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A Peterson avenue to 5-alkenyloxazoles

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ABSTRACT

The $TiCl_4$-promoted Peterson olefination of aldehydes with readily available 5-(trimethylsilyl)methyloxazoles furnishes 5-alkenyloxazoles (mostly *E*-isomers).

Ongoing research on the synthesis of oxazole-containing natural products[1] revealed a need for an expeditious route to 2-alkyl-(*E*)-5-alkenyl-4-oxazole-carboxylic esters, **1** (Fig. 1). Surprisingly, the CAS database records only two compounds of this general type, **2** and **3**, both of which are described in a patent that reports antiviral activity for such structures.[2] The scant precedent for structures **1** reflects a more general lack of information regarding the synthesis of 5-alkenyl-oxazoles. Such heterocycles have been primarily obtained by Pd-mediated coupling reactions of 5-halooxazoles.[3] A recent method for the assembly of 4-alkyl-5-acyloxazoles provides a route to corresponding 5-alkenyl-oxazoles by carbonyl reduction and dehydration of the intermediate alcohol.[4] However, the products thus obtained lack a 4-COOR substituent. A noteworthy alternative involves the de novo construction of the heterocyclic framework through cycloisomerization–elimination of *N*-propargyl amides **4** (Fig. 2),[5] but again, the ensuing 5-alkenyl-oxazoles lack the desired 4-COOR group. A variant of that method leads to 2-alkyl-4-carbalkoxy-5-vinyl oxazoles **6** by cyclization of *N*-acyl-2-(3-methoxy-1-propynyl) glycinates (**4**, Z = $COOR^3$).[6] Unfortunately, products **6** are accompanied by variable quantities of 5-(2-methoxyethyl)-oxazoles **7**, to the detriment of overall efficiency. It should be noted that contrary to the case of the 5-isomers, the chemistry of 2- and 4-alkenyl-oxazoles is fairly well developed.[7]

Our interest in compounds **1**, the paucity of methods for their assembly, and their biological relevance[1,8] induced us to research a new synthetic route. In principle, the requisite oxazoles could be prepared through olefination chemistry, and an option in that respect would be a Wittig reaction of an oxazole-based phosphorane or phosphonate. However, a search of the CAS database retrieved no record of phospho-oxazole substructures **8** or **9** (Fig. 3). Motif **10** is documented in only seven compounds,[9] none of which are serviceable in the present case. By contrast, more than 100 examples each of 2- and 4-phosphorylmethyl oxazoles **11** and **12** are known, and many Wittig reactions with such agents have been described.[10]

Alternatively, the chemistry of Ref. 6 provides facile access to 5-(trimethylsilyl)methyloxazoles such as **19** and **20** (Scheme 1). We surmised that these could undergo Peterson olefination[11] with aldehydes, thereby affording the desired **1**. On the other hand, Peterson reactions with hetero-aromatic donors are quite rare. Moreover, they appear to have been documented only in the pyridine series.[12] Because no examples of like reactions in the oxazole domain appear to exist, a feasibility study was carried out but using **19** and **20**.

The deprotonation of the foregoing oxazoles occurred regioselectively at the CH_2TMS group upon treatment with LDA or LHMDS (THF, −78 °C, 20–30 min, Scheme 2), as apparent from the virtually

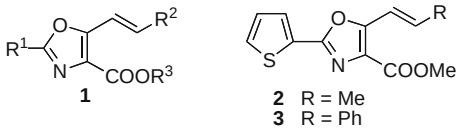

Figure 1. 5-Alkenyloxazoles of interest in this study (**1**) and recorded examples thereof (**2–3**).

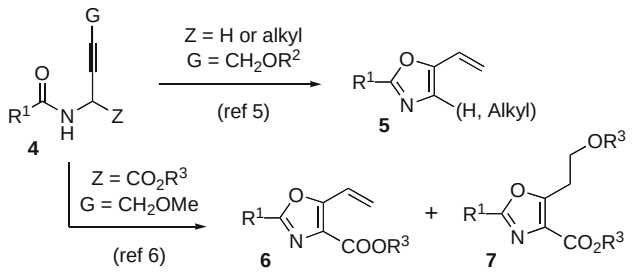

Figure 2. 5-Alkenyloxazoles via isomerization–elimination of propargylamides.

