A new and efficient method for the synthesis of pyrazolo[3,4-d] pyrimidines catalyzed by iodine

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Abstract. Substituents of fully new pyrazolo[3,4-d] pyrimidines were synthesized. The synthesis starts with cyanomethylphenylketone that reacts with phenyl hydrazine to produce the corresponding aminopyrazole. The latter undergoes a cyclocondensation with N,N'-bis(arylmethylidene)arylmethane, yielding the final product. Both synthetic steps are high yielding (the overall yields between 65-78%). The newly synthesized compounds were characterized by 1H NMR, 13C NMR, and elemental analysis.

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1. Introduction
Heterocycles, especially nitrogen-containing ones, can be found in a vast range of natural products and biologically active compounds [1, 2]. Such systems are often characterized by potent physiological properties and are common in various pharmaceuticals and naturally occurring compounds [2].

Among heterocyclic compounds containing one or more nitrogen atoms, fused pyrimidines have attracted considerable attention in recent years due to their many applications, usually as biologically active systems [3]. Pyrazolo[3,4-d] pyrimidines are one category of these fused pyrimidines encompassing an array of pharmacological activities such as anticancer [4], antiviral [5], antimicrobial [6], herbicidal, pesticides, cardiovascular activities, anti-inflammatory [7], radioprotectant [4], and so on (Figure 1). Based on these compounds, different types of drugs and drug-like molecules, such as Allopurinol, have been discovered and are currently used for treating various diseases.

More specifically, pyrazolo[3,4-d] pyrimidines are frequently reported as Tyrosine Kinase (TK) inhibitors [8]. In fact, it is believed that molecules capable of inhibiting protein kinases, a series of widely used participants in cellular activities, have a crucial role in tumor development and progression [9–11]. Therefore, they are very important for targeted cancer therapy.

On the basis of these considerations, we intend to synthesize a new family of pyrazolo[3,4-d]pyrimidines scaffolds bearing substituents at Positions 1, 3, 4, and 6 (Scheme 1). A scan of the recent literature shows clearly that many different types of organic transformations can be catalyzed by molecular iodine [12–14]. In fact, due to its low cost, high catalytic activity and ready availability, as well as its nonmetallic, nontoxic, and environmentally benign nature, L2 has been employed for a diverse range of reactions including a synthesis of various heterocycles [12–15]. Using this
Lewis acid as a catalyst, high regioselectivity and chemoselectivity can be achieved in the reactions [14].

Further to our studies on the synthesis of potentially biologically active molecules and with iodine-catalyzed reactions [16], this study aims to report the development of one-pot reaction to form pyrazolo[3,4-d]pyrimidines via the reaction of 1,3-diphenyl-1H-5-aminopyrazole with N,N'-bis(arylmethylidene)arylmethan derivatives catalyzed by molecular iodine. To the best of the author’s knowledge, it is the first report on such a reaction that results in the formation of pyrazolo[3,4-d]pyrimidine and its derivatives. This reaction leads to good yields in a short time at moderate temperatures.

2. Results and discussion

The reaction sequences employed for the synthesis of different pyrazolo[3,4-d]pyrimidines are outlined in Scheme 2, as explained in the experimental section.

To optimize the reaction conditions, the reaction of 5-aminopyrazole 1a with bisimine 2a was selected as the model reaction. The results are summarized in Table 1. Initially, different solvents were employed in the presence of 10 mol% of the catalyst (entries 1-5). According to the results, DMSO showed the best activity as a solvent because of its better solubility for the reagents (entry 4). In addition, a control experiment was performed under a neat condition. According to the results, longer reaction time and lower yield do not form an optimal condition compared to reactions performed in the presence of an organic solvent.

