# Synthesis of Novel 2-Substituted Thiadiazole Derivatives

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**Summary**: Seven mild, efficient and novel inhibitors were obtained in good to excellent yield by addition of Thiadiazole derivatives with an acids/molecular sieve system at moderate temperature (50°C). The structures of the prepared compounds are characterized by IR and [1]HNMR Spectroscopy, and the catalyst can be recovered by filtration and reused several times. The resulted showed that the process was then applied to [1, 3, 4] thiadiazde derivatives using 0.75 g of Catalyst for acids and performing the reactions at 50 ℃ for 1 hour with sulfuric acid as solvent ( 15mL, 70% ). We have shown for the first time that a heterogeneous catalyst, namely commercially available $AlPO_4$–5 and SBA–15 molecular sieve, can be successfully and efficiently utilized for the highly selective synthesis of **3**. Moreover, the use of sulfuric acid as solvent, the high atom economy, and the possibility of recycling the catalyst for several runs, make this approach practical and environmentally acceptable.

Keywords: Inhibitors; Molecular sieve; Heterogeneous catalyst; [1, 3, 4] Thiadiazole; Environmentally.

## Introduction

Thiadiazole compounds constitute one of the most important heterocyclic families [1]. Synthesis of Thiadiazole and their derivatives have attracted considerable attention due to their significant antibacterial [2], Anticancer [3] and anti-tuberculosis [4] activities. It has been observed that compared with heterocyclic molecule only nitrogen and sulfur, molecule including both nitrogen and sulfur atoms has excellent anti-inhibition [5]. Some years ago, the new type of both nitrogen and sulfur thiadiazole compounds were synthesized through addition and amide two-step reaction. The title compounds have excellent anti-corrosion performance, was very suitable for water based metal at a pH of 5-10 aqueous solution [6].

To address the challenges posed by the pollution prevention efforts and waste minimization, several strategies have been worked out. Green synthetic approach [7, 8] holds out is provided a method, which is not only for the reducing of byproducts, the saving energy consumption, the waste "zero emissions", but also in the exploit of a new method to get the new material which is not previously available [9]. Over the past decades, organic chemists using the heterogeneous catalytic systems to synthesized new compounds were becoming the important synthetic processes. Using this method, Organic chemical synthesis process will be reducing of byproducts, the saving energy consumption, the waste "zero emissions". In fact, this is provided an undoubted advantages from both an environment and an economic point of view when the using of heterogeneous catalytic systems, Research confirmed that the E–factor value can up to 50(kg of byproducts/kg of product).

In view of the great advantages of heterogeneous catalysis, their potential to reduce the separation energy costs and the amount of byproducts as a part of our endeavor towards eco-friendly has clean synthesis. Through our unremitting efforts, a provide a simple, efficient and inexpensive one-pot method for the novel thiadiazole derivatives synthesized using 2-substituted [1, 3, 4] thiadiazole, P2O5 and chloroacetic acid as materials by using XH-200A computer microwave solid-liquid phase synthesizer, although the compounds can improve the anti-corrosion efficiency, but it is different to prepared on a large scale [10]. Therefore, the synthesis of thiadiazole derivatives in heterogeneous catalysis was explored.

## Experimental

### *Materials and apparatus*

In this study, Oleic acid, Crotonic acid and acrylic acid as well as 3-Phenyl-2-propenoic acid were purchased either from SHANG HAI BOER CHEMICAL REAGENT CO., LTD or from Tianjin No.3 Chemical Reagent Factory. The molecular sieve was purchased from JEC, while [1, 3, 4] Thiadiazole derivatives was synthesized according to the literature reports. The addition reaction was carried out in a Magnetic stirred tank. [1]HNMR spectra

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($CDCl_3$, 400 MHz) were recorded on a Bruker AVANCE-400MHz with TMS as an internal standard. IR spectra were obtained on a Nicolet 5DX FT-IR spectrophotometer in the region 4000-400 $cm^{-1}$ using KBr discs. Thin layer chromatography ( T L C ) on commercial GF254 silica-backed plates of reactions. Melting was determined by an RK1 microscopic melting apparatus (uncorrected). All products were characterized by spectral and physical data.

