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A direct preparation of silyl oxazoles: a dramatic chemoselectivity difference between R_3SiOTf and R_3SiCl

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Abstract—General, highly selective silylation conditions for the ambident oxazole anion (isocyano enolate) have been found. The chemoselectivity between *O*-silylation and *C*-silylation changed from <1:99 to >99:1 upon switching from R_3SiCl to R_3SiOTf.

Oxazoles are common heterocycles in a wide variety of natural products possessing biological activity and also are widely used intermediates for functional group transformations.[1] Preparation of 2-substituted oxazoles via *C*-2 lithiation and quenching with an electrophile has been studied extensively but proved to be less straightforward than with typical arylmetallated species.[2] The *C*-2 oxazole anion has a well-documented mobile equilibrium between **2a** and **2b** that has complicated the subsequent reactions (Fig. 1).[3]

Creative solutions to this mobile equilibrium problem have included pre-complexation of the oxazole with borane[4] and transmetallation to the organozinc complexes.[5] *C*-2 Silyl oxazoles react in the ring-closed form and have been shown to couple with aldehydes, acyl iminium salts and acid chlorides.[6] Previous preparations of *C*-2 silyloxazoles involved a two-step process of initial *O*-silylation to give **3a** followed by a thermal 1,5 silyl migration to the *C*-2 silyloxazole **3b**. Unfortunately, this process has not proved general for other oxazole substrates and has limited their use in syntheses.[7,8]

As part of the synthetic efforts to support a drug development program at Merck, a synthesis of a *gem*-dimethylamino substituted pyridyl oxazole **6** was needed (Fig. 2).[9] One option for synthesizing **6** was an

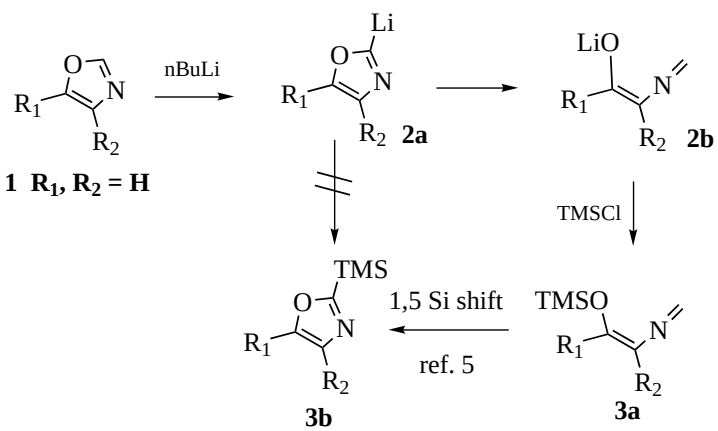

Figure 1.

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ipso-substitution of an iminium species **5** onto the silyloxazole **4a**. In order to explore this route, a practical synthesis of the silyloxazole **4a** was required.

As expected using Dondoni's methodology for preparing *C*-silyloxazoles, metallation of compound **7** followed by quenching with R_3SiCl gave exclusive *O*-silylation (**4b**). However, all attempts to effect thermal isomerization to **4b** were unsuccessful. Only desilylation or no reaction at all was observed under a variety of conditions, including thermal as well as acid or base catalysis.

The initial silylation conditions were then investigated with the goal of altering the product ratio (Table 1). The metallation of the pyridyl oxazole was achieved chemoselectively with a variety of bases as evidenced by deuterium labeling studies, using isopropylmagnesium chloride, LDA, *n*BuLi or potassium *t*-butoxide. Greater than 90% deuterium incorporation was observed for each base. Upon quenching the various metallated oxazoles with TBSCl, no change in the relative *O*/*C* ratios were observed. Even premixing TBSCl with the oxazole, followed by slow LDA addition, gave complete *O*-silylation within the limits of detection. The presence or absence of TMEDA did not affect the *O*/*C* ratio. Some change in selectivity occurred with the potassium isocyano enolate, yet large amounts of enolsilyl ether still contaminated the desired *C*-silyl compound. Finally, when TBSOTf (entries 9 and 10) was added to the magnesiated or lithiated oxazole, complete *C*-2 silylation within the limits of detection was observed. This dramatic reversal of selectivity has not been previously reported in the literature to the best of our knowledge, and prompted examination of the scope and mechanism of this unexpected highly selective silylation.

