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# ZINC-MEDIATED FACILE AND EFFICIENT CHEMOSELECTIVE *S*-ALKYLATION OF 5-ARYL-1,3,4-OXADIAZOLE-2-THIOLS IN THE ABSENCE OF BASE

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***Zinc-mediated facile and efficient chemoselective S-alkylation of 5-aryl 1,3,4-oxadiazole-2-thiols in the presence of a catalytic amount of tetra butyl ammonium iodide was described. The reaction was performed under neutral conditions. The chemoselectivity of the alkylation was confirmed by NMR spectroscopy and x-ray crystallography.***

***Keywords***: Alkylation; chemoselectivity; oxadiazole; piperazines; zinc

## INTRODUCTION

The 1,3,4-oxadiazole derivatives are useful in the fields of medicinal and pesticide chemistry as well as in polymer science.[1–4] The 1,3,4-oxadiazole ring is associated with many types of biological activities such as HIV integrase inhibitory,[5] anti-inflammatory,[6–8] antibacterial and antifungal,[9–11] and hypoglycemic[12] activities. In particular, mercapto substituted-1,3,4-oxadiazole derivatives are found to show anti-hepatitis B virus (HBV) activity.[13]

*N*-Arylpiperazines are considered ''privileged'' templates in drug discovery.[14] Piperazines are important pharmacophores found in many drugs, such as the Merck HIV protease inhibitor Crixivan.[15] Aryl piperazines are regarded as potential therapeutics for anxiety and depression.[16]

The *S*-alkylation of 5-substituted-1,3,4-oxadiazole-2-thiols has been reported with various bases such as $K_2CO_3$,[17] NaOH,[18] KOH,[19] $Et_3N$,[20] NaOMe,[21] and NaOAc.[22] The synthetic utility of zinc is well established in the literature for various chemical reactions. Zinc has drawn the attention of many researchers because it is easily availabile, inexpensive, and nontoxic.[23] As a part of our continuing efforts to develop simple, efficient, economical,

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and environmentally benign synthetic methods using zinc dust,[24] we have demonstrated a convenient zinc-mediated method for the *S*-alkylation of 5-aryl-1,3,4-oxadiazole-2-thiol with 1-(3-chloropropyl)-4-substituted piperazines in the absence of base.

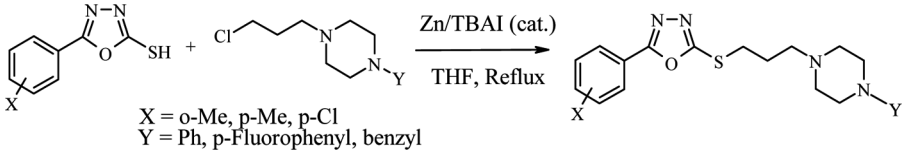
## RESULTS AND DISCUSSION

We have carried out zinc-mediated *S*-alkylation of 5-aryl-1,3,4-oxadiazole-2-thiols with 1-(3-chloropropyl)-4-substituted piperazines in the absence of base (Scheme 1). The products were obtained in excellent yields and high purity.

The oxadiazole thiol was alkylated with 1-(3-chloropropyl)-4-substituted piperazines using $K_2CO_3$ and a catalytic quantity of tetra butyl ammonium iodide (TBAI), which in acetonitrile solvent gave the product in good yield. The same reaction in the presence of zinc dust did not form the alkylated product. Equimolar quantities of various 5-substituted-1,3,4-oxadiazole-2-thiols were reacted with 1-(3-chloropropyl)-4-substituted piperazines in the presence of zinc dust and catalytic amounts of TBAI in tetrahydrofuran (THF) solvent, which produced exclusively the *S*-alkylated product in excellent yield with high purity (Table 1). The reaction was also investigated for the possibility of using zinc dust in catalytical or less than stoichiometric quantities. High yields of the products with excellent purity were obtained with 1 equivalent of zinc dust. The products were characterized by their spectral data. The $^1$H NMR spectrum is the indicative for the determination of the *S*-alkylated isomer. The $^1$H NMR of the compound in entry 5 showed a chemical shift at δ 3.37, which is typical[25] for *S*-$CH_2$ protons.

