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Efficient and Regioselective One-Pot Synthesis of 3-Substituted and 3,5-Disubstituted Isoxazoles

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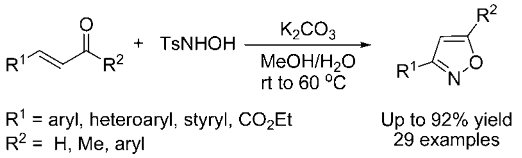
ABSTRACT



A series of 3-substituted and 3,5-disubstituted isoxazoles have been efficiently synthesized in moderate to excellent yields by the reaction of *N*-hydroxyl-4-toluenesulfonamide with α,*β*-unsaturated aldehydes/ketones. This novel strategy is associated with readily available starting materials, mild conditions, high regioselectivity, and wide scope.

The isoxazole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with vital medicinal value.[1] The development of new methods for their synthesis is therefore an area of considerable ongoing interest.[2−9]

In general, isoxazoles were obtained by two major routes:[2,3] [3 + 2] cycloaddition of alkenes/alkynes with nitrile oxides and the reaction of hydroxylamine with a three-carbon atom component. Recently, Fokin's group described a series of novel routes to 3,5- and 3,4-disubstituted isoxazoles through transition-metal-catalyzed [3 + 2] cycloaddition.[4] The reaction of α-acetylenic ketones, a three-carbon atom component, with methoxylamine to give highly substituted

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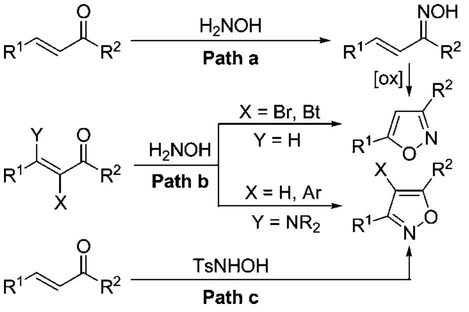
isoxazoles has also been introduced by Larock.[5] However, the development of new routes for the direct and highly regioselective synthesis of this kind of compounds from simple starting materials remains a challenge for organic chemists.

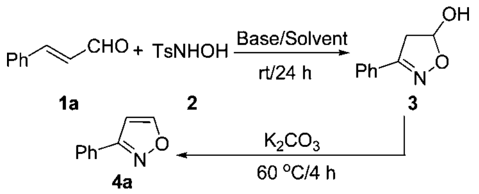
α,β-Unsaturated carbonyl compounds are widely used as the three-carbon atom component in the synthesis of isoxazoles.[2,6−8] Oxidation of α,β-unsaturated oximes to give 3,5-disubstituted isoxazoles has been reported on a small number of substrates (Scheme 1, path a).[6] The reaction of hydroxylamine with α,β-unsaturated carbonyl compounds bearing a leaving group is a very prevalent strategy to prepare these heterocycles in the literature (Scheme 1, path b).[7] 3,5-Diarylisoxazoles were also synthesized regioselectively by the reaction of chalcones with hydroxylamine hydrochloride using K_2CO_3 as solid support under microwave conditions.[8] However, these methods usually are of limited scope and use harsh conditions or starting materials which are not readily available. Thus, a simple and efficient method for synthesis of isoxazoles from readily available starting materials would be a welcome advance. In this paper, we report a simple, versatile, and regioselective methodology to access a wide array of 3-substituted and 3,5-disubstituted isoxazoles directly from α,β-unsaturated aldehydes/ketones and *N*-hydroxyl-4-toluenesulfonamide (TsNHOH)[10] **2** (Sheme 1, path c).

Scheme 1. Synthesis of Isoxazoles



Our initial study began with the reaction of cinnamaldehyde **1a** and TsNHOH **2** (Table 1). The 5- hydroxyl-3-phenylisoxazoline **3** was isolated in a low yield with no other products when **1a** and 1.0 equiv of **2** were treated with sodium methoxide in methanol (entry 1, 66% of the starting material was recovered). Since isoxazoline **3** can be conveniently converted to isoxazole **4a** by dehydration according to the literature,[11] we focused on optimizing the conditions to obtain **3**. When 4.0 equiv of **2** was used, we were pleased to find that the yield experienced a dramatic upgrade to 89% (entry 2). Then the yield was further optimized by varying the base and solvent.[12] After extensive screening of reaction conditions, we concluded that the most efficient set of conditions employs 1.0 equiv of **1**, 4.0 equiv of **2**, and 5.0 equiv of K_2CO_3 in MeOH/H_2O at room temperature (entry 5). Addition a small quantity of water was believed to be necessary as it could efficiently increase reaction rate. Under these conditions, product **3** was obtained in 92% yield, and we readily obtained **4a** in 79% total yield by treating **3** with K_2CO_3 under 60 °C in one pot.

