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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6849–6851

A tandem oximation–cyclization route to Δ^2-isoxazolines

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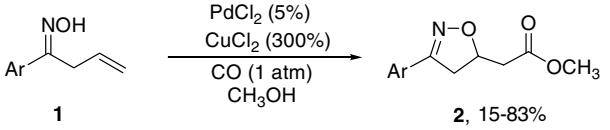
Received 25 January 2007; revised 18 July 2007; accepted 23 July 2007
Available online 27 July 2007

Abstract—3,5-Disubstituted Δ^2-isoxazolines can be prepared from the corresponding β,γ-unsaturated ketones by treatment with hydroxylamine hydrochloride and sodium hydroxide. Evidence indicates that the mechanism of this reaction involves the formation of three intermediates; oximation of the ketone, rearrangement of the alkene, and intramolecular Michael addition of the resulting α,β-unsaturated oxime.

ISO-1 (an antagonist of the proinflammatory cytokine MIF and a potential therapeutic agent for Type 1 diabetes;[1] see Scheme 1: **2**, Ar = *p*-HOPh) has been prepared via the 1,3-dipolar cycloaddition of a nitrile oxide with an appropriately substituted alkene.[2] While the 1,3-dipolar cycloaddition provides a convenient and rapid route to this general class of compound, we envisioned an alternate route to ISO-1, and to the preparation of the Δ^2-isoxazoline ring system in general, via a palladium-mediated nucleometalation/methoxycarbonylation reaction (Scheme 1). We have recently shown[3] that this reaction provides the desired isoxazolines (including ISO-1) in good yield and with complete regiochemical control during the ring closing step. The reaction, as evidenced by the location of the ester functionality in the product, most likely proceeds via a favored 5-exo-trig ring closure to form the isoxazoline ring system.

During the preparation of the β,γ-unsaturated oximes (**1**) used in that study, we noticed two interesting, and unexpected, outcomes. The first of those outcomes was



1 **2**, 15-83%

Scheme 1. Palladium-mediated formation of the Δ^2-isoxazoline ring.

realized during the pyridinium chlorochromate (PCC)[4] oxidation of the corresponding 1-aryl-3-buten-1-ols. In every case examined, the product mixture was found, by spectroscopic methods, to contain 1–10% of the original aromatic aldehyde. For example, PCC oxidation of 1-phenyl-3-buten-1-ol gave benzaldehyde (7%) and 1-phenyl-3-buten-1-one (90%). Apparently, the formation of the aldehyde arises via a Cope-type rearrangement of the 3-buten-1-ol functionality in the course of the oxidation.[5] Attempts to eliminate the formation of this byproduct by buffering the PCC oxidation, changing the temperature of the reaction, and by other methods were entirely unsuccessful.

Briefly warming a 50% aqueous ethanol solution of the β,γ-unsaturated ketone made from the PCC oxidation of the corresponding alcohol with hydroxylamine hydrochloride and sodium acetate gave the expected oximes, **1**, in excellent yield after extractive isolation.[6] These oximes were subjected to the palladium-mediated reaction as previously described.[3] However, when sodium hydroxide was employed in the oximation reaction to liberate the free base of hydroxylamine, the corresponding 3-substituted-5-methyl-Δ^2-isoxazoline (**3**) was isolated as the major component of the product mixture (Scheme 2; Table 1). It was determined that 1.1 equiv of hydroxylamine hydrochloride and 2.1 equiv of sodium hydroxide produced the isoxazoline in optimum yield.[7] Many of these 3,5-disubstituted Δ^2-isoxazolines have been prepared previously by the 1,3-dipolar cycloaddition route.[8]

The byproducts of this reaction were isolated and identified spectroscopically in order to discern the

Keywords: Isoxazolines; Tandem reactions; Cyclization; Heterocycle synthesis.
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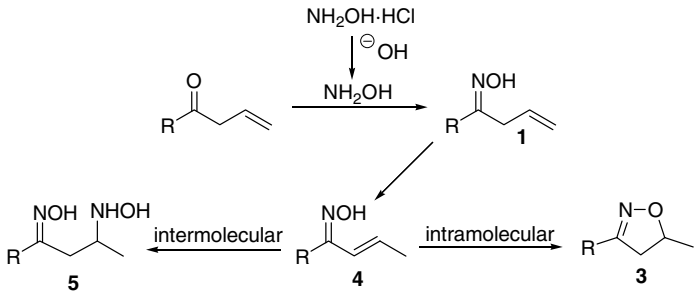
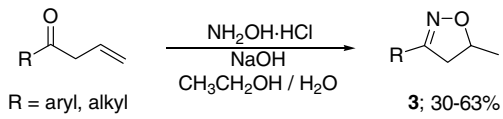
doi:10.1016/j.tetlet.2007.07.146



Scheme 2. Proposed steps in the title reaction.

