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Regioselective Synthesis of 3-Arylamino- and 5-Arylaminoisoxazoles from Enaminones

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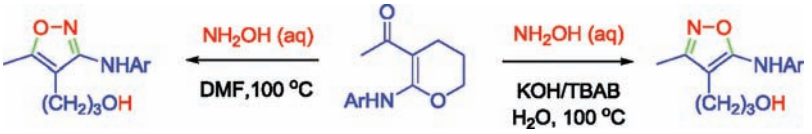
ABSTRACT



A highly regioselective synthesis of 3-arylamino- and 5-arylaminoisoxazoles from enaminones based on reaction condition selection is reported. 3-Arylaminoisoxazoles were produced by treating enaminones with aqueous hydroxylamine in DMF at 100 °C, whereas 5-arylaminoisoxazoles were synthesized by subjecting enaminones to aqueous hydroxylamine in the presence of KOH and TBAB in water under reflux. A mechanism for the regioselective synthesis of 3-arylamino- and 5-arylaminoisoxazoles is proposed.

The vast number of bioactive natural products and pharmaceutical drugs based on the isoxazole ring system,[1] such as valdecoxib, leflunomide, and cloxacillin, has become very important areas of research in natural product and pharmaceutical chemistry.[2] In addition, isoxazoles are widely used as key intermediates in the preparation of natural products and related structures.[3] So far, extensive work has generated many approaches for the synthesis of isoxazoles,[4] based on either (i) intermolecular [2 + 3] cycloadditions of 1,3-dipoles to alkynes[5] or (ii) condensations of hydroxylamine with β-diketone equivalent three carbon 1,3-electrophilic units bearing *sp* or sp^2 carbons, such as propargylic ketones, enones, and α,β-unsaturated nitriles.[6] However, the appealing generality of these methods is somewhat vitiated because of the frequent formation of a regioisomeric mixture of unsymmetrical isoxazoles in these reactions. Therefore, several elegant methods for the regioselective synthesis of isoxazoles have been reported by altering the electrophilicity of the terminal carbons in the C_3 units,[7] controlling the pH of the reaction medium and the reaction conditions,[8] or introducing bromo/benzotriazolyl moieties at the α-position of α,β-unsaturated ketones as the leaving groups that allow for the direct transformation

(1) (a) Lang, S. A.; Lin, Y.-I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. M., Potts, K. T., Eds.; Pergamon Press: New York, 1984; Vol. 6, p 61. (b) Sutharchanadevi, M.; Murugan, R. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U. K., 1996; Vol. 3, p 221. (c) Cicchi, S.; Cordero, F. M.; Giomi, D. *Prog. Heterocycl. Chem.* **2003**, *15*, 261.

(2) (a) Sperry, J.; Wright, D. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723. (b) Frolund, B.; Jorgensen, A. T.; Tagmose, L.; Stensbol, T. B.; Vestergaard, H. T.; Engblom, C.; Kristiansen, U.; Sanchez, C.; Krogsgaard-Larsen, P.; Liljefors, T. *J. Med. Chem.* **2002**, *45*, 2454. (c) Lee, Y.; Park, S.; Kim, B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1126.

(3) (a) Manning, J.; Davies, H. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (b) Baraldi, P.; Barco, A.; Benetti, S.; Pollini, G.; Simoni, D. *Synthesis* **1987**, 857.

(4) For reviews, see: (a) Jäger, V.; Colinas, P. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Ed.; Wiley: Hoboken, NJ, 2002; Vol. 59, p 361. (b) Wakefield, B. J. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Shaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol. 11, p 229. (c) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925.

(5) (a) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839. (b) Hansen, T. V.; Wu, P.; Fokin, V. V. *J. Org. Chem.* **2005**, *70*, 7761.

(6) (a) Bandiera, T.; Grünanger, P.; Albini, F. M. *J. Heterocycl. Chem.* **1992**, *29*, 1423. (b) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203. (c) Vicentini, C. B.; Verones, A. C.; Poli, T.; Guarneri, M.; Giori, P.; Ferretti, V. *J. Hetercycl. Chem.* **1990**, *27*, 1481. (d) Cuadrado, P.; Gonzalez-Nogal, A. M.; Valero, R. *Tetrahedron* **2002**, *58*, 4975. (e) He, Y.; Lin, N.-H. *Synthesis* **1994**, 989. (f) Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015. (g) Nitz, T. J.; Volkots, D. L.; Aldous, D. J.; Oglesby, R. C. *J. Org. Chem.* **1994**, *59*, 5828.

