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Pravin C. Patil, Frederick A. Luzzio, Donald R. Demuth

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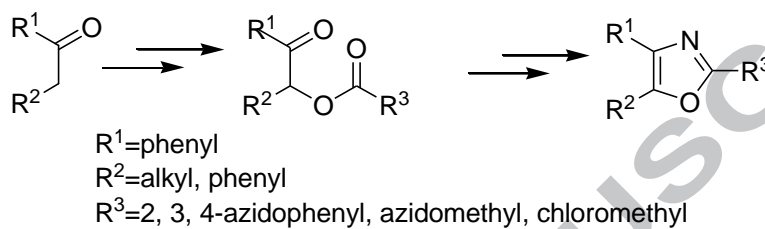
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## Oxazoles for click chemistry II: synthesis of extended heterocyclic scaffolds

Pravin C. Patil<sup>a</sup>, Frederick A. Luzzio<sup>a,\*</sup> and Donald R. Demuth<sup>b</sup>

<sup>a</sup>Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky, 40292, USA

<sup>b</sup>Department of Periodontics, Endodontics and Dental Hygiene, University of Louisville School of Dentistry, 501 S. Preston St. Louisville, Kentucky, 40292 USA

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### ABSTRACT

New routes to 2, 4, 5-trisubstituted oxazoles were established whereby the substitution pattern was established by the structure of the starting nonsymmetrical acyloins. 2-Chloromethyl-4, 5-disubstituted oxazoles were prepared by refinements of an earlier described process whereby chloroacetyl esters of symmetrical and non-symmetrical acyloins were cyclized using an ammonium acetate/acetic acid protocol. After substitution is effected, the azide moiety is then installed by substitution under mild conditions. While dibrominated and iodinated phenyloxazoles are required for further synthetic elaboration, the cyclization reaction was found to be very sensitive to the relative positions of the halogens in the starting materials.

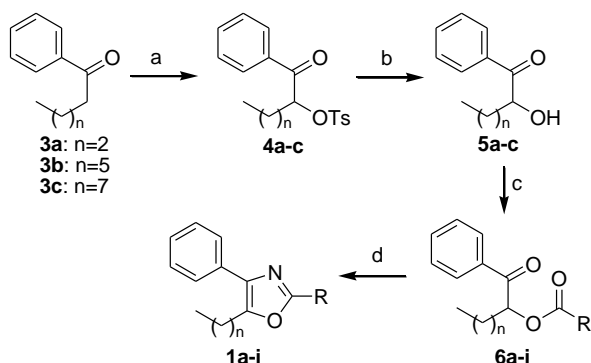
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### 1. Introduction

The oxazole structural motif plays a central role in medicinal and natural products chemistry.<sup>1</sup> Apart from the major classical name reactions and contemporary strategies used in preparing the oxazole nucleus, there remains unique opportunities for elaborating this central framework to provide a plethora of synthetic targets.<sup>2</sup> Moreover, in the area of peptidomimetics, oxazole-based scaffolds, backbones and amino acid analogues continue to provide a diverse array of compounds for pharmacological evaluation in numerous therapeutic areas.<sup>3</sup> We are presently conducting studies entailing the inhibition of dental biofilm formation using both the trisubstituted oxazole scaffold and the techniques of click chemistry. *Porphyromonas gingivalis* is a major pathogen associated with periodontal disease and this organism colonizes the dental biofilm by interacting with oral streptococci. Demuth and Sissons previously showed that this interaction is inhibited by a peptide comprised of two distinct structural motifs which block the interaction of minor fimbrial antigen (Mfa) of *P. gingivalis* with the antigen I/II (AgI/II) of oral streptococci.<sup>4</sup> Consequently, the design and study of small-molecule, non-peptide based inhibitors of the Mfa/AgI/II interaction can involve the employment of two heterocyclic scaffolds, one being a substituted oxazole, which may be joined

