Organic LETTERS

Letter

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Michael Addition of Soft Carbon Nucleophiles to Alkylidene Isoxazol-5-ones: A Divergent Entry to β-Branched Carbonyl Compounds

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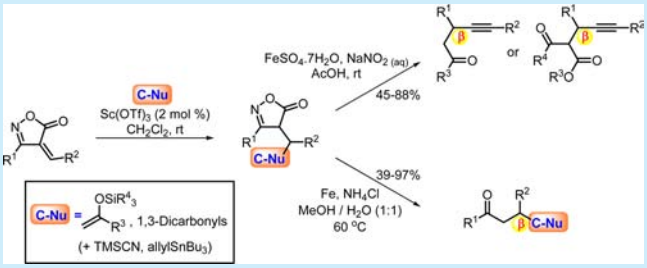
Supporting Information

ABSTRACT: A novel, divergent strategy toward the synthesis of β-branched (and linear) carbonyl compounds is developed by taking advantage of alkylidene isoxazol-5-ones as key building blocks. The yields obtained range from good to excellent, therefore making the described methods attractive options for building such molecules.



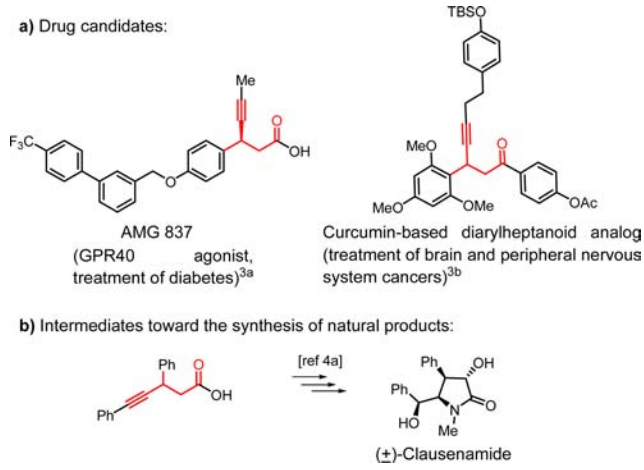
β-Branched carbonyl compounds are important motifs commonly employed en route to the synthesis of numerous complex structures.[1] The preparation of such compounds typically relies on a catalyzed conjugate addition of a nucleophile to a suitable Michael acceptor.[2] However, the use of such strategies can be eventually hampered by the lack of reactivity or incompatibility between the partners and the catalyst employed or by the difficulty in synthetically accessing either of the partners needed. Furthermore, the development of new strategies to build molecules is an extremely important endeavor in organic synthesis. This is not only a matter of intellectual exercise but also a way to expand the chemist's toolbox to tackle new problems.

In this regard, the assembly of 3-substituted pent-4-yn-1-oyl motifs can be seen as an emblematic case study of a β-branched carbonyl compound. Often, this is a fragment found in prominent candidate molecules tested as pharmaceuticals[3] and in building blocks employed toward natural products[4] (Scheme 1). Classically, the synthesis of such fragments involves the conjugate addition of metal acetylides to α,β-unsaturated carbonyl compounds. Numerous stoichiometric and catalytic, racemic, and enantioselective versions employing Al,[5] Zn,[6] Ru,[7] Rh,[8] and Cu,[9] among other agents,[10] have been described (Scheme 2, eq 1).

Herein, we report a new strategy toward these molecules, based on a rather underexplored transformation: the Zard alkynylation (Scheme 2, eq 2).[11] This transformation is particularly useful when coupled with the conjugate addition of nucleophiles to alkylidene isoxazol-5-ones, because it allows access to a highly modular route toward densely functionalized alkynes.[12]

With this mindset, we devised that the addition of silyl enol ethers **2** to alkylidene isoxazol-5-ones **1**, followed by the nitrosative degradation of the generated isoxazol-5-one intermediate **3**, can be a general valuable route toward pent-4-yn-1-oyl derivatives **4** (Scheme 2, eq 3).

Scheme 1. Examples of Compounds Containing the Pent-4-yn-1-oyl Motif Found in (a) Drug Candidates and in (b) Building Blocks toward Natural Products



Toward this goal, the addition of **2a** to **1a** was studied as a model reaction, thus leading to the functionalized isoxazol-5-one **3a**. A brief screening of different metal triflates revealed the pronounced activity of $Sc(OTf)_3$ as a catalyst (Table 1).

Once we had the optimal conditions for this transformation at hand, we demonstrated the viability of the subsequent alkynylation from **3a** to **4a**, which produced an 83% combined yield for two steps (Table 2, entry 1). At this moment, we were eager to investigate the scope of this new protocol.