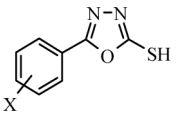
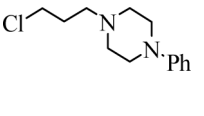
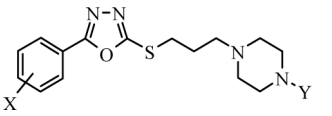
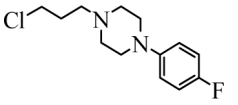
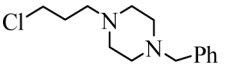
X-ray crystallography was undertaken on a representative compound (entry 5) to further confirm the structural isomer. A crystal of compound (entry 5) was grown by slow evaporation from hexane and the chloroform mixture, and the *S*-alkylated isomer was proved by single-crystal x-ray analysis of the compound (entry 5, Fig. 1).

The reusability of zinc dust was studied for entries 3 and 8 (Table 2). The zinc dust was reactivated and reused in further runs, and no remarkable loss in activity was observed. (Used zinc was treated with 10% HCl, washed with water and acetone, and dried in an oven for 2 h at 120–130 °C.) This makes the process more economical.




**Scheme 1.** Synthesis of 5-aryl-2-*S*-alkylated-1,3,4-oxadiazole.

**Table 1.** 5-Substituted-2-[3-(4-arylpiperazinyl)] propylthio-1,3,4-oxadiazoles

| Entry | Oxadiazole thiol | Piperazine | Product[a] | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|
| |  |  |  | | |
| 1 | X = o-Me | | X = o-Me, Y = Ph | 55 | 85 |
| 2 | X = p-Me | | X = p-Me, Y = Ph | 55 | 95 |
| 3 | X = p-Cl | | X = p-Cl, Y = Ph | 45 | 90 |
| | |  | | | |
| 4 | X = o-Me | | X = o-Me, Y =  | 50 | 88 |
| 5 | X = p-Me | | X = p-Me, Y =  | 40 | 92 |
| 6 | X = p-Cl | | X = p-Cl, Y =  | 40 | 90 |
| | |  | | | |
| 7 | X = o-Me | | X = o-Me, Y = Bn | 60 | 84 |
| 8 | X = p-Me | | X = p-Me, Y = Bn | 60 | 88 |
| 9 | X = p-Cl | | X = p-Cl, Y = Bn | 55 | 90 |

[a]All products were characterized by $^1$H NMR, ESI-HRMS, and IR spectroscopy.
[b]Isolated yields after column chromatography.

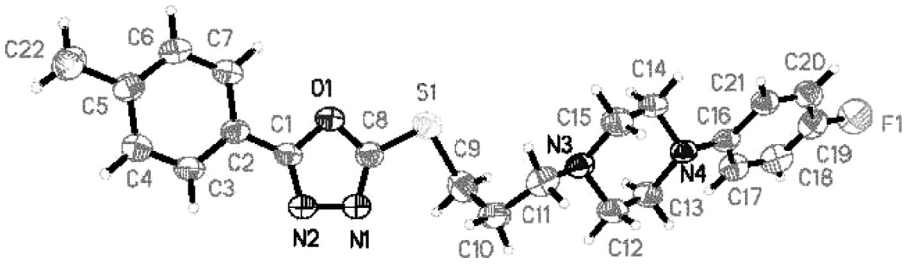



**Figure 1.** X-ray crystal structure (entry 5). Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii.

**Table 2.** Recyclability studies of zinc dust for entries 3 and 8

| Run | Yield (%) of **3** | Yield (%) of **8** |
|---|---|---|
| 1 | 90 | 88 |
| 2 | 87 | 88 |
| 3 | 86 | 85 |
| 4 | 84 | 82 |
| 5 | 84 | 82 |

## CONCLUSION

In conclusion, we have demonstrated an easy, convenient, and highly efficient approach for the chemoselective synthesis of 5-aryl-2-*S*-alkylated-1,3,4-oxadiazole derivatives. The reaction was performed using zinc dust as a recyclable catalyst with a catalytic amount of TBAI under neutral conditions. The products were obtained in good yields with excellent purity, and the workup is easy, thus making the process simple, economical, environmentally benign, and useful in organic synthesis.

