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One-pot Alkynylation of Azaaryl Aldehydes and Spontaneous Base free Rearrangement into Enone Esters: an Autoinductive Mechanism

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Abstract: A direct synthesis of γ -oxo- α , β -unsaturated esters has been developed. When heteroaromatic aldehydes are reacted with deprotonated ethyl propiolate, in the presence of Me₂Zn or BuLi, the newly formed propargylic alcohol rearranged spontaneously to give the corresponding unsaturated keto-ester. Isotope labeling, allenol intermediate trapping and crossover experiments provided insight into the reactive sequence and suggest an autocatalytic mechanism.

Introduction

Chiral propargylic alcohols are important and versatile synthetic intermediates. They can be converted to a wide variety of chemical functions.^[1-7] Sato reported the first synthesis of enantiopure alkynyl alcohol by adding lithium trimethylsilyl acetylene in the presence of a chiral amino-alcohol.^[8] Later, Soai described the use of zinc-alkynyl complexes to access enantioenriched propargylic alcohols.^[9] Thereafter, several ligands have been used successfully for this reaction.[2-3, 10-15] The presence of different functional groups allows rapid diversification and large libraries of compounds can be prepared from this type of intermediates. They can also undergo cycloadditions with various substrates to yield complex structures.^{[[16-17]]} Propargylic alcohols can undergo isomerization to provide a, \beta-unsaturated carbonyl compounds. Such compounds represent a valuable and versatile class of synthetic intermediates in organic synthesis.

The isomerization process can occur through the Meyer-Schuster and Rupe rearrangement, in which a 1,3- or 1,2-shift of the hydroxyl group of the propargylic alcohol takes place, which usually require harsh acidic conditions.^[18-19] Secondary propargylic alcohols, in particular, can also isomerize into α , β -unsaturated carbonyl compounds through a redox isomerization. The first example of such an isomerization was reported by Nineham and Raphael in 1949, at high temperatures in the presence of Et₃N.^[20] Since then, other bases such as DABCO, KOH or NaHCO₃ have also been used in this reaction, promoting the rearrangement of secondary propargylic alcohols into enones.^[21-26] It is assumed that such rearrangement occurs via an allene intermediate.

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The same rearrangement has been observed on propargylic alcohols bearing a CF_3 group on the alkyne.^[27-28] Many other methods involving the use of transition metals such as Pd, Ru, Rh, Ir have been developed for the isomerization of propargylic alcohols to enones.^[29-33] All these methods require first forming and isolating the propargylic alcohol and then submitting it to the rearrangement conditions. However, in 2006, Wang et al. developed a one pot alkynylation-isomerization-alkynylation sequence for coupling aldehydes and alkynes without a transition metal catalyst for the synthesis of 1-en-4-yn-3-ols.^[34] The reaction was promoted by KO^tBu and provided a rapid access to (E)-1-en-4-yn-3-ol and (Z)-2-en-4-yn-1-ol compounds. However, the reaction was limited to substituted phenyl acetylenes. Moreover, the synthesis of heterocyclic chalcones accomplished from has been pyridine-2-carbaldehyde derivatives, secondary amines, and alkynes with CuNPs/C as catalyst.[35-36]



Scheme 1. Spontaneous redox isomerization.

We have recently reported on the use of the Soai's autocatalyst in the asymmetric alkynylation of azaaryl aldehydes with various zinc acetylinides.^[37-39] During our investigations, an interesting rearrangement was observed with electron deficient alkynes under the same reaction conditions, which gave rise to heteroaromatic enone. Such isomerization occurred spontaneously in situ without the addition of any base or transition metal. Herein, we report our preliminary mechanistic study of the direct formation of γ -oxo- α , β -unsaturated ester from heteroaromatic aldehydes.

Results and Discussion

When pyridine-2-carboxaldehyde was treated with the zinc anion of ethyl propiolate in the presence of an amino-alcohol, the expected propargylic alcohol was not obtained. Instead, the γ oxo- α , β -unsaturated ester **1** was isolated in 30% yield (Scheme 1). Notably, both Me₂Zn and *n*-BuLi can be used for the generation of the acetylinides. In some cases, this operation is simplified by *n*-BuLi providing cleaner reactions and shorter reaction times. However, in contrast to previously reported examples we noticed that in our case the use of a base was not

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required, although a catalytic amount of aminoalcohol is used to activate Me_2Zn , but only for the alkynylation step. Thus, various azaaryl aldehydes were considered to explore the scope of this rearrangement (Table 1).

