An efficient preparation of 2-alkyl-oxazoles from 2-iodooxazoles

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ABSTRACT

An efficient synthesis toward 2-alkyl substituted oxazoles has been achieved through Suzuki cross-coupling reaction. Treatment of various alkyl iodides with 9-MeO-BBN, followed by in situ palladium-catalyzed carbon–carbon formation with 2-iodooxazoles obtained the 2-alkyl substituted oxazoles in good to excellent yields. Regioselective C2-alkylation on 2,4-di-iodooxazole under the same reaction conditions was firstly disclosed.

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Oxazoles are widely distributed in natural products, and many of them possess significant biological activities including antifungal, cytotoxic, and anthelmintic properties.¹ Oxazoles have also been utilized as important building blocks in organic syntheses and drug developments.^{2,3} The potent biological activity and the prevalence of oxazoles in natural products and drug candidates have stimulated intensive interests in the synthesis of these heterocycles.^{2b,2d–g}

As an important structural motif, 2-alkyl substituted oxazole ring has been found in many oxazole-containing natural products, including the phenoxan,^{1g} noricumazoles,⁴ hennoxazoles,^{1f} and lei-dolides A & B.^{1d} Conventional synthesis of 2-alkyl oxazoles was conducted in multistep reaction,^{2f,5} and to the best of our knowledge, direct alkylation at the C2 position is challenging and has very limited success to date.⁶ Due to the structural significance in drug development, it has a strong demanding to explore new synthetic methodologies to access this highly functionalized heterocycles in a straightforward and efficient way. Herein, we wish to report our result for the synthesis of 2-alkyl-oxazole via Suzuki–Miyaura cross-coupling reaction between 2-iodooxazoles and alkylboronates.

In our efforts toward the total synthesis of lei-dolides (Fig. 1), showing potential cytotoxicity against HCT-116 human colon carcinoma cells,^{1d} we have recently reported the stereoselective synthesis of the C22–C31 fragment of lei-dolide A employing a diastereoselective Seebach alkylation and a Brown's P2-Ni catalyzed *cis*-alkyne semihydrogenation in the presence of a vinyl iodide.⁷ To build fragments C1–C17 of lei-dolide A, we eagerly

required a method for the facile assembly of this densely functionalized 2-alkyl-substitution oxazole derivative, exemption from multistep construction of the oxazole ring.

The exploration started from a direct alkylation on oxazole C-2 position through C-2 lithiation and a subsequent quenching with an electrophile, using ethyl oxazole-4-carboxylate (**3**) and iodo-methane (**4**) as the testing system. Treatment of **3** with lithium base (LiHMSD or *t*-BuLi) in anhydrous THF, with or without 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), resulted in the recovery of major starting materials. In order to exclude the electron-withdrawing effect of carboxylate at C4-position, TBS group protected substrate 4-(*tert*-butyl-dimethylsilyloxy)methyloxazole (**5**) was applied, unfortunately, no desired product was observed. Attempted C-2 alkylation on oxazole through lithium-halogen exchange for ethyl 2-iodooxazole-4-carboxylate (**6**)⁸ in the presence of lithium reagent and **4** also failed to generate the desired 2-methyl oxazole-4-carboxylate. It seems that trapping 2-lithiooxazole with **4** was more difficult than we expected due to the mobile equilibrium⁹ between oxazole anion **7a** and α -isocyano enolate **7b** (Scheme 1).

We then turned our attention to the palladium-catalyzed B-alkyl Suzuki–Miyaura cross-coupling, as shown in Table 1.¹⁰ Initial studies were focused on the screening of a suitable coupling condition between 1-iodobutane (**8a**) and oxazolyl substrate **6**. Several common palladium catalyst precursors, such as Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, and Pd(dba)₂ were tested, and did not give encouraging results under the standard Suzuki coupling conditions (entries 1–3). Fortunately, we found that Pd(OAc)₂ in the presence of AsPh₃ and K₃PO₄ provided the desired product **9a** in 37% yield (entry 6). Inspired by this finding, we next investigated other coupling reagents and conditions, and were pleased to find that Pd(dppf)Cl₂

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Figure 1. Structures of leiodolides A and B.

Scheme 1. Attempted C-2 alkylation on oxazole using lithium reagents.

could generate the desired product **9a** in 75% yield (entry 7). Thus an optimized coupling reaction was established as follows: To a solution of alkyl iodide (1.3 equiv) and 9-methoxy-BBN (3.42 equiv) in Et_2O (1 mL) at -78°C was added $t\text{-BuLi}$ (3.0 equiv) rapidly. After 5 min, THF (1 mL) was added. The solution was stirred for 30 min at -78°C and then allowed to warm to room temperature over 1 h. In a separate flask, 2-iodooxazole (0.094 mmol, 1.0 equiv) was taken up in 1 mL of DMF to which $\text{Pd}(\text{dppf})\text{Cl}_2$ (10%), AsPh_3 (15%), Cs_2CO_3 (4.0 equiv), and H_2O (24.0 equiv) were added sequentially. Then the ethereal solution of alkyl boronate was transferred into the DMF solution, and the resulting mixture was stirred for 12 h (entry 9).

We also investigated the scope and limitation of this reaction by treatment of various alkyl halides with iodooxazole derivatives

(Table 2). Coupling of **6** with alkyl iodides, with or without branched chain structures, afforded the products in good to excellent yields (entries 1–6) under the above optimized reaction conditions. Previously failed coupling reaction between **6** and iodomethane through lithium-halogen exchange was also achieved in moderate yield (61%, entry 3). More importantly, the valuable building block **8f**¹¹ in our synthesis of leiodolide A also accomplished the corresponding alkyl oxazole **9f** in 92% yield (entry 6). However, reaction of the alkyl or benzyl bromide (entries 7–8), as well as the secondary iodide (entry 9), with oxazole **6** was proved to be inefficient under current conditions.¹² The same procedure performed on other functionalized iodooxazole substrates, such as oxazolyl compound **10**, also furnished good results suggesting a wide substrate adaptability of this method (entry 10).

