Microwave assisted, Mont. K10 clay catalyzed solvent-free green synthesis of thiadiazine and quinazolinone derivatives from pyrazole aldehydes and 2-amino amides

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Abstract: Montmorillonite K10 has been found as a green catalyst for the synthesis of cyclized thiadiazine and quinazolinones derivatives under microwave irradiation and solvent free condition. The scope of the reaction has been demonstrated for a number of pyrazole aldehyde with O-aminoamides such as 2-amino sulfonamide and 2-amino benzamide. The reaction afforded a title compounds within few minutes of irradiation in excellent yield. Synthetic utility of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-iodo-2,3-dihydroquinazolin-4(1H)-one has been demonstrated by synthesizing 2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl-2,3-dihydroquinazolin-4(1H)-one under Suzuki coupling reaction protocol. A plausible mechanism for the formation of product is provided.

Keywords: Microwave irradiation, Montmorillonite K10, pyrazole aldehyde, O-aminoamides, Quinazolinone.

1. INTRODUCTION

Montmorillonite K10 clay has been known for its tunable Brønsted and Lewis acidities and widely used as an environmentally friendly catalyst in synthetic organic chemistry [1-3]. The Mont. K10 clay offered several advantages in comparison with other catalysts, such as non-corrosive properties, non-toxic, low cost and ease of handling [4-6]. Moreover, it could be easily separated and recycled, which made it an excellent heterogeneous green catalyst [7-9]. It has been found to be an active catalyst in many types of reactions such as cationic ring-opening polymerization [10,11], esterification [12], acetylation [13], isomerization [14], cyclization, and other reactions [15-17]. As a solid acid catalyst, Montmorillonite K10 clay has a great potential to catalyze dehydration reactions [18-20].

In the modern organic synthesis, reducing reaction time, minimizing solvent use and eliminating the occurrence of side reactions are a focus of research, which also fulfills the concept of green chemistry methodologies [21,22]. Microwave-assisted organic synthesis is a matured technique in green chemistry that improves reaction rate and yields. The microwave method provides offers higher selectivity, simplicity of operation, energy efficiency, drug discovery and multi-step reaction compared to conventional method [23,24].

Quinazolinones are well known N-heterocyclic motifs and found significance in wide range of utility and found in pharmaceutical and particularly, these structures are mostly associated with anticancer activity, for example, Gefitinib is a tyrosine kinase inhibitor drug, like gefitinib, Erlotinib also receptor tyrosine kinase inhibitor which act on the (EGFR), while Lapatinib is a U.S. FDA approved drug used for the treatment of breast cancer and other solid tumors [25-27]. Alfuzosin is used for the treatment of benign prostatic hyperplasia and Doxazosin is used for the treatment of prostate enlargement and high blood pressure and also this scaffold is associated with anti-hypertensive [28], anti-malarial [29], anti-bacterial [30], anti-inflammatory, anti-fungal [31], anti-tuberculosis properties. Given the significant value of quinazolinones and the analogs, various methods have been developed by using transition metals such as copper [32], iridium [33], manganese [34], silver [35], vanadium [36] and cyanuric chloride [37], cationic amberylyst-15 resin [38], clays [39], PTSA [40], starch sulfate [41] and TFA [42] were employed as catalyst. Despite having various methods to synthesis quinazolinones, it is limitedly explored by the use of green chemistry protocol and thus prompted us to explore the prospect of Mont. K10 (MK-10) clay as a green catalyst. Hence, herein we report the MK-10clay catalyzed the synthesis of highly functionalized title compounds from O-aminoamides under solvent-free microwave irradiation.
II. EXPERIMENTAL

Materials

All the reactions were carried out in an oven-dried glassware. All the microwave irradiation reactions were performed on a CEM Discover-300 microwave synthesiser. Progress of reactions was monitored by Thin Layer Chromatography (TLC), while purification of crude compounds was done by column chromatography using silica gel (mesh size 100-200). Melting points reported are uncorrected. The NMR spectra were recorded on Bruker-400 MHz NMR spectrometer (400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR) with CDCl$_3$ or (CD$_3$)$_2$SO as the solvent and TMS as internal reference. Integrals are in accordance with assignments; Coupling constants were reported in Hertz (Hz). All the $^{13}$C spectra reported are proton-decoupled. Chemical shifts are presented in $\delta$ scale. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). FTIR spectra were recorded on a Perkin-Elmer RX-I FT-IR and absorbencies are reported in cm$^{-1}$. HRMS analyses were recorded using Q-T of Micro mass spectrometer (different mass analyses based on availability of instruments). Yields refer to quantities obtained after chromatography.