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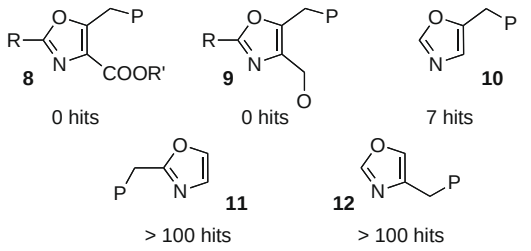
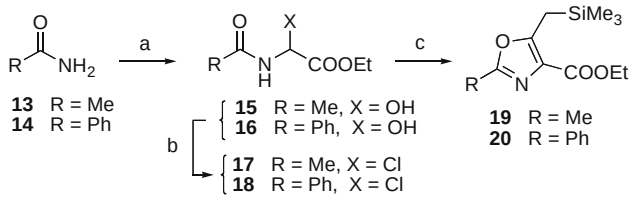
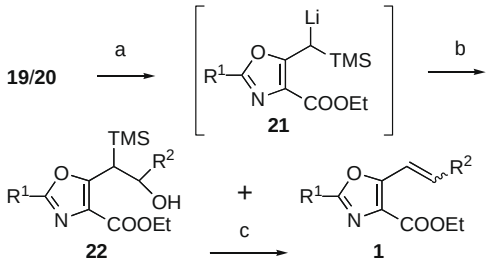


Figure 3. Oxazole-based Wittig-type reagents recorded in the CAS database.

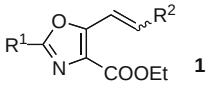


Scheme 1. Reagents and conditions: (a) OHC–COOEt, THF, reflux, 99%; (b) neat $SOCl_2$, rt, 99%; (c) Me_2Al–CC–TMS, THF, 0 °C, 3 h, 45% (chrom.) for **19**, 46% (chrom.) for **20**.



Scheme 2. Reagents and conditions: (a) LDA or LHMDS (see text), THF, −78 °C, 20–30 min; (b) R^2–CHO, then $TiCl_4$ in CH_2Cl_2, −78 °C to rt; (c) TsOH·H_2O, toluene, reflux, 40–80% overall.

Table 1
5-Alkenyloxazoles obtained by the new procedure



Entry	Base	R^1	R^2	Yield%[a] (*E*:*Z*)	Yield%[b] (*E*:*Z*)
1a	LDA	Ph	Et	50 (9:1)	79 (9:1)
1b	LDA	Ph	Ph–CH_2–CH_2	57 (4:1)	71 (7:3)
1c	LDA	Ph	4-MeO–C_6H_4	35 (7:3)	74 (7:3)
1d	LDA	Ph	2-Me–C_6H_4	40 (1:1)	53 (1:1)
1e	LDA	Ph	4-Cl–C_6H_4	60 (7:3)	74 (6:1)
1f	LDA	Ph	4-NC–C_6H_4		57 (4:1)
1g	LDA	Ph	3-Me–C_6H_4		78 (9:1)
1h	LDA	Ph	2-Furyl		50 (4:1)
1i	LHMDS	Ph	Ph	45 (4:1)	83 (3:1)
1j	LHMDS	Me	Ph–CH_2–CH_2	26 (3:2)	46 (3:2)
1k	LHMDS	Me	4-Cl–C_6H_4	38 (*E*)	46 (*E*)
1l	LHMDS	Me	2-Thienyl	44 (*E*)	77 (*E*)

[a] Yield and *E*/*Z* isomer ratio of chromatographically purified alkenyloxazoles obtained from a sequence that omitted the TsOH treatment (see text).
[b] Yield and *E*/*Z* isomer ratio (after chromatography) for a sequence that included the TsOH treatment prior to isolation of the product (see text).

