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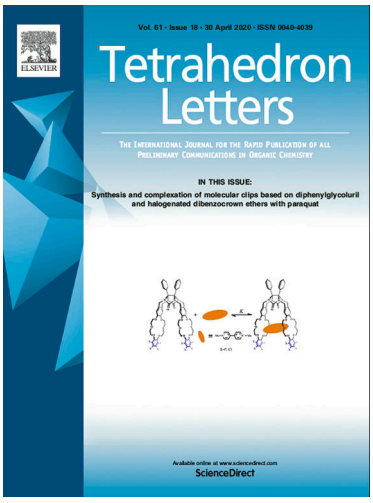

A Novel Synthetic Method of 2,4-Disubstituted Oxazoles Using Carboxylic Acid-derived $Bu_2Sn[OC(O)R]_2$

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PII: S0040-4039(20)30426-3
DOI: https://doi.org/10.1016/j.tetlet.2020.151983
Reference: TETL 151983

To appear in: *Tetrahedron Letters*

Received Date: 19 March 2020
Revised Date: 24 April 2020
Accepted Date: 27 April 2020

Please cite this article as: Yoneyama, H., Oka, N., Usami, Y., Harusawa, S., A Novel Synthetic Method of 2,4-Disubstituted Oxazoles Using Carboxylic Acid-derived $Bu_2Sn[OC(O)R]_2$, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.151983

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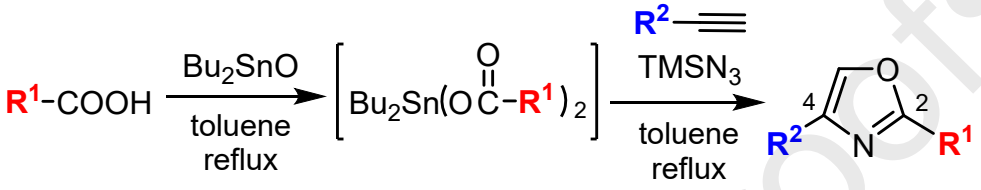

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2,4-Disubstituted oxazoles
$TMSN_3$
$Bu_2Sn[OC(O)R]_2$
Carboxylic acids

ABSTRACT

A novel synthetic method for the preparation of 2,4-disubstituted oxazoles was developed, entailing the reaction of dibutyltin diacylates $Bu_2Sn[OC(O)R]_2$ with 1-substituted acetylenes and $TMSN_3$ to afford a range of 2,4-disubstituted oxazoles in good yields.

1. Introduction

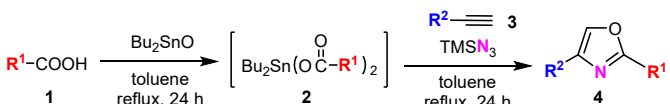
Considerable efforts have been directed towards the development of regioselective syntheses of substituted oxazoles over the years, as various substituted oxazoles were found in natural products and synthetic pharmaceutical molecules.[1] 2,4-disubstituted oxazoles, in particular are common structural elements in a wide variety of biologically relevant natural products, including neopeltolide A (antiproliferative), hennoxazole A (antiviral) and leucascandrolide A (cytoxic and antifungal).[2]

The biosynthesis of 2,4-disubstituted oxazoles entails the cyclodehydration and oxidation of serine or threonine moieties in peptide derivatives.[3] In this context, the oxidation of unsaturated oxazolines from *N*-acylserines and cyclodehydration of α-acylamino aldehydes derived from amino acids have been reported.[4,5] Another efficient strategy is the preparation of various pre-formed 2,4-difunctionalized oxazole units, which could be sequentially elaborated under metal-catalyzed cross coupling conditions to provide a range of 2,4-disubstituted oxazoles.[6] Additionally, metal catalyzed conversion of α-diazocarbonyl compounds[7] or multi-component coupling[8] from ketones have been devised for the synthesis of 2,4-disubstituted oxazoles. Although numerous procedures have been reported for the synthesis of oxazoles, straightforward and expedient approaches to 2,4-disubstituted oxazoles remain scarce. In this paper, we report a novel synthetic method of 2,4-disubstituted oxazoles **4** using dibutyltin diacylates {$Bu_2Sn[OC(O)R]_2$, **2**}, which are directly prepared from carboxylic acids **1** (Scheme 1). To the best of our knowledge, synthetic methodology for the assembly of 2,4-disubstituted oxazoles starting from carboxylic acids has not been reported thus far.