*Synthesis of the title compounds* **3a-3g.**

The title compounds 3a–3g were synthesized by the method outlined in Scheme 1. The title compounds 3a,3c–3e and 3g were crystallized from ethanol; 3b and 3f were crystallized from ethyl acetate.

*9-(5-methyl-1,3,4-thiadiazol-2-ylthio) octadecanoic acid* **(3a)**：To a stirred solution of 2-Mercapto-5-methyl–[1, 3, 4] Thiadiazde in Sulfuric acid (15mL 70%) was added molecular sieve ( 0.75 g ). The mixture was stirred at room temperature for 10 min, and the corresponding weight of Oleic acid was added dropwise to the solution and the mixture was heated to 50℃ and allowed to react for 2 h (external water bath) under continuous stirring (20 rpm). The reaction was then stopped by cooling, and water was added to the reaction mixture. The product was extracted with ethanol, and the acid was transferred to the aqueous phase by extraction with 10% NaOH. The pH of the collected NaOH extract was adjusted to pH = 1 by adding aqueous HCl and placed into an ice bath. The precipitate formed was collected by filtration and dried, recrystallized form ethanol. Yield: 74.3 %; mp: 179-181°C. $^1$HNMR ($CDCl_3$, 400MHz): δ: 1.01 (s, 3H, $-CH_3$), 1.24 (s, 30H, 15–$CH_2$–), 1.54(d, *J*=5, 3H, $-CH_3$) 2.27–2.29(m, *J*=8.2, 2H, tert–H)，11.86(s, 1H, –COOH). IR (KBr): 3496, 3049, 2963, 2867, 1707, 1648, 1553$cm^{-1}$.

*2-(5-methyl-1,3,4-thiadiazol-2-ylthio) propanoic acid* **(3b):** Yield: 70.9 %; mp: 124–125℃. $^1$HNMR ($CDCl_3$, 400MHz): δ: 2.26(s,3H, $-CH_3$), 2.88–2.90(d, *J*=8, 3H, $-CH_3$), 3.40–3.41(d, *J*=4, 1H, tert–H), 2, 9.51(s, 1H, –COOH). IR (KBr): 3321, 3098, 2862, 2696, 2417, 1636, 1594, 1490 $cm^{-1}$.

*9-(5-mercapto-1,3,4-thiadiazol-2-ylthio)octa decanoic acid* **(3c):** Yield: 40.1 %; mp: 196–198℃. $^1$HNMR ($CDCl_3$, 400MHz): δ: 1.06 (s, 3H, $-CH_3$), 1.23 (s, 30H, 15–$CH_2$–), 2.26– 2.28(m, *J*=8.2, 2H, tert–H)， 7.26 (d, *J*=5, 1H, –SH), 11.86(s, 1H, –COOH). IR (KBr): 3422, 3032, 2861, 2538, 2491, 1698, 1463, 1465, 1379$cm^{-1}$.

*2-(5-mercapto-1,3,4-thiadiazol-2-ylthio)pro panoic acid* **(3d)**：Yield: 69.8 %; mp: 132–134℃. $^1$HNMR ($CDCl_3$, 400MHz): δ: 2.89–2.91 (d, *J*=8, 3H, $-CH_3$), 3.41–3.42 (d, *J*=4, 1H, tert–H), 7.26 (s,1H, –SH), 9.69 (s, 1H, –COOH). IR (KBr): 3502, 3169, 2861, 2638, 1751, 1598, 1463, 1465 $cm^{-1}$.