We were pleased to find that when silyl enol ether **2a** is further treated with a number of alkylidene isoxazolones **1b−d**, followed by nitrosative degradation, the corresponding alkynes **4b−d** are always produced in good combined yields of 71−88%

Received: April 7, 2015
Published: April 30, 2015

DOI: 10.1021/acs.orglett.5b01004
Org. Lett. 2015, 17, 2490−2493

Scheme 2. General Picture: (a) Traditional Approach toward 3-Substituted Pent-4-yn-1-oyl Derivatives; (b) The Zard Alkynylation; (c) Our Proposed Synthetic Approach toward 3-Substituted Pent-4-yn-1-oyl Structures

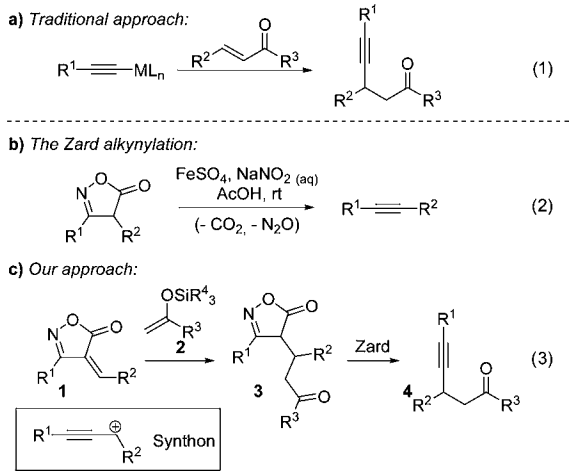
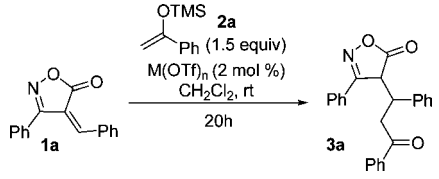


Table 1. Exploration of Metal Triflates



entry	$M(OTf)_n$	yield (%)[a]
1	–	9
2	$Zn(OTf)_2$	15
3	$Mg(OTf)_2$	20
4	$Sn(OTf)_2$	66
5	$Sc(OTf)_3$	90

[a]Estimated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

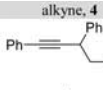
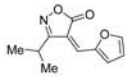
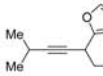
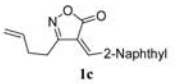
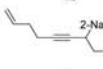
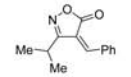
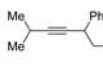
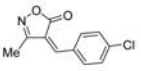
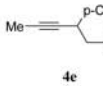
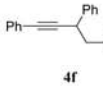
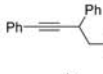
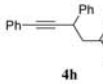
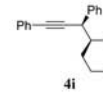
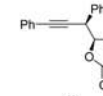
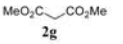
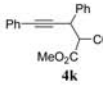
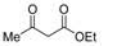
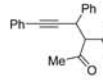
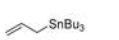
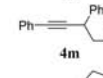
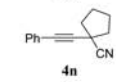
(Table 2, entries 2–4). In addition, numerous silyl enol ethers **2b–f** can be also efficiently employed as nucleophiles (Table 2, entries 5–10). Interestingly, not only ketones but also esters can be accessed by this methodology, as evidenced by the synthesis of **4h** in 74% yield (Table 2, entry 8). This reaction is found to be highly diastereoselective when cyclic silyl enol ether **2e** is employed (Table 2, entry 9). The relative stereochemistry of compound **4i** was assigned based on the X-ray single-crystal analysis of the isoxazol-5-one intermediate **3i**, which is also obtained as a single diastereoisomer (Figure 1; see also Supporting Information (SI) for more details).[13]

Furthermore, this method also allows the use of silyl dienol ether **2f**, thus affording the corresponding lactone in an 84% yield over two steps (Table 2, entry 10).[14]

In addition, under the same reaction conditions, 1,3-dicarbonyl compounds **2g** and **2h**, as well as allyltributyl stannane **2i** and trimethylsilyl cyanide **2j**, can also be used, thus further demonstrating the viability of other soft carbon nucleophiles in this strategy (Table 2, entries 11–14). Concerning the reaction times, all these reactions can be performed in the range 20–36 h (see SI for more details).

