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# 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].

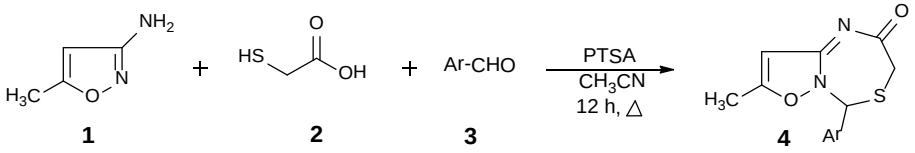
The use of solid acid catalyst has gained importance in organic synthesis because of their several advantages such as operational simplicity, non-toxicity, reusability, low cost, and easy isolation after completion of the reaction. Careful literature analyses revealed that *PTSA* acts as a mild, useful, 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-arlyl-3,5-dihydro-2*H*-isoxazolo[2,3-*c*][1,3,5]thiadiazepin-2-ones **4** in excellent yields (**Scheme 1**).




**1** **2** **3** **4**

| **4** Ar | |
|---|---|
| a, $C_6H_5$ | f, 2-$ClC_6H_4$ |
| b, 2-$CH_3C_6H_4$ | g, 2,4-$Cl_2C_6H_3$ |
| c, 4-$CH_3C_6H_4$ | h, 4-$ClC_6H_4$ |
| d, 2-$OCH_3C_6H_4$ | i, 4-$NO_2C_6H_4$ |
| e, 4-$OCH_3C_6H_4$ | j, 3,4-$OCH_2OC_6H_3$ |

**Scheme 1.** Multi-component synthesis of isoxazolo[2,3-*c*][1,3,5]thiadiazepin-2-ones catalyzed by *PTSA*.

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 $InCl_3$, *L*-Proline, $I_2$, CAN, $FeCl_3$, $ZnCl_2$ 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, $CH_3CN$, MeOH, 1,4-dioxane, DCM, EtOAc, $H_2O$, THF, DMSO and Toluene. Among the different solvents tested in this reaction, $CH_3CN$ 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 1.** Effect of different catalysts on the synthesis of novel new isoxazolo [2,3-*c*][1,3,5]thiadiazepin-2-ones 4.

| Entry | Catalyst | Yield* (%) |
|---|---|---|
| 1 | None | - |
| 2 | $InCl_3$ | 20 |
| 3 | *L*-proline | 32 |
| 4 | PTSA | 90 |
| 5 | $I_2$ | 18 |
| 6 | CAN | 62 |
| 7 | $FeCl_3$ | 36 |
| 8 | $ZnCl_2$ | 15 |
| 9 | Silica gel | 10 |

*Isolated and optimized yields.

**Table 2.** Effect of the amount of catalyst and the solvent for the synthesis of novel new isoxazolo[2,3-*c*][1,3,5]thiadiazepin-2-ones 4.

| Entry | Solvent | Catalyst loading (%) | Yield* (%) |
|---|---|---|---|
| 1 | DMF | 10 | 42 |
| 2 | $CH_3CN$ | 5 | 72 |
| 3 | $CH_3CN$ | 10 | 90 |
| 4 | $CH_3CN$ | 15 | 90 |
| 5 | EtOH | 10 | 50 |
| 6 | 1,4-dioxane | 10 | 45 |
| 7 | DCM | 10 | - |
| 8 | EtOAc | 10 | 25 |
| 9 | $H_2O$ | 10 | - |
| 10 | THF | 10 | - |
| 11 | DMSO | 10 | 30 |
| 12 | Toluene | 10 | - |

*Isolated and optimized yields.

(Ar = 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 2-$ClC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-$ClC_6H_4$, 4-$NO_2C_6H_4$ and 3,4-$OCH_2OC_6H_3$). 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 isxoazole 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 $CH_3CN$ 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.

