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

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\section*{Abstract}
In this work, multicomponent synthesis of mono and bis spiropyrazolopyridines 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 \textsuperscript{1}H, \textsuperscript{13}C 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 xantine 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. $^1\text{H}$ and $^{13}\text{C}$ 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-diazeniabicyclo[2.2.2]octane chloride (DSDABCO)

A flask (500 mL) charged with 1,4-diazeniabicyclo[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. $^1\text{H}$ NMR (400 MHz, CDCl$_3$): $\delta = 3.09$ (s, 12H), 15.05 (s, 2H) ppm. $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$): $\delta = 32.7$ ppm. Anal calc. For C$_6$H$_{14}$Cl$_2$O$_6$S$_2$: C, 20.87; H, 4.09; N, 8.11. Found: C, 20.85; H, 4.12; N, 8.09.

![Structure of DSDABCO](image-url)

**Figure 1.** Structure of DSDABCO

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

A mixture of isatine 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) (ν_max/cm⁻¹): 3430, 2925, 1685, 1540, 1367. ¹H NMR (DMSO-d₆, 400 MHz): 1.56 (s, 3H), 7.25-7.29 (m, 4H), 7.47 (m, 2H), 7.53 (m, 2H), 11.58 (s, 2H); ¹³C NMR (DMSO-d₆, 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 C₂₁H₁₄N₄O₂: 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) (ν_max/cm⁻¹): 3450, 2965, 1687, 1611, 1560, 1379. ¹H NMR (DMSO-d₆, 400 MHz): 1.53 (s, 3H), 7.20-7.26 (m, 4H), 7.77 (m, 2H), 8.53 (m, 1H), 11.58 (s, 2H); ¹³C NMR (DMSO-d₆, 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 C₂¹H₁₃ClN₄O₂: 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) (ν_max/cm⁻¹): 3045, 2965, 1679, 1571, 1608, 1352. ¹H NMR (DMSO-d₆, 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). ¹³C NMR (DMSO-d₆, 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, 143.35, 145.36, 147.15, 153.64, 177.43, 190.23. Anal. Calcd. For C₄₇H₃₆N₈O₄: 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) (ν_max/cm⁻¹): 3068, 2933, 1710, 1577, 1602, 1346. ¹H NMR (DMSO-d₆, 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. ¹³C NMR (DMSO-d₆, 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_{2}N_{8}O_{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-diazeniabicyclo[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 DSDABCD 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     | ZnCl₂     | reflux      | 24       | -         |
| 3     | K10       | reflux      | 18       | 35        |
| 4     | L-proline | reflux      | 8        | 63        |
| 5     | [BMIm][PF₆] | 60 °C | 8        | 68        |
| 6     | [BMIm] Br | 60 °C | 10       | 72        |
| 7     | [BMIm] HSO₄ | 60 °C | 10       | 79        |
| 8     | [BDBDMIm] Br [24] | 60 °C | 6        | 78        |
| 9     | [BDBDMIm] 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, $^1$H NMR and $^{13}$C 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 DSDABCD 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 DSDABCD. This procedure offer advantages such as reduced reaction time, mild reaction condition, productivity and higher yield and ease of
execution. This simple process makes 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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