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Three-Component Synthesis of Highly Functionalized 5-Acetyloxazoles

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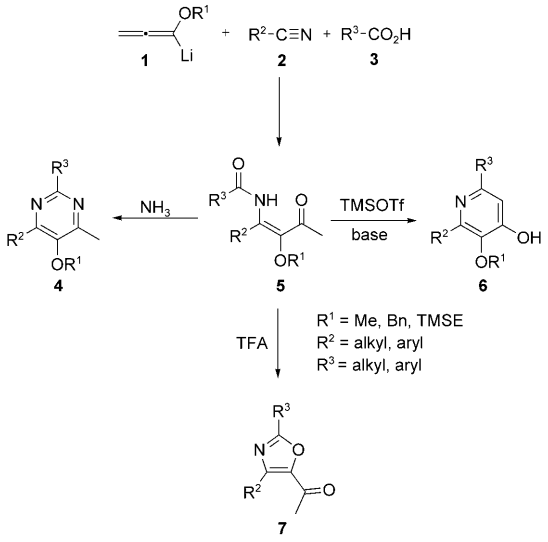
The occurrence of the oxazole subunit in architecturally complex structures and their use in functional materials contributed to an ongoing interest in this class of heterocycles. More precisely, oxazole derivatives have found industrial application as scintillator and laser dyes.[1] Owing to their important biological activities alkaloids with oxazole moieties have attracted much attention in drug development as potent antitumor, antibacterial, antiviral or antifungal agents.[2] To date, a variety of synthetic methods for oxazoles has been reported.[1,3,4] One of the most widely used syntheses of 2,5-di- and 2,4,5-trisubstituted oxazoles is the cyclodehydration of α-acylamino-ketones known as Robinson–Gabriel reaction.[5] Most of the Robinson–Gabriel based methods require harsh dehydrating agents and the direct introduction of different functional groups in 2-, 4- or 5-position is quite rare.

In our previous work we reported on the high utility of alkoxyallenes **1** as C-3 building blocks in the synthesis of heterocyclic compounds as intermediates of natural products or other interesting products.[6] Enamides, such as **5**, are readily accessible in one step by a novel three-component synthesis using lithiated alkoxyallenes, nitriles and carboxylic acids as key components. The mechanism of the enamide formation has already been discussed in former publications.[7] Recently, we have demonstrated that enamides **5** are ideal precursors for the synthesis of highly functionalized 4-methylpyrimidines[8] **4** and 4-hydroxypyridine derivatives[9] **6** using either ammonium salts or trimethylsilyl trifluoromethanesulfonate and base (Scheme 1). Herein, we describe reaction conditions that easily convert alkoxy-substituted enamides **5** to 2,4-substituted 5-acetyloxazoles **7**.[10] This method easily allows the incorporation of different substituents in 2- and 4-position of the resulting oxazoles.



Scheme 1. Synthesis of 4-methylpyrimidines **4**, 4-hydroxypyridines **6**, and 5-acetyloxazole derivatives **7** via alkoxy-substituted enamides **5** starting from lithiated alkoxyallenes **1**, nitriles **2** and carboxylic acids **3**.

Following the reported procedure enamides **5a–i** could be obtained in moderate to good yields. As depicted in Table 1 (entries 1–7) benzyloxy- or trimethylsilylethoxy-protected allenes reacted with benzonitrile and different carboxylic acids in yields between 21 and 75%. In case of $R^3 = CF_3$ (entry 1) enamide **5a** could be isolated in 40% together with the corresponding 4-hydroxypyridine **6** as a side product in 36% yield. The different solubilities of the aromatic or heteroaromatic carboxylic acids (entries 2–5) might be the reason why the yields vary in a range of 24 and 75% (in general not optimized). While benzoic acid and 2-thiophene carboxylic acid could be dissolved in diethyl ether or THF before adding to the reaction mixture, picolinic acid was only soluble in DMF and precipitated immediately at −78 °C. The reaction was also performed with propiolic acid and pyruvic acid giving products with an alkynyl or an acetyl moiety in low yields (21 and 28%, entries 6 and 7).

