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New four-component condensations leading to 2,4,5-trisubstituted oxazoles☆

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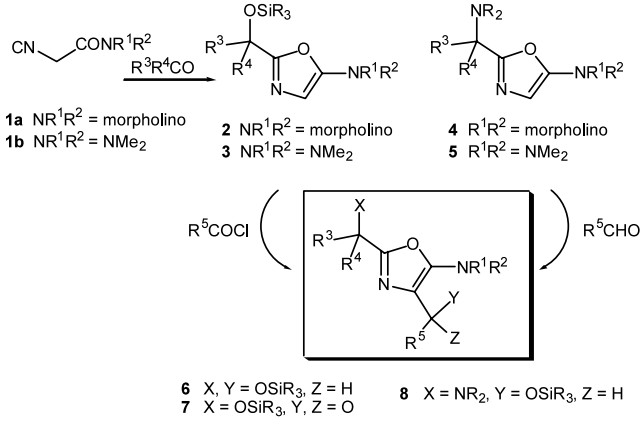
Abstract—A one-pot reaction leading to the title compounds has been developed based on the in situ acylation and hydroxyarylation of 5-aminooxazoles at the 4-position of the heterocycle.

Multiple component condensations play a central role in combinatorial chemistry and diversity oriented synthesis.[1] Such reactions, 'in which three or more reactants come together in a single reaction vessel to form a new product that contains portions of all the components,'[2] remain relatively rare in organic chemistry, but are instrumental in assembling libraries of small molecules used in pharmaceutical discovery and development.

In the preceding paper, we describe two useful three-component condensations of isocyanoacetamides **1** and carbonyl compounds with either chlorosilanes or amines and an appropriate acid promoter (Scheme 1).[3] The former reaction leads to 2-oxyalkyl-5-aminooxazoles (e.g. **2**, **3**) and the latter to 2-aminoalkyl-5-aminooxazoles (e.g. **4**, **5**).

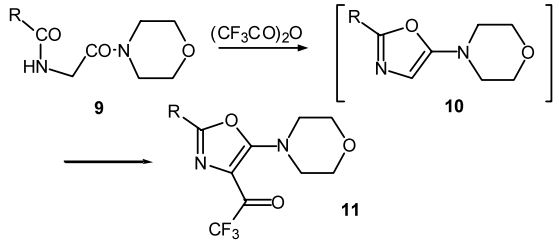
Here we demonstrate that the 4-position of such oxazoles can be further substituted using aldehydes or acid chlorides to afford a broad array of 2,4,5-trisubstituted oxazoles **6**–**8**. Besides being active pharmacophores in their own right,[4] such heterocycles can also serve as precursors for oxazolines[5] and pyrrolopyridines,[6] as well as hexasubstituted benzenes.[7] Moreover, by appropriate adjustment of reaction conditions it is possible to prepare polysubstituted oxazoles like **6**–**8** in one reaction vessel by four- and even five-component condensations incorporating diversity elements from several building blocks.

Electrophilic substitution at C-4 in 5-aminooxazoles was first demonstrated in the trifluoroacetic anhydride-promoted cyclization of α-acylaminoamides **9** (Scheme 2). Under the conditions reported, the initially formed



1a NR^1R^2 = morpholino
1b NR^1R^2 = NMe_2
2 NR^1R^2 = morpholino
3 NR^1R^2 = NMe_2
4 R^1R^2 = morpholino
5 R^1R^2 = NMe_2
6 X, Y = $OSiR_3$, Z = H
7 X = $OSiR_3$, Y, Z = O
8 X = NR_2, Y = $OSiR_3$, Z = H

Scheme 1.



Scheme 2.

☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)01751-9

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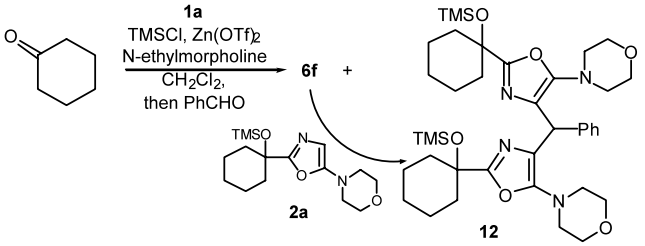
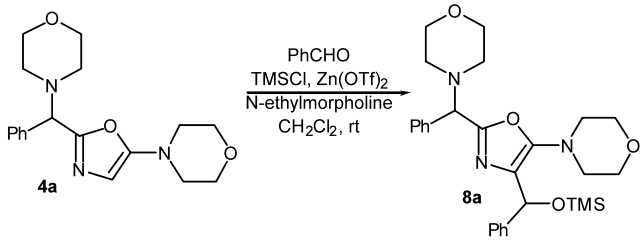


Scheme 3.



Scheme 4.

