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# Condensation of Vilsmeier salts, derived from tetraalkylureas, with amidoximes: a novel approach to access *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines

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ABSTRACT

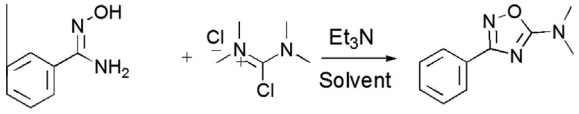
A novel approach, condensation of Vilsmeier salts and amidoximes, to access *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines has been developed. By this approach, a broad range of *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines, including aromatic, heteroaromatic, and aliphatic substituents, can be synthesized in good to high yields (up to 82%) under mild reaction conditions.



Oxadiazoles and their derivatives have been widely applied into natural products and drug intermediates such as antirhinovirus agents and anticonvulsants and analgesic agents.[1] Because of the biologic activities they exhibit, this kind of heterocyclic compounds have continuous interests in organic synthesis. Especially, *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines, not only has been reported as a pharmacologically active compound[2], but also can be used as ligands of $PdCl_2$ and other metal salts[3] with useful properties.[3]

A variety of synthetic methods for the preparation of 1,2,4-oxadiazoles have been reported[4]; these methods for the construction of 1,2,4-oxadiazole skeleton are mainly based on the coupling reaction of amidoximes with activated carbonyl compounds under harsh conditions.[5] However, the synthetic investigation of 5-dialkylamino substituted-1,2,4-oxadiazoles is limited.[4f,6] To the best of our knowledge, the introduction of an *N*,*N*-dialkylamino substitutent at the 5 position of a 1,2,4-oxadiazole core is usually carried out through the nucleophilic displacement of 5-chloro- or 5-trichloromethyl-1,2,4-oxadiazole by a secondary amine.[6g] A straightforward formation of 5-dialkylamino substituted-1,2,4-oxadiazoles can be realized by the condensation of *N*-hydroxylguanidines and carboxylic acids.[6h] In addition, 5-dialkylamino substituted-1,2,4-oxadiazoles, as by-products, have also been obtained in the reaction of *S*-methylated acylthioureas with hydroxylamine.[7] As our continuous efforts on constructing heterocyclic compounds using Vilsmeier salts as building blocks,[8] herein, we will disclose that condensation of Vilsmeier salts (derived from tetralkylureas) with amidoximes[9] could provide a novel approach to access *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines in good to high yields under mild reaction conditions.

**Table 1**
Screening studies of the reaction[a] of **1a** and **2a** with various conditions




1a 2a 3a

| Entry | Mole ratio of **1a**:**2a** | Solvent | Temp (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 1:2 | $CH_3CN$ | rt | 4 | 59 |
| 2 | 1:2 | THF | rt | 4 | 43 |
| 3 | 1:2 | Acetone | rt | 4 | 78 |
| 4 | 1:2 | DCM | rt | 4 | 81 |
| 5 | 1:1 | DCM | rt | 4 | 46 |
| 6 | 1:1.5 | DCM | rt | 4 | 74 |
| 7 | 1:2 | DCM | Reflux | 4 | 80 |
| 8 | 1:2.5 | DCM | rt | 4 | 81 |

[a] All the reactions were performed on the ratio **1**:**2** of **2a**:$Et_3N$.
[b] Isolated yields.

Initially, we investigated the condensation of benamidoxime and *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium chloride **2a** for reaction optimization, including extensive screening of solvent,

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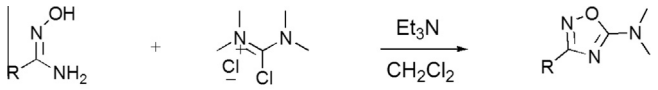
**Table 2**
Scope of synthesis of aromatic, heterocyclic, and aliphatic 5-amine-1,2,4-oxadiazoles[a]