General procedure for synthesis of 3a

To a mixture of pyrazole aldehyde 1a-c (1.0 mmol), 2-amino benzamide 2a-c (1.0 mmol) were microwave irradiated (standard mode) in the presence of montmorillonite K10 clay (1.0 mmol) at 100 W for 3 min. After the completion of the reaction (monitored by TLC), MK10 clay was filtered off using celite bed/Silica bed. The crude product was purified on a silica gel column to afford corresponding cyclic quinazolinone and thiadiazine 3a-3o in very good yields (Eluent: n-Hexane/EtOAc). All the compounds 3a-3o were thoroughly characterized by 1H NMR, 13CNMR, IR and HRMS.

General procedure for Suzuki coupling of compound 5a

To a compound 3 (1 equiv.) in mixture of 1, 4-dioxane and methanol (3:1) and phenyl boronic acid 6 (1.5 equiv.) was added followed by K$_2$CO$_3$, Pd(PPh$_3$)$_4$ catalyst. The mixture was stirred for 4 h at 70 °C. After the completion of the reaction (monitored by TLC), the mixture was extracted with ethyl acetate, washed with dil. HCl and distilled water. The combined organic layer was dried over anhydrous Na$_2$SO$_4$. Solvent was removed under vacuum and crude was purified by silica gel column chromatography to afford pure Suzuki coupled compound 5a. The compounds 5b-5j were also synthesized by using this procedure.

III. RESULT AND DISCUSSION

Initially, a slurry made up of 1 equivalent of pyrazole aldehyde (1a) and 1 equivalent of 2-amino sulfonamide (2a) and 20 w/w MK-10 was microwave irradiated (50 watts) for 3 minute afforded 3-(1,3-diphenyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-benz[e][1,2,4]thiadiazine 1,1-dioxide (3a) in 30% yield (Table 1, entry 1). Compound 3a was thoroughly characterized by spectroscopic method (See SI). In order to optimize the reaction condition for the synthesis of 3a, parameters such as microwave power and irradiation time, mole ratio of reactants and percentage load of catalyst were considered. Thus, a reaction of 1:1 ratio of compound 1a and 2a and 50 w/w of MK-10 without any solvent was microwave irradiated at 50 W for 3 min, afforded product 3a only in 30% yield (Table 1, Entry 2). Repeating the reaction with increased power level 100 W for two minutes afforded increased yield of 3a (50%) (Table 1, Entry 3). The reaction with increased 100 w/w catalyst for nine minutes the yield of 3a (90%) (Table 1, Entry 5). To optimize the catalyst load, reactions with 50 w/w and 200 w/w percent catalyst afforded 85% and 90% yield of 3a, respectively indicates lower load of catalyst decreased the yield while higher load did not alter the yield and hence 100 w/w catalyst loads is optimum (Table 1, Entries 6 and 7). Increasing the microwave power level and change of the mole of catalyst afforded the desired product 3a in decreased or no improvement in the yield (Table 1, Entries 7-10). Hence, conditions shown in entry 5 of Table 1 were found to be optimum.

Encouraged by the preliminary results and in order to demonstrate the scope of the method, the reaction was elaborated to other amino amides 2a-c (Table 2). The reaction afforded compounds 3a-o in very good to excellent yields. The scope of the reaction summarized in Table 2. It should be noted that various para-substituted pyrazole aldehyde like methoxy, chloro, bromo and nitro groups were well tolerated to sulfonamide gave the corresponding thiadiazine (3a-3e) in good to excellent yields, subsequently, para-iodo amino amides was also examined, the reaction proceeds smoothly and offered the corresponding products (3f-3j) in good to excellent yields. Further, 2-amino benzamide also well tolerated under the reaction conditions and provided corresponding products (3k-3o) in good yields.