Table 1. Optimization of Reaction Conditions from **1a** and **2**



entry[a]	base	solvent	yield of 3[b] (%)
1[c]	MeONa	MeOH	31
2	MeONa	MeOH	89
3	KOH	MeOH	61
4	K_2CO_3	MeOH	89
5[d,e]	K_2CO_3	MeOH/H_2O	92
6[d,e]	NaOH	MeOH/H_2O	86
7[d]	Na_2CO_3	MeOH/H_2O	43
8[d]	NaOAc	MeOH/H_2O	NR[f]
9	Et_3N	MeOH	46
10	DIPA	MeOH	37
11	K_2CO_3	CH_2Cl_2	NR[f]
12	K_2CO_3	THF	NR[f]
13	K_2CO_3	MeCN	trace

[a] General reaction conditions: **1a** (0.20 mmol), **2** (0.80 mmol), and base (1.00 mmol) in 2 mL of solvent. [b] Isolated yied based on **1a**. [c] **2** (0.20 mmol) and base (0.4 mmol). [d] MeOH (vol)/H_2O (vol) = 9:1. [e] Reaction time: 10 h. [f] NR= no reaction.

With the optimal experimental conditions, the scope of the isoxazole formation was explored using various enals. As shown in Table 2, the 3-substituted isoxazoles were readily obtained in moderate to excellent yields by this method. In general, substrates containing an electron-withdrawing group are more active and offer higher yields (entries 2, 5, and 7) and *ortho*-substituted substrates are less active and result in lower yields (entries 3, 6, 8, and 10).

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(12) Other *N*-hydroxylsulfonamides such as *N*-hydroxylbenzenesulfonamide or *N*-hydroxylmethanesulfonamide were also tried, but superior results were abtained with TsNHOH **2**.

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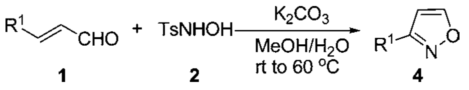
Table 2. 3-Substituted Isoxazoles Prepared from Enals



entry[a]	R^1	products	yield[b] (%)
1	**1a**, R^1 = Ph	**4a**	79
2[c]	**1b**, R^1 = 4-NO$_2$-C$_6$H$_4$	**4b**	88
4	**1d**, R^1 = 4-MeO-C$_6$H$_4$	**4d**	73
5	**1e**, R^1 = 4−Cl-C$_6$H$_4$	**4e**	85
6	**1f**, R^1 = 2−Cl-C$_6$H$_4$	**4f**	67
7	**1g**, R^1 = 4−Br-C$_6$H$_4$	**4g**	86
8	**1h**, R^1 = 2−Br-C$_6$H$_4$	**4h**	70
9	**1i**, R^1 = 4-Me-C$_6$H$_4$	**4i**	71
10	**1j**, R^1 = 2-Me-C$_6$H$_4$	**4j**	57
11[d]	**1k**, R^1 = 4-Me$_2$N-C$_6$H$_4$	**4k**	45
12	**1l**, R^1 = 2-furyl	**4l**	74
13[d]	**1m**, R^1 = styryl	**4m**	41
14[e]	**1n**, R^1 = EtO$_2$C	**4n**	50

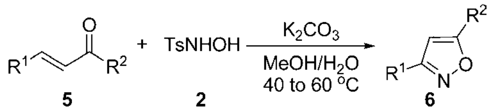
[a] General reaction conditions: **1** (0.20 mmol), **2** (0.80 mmol), and base (1.00 mmol) in 2 mL of solvent at rt, 10 h, then 60 °C, 4 h. [b] Isolated yield based on **1**. [c] rt, 1 h, then 60 °C, 1 h. [d] 40 °C, 2 days, then reflux, 24 h. [e] The product was synthesized by a two-step procedure; for details, see the Supporting Information.

However, no desired product was observed when the crotonaldehyde or acrolein was used as substrate. These differences indicated that an unsaturated carbon substituent attached to the 3-position of the aldehydes is necessary for this protocol. We then confirmed this hypothesis by using 3-vinylacrolein **1m** and 3-ester acrolein **1n** as substates. Under modified conditions, the desired products **4m** and **4n** were obtained, which were hard prepare by other methods (entries 13 and 14).[13f] In addition, heteroaromatic-substituted acrolein **1l** was also tolerable in this procedure to give good yield (entry 12).

It is worthwhile to point out that the synthesis of 3-substituted isoxazoles has been scarcely reported in the literature; the few methods involve [3 + 2] cycloaddition of an acetylene equivalent,[11a,13a−c] use of Grubbs catalyst,[13d] or the use of reagents that are not readily available.[13e,f] Obviously, our novel strategy provides a more simple and facile route to this type of compounds.