1 2a 3

| Entry | Substrate (**1a**–**1p**) | Product (**3a**–**3p**) | Yield (%) |
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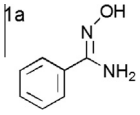
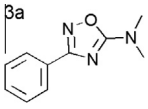
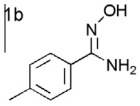
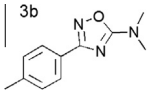
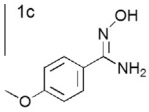
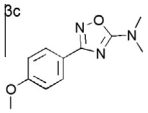
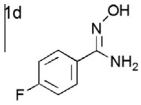
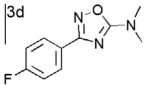
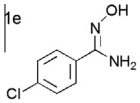
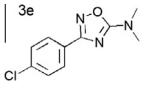
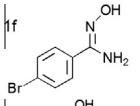
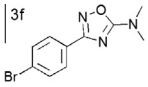
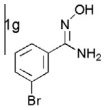
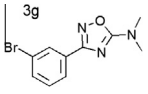
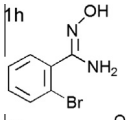
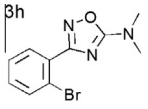
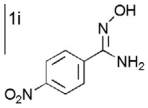
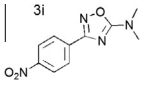
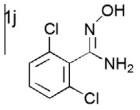
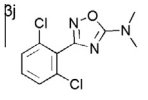
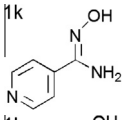
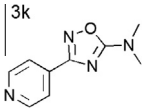
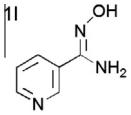
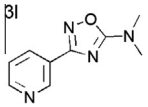
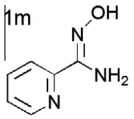
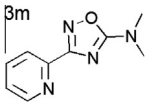
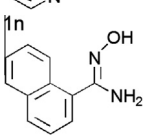
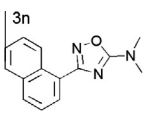
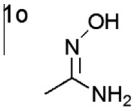
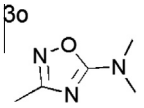
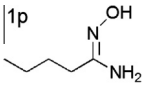
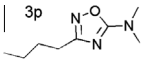
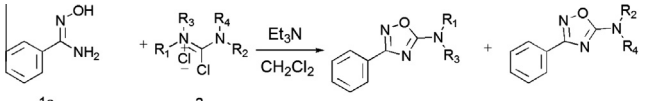
| 1 |  |  | 81 |
| 2 |  |  | 82 |
| 3 |  |  | 78 |
| 4 |  |  | 72 |
| 5 |  |  | 76 |
| 6 |  |  | 76 |
| 7 |  |  | 73 |
| 8 |  |  | 57 |
| 9 |  |  | 74 |
| 10 |  |  | 64 |
| 11 |  |  | 62 |
| 12 |  |  | 72 |
| 13 |  |  | 75 |
| 14 |  |  | 32 |

**Table 2** (*continued*)

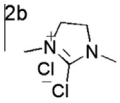
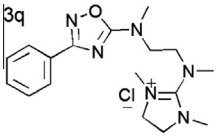
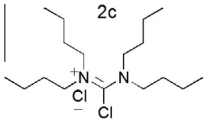
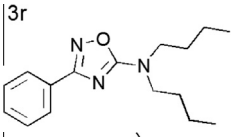
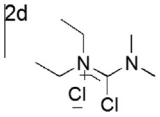
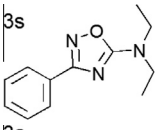
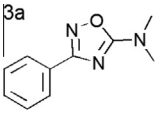
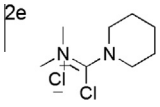
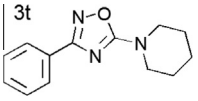
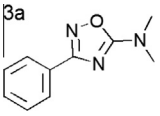
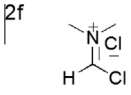
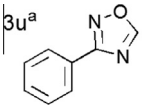
| Entry | Substrate (**1a**–**1p**) | Product (**3a**–**3p**) | Yield (%) |
|---|---|---|---|
| 15 | 1o  | 3o  | 40[b] |
| 16 | 1p  | 3p  | 56 |

[a] All the reactions were performed on 2 mmol scale with **1**:**2** of **1**:**2a** and 4 equiv base in 10 ml solvent in room temperature for 4 h.
[b] The reactions were performed in solvent of acetone.