To explain the diverse product obtained, a plausible mechanism for the formation of cyclized products are discussed in Scheme 1. The cyclized thiadiazine and quinazolinone formation under the influence of MK10 may be explained by the initial formation of...
Imine intermediate A from anthranilamide/sulfonamide B with pyrazole aldehyde C subsequently undergoes nucleophilic attack by the amide nitrogen to yield corresponding cyclized thiadiazine and quinazolinone D.[43]. The effectiveness of this methodology was further scrutinized by a gram scale synthesis of D under optimized reaction condition without notable decrease in the yield (85%) (Scheme 2).

The nature of structure and diversity of the products obtained prompted us to examine the synthetic utility via Suzuki-coupling [44]. Thus, the reaction between E and phenyl boronic acid F in methanol under the influence of Et3N and palladium catalyst for 24h at 70°C afforded biphénylderivative G only in 20% yield (Table 3, Entry 1). Then, the change of the base NaH, the yield of the 5a improved to 30%. However, the change of solvent 1,4-dioxane + methanol (3:1) and base KHCO3 afforded an optimum yield of 5a in 90% yield (Scheme 3) (Table 3, Entry 5). Having optimized condition in hand, the method has been demonstrated by preparing a number of biphényl appended Suzuki coupled products (5a-j) have been prepared in very good yield (table 4).

In this study, palladium catalyst reacts with 6-iodo-quinazolinone E to formation of organo palladium (II) complex intermediate B. This intermediate B react with boronic acid in the presence of base K2CO3 to formation of another palladium (II) complex intermediate C. In this intermediate intramolecular reductive elimination of palladium (II) convert to palladium (0) and formation of biphényl compound 5a.

3-(1,3-diphenyl-1H-pyrazol-4-yl)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (3a):
White powder; 90% yield; Rf (30% EtOAc-Hexane): 0.53, M.P: 228-232 °C. FTIR (KBr) νmax: 3363, 3229, 2983, 1737, 1664, 1486, 1373, 1240, 1186, 1164, 1155, 1154, 603 cm⁻¹; 1H NMR (400MHz, DMSO-d6): δ 8.91 (s, 1H), 8.43 (s, 1H), 7.83 (t, J = 7.7 Hz, 2H), 7.69 – 7.63 (m, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.58 – 7.51 (m, 2H), 7.51 – 7.46 (m, 2H), 7.42 (dd, J = 7.5, 2.2 Hz, 3H), 7.38 – 7.32 (m, 1H), 7.32 – 7.28 (m, 1H), 7.26 (s, 1H), 6.90 (dd, J = 8.4, 2.8 Hz, 1H), 5.92 (s, 1H). 13C NMR (100MHz, DMSO-d6): δ 164.1, 150.9, 148.0, 139.8, 139.4, 132.5, 131.6, 129.8, 129.7, 129.4, 129.0, 128.4, 128.3, 126.7, 126.5, 126.4, 125.7, 125.4, 120.4, 118.4, 115.8, 115.4, 60.3. HRMS-ESI: Calcd. for C29H16N4O3S [M+] m/z: 442.1150; Found: 442.1198.

2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl-3,4-dihydroquinazolin-4(1H)-one (5a):
Brown powder; 92% yield; Rf (30% EtOAc-Hexane): 0.44, M.P: 182-186 °C. FTIR (KBr) νmax: 3363, 3229, 2983, 1737, 1664, 1486, 1373, 1240, 1043, 760, 607 cm⁻¹; 1H NMR (400MHz, DMSO-d6): δ 8.91 (s, 1H), 8.43 (s, 1H), 7.98 (t, J = 4.7 Hz, 3H), 7.83 (d, J = 6.5 Hz, 2H), 7.69 – 7.63 (m, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.58 – 7.51 (m, 2H), 7.51 – 7.46 (m, 2H), 7.42 (dd, J = 7.5, 2.2 Hz, 3H), 7.38 – 7.32 (m, 1H), 7.32 – 7.28 (m, 1H), 7.26 (s, 1H), 6.90 (dd, J = 8.4, 2.8 Hz, 1H), 5.92 (s, 1H). 13C NMR (100MHz, DMSO-d6): δ 164.1, 150.9, 148.0, 139.8, 139.4, 132.5, 131.6, 129.8, 129.7, 129.4, 129.0, 128.4, 128.3, 126.7, 126.4, 125.7, 125.4, 120.4, 118.4, 115.8, 115.4, 60.3. HRMS-ESI: Calcd. for C29H16N4O3 [M+] m/z: 442.1794; Found: 442.1798.

