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Catalyst-free Synthesis of Mono and Bis Spiro Pyrazolopyridines in DSDABCO as a Novel Media

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ABSTRACT

In this work, multicomponent synthesis of mono and bis spiro-pyrazolopyridines from isatin derivatives, indanedione and 3-methyl-5-aminopyrazole at the presence of 1,4-disulfo-1,4-diazoniabicyclo[2.2.2]octane chloride (DSDABCO) as a novel ionic liquid media is reported. The present methodology offers several advantages such as simple procedure, mild conditions, excellent yields, green media and reduced environmental consequences. The ionic liquid was recovered and reused. The structures of the synthesized spiro-pyrazolopyridine compounds were confirmed by ¹H, ¹³C NMR and FTIR spectral data and elemental analyses.

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Graphical Abstract

Introduction

The pyrazolopyridine ring system represents the core skeleton of a pharmaceutically important class of heterocyclic compounds possessing a broad range of biological activities, such as potent cyclin kinase 1 (CDK1) inhibitor [1], HIV reverse transcriptase inhibitor [2], CCR1 antagonists [3], protein kinase inhibitors [4], inhibitors of cGMP degradation [5], inhibitors of xanthine oxidases [6], cardiovascular [7], potent vasodilator [8], anti-malarial [9], anti-proliferative [10], anti-microbial [11], anti-viral [12], anxiolytic [13], anti-inflammatory [14], anti-leishmanial [15], hypoglycemic [16], and anti-tumor agents [17].

Compounds with spiro skeleton not only constitute subunits in numerous alkaloids, but also are templates for drug discovery and have been used as scaffolds for combinatorial libraries [18]. On the other hand, isatin is a privileged lead molecule for designing potential bioactive agents and its derivatives have been shown to possess a broad range of bioactivity as many of which have been assessed as anti-tumor [19], anti-fungal [20] and anti-HIV [21]. To enhance the activity of isatin, it is a hot topic to construct isatin containing pyrazolopyridine moiety in green, efficient and simple condition.

Ionic liquids have been applied as green media in organic synthesis because of their unique properties. They have a wide liquid range, good solvating capability, negligible vapour pressure are easy to recycle. Moreover, their hydrophobicity/hydrophilicity can be tuned by appropriate modification of the anion or cation. There has earned them the sobriquet designer solvents [22-24].

Experimental

Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures. Melting points were measured on an electrothermal 9100 apparatus. IR spectra were determined on a Shimadzu FT-IR 8600 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker 400 DRX Avance instrument at 500 and 125 MHz. Elemental analyses were recorded on a Carlo-Erba EA1110CNNO-S analyzer.

Procedure for the preparation of 1,4-disulfo-1,4-diazoniabicyclo[2.2.2]octane chloride (DSDABCO)

A flask (500 mL) charged with 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.1 mol) was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (0.2 mol) and a gas outlet tube which was dipped into water to dissolve the generated HCl gas during the reaction. The flask was put into an ice bath and chlorosulfonic acid was added dropwise over a period of 20 min, and the resulting mixture was stirred slowly for another 20 min. The temperature of the mixture was brought up to the room temperature and was stirred for an additional 60 min. After completion of the reaction, the mixture was washed with diethyl ether (3×10 mL). The organic product was extracted from liquid phase and evaporated under vacuum to produce desired ionic liquid.

Analytical data for DSDABCO: yellow oil. ^1H NMR (400 MHz, CDCl_3): δ = 3.09 (s, 12H), 15.05 (s, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 32.7 ppm. Anal. calc. For $\text{C}_6\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_6\text{S}_2$: C, 20.87; H, 4.09; N, 8.11. Found: C, 20.85; H, 4.12; N, 8.09.

Figure 1. Structure of DSDABCO

General procedure for the synthesis of mono and bis spiro-pyrazolopyridines using ionic liquid DSDABCO

A mixture of isatin derivatives (1 mmol), indanedione (1 mmol) and 3-methyl-5-aminopyrazole (1 mmol) and DSDABCO (0.2 mmol) were stirred at room temperature for the required reaction times (1-2 h). The progress of the reaction was monitored by TLC (EtOAc: petroleum ether 1:2). After

completion of reaction, as indicated by TLC, the ionic liquid was separated by extraction with 2×15 mL of water. The solid residue was separated by column chromatography in 82-92% yields.

The selected spectral data

3-methyl-1H-spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3'-indoline]-2',5(10H)-dione (5a)

Red solid; dec 267-268 °C; FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3430, 2925, 1685, 1540, 1367. ^1H NMR (DMSO- d_6 , 400 MHz): 1.56 (s, 3H), 7.25-7.29 (m, 4H), 7.47 (m, 2H), 7.53 (m, 2H), 11.58 (s, 2H); ^{13}C NMR (DMSO- d_6 , 100 MHz): 27.83, 30.32, 105.13, 118.94, 133.17, 135.48, 135.97, 136.76, 140.03, 140.63, 141.06, 143.51, 143.87, 144.87, 146.57, 147.00, 147.94, 149.20, 149.23, 175.65, 189.24. Anal. Calcd. For $\text{C}_{21}\text{H}_{14}\text{N}_4\text{O}_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.27; H, 3.88; N, 15.79.