Importantly, the pent-4-yn-1-ones produced are valuable intermediates for the synthesis of a number of relevant building blocks. For instance, in the presence $AuCl_3$ (5 mol %), under

Table 2. Substrate Scope of Alkynes, through the Use of Different Soft Carbon Nucleophiles

entry	isozaxol-5-one, 1	nucleophile, 2	alkyne, 4	yield (%)[a]
1	 1a	 2a	 4a	83
2	 1b	2a	 4b	88
3	 1c	2a	 4c	71
4	 1d	2a	 4d	82
5	 1e	 2b	 4e	61
6	1a	2b	 4f	72
7	1a	 2c	 4g	66
8	1a	 2d	 4h	74
9	1a	 2e	 4i	62[b] (dr >19:1)[c]
10	1a	 2f	 4j	84 (dr 5.7:1)[c]
11	1a	 2g	 4k	45
12	1a	 2h	 4l	58 (dr 1.1:1)
13	1a	 2i	 4m	60
14	 1f	TMSCN 2j	 4n	70

[a]Isolated material, reported for two steps. [b]Michael addition performed with 3 equiv of silyl enol ether and 10 mol % of $Sc(OTf)_3$. [c]Major diastereoisomer shown.

the reflux of methanol, substrate **4a** undergoes hydration to afford diketone **5**, which can subsequently follow a Paal–Knorr cyclization, promoted by HCl, to afford the corresponding furan **6** (Scheme 3).

Continuing our investigation, we imagined that due to the weak N–O bond strength, one would be able to selectively

DOI: 10.1021/acs.orglett.5b01004
Org. Lett. 2015, 17, 2490–2493

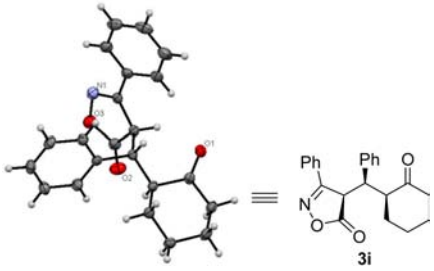
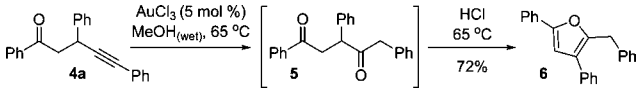


Figure 1. X-ray single-crystal structure of **3i**.

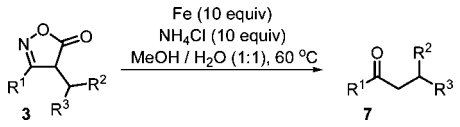
Scheme 3. An Illustrative Synthetic Application of Pent-4-yn-1-one 4a

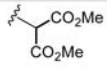
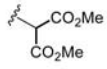


cleave the isoxazol-5-one ring, therefore triggering the formation of novel, interesting carbonyl derivatives.[15]

Indeed, this is true. In this context, we report herein an unprecedented decarboxylation protocol of isoxazol-5-ones, through the use of inexpensive iron as a reducing agent. In this process, linear and branched isoxazol-5-ones produce similar results, thus affording ketones **7a–h** in good and excellent yields (72–98%) (Table 3). Overall, this new method allows

Table 3. Disclosure of a Novel Decarboxylation Protocol of Isoxazol-5-ones



entry	R^1	R^2	R^3	product number	yield (%)[a]
1	Ph	Ph		**7a**	75
2	^{i}Pr	2-Naphthyl		**7b**	84
3	Ph	Ph	allyl	**7c**	72
4	^{i}Pr	2-Naphthyl	allyl	**7d**	98
5	Et	H	Ph	**7e**	93
6	^{i}Pr	H	2-Naphthyl	**7f**	80
7	^{i}Pr	H	2-furyl	**7g**	72
8	^{i}Pr	H	Ph	**7h**	85

[a]Isolated material.

the use of alkylidene isoxazol-5-ones as activated Michael acceptors, which, after the desired 1,4-addition, can be converted to the corresponding ketones.

In summary, we developed two new strategies to access β-branched carbonyl compounds via the conjugate addition of several soft carbon nucleophiles to alkylidene isoxazol-5-ones. The subsequent step takes advantage of either a nitrosative cleavage leading to the corresponding β-branched alkynyl ketones or a decarboxylative transformation, which releases the corresponding ketone.

Concerning the synthesis of alkynes, the strategic use of the Zard alkynylation can be highlighted as an important shift from traditional disconnections, where the alkyne moiety is actually synthesized, instead of being added as a part of a preformed reactive moiety.

Currently, we are investigating viable asymmetric strategies related to the transformations disclosed in this work. Our progress in this area will be reported in due time.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures, spectral data of products, and copies of the ^{1}H and ^{13}C NMR spectra are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01004.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge Fapesp for an undergraduate research fellowship to N.M.R.C. (2014/15718-7) and a research grant to I.D.J. (2013/09680-4). The authors are in debt to Profs. Luiz C. Dias, Carlos R. Correia, and Ronaldo A. Pilli (Unicamp, Brazil) for generous donations of chemicals. We would like to thank Prof. Marcos N. Eberlin (Unicamp, Brazil) for HRMS analyses and Dr. Déborah Simoni (Unicamp, Brazil) for X-ray single-crystal analysis. We dedicate this work to Prof. Samir Zard (École Polytechnique, France), with respect and admiration.

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DOI: 10.1021/acs.orglett.5b01004
Org. Lett. 2015, 17, 2490−2493