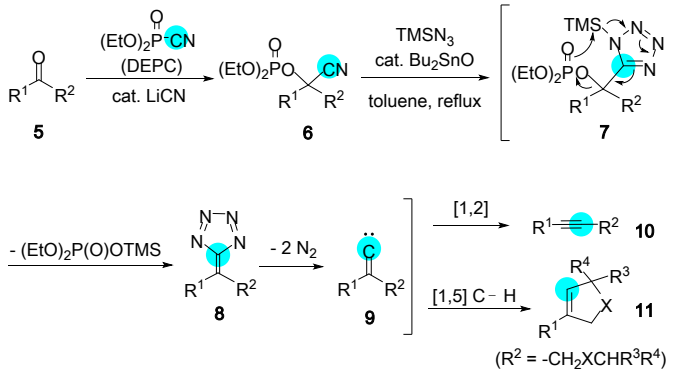
Scheme 1. Transformation of carboxylic acids **1** into 2,4-disubstituted oxazoles **4** via dibutyltin diacylates **2**.

2. Results and discussion

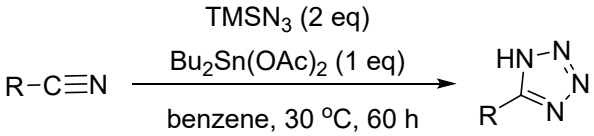
The treatment of a range of carbonyl compounds **5** with diethyl phosphorocyanidate (DEPC)[9] in the presence of a catalyst readily afforded cyanophosphates (**6**, CPs) under non-aqueous conditions.[9] CPs have been extensively utilized as useful synthetic intermediates in organic synthesis.[9] As part of our ongoing studies on the synthetic applications of CPs, we recently demonstrated the efficient transformation of carbonyl compounds **5** into homologous alkynes **10**[10] or five-membered unsaturated cyclic compounds **11** under neutral conditions,[11] in which the fragmentation of tetrazolylphosphates **7** derived from CPs **6** generated alkylidene carbenes **9**, as illustrated in Scheme 2.[12]



Furthermore, we recently reported a mild and efficient alternative reagent system for tetrazole-synthesis, in which the treatment of various nitriles with $TMSN_3$ and $Bu_2Sn(OAc)_2$ at 30 °C in benzene for 60 h yielded the corresponding 5-substituted 1*H*-tetrazoles in excellent yields (Scheme 3).[13] Therefore, we focused our attention on the reaction of this reagent system with CPs.

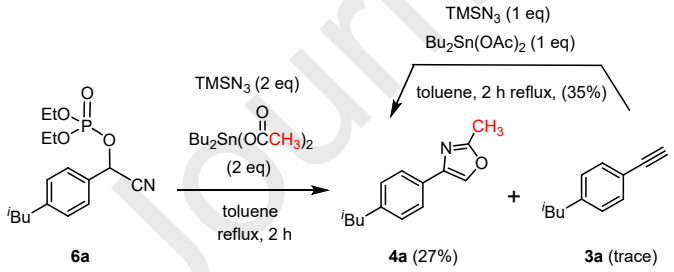


Scheme 2. Synthesis of homologous alkynes **10** or five-membered unsaturated cyclic compounds **11** from ketones **5** via CPs **6**



Scheme 3. Formation of 5-substituted tetrazoles from nitriles using $TMSN_3/Bu_2Sn(OAc)_2$

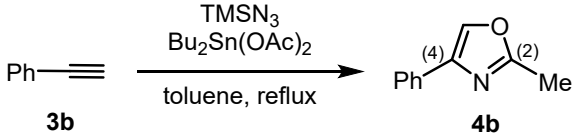
Initially, when the reaction of CP **6a** with $TMSN_3$ (2 eq) and commercially available $Bu_2Sn(OAc)_2$ (2 eq) was performed in refluxing toluene for 2 h, 4-(4-isobutylphenyl)-2-methyl oxazole (**4a**) was unexpectedly produced in 27% yield, together with alkyne **3a** in trace amounts (Scheme 4). We consideded that the production of oxazole **4a** might be caused by the overreaction of alkyne **3a** with $TMSN_3/Bu_2Sn(OAc)_2$. Indeed, the reaction of alkyne **3a** with $TMSN_3$ (1 eq)/$Bu_2Sn(OAc)_2$ (1 eq) in refluxing toluene for 2 h afforded the oxazole **4a** (35%), as shown in Scheme 4. Based on this experiment, we envisaged that alkynes **3** could be transformed directly into 2,4-disubstituted oxazoles **4** employing $TMSN_3$ and dibutyltin diacylate $Bu_2Sn[OC(O)R)]_2$.



