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A direct route to 2-alkyl-4-carbethoxy-5-vinyloxazoles

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ABSTRACT

The reaction of an α-chloroglycinate ester with the dimethylaluminum acetylide derivative of phenyl propargyl ether provides the corresponding 5-vinyloxazole in 40–50% yield.

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An ongoing program in this laboratory centers on the synthesis of oxazole-containing natural products[1] through the application of the oxazole-forming reaction shown in Scheme 1.[2] This technique involves the reaction of a readily available α-chloroglycinate ester, **3**, with a dimethylaluminum acetylide, **5**, leading to an alkynylglycinate ester, **6**. While the latter is isolable, its propensity to undergo cycloisomerization to an oxazole is such that one may conveniently allow it to advance to **7** in situ. The process thus combines the conversion of propargylic amides into oxazoles[3] with the considerably more facile cycloisomerization of alkynylglycinate esters.[4]

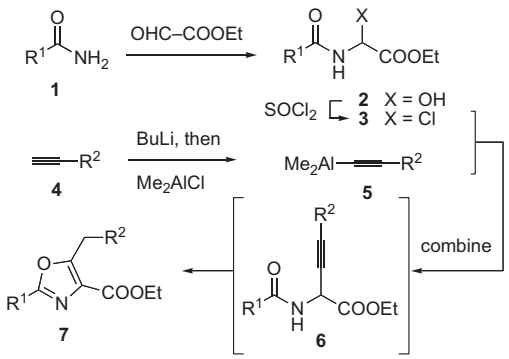
We note that the isomerization of propargylamides to oxazoles has more recently been induced through the agency of Au[5] and Pd[6] catalysis. In addition, an 'oxidative' variant of the process has been devised, in which a hypervalent iodine reagent triggers the conversion of propargylamides into 5-hydroxymethyl oxazole derivatives.[7] Of course, the continuing search for such diverse avenues to oxazoles reflects the importance of these heterocycles in natural products[8] and medicinal chemistry.[9]

The objectives of our own research made it desirable to achieve the direct conversion of **3** into a 4-carbethoxy-5-vinyloxazole. It should be noted that 5-alkenyloxazoles in general are scantily documented in the literature. Known methods for their synthesis encompass Pd-mediated coupling reactions,[10] hydride reduction of 5-acyloxazoles followed by dehydration of the resulting alcohols,[11,12] Peterson reaction of 5-(trimethylsilyl)methyl-oxazoles,[13] 'long range Pummerer cyclization' of appropriate sulfur-substituted propargylamides,[14] olefin metathesis of preformed 5-alkenyloxazole substrates,[15] and Wittig reaction of 5-formyloxazoles.[16]

The 5-vinyloxazole system is particularly rare, a mere 17 examples thereof having been recorded in the CAS database as of this writing.[17] A route to 5-vinyloxazoles lacking a 4-COOR substituent was devised by Wipf in the form of a base-promoted conversion of propargylamides **7** into **8** (Scheme 2).[18] In accord with this precedent, we found that the dimethylaluminum acetylide derived from methyl propargyl ether reacts with **3** to furnish some **10** as a minor product (ca. 20%) that accompanied the 'normal' oxazole **9** (40–60%).[2]

Initial attempts to enhance the formation of **10** aimed to induce elimination of MeOH from **9** by the action of strong base (*t*BuOK/DMSO or LDA. The COOR group activates the C-5 methylene for deprotonation).[19] All these efforts met with failure: in most cases, base treatment had no effect on **9**. This suggested that in all likelihood the events responsible for the generation of **10** occur prior to the formation of **9**. A mechanistic possibility is that the intermediate alkynylglycinate **11** undergoes in situ conversion into a mixture of **12** (product of alkyne–allene isomerization) and **13** (product of MeOH elimination; Scheme 3). An ensuing electrocyclic process then yields **9** from **12** and **10** from **13**. If this were the case, then the replacement of the OMe group in **10** with a better nucleofuge would favor the formation of cumulene **13**, ergo that of **10**.

A summary of experiments designed to probe the foregoing hypothesis appears in Scheme 4. Dimethylaluminum acetylides derived from methyl or benzyl propargyl ether reacted with test substrate **3a** to give **10a** in an identical 21% yield. Oxazole **10a** is an important building block in an ongoing synthetic study. The yield of **10a** dropped to a disappointing 13% with the Me_2Al derivative



Scheme 1. An oxazole-forming reaction (Ref. 2).

