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Graphical Abstract

Transition metal free synthesis of 2,4,6-trisubstituted pyrimidines via Cope-type hydroamination of 1,4-diarylbuta-1,3-diynes

Raju Singha and Jayanta K. Ray*

\[ \text{Ar} - \equiv - \equiv - \text{Ar} + \text{HN} \rightarrow \text{NH}_2\text{HCl} \rightarrow \text{Ar} \equiv \equiv \text{Ar} \]

\[ \text{R} = \text{H, Me, Ph} \]

Et\text{3}N, DMSO, heat

15 examples
46-88% yield

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Transition metal free synthesis of 2,4,6-trisubstituted pyrimidines via Cope-type hydroamination of 1,4-diarylbuta-1,3-diynes

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We have developed an efficient and transition metal free methodology for the synthesis of 2,4,6-trisubstituted pyrimidines by the Cope-type hydroamination reaction of 1,4-diarylbuta-1,3-diynes with amidines in DMSO solvent.

Pyrimidine motifs are one of the most important heterocycles, from both chemical and pharmaceutical points of view.1 Different substituted pyrimidines are highly bio-active and have proven to display antitumor, antibacterial, antifungal, antimalarial and anticonvulsant activities.2 Pyrimidine skeletons are also present in biological systems such as nucleic acids.3 Furthermore, different conjugated pyrimidines have luminescence properties and thus, they are also used in organic light emitting devices (OLED)4 and molecular wires.5 Due to such great importance of pyrimidine nucleus, a number of methods have been reported in literature for their synthesis; however most of them are associated with the complex starting materials or the use of different metal catalyst.6

Recently a number of methods have been reported in literature for the transition metal free synthesis of important heterocycles.7 In last decade, Beauchemin and co-workers had reported the uncatalyzed intermolecular Cope-type hydroamination reactions of alkynes/alkenes with hydrazine/hydroxylamine to form imine.8 Later on Bao and co-workers have synthesized isoxazoles and pyrazoles using the Cope-type hydroamination reactions.9

Recently Neuville and co-workers have synthesized 1,2,4-trisubstituted imidazoles by the reaction of terminal alkynes and amidines and in presence of copper catalyst (Scheme 1).10 Amides are an important class of organic compounds which can serve as a base or an ambidentate nucleophile or a bidentate nucleophile depending upon the reaction conditions.11 Herein, we have synthesized 2,4,6-trisubstituted pyrimidines via catalyst free Cope-type hydroamination reaction of 1,4-diarylbuta-1,3-diynes with amidines where the amidines acts as a bidentate nucleophile. Initially, we chose 1,4-diphenylbuta-1,3-diyne (1a) and acetonitrile hydrochloride as model substrates to optimize the reaction conditions. Reaction of the substrates in toluene solvent and in presence of triethylamine base under refluxing condition did not give any product. Similarly DMF also failed to produce any result even at 120 °C. Then we heated the substrates in DMA solvent at 140 °C and it gave the desired product 4-phenylpyrimidine (2a) in 13% yield. Under the same reaction condition, DMSO solvent produced the product 2a in 32% yield. Thus the DMSO solvent was promoting the reaction most efficiently.12 When the temperature was increased to 150 °C, the yield of the reaction was improved to 62% within 24 hours.

On further increasing the temperature to 160 °C, the yield slightly increased to 65%. Then we used different carbonate and acetate bases but they gave lower yields. All the results are shown in Table 1.

Table 1: Screening of the reaction conditions *

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Temp.(°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>Et₃N</td>
<td>110</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>Et₃N</td>
<td>120</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>DMA</td>
<td>Et₃N</td>
<td>140</td>
<td>48</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>Et₃N</td>
<td>140</td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>Et₃N</td>
<td>150</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>Et₃N</td>
<td>160</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>NaOAc</td>
<td>160</td>
<td>24</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>160</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>K₂CO₃</td>
<td>160</td>
<td>24</td>
<td>46</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1,4-diphenylbuta1,3-diyne (0.5 mmol), acetonitrilehydrochloride (3.0 equiv.), base (3.0 equiv.), solvent (5 mL).*Isolated yield.
From Table 1, we concluded that the optimized reaction conditions were 1,4-diphenylbuta-1,3-diyne (0.5 mmol), acetamide hydrochloride (3 equiv), triethylamine (3 equiv.), DMSO (5 mL) and heated at 160 °C for 24 h. Once we got the optimized reaction condition, then we applied this on different 1,4-diarylbuta-1,3-diyne to examine the scope of the reaction. We have synthesized a number of 2,4,6-trisubstituted pyrimidines \(^\text{13,14}\) and the results are shown in Table 2.

