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Construction of previously inaccessible 2-amino-4-benzyl substituted oxazoles

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Abstract—A process for the synthesis of 2-amino-4-benzyl-oxazoles is reported.

2-Amino-oxazoles are generally constructed by Harrison's procedure, which involves a sodium hydroxide mediated addition of cyanamide to an α-substituted α′-hydroxyketone, Figure 1.[1] However, when this process is applied to an α-aryl-α′-hydroxyketone, the anticipated product does not form. This observation can most likely be attributed to an undesired enolization, which leads to a complicated mixture of condensation products. Nevertheless, our need for 2-amino-4-benzyl-oxazoles motivated us to develop a strategy for their construction.[2]

Addition of the crude benzyl-cyanamide **1**, procured by treatment of cyanogen bromide with benzyl amine, to a dimer of dihydroxyacetone **2** (0.5 M in THF–H_2O/1:1 with 0.5 equiv NaOH) affords the isolable 2-amino-oxazole **3** (Scheme 1). However, it is more efficient to subject the alcohol **3** to immediate silylation (0.5 M in CH_2Cl_2, 1.1 equiv imidazole, cat. DMAP, 1.1 equiv TBSCl). In this manner, siloxyoxazole **4** arises from benzylamine in a respectable 53% isolated yield after purification (Hex–EtOAc/85:15).

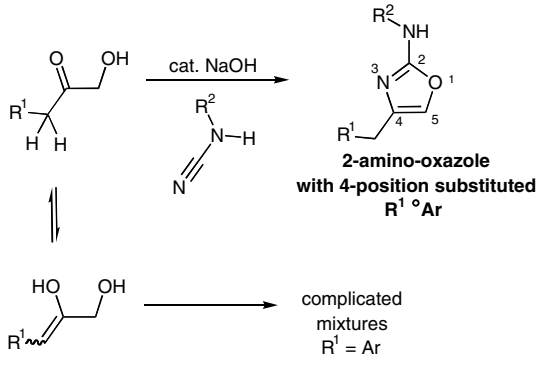
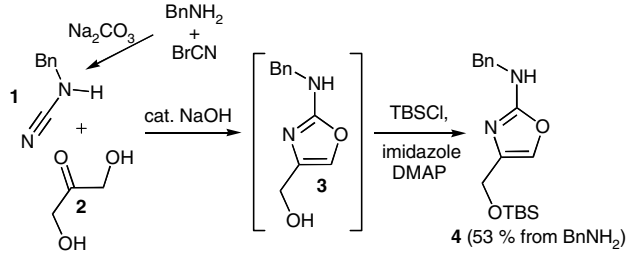
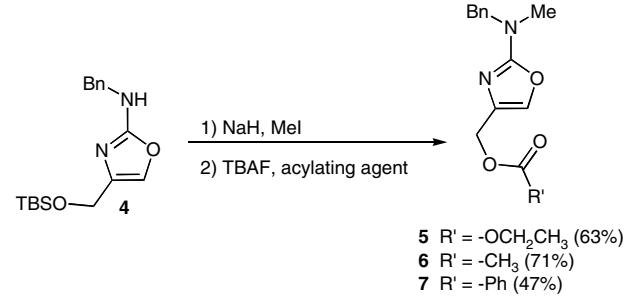


Figure 1. Harrison's synthesis of 2-amino-oxazoles.

After considerable experimentation, the acyl derivatives **5**–**7** were constructed in a single pot from **4** (Scheme 2).



Scheme 1. Synthesis of the oxazole.



Scheme 2. Formation of acyl derivatives.

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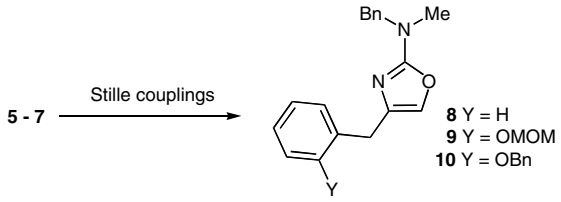
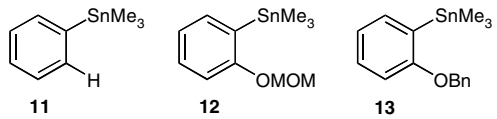
Table 1. Couplings of oxazoles **5**–**7** with aryl nucleophiles



Entries	SM	Conditions	Aryl-Nuc	Prd	Yield (%)
1	**6**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **11**	**8**	0
2	**6**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **12**	**9**	0
3	**7**	3 equiv CuBr	5.0 equiv PhMgBr	**8**	38
4	**7**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **11**	**8**	30
5	**7**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **12**	**9**	52
6	**7**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **13**	**10**	37
7	**5**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **13**	**10**	62
8	**5**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **12**	**9**	83
9	**5**	0.2 equiv $Pd_2(dba)_3$, 3 equiv LiCl	1.3 equiv of **11**	**8**	70

Attempts to methylate *only* the amine functionality in **3** or acylate *only* the hydroxyl residue in **3** were unsuccessful. However, this problem was eventually solved in the following fashion. The –OTBS ether **4** (0.2 M in THF, 0 °C) is first subjected to MeI (1.1 equiv) and NaH (1.5 equiv). After 3.5 h, the organic layer is separated and dried over Na_2SO_4. This crude material is then concentrated in vacuo and sequentially treated (neat) with TBAF (1.1 equiv 1.0 M in THF, 0 °C, 2 h) and ethylchloroformate (1.5 equiv) along with DMAP (1.5 equiv). Work-up and chromatography affords **5** in a 63% overall yield from **4**. The acetate **6** and benzoate **7** are produced in 71% and 47% using similar conditions with acetic anhydride and benzoyl chloride, respectively.

The displacement of these carbonylated materials **5**–**7** by various types of metal nucleophiles was then investigated.[3] As the ethyl carbonate **5** had initially proven very difficult to prepare, we began studying the reactivity of the acetate **6** and the benzoate **7** (Table 1). The acetate **6** proved unreactive (Table 1, entries 1–2). However, addition of PhMgBr (5.0 equiv, 1.0 M in THF) to the benzoate **7** (0.67 M in THF, 60 °C) containing CuBr (3.0 equiv) affords the benzylated oxazole **11** in moderate yields (38%, entry 3).[3] Unfortunately, this protocol does not transfer to aryl Grignard species expressing an *ortho* substituent on the aryl-ring. However, the aryl stannanes **11**–**13**, are effective coupling partners. Hegedus's coupling conditions (0.2 equiv $Pd_2(dba)_3$, 3.0 equiv LiCl, 1.3 equiv of $ArSnMe_3$, 0.67 M NMP) are particularly successful providing substituted oxazoles **8**–**10** in greater than 60% yield from the starting oxazole carbonate **5** (Table 1, entries 7–9).[4] The benzoate **7** can also be used in these processes, but the yields of the benzylated oxazole are significantly lower (Table 1, entries 4–6).



In principle, palladium mediated couplings of the oxazole carbonate **5** with other nucleophiles[5] could lead to a great many types of 4-substituted oxazoles that could not be previously addressed by the Harrison condensation strategy alone. We anticipate future application of the 2-amino-oxazole **10** as a 2π component in inverse demand Diels–Alder reactions with *o*-quinone methides in lieu of a previous example that has been noted with furan.[6]

Acknowledgements

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