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Facile synthesis of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles from acylthiourea

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ABSTRACT

Facile and selective synthesis of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles starting from *N*-acylthioureas has been demonstrated. The regio-selectivity is achieved by simply selecting an appropriate base used for the generation of hydroxyl amine from the corresponding hydrochloride salt. This method also avoids the use of toxic cyanogen bromide. The structure of the synthesized oxadiazoles has been resolved by tandem mass spectral studies.

Oxadiazoles, show wide range of application as drugs in pharmaceuticals.[1,2] Conventionally, 3,5-disubstituted 1,2,4-oxadiazoles are synthesized by coupling of amidoximes with activated carbonyl compounds, yielding *O*-acyl amidoximes followed by dehydrative cyclization carried out under harsh conditions (Scheme 1).[3] Alternatively, these are synthesized by the reaction of acylamidines with hydroxylamine[4] as shown in Scheme 1.

Though there are many literature reports for the preparation of 3,5-aryl/alkyl 1,2,4-oxadiazoles,[5] relatively less is known on 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles synthesis,[6] which are also pharmaceutically important molecules.[7] The most common methods for the preparation of the latter not only involve the use of toxic and corrosive cyanogen bromide but are also inefficient, poor yields being generally obtained (Scheme 2).[8] In this Letter, we report a cyanogen bromide-free, simple and selective method for the synthesis of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles from *N*-acyl thiourea derivatives.

At the beginning of our study, commercially available benzoylisothiocyanate **1a** was coupled with piperidine **2a** in $CHCl_3$ at room temperature for 1 h to yield the *N*-benzoyl-*N*′,*N*′-piperidine thiourea **3a** (Scheme 3).[9] Addition of hexane to the reaction mixture gave **3a** as a solid and was separated by simple filtration in 89% yield. **4a** was *S*-methylated using methyl iodide and potassium carbonate (K_2CO_3) at room temperature (25 °C) in THF to get the corresponding *S*-methylated acylthiourea **4a** in 85% yield.[10]

In an attempt to synthesize hydroxy guanidine **5a**, *S*-methylated acylthiourea **4a** was treated with a solution of hydroxylamine prepared by neutralizing hydroxylamine hydrochloride with methanolic potassium hydroxide.[11] Surprisingly, the reaction yielded two compounds in 80% overall yield, which were separated in equal amounts (~1:1) by column chromatography.

While the molecular mass of the two isolated compounds were the same, the mass spectra of neither of the compounds matched with that of the expected **5a**. In fact, the mass spectra of the isolated compounds were matching with that of the cyclized product, that is, 1,2,4-oxadiazole **7a**. The NMR spectra of the two compounds also showed no significant difference indicating that the compounds are structurally similar. Based on these results, structures of **7a** and **8a** were proposed for the two compounds, respectively. This was later confirmed by tandem mass spectral analysis (Fig. 1).[12] The reaction protocol was repeated with the morpholine analog **4b** under similar reaction conditions resulting in the oxadiazoles **7b** and **8b**, respectively, in equal amounts.

The formation of both **7a** and **8a** is possible only if hydroxylamine is reacting with **4a** at both N and O ends. This would be possible when a strong base such as methanolic KOH is used for the generation of free base from hydroxylamine hydrochloride as this could possibly generate NH_2O^- (aminoxide anion) along with hydroxylamine. Hydroxylamine could react at the nitrogen end to give **7a** while aminoxide ion could react at the oxygen end to give **8a** (Scheme 3).

Having this in mind we thought of using a milder base, such as sodium acetate for generating hydroxylamine free base from $NH_2OH{\cdot}HCl$. This approach would avoid the formation of the intermediate **6a** that would lead to **8a**. Indeed, the reaction of **4a** with $NH_2OH{\cdot}HCl$ in the presence of NaOAc, provided the desired oxadiazole **7a** in 80% yield with no unwanted regioisomer **8a**. Encouraged