The same sequence can be applied to enones as well, affording the 3,5-disubstituted isoxazoles regiospecificly in 42−92% yields (Table 3, entries 1−13). However, because of the lower activity compared to enals, preparation of 3,5-disubstituted isoxazoles from enones required higher temperature and longer reaction time. Heteroaromatic substituted chalcones were shown as good substrates for this reaction (entries 10 and 11). Previously, **6k** had been prepared as one of the two regioisomers from the reaction between 1-(2-pyridyl)-3-phenyl-1,3-propanedione and hydroxylamine,[14a,b] Suzuki coupling reaction of 2-(5-iodoisoxazol-3-yl)pyridine with phenylboronic acid,[14c] or a two-step procedure from 2-cinnamoylpyridine.[14d] 3-Vinyl- and 3-ester-substituted enones **5n**/**5o** were also suitable substrates as enals **1m**/**1n** for this procedure (entries 14 and 15).

Table 3. 3,5-Disubstituted Isoxazoles Prepared from Enones



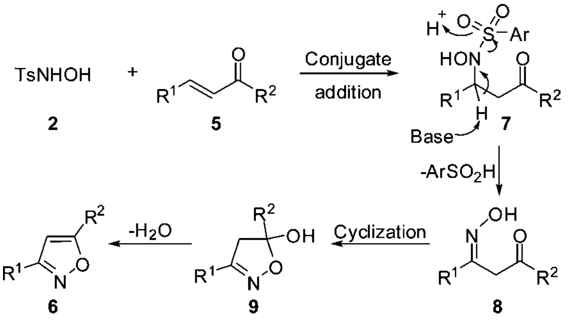
entry[a]	R^1, R^2	products	yield[b] (%)
1[c]	**5a**, R^1 = Ph, R^2 = Me	**6a**	75
2[c]	**5b**, R^1 = 4-Me-C$_6$H$_4$, R^2 = Me	**6b**	64
3	**5c**, R^1 = 4-NO$_2$-C$_6$H$_4$, R^2 = Me	**6c**	91
4	**5d**, R^1 = 4-Cl-C$_6$H$_4$, R^2 = Me	**6d**	72
5	**5e**, R^1 = 4-Br-C$_6$H$_4$, R^2 = Me	**6e**	69
6[c]	**5f**, R^1 = Ph, R^2 = Ph	**6f**	63
7[c]	**5g**, R^1 = 4-MeO-C$_6$H$_4$, R^2 = Ph	**6g**	59
8[c]	**5h**, R^1 = 4-Cl-C$_6$H$_4$, R^2 = Ph	**6h**	54
9[c]	**5i**, R^1 = 4-Br-C$_6$H$_4$, R^2 = Ph	**6i**	42
10	**5j**, R^1 = 2-furyl, R^2 = Ph	**6j**	71
11[d]	**5k**, R^1 = 2-pyridyl, R^2 = Ph	**6k**	82
12[d]	**5l**, R^1 = Ph, R^2 = 4-NO$_2$-C$_6$H$_4$	**6l**	44
13[d]	**5m**, R^1 = 4-Cl-C$_6$H$_4$, R^2 = 4-NO$_2$-C$_6$H$_4$	**6m**	92
14[e]	**5n**, R^1 = styryl, R^2 = Ph	**6n**	43
15[f]	**5o**, R^1 = EtO$_2$C, R^2 = Ph	**6o**	65

[a] General reaction conditions: **1** (0.20 mmol), **2** (1.50 mmol), and base (1.60 mmol) in 2 mL of solvent at 40 °C, 24 h, then 60 °C, 10 h. [b] Isolated yield based on **5**. [c] Some of the starting material was recovered, and yield was based on recovered starting materials; for details see the Supporting Information. [d] 40 °C, 10 h, then reflux, 4 h. [e] 40 °C, 2 days, then reflux, 24 h. [f] The product was synthesized by a two-step procedure; for details see the Supporting Information.

The reaction is highly regioselective. By comparison with previously reported data and by NMR studies, the products were determined to be 3-substituted and 3,5-disubstituted isoxazoles, and no regioisomers were formed in all cases.[15] This excellent result is attributed to the tosyl moiety, which renders the hydroxylamine's nitrogen atom more nucleophilic in conjugate addition.[10] Thus, the reaction pathway of our methodology was proposed as follows (Scheme 2):[2b,8,16] (a) conjugate addition adduct **7** was formed through the reaction of substrate **5** with *N*-hydroxylsulfonamide **2**; (b) elimination of tosyl moiety and cyclization to generate intermediate 5-hydroxylisoxazoline **9**; (c) dehydration of **9** to give product **6**.

In summary, an efficient and regioselective one-pot synthesis of 3-substituted and 3,5-disubstituted isoxazoles

Scheme 2. Proposed Reaction Pathway



has been developed from readily available α,β-unsaturated aldehydes/ketones under very mild conditions. The novel procedure involved regioselective conjugate addition, elimination of tosyl moiety, cyclization, and dehydration. Our new strategy presents step-economic construction of isoxazoles, especially 3-substituted isoxazoles which are not easy to prepare by other means. Moreover, utility of tosyl, which preformed as a good leaving group in the reaction, offered a great advantage in allowing **2** for the conjugate addition to afford the target regioselectively. Further investigations toward the related reaction, as well as the synthetic applications of this transformation, are currently underway in our laboratory.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For details, see the Supporting Information.

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