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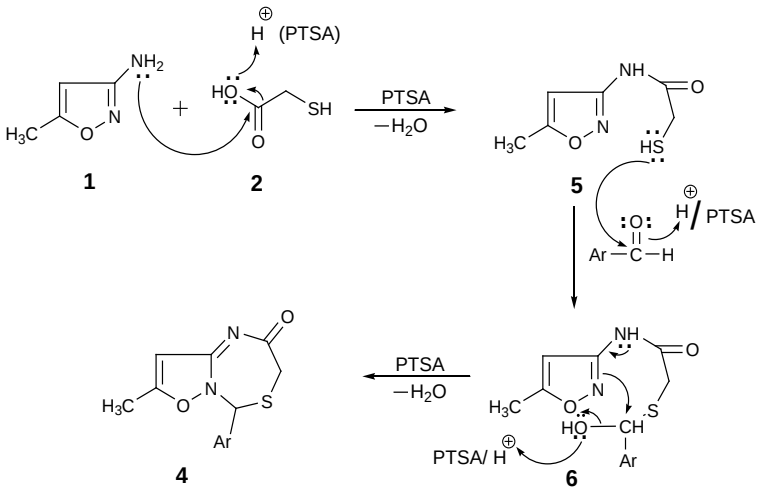


**Scheme 2.** Plausible mechanism for the formation of isoxazolo[2,3-*c*][1,3,5] thiadiazepin-2-ones 4.

## 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. $^1$H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. $^{13}$C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm ($\delta$) 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-2*H*-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** (1 mmol) in $CH_3CN$ (15 mL), was added mercapto acetic acid **2** (1 mmol), and *PTSA* (10 mol%). The reaction mixture was refluxed with stirring at 50˚C for 4 h, and freshly distilled benzaldehyde **3** (1 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)

8-*Methyl*-5-*phenyl*-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4a**).

Brown solid; mp 138˚C - 140˚C. IR (KBr): 1680 (C=O), 1620 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.25 (s, 3H, $CH_3$), 4.27 (s, 2H, $CH_2$), 5.20 (s, 1H, NCHAr), 6.21 (s, 1H, isoxazole-H), 6.95 - 7.50 (m, 5H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 12.11, 39.57, 66.05, 81.36, 128.75, 129.55, 129.87, 130.05, 131.25, 138.66, 160.32, 167.58, 193.47. MS (ESI): *m*/*z* = 261 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 60.00; H, 4.61; N, 10.76. Found. C, 60.05; H, 4.60; N, 10.77%.

8-*Methyl*-5-(2-*methylphenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4b**).

Brown solid; mp 147˚C - 149˚C. IR (KBr): 1677 (C=O), 1615 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.21 (s, 3H, isoxazole-$CH_3$), 2.40 (s, 3H, Ar-$CH_3$), 4.25 (s, 2H, $CH_2$), 5.45 (s, 1H, NCHAr), 6.32 (s, 1H, isoxazole-H), 6.85 - 7.44 (m, 4H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 12.00, 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 $C_{14}H_{14}N_2O_2S$: C, 61.31; H, 5.10; N, 10.21. Found. C, 61.35; H, 5.07; N, 10.22%.

8-*Methyl*-5-(2-*methylphenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4c**).

Brown solid; mp 155˚C - 157˚C. IR (KBr): 1675 (C=O), 1625 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.25 (s, 3H, isoxazole-$CH_3$), 2.38 (s, 3H, Ar-$CH_3$), 4.30 (s, 2H, $CH_2$), 5.55 (s, 1H, NCHAr), 6.25 (s, 1H, isoxazole-H), 6.90 (d, 2H, ArH), 7.15 (d, 2H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 12.55, 25.60, 39.75, 67.05, 83.38, 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 $C_{14}H_{14}N_2O_2S$: C, 61.31; H, 5.10; N, 10.21. Found. C, 61.33; H, 5.14; N, 10.24%.

8-*Methyl*-5-(2-*methoxyphenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4d**).