5'-chloro-3-methyl-1H-spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3'-indoline]-2',5(10H)-dione (5b)

Red solid; dec 253-255 °C; FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3450, 2965, 1687, 1611, 1560, 1379. ^1H NMR (DMSO- d_6 , 400 MHz): 1.53 (s, 3H), 7.20-7.26 (m, 4H), 7.77 (m, 2H), 8.53 (m, 1H), 11.58 (s, 2H); ^{13}C NMR (DMSO- d_6 , 100 MHz): 28.00, 32.78, 107.90, 117.43, 123.45, 123.78, 132.11, 133.87, 135.79, 136.96, 140.57, 141.65, 142.08, 142.63, 143.44, 142.85, 145.15, 157.91, 159.98, 175.01, 188.51. Anal. Calcd. For $\text{C}_{21}\text{H}_{13}\text{ClN}_4\text{O}_2$: C, 64.87; H, 3.37; N, 14.41. Found: C, 64.76; H, 3.28; N, 14.49.

1,1'-(pentane-1,5-diyl)bis(3-methyl-1H-spiro[indeno[1,2-b]pyrazolo[3,4-e]pyridine-4,3'-indoline]-2',5(10H)-dione (6b)

Brown solid; dec 295-297 °C; FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3045, 2927, 1679, 1571, 1608, 1352. ^1H NMR (DMSO- d_6 , 500 MHz): 1.53 (s, 6H), 1.78 (s, 6H), 3.76 (s, 4H), 6.92-6.99 (m, 4H), 7.11-7.14 (m, 2H), 7.19 (d, $J = 6.8$ Hz, 2H), 7.21-7.26 (m, 2H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.71-7.77 (d, $J = 6.4$ Hz, 2H), 11.59 (s, 2H), 12.31 (s, 2H). ^{13}C NMR (DMSO- d_6 , 100 MHz): 18.83, 23.42, 26.94, 29.31, 48.42, 103.18, 103.54, 107.83, 109.11, 113.17, 113.89, 117.01, 123.45, 123.85, 127.24, 129.83, 131.52, 131.83, 140.05, 143.85, 145.36, 147.15, 153.64, 177.43, 190.23. Anal. Calcd. For $\text{C}_{47}\text{H}_{36}\text{N}_8\text{O}_4$: C, 72.67; H, 4.67; N, 14.42. Found: C, 72.66; H, 4.63; N, 14.38.

1,1'-(hexane-1,6-diyl)bis(5'-chloro-3-methyl-1H-spiro[indeno[1,2-b]pyrazolo[3,4-e]pyridine-4,3'-indoline]-2',5(10H)-dione (6d)

Brown solid; dec 300-303 °C; FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3068, 2933, 1710, 1577, 1602, 1346. ^1H NMR (DMSO- d_6 , 400 MHz): 1.10 (m, 4H), 1.18 (m, 4H), 1.35 (s, 6H), 3.34 (m, 4H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.34 (m, 4H), 7.47 (m, 4H), 7.92 (m, 2H) ppm. ^{13}C NMR (DMSO- d_6 , 100 MHz):

19.88, 23.42, 27.55, 30.33, 47.37, 103.15, 105.71, 107.19, 117.45, 117.82, 119.53, 123.02, 127.46, 127.48, 135.14, 137.92, 141.36, 145.43, 147.26, 147.38, 149.25, 151.43, 155.98, 173.82, 190.14. Anal. Calcd. For $C_{48}H_{36}Cl_2N_8O_4$: C, 67.06; H, 4.22; N, 13.03. Found: C, 67.14; H, 4.26; N, 13.05.

Results and discussion

In our interest for the development of green synthetic strategies to obtain heterocyclic pharmaceutical compounds [24-39], we have concentrated on synthesis of the first multi-component synthesis of spiro-pyrazolopyridines *via* 5-aminopyrazole, isatin derivatives and indane-1,3-dione in the presence of 1,4-disulfo-1,4-diazoniabicyclo[2.2.2]octane chloride (DSDABCO) as a novel ionic liquid. Furthermore, to improve the pharmaceutical properties of pyrazolopyridines, we were triggered to prepare novel bis spiro-pyrazolopyridines.

