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A Versatile Entry to 3-Unsubstituted 2-Isoxazolines

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Abstract: A new catalytic method for the preparation of 3-unsubstituted 2-isoxazolines is reported. The isoxazolines are easily prepared from the aliphatic α,β-unsaturated aldehydes and simple oximes in the presence of an anilinium salt catalyst.

Key words: aldehydes, oximes, catalysis, heterocycles, isoxazoline

2-Isoxazoline heterocycles are typically and most conveniently prepared by the 1,3-dipolar cycloaddition between alkenes and nitrile oxides.[1] Other methods including the reaction of α,β-unsaturated carbonyl compounds with hydroxylamine salts have been employed but with limited success.[2] Due to the lack of good preparative methods, a very limited range of 3-unsubstituted compounds has been reported in the literature. The 1,3-cycloadditions of fulminic acid or silyl nitronates with activated olefins appear to be the only straightforward methods for the preparation of these compounds.[3,4] A single example of a reaction between hydroxyurea and crotonaldehyde to give 5-methyl-2-isoxazoline has been reported.[5] Recently, Pennicott el al. also disclosed a method for obtaining these compounds from *O*-propargylic hydroxylamines.[6] Herein we report a new catalytic method for the preparation of 3-unsubstituted 2-isoxazolines directly from α,β-unsaturated aldehydes and oximes. The reaction complements the existing methods nicely as it allows easy preparation of compounds bearing a nonstabilizing substituent at the 5-position of the heterocycle.

Recently, Jørgensen and co-workers published an enantioselective method for conjugate addition of oximes to α,β-unsaturated aldehydes.[7] During our own study of similar reactions, we encountered problems that arose from the reversibility of the addition. We anticipated that these problems could be circumvented by developing a catalyst that would cyclize the conjugate addition product directly to a more stable 2-isoxazoline. The work of Jaquier et al.[5] and the recent communication by the Dawson group[8] suggested that this could be well achieved using a suitable amine salt that would be able to catalyze both the conjugate addition and the cyclization step.

Initially, we chose to examine the reaction between 2-hexenal **8** and acetone oxime **9a** in the presence different amine salts. Acetone oxime was chosen as the oxime partner due to its practical utility and sensitivity towards hydrolysis.[9] Table 1 shows the NMR yield of **10** after 3 hours when different combinations of bases and acids were employed as catalysts. (Figure 1)

Screens quickly revealed that the desired reaction could indeed be achieved and both the acid and the base played a significant role in the process. The reaction proceeded

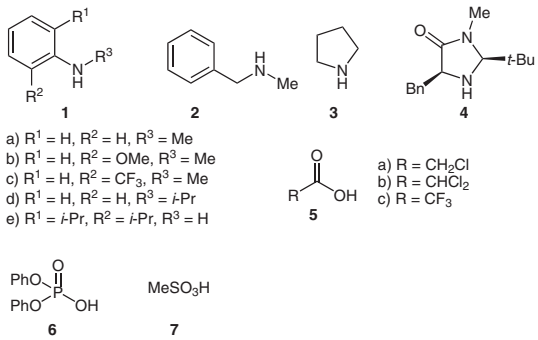
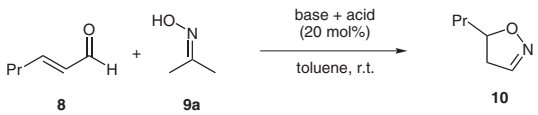


Figure 1 Selected amines and acids used in the catalyst screening

Table 1 Screen of Different Base and Acid Combinations in the 2-Isoxazoline Formation [a]



	Acid (Yield of **10**, %)				
Base	**5a**	**5b**	**5c**	**6**	**7**
1a	8	35	48	76	38
1b			42	46	
1c			61	45	
1d			51	31	
1e			69	43	
2			23	16	
3			11	10	
4	0	29	57	74	38

[a] The reactions were performed by mixing aldehyde (0.24 mmol), oxime (0.2 mmol), base (0.04 mmol), and acid (0.04 mmol) in toluene (1 mL) at r.t. NMR yield of **10** after 3 h is given. 4-Bromoanisole or 3,5-bis(trifluoromethyl)bromobenzene were used as internal standards.

