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A One-Pot Approach to Δ^2-Isoxazolines from Ketones and Arylacetylenes

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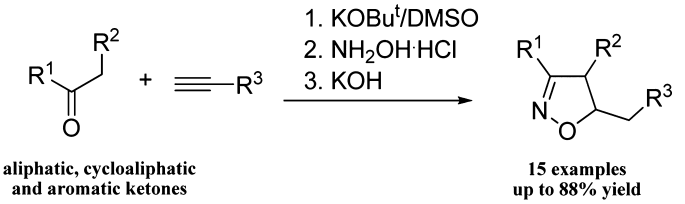
ABSTRACT



The sequential reaction of ketones with arylacetylenes and hydroxylamine in the presence of KOBu^t/DMSO followed by the treatment of the reaction mixture with H_2O and KOH leads to Δ^2-isoxazolines in up to 88% yield.

The Δ^2-isoxazoline structural unit is a frequently met active pharmacophore in numerous biologically important molecules including those possessing antifungal,[1] antibacterial,[2] antitubercular,[3] siderophore,[4] antidepressant,[5] and β-galactosidase inhibiting properties.[6] Some of them exhibit promising antiviral activity, e.g. toward hepatitis A and herpes.[7] Generally, Δ^2-isoxazolines are recognized as valuable building blocks in organic synthesis,[8] particularly as chiral ligands.[9] Along this line, they are readily convertible into diverse key synthetic structures such as β-amino acids,[10] β-hydroxy nitriles,[11] and β-hydroxy ketones.[12] The high reactivity of the N−O bond paves a short and easy route to pharmaceutically rewarding γ-aminoalcohols, known for their antitubercular activity.[13] Δ^2-Isoxazolines are also applied in the synthesis of natural products.[14] No wonder, the building up of a Δ^2-isoxazoline moiety invokes ever-growing synthetic efforts.

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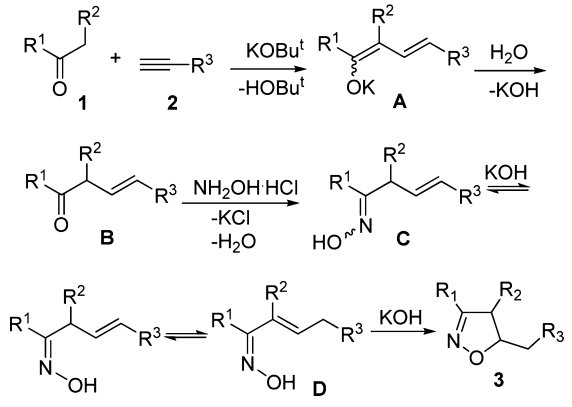
Commonly, isoxazoline derivatives are constructed by 1,3-dipolar cycloaddition of alkenes to nitrile oxides generated in situ by dehydration of nitro compounds[15] or dehydrogenation of oximes.[3b,15a,15b,16] 3-Acetyl- and 3-benzoyl isoxazolines were synthesized by the reaction of alkenes with acetone or acetophenone in the presence of $(NH_4)_2Ce(NO_3)_6$ or $(NH_4)_2Ce(NO_3)_5 \cdot 4H_2O$[17] involving the intermediate nitro ketones which were further oxidized to the nitrile oxides. Δ^2-Isoxazolines are also formed via base-catalyzed or catalyst-free cyclization of α,β-unsaturated ketones with hydroxylamine.[2,7,18] Isoxazolinylacetates were synthesized from oximes of β,γ-unsaturated ketones by their palladium-mediated nucleometalation/methoxycarbonylation.[19] The same oximes when subjected to palladium-catalyzed [$Pd(dba)_3$/phosphine/NaOBu^t] carboetherification together with arylbromides gave 3-aryl-5-benzyl Δ^2-isoxazolines.[20]

Here we report a new general one-pot strategy for the synthesis of 5-benzyl Δ^2-isoxazolines **3** from ketones **1** and arylacetylenes **2** (Table 1).

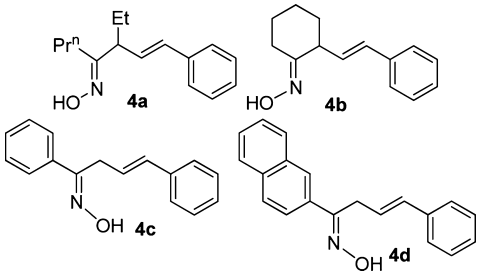
The overall reaction is implemented as follows: to the mixture of ketone **1** and arylacetylene **2** in the KOBu^t/DMSO system, kept at 100 °C for 30 min, water and hydroxylamine hydrochloride are added at 70 °C, and after 1.5−3.5 h the reaction mixture is treated with KOH at the same temperature (70 °C) for 30 min.

Apparently, the assembly of Δ^2-isoxazolines **3** comprises the following key steps (Scheme 1): the potassium dienolates **A**, the adducts of ketones to arylacetylenes,[21] react with $NH_2OH \cdot HCl$ to give the oximes of β,γ-unsaturated ketones **C** (via the intermediate formation of the corresponding ketones **B**) undergoing the final ring closure, likely via the preliminary prototropic rearrangement to oximes of the corresponding (*Z*)-α,β-unsaturated ketones **D**.

Scheme 1. Plausible Key Steps of One-Pot Assembly of 5-Benzyl Δ^2-Isoxazolines **3** from Ketones **1**, Acetylenes **2**, and Hydroxylamine



This rationale has been proven by the synthesis of oximes **C** (**4a**−**d**) from (*E*)-β,γ-unsaturated ketones **B**, isolated from the reaction mixture under the same conditions, and hydroxylamine hydrochloride. The oximes of dialkyl and cycloalkyl ketones (such as **4a,b**) are selectively formed as *E,E* isomers, while alkylaryl ketones are oximated to *Z,E* isomers (such as **4c,d**), also stereoselectively.