complete deuteration of the CH_2TMS substituent upon a D_2O quench. The regioselectivity observed in the lithiation of **19** is unquestionably due to the activating effect of the TMS group. Indeed, the metallation of 2,4-dimethyloxazole-4-carboxylates is infamously non-regioselective.[13] The resulting organometallics **21** proved to be poor nucleophiles. In particular, they added inefficiently even to aldehydes. Past experience with similar difficulties[1f] suggested that the use of a Lewis acid activator of the carbonyl acceptor might circumvent the problem. Indeed, $TiCl_4$ emerged as an effective promoter of the addition of **21** to both aromatic and aliphatic aldehydes. The ensuing reaction afforded a mixture of *E* (dominant) and *Z* isomers of the desired **1**, plus variable quantities of adducts **22**, which had failed to undergo elimination. This is not surprising in light of the retarding effect of oxophilic metal ions on the Peterson elimination of 1,2-silanols.[14] A complete conversion of **22** into **1** occurred smoothly upon treatment of such crude mixtures with TsOH in refluxing toluene.[15] In some cases, such a treatment more than doubled the overall yield of desired **1**.

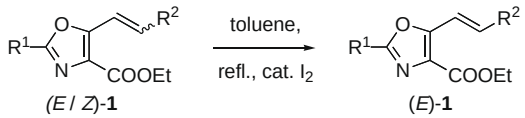
The base of choice for reactions of phenyl substrate **20** was found to be LDA, while LHMDS was preferred with methyl oxazole **19**. The latter base also gave improved yields in the reaction of **20** with PhCHO. It seems imprudent to venture simplistic explanations for such observations. The aldehydes were best introduced into a cold (−78 °C), preformed solution of **21** in one portion, either in neat forms (liquids) or as concentrated THF solutions (solids), immediately followed by the addition of $TiCl_4$ (1 M solution in CH_2Cl_2). Aqueous workup and subsequent TsOH treatment of the crude product afforded oxazoles **1** (*E*/*Z* mixtures), which then were chromatographically purified.[16]

Table 1 lists the 5-alkenyl-oxazoles obtained through the new procedure. The first yield column in this table reports the yields of **1** obtained from a sequence that omitted the TsOH treatment; the second one tabulates the yields of **1** arising from a preparation that included such a step. Available data suggest that the reaction performs adequately with both aliphatic and aromatic aldehydes. The latter substrates may indifferently carry substitution at the *ortho*, *meta*, and *para* positions and incorporate electron-donating or electron-withdrawing groups. Representative heteroaromatic aldehydes, such as 2-furaldehyde and 2-thienaldehyde, participate normally in the reaction. Unfortunately, ketones such as acetone and cyclohexanone failed to combine with **21** even in the presence of $TiCl_4$. At this time, we are unable to remedy such a limitation.

On a final note, mixtures of *E*- and *Z*-isomers of **1** may be strongly enriched in (*E*)-alkene (>95% by integration of ^1H NMR spectra) by refluxing in toluene in the presence of a catalytic amount of I_2 (Table 2).[17,18]

In summary, we have shown that readily available 5-(trimethylsilyl)methyl-oxazole-4-carboxylate esters are useful for the Peterson synthesis of (*E*)-5-alkenyl oxazoles. Applications of this chemistry to problems in total synthesis will be described in due course.

Table 2
Equilibration of (*E*/*Z*)-1 to the (*E*)-isomer



Entry	R^1	R^2	Initial *E*/*Z* ratio	Final *E*/*Z* ratio
1d	Ph	2-Me–C_6H_4	1:1	*E* only detectable
1i	Ph	Ph	3:1	96:4
1j	Me	Ph–CH_2–CH_2	1.5:1	96:4

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Supplementary data

Supplementary data (experimental procedures and spectral data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.076.