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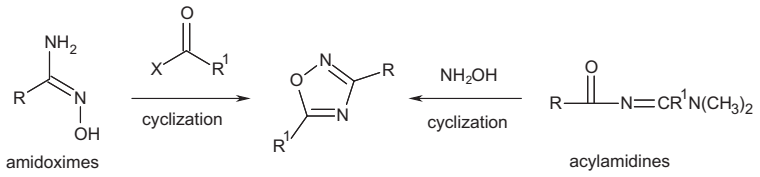
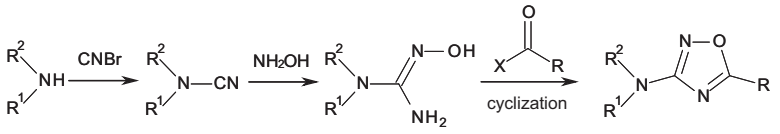
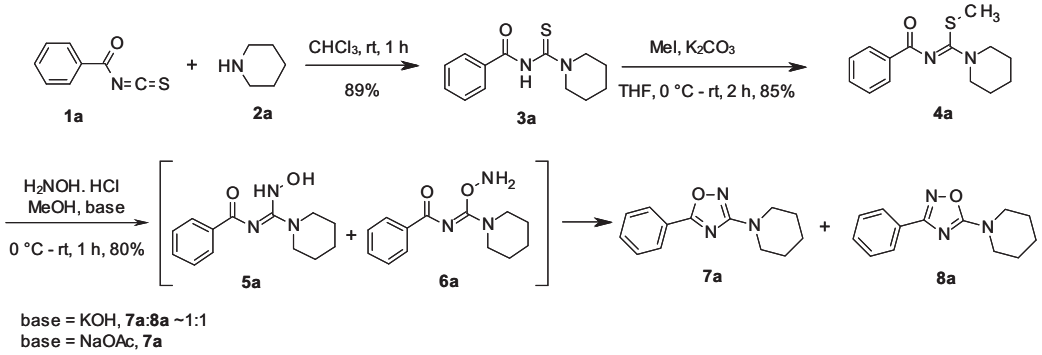


Scheme 1. Preparation of 3,5-disubstituted 1,2,4-oxadiazoles.



Scheme 2. Conventional method for the preparation of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles.



Scheme 3. Synthesis of 5-phenyl-3-(1-piperidyl)-1,2,4-oxadiazole.

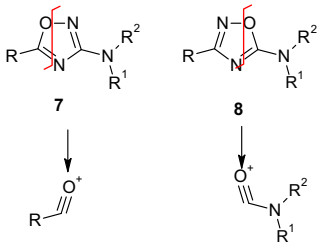
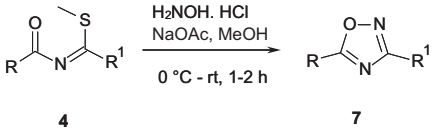
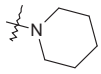
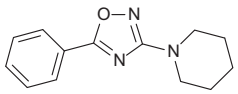
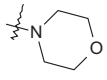
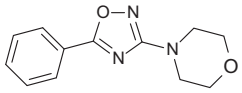


Figure 1. Proposed LC–MSMS fragmentation pathway of isomers **7** and **8**.

by the above results, the reactions were repeated with different acylisothiocyanates and primary or secondary amines to prepare a series of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles **7a–h** (Table 1). Some of the acylisothiocyanates **1**, which were not commercially available, were generated in situ by the reaction of ammoniumthiocyanate with the corresponding acyl chlorides **9**. The reaction of acylisothiocyanates with different amines using reported protocol[9] provides the corresponding acylthioureas **3** in 80–90% yield. In a subsequent step, the produced acylthiourea **3** was treated with methyl iodide to provide the corresponding *S*-methylated derivatives **4** in 80–85% yield (Scheme 4).[13] The *S*-methylated derivatives were found to be stable for couple of weeks at ambient temperature.