together via a “click” reaction. In a prior communication<sup>5</sup> we detailed a route to the inhibitory 4, 5-diaryl-2-azidoaryl- and 4, 5-diaryl-2-azidoalkyl oxazole scaffolds, and we now describe extensions of our methodology which enables access to a great many substituted oxazoles having diverse functionality and extended heterocyclic frameworks. Our initial route entailed the cyclization of azidoalkyl- or azidoaryl esters of benzoin with ammonium acetate in acetic acid (115°C/3h) thereby affording the corresponding 2-azidoaryl- or 2-azidoalkyl-4, 5-diphenyl-oxazoles. We also discovered that cyclizations of benzoin esters could be accomplished by treatment with thiourea (DMF/150°C); however, these conditions were not compatible with either alkyl or aryl azides and provided complex mixtures. Essentially, the intermediate azido esters were pre-formed before the final cyclization to the target oxazole and the basic scheme relied on both the preparation of the starting haloalkyl esters and substitution of halide with azide. We now report an extension of the cyclization methodology to 2-(azidophenyl)-4-phenyl-5-alkyloxazoles **1a-i** along with the corresponding 2-azido-methyl-4-phenyl-5-alkyloxazoles **2a-c**. The use of the symmetrical diaryl acyloin as a starting material was detailed in our previous communication and the use of which established the basic strategy and provided the 2-alkyl- or 2-aryl-4, 5-diphenyl substitution in the target heterocycle.<sup>5</sup> The scheme toward the 2-azidophenyl- and 2-azidomethyl-4-phenyl-5-alkyl-substituted oxazoles detailed herein required a somewhat different strategy

\* Corresponding author. Tel.: +0-502-852-7323; fax: +502-852-8149; e-mail: [faluzz01@louisville.edu](mailto:faluzz01@louisville.edu)

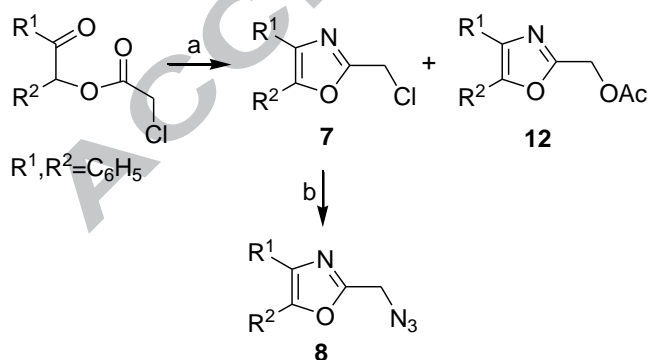
**Scheme 1.** Synthesis of 2-azidophenyl-4-phenyl-5-alkyloxazoles (n=2, 5, 7) from non-symmetrical acyloins:**Reagents/Conditions:**

(a) Oxone/4-iodotoluene, p-TsOH/MeCN/16h, 60°C.  
 (b) LiOH/H<sub>2</sub>O/DMF/16h, 5°C to rt.  
 (c) TEA/DMAP/CH<sub>2</sub>Cl<sub>2</sub>/16h, 5°C to rt.  
 (d) NH<sub>4</sub>OAc/HOAc/3h, 115°C

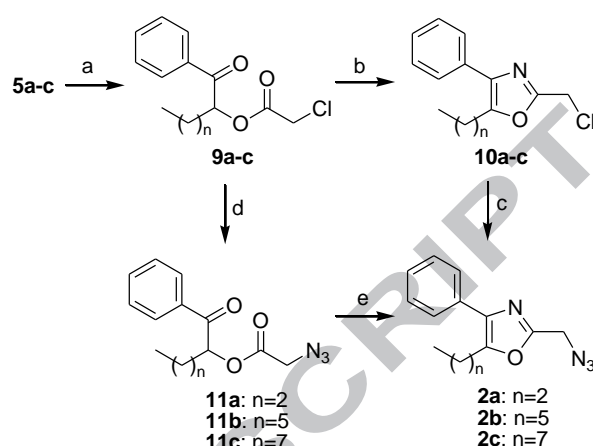
**1a, 6a:** n=2, R=2-azidophenyl  
**1b, 6b:** n=2, R=3-azidophenyl  
**1c, 6c:** n=2, R=4-azidophenyl  
**1d, 6d:** n=5, R=2-azidophenyl  
**1e, 6e:** n=5, R=3-azidophenyl  
**1f, 6f:** n=5, R=4-azidophenyl  
**1g, 6g:** n=7, R=2-azidophenyl  
**1h, 6h:** n=7, R=3-azidophenyl  
**1i, 6i:** n=7, R=4-azidophenyl

