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An Environmental Friendly Approach for the Synthesis of Spiro[indoline-3′,2-quinazoline]2′,4(3*H*)-dione Using 1-Methylimidazolium Hydrogen Sulfate, as Reusable Catalyst

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A facile and environmentally benign procedure for the synthesis of 3-aryl-1*H*-spiro[indoline-3′,2-quinazoline]2′,4(3*H*)-dione from isatoic anhydride, aromatic amines and isatin derivatives in Brønsted acidic ionic liquid, 1-methylimidazolium hydrogen sulfate, was reported. The ability to reuse the ionic liquid, the high yield, short reaction time and ease of purification are the important features of this process.

Keywords: Isatin; Isatoic anhydrid; Spiro[indoline-quinazoline]one; 1-Methylimidazolium hydrogen sulfate; Multi component reaction.

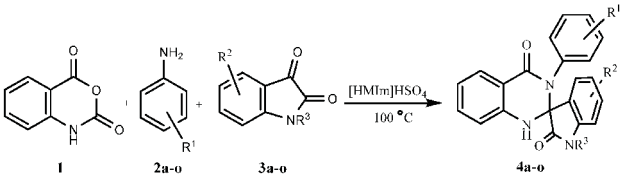
Heterocycles containing the quinazoline ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds. Recently, much attention has been focused on the synthesis of 2,3-dihydroquinazolin-4(3*H*)-ones, because of their interesting biological and pharmaceutical activities, such as antifertility, antibacterial, antifungal, analgesic, antitumor, anticancer and herbicide.[1-3]

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[4] Also, the C-3-spiro-oxindol framework system is the core structure of many pharmacological agents and natural alkaloids.[5] Furthermore, it has been reported that sharing the indole 3-carbon atom in the formation of spiroindoline derivatives can highly enhance biological activity.[6]

In recent years, ionic liquids have attracted intensive interests as a possible replacement of traditional solvents and catalyst for organic reactions, particularly in the area of green chemistry, due to their advantageous properties, including negligible vapor pressure and high thermal and chemical stability.[7]

In continuation of our efforts for the synthesis of spiro[oxindole-quinazoline][8] and our interest in using Brønsted acidic ionic liquid, 1-methylimidazolium hydrogen sulfate ([HMIm]HSO_4 as an effective catalyst for the synthesis of organic compound,[9] herein, a facile procedure was introduced for the synthesis of 3-aryl-1*H*-spiro[indoline-3′,2-quinazoline]2′,4(3*H*)-dione (**4a-o**) from isatoic anhydride **1**, aromatic amines **2a–o** and isatin derivatives using [HMIm]HSO_4, as a catalyst (Scheme I).

Scheme I Synthesis of 1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-diones



Owing to the versatile biological activities of 2,3-dihydroquinazoline-4(3*H*)-ones numerous classical methods for the synthesis of these compounds have been reported.[10-14] Recently, synthesis of 1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-dione via a reductive cyclization of 2-nitrobenzamid with isatin in presence of $SnCl_2.2H_2O$ was reported.[15] Also, Mohammadi et al. have reported the synthesis of the same compounds by refluxing of primary amines, isatin and isatoic anhydride[16] or 2-amino-*N*-phenylbenzamide[17] in the presence of alum ($KAl(SO_4).12H_2O$) as catalyst in EtOH.

However, there are disadvantages for these reports due to long reaction time (6-11 h) and use of unrecoverable solvent and catalyst. One of the most important strategies can be used to overcome these problems is to perform these reactions in the presence of ionic liquids.

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In order to find the optimum conditions, for the formation of 3-phenyl-1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-dione (**4a**), we study the reaction of isatoic anhydride (1 mmol), aniline (1.2 mmol) and isatin (1 mmol) in the presence of 0.5 mmol of various ionic liquids such as 1-buthyl-3-methyimidazolium bromide ([BMIm]Br), 1-buthyl-3-methyimidazolium hydrogen sulfate ([BMIm]HSO_4), 1-methyl-2-pyrolidonium hydrogen sulfate ([NMP]HSO_4) at 90 °C (Table 1, entry 1-3). The results show that, after three hours trace amount of products were obtained. However, when the reaction was carried out in the presence of [HMIm]HSO_4, **4a** was obtained in good yields after two hours (Table 1, entry 4).

The amount of [HMIm]HSO_4 and temperature of reaction was examined, and the results were summarized in Table 1 (entry 4-10). It could be seen that 0.5 mmol [HMIm]HSO_4 at 100 °C gave the best yield (94%) at least time (Table 1, entry 5).

