A New Convergent Approach to α-Branched Alkynes

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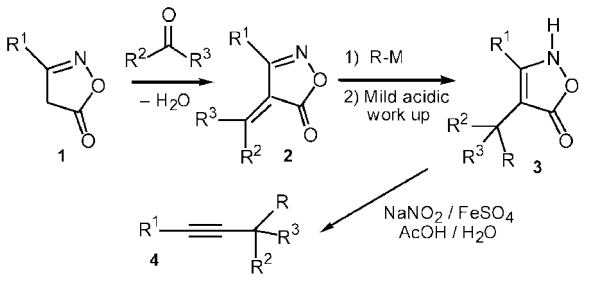
Abstract: A variety of α-branched alkynes can be easily assembled by a Knoevenagel type condensation of 4-unsubstituted isoxazolin-5-ones with aldehydes or ketones, followed by conjugate addition of an organometallic reagent and nitrosative cleavage of the heterocyclic ring.

Key words: alkynes, isoxazolin-5-ones, Knoevenagel condensation, conjugate addition

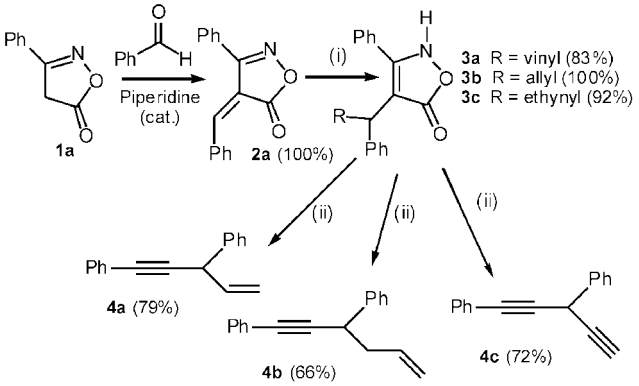
Alkynes play a central role in organic synthesis. Their rich and varied chemistry, highlighted by their amazing ability to participate in a vast number of transition metal mediated transformations, has frequently been exploited in the total synthesis of natural and unnatural products of all types and complexities.[1] Finding new, flexible methods for creating the carbon-carbon triple bond remains therefore a worthwhile endeavour. We now describe a simple, convergent strategy that allows access to α-branched alkynes including those with adjacent quaternary centres.

Our approach, outlined in Scheme 1, relies on the conjugate addition of an organometallic species to a 4-alkylidene-isoxazolin-5-one **2**, followed by the nitrosative cleavage of the heterocyclic ring to create the C-C triple bond, a reaction we discovered a few years ago.[2] A combination of sodium nitrite, aqueous acetic acid, and ferrous sulfate is used to accomplish the second transformation, the last reagent being required to generate nitric oxide in the medium and thus suppress, through the persistent radical effect, the unwanted formation of isoxazolidinone dimers by radical-radical coupling.[2a]

4-Unsubstituted isoxazolinones **1** are known to undergo a Knoevenagel type condensation with aldehydes and ketones to give 4-alkylidene derivatives **2**.[3] Surprisingly, the ability of such highly electrophilic condensation products to act as acceptors for organometallic reagents has hardly been examined in the past. The rare existing reports describe the addition of Grignard reagents to 4-arylidene derivatives (**2**, R^2 = Ar; R^3 = H) obtained by condensation of **1** with aromatic aldehydes.[4] We have now found that by the appropriate selection of the organometallic reagent, this conjugate addition acquires a much wider scope and can be exploited for the preparation of α-branched alkynes with a range of interesting substitution patterns, including quaternary centres which are difficult to prepare by more traditional routes.



Scheme 1



Scheme 2 Conditions (i) Vinyl MgBr or allyl MgBr or ethynyl MgBr–THF, –70 °C. (ii) $NaNO_2$–$FeSO_4$–AcOH–H_2O, r.t.

