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Exploring the chemistry of isoxazol-5-ones: a divergent approach towards β-branched carbonyl compounds.[a]

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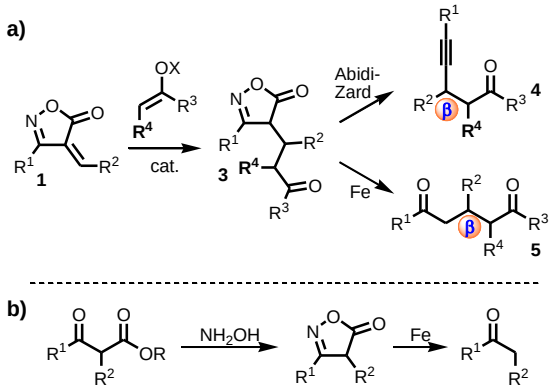
Introduction

Due to the common presence of β-branched carbonyl compounds in organic synthesis, the research for new methods to assemble these molecules is an important endeavor. In this context, we envisaged two new strategies to access such structures, by taking advantage of the chemistry of a rather underexplored class of heterocycle: isoxazol-5-ones.

In our first strategy, we were particularly interested in the synthesis of compounds containing the 3-substituted pent-4-yn-1-oyl moiety, which represents an interesting case-study of β-functionalized carbonyl compounds, due to its presence in natural products, drug candidates and numerous reactive intermediates. The development of this chemistry involves the Michael addition of enolates to alkylidene isoxazol-5-ones, followed by the Abidi-Zard nitrosative degradation, to unmask the alkyne structure (Scheme 1a).

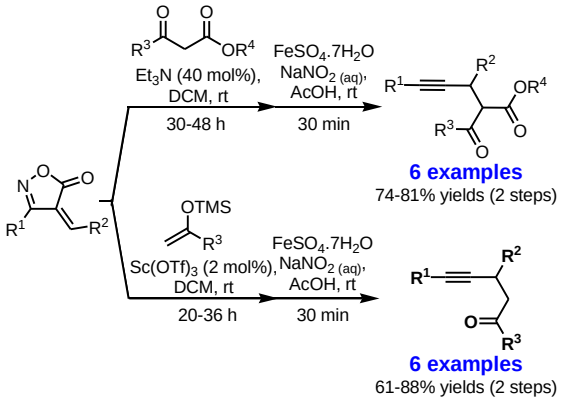
In our second strategy, we used alkylidene isoxazol-5-ones as a source for ketone functional groups, by employing iron as an inexpensive reducing agent (Scheme 1a). Interestingly, this last strategy allows the access to a new dealkoxycarboxylation protocol of β-ketoesters (Scheme 1b).



Scheme 1: a) Divergent approach to β-branched carbonyl compounds; b) A new entry to a dealkoxycarboxylation protocol of β-ketoesters.

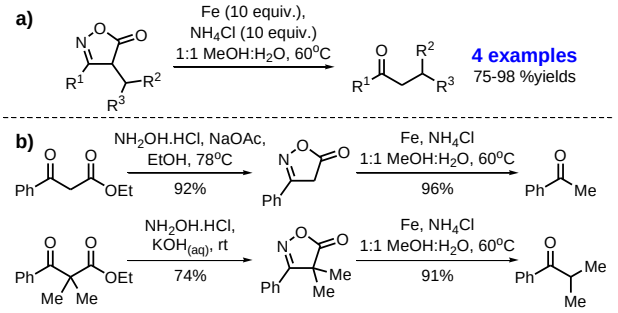
Results and Discussion

For the synthesis of β-substituted pent-4-yn-1-oyl compounds, we used both *in-situ* generated enolates, by the combination of Et_3N (40 mol%) and malonates or β-ketoesters; and preformed enolates, by the combination of $Sc(OTf)_3$ (2 mol%) and enol silyl ethers (Scheme 2).



Scheme 2: Synthesis of pent-4-yn-1-ones.

A decarboxylation approach employing isoxazol-5-ones was also established. In the presence of Fe, NH_4Cl and a 1:1 mixture H_2O:MeOH, under heating, this heterocycle decarboxylates to reveal a ketone functional group (Scheme 3a). We took advantage of this reactivity to disclose an unprecedented dealkoxycarboxylation of β-ketoesters (Scheme 3b).



Scheme3: a) Decarboxylation approach of isoxazol-5-ones. b) New dealkoxycarboxylation of β-ketoesters.

Conclusions

Isoxazol-5-ones are versatile motifs in organic chemistry. They serve as masked alkynes and ketone functional groups. One can also take advantage of such heterocycles to decarboxylate β-ketoesters.

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