Oximes **4a**−**d** do readily cyclize to the corresponding Δ^2-isoxazolines thus confirming the easy isomerization of both the oxime (for oximes of *E,E* configuration) and β,γ-ethylenic moiety as the above rationale suggests.

As seen from Table 1, this strategy is effective for a great diversity of ketones **1** such as dialkyl (entries 1−4), cycloalkyl (entries 5−7), and alkylaryl (entries 8−15), as well as for a variety of arylacetylenes. Acylated condensed aromatics (entry 14) and fluorine derivatives (both ketones and acetylenes) fairly tolerate the reaction conditions and also afford the desired products in good yields (entries 10, 11, 13), thus proving the generality of the strategy elaborated. The variable yields appear to be indicative of the fact that as shown above the overall process involves at least five separate mechanistic steps (Scheme 1): addition of ketones to arylacetylenes, oximation of the resulted β,γ-unsaturated ketones, *E*→*Z* isomerization of the oximes (for oximes of alkyl- and cycloalkyl ketones), prototropic rearrangement of oximes of β,γ-unsaturated ketones to oximes of α,β-unsaturated ketones, and their final cyclization.

The synthetic meaning of the strategy developed is augmented by the fact that it allows preparation of 5-benzyl Δ^2-isoxazolines. The interest in the latter is growing rapidly because they are active against *Mycobacterium tuberculosis* $H_{37}Ra$ and $H_{37}Rv$[3b] and possess antistress activity in acute stress (AS) induced peripheral changes.[16] Also, they activate both estrogen receptor α and β (ERα, ERβ).[22] Currently, 5-benzyl-3-phenyl Δ^2-isoxazolines are synthesized by the traditional methods, e.g. hetero-Diels−Alder reactions of aromatic aldoximes with alkenes.[3b,16,22]

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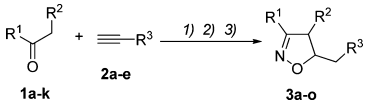
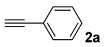
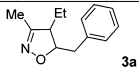
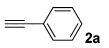
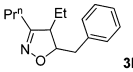
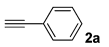
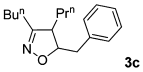
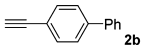
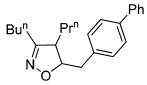
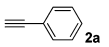
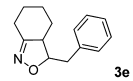
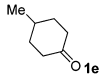
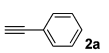
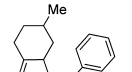
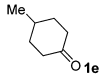
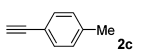
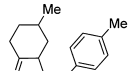
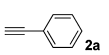
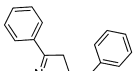
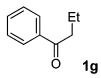
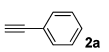
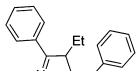
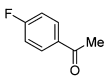
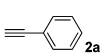
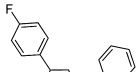
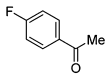
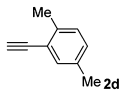
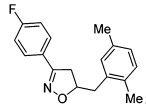
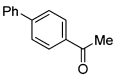
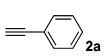
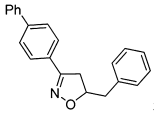
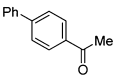
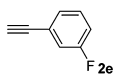
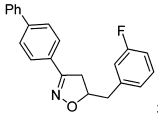
Table 1. One-Pot Synthesis of 5-Benzyl Δ^2-Isoxazolines **3** from Ketones **1** and Arylacetylenes **2**[a]



entry	ketone	acetylene	Δ^2-isoxazoline	yield (%)[b]
1	 1a	 2a	 3a	59
2	 1b	 2a	 3b	61
3	 1c	 2a	 3c	53
4	 1c	 2b	 3d	56
5	 1d	 2a	 3e	61
6	 1e	 2a	 3f	58
7	 1e	 2c	 3g	58
8	 1f	 2a	 3h	74
9	 1g	 2a	 3i	88
10	 1h	 2a	 3j	50
11	 1h	 2d	 3k	45
12	 1i	 2a	 3l	80
13	 1i	 2e	 3m	48
14	1j	2a	3n	65
15	1k	2a	3o	78

[a] Reagents and conditions: (1) ketone **1** (5 mmol), arylacetylene **2** (5 mmol), $KOBu^t$ (6 mmol), DMSO (10 mL), 100 °C, 30 min; (2) H_2O (5 mmol), $NH_2OH \cdot HCl$ (6 mmol), 70 °C, 1.5–3.5 h; (3) KOH (5 mmol), 70 °C, 30 min. [b] Isolated yield after column chromatography or recrystallization.

Therefore, involving other readily available starting materials such as ketones and arylacetylenes for the synthesis of 5-benzyl Δ^2-isoxazolines contributes considerably to their accessibility and structural variety.

In conclusion, a one-pot general strategy for the synthesis of 5-benzyl Δ^2-isoxazolines, synthetically and pharmaceutically important heterocycles, from ketones, arylacetylenes, and hydroxylamine has been developed. The strategy is applicable for the preparation of 5-benzyl Δ^2-isoxazolines with both aliphatic and aromatic substituents at C-3 of the isoxazoline ring due to the great variety of starting ketones controlling these substituents' structures.

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Supporting Information Available. Experimental procedure, characterization data, and copies of spectra for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

The authors declare no competing financial interest.