(7) (a) Rahman, A.; Vishwakarama, J. N.; Yadav, R. D.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 247. (b) Rudorf, W. D.; Augustin, M. *J. Prakt. Chem.* **1978**, *320*, 585. (c) Dornow, A.; Dehmer, K. *Chem. Ber.* **1967**, *100*, 2577. (d) Gompper, R.; Topfl, W. *Chem. Ber.* **1962**, *95*, 2881.

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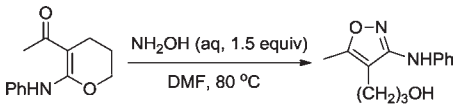
of the initially formed isoxazolines into the aromatic isoxazoles.[9] Neverthless, the development of new methods for the highly regioselective synthesis of isoxazoles from the same precursors is still a challenge for organic chemists.[10]

On the other hand, enaminones and related compounds possessing the conjugated system N—C=C—C=O are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.[11] During the course of our studies on the chemistry of enaminones, we developed efficient synthesis of pyrrolin-4-ones,[12] 2,3-dihydrofurans,[13] pyrimidin-4(3*H*)-ones,[14]pyridin-2(1*H*)-ones,[15] cyclophosphamides,[16] and pyranoquinolines[17] from various enaminones. In connection with these studies, we investigated the reactions of cyclic enaminones, 2-arylamino-3-acetyl-5,6-dihydro-4*H*-pyranes, with aqueous hydroxylamine under different conditions. As a result, we achieved regioselective synthesis of 3-arylamino- and 5-arylaminoisoxazoles by controlling the reaction conditions. Herein, we wish to report our preliminary results and present the involved mechanisms.

The substrates, cyclic enaminones **1**, were synthesized from commercially available *β*-oxo amides and 1,3-dibromopropane in excellent yields according to our published procedure.[15c] With substrates **1** in hand, we selected **1a** as the model compound to examine its behavior under different conditions. Upon treatment of **1a** with aqueous hydroxylamine (1.5 equiv) in DMF at 80 °C for 14.0 h, the reaction proceeded smoothly as indicated by TLC and furnished a white solid after workup and purification (column chromatography). The product was characterized as 3-[5-methyl-3-(phenylamino)isoxazol-4-yl]propan-1-ol **2a** (68% yield) on the basis of its spectral and analytical data (Scheme 1).

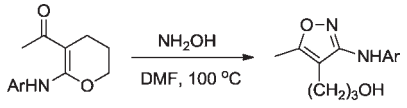
Scheme 1. Reaction of **1a** with NH_2OH in DMF



1a **2a**

The optimization of the reaction conditions, including reaction temperature, time and solvents, were then investigated. The reaction of **1a** with hydroxylamine could proceed in other solvents, such as C_2H_5OH, CH_3OH, and water, but the conversion was very low. When **1a** and hydroxylamine were subjected to water in the presence of TBAB under reflux, **2a** was obtained in 52% yield along with recovery of **1a** (33%). After a series of experiments, the optimal results could be obtained when the reaction of **1a** and aqueous hydroxylamine (1.5 equiv) were conducted in DMF at 100 °C for 12.0 h, whereby the yield of **2a** reached 83% (Table 1, entry 1).

Table 1. Reaction of Enaminones **1** with NH_2OH in DMF[a]



1 **2**

entry	**1**	Ar	**2**	yield[b] (%)
1	**1a**	C_6H_5	**2a**	83
2	**1b**	4-MeC_6H_4	**2b**	80
3	**1c**	4-$MeOC_6H_4$	**2c**	77
4	**1d**	4-ClC_6H_4	**2d**	86
5	**1e**	4-$CF_3C_6H_4$	**2e**	74
6	**1f**	2,4-$Me_2C_6H_3$	**2f**	79

[a] Reagents and conditions: **1** (1.0 mmol), NH_2OH (aq, 1.5 mmol), DMF (5 mL), 100 °C, 10.0–13.0 h. [b] Isolated yield.