5-aminooxazole **10** reacted with excess anhydride to furnish **11**.[8] To explore the scope and generality of such enamine-like substitutions, the behavior of 5-aminooxazoles **2**–**5** was investigated in reactions with a variety of electrophiles.

An earlier observation[3] that the 5-aminooxazole formed in the reaction of **1a** with benzaldehyde underwent a second carbonyl addition at C-4 led us to investigate a one-pot, four-component process involving the serial condensation of **1** with two different carbonyl compounds using $R_3SiCl/Zn(OTf)_2$ as promoter. Reaction of **1a** with cyclohexanone and benzaldehyde led to the trisubstituted heterocycle **6f** (18–20%) as well as a second product, bis-oxazole **12** (20%, Scheme 3), which likely arose by condensation of **6f** with **2a**.

Adding more *N*-ethylmorpholine with the second carbonyl compound suppressed formation of **12**, raising the yield of **6f** to 55%. Replacing TMSCl with Et_3SiCl and adding supplemental $Zn(OTf)_2$ gave **6f** in 72% yield. However, reactions with the more electron rich isonitrile **1b** gave predominantly dimers like **12** and higher-order condensation products. Table 1 summarizes condensations using **1a** with a variety of aldehydes and ketones demonstrating the scope of this new MCC reaction.

Aromatic aldehydes gave the best results in the second condensation step, since enolizable aliphatic aldehydes or ketones rapidly formed the corresponding enol silyl ether derived from $(CH_3)_3SiCl$ or Et_3SiCl.[9] Those conditions led to the results summarized in Table 1.

Substituted 5-aminooxazoles like **4a** (Scheme 1) prepared by reaction of **1a** with iminium ions also gave trisubstituted oxazoles with aromatic aldehydes (Scheme 4). The formation of **8a** in 54% yield from **4a** demonstrated that cross-condensation products could be prepared that introduced both nitrogen and oxygen functionality around the heterocyclic core. In this instance, the serial, one-pot process gave **8a** directly from **1a** in only 19% yield.

The acylation of substituted 5-aminooxazoles was also investigated (Table 2). Oxazoles **2** and **3** reacted with a broad range of aliphatic and aromatic acid chlorides, including crotonyl, cinnamoyl, phenoxyacetyl, and phenacetyl chlorides, giving products **7a**–**k** in good yields. By contrast, acylations of diaminooxazoles **4** and **5** were problematic, and formed decomposition products likely arising from acylammonium complexes of the benzylic nitrogen substituent.

Since in some cases similar reaction conditions could be used for heterocycle-forming and subsequent ring acylation steps, it was of interest to investigate a one-pot, four-component process for assembling trisubstituted oxazoles **7** (Scheme 5) using an isonitrile, carbonyl compound, silane, and acid chloride

Several successful examples are shown in Table 3. In the one-pot procedure, both C–C bond-forming steps are promoted using $Zn(OTf)_2/Et_3SiCl$/*N*-ethylmorpholine. As expected (entries 1 and 2), using Et_3SiOTf in place of $Zn(OTf)_2/Et_3SiCl$ gave similar results.[10] The desired trisubstituted oxazoles were obtained pure by careful flash column chromatography.

Table 1. One-pot synthesis of trisubstituted oxazoles **6**[a]

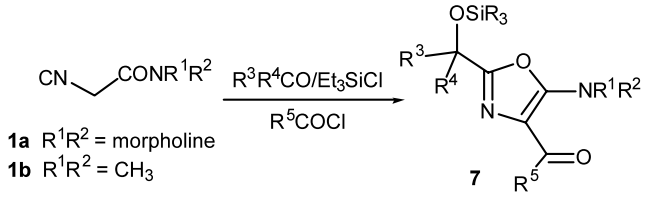
RNC	R^3COR^4/R_3SiCl	R^5CHO/R_3SiCl	Product (yield)
1a	$(CH_3)_3CCHO/Et_3SiCl$	$PhCHO/Et_3SiCl$	**6a** (51%)
1a	$Ph(CH_2)_2CHO/Et_3SiCl$	$PhCHO/Et_3SiCl$	**6b** (61%)
1a	PhCHO/TMSCl	PhCHO/TMSCl	**6c** (54%)
1a	$PhCHO/Et_3SiCl$	$PhCHO/Et_3SiCl$	**6d** (40%)
1a	*p*-$MeOC_6H_4CHO/Et_3SiCl$	*p*-$MeOC_6H_4CHO/Et_3SiCl$	**6e** (43%)
1a	Cyclohexanone/TMSCl	PhCHO/TMSCl	**6f** (55%)
1a	Cyclohexanone/Et_3SiCl	$PhCHO/Et_3SiCl$	**6g** (72%)
1a	Cyclohexanone/Et_3SiCl	*p*-$MeOC_6H_4CHO/Et_3SiCl$	**6h** (35%)
1a	Cyclohexanone/Et_3SiCl	*p*-ClC_6H_4CHO/Et_3SiCl	**6i** (50%)
1a	Cyclohexanone/TMSCl	$PhCHO/Et_3SiCl$	**6j** (54%)

[a] *Conditions*: (i) $Zn(OTf)_2$ (0.5 equiv.), R_3SiCl (2 equiv.), *N*-ethylmorpholine, (2.1 equiv.) CH_2Cl_2, R^3R^4CO (1.3 equiv.), rt, 2 h; (ii) *N*-ethylmorpholine (3 equiv.), R_3SiCl (2 equiv.), R^5CHO (1.5 equiv.), $Zn(OTf)_2$ (0.5 equiv.), 12 h.