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Responsible for X-ray crystal structure analysis.

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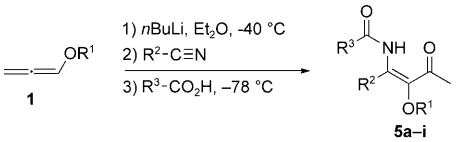
Table 1. Three-component synthesis of enamides **5a–i** starting from alkoxyallenes **1**.



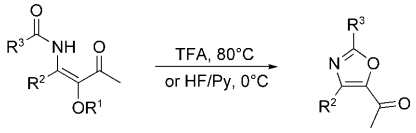
Entry	R^1	R^2	R^3	Product	Yield[a] [%]
1	Bn	Ph	CF_3	**5a**	40[b]
2	Bn	Ph	Ph	**5b**	54[8]
3	Bn	Ph	2-pyridyl	**5c**	27
4	TMSE	Ph	2-pyridyl	**5d**	24
5	TMSE	Ph	2-thienyl	**5e**	75
6	TMSE	Ph	C≡CH	**5f**	21
7	TMSE	Ph	acetyl	**5g**	28
8	Bn	n-C_9H_{19}	Ph	**5h**	27
9	TMSE	*c*Pr	*c*Pr	**5i**	75

[a] Reaction conditions: 1) Alkoxyallene (1.0 or 3.0 equiv), *n*BuLi (1.1 or 2.7 equiv), Et_2O, −40 °C, 20 min. 2) Nitrile (1.5 or 1.0 equiv), 30 min at −40 °C. 3) −78 °C, 4 h, then carboxylic acid (3.0 or 6.0 equiv), warm up to RT overnight. TMSE = trimethylsilylethyl, *c*-Pr = cyclopropyl. [b] In addition 36 % pyridinol **6** isolated as side product.

Changing the nitrile to *n*-nonylnitrile and treatment with benzoic acid gave only poor yields (27 %, entry 8). Gratifyingly, the use of cyclopropylnitrile and cyclopropane carboxylic acid as components afforded the expected product in high yields (75 %, entry 9).

The cyclization of enamides **5a–i** to the corresponding oxazole derivatives was carried out in a sealed tube with an excess of trifluoroacetic acid acting as solvent and reagent. After heating at 80 °C for 15–20 min the corresponding 5-acetyloxazoles **7a–h** were obtained in moderate to very good yields (Table 2, entries 1–9, 39–99 %). Noteworthy, not only electron-withdrawing heteroaryl groups can be introduced to the C-2 position in similar yields, but also alkynyl or acetyl substituents are possible at this ring position (entries 6 and 7). The C-4 position is not restricted to aromatic substituents as oxazoles with an unbranched alkyl chain or a cyclopropyl substituent could also be prepared (entries 8 and 9). To compare the reactivity of benzyl and trimethylsilylethyl-protected enamides we prepared enamides **5c** and **5d** (Table 1, entries 3 and 4) with identical substituents R^2 and R^3. Entries 3 and 4 of Table 2 reveal higher yields of the corresponding oxazole **7** starting from the trimethylsilylethyl-protected enamide **5**. Attempts to apply fluoride reagents, such as HF/pyridine, to trimethylsilylethyl-protected enamides, such as **5i**, were successful, but the yield of **7h** could not be increased.

Table 2. Synthesis of oxazole derivatives **7a–h**.



Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	Bn	Ph	CF_3	**7a**	74
2	Bn	Ph	Ph	**7b**	48
3	Bn	Ph	2-pyridyl	**7c**	64
4	TMSE	Ph	2-pyridyl	**7c**	99
5	TMSE	Ph	2-thienyl	**7d**	68
6	TMSE	Ph	C≡CH	**7e**	57
7	TMSE	Ph	acetyl	**7f**	39
8	Bn	n-C_9H_{19}	Ph	**7g**	51
9	TMSE	*c*Pr	*c*Pr	**7h**	67, 34[b]

Reaction conditions: [a] TFA (excess), sealed tube, 80 °C, 15–20 min. [b] HF/Py (3.0 equiv), 0 °C, 1 min.