Having established the optimal conditions for the ring-opening/recyclization process, we aimed to determine its scope with respect to the amide motif of cyclic enaminones **1**. Thus, a series of reactions of substrates **1b–f** and aqueous hydroxylamine was carried out under identical conditions as described for **2a** (Table 1, entry 1), and some of the results are summarized in Table 1. It was observed that all the reactions proceeded smoothly to afford the corresponding 3-arylaminoisoxazoles **2b–f** in moderate to good yields (Table 1, entries 2–6). In all these cases, the other regioisomeric products were not even detected. Therefore, we provided a facile regiospecific synthesis of 3-aminoisoxazoles of type **2**.

To gain insight into the mechanism of the ring-opening/recyclization reaction of **1**, a separate experiment was carried out. The reaction of **1d** and hydroxylamine (aq, 1.5 equiv) was performed at 70 °C for 1.5 h and then

(8) (a) Katritzky, A. R.; Barczynski, P.; Ostercamp, D. L.; Yousaf, T. I. *J. Org. Chem.* **1986**, *51*, 4037. (b) Jacobsen, N.; Kolind-Andersen, H.; Christensen, J. *Can. J. Chem.* **1984**, *62*, 1940. (c) Purkayastha, M. L.; Ila, H.; Junjappa, H. *Synthesis* **1989**, 20.

(9) (a) Borkhade, K. T.; Marathey, M. G. *Indian J. Chem.* **1970**, *8*, 796. (b) Kashima, C.; Yoshihara, N.; Shirai, S. I. *Heterocycles* **1981**, *16*, 145. (c) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787. (d) Kashima, C.; Shirai, S.-I.; Yoshiwara, N.; Omote, Y. *J. Chem. Soc. Chem., Commun.* **1980**, 826. (e) Kashima, C.; Yoshiwara, N.; Shirai, S.-I.; Omote, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 1455.

(10) (a) Sobenina, L. N.; Drichkov, V. N.; Mikhaleva, A. b. I.; Petrova, O. V.; Ushakov, I. A.; Trofimov, B. A. *Tetrahedron* **2005**, *61*, 4841. (b) Pavlik, J. W.; Lowell, J. A.; Ervithayasuporn, V. *J. Heterocycl. Chem.* **2005**, *42*, 1253.

(11) For reviews, see:(a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277. (b) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463. (c) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.

(12) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345.

(13) Zhang, R.; Liang, Y.; Zhou, G.; Wang, K.; Dong, D. *J. Org. Chem.* **2008**, *73*, 8089.

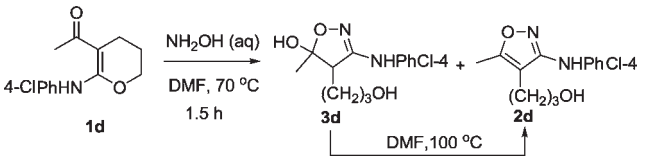
(14) Zhang, R.; Zhang, D.; Liang, Y.; Zhou, G.; Dong, D. *J. Org. Chem.* **2011**, *76*, 2880.

(15) (a) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504. (b) Zhang, R.; Zhang, D.; Liang, Y.; Dong, D. *Synthesis* **2009**, 2497. (c) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593.

(16) Xiang, D.; Huang, P.; Wang, K.; Zhou, G.; Liang, Y.; Dong, D. *Chem. Commun.* **2008**, 6236.

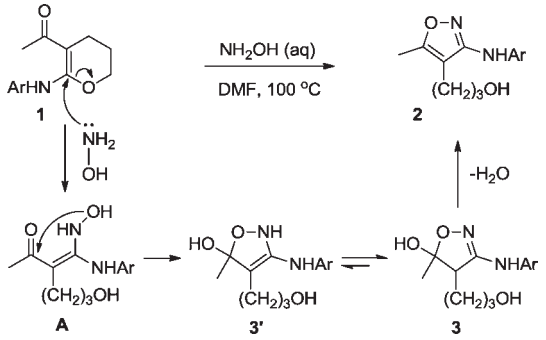
(17) Xiang, D.; Xin, X.; Liu, X.; Santosh, K.; Dong, D. *Synlett.* **2011**, 2187.

