One-Pot Three Component Domino Reaction for the Synthesis of Novel Isoxazolo[2,3-c][1,3,5]Thiadiazepin-2-Ones Catalyzed by PTSA—A Green Chemistry Approach

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Abstract

The synthesis of novel isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones has been achieved in excellent yields by one-pot three-component Domino reaction without the production of toxic waste products by using p-toluene sulfonic acid (PTSA) as a Lewis acid catalyst. PTSA plays a crucial role in the success of the reaction, as well as for increasing reaction rate.

Keywords

Multi-Component Green Synthesis, Isoxazolo[2,3-c][1,3,5]Thiadiazepin-2-Ones, PTSA

1. Introduction

Multi-component reaction (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation [1] [2] and are important owing to their synthetic efficiency [3] [4]. In times, where a premium is put on speed, diversity and efficacy in the drug discovery process [5], MCR strategies offer significant advantages over conventional linear type syntheses. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. MCRs

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offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations, and allow savings of both solvents and reagents. As a result, it requires minimum effort, which minimizes the environmental loading and is acceptable from a “Green Chemistry Point of View”.

In recent years, the discovery of novel MCRs, has been increasingly active area of research yielding novel chemical scaffolds for drug discovery. Thus, the development of new multi-component reaction is a popular area of research in current organic chemistry [6]. In the past decade, there have been tremendous development in three and four component reactions and great efforts continue to be made to develop new multi-component reactions [7]-[11].

The use of solid acid catalyst has gained importance in organic synthesis because of their several advantages such as operational simplicity, non-toxicity, reusability, low cost, and easy isolation after completion of the reaction. Careful literature analyses revealed that PTSA acts as a mild, useful, non-toxic and inexpensive Lewis acid catalyst which makes the multi-component synthesis convenient, more economic and environmentally benign. The mild reaction condition, operational simplicity, and the excellent yields make the PTSA more versatile. In recent years, the use of PTSA as a catalyst has received considerable attention in organic transformations [12]-[15]. Especially it makes the reaction rapid, facile and efficient and is devoid of unnecessary derivatization and generation of hazardous substances.

The synthesis of compounds belonging to seven membered ring heterocyclic thiadiazepine series constitutes an important research area due to their impressive array of diverse biological activities such as antimicrobial, analgesic, anticoagulant, and antidepressant properties [16]-[19]. Besides this, biological activities of isoxazoles have made them a focus of medicinal chemistry over the years [20]-[22].

Based on the versatile bioactivities of thiadiazepines and isoxazoles, it is promising that the investigation of isoxazole scaffold with thiadiazepine segment might result in the discovery of new drug candidates with unknown or enhanced bioactivities. However, the design of thiadiazepine implanted with isoxazole frame work for medicinal properties has been less recognized, and no report is available on the synthesis of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones. Therefore, the development of facile approach to access these novel targets with structural diversity is highly desirable and valuable for medicinal chemistry and drug discovery. In view of this, and as a sequel to our work on multi-component isoxazole based drug syntheses [23]-[30], we herein, report one-pot three-component Domino reaction for the synthesis of novel thiadiazepines embedded with isoxazole motif via multi-component reaction catalyzed by environmentally friendly PTSA.

2. Results and Discussion

The three-component Domino reaction of 3-amino-5-methylisoxazole 1, mercapto acetic acid 2, and various substituted aromatic aldehydes 3 in acetonitrile in presence of PTSA was carried out under refluxing for 8 h to afford the corresponding novel new 8-methyl-5-aryl-3,5-dihydro-2H-isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones 4 in excellent yields (Scheme 1).

![Scheme 1. Multi-component synthesis of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones catalyzed by PTSA.](image-url)
To establish feasibility of the strategy and optimize reaction conditions, different solvents in presence of PTSA as inexpensive and readily available catalyst and various other Lewis acid catalysts including InCl₃, L-Proline, I₂, CAN, FeCl₃, ZnCl₂ and silica gel were screened. The best overall yield (90%) was obtained with PTSA (10 mol %), whereas without PTSA the product is not formed (Table 1).

The reaction was also explored by utilizing different solvents such as DMF, EtOH, CH₃CN, MeOH, 1,4-dioxane, DCM, EtOAc, H₂O, THF, DMSO and Toluene. Among the different solvents tested in this reaction, CH₃CN is found to be more effective in terms of excellent yield and less reaction time (Table 2).