In order to test the generality of this silylation duality, several other oxazole substrates and different silylating reagents were examined. As can be seen from Table 2, the size of the silylation reagent did not affect the partition between *O*- and *C*-silylation, with TMS, TBS and TIPS chlorides and triflates showing equally selective results (>99:1 selectivity, entries 1, 3–5 and 10). As the trimethylsilyl oxazoles proved to be completely unstable to water and the TBS derivatives only marginally stable, only the TIPS derivatives were prepared for each of the oxazoles (**8**, **12**,[10] **1**, **13**) tested. The tri-isopropylsilyloxazoles were very stable to aqueous workups and column chromatography, and purification without the extensive decomposition seen with the other derivatives was possible. Benzoxazole (**13**) metallation led to a aromaticity-stabilized isocyano phenolate anion, and might have been predicted to give only *O*-silylation regardless of silylation reagent. However, selective differential (*O*,*C*) silylation occurred with both the triflate and the chloride (entries 18 and 19) in line

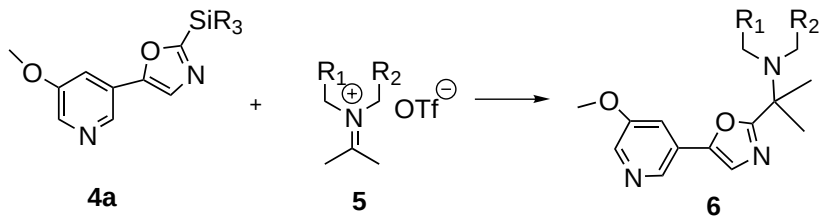
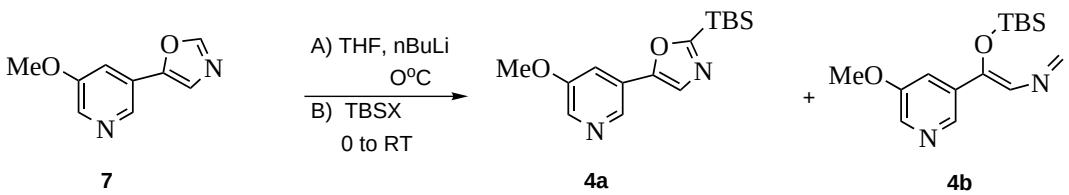


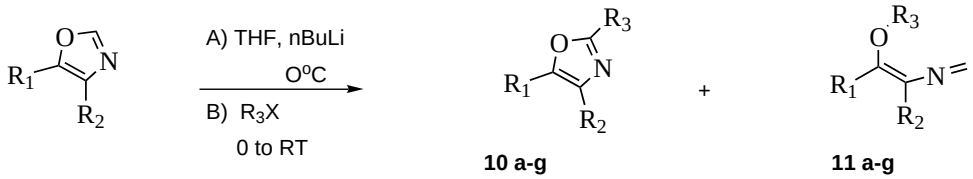
Figure 2.

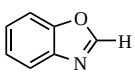
Table 1.



Entry	Base	Solvent	Temp. (°C)	Silylating reagent	Ratio (**4a**:**4b**)
1	*n*BuLi	THF	−5	TBSCl	<1:99
2	*n*BuLi	THF (1 equiv. TMEDA)	−5	TBSCl	<1:99
3	LDA	THF	−5	TBSCl	<1:99
4	LDA	THF	−5	Inverse TBSCl	<1:99
5	*i*PrMgCl	THF (1 equiv. TMEDA)	−5	TBSCl	<1:99
6	KOtBu	THF	−20	TBSCl	2.4:1
7	KOtBu	THF	0	TBSCl	1:1
8	*i*PrMgCl	THF/DMPU (2:1)	−5	TBSOTf	1:3
9	*i*PrMgCl	THF	−5	TBSOTf	>99:1
10	*n*BuLi	THF (1 equiv. TMEDA)	−5	TBSOTf	>99:1

Table 2.