**Table 2**: synthesis of different 2,4,6-trisubstituted pyrimidines \(^\text{a,b}\)

<table>
<thead>
<tr>
<th>Ar = Cyclic group</th>
<th>Reactions</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph Ph</td>
<td>2g, Y = 63%</td>
<td></td>
</tr>
<tr>
<td>F F</td>
<td>2h, Y = 60%</td>
<td></td>
</tr>
<tr>
<td>Cl F</td>
<td>2i, Y = 61%</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>2j, Y = 82%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>2k, Y = 80%</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>2l, Y = 88%</td>
<td></td>
</tr>
<tr>
<td>F F</td>
<td>2m, Y = 46%</td>
<td></td>
</tr>
<tr>
<td>F F</td>
<td>2n, Y = 62%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>2o, Y = 76%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1,4-diarylbuta-1,3-diyne (0.5 mmol), benzamidinehydrochloride/formamidineacetate (3.0 equiv.), Et,\text{N} (3.0 equiv.), DMSO (5 mL) and heated at 160 °C for 24 h. \(^b\) Isolated yield.

As shown in Table 2, except 2d, the yield of the products were moderate to excellent. For the electron rich 1,4-diarylbuta-1,3-diyne (Table 2, entry 2d) the yield was lower and for the electron poor 1,4-diarylbuta-1,3-diyne (Table 2, entries 2c, 2e and 2f), the yields were higher. This result implies that, the electron deficient 1,4-diarylbuta-1,3-diyne are the suitable substrates for this reaction.

**Scheme 2**: The X-ray crystal structure of compound 2c

The structures of the tri-substituted pyrimidines were unambiguously confirmed from the X-ray crystal structure of the compound 2c (CCDC 990434) (Scheme 2).

After confirming the structure of the compound 2,4,6-trisubstituted pyrimidines, different 1,4-diarylbuta-1,3-diyne were subjected to reaction with benzamidinehydrochloride or formamidineacetate to test the generality of this synthetic protocol. The results are shown in Table 3.

**Scheme 3**: Plausible rational for the formation of 2,4,6-trisubstituted pyrimidines.
According to our experimental results and literature reports\(^8\), a plausible reaction mechanism is shown in Scheme 3. At first the amidine hydrochloride reacted with triethylamine to give free amidine. Then the intramolecular Cope-type hydronamination reaction occurred between the diyne (I) and amidine to give the ionic intermediate A, which then transformed to the intermediate B via a proton transfer process. Then the intermediate B converted to the intermediate C through the isomerisation process. Then intermediate C gave the final product 2,4,6-trisubstituted pyrimidines (2) via the intramolecular electrophilic addition reaction.

In conclusion, we have developed a novel and straight forward method for the synthesis of 2,4,6-trisubstituted pyrimidines using the readily available starting materials, 1,4-diarylbuta-1,3-dienes and amidines. This methodology will be very much useful in organic synthesis because of its simple reaction condition, moderate to good yield, readily available starting materials and catalyst free reaction condition.

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Notes and references

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† Electronic Supplementary Information (ESI) available: The detailed experimental procedures, characterisation data and the copies of \(^1\)H and \(^13\)C NMR spectra are available in supporting information. See DOI: 10.1039/b000000x/


13. General procedure for the synthesis of 2,4,6-trisubstituted pyrimidines: The 1,4-diarylbuta-1,3-diene (0.5 mmol), acetamidine/benzamidine hydrochloride (1.5 mmol) were taken in a round bottomed flask fitted with a condenser and then triethyl amine (1.5 mmol) and dimethyl sulfoxide (5 mL) were added. Then the reaction mixture was heated at 160 °C under air balloon for 24 h. Then the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and then evaporated under reduced pressure. The crude product was then purified by column chromatography using silica gel (60 mesh) and petroleum ether/ethylacetate (20:1) as eluent.

14. Spectral data of the representative compound 4-benzyl-2-methyl-6-phenylpyrimidine (2a): Yellow liquid; Yield 65%; \(^1\)H NMR (CDCl$_3$), 200 MHz: δ: 2.81 (3H, s), 4.16 (2H, s), 7.30-7.35 (5H, m), 7.44-7.47 (4H, m), 7.94-7.99 (2H, m); \(^13\)C NMR (CDCl$_3$), 50 MHz: δ: 26.3 (CH$_3$), 44.3 (CH$_2$), 113.3 (CH), 127.1 (CH), 127.5 (2 x CH), 129.0 (2 x CH), 129.1 (2 x CH), 129.5 (2 x CH), 130.9 (CH), 137.2 (C), 137.7 (C), 164.9 (C), 168.0 (C), 169.7 (C); HRMS (ESI) calculated for C$_{25}$H$_{26}$N$_2$ [M + H]$: 371.1868; found: 361.1387.