Brown solid; mp 150˚C - 152˚C. IR (KBr): 1680 (C=O), 1620 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.20 (s, 3H, isoxazole-$CH_3$), 3.75 (s, 3H, $OCH_3$), 4.26 (s, 2H, $CH_2$), 5.33 (s, 1H, NCHAr), 6.15 (s, 1H, isoxazole-H), 6.90 - 7.45 (m, 4H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 12.01, 40.33, 55.65, 67.32, 82.75, 128.80, 129.66, 130.05, 132.33, 135.50, 140.05, 167.32, 168.06, 195.50. MS (ESI): *m*/*z* = 291 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.82; N, 9.65. Found. C, 57.96; H, 4.85; N, 9.68%.

8-*Methyl*-5-(4-*methoxyphenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4e**).

Brown solid; mp 159˚C - 161˚C. IR (KBr): 1670 (C=O), 1622 (C=N) cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.26 (s, 3H, $CH_3$), 3.80 (s, 3H, $OCH_3$), 4.40 (s, 2H, $CH_2$), 5.56 (s, 1H, NCHAr), 6.20 (s, 1H, isoxazole-H), 6.90 (d, 2H, ArH), 7.20 (d, 2H, ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 12.35, 40.55, 54.60, 66.95, 82.88, 128.95, 130.05, 130.65, 132.35, 136.00, 139.95, 165.32, 168.05, 194.55. MS (ESI): *m*/*z* = 291 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.82; N, 9.65. Found. C, 57.90; H, 4.80; N, 9.64%.

8-*Methyl*-5-(2-*chlorophenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4f**).

Orange solid; mp 171˚C - 173˚C. IR (KBr): 1680 (C=O), 1625 (C=N) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.20 (s, 3H, $CH_3$), 4.25 (s, 2H, $CH_2$), 5.52 (s, 1H, NCHAr), 6.23 (s, 1H, isoxazole-H), 6.86 - 7.22 (m, 4H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 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 $C_{13}H_{11}N_2O_2SCl$: C, 53.06; H, 3.74; N, 9.52. Found. C, 53.04; H, 3.72; N, 9.55%.

8-*Methyl*-5-(2,4-*dichlorophenyl*)-3,5-*dihydro*-2*H*-*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, $CDCl_3$): $\delta$ = 2.25 (s, 3H, $CH_3$), 4.36 (s, 2H, $CH_2$), 5.50 (s, 1H, NCHAr), 6.15 (s, 1H, isoxazole-H), 7.00 - 7.50 (m, 3H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 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 $C_{13}H_{10}N_2O_2SCl_2$: C, 47.56; H, 3.04; N, 8.53. Found. C, 47.55; H, 3.08; N, 8.55%.

8-*Methyl*-5-(4-*chlorophenyl*)-3,5-*dihydro*-2*H*-*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, $CDCl_3$): $\delta$ = 2.25 (s, 3H, $CH_3$), 4.33 (s, 2H, $CH_2$), 5.50 (s, 1H, NCHAr), 6.22 (s, 1H, isoxazole-H), 7.00 (d, 2H, ArH), 7.35 (d, 2H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 12.45, 40.80, 63.95, 82.22, 127.75, 129.00, 131.52, 136.60, 138.75, 143.65, 165.50, 169.00, 194.05. MS (ESI): *m*/*z* = 295 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{11}N_2O_2SCl$: C, 53.06; H, 3.74; N, 9.52. Found. C, 53.10; H, 3.77; N, 9.51%.

8-*Methyl*-5-(4-*nitrophenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4i**).

Orange solid; mp 202˚C - 204˚C. IR (KBr): 1680 (C=O), 1622 (C=N) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.23 (s, 3H, $CH_3$), 4.28 (s, 2H, $CH_2$), 5.51 (s, 1H, NCHAr), 6.25 (s, 1H, isoxazole-H), 7.02 (d, 2H, ArH), 7.55 (d, 2H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 12.22, 39.85, 63.55, 82.25, 128.00, 129.52, 130.99, 135.05, 139.62, 144.65, 165.52, 168.08, 195.00. MS (ESI): *m*/*z* = 306 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.60; N, 13.77. Found. C, 51.18; H, 3.62; N, 13.79%.