*9-(5-amino-1,3,4-thiadiazol-2-ylthio)octade canoic acid* **(3e):** Yield: 65.1 %; mp: 194–195℃. $^1$HNMR ($CDCl_3$, 400MHz): δ: 1.16 (s, 3H, $-CH_3$), 1.26 (s, 30H, 15–$CH_2$–), 2.27– 2.29(m, *J*=8.2, 2H, tert–H)， 4.02–4.04 (m, 2H,– $NH_2$)11.37(s, 1H, –COOH). IR (KBr): 3487, 3140, 2879, 2867, 1707, 1648, 1553 $cm^{-1}$.

*2-(5-methyl-1,3,4-thiadiazol-2-ylthio)butano ic acid* **(3f):** Yield: 70.6 %; mp: 183–184 ℃. $^1$HNMR ($CDCl_3$, 400MHz): δ: 1.11–1.22 (m, *J*=5.2, 3H, $-CH_3$), 1.54 (s, 3H,$-CH_3$), 2.49–2.50 (d, *J*=4, 2H, $-CH_2$–), 3.00–3.03 (d, *J*=12, 1H, tert–H), 10.99(s, 1H, –COOH). IR (KBr): 3386, 3265, 2963, 2867, 1787, 1694, 1543$cm^{-1}$.

*2-(5-methyl-1,3,4-thiadiazol-2-ylthio)-2-phe nylacetic acid* **(3g):** Yield: 63.4 %; mp: 187–188 ℃. $^1$HNMR ($CDCl_3$, 400MHz): δ: 1.49 (s, 3H,$-CH_3$), 2.45–2.46 (d, *J*=4, 2H, $-CH_2$–), 3.01–3.03 (d, *J*=8, 1H, tert–H),7.31–7.33 (m, *J*=8.2, 5H, –Ar) 10.99(s, 1H, –COOH). IR (KBr): 3485, 3149, 2963, 2854, 1797, 1568, 1593$cm^{-1}$.

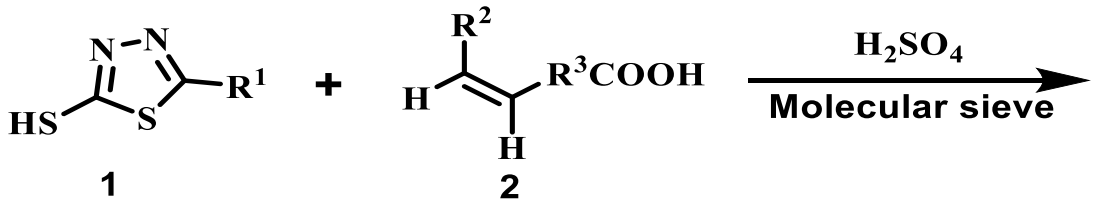
**Results and Discussion**

Heterocyclic compounds **3** were utilized as the stainless steel surface anti-corrosion, generally this compounds were synthesized by reacting with [1, 3, 4] thiadiazde derivatives and unsaturated acid, The process can also afford the **4** (Scheme 1).

The chemical activity of two kinds of molecular sieve, $AlPO_4$–5 molecular sieve and SBA–15 molecular sieve was tested in the specific reactor between 2–mercapto–[1, 3, 4] thiadiazde ( 1.32 g 10mmol ) and unsaturated acid oleic acid at 45 °C for 1 hour. The chemical reaction results are reported in Table-1.

Table-1: Synthesis of 3 Promoted by Heterogeneous Basic Catalysts.

| | Heterogeneous Catalyst | Yield ( % ) | Selectivity ( % ) |
|---|---|---|---|
| 1 | none | 0 | - |
| 2 | $AlPO_4$–5 | 75 | 99 |
| 3 | SBA–15 | 61 | 98 |