In the second stage, the amount of the iodine required for catalyzing the reaction was optimized. The reaction was carried out in the presence of different amounts of the catalyst (entries 4 and 7-9). In the first step, 5 mol% of catalyst was used that afforded unsatisfactory yield (entry 7). The increasing amount of catalyst up to 20 and 50% had a detrimental effect on the products’ yields (entries 8 and 9). In the absence of a catalyst, no product was formed (entry 10). Finally, it was shown that the best results were obtained using 10 mol% of iodine as a catalyst with a reasonable yield (entry 4).

At our next attempt, the effect of temperature was examined. For this purpose, the reaction was performed at room temperature, 80, and 100°C (entries 4, 11 and 12). According to Table 1, the best temperature for this synthesis is 80°C with higher conversion in shorter times.

By using these optimized reaction conditions, an attempt was made to expand the scope of the reaction. The results are summarized in Table 2. As observed, the reaction of 1,3-diphenyl-1H-5-aminopyrazole with various types of N,N'-bis(arylmethylidene)arylmethan was performed. According to the results, all the products were produced with good yields in approximately short times.

A designed series of molecules were characterized by 1H NMR, 13C NMR, and elemental analysis. The 1H NMR spectrum of 3b showed two sharp singlet signals at δ = 2.29 and 2.38 ppm that can be attributed to two CH3 groups, and the aromatic hydrogens of phenyl groups appeared between δ 6.96 and 8.54 ppm.

The possible pathway for this reaction is shown in Scheme 2. The activation of the imine bond occurred in the presence of iodine as the catalyst. The nucleophilic attack of carbon atom in the cyclic enamine to the activated imine bond resulted in the formation of intermediate A. The conversion of intermediate A to B occurred through the imine-enamine tautomerism. The nucleophilic attack of enamine nitrogen to the benzyl carbon resulted in the hydrolysis of the imine bond followed by the formation of six-membered cyclic pyrimidine. Finally, aromatization of C is done in the presence of iodine.
Scheme 2. Proposed mechanism for the synthesis of pyrazolo[3,4-d]pyrimidin.

Table 1. Optimization of reaction conditions for the synthesis of 1,3,4,6-tetraphenyl-1H-pyrazolo[3,4-d]pyrimidine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst (mol%)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>10</td>
<td>Reflux</td>
<td>12</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>CH3CN</td>
<td>10</td>
<td>Reflux</td>
<td>12</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>10</td>
<td>Reflux</td>
<td>12</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>10</td>
<td>100</td>
<td>3</td>
<td>85</td>
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<tr>
<td>5</td>
<td>DMSO</td>
<td>10</td>
<td>100</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>Neat</td>
<td>10</td>
<td>150</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>5</td>
<td>100</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>DMSO</td>
<td>20</td>
<td>100</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>50</td>
<td>100</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>-</td>
<td>100</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>DMSO</td>
<td>10</td>
<td>80</td>
<td>3</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>DMSO</td>
<td>10</td>
<td>r.t.</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

*: isolated yield.

3. Conclusions

An iodine-catalyzed reaction for the formation of pyrazolo[3,4-d]pyrimidine derivatives through a single-step, one-pot reaction was described for the first time. A clean procedure with low catalysis was presented that led to good yields in a short reaction time, and the use of molecular iodine as a non-toxic, non-corrosive, commercially available, and inexpensive catalyst is another advantage of this procedure. Therefore, it can be considered an efficient and attractive strategy for the synthesis of additional pyrazolo[3,4-d] pyrimidine derivatives. Finally, the synthesized compounds are potentially active drugs as tyrosine kinase inhibitors. Fur-
Table 2. Synthesis of pyrazolo[3,4-d]pyrimidine derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>5-Aminopyrazole</th>
<th>Bisimine</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
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<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td>2.5</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
<td>5.5</td>
<td>66</td>
</tr>
<tr>
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<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
<td>3.5</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
<td>5</td>
<td>70</td>
</tr>
</tbody>
</table>

*: Reaction condition: 5-Aminopyrazole (1 mmol), Bisimine (1 mmol), Iodine (10 mol%), DMSO (3 ml).

b: isolated yield.