8-*Methyl*-5-(3,4-*methylenedioxyphenyl*)-3,5-*dihydro*-2*H*-*isoxazolo*[2,3-*c*][1,3,5]*thiadiazepin*-2-*one* (**4j**).

Brown solid; mp 164˚C - 166˚C. IR (KBr): 1675 (C=O), 1640 (C=N) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.25 (s, 3H, $CH_3$), 3.90 (s, 2H, $OCH_2O$), 4.30 (s, 2H, $CH_2$), 5.50 (s, 1H, NCHAr), 6.15 (s, 1H, isoxazole-H), 7.00 - 7.45 (m, 3H, ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 12.25, 40.05, 66.95, 72.05, 83.05, 128.27, 130.33, 131.65, 132.85, 139.88, 141.07, 163.35, 165.05, 193.58. MS (ESI): *m*/*z* = 305 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{12}N_2O_4S$: C, 55.26; H, 3.94; N, 9.21. Found. C, 55.23; H, 3.92; N, 9.20%.

## References


[1] Kappe, C.O. (2000) Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Accounts of Chemical Research*, **33**, 879-888. http://dx.doi.org/10.1021/ar000048h

[2] Zhu, J. and Bienayne, H. (2005) Multi-Component Reactions. Wiley-VCH-Wenkein, Germany. http://dx.doi.org/10.1002/3527605118

[3] Ramon, D.J. and Yus, M. (2005) Asymmetric Multi-Component Reactions (AMCRs): The New Frontier. *Angewandte Chemie International Edition*, **44**, 1602-1634. http://dx.doi.org/10.1002/anie.200460548

[4] Volla, C.M.R., Atodiresei, I. and Rueping, M. (2014) Catalytic C-C Bond Forming Multi-Component Cascade or Domino Reaction: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis. *Chemical Reviews*, **114**, 2390-2431. http://dx.doi.org/10.1021/cr400215u

[5] Stevens, M., Pannecouque, C. and De Clercq, E. (2003) Inhibition of Human Immunodeficiency Virus by a New Class of Pyridine Oxide Derivatives. *Antimicrobial Agents and Chemotherapy*, **47**, 2951-2957. http://dx.doi.org/10.1128/AAC.47.9.2951-2957.2003

[6] Menendez, J.C. (2006) Multicomponent Reactions. *Synthesis*, **15**, 2624. http://dx.doi.org/10.1055/s-2006-949153

[7] Bertozzi, F., Gustafsson, M. and Olsson, R. (2002) A Novel Metal Iodide Promoted Three-Component Synthesis of Substituted Pyrrolidines. *Organic Letters*, **4**, 3147-3150. http://dx.doi.org/10.1021/ol0264814

[8] Bagley, M.C., Cala, J.W. and Bower, J. (2002) A New One-Pot Three-Component Condensation Reaction for the Synthesis of 2,3,4,6-Tetrasubstituted Pyridines. *Chemical Communications*, **6**, 1682-1683. http://dx.doi.org/10.1039/b203900a

[9] Huma, H.Z.S., Halder, R., Kalra, S.S., Das, J. and Iqbal, J. (2002) Cu(I)-Catalyzed Three Component Coupling Protocol for the Synthesis of Quinoline Derivatives. *Tetrahedron Letters*, **43**, 6485-6488. http://dx.doi.org/10.1016/S0040-4039(02)01240-6

[10] Domling, A. and Ugi, I. (2000) Multicomponent Reactions with Isocyanides. *Angewandte Chemie International Edition*, **39**, 3168-3210. http://dx.doi.org/10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U

[11] Yu, L., Chen, B. and Huang, X. (2007) Multicomponent Reactions of Allenes, Diaryl Diselenides, and Nucleophiles in the Presence of Iodosobenzene Diacetate: Direct Synthesis of 3-Functionalized-2-Arylselenyl Substituted Allyl Derivatives. *Tetrahedron Letters*, **48**, 925-927. http://dx.doi.org/10.1016/j.tetlet.2006.12.026

[12] Khosropour, A.R., Khodaei, M.M. and Moghannian, H. (2005) A Facile, Simple and Convenient Method for the Synthesis of 14-Alkyl or Aryl-14-*H*-Dibenzo[*a*,*j*]xanthenes Catalyzed by *p*TSA in Solution and Solvent-Free Conditions. *Synlett*, No. 6, April, 955-958.