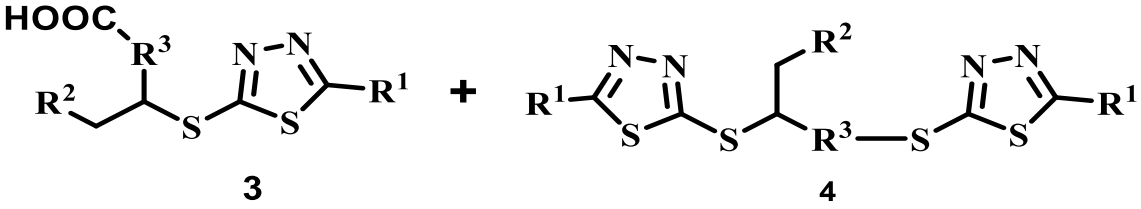



**1a:** $R^1=CH_3$ **2a:** $R^2=CH_3(CH_2)_7$, $R^3=(CH_2)_7$

**1b:** $R^1=SH$ **2b:** $R^2=H$, $R^3=0$

**1c:** $R^1=NH_2$ **2c:** $R^2=CH_3$, $R^3=0$

**2d:** $R^2=C_6H_5$-, $R^3=0$




**3a, 4a:** $R^1=CH_3$, $R^2=CH_3(CH_2)_7$, $R^3=(CH_2)_7$

**3b, 4b:** $R^1=CH_3$, $R^2=H$, $R^3=0$

**3c, 4c:** $R^1=SH$, $R^2=CH_3(CH_2)_7$, $R^3=0$

**3d, 4d:** $R^1=SH$, $R^2=H$, $R^3=0$

**3e, 4e:** $R^1=NH_2$, $R^2=CH_3(CH_2)_7$, $R^3=0$

**3f, 4f:** $R^1=CH_3$, $R^2=CH_3$, $R^3=0$

**3g, 4g:** $R^1=CH_3$, $R^2=C_6H_5$-, $R^3=0$

Scheme-1: The chemical reaction of products between unsaturated acids and [1, 3, 4] thiadiazde derivatives.

As can be seen from Table-1, both of the $AlPO_4$–5 and SBA–15 catalysts were able to enhanced the reaction yield, while affording exclusively compound **3** provided with excellence selectivity, the products of structure were assign based on IR and $^1$H-NMR.

Three parameters of optimal reaction conditions are given with special regard to reaction time, reaction temperature and amount of catalyst.

*The effort of reaction time*

Firstly the model reaction was analyzed by examining the yield of product **3** versus time; the reaction was carried out over Two hours and TLC analysis was performed every 30 min (Fig. 1).

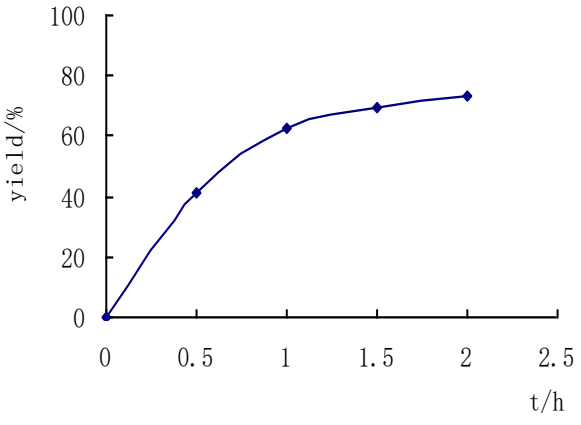



Fig. 1: Reactivity of thiadiazde and oleic acid in the presence of heterogeneous catalyst at 50 °C as a function of time.

It was found that, the yield of **3** continuously increases with the reaction time; after 1 h, however, the increase becomes very slow, and after 2 h the curve turns to saturation. This indicates that the reaction reached its maximum yield, and further extension in reaction time does not result in further enhancement of the yield.

