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A general synthesis of 2-substituted-5-aminooxazoles: building blocks for multifunctional heterocycles☆

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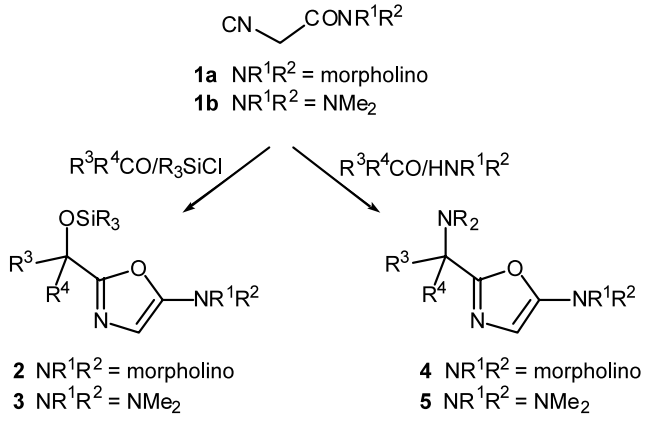
Abstract—Condensation of unsubstituted isocyanoacetamides with aldehydes and ketones, or their derived iminium ions, leads to 2-substituted-5-aminooxazoles, which are useful compounds for drug discovery programs.

Recently, as part of a program to develop new multiple component condensation (MCC) reactions for combinatorial chemistry, we described a new silyl-promoted variant of the Passerini condensation. In that reaction, simple carbonyl compounds combined with ethyl isocyanoacetate to afford 2-substituted-5-ethoxyoxazoles in a one-pot process that involved nucleophilic participation by the carboethoxy group.[1] Naturally-occurring oxazoles are widely distributed as subunits of biologically active natural products,[2] particularly as 2,4,5-trisubstituted heterocycles.[3] Synthetically produced oxazoles also show very favorable pharmacophore profiles in drug discovery programs.[4] However relatively few general methods have been developed that can be used to prepare substituted oxazoles, and most rely on reactive building blocks such as α-halo or α-aminoketones and their derivatives.[5]

To explore the utility of silyl-promoted isonitrile condensations in making combinatorial libraries of diversely functionalized 2,4,5-trisubstituted oxazoles, it was of interest to investigate reactions of isocyanoacetamides like **1**, which would form electron-rich 5-aminooxazoles that should be prone to further substitution at the 4-position of the ring. Here we report successful carbonyl and iminium ion condensations of isonitriles **1** to afford silyloxyalkyloxazoles (e.g. **2**, **3**) and aminoalkyloxazoles (**4**, **5**), respectively. In the following paper, we demonstrate the utility of heterocycles **2**–**5** in assembling a broad array of 2,4,5-trisubstituted oxazoles in new one-pot, four-component condensations.

In 2001, French researchers reported that alkyl-substituted isocyanoacetamides condensed with electrophilic iminium ions, prepared in situ from carbonyl compounds and primary or secondary amines, to afford oxazoles.[6] However, the French group did not investigate reactions of unsubstituted isocyanoacetamides, despite their prospective utility, because of concerns about the potential for competing nucleophilic substitution at both the isonitrile and the active methylene carbons in **1**. It was also unclear whether isocyanoacetamides were sufficiently nucleophilic to condense with the cognate carbonyl compounds themselves, which are less electrophilic than their derived iminium ions.

In fact, isocyanoacetamides **1a** and **1b**[7] reacted with simple carbonyl compounds in the presence of R_3SiCl,



Scheme 1.

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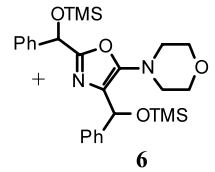
$Zn(OTf)_2$ and *N*-ethylmorpholine (NEM) to form 2,5-disubstituted oxazoles **2** (Scheme 1). The method was general in scope, successfully affording the desired condensation product using representative carbonyl compounds.[8] Both trimethylsilyl chloride and triethylsilyl chloride proved to be effective promoters, Moreover, despite initially-expressed concerns about the reactivity of unsubstituted isocyanoacetamides, no products derived from alkylation at the active methylene carbon of **1** were detected.

In the reaction of **1a** with benzaldehyde, the desired adduct **2g** was only formed at 0°C and in 29% yield, along with an unexpected product **6** (Table 1) in 20% yield, which likely arose by a second condensation of benzaldehyde at the 4-position of **2g**. This side reaction proved to be general with aromatic aldehydes.