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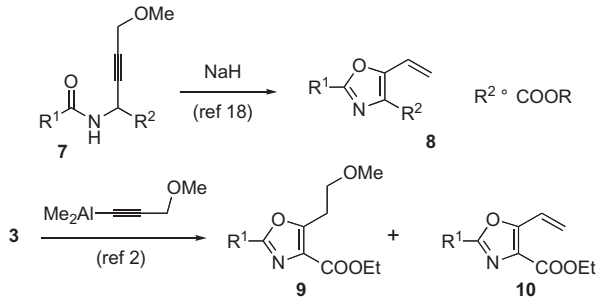


Scheme 2. 5-Alkenyloxazoles via isomerization–elimination of propargylamides.

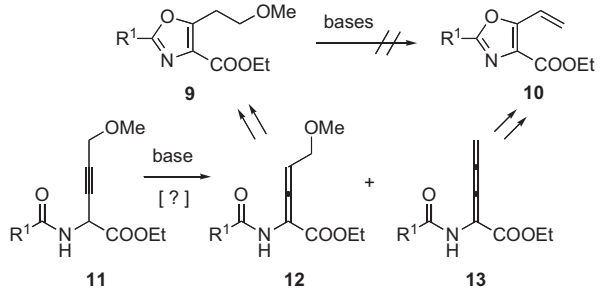
of propargyl chloride, apparently due to facile degradation of the organometallic agent. Inspired by the work of Schweitzer,[20] we then tested a phenoxy nucleofuge. Happily, lithiation (*n*-BuLi) of phenyl propargyl ether, transmetallation to Me_2AlCl, and reaction of the resultant with **3a** afforded **10a** as the sole product in 55% yield after chromatography.

The successful preparation of **10a** may be regarded as a major application of the new route to 5-vinyloxazoles, given the projected usefulness of structurally related heterocycles in medicinal (e.g., preparation of peptidomimetics) and natural product (assembly of key subunits of various antibiotic substances) chemistry. Accordingly, included herein are detailed procedures for its preparation accompanied by full characterization data.[21]

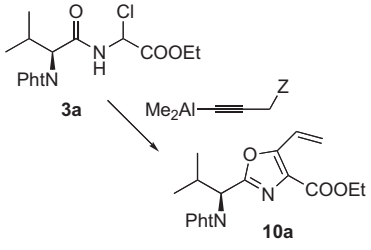
Additional examples of the new 5-vinyloxazole synthesis from the known[2,22,23] chloroglycinates **3b–d** and **3f–g** appear in Table 1. In most cases, the sole discernible product of these reactions was **10**, but occasionally, traces (<10%, not characterized) of a byproduct, probably an oxazole of the type **9**, were also observed. The low yield obtained with **3g** is consistent with previous observations indicating that chloroglycinates arising from α,β-unsaturated amides are poor substrates for the present oxazole-forming process.[22]

Attempts to further improve the reaction by enhancing the nucleofugal aptitude of the phenoxy segment (introduction of electron-withdrawing substituents) gave disappointing results. This was apparently due to the lability of the resulting aluminum acetylides. For instance, experiments involving 4-chlorophenyl propargyl ether and 2,4,6-trichlorophenyl propargyl ether in lieu of phenyl propargyl ether afforded the target vinyloxazoles in substantially diminished yields (ca. 15–20%). Consequently, such a line of research was pursued no further.[24]

In summary, the use of an acetylenic alane derived from phenyl propargyl ether permits the direct conversion of chloroglycinates **3** into 5-vinyloxazoles **10** in synthetically useful yield. Applications of this chemistry in synthesis are being evaluated and will be described in due course.



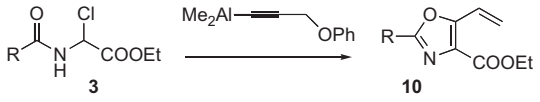
Scheme 3. Possible mechanism of 5-vinyloxazole formation.



Z	yield (%)[a]
OMe	21
OBn	21
Cl	13
OPh	55

Scheme 4. Effect of nucleofuge Z on the yield of **10a**.

Table 1
5-Vinyloxazoles obtained by the new procedure



Entry	R	Yield[a] (%)
b	Me	41
c	*cyclo*-C_6H_{11}	50
d	Ph	36
e	Bn	39
f	$PhSCH_2$	41
g	(*E*)-Ph–CH=CH	<10%

[a] Yield of chromatographically purified vinyloxazoles.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data, ^1H and ^{13}C and NMR spectra of the new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.130.