Table 2. Condensations of oxazoles **2** and **3** with acid chlorides[a]

Oxazole	Acid chloride	Product	% Yield
2a R = Et R_3, $R_4 = (CH_2)_5$	Butyryl	**7a** $R^5 = n\text{-}C_3H_7$ NR_2 = morph	74
2a	Isobutyryl	**7b** $R^5 = i\text{-}C_3H_7$ NR_2 = morph	68
2b R = Et R^3 = H $R^4 = n\text{-}C_9H_{19}$	Butyryl	**7c** $R^5 = n\text{-}C_3H_7$ NR_2 = morph	70
3a R = Et R^3 = H, $R^4 = Ph(CH_2)_2$	Acetyl	**7d** $R^5 = CH_3$ $NR_2 = NMe_2$	72
3b R = Et $R^3R^4 = (CH_2)_5$	Benzoyl	**7e** R^5 = Ph $NR_2 = NMe_2$	71
3b	Acetyl	**7f** $R^5 = CH_3$ $NR_2 = NMe_2$	74
3b	Butyryl	**7g** $R^5 = n\text{-}C_3H_7$ $NR_2 = NMe_2$	63
3b	Crotonyl	**7h** $R^5 = CH_3CH$=CH $NR_2 = NMe_2$	35
3b	Cinnamoyl	**7i** R^5 = PhCH=CH	79
3b	$PhOCH_2COCl$	**7j** $R^5 = PhOCH_2$ $NR_2 = NMe_2$	77
3b	$PhCH_2COCl$	**7k** R^3 = H $R^4 = PhCH_2$	47

[a] *Conditions*: $Zn(OTf)_2$ (0.3 equiv.), RCOCl (2.5 equiv.), pyridine (3.5 equiv.), 1:1 CH_2Cl_2/THF, rt.



Scheme 5.

In summary, the synthesis of highly substituted oxazoles from isonitriles can be achieved in a convergent approach that uses aldehydes and ketones as well as chlorosilanes and acid chlorides as inputs. In one example a five-component condensation was successfully implemented involving the combination of isonitrile **1a** with two different carbonyl compounds and two different chlorosilanes to afford compound **6j**. The ready availability of these well-known families of compounds should make it possible to assemble libraries of pharmaceutically interesting heterocyclic systems from simple starting materials.

Table 3. One-pot, four-component condensation leading to trisubstituted oxazoles **7** (R = Et)[a]

RNC	R^3R^4CO	R^5COCl[a]	Product	% Yield
1a	Cyclohexanone	Butyryl-Cl (A)	**7a** R^3, $R^4 = (CH_2)_5$ $R^5 = n\text{-}C_3H_7$	43
1a	Cyclohexanone	Butyryl-Cl (B)	**7a**	48
1a	Pivalaldehyde	$PhOCH_2$-COCl (C)	**7l** R^3 = H $R^4 = (CH_3)_3C$ $R^5 = PhOCH_2$	35
1b	Hydrocinnam-aldehyde	Acetyl-Cl (A)	**7d** R^3 = H $R^4 = Ph(CH_2)_2$ $R^5 = CH_3$	35
1b	Isobutyr-aldehyde	Cinnamoyl-Cl (A)	**7m** R^3 = H $R^4 = i\text{-}C_3H_7$ R^5 = PhCH=CH	36

[a] *Conditions*: (A) (i) $Zn(OTf)_2$ (0.3 equiv.), *N*-ethylmorpholine (1.6 equiv.), Et_3SiCl (1.2 equiv.), R^3R^4CO (1.2 equiv.), CH_2Cl_2, rt, 2 h, (ii) pyridine (3.5 equiv.), R^5COCl (2.5 equiv.), THF, rt; (B) Et_3SiOTf (1.2 equiv.) replaced $Zn(OTf)_2$ and Et_3SiCl; (C) TMSCl replaced Et_3SiCl.

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9. Reactions using cinnamaldehyde as the second carbonyl component afforded the corresponding dimer **12** and other higher-order condensation products.
10. Representative procedures, as well as spectroscopic and physical characterization data for new compounds are included in Supplementary Data, which is available on the Web.