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# Synthesis of 2-(*N*-formyl)-5-aryl/aryloxymethyl-1,3,4-thiadiazoles with potential bioactivity in PEG-400

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**Abstract**

An environmental benign procedure for synthesis of 2-(*N*-formyl)-5-aryl/aryloxymethyl-1,3,4-thiadiazoles has been developed by reaction of 2-amino-5-aryl/aryloxymethyl-1,3,4-thiadiazoles with formic acid in PEG-400. The key advantages of this protocol are the shorter reaction time, higher yields, lower cost, simple workup, and environment-friendly compared to conventional organic solvent reaction. The present method does not involve any hazardous organic solvent or catalyst.
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The 1,3,4-thiadiazole derivatives have attracted continuing interest over the years because of their varied biological activities, such as antituberculosis, anticancer, antibacterial, antifungal and anticonvulsant activities [1–7]. 2-Amino-1,3,4-thiadiazoles of 1,3,4-thiadiazole derivatives provided a useful method for the synthesis of 1,3,4-thiadiazoles, it has been used for synthesis of various compounds possessing biological activities as intermediates [8–11]. On the other hand, formamides are valuable intermediates in the construction of various pharmaceutically important compounds and useful reagents in Vilsmeier formylation reactions. Besides, formamides can catalyze several organic transformations as Lewis bases. The formyl group is also an important protecting group of amines in peptide synthesis [12–17]. Based on the principle of superposition, a higher biological activity compound may be obtained by connecting 1,3,4-thiadiazole and formamides groups in one molecule. Here, we report an environmental benign synthesis of such compounds.

Developing green chemical reactions is one of the most important purposes of modern organic synthesis. Polyethylene glycol (PEG) and its monomethyl ethers have emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents, and recyclability [18]. On the other hand, PEGs are inexpensive, completely non-halogenated, and low toxic. Recently, PEGs have received considerable attention in synthetic organic chemistry as green organic solvent [19–23]. In the present conversion, it has efficiently been utilized for the preparation of various *N*-formyl compounds [12].

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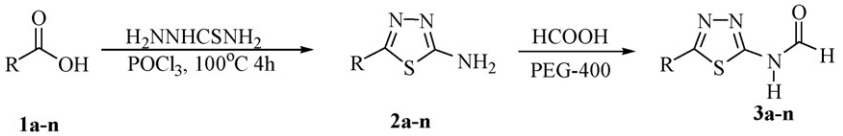
As part of our ongoing interest in the 2-amino-5-aryl/aryloxymethyl-1,3,4-thiadiazoles for synthesis of various compounds as intermediates [20,24] and taking all the above-mentioned evidence into account, a series of novel 2-(*N*-formyl)-5-aryl/aryloxymethyl-1,3,4-thiadiazoles were designed and synthesized.

## 1. Result and discussion

As described in Scheme 1, the starting material 2-amino-5-aryl/aryloxymethyl-1,3,4-thiadiazoles **2a–n** were synthesized as the previous work [25]. When 2-amino-5-aryl/aryloxymethyl-1,3,4-thiadiazoles and HCOOH are stirred at room temperature or heated without any solvent, the product was not found and all starting materials were recovered. Then we tested the model reaction **3a** (A mixture of 2-amino-5-phenoxymethyl-1,3,4-thiadia-zoles and HCOOH was heated in PEG-400) and found that the reaction proceeded under polyethylene glycol (PEG) and gave high yield, so we haven't further studied for other solvent. The compound **3a** was confirmed by IR, $^{1}$H NMR, $^{13}$C NMR. The IR spectrum of **3a** displayed bands at 3163 $cm^{-1}$ and 1693 $cm^{-1}$ due to –NH– and –C=O stretching frequencies, respectively. The $^{1}$H NMR spectrum of **3a** exhibited one singlet at $\delta$ 5.46 which accounts for two methylene protons on the $-OCH_2-$protons. A singlet at $\delta$ 8.74 accounts for the –CHO proton and a singlet about $\delta$ 12.78 is due to the –NH–proton. The $^{13}$C NMR displayed peaks at $\delta$ 64.6 ($CH_2$), 114.8 (2C), 122.1, 129.8 (2C), 157.4, 158.5, 161.9 (C=O).