Iminium salts, prepared in situ from carbonyl compounds and amines,[9] also reacted smoothly with the isonitriles **1a** and **1b** as shown in Table 2. No deleterious side reactions were noted involving the active methylene group of **1**, either using morpholine or the more basic dimethylamine to generate reactive iminium electrophiles. The reaction worked most conveniently in methanol at rt (Table 2), but could also be conducted in less polar solvents such as CH_2Cl_2 or toluene at reflux.

Table 1. Silyl-promoted condensations of isocyanoacetamides **1a** and **1b** with aldehydes and ketones[a]

RNC	Carbonyl compound	R_3SiCl	Product	% Yield
1a	$(CH_3)_3CCHO$	TMSCl	**2a** $R^3=H$, $R^4=(CH_3)_3C$	84
1a	$Ph(CH_2)_2CHO$	TMSCl	**2b** $R^3=H$, $R^4=Ph(CH_2)_2$	74
1a	$CH_3(CH_2)_8CHO$	TMSCl	**2c** $R^3=H$, $R^4=n\text{-}C_9H_{19}$	82
1a	$CH_3(CH_2)_8CHO$	Et_3SiCl	**2d** $R^3=H$, $R^4=n\text{-}C_9H_{19}$	72
1a	Cyclohexanone	TMSCl	**2e** R^3, $R^4=(CH_2)_5$	79
1a	Cyclohexanone	Et_3SiCl	**2f** R^3, $R^4=(CH_2)_5$	77
1a	PhCHO	TMSCl 0°C	**2g** $R^3=H$, $R^4=Ph$	29
			 **6**	20
1b	$Ph(CH_2)_2CHO$	Et_3SiCl	**3a**	73
1b	Cyclohexanone	Et_3SiCl	**3b**	80

[a] *Conditions*: $Zn(OTf)_2$ (0.3 equiv.), R_3SiCl (2 equiv. for **1a**, 1.6 equiv. for **1b**), NEM, (2.1 equiv.) CH_2Cl_2, carbonyl compound (1.3 equiv.), rt.

Table 2. Condensations of isocyanoacetamides **1a** and **1b** with iminium salts

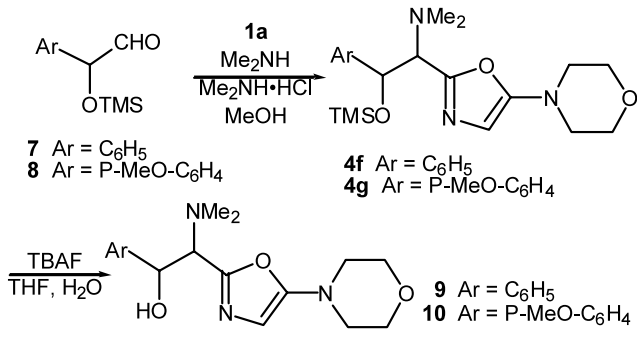
RNC	R^3R^4CO	Amine (cond)[a]	Product	% Yield
1a	PhCHO	Morph	**4a** $R^3=H$, $R^4=Ph$ $NR_2=morph$	88
1a	PhCHO	Me_2NH	**4b** $R^3=H$, $R^4=Ph$ $NR_2=NMe_2$	92
1a	$p\text{-}MeOC_6H_4\text{-}CHO$	Morph	**4c** $R^3=H$, $R^4=p\text{-}MeOC_6H_4$ $NR_2=morph$	82
1a	$Ph(CH_2)_2CHO$	Morph	**4d** $R^3=H$, $R^4=Ph(CH_2)_2$ $NR_2=morph$	92
1a	Cyclohexanone	Morph	**4e** R^3, $R^4=(CH_2)_5$ $NR_2=morph$	92
1b	Cyclohexanone	Morph	**5a** R^3, $R^4=(CH_2)_5$ $NR_2=morph$	80
1b	PhCHO	Me_2NH	**5b** $R^3=H$ $R^4=Ph$ $NR_2=Me_2N$	73
1b	$p\text{-}MeOC_6H_4\text{-}CHO$	Me_2NH	**5c** $R^3=H$, $R^4=p\text{-}MeOC_6H_4$ $NR_2=Me_2N$	75

[a] *Conditions*: R^3R^4CO (1.2 equiv.), amine (1.2 equiv.), $Et_3N{\cdot}HCl$ (1 equiv.), CH_3OH, rt, 12 h.

