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Synthesis of 5-hydroxy-Δ^1-pyrrolines from aryl isoalkyl ketoximes and acetylene in a tuned superbase medium

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ABSTRACT

The reaction between aryl isoalkyl ketoximes and acetylene under atmospheric pressure was applied to the synthesis of 5-hydroxy-Δ^1-pyrrolines, containing aromatic substituents at the carbon–nitrogen double bond, in moderate yields. A crucial factor for the synthesis is the accurate tuning of the system basicity to prevent further dehydration of the target compounds to 3*H*-pyrroles.

Introduction

Δ^1-Pyrrolines are of interest due to their abundance in natural products[1] and living organisms.[2] Furthermore, a number of unnatural Δ^1-pyrrolines have been used as synthons for new drugs[3] and intermediates in the synthesis of biologically active compounds,[4] light-driven switches,[5] and boranil fluorophores.[6]

Despite the advances in methods to synthesize the Δ^1-pyrroline scaffold (e.g., by intramolecular cyclizations of bifunctional compounds and multi-component cyclizations,[7] 1,3-dipolar cycloadditions,[8] photo- and thermo-induced[9,10] reactions), the synthesis of hydroxy-substituted pyrrolines, particularly 5-hydroxy-Δ^1-pyrrolines (3,4-dihydro-2*H*-pyrrol-2-ols) with aromatic substituents, is much less developed. To date, only three preparative methods for their synthesis have been reported. The first based on the reaction between 1,4-diketones and liquid ammonia was put into practice by Sammes and co-workers[11] and was shown to be reliable in recent work.[12] Two other methods have been published recently, though they give access exclusively to condensed 5-hydroxypyrrolines[13] or 5-hydroxypyrroline-3,3-dicarbonitriles.[14] Other relevant examples are also known.[15] Among these is the reaction of isopropyl phenyl ketoxime with acetylene in the presence of NaOH in DMSO to afford 3,3-dimethyl-2-phenyl-5-hydroxypyrroline in 26% yield.[15e]

It is common knowledge that ketoximes having methyl and methylene substituents at the α-position to the oxime functional group react with acetylene in a KOH/DMSO system to give 1*H*-pyrroles (Trofimov's reaction[16]) via dehydration of the intermediate 5-hydroxypyrrolines, which can occur without acetylene. However, when using ketoximes with only one C–H bond adjacent to the oxime functional group, further vinylation of the hydroxy group with acetylene in pyrrolines **E** (Scheme 1) has been proven to be an imperative step in the assembly of the 3*H*-pyrrole core.[17]

It is assumed that 5-hydroxypyrrolines could be chemoselectively obtained (i.e., undesirable dehydration could be hindered) provided that the basicity of the MOH (M = Na, K)/DMSO superbase systems could be tuned to suppress their vinylation without significant hindrance of the preceding reaction steps.

Although only one representative of the hydroxypyrroline series, namely 3,3-dimethyl-2-phenyl-5-hydroxypyrroline, as an intermediate in the synthesis of 3*H*-pyrrole has been occasionally reported,[15e,17,18] the feasibility of a general synthesis of 5-hydroxypyrrolines from aryl(hetaryl) isoalkyl ketoximes and acetylene remained obscure. Our previous investigations provided a deeper insight[17] into the mechanism of 3*H*-pyrrole synthesis and allowed us to propose that these intermediates could be isolated as major products provided that the subsequent vinylation of the hydroxy group could be suppressed. Indeed, as shown herein, this goal is achievable by tuning the catalytic system so that the catalyst becomes inactive during the vinylation stage.

Due to the straightforward preparation of aromatic or heteroaromatic ketoximes with isoalkyl groups via acylation, this

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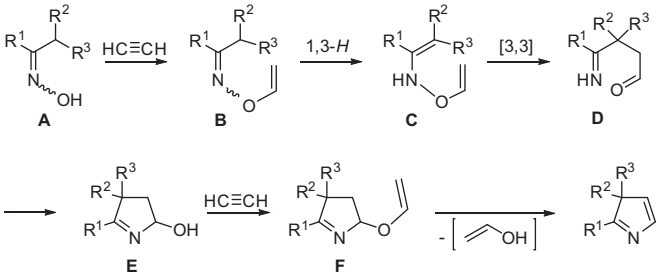


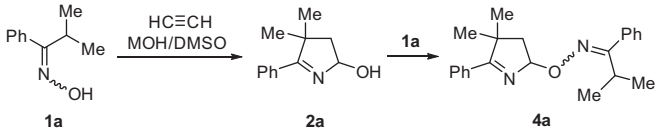
Scheme 1. 3*H*-Pyrrole synthesis from aryl(hetaryl) isoalkyl ketoximes and acetylene.

methodology has the potential to become the first general route to 5-hydroxypyrrolines with aromatic and heteroaromatic substituents at the carbon–nitrogen double bond.

