ORGANIC LETTERS

2002
Vol. 4, No. 17
2905−2907

Ethyl 2-Chlorooxazole-4-carboxylate: A Versatile Intermediate for the Synthesis of Substituted Oxazoles

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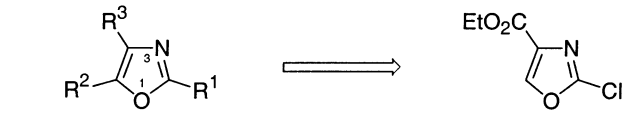
Received June 2, 2002

ABSTRACT



2

R^1 = Ar, Het, alkenyl

R^2 = H, Ar, Het, alkenyl, alkynyl

R^3 = H, CO_2H, Ar, Het, alkenyl, alkynyl

By using a sequence of regiocontrolled halogenation and palladium-catalyzed coupling reactions, the synthesis of variously substituted oxazoles from ethyl 2-chlorooxazole-4-carboxylate (2) was accomplished. The methodology was applied to the synthesis of a series of 2,4-disubstituted, 2,5-disubstituted, and 2,4,5-trisubstituted oxazoles.

The discovery of natural products containing one or more oxazole units has stimulated interest in the chemistry and synthesis of these heterocycles.[1] The first naturally occurring oxazoles to be isolated were relatively simple 2,5-disubstituted oxazoles such as annuloline[2] and balsoxin.[3] 2,5-Diaryloxazoles are also of considerable interest due to their ability to scintillate or emit light in the presence of ionizing radiation.[4] In recent years, a wide variety of biologically important 2,4-disubstituted oxazoles have been isolated including the phorboxazoles,[5] the ulapaulides,[6] the virginiamycins,[7] and the calyculins.[8] As a consequence a number of contemporary strategies for the construction of 2,4-disubstituted oxazoles have emerged.[9] Trisubstituted oxazoles are relatively rare but include diazonamide A, a secondary metabolite of *Diazona chinensis*, which shows potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines.[10] As part of a medicinal chemistry program, we required a flexible route that would give high-yielding and rapid access to a series of substituted oxazoles. A method involving a sequence of regiocontrolled halogenation followed by palladium-catalyzed coupling, based upon a readily available oxazole scaffold, was identified as an attractive possibility.[11] There was limited literature precedent for the elaboration of the oxazole nucleus with palladium-catalyzed coupling reactions[12] and the previously

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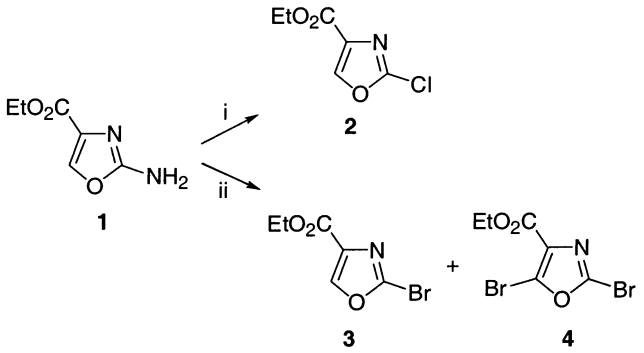
10.1021/ol0262800 CCC: $22.00
Published on Web 07/23/2002

unreported ethyl 2-chlorooxazole-4-carboxylate (**2**) and the 2-bromo analogue **3** were identified as potential precursors. The synthesis of the halooxazoles **2** and **3** is outlined in Scheme 1. Ethyl 2-aminooxazole-4-carboxylate (**1**) was

Scheme 1[a]



[a] Reaction conditions: (i) ^{t}BuONO (1.5 equiv), $CuCl_2$ (1.5 equiv), CH_3CN, 80 °C (83%); (ii) ^{t}BuONO (1.5 equiv), $CuBr_2$ (1.5 equiv), CH_3CN, 80 °C (**3**, 21%, **4**, 16%).

prepared, on a 100-g scale, by the condensation of ethyl bromopyruvate and urea at 100 °C.[13] The 2-aminooxazole **1** was then treated with 1.5 equiv of *tert*-butyl nitrite and copper(II) chloride in acetonitrile yielding 2-chlorooxazole **2** in 83% yield.[14] Replacing the copper(II) chloride with copper(II) bromide gave a low yield of a separable mixture of 2-bromooxazole **3** and the 2,5-dibromooxazole **4**. In an attempt to improve the selectivity for the formation of either **3** or the potentially useful dibromide **4**, the stoichiometry of the reagents and temperature of the reaction were varied. However, similar product distributions and low isolated yields were the result. Under similar reaction conditions, Doyle has observed that the reaction of anilines also gave byproducts due to substitution of bromide either ortho or para to the original amine substituent.[14]

With a large quantity of the chlorooxazole **2** in hand, its palladium-catalyzed cross-coupling reactions with a variety of organometallic reagents were examined. Under standard Suzuki conditions[15] and 1 equiv of phenylboronic acid, coupling at the 2-position was observed, affording **5a** in 87% isolated yield (entry 1, Table 1). The Stille coupling reaction was investigated next.[12c,16] With use of standard conditions