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16. *Representative procedure for the Peterson olefination with* **20**: preparation of compound **1a**. Commercial *n*-BuLi solution (1.6 M in hexanes, 230 μL, 1.4 mmol) was added dropwise to a cold (−78 °C) solution of diisopropylamine (50 μL, 360 mmol, 1.1 equiv) in dry THF (300 μL) under argon. The resultant was stirred at (−78 °C) for 30 min, then, a dry THF (600 μL) solution of **20** (100 mg, 330 mmol, 1.0 equiv) was added dropwise, and the mixture was stirred for 30 min. Neat propionaldehyde (100 μL, 1.4 mmol, 4.2 equiv) was added rapidly in one portion, followed by commercial $TiCl_4$ in CH_2Cl_2 (1 M, 360 μL, 360 mmol), and the mixture was stirred for 5 h at −78 °C. Deionized H_2O (200 μL) was cautiously added and the solution was warmed to rt. The mixture was extracted three times with diethyl ether (20 mL). The combined extracts were washed with deionized H_2O (15 mL), dried ($MgSO_4$), filtered, and concentrated. A toluene (3 mL) solution of the crude residue plus $TsOH{\cdot}H_2O$ (63 mg, 330 mmol) was refluxed for 20 min under Ar, then it was cooled and evaporated. The residue was partitioned between Et_2O (20 mL) and aq satd $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with more Et_2O (15 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatographic purification of the residue (20% EtOAc in hexane) yielded 71 mg (79%) of **1a,** white solid, 9:1 mixture of *E*- and *Z*-isomers. ^1H (*E*-isomer): 8.10–8.13 (m, 2H), 7.45–7.48 (m, 3H), 6.98 (dt, J_1 = 16.1, J_2 = 1.5, 1H), 6.73 (dt, J_1 = 16.1, J_2 = 6.5, 1H), 4.45 (q, J = 7.1, 2H), 2.36 (m, 2H), 1.44 (t, J = 7.1, 3H), 1.16 (t, J = 7.4, 3H); ^1H (*Z*-isomer): 8.10–8.13 (m, 2H), 7.45–7.48 (m, 3H), 6.90 (dt, J_1 = 14.4, J_2 = 1.7, 1H), 6.01(dt, J_1 = 11.9, J_2 = 7.5, 1H), 4.45 (q, J = 7.1, 2H), 2.70 (m, 2H), 1.43 (t, J = 7.1, 3H), 1.19 (t, J = 7.6, 3H); ^{13}C: 162.31, 159.39, 154.46, 140.42, 130.89, 128.70, 126.96, 126.80, 126.51, 114.95, 61.13, 26.26, 14.38, 12.84; IR: 1710.4; HRMS: calcd for $C_{16}H_{17}NO_3$ Na 294.1106, found 294.1100. Chromatography of the crude Peterson mixture before TsOH treatment had afforded **1a** in only 50% yield. See the Supplementary data for additional details.
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18. *Representative procedure for the isomerization of mixtures of geometric isomers*: (*E*)-**1i.** A toluene (300 mL) solution of a 3:1 mixture of (*E*)- and (*Z*)-**1i** (16 mg, 50 mmol) and a small crystal of I_2 (0.6 mg, ca. 5 mol %) was refluxed under Ar for 18 h. The mixture was diluted with Et_2O (20 mL) and washed with aq satd $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with more Et_2O (15 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to provide 16 mg (100%) of **1i**, as a 96:4 mixture of (*E*) and (*Z*)-isomers (integration of ^1H NMR spectrum). White solid, mp 114–116 °C. ^1H: 8.17–8.20 (m, 2H), 7.68 (d, 1H, J = 16.4), 7.62–7.33 (m, 9H), 4.49 (q, 2H, J = 7.1), 1.48 (t, 3H, J = 7.2). ^{13}C: 162.2, 159.9, 154.4, 135.8, 134.5, 131.1, 129.2, 128.9, 128.8, 128.7, 127.3, 127.0, 126.4, 113.2, 61.3, 14.4. See Supplementary data for additional information.