*The effort of reaction temperature*

In a second series of experiments the reaction temperature was examined. After screening many temperature systems, we pursued the addition reaction of oleic acid by the [1, 3, 4] thiadiazde derivatives at temperature systems in detail. As shown, at more elevated temperature (studied up to 100 °C), no **3** could be observed, and **4** was the only isolate products. In the absence of cat, we have not observed the appearance of the product **3**. Compound **3** initially formed clearly are further transformed by its esterification of excess oleic acid to **4**. However, lower temperature results in a gradual increase in yield of **3**. **3** became significant at 75 °C and were formed exclusively at 60 °C. The optimized results are summarized in Table-2. The results show that the reaction could be carried out at moderate temperature in good to excellent yields, without the formation of a significant amount of **4**, which are readily formed at higher temperature.

Table-2: Addition reaction of 2–Mercapto–5–Methyl–[1, 3, 4] thiadiazde with oleic acid in the presence of catalyst

| T ℃ | Product yield % | |
|---|---|---|
| | 3 | 4 |
| 100 | trace | 25 |
| 75 | 15 | 18 |
| 60 | 50 | trace |
| 50 | 75 | trace |

*The effort of amount of catalyst*

Finally, the effect of the amount of catalyst on the reaction yield was also taken into account with the aim of examining the possibility of using the minimum amount of Heterogeneous catalyst. The optimized results are summarized in Table-3.

Table-3: Effect of the amount of catalyst in the Synthesis of 3 at 50 °C.

| Entry | Amount of catalyst | Yield ( % ) of 3 | Selectivity ( % ) for product |
|---|---|---|---|
| 1 | 0.25 | 57 | 97 |
| 2 | 0.50 | 68 | 98 |
| 3 | 0.75 | 73 | 99 |
| 4 | 1.00 | 74 | 99 |

As can be concluded from the results depicted in table3, lowering the amount of Catalyst from 1.00 to 0.75 g gives the same quantitative yield of **3**. However, lowering the amount of catalyst further reduces the yield.

To explore the scope of our method, a variety of Thiadiazole derivatives were investigated to react with Oleic acid catalyzed by Molecular sieve, and the results are summarized in Table-4.

As shown in Table-4, the corresponding compounds **3a, 3b, 3d–3g** were obtained in good yields without the formation of possible byproducts **4**. Only 2, 5–dimercapto-1, 3, 4-thiadiazole (**1 c**) gave **3** in low yield (Table **4**, entry **3**), and the catalyst could be reused several times without any loss of activity.

Table-4: Preparation of 3 from Thiadiazole derivatives with Oleic acid catalyzed by Molecular sieve.

| Entry | $R^1$ | $R^2$ | $R^3$ | Yield ( % ) | Ratio3:4 |
|---|---|---|---|---|---|
| 1 | $CH_3$ | $CH_3(CH_2)_7$ | $(CH_2)_7CO$ | 74.3 | 100:0 |
| 2 | $CH_3$ | H | CO | 72.9 | 100:0 |
| 3 | SH | $CH_3(CH_2)_7$ | $(CH_2)_7$ CO | 40.1 | 62:38 |
| 4 | SH | H | CO | 69.8 | 100:0 |
| 5 | $NH_2$ | $CH_3(CH_2)_7$ | $(CH_2)_7CO$ | 65.1 | 100:0 |
| 6 | $CH_3$ | $CH_3$ | CO | 70.6 | 100:0 |
| 7 | $CH_3$ | $C_6H_5$– | CO | 63.4 | 100:0 |

## Conclusion

From the results obtained to far, the process was then applied to [1, 3, 4] thiadiazde derivatives using 0.75 g of Catalyst for acids and performing the reactions at 45 °C for 1 hour. We shown that the heterogeneous catalyst, namely commercially available $AlPO_4$–5 and SBA–15 molecular sieve, can be successfully and efficiently utilized for the synthesis of **3**. Moreover, the use of sulfuric acid as solvent, which is not only for the reducing of byproducts, the saving energy consumption, the waste "zero emissions", provided an undoubted advantages from both an environment and an economic point of view when the using of heterogeneous catalytic systems.

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