[13] Nadaraj, V., Selvi, S.T. and Sasi, R. (2006) Microwave-Assisted Synthesis of Quinoline Alkaloids: 4-Methoxy-1-Methyl-2-Quinolinone and Its Analogs. *Arkivoc*, **2006**, 82-89. http://dx.doi.org/10.3998/ark.5550190.0007.a11

[14] Maluindarante, M.P.D. and Wimalsena, K. (1998) Detailed Characterization of *p*-Toluenesulfonic Acid Monohydrate as a Convenient, Recoverable, Safe, and Selective Catalyst for Alkylation of the Aromatic Nucleus. *The Journal of Organic Chemistry*, **3**, 2858-2866.

[15] Longhi, K., Moreira, D.N., Marzari, M.R.B., Floss, V.M., Bonacorso, H.G., Zanatta, N. and Martins, M.A.P. (2010) An Efficient Solvent-Free Synthesis of *NH*-Pyrazoles from *β*-Dimethylaminovinylketones and Hydrazine on Grinding. *Tetrahedron Letters*, **51**, 3193-3196. http://dx.doi.org/10.1016/j.tetlet.2010.04.038

[16] Kazuo, O. and Yoh-Ichi, M. (1992) Synthesis and Antiarrhythmic Activity of 2, 5-Disubstituted 2,3-Dihydro-1,2,5-Benzothiadiazepin-4(5H)-One-1,1-Dioxides. *Chemical & Pharmaceutical Bulletin*, **40**, 2442-2447. http://dx.doi.org/10.1248/cpb.40.2442

[17] Kidwai, M., Sapra, P., Misra, P., Saxena, R.K. and Singh, M. (2001) Microwave Assisted Solid Support Synthesis of Novel 1,2,4-Triazolo[3,4-*b*]1,3,4-Thiadiazepines as Potent Antimicrobial Agents. *Bioorganic & Medicinal Chemistry*, **9**, 217-220. http://dx.doi.org/10.1016/S0968-0896(00)00245-5

[18] Anusha, D., Rubig, S. and Sarita, K. (2006) Microwave Enhanced Solid Support Synthesis of Fluorine Containing Benzopyrano-Triazolo-Thiadiazepines as Potent Antifungal Agents. *Bioorganic & Medicinal Chemistry*, **14**, 1303-1308. http://dx.doi.org/10.1016/j.bmc.2005.09.057

[19] Geeta, A.S., Vijayaraj, R., Kumar, T.R. and Anand, R.S. (2011) Synthesis of Certain 3-Pyridyl [1,2,4]Triazolo[3,4-*b*][1,3,4] Thiadiazepines and Evaluation of Their Possible Biological Activities. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, **2**, 155-159.

[20] Daidone, G., Raffa, D., Maggio, B., Plescia, F., Cutuli, V.M.C., Mangano, N.G. and Caruso, A. (1999) Synthesis and Pharmacological Activities of Novel 3-(Isoxazol-3-yl)-Quinazolin-4(3*H*)-One Derivatives. *Archiv der Pharmazie*, **332**, 50-54.