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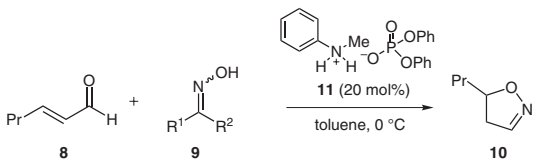
efficiently only when acids and bases of suitable pK_a and pK_{aH} value were employed. Different *N*-alkylanilines together with trifluoroacetic acid or diphenylphosphate (DPP) gave the best results. The imidazolidinone base **4** was also very efficient in promoting the reaction with the same acids. However, only racemic products were obtained in these conditions, and as such we decided to focus on cheaper and simpler alternatives, particularly on the *N*-methylaniline (**1a**). After solvent screens, toluene emerged as the solvent of choice for the reaction, although other nonpolar solvents, such as chlorinated hydrocarbons or dioxane may also be used. In temperature screens, running the reaction at 0 °C gave optimal results.

Selection of the oxime reagent significantly affects the reaction rate. In general, small, low-molecular-weight oximes are ideal starting materials, since the parent ketone is easy to separate afterwards from the reaction mixture. Various oximes turned out to be reactive in the conditions developed (Table 2). Of the oximes tested, diethylketone oxime **9c** possessed the best combination of reactivity, stability, and practical utility in our conditions. Most oximes, excluding the most sterically hindered compounds such as **9d**, are capable hydroxylamine donors for the reaction. It should be stressed that acetone oxime and acetaldehyde oxime may be viable alternatives when the product must be purified by distillation.[10]

The generality of the reaction was explored with a variety of α,β-unsaturated aldehydes (Table 3).

Table 2 Oxime Screen for Isoxazoline Synthesis



8 9 10

Oxime	R^1	R^2	NMR yield (%)[a]
9a	Me	Me	74
9b	-$(CH_2)_4$-		38
9c	Et	Et	78
9d	*t*-Bu	Me	0
9e	Ph	Me	4
9f	Me	H	46
9g	Ph	H	19
9h	4-$MeOC_6H_4$	H	22
9i	4-$NO_2C_6H_4$	H	8
9j	PhHC=CH	H	34

[a] The reactions were performed with aldehyde (0.24 mmol), oxime (0.2 mmol), and aniline salt **11** (0.04 mmol) in toluene (1 mL) at 0 °C. NMR yield after 6 h is given.

The method appears to be fairly general, affording the 2-isoxazoline products in moderate to good yields. The conditions are also compatible with more sensitive functionalities (entries 4 and 8) and steric hindrance in the β-position is also tolerated (entry 5). However, in common with other O- and N-additions to unsaturated aldehydes, the method is limited to the use of aliphatic α,β-unsaturated aldehydes. Substrates with further conjugation in the β-position were unreactive. Employing α-acroleins as reaction partners also failed, even when salts of primary amine **1e** were used as catalysts.[11]

According to our hypothesis, the reaction mechanism involves an initial iminium-catalyzed conjugate addition of oxime to the α,β-unsaturated aldehyde followed by the cyclization step that proceeds through hydrolysis of the formed *O*-alkyloxime. In preliminary NMR studies, we have observed that the concentration of the conjugate addition product rises rapidly and then falls as the concentration of the 2-isoxazoline product rises.[12] However, the other mechanistic pathways, such as an oxime transfer between the aldehyde and the oxime, followed by an unfavorable 5-*endo*-trig cyclization, cannot be ruled out.[13]