and required the preparation and employment of non-symmetrical acyloins **5a-c** as starting materials. Aromatic- aliphatic ketones were employed in the preparation of non-symmetrical acyloins through a two-step procedure involving oxidation-tosylation (Scheme 1). Hence, α-tosylation of ketones **3a-c** (oxone/4-iodotoluene/p-toluenesulfonic acid/acetonitrile/ 16h, 60°C) provided the tosylates **4a-c**.<sup>6,7</sup> Base-mediated hydrolysis (LiOH/H<sub>2</sub>O/DMF/16h, 5°C to rt) of the intermediate tosylates **4a-c** afforded the nonsymmetrical acyloins **5a-c**.<sup>7,8</sup> The acyloins **5a-c** were then acylated with the appropriate acid chloride to afford the intermediate acyclic esters **6a-i**. The acyclic esters **6a-i** were then cyclized with ammonium acetate in acetic acid to provide the trisubstituted oxazoles **1a-i**.<sup>8</sup>

During earlier studies of the synthesis of the 2-azidomethyl-4, 5-diphenyloxazole **8** we discovered that cyclization of the

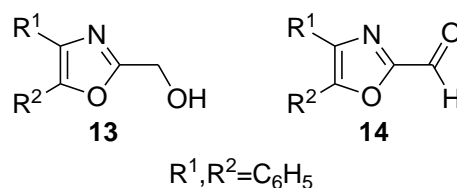
**Scheme 2:** Cyclization of benzoin chloroacetate

**Reagents/Conditions:** (a) NH<sub>4</sub>OAc/HOAc/115°C, 3h.  
 (b) NaN<sub>3</sub>/DMF/rt, 3h.

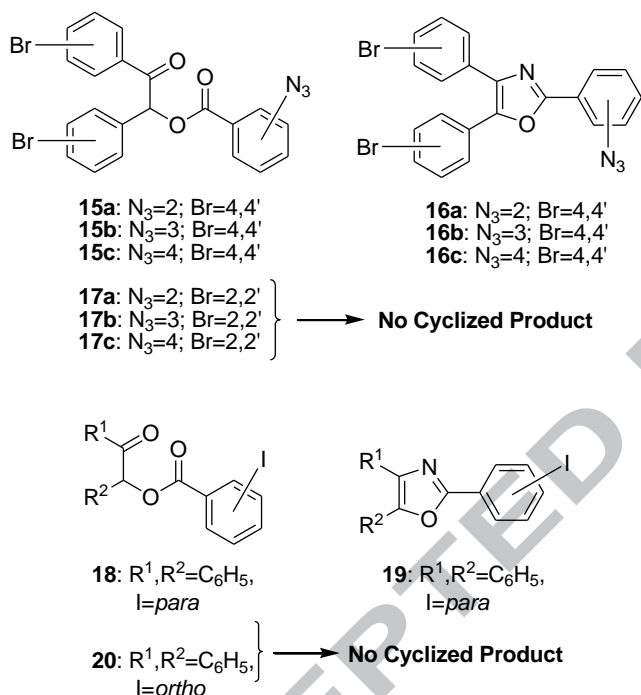
**Scheme 3.** Synthesis of 2-azidomethyl-4-phenyl-5-alkyloxazoles (n=2,5,7):

**Reagents/Conditions:** (a) chloroacetyl chloride/TEA/DMAP/CH<sub>2</sub>Cl<sub>2</sub>/ 5°C to rt, 16h. (b) NH<sub>4</sub>OAc/HOAc/115°C, 3h. (c) NaN<sub>3</sub>/DMF/rt, 2h. (d) NaN<sub>3</sub>/DMF/rt, 2h. (e) NH<sub>4</sub>OAc/HOAc/115°C, 3h.