[21] Talley, J.J., Brown, D.L., Carter, J.S., Graneto, M.J., Koboldt, C.M., Masferrer, J.L., Perkins, W.E., Rogers, R.S., Shaffer, A.F., Zhang, Y.Y., Zweifel, B.S. and Seibert, K. (2000) 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, Valdecoxib: A Potent and Selective Inhibitor of COX-2. *Journal of Medicinal Chemistry*, **43**, 775-777. http://dx.doi.org/10.1021/jm990577v

[22] Li, W.T., Hwang, D.-R., Chen, C.-P., Shen, C.-W., Huang, C.-L., Chen, T.-W., Lin, C.-H., Chang, Y.-L., Chang, Y.-Y., Lo, Y.-K., Tseng, H.-Y., Lin, C.-C., Song, J.-S., Chen, H.-C., Chen, S.-J., Wu, S.-H. and Chen, C.-T. (2003) Synthesis and Biological Evaluation of *N*-Heterocyclic Indolyl Glyoxylamides as Orally Active Anticancer Agents. *Journal of Medicinal Chemistry*, **46**, 1706-1715. http://dx.doi.org/10.1021/jm020471r

[23] Rajanarendar, E., Govardhan Reddy, K., Shivarami Reddy, A. and Nagi Reddy, M. (2012) Brownsted Ionic Liquid [HMim]$BF_4$ Promoted Simple and Efficient One-Pot Green Synthesis of Isoxazolyl-1,3-Benzoxazines at Ambient Temperature. *Green Chemistry Letters and Reviews*, **5**, 699-705. http://dx.doi.org/10.1080/17518253.2012.700736

[24] Rajanarendar, E., Nagi Reddy, M. and Ram Murthy, K. (2010) Multi-Component Synthesis of Methylene Bis-Isoxazolo[4,5-*b*]Pyridine-*N*-Oxides. *Chinese Chemical Letters*, **21**, 927-930. http://dx.doi.org/10.1016/j.cclet.2010.03.014

[25] Rajanarendar, E., Venkateshwarlu, P. and Ram Krishna, S. (2012) Ceric Ammonium Nitrate Catalyzed One-Pot Synthesis of Novel Isoxazolyl-Hexahydroquinindolinones Cerammoniumnitrat Katalysierten One-Pot Synthese von Neuartigen Isoxazolyl-Hexahydroquinindolinones. *Heterocyclic Letters*, **2**, 283-289.

[26] Rajanarendar, E., Thirupathaiah, K., Ram Krishna, S. and Kishore, B. (2013) Green Chemistry Approach to Fast and Highly Efficient One-Pot Synthesis of Bis-Isoxazolyl-1,2,5,6-Tetrahydropyridine-3-Carboxylates. *Green and Sustainable Chemistry*, **3**, 9-18. http://dx.doi.org/10.4236/gsc.2013.32A002

[27] Rajanarendar, E., Goverdhan Reddy, K. and Ram Krishna, S. (2015) A Facile One-Pot Synthesis of Highly Functionalized Isoxazolyl Imidazo[1,2-*a*]Pyridines through CuI-Promoted Cyclization. *Journal of Heterocyclic Chemistry*, **52**, 660-668. http://dx.doi.org/10.1002/jhet.2146

[28] Rajanarendar, E., Nagi Reddy, M., Govardhan Reddy, K. and Rama Krishna, S. (2012) *L*-Proline Catalyzed Efficient

One-Pot Three-Component, Aza-Diels—Alder Reactions on Nitrostyryl Isoxazoles: A Facile Synthesis of New Isoxazolyl Tetrahydroquinolines and Isoxazolo[2, 3-*a*] Pyrimidines. *Tetrahedron Letters*, **53**, 2909-2913. http://dx.doi.org/10.1016/j.tetlet.2012.04.002

[29] Rajanarendara, E., Nagi Reddy, M. and Raju, S. (2011) An Efficient One-Pot Synthesis of Polyhydroquinolines *via* Hantzsch Condensation Using *L*-Proline as Catalyst. *Indian Journal of Chemistry—Section B*, **50B**, 751-755.

[30] Rajanarendar, E., Nagi Reddy, M. and Shaik, F.P. (2011) An Efficient One Pot Three Component Synthesis of New Isoxazolyl Polyhydroacridine-1,8-Diones in an Ionic Liquid Medium. *Indian Journal of Chemistry—Section B*, **50B**, 245-252.