Notably, the reaction can also be promoted by acid alone, in which case the reaction proceeds at a comparable rate to the amine-catalyzed reaction but only after an initial induction period. This behavior indicates that a new catalytic species is generated under these conditions.[14] This species could also play a role in our difficulties in obtaining enantioenriched products.[15]

In conclusion, we have developed a simple anilinium salt catalyzed method for the preparation of 5-substituted 2-isoxazolines from α,β-unsaturated aldehydes and readily available oximes. Our method complements the existing methods by enabling the preparation of a variety of 3-unsubstituted 2-isoxazolines, and requires no further stabilization at the 5-position of the heterocycle. Mechanistic studies to test our mechanistic hypothesis are under way and will be published later along with the full account of this work.

Acknowledgment

TEKES and Graduate School of Organic Chemistry and Chemical Biology are acknowledged for material and financial support. We thank Dr. Jari Koivisto for NMR assistance.

References and Notes

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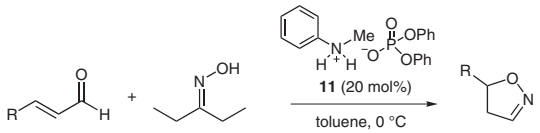
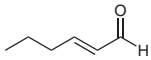
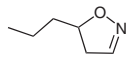
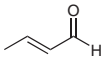
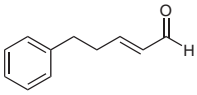
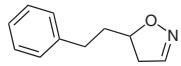
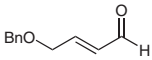
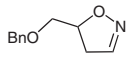
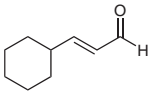
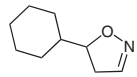
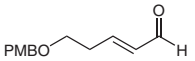
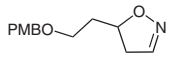
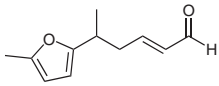
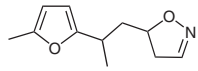
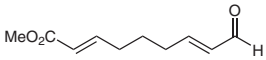
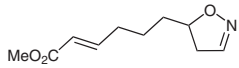
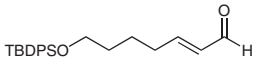
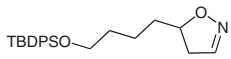
(3) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291.

Table 3 Synthesis of 2-Isoxazolines[17–21]



8 **9c** **10**

Entry		Aldehyde		Product	Time (h)	Yield (%)[a]
1	**8a**		**10a**		6	80[b]
2	**8b**		**10b**		6.5	55[c]
3	**8c**		**10c**		6.5	86
4	**8d**		**10d**		15.5	63
5	**8e**		**10e**		6.5	73
6	**8f**		**10f**		7	73
7	**8g**		**10g**		14.5	83[d]
8	**8h**		**10h**		15	73
9	**8i**		**10i**		7.5	82

[a] Yields refer to isolated and chromatographically purified products.
[b] NMR yield after 6 h is given.
[c] The reaction was performed in $CHCl_3$ using 10 mol% of **11** in 20 mmol scale using acetaldehyde oxime **9f** as oxime reactant. The yield refers to distilled product.
[d] 1:1 mixture of diastereomers.