Scheme 4. Reaction of CP **6a** with $TMSN_3/Bu_2Sn(OAc)_2$

We therefore investigated the reaction of ethynylbenzene (**3b**) with $TMSN_3$ (1 eq) in the presence of a catalytic amount of $Bu_2Sn(OAc)_2$ in refluxing toluene for 2 h, which yielded 2-methyl-4-phenyloxazole (**4b**) in low yields (Table 1, entries 1–2). Increasing the amount of $Bu_2Sn(OAc)_2$ and extending the reaction time led to an improved yield of **4b** (60 %) (entry 4). Furthermore, the use of 2 eq of $TMSN_3$ afforded the oxazole **4b** in 66% yield (entry 6).

Table 1. Reaction of ethynylbenzene **3b** with $TMSN_3$/ $Bu_2Sn[OC(O)R)]_2$

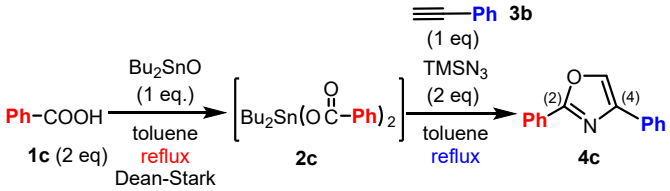


1	1	0.1	2	trace
2	1	0.5	2	14
3	1	1	2	35
4	1	1	4	60
5	2	1	4	66

[a]RT: reaction time

Next, the synthesis of 2,4-diphenyloxazole (**4c**) was attempted using $Bu_2Sn[OC(O)Ph]_2$,[14] which was prepared *in situ* from an azeotrope of benzoic acid (2 eq) and Bu_2SnO (1 eq) in refluxing toluene, implementing a Dean–Stark water separator for 12 h (Table 2). Subsequently, **3b** (1 eq) and $TMSN_3$ (2 eq) were added to the resulting $Bu_2Sn[OC(O)Ph]_2$ solution in toluene. The resulting mixture was further refluxed for 4 h to yield **4c** (36%) (entry 1). Furthermore, the extension of both reaction times (RTs) to 24 h significantly improved the yield of **4c** to 97% (entry 4).

Table 2. Reaction of ethynylbenzene **3b** with $TMSN_3$/ $Bu_2Sn[OC(O)Ph]_2$

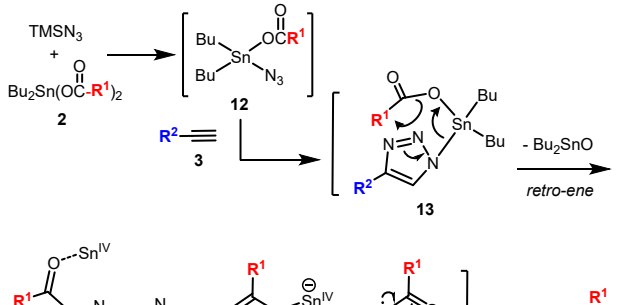


entry	RT (h)	RT (h)	yield (%)[a]
1	**12**	**4**	**36**
2	**12**	**24**	**64**
3	**20**	**2**	**24**
4	**24**	**24**	**97**

[a]The yield was based on ethynylbenzene.

Applying the synthetic procedure from above (Table 2, entry 4), various carboxylic acids **1** were transformed into 2,4-disubstituted oxazoles **4** via reaction of **2** with mono-substituted acetylenes **3** and $TMSN_3$ (Table 3).[15] In cases of benzoic acids **1d**–**h** containing *para (p)*-functional groups (Me, OMe, Cl, CF_3, and NO_2) and 2-thiophene-2-carboxylic acid **1i**, the corresponding oxazoles **4d**–**i** were readily obtained in yields of 60–96%. Subsequently, the effect of functional groups at the *p*-position of ethynyl benzenes **3** was examined. *p*-Substituted Me, MeO, and Cl derivatives afforded the respective 2-phenyl-4-(*p*-substituted phenyl) oxazoles **4j** (98%), **4k** (81%), and **4l** (76%) in high yields, while *p*-substituted with electron-withdrawing groups, such as 1-ethynyl-4-nitrobenzene **3m** afforded the corresponding oxazole **4m** in only 30% yield. Meanwhile, the present method proved suitable for the the formation of dimethylamino-containing 2,4-biphenyloxazoles **4n** (28%) and **4o** (55%). 2-Phenylpropyl-, 2-cyclohexyl-, and 2-adamantyl-4-phenyl oxazoles **4p** (72%), **4q** (56%) and **4r** (39%), respectively, as well as 4-phenethyl- and 4-cyclohexyl-2-phenyl oxazoles **4s** (64%) and **4t** (41%) could be prepared in moderate to high yields. The oxazole **4u** (78%) bearing a vinyl function could be also prepared. Furthermore, *N*-Boc-L-protected proline (**1v**) was also converted to the corresponding oxazole **4v** (73%, 99% ee)[16] with retention of the enantiomeric purity at the α-chiral carbon, as determined by the Mosher method.[17] Interestingly, the present method was applicable to the formation of 2,4-dialkyloxazoles **4w** (48%) and **4x** (27%), while other currently available synthetic methods[3-8] have not been successful in the direct formation of 2,4-dialkyloxazoles when both R^1 and R^2 are aliphatic.[7b]