Compound **2a**, prepared quantitatively as one geometrical isomer (presumably the one shown) by condensation of commercially available 3-phenyl-isoxazolin-5-one with benzaldehyde in the presence of a small amount of piperidine, reacted smoothly with allyl, vinyl, and ethynyl magnesium bromides to give the corresponding adducts **3a–c** and thence alkynes **4a–c** upon nitrosative cleavage (Scheme 2). Such enynes and diynes are useful substrates in a number of transition metal mediated transformations.[5] Both the organometallic reagents and the initial substitution pattern on the heterocyclic ring can be varied, as illustrated by the examples compiled in the Table (the yields shown are for the two steps, since in most cases the adduct from the reaction with the organometallic reagent was not purified). We were pleased to find that organozinc reagents also underwent the addition smoothly. The much greater tolerance of organozinc reagents with respect to the presence of functional groups opens up many possibilities for the synthesis of α-branched yet usefully function-

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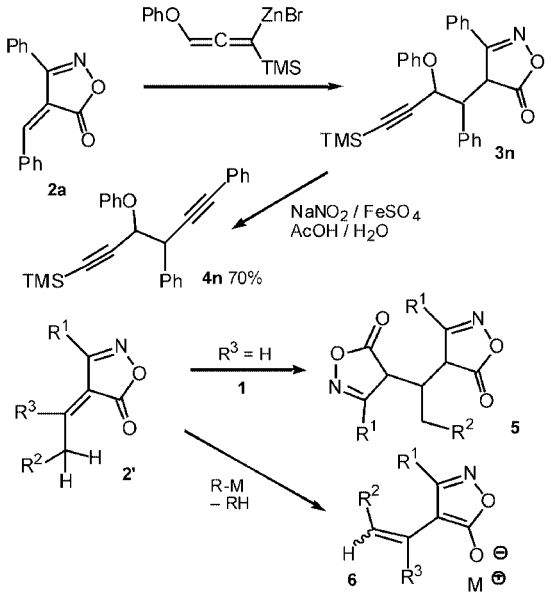
alised alkynes.[6] The addition of allenylzinc reagent leading to alkyne **4n** pictured in Scheme 3 is of special interest because essentially one diastereoisomer was obtained, but of as yet undetermined relative stereochemistry. Moreover, the survival of the relatively fragile trimethylsilylalkyne portion of the molecule constitutes a further testimony to the mildness of the nitrosative cleavage of the isoxazolinone ring.



Scheme 3

In the case of organometallic additions to 4-alkylidene-isoxazolin-5-one **2′** derived from aliphatic ketones, the difficulties we encountered resulted from the acidity of the γ-hydrogens and the ready formation of the corresponding salts **6**. Grignard reagents did not therefore add well; however, the less basic organozinc and organocopper reagents proved satisfactory allowing the convenient creation of quaternary centers (examples **4l** and **4m**). In the case of aliphatic aldehydes, one further complication appears to be the easy formation of bis-addition products **5**.[3] One notable exception is cyclopropane-carboxaldehyde whose derivative could be transformed cleanly into alkyne **4i** possessing a rare substitution pattern.

Despite some of the limitations we have so far observed and which we are attempting to circumvent, this approach to α-branched alkynes is straightforward,[8] quite flexible, and provides structures only tediously accessible otherwise. The 4-alkylidene-isoxazolin-5-ones represent in fact practical synthetic equivalents of propargyl cations. One further aspect worth underlining concerns the possibility of controlling the absolute stereochemistry by using chiral ligands in conjunction with the organozinc reagents.[7]