(4) (a) Torssell, K.; Zeuthen, O. *Acta Chem. Scand. Ser. B* **1978**, *32*, 118. (b) Sharma, S. C.; Torssell, K. *Acta Chem. Scand. Ser. B* **1979**, *33*, 379. (c) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2247.
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(8) Dirksen, A.; Hackeng, T. M.; Dawson, P. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 7581.
(9) Acetone oxime has previously been used as a transoximation reagent. See: Juskowiak, M.; Krzyzanowski, P. *J. Prakt. Chem.* **1989**, *331*, 870.
(10) For the preparation of volatile **10a**, the use of acetaldehyde oxime under modified conditions is recommended. See ref. 21.
(11) Erkkilä, A.; Pihko, P. M.; Clarke, M.-R. *Adv. Synth. Catal.* **2007**, *349*, 802.
(12) In control experiments, the reaction products did not equilibrate to starting materials when exposed to the reaction conditions [e.g., 3-pentanone (30 mol%), catalyst (50 mol%), r.t., 3 h].
(13) A related reaction for the preparation of 3-substituted 2-isoxazolines from β,γ-unsaturated ketones has been proposed to follow this mechanism. See: Norman, A. L.; Shurrush, K. A.; Calleroz, A. T.; Mosher, M. D. *Tetrahedron Lett.* **2007**, *48*, 6849.
(14) We initially believed that this species is hydroxylamine. However, in control experiments, hydroxylammonium diphenylphosphate turned out to be relatively poor catalyst for the reaction, and exhibited a similar induction period than acid catalysts.
(15) Moderate enantioselectivities (up to 63%) could be obtained using a chiral imidazolidinone base along with strong acids

in colder temperatures. However, in these cases, the reaction rate and conversion were poor. Attempts to obtain enantioenriched products in the presence of chiral phosphoric acids failed. These studies will be reported separately.

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(17) **General Procedure for the Preparation of 2-Isoxazolines Using Diethylketone Oxime**
To a solution of amine salt **11** (37.1 mg, 0.1 mmol, 20.7 mol%) in toluene (2.5 mL) at 0 °C was added aldehyde (0.6 mmol, 120 mol%). After 4 min, diethylketone oxime (55 μL, 0.5 mmol, 100 mol%) was added and the mixture was stirred at 0 °C for the indicated period of time. The reaction mixture was diluted with Et_2O (15 mL), washed with sat. $NaHCO_3$ (5 mL), and 5% oxalic acid (2 × 5 mL). The layers were separated. The acidic and basic aqueous layers were back-extracted separately with Et_2O (2 × 6 mL and 5 mL, respectively). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to a volume of 1–2 mL. The residue was purified by column chromatography.

(18) **Analytical Data of Compound 10c**
Reaction time: 6.5 h; yield 0.076 g (86%); eluent: gradient: 10–30% MTBE in hexane; R_f = 0.35 (40% EtOAc in hexane). IR (film): 3062, 3026, 2924, 2589, 1600, 1495, 1454, 1275, 843 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2 H), 7.21–7.18 (m, 3 H), 7.12 (t, 1 H, J = 1.8 Hz), 4.52 (m, 1 H), 3.04 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 10.5 Hz, J_3 = 17.4 Hz), 2.80 (ddd, 1 H, J_1 = 5.6 Hz, J_2 = 9.5 Hz, J_3 = 13.9 Hz), 2.72 (ddd, 1 H, J_1 = 6.9 Hz, J_2 = 9.3 Hz, J_3 = 13.9 Hz), 2.62 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 7.8 Hz, J_3 = 17.4 Hz), 2.01 (dddd, 1 H, J_1 = 5.6 Hz, J_2 = 7.9 Hz, J_3 = 9.3 Hz, J_4 = 13.6 Hz), 1.83 (dddd, 1 H, J_1 = 5.2 Hz, J_2 = 6.9 Hz, J_3 = 9.5 Hz, J_4 = 13.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 145.9, 141.1, 128.5, 126.0, 77.8, 40.5, 36.9, 31.8. HRMS (ESI^+): *m/z* calcd for [$C_{11}H_{13}NO$ + H]: 176.1075; found: 176.1070.