A plausible mechanism of this reaction is proposed in Scheme 5. The mechanism of the Bu_2SnO-catalyzed $TMSN_3$-nitrile cycloaddition for tetrazole synthesis has been studied in detail.[18] By analogy with the reaction, $TMSN_3$ and dibuthyltin diacylate **2** form a tetracoordinate organotin (IV) intermediate **12**, and the subsequent [2+3] cycloaddition with acetylene **3** leads to an intermediate *N*-[dibutyl(*O*-acyl)stannyl]triazole **13**. This intermediate undergoes expulsion of stable dibutyltin oxide through an intramolecular retro-ene process to give *N*-(acyl)triazole **14**. Loss of N_2 forms the carbocation complex intermediate **15a** or diradical species **15b** and spontaneous cyclization produces the desired 2,4-disubstituted oxazole **4**.[19]



Scheme 5. A plausible mechanism for the conversion of dibutyltin diacylates **2** to 2,4-disubstituted oxazoles **4**.

Conclusions

In this study, we demonstrated that reaction of $Bu_2Sn[OC(O)R]_2$ with mono-substituted acetylenes/$TMSN_3$ furnishes a range of 2,4-disubstituted oxazoles in moderate to excellent yields.[15] $Bu_2Sn[OC(O)R]_2$ can be readily prepared from various carboxylic acids, which have not been used as substrates in the synthesis of 2,4-disubstituted oxazoles thus far. Dimethyl amino groups as well as *N*-Boc-L-protected proline remain intact. In addition, the present method was successfully applied for the assembly of 2,4-dialkyloxazoles. Therefore, this methodology is general and applicable to the synthesis of a broad range of 2,4-disubstituted oxazole derivatives, which can be assessed for biological activity, and used as starting points for the development of biologically active molecules. The further investigation for the mechanism and applications are in progress in our laboratory.

Acknowledgments

We would like to thank Professor Emeritus T. Shioiri at Nagoya City University for providing encouragement. We thank Ms. M. Yoshii, Ms. H. Kusuki, and Ms. M. Satake at our lab for their technical supports.

Supplementary Material

Supplementary data to this article can be found online at ----------.