Scheme 2. Reaction of **1d** with NH_2OH in DMF



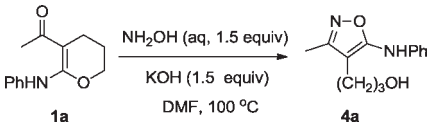
quenched with brine. A main product was obtained, which was characterized as 3-[(4-chlorophenyl)amino]-4-(3-hydroxypropyl)-5-methyl-4,5-dihydroisoxazol-5-ol **3d** in 65% yield; meanwhile, 3-aminoisoxazole **2d** was obtained in 12% yield (Scheme 2). It is worth noting that **3d** could be converted into **2d** in 94% yield upon treatment in DMF at 100 °C.

Scheme 3. Plausible Mechanism for the Synthesis of Isoxazoles **2** from Enaminones **1** and NH_2OH



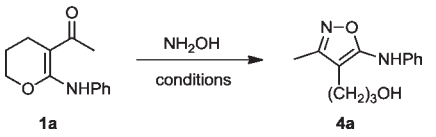
On the basis of the obtained results and our previously reported work,[12−16] a plausible mechanism for the synthesis of 3-aminoisoxazoles **2** is presented in Scheme 3. The ring-opening reaction of enaminone **1** is triggered by the attack of *N*-nucleophile, hydroxylamine, to generate intermediate **A**,[10a] followed by intramolecular cyclization to formation of intermediates **3′** and **3**,[8a,18] and subsequent elimination of a water molecule to afford isoxazole **2**.

Scheme 4. Reaction of **1a** with NH_2OH in DMF in the Presence of KOH



The above findings encouraged us to envisage that under appropriate conditions, the regioselective synthesis of 5-arylaminoisoxazoles may be realized. Thus, enaminone **1a** was treated with hydroxylamine (aq, 1.5 equiv) in DMF in the presence of KOH (1.5 equiv) at 100 °C. The reaction proceeded smoothly and furnished a product, after workup and purification by column chromatography, which was characterized as 3-[3-methyl-5-(phenylamino) isoxazol-4-yl]propan-1-ol **4a** (72% yield) on the basis of its spectral and analytical data (Scheme 4).

Table 2. Reaction of **1a** with NH_2OH under Different Conditions[a]



					yield[b] (%)	
entry	solvent	catalyst	temp (°C)	additive	**2a**	**4a**
1	DMF	none	100	KOH	0	72
2	EtOH	none	80	KOH	0	67
3	MeOH	none	65	KOH	0	64
4	H_2O	none	100	KOH	0	51
5	H_2O	TBAB	100	KOH	0	84
6	H_2O	TBAB	100	K_2CO_3	32	25
7	H_2O	TBAB	100	Et_3N	26	34
8	H_2O	TBAB	100	HCl	0	0

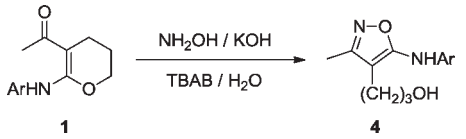
[a] Reagents: **1a** (1.0 mmol), NH_2OH (aq, 1.5 mmol), solvent (10 mL), catalyst (0.1 mmol), additive (1.5 mmol). [b] Isolated yields.

The optimization of the 5-arylaminoisoxazole synthesis, including reaction solvents, time, and base or acid as additive, was then investigated. With KOH as base, the reaction of **1a** could proceed in other solvents, such as EtOH, MeOH, or water (Table 2, entries 2−4). Interestingly, when **1a** was treated with hydroxylamine (aq, 1.5 equiv) in water in the presence of KOH (1.5 equiv) and phase transfer catalyst tetrabutylammonium bromide (TBAB, 0.1 equiv) at 100 °C, the reaction could furnish **4a** in 84% yield (Table 2, entry 5). However, in the presence of a weak base, such as K_2CO_3 or Et_3N, the reaction of **1a** formed a mixture, a pair of regioisomers **2a** and **4a** along with recovery of some intact starting material **1a** (Table 2, entries 6 and 7). No reaction was observed when aqueous HCl was employed instead of base (Table 2, entry 8).