(19) **Analytical Data of Compound 10d**
Reaction time: 15.5 h; yield 0.061 g (63%); eluent: 10–30% MTBE in hexane; R_f = 0.25 (50% EtOAc in hexane). IR (film): 3419, 3064, 3031, 2918, 2852, 1726, 1602, 1496, 1453, 1367, 1114, 1027, 838 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 7.12 (t, 1 H, J = 1.8 Hz), 4.71 (dtdd, 1 H, J_1 = 0.5 Hz, J_2 = 5.0 Hz, J_3 = 7.4 Hz, J_4 = 10.7 Hz), 4.58 (s, 2 H), 3.58 (dd, 1 H, J_1 = 5.0 Hz, J_2 = 10.4 Hz), 3.52 (dd, 1 H, J_1 = 5.0 Hz, J_2 = 10.4 Hz), 3.04 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 10.7 Hz, J_3 = 17.6 Hz), 2.90 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 7.4 Hz, J_3 = 17.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 137.8, 128.4, 127.71, 127.67, 77.1, 73.5, 70.7, 37.8. HRMS (ESI^+): *m/z* calcd for [$C_{11}H_{13}NO_2$ + H]: 192.1025; found: 192.1028.

(20) **Analytical Data of Compound 10h**
Reaction time: 15 h; yield 0.072 g (73%); eluent: gradient 50–65% MTBE in hexane; R_f = 0.23 (30% MTBE in hexane). IR (film): 2949, 2862, 2738, 1723, 1690, 1657, 1436, 1273, 1161, 1128, 974 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (t, 1 H, J = 1.7 Hz), 6.93 (td, 1 H, J_1 = 7.0 Hz, J_2 = 15.6 Hz), 5.82 (td, 1 H, J_1 = 1.6 Hz, J_2 = 15.6 Hz), 4.50 (m, 1 H), 3.70 (s, 3 H), 3.05 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 10.5 Hz, J_3 = 17.4 Hz), 2.60 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 7.9 Hz, J_3 = 17.4 Hz), 2.25 (m, 2 H), 1.72–1.47 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 148.6, 145.8, 121.4, 78.2, 51.4, 40.5, 34.5, 31.8, 24.0. HRMS (ESI^+): *m/z* calcd for [$C_{10}H_{15}NO_3$ + Na]: 220.0950; found: 220.0946.

(21) **Synthesis of Compound 10b**
To a solution of salt **11** (0.743 g, 2.08 mmol, 10.4 mol%) in $CHCl_3$ (50 mL) at 0 °C was added crotonaldehyde (1.99 mL, 24 mmol, 120 mol%). After 6 min, acetaldehyde oxime (1.23 mL, 20 mmol, 100 mol%) was added. The ice bath was removed and the reaction mixture was stirred at r.t. After 6 h, the reaction mixture was washed with 10% oxalic acid solution (10 mL) and then with 5% oxalic acid (30 mL, 20 mL). Hexanes (10 mL) was added[22] and the layers were separated. The organic layer was washed with sat. $NaHCO_3$ (20 mL) and both acidic and basic aqueous phases were back-extracted separately with Et_2O (50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated by distillation. The dark brown residue was distilled under reduced pressure (15 mmHg, water-aspirator vacuum) to give 0.871 g (51%) of **10b** as colorless liquid (purity >95% by ^1H NMR).
Analytical Data of Compound 10b
Bp 52 °C/15 mmHg (lit. 65 °C/25 mmHg);[16] R_f = 0.57 (50% EtOAc in hexane, $KMnO_4$ stain). IR (film): 2976, 2918, 1680, 1641, 1599, 1438, 1379, 1275, 843 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (br s, 1 H), 4.71–4.60 (m, 1 H), 3.07 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 10.3 Hz, J_3 = 17.3 Hz), 2.57 (ddd, 1 H, J_1 = 1.8 Hz, J_2 = 7.7 Hz, J_3 = 17.3 Hz), 1.32 (d, 3 H, J = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 74.8, 42.0, 20.7. HRMS (ESI^+): *m/z* calcd for [C_4H_7NO – H]: 84.0449; found: 84.0453.

(22) The catalyst is highly soluble in chlorinated solvents, but less soluble in hydrocarbons. Addition of hexanes assists in catalyst removal. The same yield has also been obtained in 50 mmol scale by direct distillation of the reaction mixture, without attempts to remove the catalyst components.