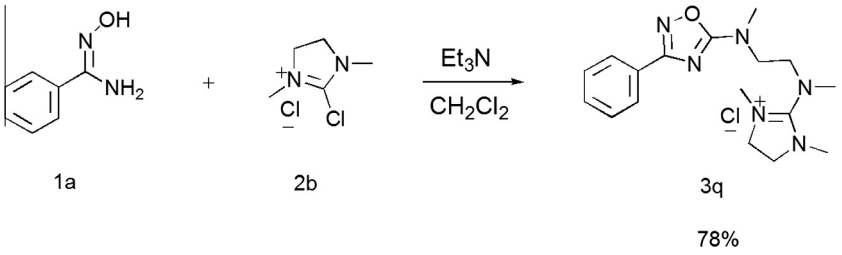
**Table 3**
Synthesis of 5-amine-1,2,4-oxadiazoles with the corresponding substrates of Vilsmeier salts



1a 2 3

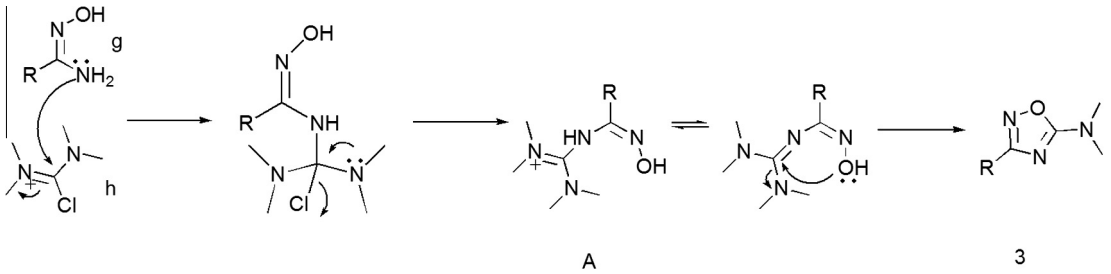
| Entry | Substrate (Vilsmeier salts **2b**–**2f**) | Product (**3q**–**3u**) | Yield (%) |
|---|---|---|---|
| 1 | 2b  | 3q  | 78 |
| 2 | 2c  | 3r  | 40 |
| 3 | 2d  | 3s  | 42 |
| | | 3a  | 12 |
| 4 | 2e  | 3t  | 45 |
| | | 3a  | 14 |
| 5 | 2f  | 3u[a]  | – |

[a] Expected product.



1a 2b 3q
78%

**Scheme 1.** Synthesis of 5-amine-1,2,4-oxadiazole via cyclic Vilsmeier salt and amidoxime.




**Scheme 2.** Mechanism for the formation of **3**.

reaction temperature, and stoichiometry. The results are summarized in Table 1. As shown, the solvent exerts an important effect on the yield of product **3a**. When using 4 equiv of $Et_3N$ as a base and 1:2 mol ratio of benamidoxime to **2a**, the reaction was completed within 4 h at an ambient temperature in dichloromethane (DCM), furnishing product **3a** in 81% yield (Table 1, entry 4). In comparison, using acetonitrile, tetrahydrofuran, or acetone as a solvent, the reaction provided product **1c** in lower yields (Table 1, entries 1–3). Decreasing the mole ratio of benamidoxime to **2a** (from 1:2 to 1:1) led to a decrease in the yield of product **3a** (from 81% to 46%, Table 1, entries 4–6). However, increasing the mole ratio up to 1:2.5 has no apparent effect on the reaction outcome (Table 1, entry 8). While the reaction ratios of **1a**:**2a** from 1:1 to 1:2.5 afforded the product **3a** in 46–81%, the ratio 1:2 gave the best yield (Table 1, entry 4). Additional increasing of temperature led to no improvement in the yield (Table 1, entry 7). After the optimization study, in terms of the reaction yields the best reaction conditions were obtained as the following: 4 equiv of $Et_3N$ as a base, 1:2 mol ratio of benamidoxime to **2a**, DCM as a solvent, and at room temperature.