4. Experimental

4.1. Materials and techniques

All materials used are commercially available, which have been purchased from Merck and used without any additional purification. 1H NMR and 13C NMR spectra were recorded on a Bruker (Avance DRX-400) spectrometer using CDCl3 as a solvent at room temperature. Chemical shifts δ were reported in ppm relative to tetramethylsilane as an internal standard. Elemental analysis was performed by a Perkin Elmer 2004 (II) CHN analyzer.

4.1.1. General synthesis procedure (for example 1a):

A mixture of phenylhydrazine (1 mmol), cyanomethylphenylketone (1 mmol), and n-butylimidazolium bromide (0.5 mmol) was stirred for 4 h at 80°C. After completion of the reaction, 10 mL of distilled water was added to the reaction mixture, resulting in the instant formation of 1,3-diphenyl-1H-5-aminopyrazole.
precipitates. Finally, these precipitates were filtered and washed two times with distilled water.

4.1.2. General synthesis procedure (for example 3a):
In a round bottom flask equipped with a magnetic bar, 1,3-diphenyl-1H-5-aminoazopyrazole (1 mmol) and N,N'-bis(arylmethylidine) arylmethan (1 mmol) were added in DMSO (3 mL) in the presence of molecular iodine (10 mol%) as the catalyst at 80°C. The reaction mixture was stirred for 2-5/5 hours, and the reaction progress was controlled by TLC (1:4; ethylacetate: n-hexane). After completion of the reaction, the mixture was cooled at room temperature, poured into a separatory funnel, extracted from water and ethyl acetate, and dried using rotary evaporator. Purification of the desired product was done using column chromatography (ethyl acetate: n-hexane: 1:4). These purified products were dried and subjected to spectral analyses for verifying their exact structures.

4.2. Spectral data

1,3,4,6-tetraphenyl-1H-pyrazolo[3,4-d]pyrimidine (3a):

Yellow Oil: Yield: 0.330g (78%); 1H-NMR (400 MHz, CDCl3): δ 7.12-7.16 (m, 2H, H-Ar), 7.22-7.28 (m, 4H, H-Ar), 7.30-7.34 (t, 3H, J = 7.4 Hz, H-Ar), 7.46-7.56 (m, 7H, H-Ar), 8.41-8.43 (d, 2H, J = 8.4 Hz, H-Ar), 8.65-8.66 (d, 2H, J = 7.6 Hz, H-Ar); 13C-NMR (400 MHz, CDCl3): δ 108.1, 117.9, 121.6, 123.7, 125.3, 126.4, 127.9, 128.9, 128.5, 128.8, 129.1, 129.5, 130.1, 130.3, 130.8, 137.0, 139.1, 146.6, 161.6, 163.2; Elemental analysis for C26H24N2O4: Calcd: C, 82.05%; H, 4.75%; N, 13.20%; Found: C, 82.43%; H, 4.29%; N, 13.28%.

4,6-di(4-methylphenyl)-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (3b):

Yellow Oil: Yield: 0.330g (75%); 1H-NMR (400 MHz, CDCl3): δ 2.29 (s, 3H, Me), 2.38 (s, 3H, Me), 6.96-6.98 (d, 2H, J = 8 Hz, H-Ar), 7.14-7.18 (t, 2H, J = 7.4 Hz, H-Ar), 7.25-7.31 (m, 8H, H-Ar), 7.43-7.45 (d, 2H, J = 7.6 Hz, H-Ar), 7.51-7.55 (t, 2H, J = 8.1 Hz, H-Ar), 8.41-8.42 (d, 2H, J = 7.6 Hz, H-Ar), 8.52-8.54 (d, 2H, J = 8.4 Hz, H-Ar); 13C-NMR (400 MHz, CDCl3): δ 30.4, 30.8, 101.9, 120.5, 122.9, 123.4, 125.3, 126.8, 127.4, 127.5, 127.8, 128.0, 128.3, 128.5, 129.3, 131.4, 133.2, 134.0, 138.0, 139.4, 140.1, 145.6; Elemental analysis for C31H26N2O4: Calcd: C, 82.27%; H, 5.35%; N, 12.38%; Found: C, 82.51%; H, 5.31%; N, 12.18%.