Results and discussion

To prove this assumption, the reaction between isopropyl phenyl ketoxime **1a** and acetylene under atmospheric pressure was investigated as a model. The following variables were tested: type of superbase system, ketoxime: base molar ratio, water content, temperature, and time (Table 1).

Initial screening of the reaction conditions was carried out using the following parameters: 0.5 mol KOH·0.5H_2O, dry DMSO, 90 °C, 4 h. Under these conditions, mainly 3*H*-pyrrole **3a** was observed (entry 2). Decreasing the molar equivalents of base led to almost full prevention of ketoxime **1a** vinylation (entry 1). Subsequently increasing the water content in the reaction mixture completely suppressed 3*H*-pyrrole **3a** formation at acceptable conversions of ketoxime **1a** to the desired 5-hydroxypyrroline **2a** (entries 3 and 4). Longer reaction times or higher reaction temperatures facilitated both vinylation of ketoxime **1a** and dehydration of 5-hydroxypyrroline **2a** (via vinylation of **2a**, entries 5 and 7, respectively). The amount of 5-hydroxypyrroline **2a** in the crude reaction mixture was increased by changing the nature of the base (NaOH instead of KOH, entry 9) but due to the significant quantity of 3*H*-pyrrole **3a** which complicates the isolation of **2a**, the isolated yield of the former was lower compared to that in entry 4. The same was observed when 1 wt % of water to DMSO was used (entry 3).



Scheme 2. Reaction of ketoxime **1a** with 5-hydroxypyrroline **2a** during the work-up process.

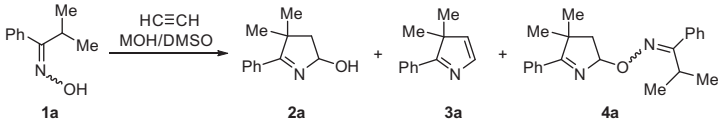
It should be noted that in the crude reaction mixture, along with expected products 5-hydroxypyroline **2a** and 3*H*-pyrrole **3a**, by-products such as 5-hydroxypyrroline ester **4a** and 4,4-dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone were also observed (earlier described[18b]). The former results from the reaction of the starting ketoxime **1a** with 5-hydroxypyrroline **2a** (Scheme 2), and is probably formed during the work-up procedure since ether **4a** was not detected by ^{1}H NMR of the reaction mixture.

To demonstrate the generality of this methodology aryl(hetaryl) isoalkyl ketoximes **1a**–**g** were tested in the reaction with acetylene under optimum conditions (0.5 mol KOH·0.5H_2O, 1 mol ketoxime, 2 wt % of water to DMSO, 90 °C, 4 h, Table 2).

As can be seen from Table 2, the one-pot synthesis of 5-hydroxypyrrolines was effective for various aryl (**1a**–**f**) substituted ketoximes providing the corresponding products in moderate yields. The reaction of 2-furylisopropyl ketoxime **1g** with acetylene proved to be more sensitive to base and hence this reaction needed to be further optimized. Under the standard conditions (0.5 equiv of KOH·0.5H_2O), mainly *O*-vinyl ketoxime **5g** was formed in 12% yield (Scheme 3), whereas at a higher base content (1.0 equiv of KOH·0.5H_2O), the crude reaction mixture represented an equimolar mixture of 5-hydroxypyrroline **2g**, starting ketoxime **1g** and 3*H*-pyrrole **3g**, from which the desired product **2g** was not easily isolated.

The synthesized compounds represent a potential useful family of building blocks, which owing to their hydroxy functional group may be widely employed for the design of diverse conjugated arene-pyrroline ensembles. This would require systematic investigation of the hydroxy functional group reactivity, which was not examined. Although it was reported[17] that 3,3-dimethyl-2-phenyl-5-hydroxypyrroline reacted with acetylene to give 3*H*-pyrrole, this transformation was mainly related to the mechanism of 3*H*-pyrrole formation. Another example is the formation of 2-phenyl-3,3-dimethylpyrroline[18a] and 4,4-dimethyl-5-phenyl-1-vinyl-

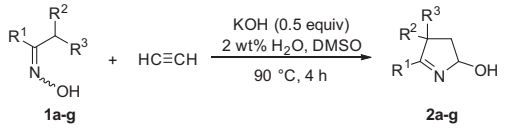
Table 1
Screening of reaction conditions for the selective synthesis of 5-hydroxypyrroline **2a**