Table 1. Palladium-Catalyzed Coupling Reactions of **2**[a]

2 **5a-d**

entry	R	conditions	time (h)	product	yield (%)
1	Ph	i	1	**5a**	87
2	vinyl	ii	4	**5b**	84
3	2-pyridyl	iii	4	**5c**	73
4	C≡CPh	iv	6	**5d**	0

[a] Reaction conditions: (i) $Pd(Ph_3P)_4$, $PhB(OH)_2$, aq K_2CO_3, PhMe, 90 °C; (ii) $Pd(Ph_3P)_2Cl_2$, CH_2═$CHSnBu_3$, dioxane, 100 °C; (iii) $Pd(Ph_3P)_4$, 2-pyridylzinc bromide, THF, 65 °C; (iv) $Pd(Ph_3P)_2Cl_2$, CuI, phenylacetylene, Et_3N, 80 °C.

and 1 equiv of vinyltributyltin, coupling at the 2-position afforded **5b** in 84% isolated yield (entry 2). The Negishi coupling reaction of **2** with 2-pyridylzinc bromide in THF at reflux gave **5c** in 73% yield (entry 3).[17] Sonogashira reaction of **2** with phenylacetylene gave a resinous material and it was not possible to isolate the expected product, **5d**, from the mixture (entry 4).[18] Low yields for the Sonogashira reaction of 2-bromothiazoles[11a,12b] and 2-iodoimidazoles[12b] have also been reported. In summary, Suzuki, Stille, and Negishi reactions with the 2-chlorooxazole **2** all gave good yields of the expected oxazoles **5a**−**c** although a Sonogashira reaction failed. In principle, the carboxylic functionality at C-4 could now be exploited by a range of synthetic maneuvers leading to a variety of 2,4-disubstituted oxazoles.

The synthesis of trisubstituted oxazoles via the installation of substituents at the 5-position was investigated next. One possibility was to utilize the 2,5-dibromooxazole **4**. It was anticipated that a palladium-catalyzed coupling reaction would be selective for the more electron-deficient 2-position and that the C-2 substituent could be introduced first. A second coupling could then be used to install the C-5 substituent. Under standard Suzuki conditions, and 1 equiv of phenylboronic acid, the dibromooxazole **4** gave a complex mixture of products. Analysis of the crude reaction mixture by ^{1}H NMR and LC-MS indicated the presence of mono- and disubstituted coupled products and also products arising from debromination of the coupled products and of the starting material. It was decided not to pursue this approach further but instead to utilize the 2,4-disubstituted oxazoles **5a**−**d** prepared earlier.

The oxazole **5a** was brominated at the 5-position by treatment with *N*-bromosuccinimide in refluxing chloroform and gave the bromide **6** in 86% yield. Under standard Suzuki

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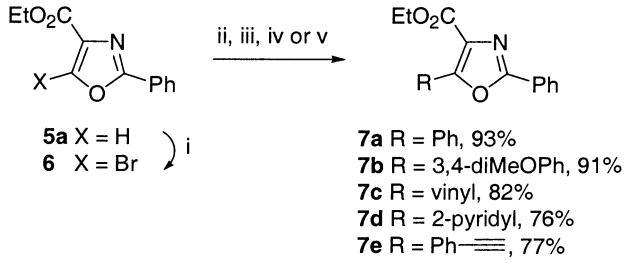
conditions and with phenylboronic acid, the 5-bromooxazole **6** proved to be reactive affording, after 4 h, **7a** in 93% yield. Similarly, 3,4-dimethoxyphenyl boronic acid gave an excellent yield of the oxazole **7b**. Standard Stille conditions and vinyltributyltin gave **7c** in 82% yield.[12e,f] Negishi coupling with 2-pyridylzinc bromide gave **7d** in 76% yield. The Sonogashira reaction, which failed with the 2-chlorooxazole **2**, gave a much cleaner reaction with **6**, affording **7e** in 77% yield (Scheme 2).[12b] In general, the palladium-catalyzed

Scheme 2[a]



[a] Reaction conditions: (i) NBS (4 equiv), $CHCl_3$, reflux, 48 h (86%); (ii) $Pd(Ph_3P)_4$, $RB(OH)_2$, aq K_2CO_3, PhMe, 90 °C, 4 h; (iii) $Pd(Ph_3P)_2Cl_2$, CH_2═$CHSnBu_3$, dioxane, 100 °C, 8 h; (iv) $Pd(Ph_3P)_4$, 2-pyridylzinc bromide, THF, 65 °C, 18 h; (v) $Pd(Ph_3P)_2Cl_2$, CuI, phenylacetylene, Et_3N, 80 °C, 18 h.