The scope and generality of this one-pot three-component synthesis of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones 4 through Domino reaction is illustrated by conducting the reaction with substituted aromatic aldehydes

<table>
<thead>
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<th>Entry</th>
<th>Catalyst</th>
<th>Yield* (%)</th>
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</tr>
<tr>
<td>2</td>
<td>InCl₃</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>L-proline</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>PTSA</td>
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<tr>
<td>5</td>
<td>I₂</td>
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<td>6</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>ZnCl₂</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>Silica gel</td>
<td>10</td>
</tr>
</tbody>
</table>

*Isolated and optimized yields.

<table>
<thead>
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<th>Entry</th>
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<th>Catalyst loading (%)</th>
<th>Yield* (%)</th>
</tr>
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</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
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</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>10</td>
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<td>4</td>
<td>CH₃CN</td>
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<tr>
<td>5</td>
<td>EtOH</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1,4-dioxane</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>DCM</td>
<td>10</td>
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<tr>
<td>8</td>
<td>EtOAc</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>H₂O</td>
<td>10</td>
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<tr>
<td>10</td>
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<td>10</td>
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</tr>
<tr>
<td>11</td>
<td>DMSO</td>
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</tr>
<tr>
<td>12</td>
<td>Toluene</td>
<td>10</td>
<td>-</td>
</tr>
</tbody>
</table>

*Isolated and optimized yields.
(Ar = 2-CH$_3$C$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, 2-OCH$_3$C$_6$H$_4$, 4-OCH$_3$C$_6$H$_4$, 2-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$ and 3,4-OCH$_2$OC$_6$H$_3$). In each case, the corresponding product 4 was isolated in excellent yield. The results indicated that this method has ability to tolerate a variety of functional groups such as methyl, methoxy (electron releasing), and halo, nitro (electron withdrawing) etc. on aromatic ring under the reaction conditions.

The plausible mechanism for the formation of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones 4, may initially involves the reaction of isoxazole amine 1 with mercapto acetic acid 2 being activated by PTSA to give the amide derivative 5. The mercapto group of 5, then attacks the carbonyl group of aromatic aldehyde, which is being activated by PTSA to give the addition product 6. The isoxazole ring nitrogen, influenced by NH group, makes a nucleophilic attack on aldehyde carbon, which subsequently undergoes dehydration to afford the title compound 4, once again by catalytic (PTSA) effect (Scheme 2).

The results demonstrate that PTSA is an efficient catalyst and plays a crucial role in the success of this reaction, as well as for increasing the reaction rate and to produce excellent yield, in CH$_3$CN solvent, because the reaction did not proceed at all in the absence of PTSA catalyst.

To the best of knowledge, this happens to be the first report on the synthesis of novel isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones. The structure of the products 4a-j have been established on the basis of spectral (IR, $^1$H NMR, $^{13}$C NMR and MS) and analytical data. Isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones 4 exhibited characteristic absorption bands at 1680 and 1620 cm$^{-1}$ due to C=O and C=N functional group stretching vibrations respectively. $^1$H NMR spectra of 4 displayed to prominent singlets at $\delta$ 4.27 and 5.50 due to CH$_2$ and NCHAr proton respectively confirming the cyclization. $^{13}$C NMR spectra of 4 is consistent with the proposed structure by displaying the absorption peaks at 39.57, 66.05, 160.32 and 193.47 due to CH$_2$, NCHAr, C=N and C=O carbons respectively. Mass spectrum of 4a fully agrees with the cyclised structure which showed the molecular ion [M+H]$^+$ peak at $m/z$ 261. Elemental analyses are in full agreement with the proposed structures by confirming elemental composition and purity of the newly synthesized compounds.

3. Conclusions

In conclusion, we demonstrated a mild and efficient PTSA catalyzed synthesis of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones using one-pot three-component Domino reaction. The results indicate that PTSA is an efficient, eco-friendly and cost-effective catalyst for this reaction. The obvious advantages of the method are 1) operational simplicity, 2) high atom economy, 3) excellent yields, and 4) products are isolated in pure form by recrystallization without intervention of chromatography. The newly synthesized isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones might exhibit interesting pharmacology activities and may act as potential drug candidates.

The authors are thankful to Head, Department of chemistry, Kakatiya University, Warangal for providing the facilities, the Director, CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad for recording spectral data.