In following study of model reaction **3a**, we examined the reaction in different conditions to find out the effect of temperature and time on the reaction. It was found that low yield was obtained at lower temperature, even if the reaction time was prolonged (entry 1). Higher yield was obtained under higher temperature and longer time (entry 7). But when the reaction solution was heated at 130 °C, such high temperature did not further improve yield. From Table 1 it can be seen that if this reaction was performed at 110 °C for 2 h, the desired product **3a** was produced in the highest yield (Table 1 entry 5, 11).

With the optimized condition in hand, a series of 2-(*N*-formyl)-5-aryl/aryloxymethyl-1,3,4-thiadiazoles were synthesized in PEG-400 with high yields without additional solvent or catalyst (Table 2) [26]. Both electron-donating and electron-withdrawing groups are tolerated in the reaction, and we found that the *N*-formylation of 5-aryl/




**1a-n** **2a-n** **3a-n**

**a**: R = $C_6H_5OCH_2$ **e**: R = 4-$ClC_6H_4OCH_2$ **i**: R = $_2$-$NO_2C_6H_4OCH_2$ **m**: R = 3-$CH_3C_6H_4$
**b**: R = 2-$ClC_6H_4OCH_2$ **f**: R = 4-$CH_3OC_6H_4OCH_2$ **j**: R = $_4$-$NO_2C_6H_4OCH_2$ **n**: R = 3-$NO_2C_6H_4$
**c**: R = 2-$CH_3C_6H_4OCH_2$ **g**: R = 2-$CH_3OC_6H_4OCH_2$ **k**: R = $C_6H_5$
**d**: R = 4-$CH_3OC_6H_4$ **h**: R = 3-$CH_3C_6H_4OCH_2$ **l**: R = $_2$-$CH_3OC_6H_4$

Scheme 1.

Table 1
Synthesis of **3a** at different temperature and time.

| Entry | Solvent | Temperature (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| **1** | PEG-400 | 25 | 2 | 10 |
| **2** | PEG-400 | 80 | 2 | 55 |
| **3** | PEG-400 | 90 | 2 | 73 |
| **4** | PEG-400 | 100 | 2 | 84 |
| **5** | PEG-400 | 110 | 2 | 94 |
| **6** | PEG-400 | 120 | 2 | 94 |
| **7** | PEG-400 | 130 | 2 | 94 |
| **8** | PEG-400 | 110 | 0.5 | 61 |
| **9** | PEG-400 | 110 | 1 | 73 |
| **10** | PEG-400 | 110 | 1.5 | 86 |
| **11** | PEG-400 | 110 | 2.5 | 93 |

[a] Isolated yield.

Table 2
Synthesis of **2a–o** refluxed in PEG-400.

| Entry | Product | R | Product | Mp (°C) | Yield[a] (%) |
|---|---|---|---|---|---|
| **1** | **3a** | $C_6H_5OCH_2$ | $C_{10}H_9N_3O_2S$ | 136–138 | 96 |
| **2** | **3b** | $2\text{-}ClC_6H_4OCH_2$ | $C_{10}H_8ClN_3O_2S$ | 250–252 | 92 |
| **3** | **3c** | $2\text{-}CH_3C_6H_4OCH_2$ | $C_{11}H_{11}N_3O_2S$ | 209–211 | 94 |
| **4** | **3d** | $4\text{-}CH_3OC_6H_4$ | $C_{10}H_9N_3O_2S$ | 247–249 | 94 |
| **5** | **3e** | $4\text{-}ClC_6H_4OCH_2$ | $C_{10}H_8ClN_3O_2S$ | 218–220 | 91 |
| **6** | **3f** | $4\text{-}CH_3OC_6H_4OCH_2$ | $C_{11}H_{11}N_3O_3S$ | 171–173 | 96 |
| **7** | **3g** | $2\text{-}CH_3OC_6H_4OCH_2$ | $C_{11}H_{11}N_3O_3S$ | 183–185 | 95 |
| **8** | **3h** | $3\text{-}CH_3C_6H_4OCH_2$ | $C_{11}H_{11}N_3O_2S$ | 190–192 | 94 |
| **9** | **3i** | $2\text{-}NO_2C_6H_4OCH_2$ | $C_{10}H_8N_4O_3S$ | 219–221 | 87 |
| **10** | **3j** | $4\text{-}NO_2C_6H_4OCH_2$ | $C_{10}H_8N_4O_4S$ | 225–227 | 89 |
| **11** | **3k** | $C_6H_5$ | $C_9H_7N_3OS$ | 201–203 | 94 |
| **12** | **3l** | $2\text{-}CH_3OC_6H_4$ | $C_9H_6ClN_3OS$ | 248–250 | 92 |
| **13** | **3m** | $3\text{-}CH_3C_6H_4$ | $C_{10}H_9N_3OS$ | 179–181 | 94 |
| **14** | **3n** | $3\text{-}NO_2C_6H_4$ | $C_9H_6N_4O_3S$ | 213–215 | 85 |