Table Synthesis of α-Branched Alkynes

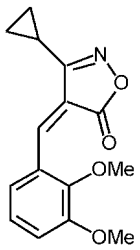
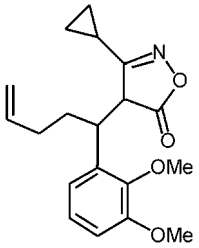
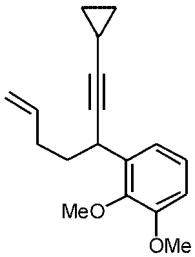
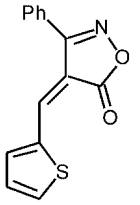
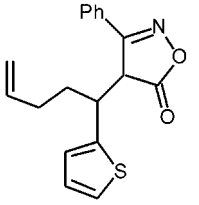
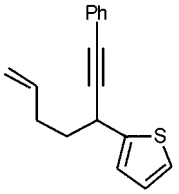
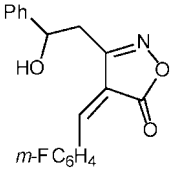
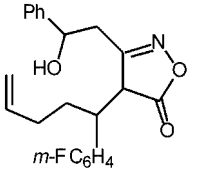
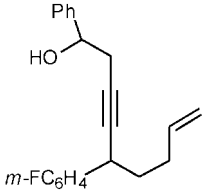
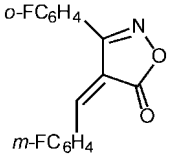
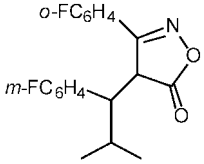
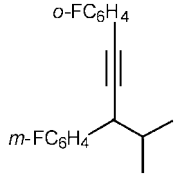
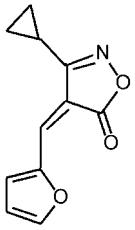
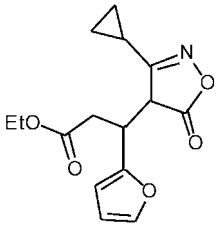
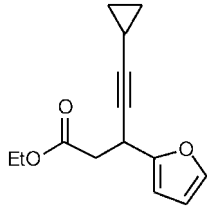
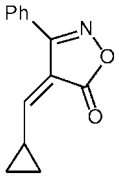
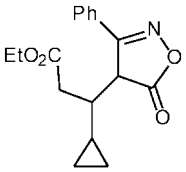
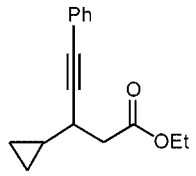
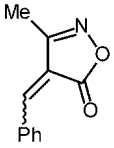
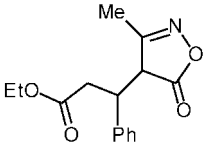
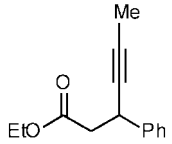
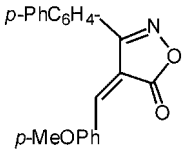
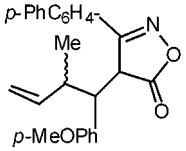
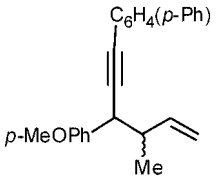
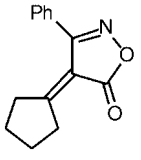
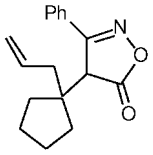
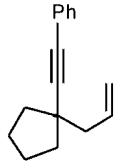
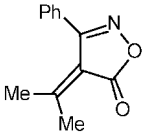
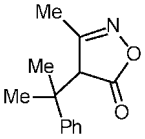
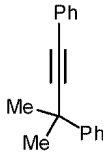
4-Alkylidene isoxazolidin-5-one **2**	Adduct **3** (Organo-metallic reagent)[a]	Alkyne **4** (yield %)
 **2d**	 **3d** (a)	 **4d** (37%)
 **2e**	 **3e** (a)	 **4e** (66%)
 **2f**	 **3f** (a)	 **4f** (31%)

Table Synthesis of α-Branched Alkynes (continued)

4-Alkylidene isoxazolidin-5-one **2**	Adduct **3** (Organo-metallic reagent)[a]	Alkyne **4** (yield %)
 **2g**	 **3g** (b)	 **4g** (35%)
 **2h**	 **3h** (c)	 **4h** (50%)
 **2i**	 **3i** (c)	 **4i** (75%)
 **2j**	 **3j** (c)	 **4j** (50%)
 **2k**	 **3k** (d)	 **4k** (56%)
 **2l**	 **3l** (e)	 **4l** (33%)
 **2m**	 **3m** (f)	 **4m** (35%)

[a] (a) CH_2=$CHCH_2CH_2MgBr$; (b) *i*PrMgCl; (c) $BrZnCH_2CO_2Et$; (d) crotyl ZnBr; (e) allyl ZnBr; (f) PhCu ($MgBr_2$).

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Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 8735. (d) Boutillier, P.; Zard, S. Z. *Chem. Commun.* **2001**, 1304. (e) Huppé, S.; Rezaei, H.; Zard, S. Z. *Chem. Commun.* **2001**, 1894. (f) Zard, S. Z. *Chem. Commun.* **2002**, in press.