4,6-di(4-methoxyphenyl)-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (3c):

Yellow Oil: Yield: 0.319g (66%); 1H-NMR (400 MHz, CDCl3): δ 3.75 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.67-6.69 (d, 2H, J = 8 Hz, H-Ar), 6.97-6.99 (d, 4H, J = 8.8 Hz, H-Ar), 7.25-7.28 (t, 2H, J = 7.4 Hz, H-Ar), 7.30-7.34 (t, 2H, J = 6.8 Hz, H-Ar), 7.51-7.54 (m, 4H, H-Ar), 8.40-8.42 (d, 2H, J = 8 Hz, H-Ar), 8.60-8.62 (d, 2H, J = 8.8 Hz, H-Ar); 13C-NMR (400 MHz, CDCl3): δ 55.4, 55.4, 106.4, 107.0, 113.3, 113.8, 117.1, 119.0, 121.5, 128.2, 128.5, 129.0, 129.1, 129.1, 130.5, 130.7, 132.0, 139.6, 140.8, 161.4, 162.0; Elemental analysis for C31H24N2O4: Calcd: C, 76.84%; H, 4.90%; N, 11.56%; O, 6.60%; Found: C, 76.91%; H, 5.11%; N, 11.27%; O, 6.71%.

4,6-di(2-chlorophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (3d):

Yellow Oil: Yield: 0.321g (65%); 1H-NMR (400 MHz, CDCl3): δ 6.95-6.98 (t, 4H, J = 7.2 Hz, H-Ar), 7.06-7.10 (t, 2H, J = 8 Hz, H-Ar), 7.26-7.35 (m, 8H, H-Ar), 7.49-7.53 (t, 4H, J = 7.6 Hz, H-Ar), 8.47-8.49 (d, 2H, J = 8.4 Hz, H-Ar); 13C-NMR (400 MHz, CDCl3): δ 108.5, 120.8, 121.4, 125.7, 127.0, 127.3, 127.8, 128.8, 128.9, 129.0, 129.1, 129.8, 130.7, 131.2, 131.8, 132.7, 134.4, 136.3, 136.1, 139.7, 156.7, 160.0, 161.6; Elemental analysis for C26H16Cl2N2O2: Calcd: C, 70.60%; H, 3.68%; Cl, 14.37%; N, 11.36%; Found: C, 70.55%; H, 3.81%; Cl, 14.22%; N, 11.42%.

1,3-diphenyl-4,6-di(2-thienyl)-1H-pyrazolo[3,4-d]pyrimidine (3e):

Yellow Oil: Yield: 0.305g (70%); 1H-NMR(400 MHz, CDCl3): δ 7.10-7.14 (m, 4H, H-Arthio), 7.27-7.34 (m, 3H, H-Ar), 7.43-7.48 (m, 3H, H-Ar), 8.11-8.12 (d, 2H, J = 4.5, H-Arthio), 8.19-8.20 (d, 2H, J = 8.1, H-Ar), 8.35-8.37 (d, 2H, J = 8.4, H-Ar); 13C-NMR (400 MHz, CDCl3): δ 107.31, 121.58, 126.48, 126.71, 128.25, 128.31, 128.45, 128.80, 129.06, 129.73, 129.87, 130.33, 130.88, 130.97, 131.69, 132.31, 133.35, 134.26, 136.90, 157.69, 164.32; Elemental analysis for C25H16N2S2: C, 68.78%; H, 3.69%; N, 12.83%; S, 14.69%; Found: C, 68.92%; H, 3.54%; N, 12.99%; S, 14.55%.

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References

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