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

Naylil M. R. Capreti (IC), Igor D. Jurberg (PQ)

Institute of Chemistry, State University of Campinas (Unicamp), 13083-970, C.P. 6154, Campinas, SP, Brazil.

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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 alkene 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 Et₃N (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, NH₄Cl and a 1:1 mixture H₂O: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).


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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