After optimizing the conditions, we next evaluated the efficiency and versatility of the [HMIm]HSO_4 as catalyst for the preparation of other spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-dione derivatives by using a variety of structurally diverse anilines and isatines. In all cases studied, the reaction proceeded smoothly to give the corresponding products **4a-o** in good to excellent yield at least time (Table 2).

A comparison of the present method with other reported in literature are shown that not only the desired products were obtained in better yields, but also the time of reactions were reduced to a remarkable extent, that show the merit of the present work in comparison with reported results in literature[16] (Table 2). Thus, the [HMIm]HSO_4 act as a suitable catalytic medium with to reaction time and yield of the products.

In the end of reaction, the ionic liquid was easily separated from the reaction medium by washing with water. After washing the solid products with water completely, the water containing ionic liquid (ionic liquid is soluble in water) was evaporated under reduced pressure and ionic liquid was recovered and reused. Table 2 shows that no considerable change in the activity of the ionic liquid was observed when it reused over three successive runs (Table 2, product **4a**).

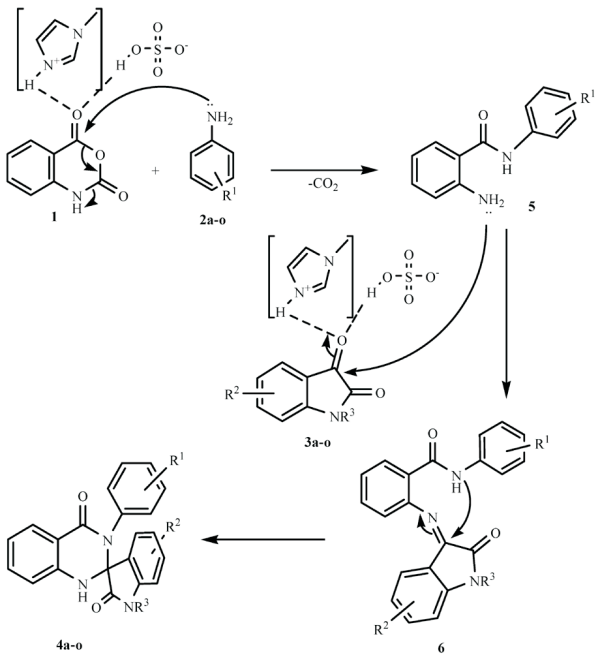
We have not established the exact mechanism for the formation of spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-diones **4**, however, a reasonable suggestion is offered in Scheme II. It is thought that, Brønsted acidic ionic liquid,

Table 1. Efects of the type and amount of ionic liquid on the formation of 4a[a]

Entry	Ionic Liquid (mmol)	T (°C)	t (min)	Yield (%)
1	[BIMm]Br (0.5)	90	180	trace
2	[BMIm]HSO_4 (0.5)	90	180	trace
3	[NMP]HSO_4 (0.5)	90	180	trace
4	[HMIm]HSO_4 (0.5)	90	120	91
5	[HMIm]HSO_4 (0.5)	100	100	94
6	[HMIm]HSO_4 (0.5)	110	75	82
7	[HMIm]HSO_4 (0.5)	120	60	75
8	[HMIm]HSO_4 (0.25)	100	120	81
9	[HMIm]HSO_4 (0.75)	100	90	84
10	[HMIm]HSO_4 (1.0)	100	90	78

[a] Reaction conditions: Isatoicanhydrid (1 mmol), aniline (1.2 mmol), isatin (1 mmol), ionic liquid [HMIm]HSO_4.

Scheme II Proposed mechanism for the synthesis of 1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-diones



[HMIm]HSO_4 can activate the carbonyl groups of isatoic anhydrid and isatin via hydrogen bonding between the carbonyl group of isatoic anhydrid or isatin and the cationic (N^+-H) or ionic component (SO_4^--H) of ionic liquid. The reaction proceeds via a cascade of condensation reactions involving formation of the intermediate **5**, which is formed *in situ* by reaction of aniline **2** with the activated carbonyl group isatoic anhydride **1**. The intermediate **5** then reacted with C-3 carbonyl of isatin to give the intermediate **6**. This intermediate undergoes a cyclocondensation reaction to af-

Table 2. Synthesis of spiro[indoline-quinazoline]ones and comparison of efficiency 1-methylimidazolium hydrogen sulfate with other report[a]