![Scheme 2. Plausible mechanism for the formation of isoxazolo[2,3-c][1,3,5]thiadiazepin-2-ones 4.](image-url)
4. Experimental Part

All the melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F 254 silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. "H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. "C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as internal standard. Mass Spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analysers.

4.1. One-Pot Three-Component Domino Reaction for the Synthesis of 8-Methyl-5-Aryl-3,5-Dihydro-2H-Isoxazolo[2,3-c][1,3,5]Thiadiazepin-2-Ones 4 Catalyzed by PTSA; Typical Procedure

To a stirred solution of 3-amino-5-methylisoxazole (1 mmol) in CH₃CN (15 mL), was added mercapto acetic acid (2 mmol), and PTSA (10 mol%). The reaction mixture was refluxed with stirring at 50°C for 2 h, and freshly distilled benzaldehyde (3 mmol) was added later to the reaction mixture, and the reaction continued for another 8 h at 50°C. After completion of the reaction (monitored by TLC), the reaction mixture was poured on to crushed ice, and the resulted precipitate was filtered and washed with cold alcohol and recrystallized from ethyl acetate to afford the pure product 4a. This procedure was followed for all other reactions.

4.2. Spectral Data of Compounds (4a-h)


Brown solid; mp 138°C - 140°C. IR (KBr): 1680 (C=O), 1620 (C=N) cm⁻¹. "H NMR (300 MHz, CDCl₃): δ = 2.25 (s, 3H, CH₃), 4.27 (s, 2H, CH₂), 5.20 (s, 1H, NCHAr), 6.21 (s, 1H, isoxazole-H), 6.95 - 7.50 (m, 5H, ArH). 13C NMR (75 MHz, CDCl₃): δ = 121.11, 39.57, 66.05, 81.36, 128.75, 129.55, 129.87, 130.05, 131.25, 136.66, 160.32, 167.58, 193.47. MS (ESI): m/z = 261 [M+H]^+. Anal. Calcd. for C₁₃H₁₂N₂O₂S: C, 61.31; H, 4.61; N, 9.76. Found. C, 60.05; H, 4.60; N, 10.77%.


Brown solid; mp 147°C - 150°C. IR (KBr): 1677 (C=O), 1615 (C=N) cm⁻¹. "H NMR (300 MHz, CDCl₃): δ = 2.21 (s, 3H, isoxazole-CH₃), 2.40 (s, 3H, Ar-CH₃), 4.25 (s, 2H, CH₂), 5.45 (s, 1H, NCHAr), 6.32 (s, 1H, isoxazole-H), 6.85 - 7.44 (m, 4H, ArH). 13C NMR (75 MHz, CDCl₃): δ = 120.00, 23.50, 40.02, 65.88, 83.35, 127.75, 128.90, 131.05, 132.33, 139.56, 140.02, 160.35, 165.49, 190.75. MS (ESI): m/z = 275 [M+H]^+. Anal. Calcd. for C₁₄H₁₄N₂O₂S: C, 61.31; H, 5.10; N, 10.21. Found. C, 61.35; H, 5.07; N, 10.22%.


Brown solid; mp 155°C - 157°C. IR (KBr): 1665 (C=O), 1625 (C=N) cm⁻¹. "H NMR (300 MHz, CDCl₃): δ = 2.25 (s, 3H, isoxazole-CH₃), 2.38 (s, 3H, Ar-CH₃), 4.30 (s, 2H, CH₂), 5.55 (s, 1H, NCHAr), 6.25 (s, 1H, isoxazole-H), 6.90 (d, 2H, ArH), 7.15 (d, 2H, ArH). "C NMR (75 MHz, CDCl₃): δ = 12.55, 25.60, 39.75, 67.05, 83.88, 128.05, 129.00, 131.35, 132.85, 140.05, 141.02, 160.55, 165.66, 191.04. MS (ESI): m/z = 275 [M+H]^+. Anal. Calcd. for C₁₄H₁₄N₂O₂S: C, 61.31; H, 5.10; N, 10.21. Found. C, 61.33; H, 5.14; N, 10.24%.