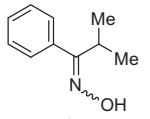
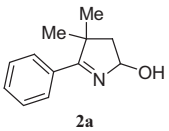
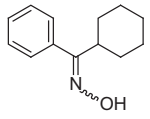
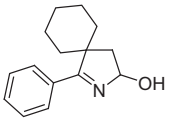
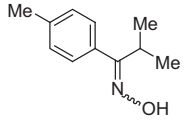
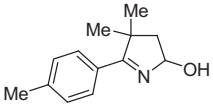
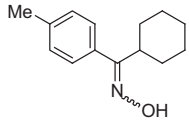
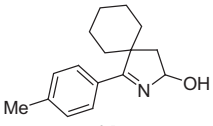
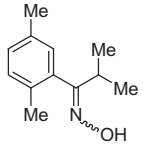
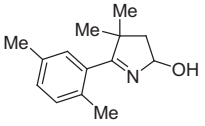
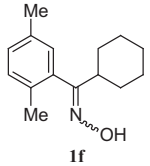
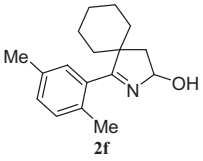
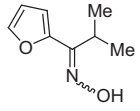
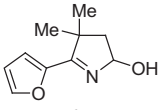
Entry	MOH, mol per 1 mol of ketoxime **1a**	Water content (wt % to DMSO)	Temperature (°C)	Time (h)	Ratio of **1a**:**2a**:**3a**:**4a**[a]
1	KOH·0.5H_2O, 0.25	0	90	4	92:2:0:6
2	KOH·0.5H_2O, 0.5	0	90	4	12:12:58:7[b]
3	KOH·0.5H_2O, 0.5	1	90	4	15:52 (23)[c]:29:4
4	KOH·0.5H_2O, 0.5	2	90	4	39:51 (44):0:10
5	KOH·0.5H_2O, 0.5	2	90	6	9:45 (11):32:10[b]
6	KOH·0.5H_2O, 0.5	2	80	4	65:22:0:13
7	KOH·0.5H_2O, 0.5	2	100	4	16:30:40:6[b]
8	NaOH, 1.0	0	90	4	21:31:40:6[b]
9	NaOH, 1.0	2	90	4	25:58 (32):12:5
10	NaOH, 1.0	3	90	4	55:29:5:11

[a] According to ^{1}H NMR data of the crude product.
[b] 4,4-Dimethyl-5-phenyl-1-vinyl-2-pyrrolidinone was detected.
[c] In brackets isolated yield of 5-hydroxypyrroline **2a**.

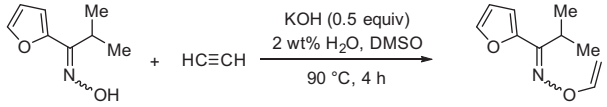
Table 2
One-pot synthesis of 5-hydroxypyrrolines **2a–g** from ketoximes **1a–g** and acetylene[a]



1a-g **2a-g**

Entry	Ketoxime **1**	5-Hydroxypyrroline **2**	Isolated yield (%)
1	 **1a**	 **2a**	44
2	 **1b**	 **2b**	35
3	 **1c**	 **2c**	31
4	 **1d**	 **2d**	29
5	 **1e**	 **2e**	31
6	 **1f**	 **2f**	38
7	 **1g**	 **2g**	See text

[a] Conditions: ketoxime **1** (12.50 mmol), KOH·0.5H_2O (0.406 g, 6.25 mmol), DMSO (50 mL), water (1.1 mL), acetylene under atmospheric pressure, 90 °C, 4 h.



1g **5g** (12%)

Scheme 3. Reaction of 2-furylisopropyl ketoxime **1g** with acetylene under standard conditions.

2-pyrrolidinone[18b] which was proposed to originate from the intermediate 3,3-dimethyl-2-phenyl-5-hydroxypyrroline without robust evidence.

Conclusions

In conclusion, we have shown that 5-hydroxy-Δ^1-pyrrolines, bearing aromatic substituents at the carbon–nitrogen double bond, can be synthesized in moderate yields by the straightforward reaction of the corresponding aryl isoalkyl ketoximes and acetylene in the presence of an appropriately tuned superbase KOH/DMSO system. Further investigations of the reaction scope and application of the compounds obtained as a pyrroline synthon are under way in our laboratory.

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The spectral data were obtained using the instrument park of Baikal Analytical Center.

Supplementary data

Supplementary data (synthetic procedure, characterization data, ^1H and ^{13}C NMR spectra of new products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.025.

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