Entry	Oxazole	Silylating conditions[c]	Major product	Ratio (**10**:**11**)	Yield[a]
1	**8** (R_1=Ph, R_2=H)	TBSOTf	**10a**	>99:1	93
2	**8**	TBSOTf (1 equiv. TMEDA)			
3	**8**	TBSCl	**11a**	<1:99	96
4	**8**	TIPSOTf[d]	**10b**	>99:1	95[b]
5	**8**	TIPSCl	**11b**	<1:99	95
6	**8**	TIPSOTf (LiCl added)	**10b**	>99:1	NA
7	**8**	TIPSCl (LiOTf added)	**11b**	<1:99	NA
8	**8**	TMSOTf (−60°C)	**10c**	>99:1	90
9	**8**	TMSOTf (−5°C)	**10c**	>99:1	NA
10	**8**	TMSCl	**11c**	<1:99	92
11	**8**	TMSCl then 0.2 equiv. TMSOTf	**11c**	<1:99	NA
12	**12** (R_1=H, R_2=Ph)	TBSOTf	**10d**	>99:1	87
13	**12**	TBSCl	**11d**	<1:99	90
14	**12**	TIPSOTf[d]	**10e**	>99:1	91[b]
15	**12**	TIPSCl	**11e**	<1:99	96
16	**1** (R_1=H, R_2=H)	TIPSOTf[d]	**10f**	>99:1	94[b]
17	**1**	TIPSCl	**11f**	<1:99	94
18	**13** 	TIPSOTf[d]	**10g**	>99:1	90[b]
19	**13**	TIPSCl	**11g**	<1:99	93

[a] Ratios and yields determined on the crude reaction mixture by NMR using an internal standard.
[b] Isolated yields.
[c] Standard conditions were addition of 1.05 equiv. *n*BuLi (1.6 M) to an inerted and cooled (–5 to –10°C) solution of the oxazole in THF (0.33 M), followed by addition of 1.05 equiv. silylation reagent at –5°C.
[d] TIPOTf purchased from Aldrich contained approx 10% of diisopropyl-*n*-propylsilyltriflate.

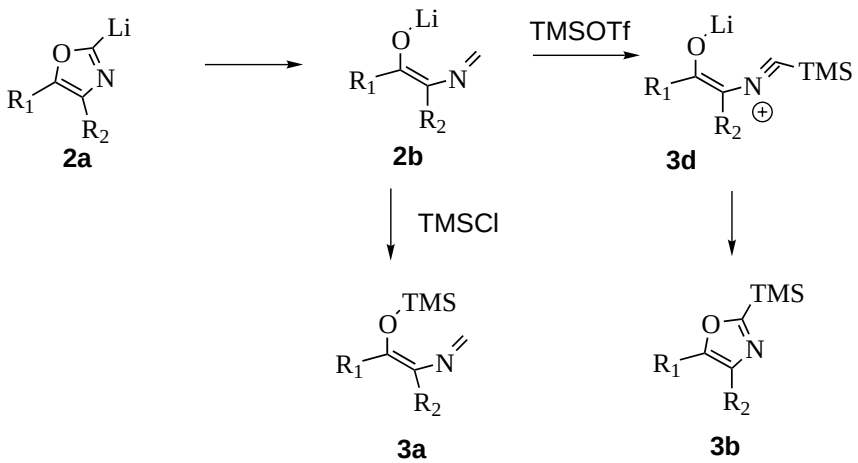


Figure 3.