## EXPERIMENTAL

Melting points were determined on a Buchi capillary melting-point apparatus. The $^1$H NMR (200 MHz and 300 MHz) were recorded on Varian Gemini and Bruker Avance spectrometers using tetramethylsilane (TMS) as an internal standard. Electrospray ionization–mass spectra (EIS-MS) were recorded on an Agilent Technologies LC/MSD SL single quadrupole (Agilent ChemStation software). High-resolution mass spectra (HRMS) were recorded on a high-resolution QSTAR XL hybrid MS/MS system (Applied Biosystems) under ESI conditions with sample solutions prepared in MeOH. Infrared (IR) spectra were recorded on a Perkin-Elmer IR 683.



### X-Ray Crystallographic Analysis

The crystal system was monoclinic, and the space group was $P2_1/c$. The unit cell dimension were as follows: a = 12.2372(10) Å, b = 10.3618(9) Å, c = 14.4945 Å, and $\beta = 105.853(1)^\circ$. Data collection yielded 19845 reflections, resulting in 3741 unique, averaged reflections, 2761 with $I > 2\sigma(I)$, and $\theta$ range: 1.73–25.00°. The structure was solved by direct methods using SHELXS-97[26] and refined by full-matrix least-squares refinement using SHELXL-97[26], leading to a final R = 0.0472, wR = 0.1182, and GOF = 1.034. Intensity data were measured on a Bruker Smart Apex with CCD area detector. CCDC 713379 contains supplementary crystallographic data for the structure.

### Typical Procedure for the Synthesis of 2-[3-(4-(4-Fluorophenyl)piperazinyl)] Propylthio-5-[4-methylphenyl]-1,3,4-oxadiazoles (Entry 5)

In a typical procedure, 5-(4-methylphenyl)-1,3,4-oxadiazole-2-thiol (1.0 g, 5.2 mmol) and 1-(3-chloropropyl)-4-(4-fluorophenyl)piperazine (1.39 g, 5.2 mmol) were taken in THF (20 ml) and mixed well for 5 min. Zinc dust (0.34 g, 5.2 mmol) and a catalytic amount of TBAI (0.0192 g, 0.052 mmol) were added. The reaction mixture was refluxed for 40 min. After completion, the reaction mixture was filtered, and the solid was washed with THF (2 × 5 ml). The combined filtrate was concentrated, and the product was purified by flash-column chromatography.

### Characterization Data for the Products, Entries 1–9

**Entry 1.** Brown viscous liquid; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.85 (d, $J = 7.3$ Hz,1H), 7.45–7.12 (m, 5H), 6.92–6.72 (m, 3H), 3.38 (t, $J = 7.3$ Hz, 2H),

3.24–3.10 (m, 4H), 2.69 (s, 3H), 2.67–2.51 (m, 6H), 2.09 (quintet, $J = 7.3$ Hz, 2H). IR (KBr): 3059, 2930, 2818, 1598, 1548, 1470, 1380, 1234, 1188, 1133, 1041, 998, 951, 761, 725, 692 $cm^{-1}$; ESI-MS: $m/z$ 395.0 (M + 1).

**Entry 2.** Light yellow solid; mp 90–92 °C; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.87 (d, $J = 7.8$ Hz, 2H), 7.30–7.13 (m, 4H), 6.90–6.73 (m, 3H), 3.37 (t, $J = 7.0$ Hz, 2H), 3.22–3.11 (m, 4H), 2.65–2.50 (m, 6H), 2.42 (s, 3H), 2.08 (quintet, $J = 7.0$ Hz, 2H). IR (KBr): 3026, 2923, 2817, 1569, 1501, 1472, 1291, 1235, 1179, 1064, 951, 824, 754, 692 $cm^{-1}$; ESI-MS: $m/z$ 395.0 (M + 1); ESI-HRMS for $C_{22}H_{26}N_4OS$: found: 394.1840; calcd: 394.1827.

**Entry 3.** White solid; mp 113–115 °C; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.94 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.26–7.14 (m, 2H), 6.90–6.75 (m, 3H), 3.39 (t, $J = 6.6$ Hz, 2H), 3.24–3.13 (m, 4H), 2.73–2.53 (m, 6H), 2.11 (quintet, $J = 6.6$ Hz, 2H). IR (KBr): 3047, 2938, 1598, 1462, 1238, 1190, 1008, 847, 753 $cm^{-1}$; ESI-MS: $m/z$ 416 (M + 1). ESI-HRMS for $C_{21}H_{23}N_4OSCl$: found: 414.9498; calcd: 414.9500.

