	60	100	55
7	[BMIM] BF_4	Alum	30	100	85
8	[BMIM] Trif	Alum	60	100	92
9	[BMIM] PF_6	Alum	30	60	70
10	[BMIM] PF_6	Alum	15	80	93
11	[BMIM] PF_6	Alum	15	100	98
12	[BMIM] PF_6	Alum	15	120	98

[a] Barbituric acid (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol), isatin (1 mmol) and catalyst (10% mol).

dine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraones **4** were synthesized by the one-pot, three-component condensation of cyclohexane-1,3-diones **1**, isatins **2** and barbituric acids **3** in excellent yields in ionic liquid media in the presence of Alum as a catalyst for 15 min. Work-up gave products **4a—4x** in 88% to 98% yields. The results are summarized in Table 4. All the products **4a—4x** are known compounds and were characterized by comparison of their ^{1}H NMR spectra and TLC with our previous synthetic products.[54]

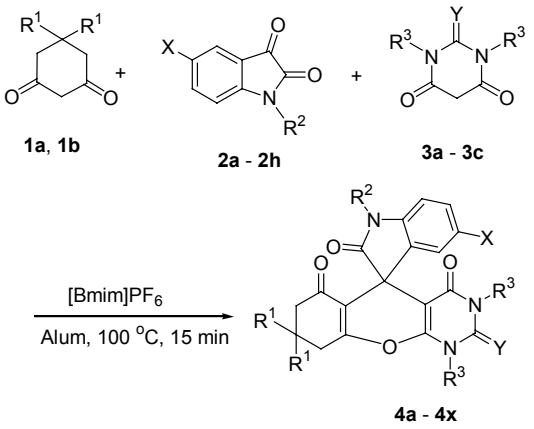

Figure 4 Synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraone derivatives.

This procedure is a convenient and simple method for the preparation of extensive chemical library for spirooxindole derivatives by accessible starting materials to find widespread application in the ground of combinatorial chemistry, and drug innovation.

We also checked the reusability of the catalyst by recovering the alum and using it for new runs and found that the catalyst could be reused several times without any decrease in the product yield. Apparently, recycling of catalyst is possible for three successive times without significant loss of activity (Table 4, Entry 4f). The catalyst can be removed from the aqueous phase by removing the water under vacuum then washing with EtOH and drying at r.t.

Table 4 Synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraone derivatives[a]

Product **4**	X	Y	R^1	R^2	R^3	Yield[b]/%
a	H	O	Me	H	H	98
b	H	O	Me	Me	H	95
c	H	O	Me	Et	H	92
d	H	O	Me	Bz	H	92
e	Br	O	Me	H	H	95
f	NO_2	O	Me	H	H	98 (98, 96, 96)[c]
g	Br	O	Me	Me	H	94
h	Me	O	Me	H	H	94
i	H	O	Me	H	Me	88
j	H	O	Me	Me	Me	88
k	NO_2	O	Me	H	Me	90
l	H	S	Me	Me	H	92
m	Br	S	Me	H	H	91
n	NO_2	S	Me	H	H	94
o	H	O	H	H	H	90
p	H	O	H	Me	H	89
q	Br	O	H	H	H	90
r	NO_2	O	H	H	H	92
s	H	O	H	Me	Me	88
t	Br	O	H	H	Me	89
u	NO_2	O	H	H	Me	89
v	H	S	H	H	H	88
w	Br	S	H	H	H	92
x	NO_2	S	H	H	H	90

[a] Barbituric acids (1 mmol), cyclohexane-1,3-diones (1 mmol), isatins (1 mmol), ionic liquid (0.1 mL) and alum (10% mol). [b] Isolated yield. [c] Isolated yield after recycling of catalyst.

We have not established an exact mechanism for the formation of products **4**, however, a reasonable possibility is shown in Figure 5.

Conclusions

In conclusion, we have reported an environmentally friendly three-component, efficient, clean and simple method for the synthesis of some new spirooxindole derivatives using readily available starting materials. This is the first report on the synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-tetraones in an ionic liquid and these new reaction conditions open an important alternative to the use of volatile organic solvents. Prominent among the advantages of this new method are short reaction times, operational simplicity, use of IL media, high yields, easy work-up procedures,

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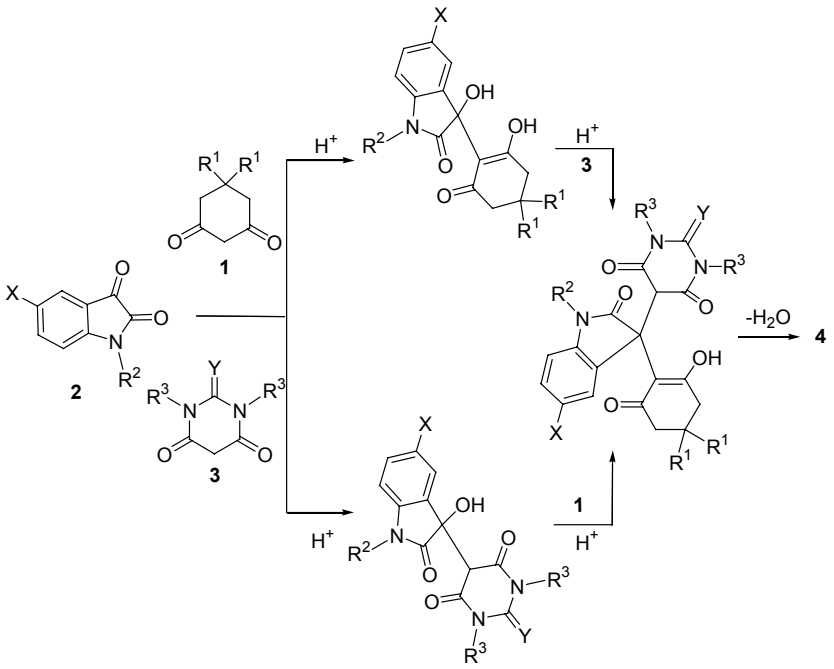

Figure 5 Proposed mechanism of the reaction.

and using of Alum as a nontoxic, easy available, recyclable and inexpensive catalyst. Moreover, the advantage of such media is that often smaller amounts of the ILs can be used compared with organic solvents in reaction; in addition, the reaction media can be recycled for several times.

Acknowledgement

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