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21. Synthesis of **10a**. A solution of *N*-phthaloyl valinamide (1.2 g, 5.0 mmol) and ethyl glyoxylate (50% w/w in toluene, 1.3 g, 6.5 mmol) was refluxed overnight, whereupon TLC (30% EtOAc/hexanes) indicated complete conversion of the starting amide into the hydroxyglycinate. The mixture was concentrated in vacuo, and the residue was triturated with 30% EtOAc in hexanes to yield 1.7 g (>99% crude yield) of the corresponding α-hydroxyglycinate, 1:1 mixture of diastereomers (^{1}H: 8.29 (d, 1H, *J* = 6.5), 8.15 (d, 1H, *J* = 6.5), 7.89–7.87 (m, 4H), 7.79–7.75 (m, 4H), 5.56 (d, 1H, *J* = 6.9), 5.44 (d, 1H, *J* = 6.9), 4.47 (d, 1H, *J* = 11.3), 4.44 (d, 1H, *J* = 11.2), 4.29–4.24 (m, 6H), 2.87–2.83 (m, 2H), 1.27 (t, 6H, *J* = 7.1), 1.11 (d, 6H, *J* = 6.5), 0.86 (d, 6H, *J* = 6.5). ^{13}C: 169.7, 169.5, 169.4, 169.3, 168.4, 134.5, 131.2, 123.8, 72.5, 72.3, 62.5, 27.6, 27.5, 19.7, 19.5, 19.4, 13.9. ESIMS: 349 $[M+H]^+$, 371 $[M+Na]^+$). A solution of this material (ca. 5 mmol) and $SOCl_2$ (15 mmol) in CH_2Cl_2 (15 mL) was stirred overnight under argon at rt, then the mixture was evaporated to dryness to leave a residue of 1.8 g of essentially pure α-chloroglycinate, 1:1 mixture of diastereomers, in quantitative yield (^{1}H: 8.56 (d, 1H, *J* = 9.5), 8.35 (d, 1H, *J* = 9.5), 7.93–7.88 (m, 4H), 7.80–7.77 (m, 4H), 6.24 (d, 2H, *J* = 9.5), 4.50 (d, 1H, *J* = 11.2), 4.48 (d, 1H, *J* = 11.2), 4.39–4.22 (m, 4H), 2.93–2.79 (m, 2H), 1.35 (q, 3H, *J* = 7.2), 1.33 (q, 3H, *J* = 7.2), 1.12 (d, 3H, *J* = 6.7), 1.10 (d, 3H, *J* = 6.7), 0.88 (d, 3H, *J* = 6.7), 0.87 (d, 3H, *J* = 6.7)). This reactive substance was not thoroughly characterized and it was used without further purification. Commercial *n*-BuLi (1.6 M in hexanes, 3.3 mL, 5.3 mmol) was added to a THF (8 mL) solution of phenyl propargyl ether (0.7 g, 5.3 mmol) at −78 °C, under Ar. The mixture was stirred at −78 °C for 20 min, then it was warmed up to 0 °C and dimethylaluminum chloride (1.0 M in hexanes, 5.3 mL, 5.3 mmol) was added. The mixture was stirred at 0 °C for 1 h, then was transferred over 15 min (syringe) to a solution of α-chloroglycinate (1.8 g, 5.0 mmol) in THF (6 mL), kept at rt. The resulting mixture was stirred at rt for 4 h; then it was diluted with $CHCl_3$, filtered through silica gel (elution with EtOAc), and concentrated in vacuo. Purification of the residue (flash chromatography on silica gel; 0.5% Et_3N in 20% EtOAc/hexanes) afforded 1.0 g (55%) of **10a**, as a colorless oil, $[\alpha]_D^{22} = -50.4$ (*c* 0.6, $CHCl_3$). IR: 1770, 1720, 1639, 1563. ^{1}H: 7.80 (dd, 2H, *J* = 5.5, 3.1), 7.69 (dd, 2H, *J* = 5.5, 3.1), 7.11 (dd, 1H, *J* = 17.7, 11.4), 5.94 (d, 1H, *J* = 17.7), 5.51 (d, 1H, *J* = 11.4), 5.13 (d, 1H, *J* = 10.3), 4.32 (q, 2H, *J* = 7.1), 3.16–3.04 (m, 1H), 1.32 (t, 3H, *J* = 7.1), 1.08 (d, 3H, *J* = 6.7), 0.93 (d, 3H, *J* = 6.7). ^{13}C: 167.3, 161.6, 159.3, 154.2, 134.3, 131.5, 127.4, 123.5, 122.0, 120.7, 61.2, 54.1, 28.5, 20.4, 19.3, 14.3. HRMS: calcd for $C_{20}H_{20}N_2O_5Na$ $M+Na^+$, 391.1270; found, 391.1268.
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