[a] Isolated yield.

aryloxymethyl-1,3,4-thiadiazoles having electron-donating groups such as methyl and methoxy in the aromatic ring occured in higher yields than having electron-withdrawing groups such as chloro and nitro groups. In particularly, for compounds with nitro, the yields were a little lower because of the stronger ability of electron-withdrawing (Table 2, entries 9, 10, 14).

In summary, we have developed a convenient method for preparation of 2-(*N*-formyl)-5-aryl/aryloxy-methyl-1,3,4-thiadiazoles. The advantages of this methodology lie in higher yields, operational simplicity, lower cost, and less pollution to environment. Moreover, this procedure will provide a good to excellent method for synthesis of 1,3,4-thiadiazoles derivatives.

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[26] General procedure for the synthesis of 2-*N*-formylation-5-aryl/aryloxymethyl-1,3,4-thiadiazoles (**3a**–**3n**): PEG-400 (2 g) was added to a mixture of thiadiazoles (1 mmol) and HCOOH (3 mmol), then the mixture was heated at 110 °C for 2 h and the progress of the reaction was monitored by TLC. After completion, the mixture was diluted with water (10 mL) and filtered. The residue was subjected to column chromatography to obtain the pure *N*-formyl thiadiazole (ethyl acetate-petroleum ether, 5:1). Selected physical and spectral (IR, $^{1}$H NMR, $^{13}$C NMR, MS, Anal.) data. **3a** Mp: 136–138 °C. IR (KBr) *ν*: 3163, 1693, 1247 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$): *δ* 12.78 (s, 1H, NH), 8.74(s, 1H, CHO), 7.35–7.02 (m, 5H, ArH), 5.45 (s, 2H, $OCH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 64.6, 114.8, 122.1, 129.8, 157.4, 158.5, 161.9. MS: *m/z* 236 ($M^+$). Anal. calcd. for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86. Found: C, 51.97; H, 3.79; N, 17.92. **3g** Mp: 183–185 °C. IR (KBr) *ν*: 3164, 1696, 1259 cm$^{-1}$. $^{1}$H NMR (400 MHz, DMSO-$d_6$): *δ* 12.75 (s, 1H, NH), 8.54(s, 1H, CHO), 7.10–6.86 (m, 4H, ArH), 5.45 (s, 2H, $OCH_2$), 3.77 (s, 3H, $OCH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): *δ* 55.7, 65.0, 112.7, 115.0, 120.8, 122.6, 146.8, 149.5, 157.9, 160.1, 161.2. MS: *m/z* 266 (M+) Anal. calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84. Found: C, 49.72; H, 4.25; N, 15.90. **3h** Mp: 190–192 °C. IR (KBr) *ν*: 3165, 1689, 1261 cm$^{-1}$. $^{1}$H NMR (400 MHz, DMSO-$d_6$): *δ* 12.77 (s, 1H, NH), 8.54(s,1H, COH), 7.22–6.81 (m, 4H, ArH), 5.48 (s, 2H, $OCH_2$), 2.28 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): *δ* 21.2, 63.9, 111.9, 115.7, 122.5, 129.5, 139.4, 157.4, 157.8, 160.1, 161.3. MS: *m/z* 249 (M+) Anal. calcd. for $C_{11}H_{11}N_3O_2S$: C, 51.00; H, 4.45; N, 16.86. Found: C, 51.08; H, 4.37; N, 12.80.