The best results were obtained in the presence of pyr·HCl or $Et_3N{\cdot}HCl$. In earlier work NH_4Cl was used to catalyze the formation of oxazoles in aprotic solvents from *C*-substituted isocyanoacetamides.[6b]

As the data in Table 2 indicate, iminium ions derived from a wide range of carbonyl compounds could be incorporated into the oxazole ring system using this method.[10] Results with dimethylamine and morpholine suggest that the method should be successful with amines of varying basicity.[11] Even base-sensitive α-silyloxy-substituted arylacetaldehydes such as **7** and **8**[12] reacted smoothly to form the corresponding heterocycles **4f** and **4g**. To confirm their structures, these adducts were deprotected in situ ($Bu_4NF{\cdot}3H_2O$) to afford aminoalcohols **9** and **10** in overall yields of 66 and 70% yield, respectively (Scheme 2). Compounds **9** and **10** were obtained as a mixture of *syn*- and *anti*-diastereomers (1:1.8 for **9**; 1:1.3 for **10**), which could be separated and whose structures were assigned based on

NMR chemical shift and coupling constant data.[13]
The route to 2-substituted-5-aminooxazoles described here generates pharmaceutically interesting heterocycles using a practical and convenient one-pot process that is amenable for use in combinatorial chemistry. The incorporation of peptidyl fragments as component substituents on either the carbonyl or isonitrile (or both)



Scheme 2.

reactants would provide swift access to mimics of natural oxazoles derived by post-translational modification of serine or threonine residues in proteins.[14]

Besides being precursors for oxazolines[15] and pyrrolopyridines,[6] functionalized 5-aminooxazoles have recently been transformed into hexasubstituted benzenes.[16] The further reactivity of oxazoles **2**–**5** and their implementation in new four-component MCC reactions is described in the following paper.

Acknowledgements

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8. *Representative procedure—preparation of* ***2a***: Pivalaldehyde (54 mg, 0.6 mmol) was added to a solution of $Zn(OTf)_2$ (91 mg), TMSCl (190 μL), and *N*-ethylmorpholine (200 μL) in CH_2Cl_2 (0.5 mL) under Ar, immediately followed by isonitrile **1a** (77 mg). The reaction mixture was stirred for 12 h at rt, then diluted with hexane (10 mL). The organic layer was washed with aqueous $NaHCO_3$ (3 mL), dried (Na_2SO_4) and concentrated. The crude products was chromatographed over SiO_2 (1:9 EtOAc:hexane) to afford **2a** as a colorless oil (0.13 g, 84%): ^1H NMR (300 MHz, C_6D_6) δ 5.92 (s, 1H), 4.51 (s, 1H), 3.34 (t, 4H, $J=4.3$ Hz), 2.50–2.70 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (75 MHz) δ 157.6, 156.6, 103.0, 77.1, 65.8, 48.5, 36.2, 26.1, –0.4; FIMS *m*/*z* 312 (M+).
9. The presence of acid (Et_3N·HCl) enabled reactions to occur smoothly at rt and prevented side reactions involving the active methylene group of **1**.
10. *Representative procedure—preparation of* ***4e***: A solution of cyclohexanone (124 μL, 1.2 mmol), morpholine (105 μL), Et_3N·HCl (27 mg), and isonitrile **1a** (154 mg) in methanol (1.5 mL) was stirred overnight. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (10 mL) and aqueous $NaHCO_3$ (5 mL). After further extraction (3×10 mL), the combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated. Chromatography of the residue (SiO_2, 1:99 CH_3OH:EtOAc) afforded **4e** as an oil (296 mg, 92%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 3.78–3.84 (m, 4H), 3.66 (br. s, 4H), 3.02–3.08 (m, 4H), 2.49 (br. s, 4H), 2.18 (br. s, 2H), 1.60–1.82 (m, 4H), 1.20–1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 157.0, 102.7, 68.0, 66.2, 60.1, 48.7, 46.8, 32.6, 25.9, 22.4; IR (film) 2930, 2850, 1610, 1555, 1455; FABMS *m*/*z* 320 (M−1).
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