with the other oxazoles. Parent oxazole[11] **1** gave selective *O*- and *C*-silylations as well (entries 16 and 17) with no detectable isomer either case.[12]

Conceptually, several different pathways can be proposed to explain the observed *C*-silyl product (**3b**, Fig. 3). With silyltriflates, *C*-silylation could occur directly

on the closed-form oxazole anion (**2a**), present in small quantities, though undetectable on the NMR timescale.[13] Alternatively, *C*-silylation of the open-form α-isocyano enolate (**2b**) could occur followed by ring-closure (Fig. 3, **3d**). The observed products are reversed from HSAB theory of *O*/*C* ambident enolate alkylations, whereby hard electrophiles react on oxygen.[14] Lastly, *O*-silylation could occur giving **3b** followed by a 1,5-silyl migration promoted by silyltriflate. However, this last pathway seems unlikely since adding silyltriflate to the enolsilyl ethers or adding lithium triflate to a quenched or unquenched crude TBSCl reaction (entry 7, Table 2) did not alter the ratios. Also, attempted isomerization of *O*-silyl to *C*-silyl with TBSOTf at rt or elevated temperatures failed as well. Mechanistic details of this unexpectedly clean *C*-silylation await further experimental efforts.

In conclusion, a novel preparation of *C*-2 silyloxazoles has been found. The generality, selectivity and yields are superior to the existing literature methods and should therefore find use in various applications.

Acknowledgements

The support of Dr. Paul J. Reider is also gratefully acknowledged.

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12. General procedure: To a dry solution of the oxazole **1** (66 uL, 1.0 mmol) in 3 ml THF (water content less than 200 ug/mL as measured by Karl Fisher titration), under a nitrogen atmosphere and cooled to −20 to −30°C, was slowly added 1.05 mmol *n*BuLi (650 uL, 1.6 M in hexanes). The anion solution was warmed to 0 to −5°C and then either silyl triflate or chloride was added to the anion solution. The mixture was then warmed to room temperature and aged 20 min. The mixture was then diluted with water and isopropylacetate, the layers cut and the organic solution concentrated to dryness. Compound **10f** ^{1}H NMR (600.13 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.21 (s, 1H), 1.41 (septet, $J=7.6$ Hz, 3H), 1.14 (d, $J=7.6$ Hz, 18H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 168.7, 140.4, 126.6, 18.3, 11.0 Compound **11f** ^{1}H NMR (399.87 MHz, $CDCl_3$) δ 6.43 (br d, $J=4.0$ Hz, 1H), 5.02 (d, $J=4.0$ Hz, 1H), 1.15 (m, 21H); ^{13}C NMR (100.55 MHz, $CDCl_3$) δ 166.2, 145.3, 95.0 (t, $J_{N14-C13}=12.8$ Hz), 17.3, 11.7.
13. The NMR of lithiated oxazole **2b** ($R_1=Ph$) was consistent with other published studies of metallated oxazoles shown to be exclusively in the open isocyanoenolate form (**2b**, $R_1=Ph$): ^{1}H NMR (399.87 MHz, d_8-THF) δ 7.68 (m, 2H), 7.15 (m, 3H), 5.20 (s, 1H); ^{13}C NMR (100.55 MHz, d_8-THF) δ 169.3, 164.6, 144.0, 129.22, 129.19, 127.5, 83.5. Magnesiation of **7** in THF/DMPU at 0°C gave the following data consistent with an open form isocyanoenolate anion: ^{1}H NMR (500.13 MHz, d_8-THF) δ 8.38 (s, 1H), 8.11 (s, 1H), 7.98 (br s, 1H), 5.45 (s, 1H), 3.90 (br s, 3H); ^{13}C NMR (125.76 MHz, d_8-THF) δ 164.1, 162.9, 156.9, 139.4, 138.6, 138.0, 117.9, 83.8, 56.6, see Refs. 5a and 5c.
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