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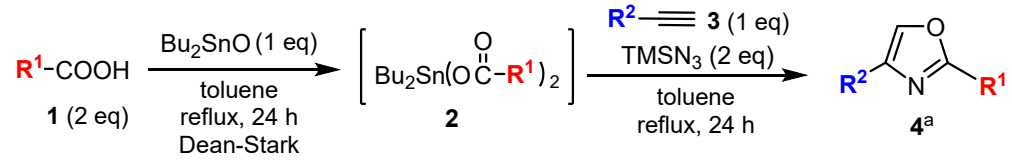
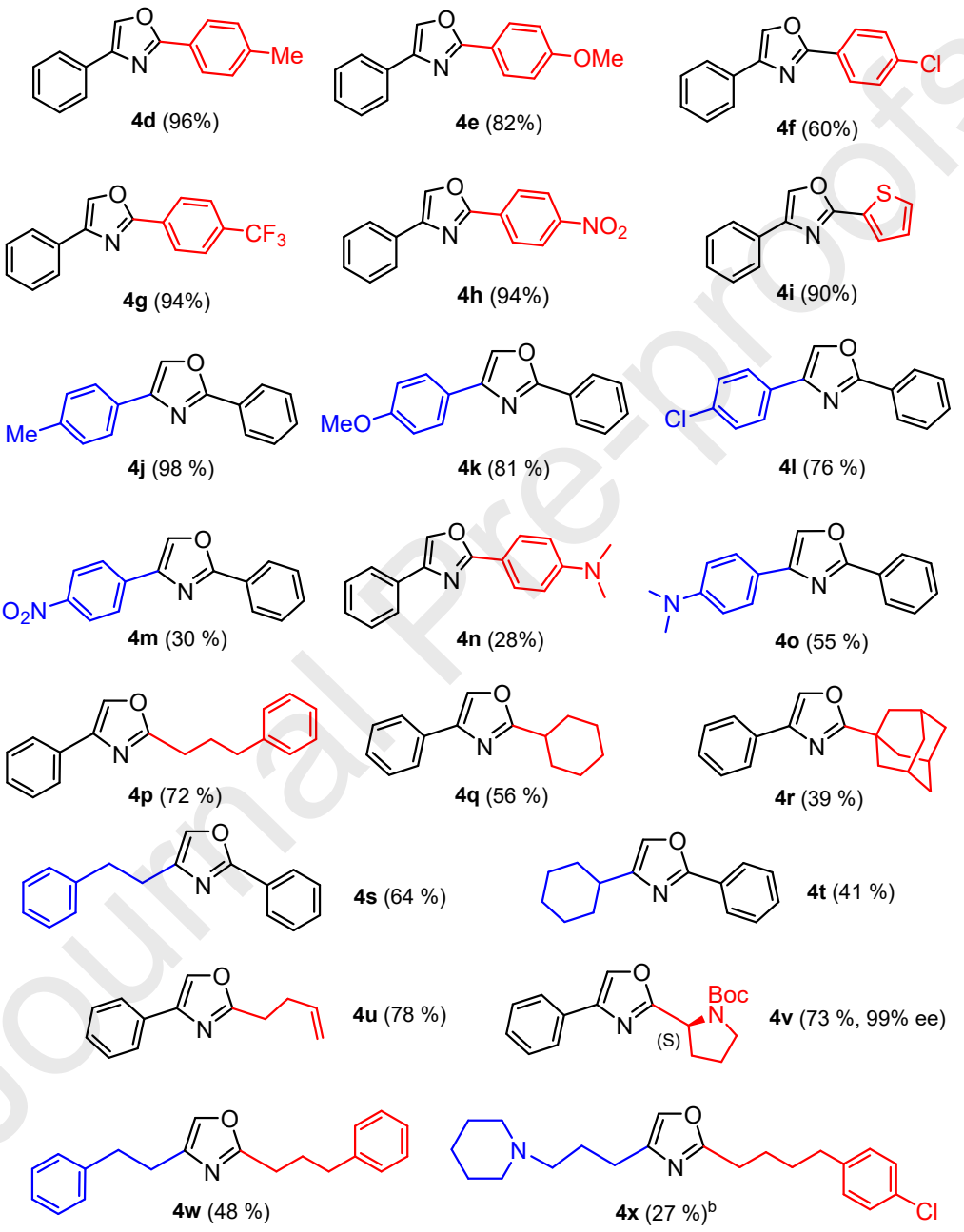
19. (a) Addition of radical inhibitors TEMPO or HQ remarkedly decreased the formation of oxazole **4**, suggesting the generation of radical species in the reaction mechanism [See Supplementary Data]. Meanwhile, in case of 4-pentenoic acid **1u**, which was likely to undergo radical cyclization, the regular oxazole **4u** (78%) bearing a vinyl group was obtained, as shown in Table 3..

Table 3. Transformation of carboxylic acids **1** into 2,4-disubstituted oxazoles **4** by the present method.





[a]The isolated yield was based on alkyne **3**. [b]**1** (4 eq), Bu_2SnO (2 eq), and $TMSN_3$ (1 eq) were used.

Highlights

1. This article describes a new synthetic method of 2,4-disubstituted oxazoles.

3. $Bu_2Sn[OC(O)R]_2$ are prepared readily from carboxylic acids.

4. The present method affords a range of 2,4-disubstituted oxazoles in good yields.

Graphical Abstract

A Novel Synthetic Method of 2,4-Disubstituted Oxazoles Using Carboxylic Acid-derived $Bu_2Sn[OC(O)R]_2$

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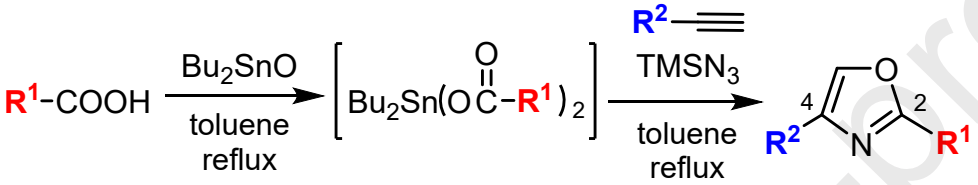

The authors declare no conflict of interest/