**Entry 4.** Yellow oily liquid; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.87 (d, $J = 7.6$ Hz, 1H), 7.42–7.26 (m, 3H), 6.97–6.77 (m, 4H), 3.38(t, $J = 6.8$ Hz, 2H), 3.14–3.04 (m, 4H), 2.71 (s, 3H), 2.65–2.50 (m, 6H), 2.10 (quintet, $J = 6.8$ Hz, 2H). IR (KBr): 2930, 2817, 1604, 1548, 1509, 1470, 1381, 1231, 1189, 1042, 1002, 951, 821, 771, 724, 671 $cm^{-1}$; ESI-MS: $m/z$ 413 (M + 1).

**Entry 5.** White solid; mp 131–133 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, $J = 7.6$ Hz, 2H), 7.26 (d, $J = 7.6$ Hz, 2H), 6.94–6.86 (m, 2H), 6.85–6.78 (m, 2H), 3.37 (t, $J = 6.8$ Hz, 2H), 3.13–3.03 (m, 4H), 2.64–2.50 (m, 6H) 2.43 (s, 3H), 2.08 (quintet, $J = 6.8$ Hz, 2H). IR (KBr): 2947, 2818, 1612, 1508, 1473, 1238, 1179, 1063, 828, 720 $cm^{-1}$; ESI-MS: $m/z$ 413.2 (M + 1); ESI-HRMS for $C_{22}H_{26}N_4OFS$: found 413.1806; calcd. 413.1811.

**Entry 6.** Pale yellow solid; mp 133–134 °C; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.94 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 6.96–6.78 (m, 4H), 3.38 (t, $J = 7.0$ Hz, 2H), 3.15–3.06 (m, 4H), 2.67–2.53 (m, 6H), 2.08 (quintet, $J = 7.0$ Hz, 2H). IR (KBr): 3089, 2938, 2818, 2776, 1603, 1510, 1459, 1356, 1238, 1184, 1087, 1007, 951, 816, 721, 693 $cm^{-1}$; ESI-MS: $m/z$ 432.8 (M + 1). ESI-HRMS for $C_{21}H_{22}ClFN_4OS$: found 432.1193; calcd. 432.1187.

**Entry 7.** Brown viscous liquid; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.86 (d, $J = 6.8$ Hz, 1H), 7.40–7.15 (m, 8H), 3.47 (s, 2H), 3.34 (t, $J = 6.8$ Hz, 2H), 2.71 (s, 3H), 2.54–2.39 (m, 10H), 2.04 (quintet, $J = 6.8$ Hz, 2H). IR (KBr): 3060, 2937, 2810, 1605, 1550, 1471, 1350, 1189, 1156, 1042, 1007, 950, 729, 700 $cm^{-1}$; ESI-MS: $m/z$ 409.0 (M + 1); ESI-HRMS for $C_{23}H_{28}N_4OS$: found 408.1997; calcd. 408.1983.

**Entry 8.** Brown solid; mp 54–56 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (d, $J = 8.3$ Hz, 2H), 7.31–7.15 (m, 7H), 3.49 (s, 2H), 3.31 (t, $J = 7.6$ Hz, 2H), 2.58–2.42 (m, 10H), 2.39 (s, 3H), 2.03 (quintet, $J = 7.6$ Hz, 2H). IR (KBr): 3028, 2941, 2803, 2768, 1962, 1654, 1613, 1556, 1468, 1407, 1344, 1286, 1179, 1136, 1066, 1006, 940, 821, 738, 694 $cm^{-1}$; ESI-MS: $m/z$ 409 (M + 1).

**Entry 9.** Light yellow solid; mp 68–69 °C. $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.93 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 8.3$ Hz, 2H), 7.32–7.15 (m, 5H), 3.48 (s, 2H), 3.34

(t, $J = 6.8$ Hz, 2H), 2.56–2.36 (m, 10H), 2.03 (quintet, $J = 6.8$ Hz, 2H). IR (KBr): 2922, 2803, 1605, 1470, 1403, 1089, 830, 727 $cm^{-1}$; ESI-MS: $m/z$ 429.8 (M + 1); ESI-HRMS for $C_{22}H_{25}ClN_4OS$: found 429.1500; calcd. 429.1515.

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