Brown solid; mp 150°C - 152°C. IR (KBr): 1660 (C=O), 1620 (C=N) cm⁻¹. "H NMR (300 MHz, CDCl₃): δ = 2.20 (s, 3H, isoxazole-CH₃), 3.75 (s, 3H, OCH₃), 4.26 (s, 2H, CH₂), 5.33 (s, 1H, NCHAr), 6.15 (s, 1H, isoxazole-H), 6.90 - 7.45 (m, 4H, ArH). "C NMR (75 MHz, CDCl₃): δ = 12.01, 40.33, 55.65, 67.32, 82.75, 128.80, 129.66, 130.55, 132.33, 135.50, 140.05, 167.32, 168.06, 195.50. MS (ESI): m/z = 291 [M+H]^+. Anal. Calcd. for C₁₄H₁₄N₂O₃S: C, 57.93; H, 4.82; N, 9.65. Found. C, 57.96; H, 4.85; N, 9.68%.


Brown solid; mp 159°C - 161°C. IR (KBr): 1670 (C=O), 1622 (C=N) cm⁻¹. "H NMR (300 MHz, CDCl₃): δ = 2.26 (s, 3H, CH₃), 3.80 (s, 3H, OCH₃), 4.40 (s, 2H, CH₂), 5.56 (s, 1H, NCHAr), 6.20 (s, 1H, isoxazole-H), 6.90 (d, 2H, ArH), 7.20 (d, 2H, ArH). "C NMR (75 MHz, CDCl₃): δ = 12.35, 40.55, 54.60, 66.95, 82.88, 128.95, 130.05, 130.65, 132.35, 136.00, 139.95, 163.32, 168.05, 194.55. MS (ESI): m/z = 291 [M+H]^+. Anal. Calcd. for C₁₄H₁₁ClN₂O₃S: C, 57.90; H, 4.80; N, 9.64%.

Orange solid; mp 171°C - 173°C. IR (KBr): 1680 (C=O), 1625 (C=N) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.20, 3H, (s, 3H, CH₃), 4.25, 2H, (s, 2H, CH₂), 5.52, 1H, (s, 1H, NCHAr), 6.23, 2H, (s, 1H, isoazole-H), 6.86 - 7.22, 2H, (m, 4H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ = 12.15, 40.55, 63.55, 82.06, 127.90, 129.56, 131.33, 138.05, 140.05, 145.55, 167.82, 169.07, 196.20. MS (ESI): m/z = 295 [M+H]⁺. Anal. Calcd. for C₁₃H₁₉N₂O₂Cl: C, 53.06; H, 3.72; N, 9.52. Found. C, 53.04; H, 3.72; N, 9.55%

8-Methyl-5-(2,4-dichlorophenyl)-3,5-dihydro-2H-isoxazolo[2,3-c][1,3,5]thiadiazepin-2-one (4g).
Orange solid; mp 192°C - 194°C. IR (KBr): 1675 (C=O), 1635 (C=N) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.25, 3H, (s, 3H, CH₃), 4.36, 2H, (s, 2H, CH₂), 5.50, 1H, (s, 1H, NCHAr), 6.15, 2H, (m, 1H, isoazole-H), 7.00 - 7.50, 3H, (m, 3H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ = 12.34, 41.05, 64.50, 83.05, 128.55, 129.76, 132.05, 139.05, 141.05, 146.65, 167.50, 168.55, 195.62. MS (ESI): m/z = 329 [M+H]⁺. Anal. Calcd. for C₁₃H₁₀N₂O₂Cl: C, 56.36; H, 3.04; N, 8.53. Found. C, 54.75; H, 3.08; N, 8.55%

8-Methyl-5-(4-chlorophenyl)-3,5-dihydro-2H-isoxazolo[2,3-c][1,3,5]thiadiazepin-2-one (4h).
Orange solid; mp 183°C - 185°C. IR (KBr): 1675 (C=O), 1630 (C=N) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.25, 3H, (s, 3H, CH₃), 4.33, 2H, (s, 2H, CH₂), 5.50, 1H, (s, 1H, NCHAr), 6.22, 2H, (m, 1H, isoazole-H), 7.00, 1H, (d, 2H, ArH), 7.35, 2H, (m, 2H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ = 12.45, 40.80, 63.95, 82.22, 127.75, 129.00, 131.52, 136.60, 138.75, 143.65, 154.50, 156.90, 194.05. MS (ESI): m/z = 295 [M+H]⁺. Anal. Calcd. for C₁₃H₁₈N₂O₂S: C, 55.26; H, 3.94; N, 9.21. Found. C, 55.23; H, 3.92; N, 9.20%.

References


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