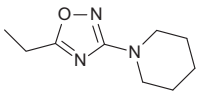
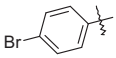
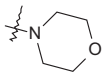
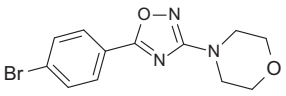
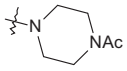
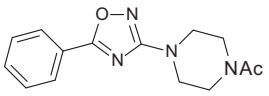
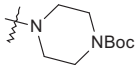
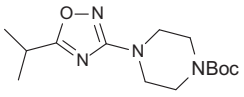
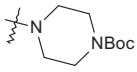
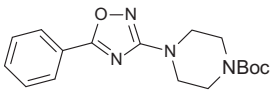
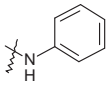
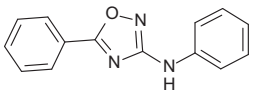
Table 1
Synthesis of different oxadiazoles **7** from the corresponding *S*-methylated acylthioureas **4**

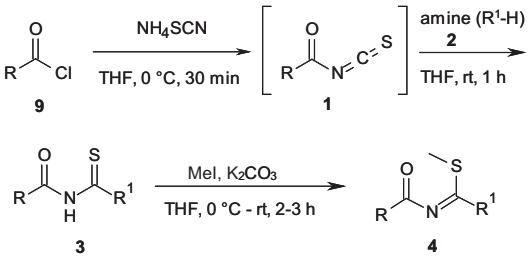


Entry	R	R^1	Oxadiazole (**7**)	Yield of **7** from **4** (%)
a				80
b				80

(*continued on next page*)

Table 1 (*continued*)

Entry	R	R^1	Oxadiazole (**7**)	Yield of **7** from **4** (%)
c				76
d				77
e				78
f				75
g				72
h				79



Scheme 4. Synthesis of *S*-methylated acylthioureas **4** starting from corresponding acyl chlorides **9**.

Finally, intermediates **4**, upon treatment with $NH_2OH{\cdot}HCl$ in the presence of NaOAc provided 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazole **7a–h** in 70–80% yield (Table 1).[13]

Based on these results, we believe that **7** or **8** can be synthesized selectively just by modifying the strength of the base. Work is under progress for the selective synthesis of **8** using this protocol.

We have demonstrated a facile and selective synthesis of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles **7** starting from the corresponding acyl chlorides in good yields**.** The reactions proceed via in situ generated hydroxy guanidines **5**. The protocol avoids the use of toxic cyanogen bromide. The structures of the regioisomers have been confirmed by tandem mass spectral studies.

Acknowledgments

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Supplementary data

Supplementary data associated (mass, ^1H and ^{13}C spectra for **7a**, **7b**, **8a**, and **8b**) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.048.

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12. Detection of the mixture of isomers were performed on an Agilent HPLC coupled through an Electrospray interphased to an Agilent 6520 Accurate-Mass Q-TOF LC/MS. Accurate mass TOF-LC mass detected two isomers **7a** and **8a** with M+H ions as 230.1288, 230.1289, respectively, and molecular formula generated as $C_{13}H_{15}N_3O$ with mass error less than 2.0 ppm for both. However, accurate mass Q-TOF LC–MS/MS shows fragmentation having unique product ion pattern via 230.1288, 105.0339 for **7a** and 230.1288, 112.0760 for **8a**. Corresponding molecular formula generated for the product ions were formyl carbocation, C_7H_5O and *N*-formyl carbocation, $C_6H_{10}NO$, respectively, with a mass error less than 5.0 ppm.
13. *General procedure for the preparation of acylthioureas* **3a–h**: Ammoniumthiocyanate (11 mmol) was added to a solution of acyl chlorides **9** (10 mmol) in THF (10 mL) at 0 °C and stirred for 30 min. Substituted amine **2** (11 mmol) was added to the above reaction mixture and was stirred at rt for about an hour until completion (monitored by TLC). The solvent was removed in vacuo and

the remaining mass was dissolved in ethylacetate. The organic layer was washed with 10% $NaHCO_3$ solution, 10% HCl, brine, and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure to afford the products as solids in 80–90% yield.

Procedure for the preparation of S-methylated acylthioureas **4a**–**h**: To a stirring solution of acylthioureas **3** (10 mmol) in THF (10 mL), MeI (30 mmol) was added followed by K_2CO_3 (11 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2–3 h. After completion of the reaction (monitored by TLC), THF was evaporated and the residue was diluted with ethylacetate. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and yielded the crude compounds in 80–85% yield, which were taken for further reaction without any purification.