chloroacetyl ester of benzoin (NH<sub>4</sub>OAc/HOAc/115°C, 3h) gave 2-chloromethyl-4, 5-diphenyl-oxazole **7**, albeit in modest yield. Substitution of **7** with azide ion (NaN<sub>3</sub>/DMF/rt, 3h) gave the azidomethyloxazole **8**. Thus, nucleophilic substitution of **7** with azide ion under mild conditions was a viable alternative to cyclization of the corresponding azidoacetyl ester as reported earlier (Scheme 2). The chloroacetyl esters of the nonsymmetrical acyloins **9a, 9b** and **9c** were cyclized in similar fashion thereby providing the corresponding 4-phenyl-5-alkyl-2-(chloromethyl) oxazoles **10a-c** (Scheme 3).<sup>8</sup> Conversion to the corresponding 2-azidomethyl compounds **2a-c** was accomplished by treating **10a-c** with sodium azide in DMF (rt).<sup>8</sup> For comparison, the conversion of chloroesters **9a-c** to the corresponding azidoesters **11a-c** (NaN<sub>3</sub>/DMF) according to our previous route was conducted smoothly.<sup>8</sup> The azidoesters **11a-c** were then cyclized to the azidomethyloxazoles **2a-c** (NH<sub>4</sub>OAc/HOAc).<sup>8</sup> When an excess of ammonium acetate/acetic acid was used during the cyclization of the chloroacetyl ester of benzoin (Scheme 2), solvolysis to the corresponding 2-acetoxymethyl oxazole **12** was a competing reaction (**7**/33%, **12**/16%). Decreasing the concentration of ammonium acetate in acetic acid while carefully monitoring the reaction progress increased the yield of the chloromethyloxazole **7** to 62% and decreased the formation of ester **12** to 5%.<sup>8</sup> Interestingly, the product acetoxy ester **12** could be hydrolyzed (K<sub>2</sub>CO<sub>3</sub>/EtOH/reflux, 2h 97%) which provided the hydroxymethyl oxazole **13** in excellent yield.<sup>8</sup> The construction of extended oxazole scaffolds might utilize the aldehyde **14** as a viable intermediate for Wittig or organometallic reaction, and to this end, **13** was oxidized to **14** with the Dess-Martin periodinane



(CHCl<sub>3</sub>/reflux, 2h, 97%).<sup>8</sup> The cyclization of the tricyclic esters to provide the triaryloxazoles using ammonium acetate in acetic acid is not without limitations and certain substitution patterns on either the benzoin portion or the benzoyl ester portion may nullify any yield of desired product. For example, the 2-azido-, 3-azido- or 4-azidobenzoyl ester of 4, 4'-dibromobenzoin **15a-c** cyclized under normal conditions (NH<sub>4</sub>OAc/HOAc, 115°C) to afford the corresponding 2-azidophenyl-(4,4'-dibromodiphenyl) oxazoles **16a-c**, but the 2-azido, 3-azido or 4-azidobenzoyl esters of 2,2'-dibromobenzoin **17a-c** do not cyclize to give the expected azidophenyl-2,2'-(dibromodiphenyl) oxazoles. Another example of steric influence resides in a comparison of the cyclization reactions of the 4-iodobenzoyl ester **18** and 2-iodobenzoyl ester **20** of benzoin. Treatment of the 4-iodobenzoyl ester **18** under normal cyclization conditions affords a clean yield (95%) of the 4-iodophenylloxazole **19**, while under the same conditions, the *ortho*-iodobenzoyl ester **20** gave none of the expected oxazole.



In summary, we have detailed a synthetic route to 2, 4, 5-trisubstituted oxazoles which are differentially substituted at the 4- and 5- positions with phenyl groups and alkyl groups respectively. The route utilizes non-symmetrical acylins as starting materials and has the advantage of not involving installation of an appendage on a pre-formed oxazole. In contrast to cyclizing azidoalkyl esters to azidoalkyloxazoles, our newly-developed strategy utilizes direct cyclization of haloalkyl esters to haloalkyloxazoles so that they may be either transformed to azides or further elaborated using other nucleophiles. We found the chloromethyloxazoles to be a valuable intermediate for the preparation of many more oxazole-based scaffolds and these studies will be reported in due course.

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## Supplementary Information

The <sup>1</sup>H, <sup>13</sup>C, FTIR and HRMS data for **6a-i**, **1a-i**, **9a-c**, **10a-c**, **11a-c**, **2a-c**, **16a-c**, **7**, **12**, **18** and **19** and experimental procedures for compounds **4a-c**, **5a-c**, **6a-i**, **1a-i**, **9a-c**, **10a-c**, **2a-c**, **11a-c**, **7**, **12**, **13**, **14** and **16a-c** can be found in the online version at <http://dxdoi.org/>

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8. See Supplementary Information for general procedures.