According to the structure determination of the 2,4-dicyclopropyloxazole derivative by X-ray diffraction **7h** possesses crystallographic C_s symmetry (Figure 1).[11] As a consequence the carbon planes of both cyclopropane rings are exactly in perpendicular orientation with respect to the oxazole ring. These antiperiplanar conformations allow favorable electronic interactions of the heteroaryl moiety with the cyclopropane rings.

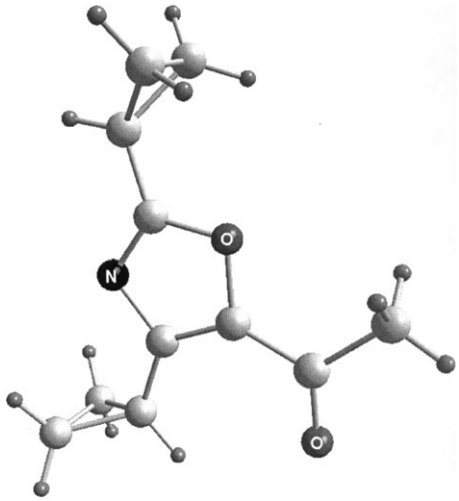
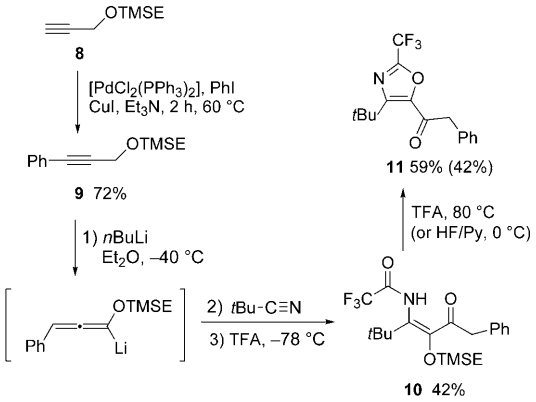


Figure 1. X-ray crystal structure of compound **7h**.

The formation of oxazole derivatives could be explained in accordance to the Robinson–Gabriel mechanism for the cyclodehydration of α-acylaminoketones. In contrast to the generally accepted mechanism of the Robinson–Gabriel reaction[12] our preliminary studies with ^{18}O-labelled enamides showed that the enol oxygen is incorporated into the oxazole ring. This discovery fits to the mechanism assumed for the conversion of *ortho*-hydroxy benzeneamides into benzoxazoles.[13]

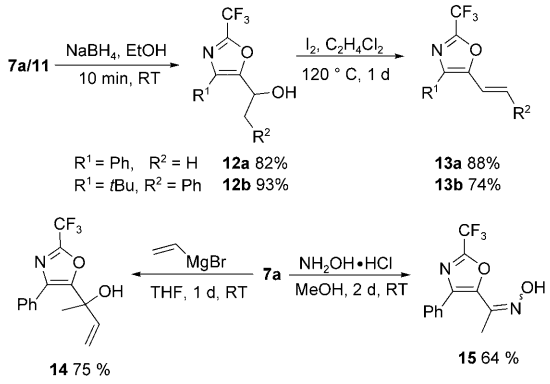
Next we focused our attention to the substituent at C-5 of the oxazole. Our method is not restricted to introduce 5-acetyl substituted oxazoles as demonstrated by the synthesis of derivative **11**. This compound could be prepared by a γ-phenyl substituted (trimethylsilylethoxy)alkyne **9**, using the general reaction conditions for the synthesis of enamides and oxazoles (Scheme 2). First, Pd-catalyzed coupling of alkyne **8**[14] with iodobenzene yielded alkyne **9** in 72 %. Direct isomerization of this compound with *n*-butyllithium



Scheme 2. Synthesis of enamide **10** and oxazole **11** starting from γ-phenyl substituted (trimethylsilylethoxy)alkyne **9**.