Products	R^1	R^2	R^3	Found[a]			Reported			Ref.
				m.p. (°C)	time (min)	Yield (%)	m.p. (°C)	time (h)	Yield (%)	
4a	H	H	H	250-2	100	94 (91,90,90)[b]	251-3	8	91	[16]
4b	*o*-Cl	H	H	293-5	80	87	-	-	-	-
4c	*m*-Cl	H	H	282-4	70	83	-	-	-	-
4d	*p*-Cl	H	H	265-7	110	91	264-6	8	85	[16]
4e	*p*-Br	H	H	215-7	120	92	213-5	8	86	[16]
4f	*p*-Me	H	H	273-5	80	90	271-3	7	93	[16]
4g	*p*-OMe	H	H	267-9	60	94	269-1	8	92	[16]
4h	*p*-Et	H	H	295-7	86	86	-	-	-	-
4i	*p*-Br	5-Br	H	298-9	35	81	-	-	-	-
4j	*m*-Cl	5-Br	H	295-7	120	94	-	-	-	-
4k	*m*-Cl	H	Ph-CH_2	222-4	90	90	-	-	-	-
4l	*p*-OMe	H	Ph-CH_2	215-8	25	92	-	-	-	-
4m	H	H	Ph-CH_2	235-6	40	90	-	-	-	-
4n	*p*-Et	H	CH_3	232-5	75	92	-	-	-	-
4o	H	H	CH_3	224-6	30	91	-	-	-	-

[a] Reaction conditions: isatoicanhydrid (1 mmol), aromatic amines (1.2 mmol), isatin (1 mmol), ionic liquid [HIMm]HSO_4 (0.5 mmol) in an oil bath at 100 ºC. [b] The yields of reaction with recycled ionic liquid after three successive runs.

ford the corresponding spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-diones **4** (Scheme II).

In conclusion, we have developed an efficient method for the synthesis of spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-diones in high yields employing Brønsted acidic ionic liquid, 1-methylimidazolium hydrogen sulfate. The application of an inexpensive, easily available and reusable ionic liquid makes this method simple, clean, practical and economically viable. Less waste, ease of product separation, descend reaction time with improved yield as compared to other reported methods are advantages of the proposed procedure.

EXPERIMENTAL

All reagents were purchased from Merck and Fluka and used without further purification. Melting points were measured on an Electro-thermal IA 9100 apparatus. IR spectra were recorded on KBr pellets on a Shimadzu FT-IR 8600 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 DRX Avance instrument at 500 and 125 MHz. Elemental analysis were carried out on a Thermo Finnigan Flash EA 1112 series instrument.

Preparation of ionic liquids: For the present study, we prepared a series of Brønsted acidic ionic liquids by the following reported procedures.[18,19,20] *(i) Preparation of 1-Methylimidazolium Hydrogen Sulfate:*[18] 1-Methylimidazole (1.59 mL, 20 mmol) and acetonitrile (5 mL) were charged into a 25 mL round-bottom flask. Then, the mixture was stirred at 0 °C for 1 min. Stoichiometric amount of concentrated sulfuric acid (97%, 1.03 g/mL) was added dropwise and the mixture stirred for 1 h at 0 °C and then stirred for 2 h at room temperature. The [HMIm]HSO_4 was washed repeatedly with diethyl ether (2.5 mL) to remove non-ionic residues and then it was dried in a vacuum evaporator. *(ii) Preparation of 1-butyl-3-methylimidazolium bromide:*[19] 1-bromobutane (2.2 mmol) and 1-Methylimidazole (2 mmol) are placed in a 20 mL beaker, mixed thoroughly and the mixture is heated intermittently in an unmodified household MW oven (Sanyo AIF-A EM-5641) at 180 W for 3 minute (until a clear single phase is obtained). The resulting ionic liquid is then cooled, washed with ether (2 × 3 mL) to remove unreacted starting materials and product dried in vacuum by a rotary evaporator to obtain the viscous clear [BMIm]Br. *(iii) Preparation of [NMP][HSO$_4$]:*[20] 1-Methyl-2-pyrolidone (20 mmol) was charged into a 250 mL flask with magnetic stirrer. Then equimolar concentrated sulphuric acid (98 wt %) was added dropwise slowly into the flask at 80 °C for 12 h. The mixture was washed with ether three times to remove non-ionic residues and dried in vacuum by a rotary evaporator to obtain the viscous clear [NMP][HSO_4]. *(iv) Preparation*

of [BMIm]HSO$_4$:[20] 1-buthyl-3-methyimidazolium hydrogen sulfate was obtained by a dropwise addition of one equivalent of concentrated sulphuric acid (98%) to solution of 1-butyl-3-methylimidazolium bromide in anhydrous methylene chloride. The reaction proceed at room temperature for 24 h with vigorous stirring. Then, the mixture was dried in vacuum by a rotary evaporator to remove the HBr and solvent to obtain the viscous clear [BMIm]HSO$_4$.