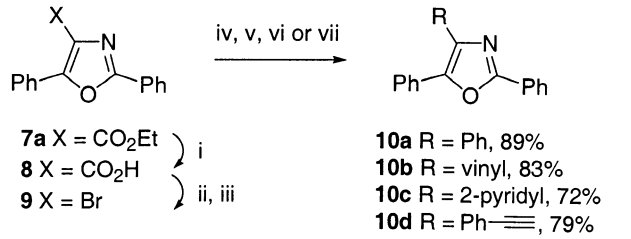
coupling reactions of the 5-bromooxazole **6** gave good yields of the expected trisubstituted oxazoles **7a**−**e** although slightly longer reaction times were required for complete conversion.

The range of trisubstituted oxazoles available by this route can be extended by manipulation of the carboxylic functionality at C-4. For example, a Hunsdiecker[19] reaction was used to introduce a halogen at the C-4 position that proved suitable for further functionalization via palladium-catalyzed processes. Thus, hydrolysis of the ester **7a** with sodium hydroxide gave the acid **8**, which was converted to the corresponding silver salt by treatment with silver nitrate and potassium hydroxide in water. Heating the silver salt in the presence of 1 equiv of bromine gave the 4-bromooxazole **9** in 79% yield. Under standard Suzuki conditions and with phenylboronic acid, the 4-bromooxazole proved to be reactive affording, after 4 h, **10a** in 89% yield. Standard Stille conditions and vinyltributyltin gave **10b** in 83% yield.[12d,h,i,j] Negishi coupling with 2-pyridylzinc bromide gave **10c** in 72% yield and Sonogashira reaction with phenylacetylene gave **10d** in 79% yield (Scheme 3). In summary, the palladium-catalyzed couplings of the 4-bromooxazole **9** with various organometallic reagents gave good yields of the expected products.

The trisubstituted oxazoles **7a**−**e** can also be exploited in the synthesis of 2,5-disubstituted oxazoles. For example, hydrolysis of the ester **7b** with sodium hydroxide in ethanol gave the acid **11** in 95% yield. Heating the acid **11** in wet DMF resulted in clean decarboxylation and gave balsoxin

(19) For a review see: Johnson, R. G.; Ingham, R. K. *Chem Rev.* **1956**, *56*, 219.

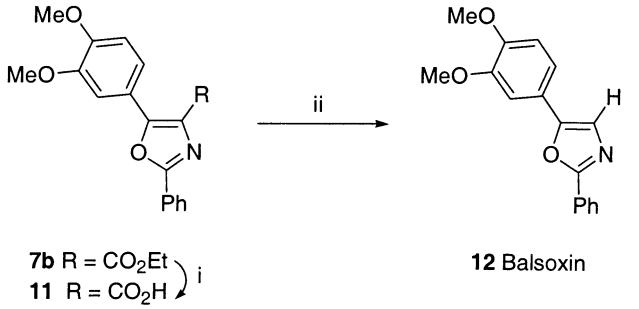
Scheme 3[a]



[a] Reaction conditions: (i) NaOH, EtOH, room temperature (97%); (ii) KOH, $AgNO_3$, H_2O; (iii) Br_2, CCl_4, 75 °C (79%); (iv) $Pd(Ph_3P)_4$, $PhB(OH)_2$, aq K_2CO_3, PhMe, 80 °C, 4 h; (v) $Pd(Ph_3P)_2Cl_2$, CH_2═$CHSnBu_3$, dioxane, 100 °C, 8 h; (vi) $Pd(Ph_3P)_4$, 2-pyridylzinc bromide, THF, 65 °C, 16 h; (vii) $Pd(Ph_3P)_2Cl_2$, CuI, phenylacetylene, Et_3N, 80 °C, 16 h.

(**12**), which has previously been isolated from the plant *A. plumieri* (Scheme 4).[3]

Scheme 4[a]



[a] Reaction conditions: (i) NaOH, EtOH, room temperature (95%); (ii) DMF−H_2O (1:1), 150 °C, 60 h (74%).

The readily available ethyl 2-chlorooxazole-4-carboxylate (**2**) proved to be a versatile scaffold for the synthesis of 2,4-disubstituted, 2,5-disubstituted, and 2,4,5-trisubstituted oxazoles. Suzuki, Stille, and Negishi coupling reactions were all successfully used to install substituents at the C-2 oxazole position. Following bromination, a second palladium-catalyzed coupling reaction was used to install substituents at the C-5 position. The carboxylic functionality at C-4 could then be exploited by a variety of synthetic transformations. For example, decarboxylation directly gave the corresponding 2,5-disubstituted oxazole; alternatively, a Hunsdiecker reaction was used to locate a bromide at the C-4 position, which was then exploited in a third palladium-catalyzed coupling reaction. The wide range of compatible organometallic reagents and the synthetic versatility of the carboxylic functionality at C-4 offers considerable flexibility for the synthesis of substituted oxazoles from a single precursor.

Supporting Information Available: Representative procedures for the preparation of **2**, **5a**, **5b**, **5c**, **6**, **7e**, **8**, **9**, **11**, and **12** and relevant spectroscopic data for compounds **2**, **3**, **4**, **5a**−**c**, **6**, **7a**−**e**, **8**, **9**, **10a**−**d**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0262800