Scheme 1. Synthesis of mono and bis spiro-pyrazolopyridines using ionic liquid DSDABCO

A possible mechanism for the synthesis of spiro-pyrazolopyridine derivatives was proposed (Scheme 2). Initially, isatin 1 was converted to active form 7 by hydrogen abstraction from ionic liquid DSDABCO as a bronsted acid. After nucleophilic attack of C-2 of indane-1,3-dione 2 to carbonyl moiety of intermediate 7 dehydration compound 8 was formed. Finally, nucleophilic attack of C-4 of 5-aminopyrazole to intermediate 8, followed by cyclization and dehydration product 5 was produced.

Scheme 2. A proposed mechanism for the synthesis of mono and bis spiro-pyrazolopyridines using ionic liquid DSDABCO

In order to optimize the model process and to understand the efficiency of media in this reaction, several classic catalysts were chosen for comparison. Initially, the reaction of isatin **1a**, indan-1,3-dione **4**, 5-aminopyrazole **5** were mixed together with 10 mL of EtOH (entries 1-4) in the present of 0.1 g solid acidic catalyst or 0.2 mmol of ionic liquids (entries 5-10). Among the tested media, we found that the ionic liquid (DSDABCO) was the best for both high yield and high reaction rate (92% yield in 1 hour). We found that 0.2 mmol of DSDABCO was enough for the synthesis of **5a** (Table 1).

Table 1. The effect of various catalysts or media on the synthesis of spiro-pyrazolopyridine **5a**

Entry	Media ^{a,b}	Temperature	Time (h)	Yield (%)
1	silica gel	reflux	24	-
2	ZnCl ₂	reflux	24	-
3	K10	reflux	18	35
4	L-proline	reflux	8	63
5	[BMIm][PF ₆]	60 °C	8	68
6	[BMIm] Br	60 °C	10	72
7	[BMIm] HSO ₄	60 °C	10	79
8	[BDBDIm] Br [24]	60 °C	6	78
9	[BDBDIm] Br [24]	r.t.	5	82
10	DSDABCO	r.t.	1	92

^a 10 mL of EtOH was used as a solvent

^b 0.2 mmol of ionic liquids were used

It is clear from Table 2. that increasing temperature has no effect in reaction time and yield. The best temperature for the synthesis of spiro-pyrazolopyridine **5a** was room temperature (Table 2).

Table 2. The effect of amount of ionic liquid DSDABCO and temperature in the synthesis of spiro-pyrazolopyridine **5a**

Entry	DSDABCO (mmol ionic liquid/ 1 mmol of substrate)	Temperature	Time (h)	Yield (%)
1	0.2	100 °C	2	91
2	0.2	80 °C	1	92
3	0.2	60 °C	1	92
4	0.3	r.t.	1	92
5	0.2	r.t.	1	92
6	0.1	r.t.	2	81

To test the generality and efficiency of DSDABCO, we checked some aldehydes with electron withdrawing and electron donating substituents (Table 3). All of the synthesized compounds in Table 3. were characterized by spectroscopic methods (IR, ¹H NMR and ¹³C NMR) and elemental analysis. To investigate the scope of this synthesis, different synthesized bis isatin and mono isatins were reacted with indane-1,3-dione and aminopyrazole in DSDABCO and the results were listed in Table 3.

Table 3. Synthesis of fused mono, bis spiro-pyrazolopyridine derivatives using ionic liquid DSDABCO

Entry	Isatin	Linkage	Product	Time (min)	Yield (%)	Dec. (°C)	Reported Dec. (°C) [31]
1	Isatin	-	5a	60	92	265-267	267-268
2	5-Cl isatin	-	5b	60	94	257-258	253-255
3	5-Br isatin	-	5c	60	95	289-291	289-290
4	Isatin	Dibromohexane	6a	90	94	266-268	267-269
5	Isatin	Dibromopentane	6b	90	93	292-294	295-297
6	Isatin	Dibromobutane	6c	90	95	298-300	297-299
7	5-Cl isatin	Dibromohexane	6d	90	96	301-303	300-303
8	5-Cl isatin	Dibromopentane	6e	90	95	307-309	308-310
9	5-Cl isatin	Dibromobutane	6f	90	95	299-301	300-303
10	5-Br isatin	Dibromopentane	6g	90	94	301-303	300-303
11	5-Br isatin	Dibromobutane	6h	90	93	301-303	300-302
12	Isatin	Benzilic	6i	120	95	290-292	288-289

^a Isolated yield

Conclusions

Finally, we develop an efficient and convenient procedure for the synthesis of novel derivatives of mono and bis spiro-pyrazolopyridines through three component synthesis of isatin derivatives, indan-1,3-dione and aminopyrazole in ionic liquid DSDABCO. This procedure offer advantages such as reduced reaction time, mild reaction condition, productivity and higher yield and ease of

execution. This simple process make this procedure economic, begin and a waste free chemical process for the synthesis of pyrazolopyridines.

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Conflict of Interest

We have no conflicts of interest to disclose.

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