General Experimental Procedure for the Preparation of Compounds 4a-o. A mixture of isatoic anhydrid (1 mmol), aromatic amines (1.2 mmol), isatin derivatives[21] (1 mmol), ionic liquid [HMIm][HSO$_4$] (0.5 mmol) was heated in an oil bath at 100 ºC for the appropriate times according to Table 2. After completion of reaction, as indicated by TLC, 20 mL distilled water was added, then the resulting solid product was filtered and dried. The crude product was recrystallized from ethanol and dried to afford powder compounds of **4a-o.**

3-(*o*-Chlorophenyl)-1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-dione (4b). Yield: 87%, Beige powder; mp 293-295 °C. IR (KBr): ν_{max} 1477, 1618, 1741, 3072, 3352, 3458 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.70 (d, *J* = 7.79 Hz, 1H), 6.73 (d, *J* = 8.06 Hz, 1H), 6.76 (t, *J* = 7.50 Hz, 1H), 6.88 (t, *J* = 7.50 Hz, 1H), 7.01-7.03 (m, 1H), 7.15-7.22 (m, 3H), 7.32 (t, *J* = 7.20 Hz, 1H), 7.40-7.43 (m, 1H), 7.51 (d, *J* = 7.41 Hz, 1H), 7.66-7.67 (m, 2H), 10.6 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 77.0, 111.0, 115.2, 115.5, 118.6, 122.9, 126.2, 126.9, 128.3, 128.7, 128.8, 130.3, 130.6, 132.1, 134.0, 134.6, 137.1, 142.8, 147.1, 163.4, 176.7 ppm. Anal. Calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18. Found: C, 67.07; H, 3.69; N, 11.21.

1′-Benzyl-3-(*m*-chlorophenyl)-1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-dione (4k). Yield: 90%, Light yellow powder, mp 222-224 ºC. IR (KBr): ν_{max} 1479, 1612, 1641, 1728, 2927, 3058, 3248 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 4.48 (d, *J* = 15.65 Hz, 1H), 4.95 (d, *J* = 15.65 Hz, 1H), 5.88 (brs, 1H, NH), 6.54 (d, *J* = 7.88 Hz, 1H), 6.69 (d, *J* = 8.02 Hz, 1H), 6.86-7.04 (m, 7H), 7.13-7.34 (m, 6H), 7.50 (d, *J* = 7.32 Hz, 1H), 7.94 (d, *J* = 7.94 Hz, 1H) ppm;^{13}C NMR (125.75 MHz, DMSO-d$_6$): δ 44.3, 77.3, 110.3, 115.4, 116.2, 120.2, 123.8, 125.7, 127.5, 127.6, 128.2, 128.5, 128.8, 129.0, 129.2, 130.2, 130.4, 131.6, 134.5, 134.6, 135.0, 139.1, 142.4, 145.1, 164.5, 173.3 ppm. Anal. Calcd for $C_{28}H_{20}ClN_3O_2$: C, 72.18; H, 4.33; N, 9.02. Found: C, 72.26; H, 4.27; N, 8.94.

1′-Methyl-3-(*p*-ethylphenyl)-1*H*-spiro[indoline-3′,2-quinazoline]-2′,4(3*H*)-dione (4n). Yield: 92%, Light yellow powder, mp 232-235 ºC. IR (KBr): ν_{max} 1512, 1614, 1641, 1726, 2982, 3056, 3282 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 1.16 (t, *J* = 7.51 Hz, 3H), 2.54 (q, 2H), 3.06 (s, 3H), 4.58 (s, 1H, NH), 6.68-6.70 (m, 2H), 6.89-6.91 (m, 2H), 6.99-7.07 (m, 4H), 7.30-7.38 (m, 2H), 7.52 (d, *J* = 7.44 Hz, 1H), 8.07 (d, *J* = 7.76 Hz, 1H) ppm; ^{13}C NMR (125.75 MHz, DMSO-d$_6$): δ 15.0, 27.5, 29.6, 77.2, 110.6, 114.3, 114.5, 117.8, 122.1, 126.2, 127.3, 127.6, 129.0, 129.4, 130.6, 133.3, 135.8, 141.2, 142.8, 146.1, 163.6, 174.3 ppm. Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.24; H, 5.57; N, 10.90.

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