Recently, Strotman et al.¹³ reported a direct arylation on di-substituted 2,4-di-iodo-oxazole (**11**) to prepare bis- and tris-oxazole molecules and demonstrated the possibility of catalyst-controlled regioselective Suzuki couplings at 2- or 4-position of **11**. Inspired by their elegant pioneer work, we studied the alkylation of **11** with different alkyl iodides under our conditions. We were pleased to find that the cross-coupling reaction was carried out smoothly affording 2-alkyl-4-iodooxazole as the only coupling product in good yields (entries 11–14). Confirmation of this selectivity was exemplified by lithiation of 4-iodooxazole **9j** with $n\text{-BuLi}$, and quenching with H_2O to obtain the known compound 2-butyloxazole.¹⁴ To the best of our knowledge, there is no literature precedent about the regioselective 2-alkylation on 2,4-di-iodo-oxazole. This result implies that the current method is applicable to the synthesis of differentially substituted 2,4-di-alkyl-oxazoles,

Table 1
Optimization for one-pot B-alkyl Suzuki cross-coupling

Entry	Reagent sources and solvent ^a	T (°C)	Time (h)	Yield ^b (%)
1	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, K_3PO_4 , H_2O , DMF	rt to reflux	12	Trace
2	$\text{Pd}(\text{PPh}_3)_4$, NaOH, H_2O , THF	rt	24	ND ^c
3	$\text{Pd}(\text{dba})_2$, AsPh_3 , Cs_2CO_3 , H_2O , DMF	rt	24	ND
4	$\text{Pd}(\text{OAc})_2$, AsPh_3 , Cs_2CO_3 , H_2O , DMF	rt	24	ND
5	$\text{Pd}(\text{dppf})\text{Cl}_2$, K_3PO_4 , H_2O , DMF	rt	12	5
6	$\text{Pd}(\text{OAc})_2$, AsPh_3 , K_3PO_4 , H_2O , DMF	rt	12	37
7	$\text{Pd}(\text{dppf})\text{Cl}_2$ (5%), AsPh_3 , Cs_2CO_3 , H_2O , DMF	rt	12	75
8	$\text{Pd}(\text{dppf})\text{Cl}_2$, AsPh_3 , K_3PO_4 , H_2O , DMF	rt	12	85
9	$\text{Pd}(\text{dppf})\text{Cl}_2$, AsPh_3 , Cs_2CO_3 , H_2O , DMF	rt	12	91

^a Unless otherwise noted, 2-iodooxazole (0.094 mmol, 1.0 equiv), $n\text{-C}_3\text{H}_7\text{CH}_2\text{-I}$ (1.3 equiv), $t\text{-BuLi}$ (3.0 equiv), 9-methoxy-BBN (3.42 equiv), Et_2O (1 mL), DMF (1 mL), the palladium catalyst precursors (10%), AsPh_3 (15%), Cs_2CO_3 (4.0 equiv), K_3PO_4 (3.0 equiv), NaOH (4.0 equiv), and H_2O (24.0 equiv) were used.

^b Isolated yield.

^c No desired product.

Table 2Pd-catalyzed B-alkyl Suzuki cross-coupling of iodooxazoles with halides^a

Entry	Iodooxazole	Alkyl halide	Product	Yield ^b (%)
1		<i>n</i> -C ₃ H ₇ CH ₂ -I (8a)	9a ^{6c}	91
2	6	<i>n</i> -C ₆ H ₁₃ CH ₂ -I (8b)	9b	89
3	6	MeI (8c)	9c ^{6c}	61
4	6	(8d)	9d	83
5	6	(8e)	9e	91
6	6	(8f)	9f	92
7	6	PhCH ₂ -Br (8g)	9g ^{6c}	7
8	6	<i>n</i> -C ₃ H ₇ CH ₂ -Br (8h)	9a	Trace
9	6	(8i)	9h	ND ^c
10		<i>n</i> -C ₃ H ₇ CH ₂ -I (8a)	9i	79
11		<i>n</i> -C ₃ H ₇ CH ₂ -I (8a)	9j	76 ^d
12	11	<i>n</i> -C ₆ H ₁₃ CH ₂ -I (8b)	9k	73 ^d
13	11	(8d)	9l	71 ^d
14	11	(8f)	9m	76 ^d

^a Unless otherwise noted, the Pd(dppf)Cl₂ (10%), AsPh₃ (15%), Cs₂CO₃ (4.0 equiv), and H₂O (24.0 equiv) were used, then the alkyl boronate solution was added and stirred for 12 h at room temperature.

^b Isolated yield.

^c No desired product.

^d No 2,4-disubstituted or 4-substituted product was observed.

and is a good complement to the existing methods for oxazole syntheses.

In conclusion, we have developed an efficient method toward 2-alkyl substituted oxazoles through alkylborane mediated Suzuki cross-coupling in good to excellent yields. The first example of palladium-catalyzed regioselective alkylation on 2,4-diiodooxazole is also disclosed. This method could provide a new facile synthetic approach toward 2,4-disubstituted oxazoles for natural product synthesis. Expansion of the protocol scope

and application of this methodology to the total synthesis of lei-odolides are currently underway in our group.

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Supplementary data

Supplementary data (experimental procedure, ^1H and ^{13}C NMR data of new compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.05.088>.

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