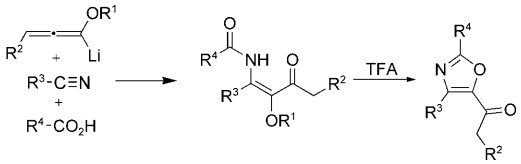
at −40 °C to the α-lithiated alkoxyallene and subsequent treatment with pivalonitrile and trifluoroacetic acid generates the enamide **10** in 42 % yield. The cyclization was either possible with trifluoroacetic acid under the general conditions or with HF/pyridine to provide the expected product **11** in 59 or 42 % yield, respectively.

Oxazoles with the 5-acetyl group are not easily available by other methods.[15] Only a few deal with the synthesis of related oxazol-5-yl ketones.[16] This functional group enables the preparation of a variety of other oxazole derivatives. The trifluoromethyl-substituted oxazoles **7a** and **11** were smoothly reduced using sodium borohydride to give the corresponding alcohols **12a–b** in very good yields (82–93 %). Subsequent dehydration employing Hibbert conditions furnished 5-alkenyl-substituted oxazoles **13a–b** in 74 and 88 % yield (Scheme 3). NMR spectroscopy confirmed the *trans*-configuration of compound **13b**. These oxazole derivatives can be starting point for further synthetic elaboration. Grignard addition of vinylmagnesium bromide to oxazole **7a** afforded compound **14** in good yield (75 %), which should be a suitable precursor for further studies leading to Diels–Alder products. Treatment of **7a** with hydroxylammonium chloride provided oxime **15** as the singular isomer in 64 % yield.



Scheme 3. Subsequent reactions of oxazole derivatives **7a** and **11**.

In conclusion, we have developed a novel and fast three-component synthesis to 2,4-disubstituted 5-acetyloxazoles using α-lithiated alkoxyallenes, nitriles and carboxylic acids as precursors. The two-step procedure allows a highly flexible substitution pattern at C-2 and C-4 position (Scheme 4). The acetyl group at C-5 can be further functionalized employing standard reactions. Scope and limitations of this method leading to highly substituted oxazole derivatives is currently under investigation.



Scheme 4. Highly flexible substitution pattern in all positions.

Experimental Section

Synthesis of enamide 5i (typical procedure): Trimethylsilylethoxyallene (4.00 g, 25.6 mmol) was dissolved in Et_2O (52 mL) and *n*-butyllithium (9.73 mL, 24.3 mmol, 2.5 M in hexanes) was added at −40 °C. After 25 min at −50 °C to −40 °C cyclopropane nitrile (0.95 mL, 12.8 mmol) was added. The solution was stirred at −40 °C for 30 min and then cooled down to −78 °C. After stirring for 4 h at this temperature cyclopropane carboxylic acid (4.06 mL, 51.2 mmol) was added and the mixture was warmed up overnight to room temperature. The mixture was quenched with satd. aq. $NaHCO_3$ solution (40 mL) and extracted twice with Et_2O (40 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:10) provided **5i** as colorless oil (2.98 g, 75 %).

Synthesis of oxazole 7h (typical procedure): Enamide **5i** (144 mg, 0.465 mmol) was added in a sealed tube and dissolved in TFA (2.0 mL). The reaction mixture was placed in a preheated oil bath (80 °C). After stirring for 15 min at this temperature water (4.0 mL) was slowly added to the reaction mixture and extracted three times with CH_2Cl_2 (4.0 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:10) provided **7h** as colorless solid (60 mg, 67 %).

Acknowledgements

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Keywords: cumulenes · cyclization · heterocycles · multicomponent reactions · oxazoles

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[11] CCDC 718587 (**7h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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