Scheme 1. Plausible mechanism for the formation of cyclized thiadiazine and quinazolinone

Scheme 2. Gram scale synthesis of 3a to biphenyl derivatives 5a-h.
The plausible mechanism for the formation of Suzuki coupled products (5a-j) is provided in Scheme 4.

Scheme 4. Plausible pathway for oxidative Suzuki coupling.

Table 1. Optimization of synthesis of compound 3a.\(^{a,b}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (W/W%)</th>
<th>MW Power (watt)</th>
<th>Irradiation time (min)</th>
<th>Yield % 3a(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MK10(20)</td>
<td>50W</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>MK10(50)</td>
<td>50W</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>MK10(50)</td>
<td>100W</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>MK10(50)</td>
<td>100W</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>MK10(100)</td>
<td>100W</td>
<td>9</td>
<td>90(^{d})</td>
</tr>
<tr>
<td>6</td>
<td>MK10(50)</td>
<td>100W</td>
<td>9</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>MK10(200)</td>
<td>100W</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>MK10(100)</td>
<td>200W</td>
<td>9</td>
<td>90</td>
</tr>
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<td>9</td>
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<td>300W</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>MK10(20)</td>
<td>100W</td>
<td>9</td>
<td>70</td>
</tr>
</tbody>
</table>

*All the reactions was carried out on a CEM Discover 300 microwave synthesizer under neat condition; \(^{b}\)Standard mode: 1a (1.0mmol), 2a (1.0mmol), 50 psi, at 100°C; \(^{c}\)Isolated yield; \(^{d}\)Optimized condition.

Table 2. Scope of the reaction\(^{a,b}\)

Pyrazole aldehyde + Amino amides \(\xrightarrow{\text{100% w/w MK10 μW (100W) 9 min}}\) Products
Products

Table 3
Optimization of synthesis of 5a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield % 5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>Et3N</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>NaH</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>1,4-Dioxane</td>
<td>NaH</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>1,4-Dioxane + MeOH</td>
<td>NaH</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1,4-Dioxane + MeOH</td>
<td>K2CO3</td>
<td>4</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>1,4-Dioxane + MeOH</td>
<td>Et3N</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>1,4-Dioxane + MeOH</td>
<td>Et3N</td>
<td>24</td>
<td>60</td>
</tr>
</tbody>
</table>

*a* All the reactions were carried out on a CEM Discover 300 microwave synthesizer under neat condition; *b* Standard mode, 100W, 50 psi, 100°C for 9min.

Table 4
Scope of the reaction

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2 equiv. of base was used in all the reaction, change of the equivalents did not change the observed product formation and yield.

Isolated yield.

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All the reaction carried out by Suzuki coupling reaction. Quinazolinone (1 equiv.), phenyl boronic acid (1.5 equiv.), palladium catalyst (10 mol%), K₂CO₃ base (2 equiv.) and mixture of solvent 1,4 dioxane + methanol (3:1) (10 ml) for 4 hrs at 70°C.

**Figure 1.** Biologically active Quinazolinones

In conclusion, we have demonstrated MK-10clay has been found as a green catalyst for the synthesis of cyclized thiadiazine and quinazolinones under microwave irradiation and solvent free condition. The catalyst utility was tested by react with a variety of pyrazole aldehyde with O-aminoamides. Plausible mechanism for the formation of products is provided. Synthetic utility of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-iodo-2,3 dihydroquinazolin-4(1H)-one 3f has been demonstrated by synthesis of highly active biphenyl heterocyclic 2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl-2,3-dihydroquinazolin-4(1H)-one 5a under standard reaction protocols.
Experimental details, 1H, 13C NMR and HRMS spectra have been provide in supporting information.

V. ACKNOWLEDGEMENT

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