Under the optimal conditions as for **4a** in Table 2, entry 5, a range of reactions of selected cyclic enaminones **1** were carried out, aiming to determine the scope of the 5-arylaminoisoxazole synthesis, and some of the results are summarized in Table 3. It was found that the reactions of **1b**−**i** bearing variable aryl amine groups could proceed efficiently to afford the corresponding 5-arylamino isoxazoles **2b**−**i** in moderate to good yields (Table 3, entries 2−8). It is worth mentioning that the structure of **4d** was elucidated by means of the X-ray single crystal analysis (Figure 1) and confirmed by its spectral and analytical data. Therefore, we provided a clean and convenient synthesis of 5-arylaminoisoxazoles based on the reaction of enaminones and

(18) Martins, M. A. P.; Beck, P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Blanco, R. F.; Peres, R.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2002**, *43*, 7005.

Table 3. Reaction of Enaminones **1** with NH_2OH in Water in the Presence of KOH[a]



1 **4**

entry	1	Ar	4	yield[b] (%)
1	**1a**	C_6H_5	**4a**	84
2	**1b**	4-MeC_6H_4	**4b**	81
3	**1c**	4-$MeOC_6H_4$	**4c**	77
4	**1d**	4-ClC_6H_4	**4d**	89
5	**1f**	2,4-$Me_2C_6H_3$	**4f**	80
6	**1g**	2-MeC_6H_4	**4g**	72
7	**1h**	2-ClC_6H_4	**4h**	83
8	**1i**	3-MeC_6H_4	**4i**	78

[a] Reagents and conditions: **1** (1.0 mmol), NH_2OH (aq, 1.5 mmol), H_2O (10 mL), TBAB (0.1 mol), KOH (1.5 mmol), 100 °C, 5.5–8.5 h. [b] Isolated yield.

hydroxylamine catalyzed by TBAB in the presence of KOH in water.

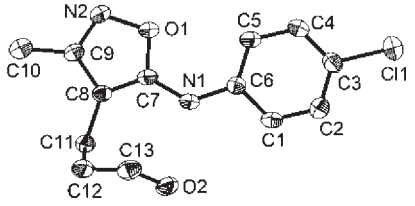
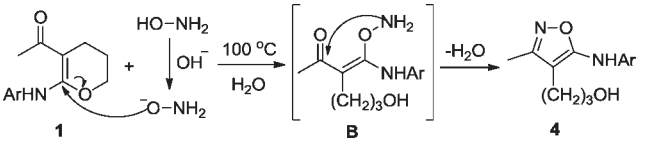


Figure 1. ORTEP drawing of **4d**.

On the basis of the above experimental results together with some literature studies, a plausible mechanism for the synthesis of 5-arylaminoisoxazoles **4** is presented in Scheme 5. In the presence of a strong base, aminohydroxy anion is formed,[19] which then, as an *O*-nucleophile, attacks the β-position of enaminone **1** to generate intermediate **B** via intermolecular nucleophilic vinylic substitution (S_NV) reaction,[10a] followed by an intramolecular cyclization to give 5-arylamino isoxazole **4** with elimination of a water molecule.[20]

Scheme 5. Plausible Mechanism for the Synthesis of Isoxazoles **4**



1 **B** **4**

In summary, we have developed a facile and efficient synthesis of 3-arylamino- and 5-arylaminoisoxazoles from readily available enaminones **1** in a highly regioselective manner by variation of the reaction conditions. This protocol is associated with readily available starting materials, mild conditions, good yields, high regioselectivity, flexible substitution patterns, and a wide range of synthetic potential of products. Further work on reaction mechanism and extension of the scope of the present protocol are currently underway in our laboratory.

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Supporting Information Available. Experimental details and analytical data for all new compounds, copies of ^1H and ^{13}C NMR spectra of **2**, **3**, and **4**, and CIF data for **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Kashima, C.; Yoshiwara, N.; Omote, Y. *Tetrahedron Lett*. **1982**, *23*, 2955.

(20) (a) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017. (b) Pavlik, J.; Lowell, J.; Ervithayasuporn, V. *J. Hetercycl. Chem*. **2005**, *42*, 1253. (c) Bonacorso, H.; Vezzosi, R.; Rodrigues, I.; Drekener, R.; Porte, L.; Flores, A.; Zanatta, N.; Martins, M. *J. Braz. Chem. Soc*. **2009**, *20*, 1370.