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(8) Typical experimental procedures: (A) *Condensation of isoxazolinones **1** with aldehydes and ketones*: To a solution of the isoxazolin-5-one (10 mmol) in propan-2-ol (20 mL) in a 100 mL round bottom flask were added the corresponding aldehyde (1.2 equiv) or ketone (2 equiv) and a catalytic amount of piperidine (ca. 0.2 mL). The resulting solution was then stirred to 50 °C in the case of aldehydes or to reflux in the case of ketones. When TLC showed complete consumption of the isoxazolinone, most of the solvent was removed under partial vacuum. In the case of aldehydes, the products generally precipitated and were isolated by a filtration and washed with petroleum ether. In the other cases, an oil was obtained which was washed with a little petroleum ether–Et_2O, 80:20, dried, and used as such in next step.
(B) *Addition of organometallic reagents to alkylidene isoxazolinone **2**. (a)Addition of Grignard reagents (compounds* **3a**–**g**): To a solution of the alkylidene isoxazolinone **2** (5 mmol) in dry THF (15 mL) cooled to –70 °C was added a solution of the Grignard reagent (5 mmol). After stirring for 15 min. at –70 °C, the mixture was allowed to warm to r.t. then hydrolyzed with dilute HCl (0.2 M; 40 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The nearly pure products **3a**–**g** were used directly in step (C). (b)*Addition of organozinc reagents (compounds* **3k**,**l***)*: To a cooled (–10 °C) solution of crotyl or allyl magnesium bromide (5.2 mmol) in dry THF (15 mL) was added under nitrogen a solution of $ZnBr_2$ (1 M/THF). The mixture was cooled to –70 °C and the alkylidene isoxazolinone **2j** or **2k** (5 mmol) was added all at once. The mixture was allowed to warm to r.t. and when TLC showed that no starting material was left, dilute HCl (0.2 M; 40 mL) was added and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with a solution of citric acid (0.1 M; 20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The nearly pure **3j**,**k** were used directly in step (C). (c)*Addition of allenylzinc (compound **3n**)*: To a cooled (–70 °C) solution of trimethylsilyl-3-phenoxyprop-1-yne (5 mmol) in dry THF (20 mL) was added dropwise a solution of *sec*-butyllithium [1.3 N] (5.1 mmol, 3.9 mL). After 10 min at –70 °C, a solution of $ZnBr_2$ (1 M; 5.1 mmol) was added dropwise. After warming to –30 °C, isoxazolinone **2a** was added and the temperature allowed to rise to r.t. At the end of the reaction (monitored by TLC), the mixture was hydrolyzed using the same work-up as in the preceding procedure. Compound **3n** thus obtained was used as such in step (C). (d) *Addition of Reformatsky's reagent (compounds **3h**,**i***) : 1,2-Dibromoethane (0.2 mL) was added to zinc dust (15 mmol) in dry THF (10 mL) while heating to reflux under nitrogen. After 2 min at reflux, the mixture was cooled down to r.t., TMSCl (0.2 mL) was added, and the solution refluxed again for 10 min. To this mixture, cooled down to r.t., was added dropwise ethyl bromoacetate (5.5 mmol). After stirring 15 min at r.t., the resulting Reformatsky's reagent was added to a cold (–10 °C) solution of isoxazolinone **2h** or **2i** (5 mmol) in THF (10 mL) then the temperature was allowed to increase to r.t. At the end of reaction (monitored by TLC) the mixture was hydrolyzed using again the same work-up as for **2j** and **2k**. The nearly pure **3h**,**i** were used directly in step (C). (e)*Addition of phenyl copper reagent (compound **3m***): To a suspension of copper bromide-dimethyl sulfide (6 mmol) under nitrogen in dry THF (20 mL) was added dropwise at –50 °C a solution of phenylmagnesium bromide (5.5 mmol). After stirring 15 min at –50 °C, isoxazolinone **2m** (5 mmol) was added and the reaction mixture was stirred while keeping the temperature below –40 °C until the TLC showed no starting material. The medium was then hydrolyzed at –60 °C with dilute HCl (0.2 M; 40 mL) and the aqueous layer extracted with ether (2 × 30 mL). The combined organic layers were washed with a solution of citric acid (0.1 M; 2 × 20 mL), brine (20 mL), and dried over $MgSO_4$. After concentrating under vacuum, the crude product was further purified by filtration on a silica pad and used directly in step C.
(C) *Synthesis of alkynes* **4a**–**n**: To a suspension of ferrous sulfate (5.56 g, 20 mmol, 5.5 equiv) in acetic acid (15 mL) was added half of a solution of sodium nitrite (2.1 g, 35 mmol, 10 equiv) in water (10 mL) under an inert atmosphere (all solutions must also be thoroughly degassed beforehand). The remainder was added simultaneously with a solution of the isoxazolinone **3** (3.5 mmol) in degassed acid acetic (15 mL) over 30 minutes at 25 °C. The set-up was then flushed with nitrogen for 30 minutes; water (150 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were then washed with dilute HCl (0.5 M), saturated $NaHCO_3$, and dried over $NaHCO_3$ (with stirring) for 45 minutes. Concentration and purification by chromatography of the residue provided alkynes **4** in the stated yields.