 Table 1. Scope of direct alkynylation-isomerization.



[a] Isolated yields. [b] NMR yield.

When pyridine-3-carboxaldehyde was subjected to the reaction conditions, the propargylic alcohol 2 was the only product isolated (entry 1). The pyridine-4-carboxaldehyde gave the unsaturated keto-ester 3 as the sole product (entry 2). The

reaction with smaller size ring suggests that the presence of an available lone pair on the nitrogen atom, acting as a base, is crucial for the rearrangement. Indeed, pyrrole derivative turned the rearrangement off (entry 3). While 1-methyl-1H-imidazole-2carboxaldehyde generated only the rearranged product 5, although in low yield, no alkynol was observed (entry 4). The isomerization did not proceed with thiazole-5-carboxaldehyde, and stopped at the propargylic alcohol (entry 6), whereas the reaction with its regio-isomer thiazole-2-carboxaldehyde gave the keto-ester 6 (entry 5). Again, in absence of a nitrogen, no rearrangement was observed with thiophene-2-carboxaldehyde (entry 7). All together these observations confirm the role of the nature of aldehyde, but also the position of the nitrogen atom in the azaaryl ring (table 1, entries 1 and 6). Among other aldehydes with N-substituent, in the reaction of electron-poor 4nitrobenzaldehyde rearrangement product 9 was isolated in 28% vield (entry 8), alongside unidentified by-products. The reaction with electron-rich 4-dimethylamino-benzaldehyde, showed no sign of rearrangement (entry 9). While the reduced availability of the lone pair for NMe₂, delocalized in the benzene ring, may account for the absence of isomerization, the strong withdrawing NO₂ may lead to increased acidity of the proparquic C-H, prone for isomerisation.

Table 2. Effect of alkyne structure on direct isomerization of alkynols.



Other alkynes were examined under the standard conditions with pyridine-4-carboxaldehyde, which gave cleaner reactions than the 2-pyridine aldehyde (Table 2). No rearrangement was observed using phenyl acetylene and TMS-acetylene. However, compound **11** was unstable and decomposed after a few hours into unidentified compounds. Remarkably, the THP-protected propargyl alcohol rearranged *in-situ* into the corresponding enone **13**.

Work up conditions were also an important factor. Acccording to literature the rearrangement is *Z*-selective and hardly detectable by NMR analysis. The *Z*-isomer is prone to rapid isomerization into a thermodynamically favored *E*-isomer at elevated temperature in presence of base. We anticipated that keeping a basic environment during the work-up would trap the kinetic product, the first formed isomer (Table 3). Under a mild alkaline environment (entry 1) the *Z*-enone was isolated as the major isomer. However, work up at lower pH favored the *E*-enone up

to 2:1 ratio, suggesting an isomerization of Z to E under acidic conditions.



Entry	Proton source	Z:E Ratio ^a
1	Sat. NaHCO _{3 aq.}	82/18
2	H ₂ O	50/50
3	1N HCl _{aq.}	35/65
4	4N HCl in dioxane	33/67
^a NMR ratio on crude mixture		

Two different mechanisms have been proposed for this reaction. Isomerization of the propargylic alcohol **14**, through a 1,3-hydride shift leading to an allenol, has been invoked to account for this transformation. (Figure 1, a).^[34] Later the same year, Koide proposed another mechanism which starts with the deprotonation of alcohol **15** (Figure 1, b).^[22,23] The cumulene intermediate can be formed by resonance and is reprotonated at the terminal site to give the allene. Subsequently, a final allenol-enone tautomer exchange gives the unsaturated keto-ester **17**.



Figure 1. Mechanisms proposed by Wang and Koide.