Table 1. Hydroxide-mediated Tandem oximation/cyclization reaction



Compound	R	Yield (%)
3a	Ph	62
3b	*p*-MePh	54
3c	*p*-MeOPh	39
3d	1-Naphthyl	30
3e	2-Naphthyl	63
3f	2-Phenylethyl	37
3g	*n*-Pentyl	51

mechanism of this unexpected ring forming reaction. With reasonable mass balance (>95%), only the following compounds were isolated in yields that varied based on specific reaction conditions: the expected β,γ-unsaturated oxime (**1**), the rearranged α,β-unsaturated oxime (**4**), the product Δ^2-isoxazoline (**3**), and an interesting β-hydroxylamino oxime (**5**). The existence of the α,β-unsaturated oxime (**4**) and the β-hydroxylamino oxime (**5**) in the reaction mixture indicates that the mechanism of the reaction proceeds via oximation (ketone → **1**), rearrangement of the alkene into conjugation (**1** → **4**), and Michael addition[9] (**4** → **3**) to form the desired isoxazoline (**3**).

Additional evidence of this mechanism was obtained by subjecting **1** (R = Ph) to the conditions of the reaction.[7] The product isoxazoline, **3a** (R = Ph), and the byproducts **4** (R = Ph) and **5** (R = Ph), were identified in proportions similar to those of the reaction of the corresponding ketone with hydroxylamine and sodium hydroxide. In a similar fashion, the isolated α,β-unsaturated oxime, **4** (R = Ph), was also submitted to the reaction conditions[7] to yield the desired product Δ^2-isoxazoline (**3a**) in 62% yield.

To explore the scope of this reaction, a series of 1-alkyl and 1-aryl substituted 3-buten-1-ones was prepared from commercially available materials by the method described previously.[3] The ketones were then subjected to the hydroxide-driven oximation reaction (Table 1). In each case, the Δ^2-isoxazolines (**3**) were obtained as the major product of the reaction mixture, with a contribution of each of the byproducts (**1**, **4**, and **5**) mentioned earlier.

In summary, treatment of substituted 3-buten-1-ones with hydroxylamine hydrochloride and sodium hydroxide gives 3,5-disubstituted Δ^2-isoxazolines (**3**) as the major product of the reaction. The reaction is applicable to the preparation of compounds with both aliphatic and aryl substituents at C-3 of the isoxazoline ring. The variable yields appear to be indicative of both the disfavored 5-endo-trig ring closure and the fact that the overall reaction involves three separate mechanistic steps: oximation, rearrangement to the conjugated alkene, and ring closure via Michael addition. Current efforts to explore this tandem reaction are being concentrated on the capture of the anion generated by Michael addition and elucidation of the effect of steric bulk in the cyclization event.

Acknowledgments

The donors of the American Chemical Society Petroleum Research Fund (ACS PRF#40443-B1) are acknowledged for partial support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.146.

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7. *The general experimental procedure*: To a 50 mL round bottom flask were added hydroxylamine hydrochloride (3.2 mmol), 1.5 mL water, 1.5 mL absolute ethanol, and solid sodium hydroxide (6.4 mmol). The mixture was stirred at room temperature while the corresponding β,γ-unsaturated ketone (2.9 mmol) was added as a solution in aqueous ethanol. The roundbottom flask was then fitted with an air-cooled reflux condenser and the solution heated to reflux for 15–30 min. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with ethyl acetate (3×50 mL). The combined extracts were washed with water (2×50 mL), brine (1×50 mL), dried over $MgSO_4$, filtered, and the solvent removed by rotary evaporation. The product isoxazoline was isolated by radial chromatography (silica gel, 9:1 hexane–ethyl acetate). For example: 3-(4′-Methylphenyl)-5-methyl-Δ^2-isoxazoline (**3b**) was isolated in 54% yield: ^{1}H NMR ($CDCl_3$) in δ: 7.54 (d, $J = 8.1$ Hz, 2H); 7.19 (d, $J = 8.1$ Hz, 2H); 4.97 (dddd, $J = 8.4$, 7.5, 6.3, 4.2 Hz, 1H); 3.55 (dd, $J = 10.2$, 4.2 Hz, 1H); 3.46 (dd, $J = 16.5$, 7.5 Hz, 1H): 3.37 (dd, $J = 10.2$, 8.4 Hz, 1H); 3.29 (dd, $J = 16.5$, 6.3 Hz, 1H); 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$) in δ: 156.4, 140.3, 129.4, 127.1, 126.5, 77.3, 41.7, 21.4, 21.0. Anal. Calcd for $C_{11}H_{13}NO$, C, 75.40; H, 7.48; N, 7.99. Found: C, 75.19; H, 7.75; N, 7.60.
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