With optimized reaction conditions in hand, we turned our attention to the scope of the reaction with respect to the amidoximes. As shown in Table 2, a variety of amidoximes, derived from aromatic, and heteroaromatic and aliphatic nitriles[4i], are competent in the reaction. Especially, aryl amidoximes bearing either electron-withdrawing or electron-donating substituents on the phenyl ring all exhibited high reactivity to give the corresponding products in good to high yields. Electron-deficient aryl amidoximes such as 4-fuloro-(Table 2, entry 4), 4-chloro-(Table 2, entry 5), 4-bromo-(Table 2, entry 6), and 4-nitro-(Table 2, entry 9) benzamidoxime were giving the corresponding products 3-substituted aromatic N,N-dimethy-1,2,4-oxadiazole-5-amines in 72–76% yields. Similarly electron-rich aryl amidoximes, such as 4-methyl- and 4-methoxylbenzamidoxime provided the desired products in excellent yields (78%, 82%, Table 2, entries 2–3). Substitution at the *para*- or *meta*-position of the phenyl ring of aryl amidoximes did not interfere with their reactivity (Table 2, entries 6 and 7). It is noteworthy that *ortho*-position substituted aryl amidoximes, 2-bromo- and 2,6-dichlorobenamidoxime, also gave the desired products in satisfied yields (57% and 64%, Table 2, entries 8 and 10). Gratifyingly, the reaction displayed high yields for heteroaromatic amidoximes **1k**, **1l**, and **1m** (72%, 62%, and 75%, Table 2, entries 11–13). In addition, the fused-ring aryl amidoxime **1n** could also apply into this reaction with yielding product **3n** in moderate yield (32%, Table 2, entry 13). However, in the case of aliphatic amidoximes, due to the poor solubility of **1o** in DCM, acetone was used as the solvent instead of DCM. To our delight, products **3o** and **3p** were afforded in isolated yields of 40% and 56%, respectively (Table 2, entries 15, 16).

In order to explore the effect of structure of Vilsmeier salts on their reactivity and selectivity of corresponding products, we also examined a range of other symmetrical and unsymmetrical Vilsmeier salts in the reactions of them with benzamidoxime **1a** under the identical conditions. Experimental results are summarized in Table 3. Of interest is the result shown in entry 1, the ring-opening of cyclic Vilsmeier salt **2b** (2-chloro-1,3-dimethylimidazolium chloride or DMC) proceeded smoothly and gave 78% yield of product **3q** with a hexaalkylguanidinium cation. And an increase in the length of alkyl chains on dialkylamino groups, as we anticipated, apparently affected the reactivity of Vilsmeier salts **2**, such as compound **2c**, ultimately leading to give 40% yield (Table 3, entry 2). A same trend was also observed when unsymmetrical Vilsmeier salts **2d** and **2e** reacted with benzamidoxime **1a**; products **3q** and **3r**, isolated from their mixtures with product **3a**, were obtained in 42% and 45% yields respectively; however, product **3a** was only given in 12% and 14% yields respectively (Table 3,entries 3 and 4). For the substrate **2f**, however, the reaction did not give the expected product under the experimental conditions.

In our previous studies[8b], we found that 2-chloro-1,3-dimethylimidazolium chloride (DMC) could convert α-amino alcohols to guanidines instead of oxazolines; And, in this work, we successfully tapped the leaving dialkylamino group on DMC using DMC itself in the reaction of DMC and benzamidoxime, and synthesized product **3q** containing a guanidinium cation (Scheme 1). Based on the above results, a possible mechanism, as shown in Scheme 2, for this transformation is proposed: initially, the nucleophilic substitution between amidoxime **g** and Vilsmeier salt **h** leads to guanidine intermediate **A**; subsequently, intermediate **A** undergoes an intramolecular nucleophilic substitution and forms product **3** in which process the dialkylamino group as a leaving group forms a guanidine with remained DMC.

In summary, a novel approach, condensation of Vilsmeier salts and amidoximes, to access *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines, has been developed. By this approach, a broad range of *N*,*N*-dialkyl-1,2,4-oxadiazol-5-amines, including aromatic, and heteroaromatic and aliphatic substituents, can be synthesized in good to high yields (up to 82%) under mild reaction conditions. Future efforts will be devoted to extending the substrate scope and exploring the application of this method in the synthesis of structurally related bioactive molecules.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes


1. (a) Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421–2436; (b) Miryan, N.I. U.S.S.R. Patent, 770050, **1985**.; (c) Akira, M; Kazuya, S; Hideki, T; Akira, M; Kazutoshi, H; Takuma, O. Eur. Pat. Appl. EP 446010 A1 19910911, **1991**.
2. Grunwald, C.; Rundfeldt, C.; Lankau, H. J.; Arnold, T.; Hofgen, N.; Dost, R.; Egerland, U.; Hofmann, H. J.; Unverferth, K. *J. Med. Chem.* **2006**, *49*, 1855–1866.
3. Bokach, N. A.; Kukushkin, V. Y.; Haukka, M.; Pombeiro, A. J. L. *Eur. J. Inorg. Chem.* **2005**, *2005*, 845–853.
4. (a) Nishiwaki, N.; Kobiro, K.; Hirao, S.; Sawayama, J.; Saigo, K.; Ise, Y.; Okajima, Y.; Ariga, M. *Org. Biomol. Chem.* **2011**, *9*, 6750–6754; (b) Amarasinghe, K. K. D.; Maier, M. B.; Srivastava, A.; Gray, J. L. *Tetrahedron Lett.* **2006**, *47*, 3629–3631; (c) Du, W.; Truong, Q.; Qi, H.; Guo, Y.; Chobanian, H. R.; Hagmann, W. K.; Hale, J. J. *Tetrahedron Lett.* **2007**, *48*, 2231–2235; (d) Kurz, T.; Lolak, N.; Geffken, D. *Tetrahedron Lett.* **2007**, *48*, 2733–2735; (e) Augustine, J. K.; Akabote, V.; Hegde, S. G.; Alagarsamy, P. *J. Org. Chem.* **2009**, *74*, 5640–5643; (f) Ispikoudi, M.; Amvrazis, M.; Kontogiorgis, C.; Koumbis, A. E.; Litinas, K. E.; Hadjipavlou-Litina, D.; Fylaktakidou, K. C. *Eur. J. Med. Chem.* **2010**, *45*, 5635–5645; (g) Makara, G. M.; Schell, P.; Hanson, K.; Moccia, D. *Tetrahedron Lett.* **2002**, *43*, 5043–5045; (h) Nicolaidesa, D. N.; Litinasa, K. E.; Vrasidasa, I.; Fylaktakidoub, K. C. *J. Heterocycl. Chem.* **2004**, *41*, 499–503; (i) Hamze, A.; Hernandez, J. F.; Fulcrand, P.; Martinez, J. *J. Org. Chem.* **2003**, *68*, 7316–7321; (j) Buscemi, S.; Vivona, N.; Caronna, T. *J. Org. Chem.* **1996**, *61*, 8397–8401.
5. Kandre, S.; Bhagat, P. R.; Sharma, R.; Gupte, A. *Tetrahedron Lett.* **2013**, *54*, 3526–3529.
6. (a) Ispikoudi, M.; Litinas, K. E.; Fylaktakidoua, K. C. *Heterocycles* **2008**, *75*, 1321–1328; (b) Kawashima, E.; Tabei, K. *J. Heterocycl. Chem.* **1986**, *23*, 1657–1660; (c) Dürüst, Y.; Yıldırım, M.; Aycan, A. *J. Chem. Res.* **2008**, 235–239; (d) Adib, M.; Bagherzadeh, S.; Mahdavi, M.; Bijanzadeh, H. R. *Mendeleev Commun.* **2010**, *20*, 50–51; (e) Krasavin, M.; Rufanov, K. A.; Sosnov, A. V.; Karapetian, R.; Godovykh, E.; Soldatkina, O.; Lavrovsky, Y.; Gakh, A. A. *Chem. Cent. J.* **2010**, *4*, 4; (f) Eloy, F.; Lenaers, R. *Helv. Chim. Acta* **1966**, *49*, 1430–1432; (g) Matthew F. WO 2008/081204, **2008**.
7. Chennakrishnareddy, G.; Debasis, H.; Jayan, R.; Manjunatha, S. G. *Tetrahedron Lett.* **2011**, *52*, 6170–6173.
8. (a) Wang, Y.; Xin, X.; Liang, Y.; Lin, Y.; Duan, H.; Dong, D. *Adv. Synth. Catal.* **2009**, *351*, 2217–2223; (b) Jia, X. D.; Duan, H. F.; Lin, Y. J.; Cao, J. G.; Liang, D. P.; Luo, X. Y.; Jiang, F.; Gao, H.; Wu, M. C. *Chem. Res. Chinese U.* **2010**, *26*, 394–397.
9. (a) Kantlehner, W.; Edelmann, K.; Gissel, A.; Scherr, O.; Vetter, J.; Wezstein, M.; Ziegler, G.; Mezger, J.; Iliev, B. *Acta Chim. Slov.* **2009**, *56*, 612–621; (b) Kawamorita, S.; Miyazaki, T.; Iwai, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 12924–12927; (c) Zare, H.; Ghanbari, M. M.; Jamali, M.; Aboodi, A. *Chin. Chem. Lett.* **2012**, *23*, 883–886.