General procedure for the preparation of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles (**7a**–**h**): NaOAc (30 mmol) was added to $NH_2OH{\cdot}HCl$ (30 mmol) in MeOH (10 mL) and stirred at 0 °C. After 20 min, *S*-methylated acylthioureas **4** (10 mmol) in MeOH (10 mL) was added to the above reaction mixture and was stirred for 1–2 h. After completion of the reaction (monitored by TLC), solvent was removed in vacuo and the reaction mass was dissolved in ethylacetate. The organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. Thereafter, the organic layer was concentrated and the resulting compound **7** was isolated, which was purified by flash column chromatography (20% of EtOAc and hexane) to yield the title compounds in 70–80% yield.

Spectral data for selected compounds: 5-phenyl-3-(1-piperidyl)-1,2,4-oxadiazole **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60–1.67 (m, 6H), 3.50–3.51 (m, 4H), 7.48–7.57 (m, 3H), 8.07–8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 24.1, 45.9, 126.1, 126.9, 127.5, 129.5, 167.5, 170.0; LC–MS *m*/*z* calcd for $C_{13}H_{16}N_3O$ 230.1 ($M+H^+$), found 230.1 ($M+H^+$).

3-Phenyl-5-(1-piperidyl)-1,2,4-oxadiazole **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62–1.70 (m, 6H), 3.65–3.67 (m, 4H), 7.43–7.49 (m, 3H), 7.99–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 24.0, 46.0, 123.8, 126.8, 127.8, 131.2, 169.8, 173.1; LC–MS *m*/*z* calcd for $C_{13}H_{16}N_3O$ 230.1 ($M+H^+$), found 230.1 ($M+H^+$).

4-(5-Phenyl-1,2,4-oxadiazol-3-yl)morpholine **7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35–3.37 (m, 4H), 3.72–3.75 (m, 4H), 7.39–7.48 (m, 3H), 7.97–7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 66.2, 124.6, 127.9, 128.9, 132.5, 170.7, 174.5; LC–MS *m*/*z* calcd for $C_{12}H_{14}N_3O_2$ 232.1 ($M+H^+$), found 232.1 ($M+H^+$).

4-(3-Phenyl-1,2,4-oxadiazol-5-yl)morpholine **8b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61–3.3.62 (m, 4H), 3.74–3.76 (m, 4H), 7.36–7.38 (m, 3H), 7.92 (m, 2H), ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.9, 66.1, 127.2, 127.6, 128.6, 130.8, 165.5, 170.0; LC–MS *m*/*z* calcd for $C_{12}H_{14}N_3O_2$ 232.1 ($M+H^+$), found 231.9 ($M+H^+$).

5-Ethyl-3-(1-piperidyl)-1,2,4-oxadiazole **7c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24–1.28 (t, *J* = 7.52 Hz, 3H), 1.55 (br , 6H), 2.65–2.72 (q, *J* = 7.52 Hz, 2H), 3.32 (br, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 20.5, 24.2, 24.9, 46.9, 170.4, 179.4; LC–MS *m*/*z* calcd for $C_9H_{16}N_3O$ 182.1 ($M+H^+$), found 182.1 ($M+H^+$).

4-[5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl]morpholine **7d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (m, 4H), 3.74 (m, 4H), 7.56–7.58 (m, 2H), 7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 66.2, 123.5, 127.4, 429.3, 132.3, 170.7, 173.7; LC–MS *m*/*z* calcd for $C_{12}H_{13}BrN_3O_2$ 311.1 ($M+H^+$), found 311.1 ($M+H^+$).

tert-Butyl 4-(5-isopropyl-1,2,4-oxadiazol-3-yl)piperazine-1-carboxylate **7f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 7.2 Hz, 6H), 1.46 (s, 9H), 3.0 (m, 1H), 3.34 (t, 4H), 3.43 (t, 4H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0, 27.7, 28.4, 44.4, 45.9, 80.1, 154.9, 170.1, 183.1; LC–MS *m*/*z* calcd for $C_{14}H_{25}N_4O_3$ 297.2 ($M+H^+$), found 297.2 ($M+H^+$).