Here, a direct application of Koide's mechanism shows some limitations in absence of additional amine in our system. In contrast, Biellman *et al.* reported that catalytic amounts of pyridine hydrochloride promoted isomerization of pyridine alkynol by ring activation at C-2 and C-4.^[40-41] Consequently, in our case, it is reasonable to envision two molecules of propargylic alcohols bearing a pyridine ring reacting with each other, one acting as the base to effect the isomerization, making the process *autocatalytic*. To identify some of the intermediates of the reaction pathway, the following reaction was visualized aiming at trapping the allenolate intermediate (Scheme 2): pyridine-2-carboxaldehyde was let to react with dimethylzinc and ethyl propiolate under standard conditions and analytical samples monitored the progress of the reaction. After complete reaction of starting materials, a second equivalent of aldehyde

was added. The only product isolated was identified as the β diketone **20**, which can only be attributed to the aldol reaction between the allenolate intermediate **18** and the pyridine-2carboxaldehyde in excess as second portion. Aldol adduct **19** was not isolated suggesting subsequent rearrangement immediately after the addition of the allenolate onto the aldehyde. We should also point that the trapping experiment was unsuccesfull with benzaldehyde.



Scheme 2. Evidence of a zinc allenoate and Deuterium-labelling experiment.

To gain further insight into the mechanism of this sequence of rearrangements, the same reaction was implemented starting from deuterated aldehyde. The D-pyridine-2-carboxaldehyde was prepared in two steps from ethyl picolinate and subjected to identical reaction conditions. The corresponding aldol adduct **21** was formed with different degrees of deuterium incorporation at the α and β positions with respect to the aldol group. Gratefully, the presence of the deuterium retarded the second rearrangement by virtue of a primary isotope effect, and we were able to isolate the product of the aldol reaction **21**, after flash chromatography, before rearranging into labeled β -diketone **22** (Scheme 2). Finally, compound **20** was isolated.



Scheme 3. Proposed mechanism for a two step rearrangement.

On the basis of the results described in scheme 2, we postulate a mechanism for the sequential rearrangement from alkynol to product **20** (Scheme 3). The pyridine within the product abstracts 4-H from **23** affording cumulene **24**, which is protonated at C2 by reaction with the protonated base to form allenoate (D)-**25**. This is supported by the observed deuterium at this position and the mechanism here is consistent with that suggested previously by Koide. In the following step, the formation of aldol compound (D)-**21** confirmed reaction of aldehyde with the intermediate (D)-**25** at C3. These results also rule out any aldol reaction of cumulene **24** at C2 with aldehyde. The second rearrangement occurs after work up presumably through the deprotonation of (D)-**21** at the picolinic position facilitated by resonance with the pyridine ring.

Abstraction of 4-H may also be effected by Me₂Zn or BuLi. However, this probability is ruled out on the basis of the observations made in scheme 2 and 3. Such transfer of deuterium atom from C4 to C2 would not be possible in such an irreversible process with a carbon base. To probe the autocatalytic mechanism a crossover reaction was devised. If this hypothesis is correct and the pyridine ring within the alkynol is the base, the isomerization may occur preferentially with resulting pyridine propargylic alcohol. Thus, an equimolar mixture of pyridine-4-carboxaldehyde and benzaldehyde was treated with an excess of nucleophilic ethyl propiolate. In contrast pyridine-2-carboxaldehyde, pyridine-4to carboxaldehyde has a more exposed N-atom and can act as a base by itself, but also in the product by preventing an intramolecular coordination in the metallated alkylol. Surprisingly, we isolated (E)-enone 3 derived from pyridine-4-carboxaldehyde along with unmodified alkynol 26 (Scheme 4). This indicates that the pyridine in neither the aldehyde nor the alkynol/enone is able to effect the deprotonation of 26. Again, remaining BuLi if any did not initiate isomerization of 26. Thus, the absence of isomerization with 26 is consistent with a self-induced isomerization into enone 3 presumably by formation of a homocomplex of pyridine-alkynols.

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Scheme 4. Cross-over reaction with benzaldehyde.

Conclusions

In summary, we have shown that the alkynylation of azaaryl aldehydes with ethyl propiolate generated propargylic alcohols which isomerized spontaneously into corresponding enones. We have gained significant mechanistic insight based on isotope labeling and were able to provide evidence for the putative allenolate intermediate by trapping it in an aldol-type reaction. The presence of the base within the alkynol product is crucial for the rearrangement, making the process autocatalytic. The conceptual novelty of this work could be integrated as a key step in related synthetic applications.

Experimental Section

See supporting information.

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Keywords: Alkyne addition • Raphael isomerisation • Enone esters • Rearrangement • Synthetic methods.

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Spontaneous Raphael rearrangement*

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Spontaneous rearrangement of heteroaromatic alkynols into enones involving an autocatalytic mechanism.

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