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Synthesis of extended oxazoles II: Reaction manifold of 2-(halomethyl)-4,5-diaryloxazoles

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ABSTRACT

2-(Halomethyl)-4,5-diphenyloxazoles are effective, reactive scaffolds which can be utilized for synthetic elaboration at the 2-position. Through substitution reactions, the chloromethyl analogue is used to prepare a number of 2-alkylamino-, 2-alkylthio- and 2-alkoxy-(methyl) oxazoles. The 2-bromomethyl analogue offers a more reactive alternative to the chloromethyl compounds and is useful in the C-alkylation of a stabilized (malonate) carbanion as exemplified by a concise synthesis of Oxaprozin.

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1. Introduction

The synthesis and utilization of extended 2-substituted-4, 5-diaryloxazoles has found interesting applications in the synthesis of natural products, medicinal chemistry and photochemistry. In natural products synthesis, the 4,5-diaryloxazole group has functioned as an effective masked carboxyl derivative and functions well when introduced during the early or late stages of a total synthesis.[1] Medicinal chemistry groups have investigated the diaryloxazole system in the design and evaluation of prostanoid analogues.[2] While the 2-substituted 4,5-diaryloxazole group responds well in photochemical reactions involving singlet oxygen, there is an inherent photochemical response exhibited by these compounds which has potential in scintillation technology.[3] Basically three to four general strategies may be followed when preparing extended oxazoles at the 2-position and all these allow for a varied pattern of substituents as well as a varied degree of substituent reactivity or functional group types (Scheme 1). Lithiation of the 2-position of 4,5-diaryloxazoles may be accomplished followed by reactions with a series of electrophiles (Eq 1, **Scheme 1**), however, the reaction may be complicated by ring-opening to the isonitrile enolate.[4] 2-methyl-4,5-diaryl-oxazoles may be deprotonated (LDA) and alkylated to provide extended, fully functionalized oxazoles at the 2-position (Eq 2, **Scheme 1**). The ring-closure strategy toward 2-extended oxazoles involves the fairly standard benzoin ester formation followed by generation of the heterocycle with ammonium acetate in acetic acid (Eq 3, **Scheme 1**).[5] Typically, the ring-closure strategy is limited by the types of substituted benzoins as well as the carboxylic acid portion of the ester which bears the soon-to-be 2-appendage at the α-position of the carbonyl. While 2-(halomethyl)oxazoles (X=Br, Cl) were first proposed as atom transfer radical polymerization (ATRP) initiators,[6] our earlier work showed their synthetic utility in preparing 2-(azidomethyl)oxazole click reactants.[5] Considering the facile formation of azides from the title compounds, we now report a

Scheme 1. Synthesis of 2-extended oxazoles (X=Cl, Br).

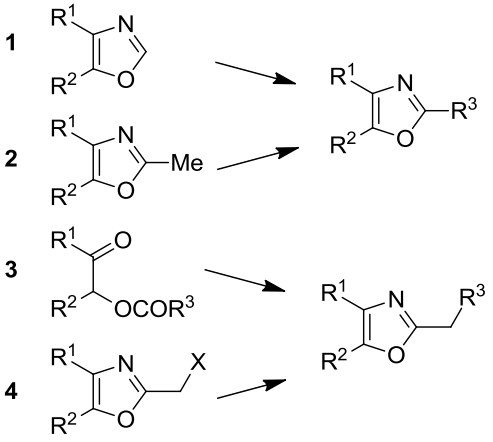

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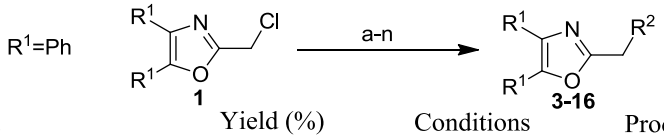
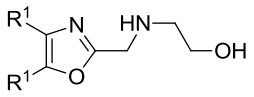
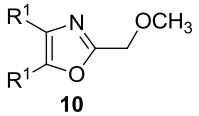
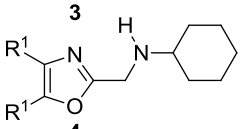
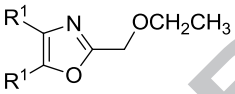
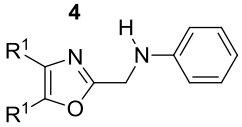
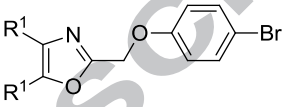
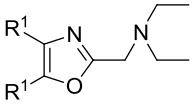
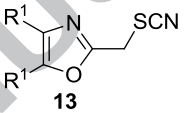
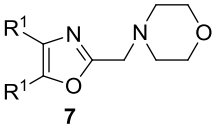
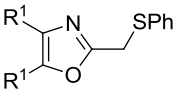
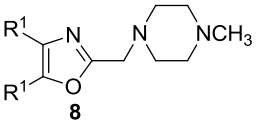
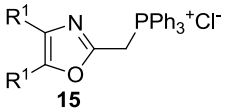
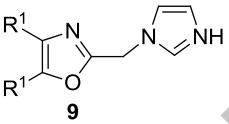
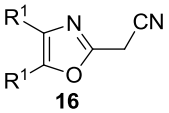
Table 1. Synthesis of Extended 2-Substituted Oxazoles



Conditions	Product	Yield (%)	Conditions	Product	Yield (%)
a	 **3**	63	h	 **10**	96
b	 **4**	40	i	 **11**	80
c	 **5**	70	j	 **12**	72
d	 **6**	81	k	 **13**	93
e	 **7**	90	l	 **14**	90
f	 **8**	80	m	 **15**	30
g	 **9**	85	n	 **16**	41

Reagents and conditions: (a) ethanolamine/ethanol/reflux/6h. (b) cyclohexylamine/TEA/THF/60°C/2h. (c) aniline/85°C/12h. (d) diethylamine/ benzene/reflux/3h. (e) morpholine/benzene/refux/8h. (f) *N*-methylpiperazine/TEA/THF/reflux/2h. (g) imidazole/NaH/DMF/5°C/2h. (h) NaOMe/ MeOH/5°C to rt/16h. (i) NaOEt/EtOH/5°C to rt/16h. (j) 4-bromophenol/K_2CO_3/DMF/100°C. (k) KSCN/acetone/ reflux/3h. (l) PhSH/NaH/DMF/ 5°C to rt. (m) PPh_3/toluene/reflux/16h. (n) NaCN/DMF/10°C to rt/16h.

diverse manifold of substitution when these halogenated compounds are reacted with appropriate nucleophiles such as amines, alkoxides, thiolates, triphenylphosphine or cyanide ion thereby providing a number of interesting intermediates (Eq 4, **Scheme 1**). In terms of fundamental nitrogen substitution on the 2-(methylene) position of oxazoles, the simplest, most unambiguous nitrogen nucleophile, i.e. azide ion, was utilized toward the goal of only providing click intermediates. Chain-lengthening of the 2-azidoalkyl group for the purpose of furnishing homologous 2-(aminoalkyl)oxazoles would necessitate oxazole closure of the corresponding homologous 2-(azidoalkyl)esters followed by reduction of the azido group. 2-(Aminoalkyl)-4,5-diphenyloxazoles have been investigated for analgesic and anti-inflammatory activity in rodent models using phenylbutazone and diethamphenazole as standards. Herein, we first show the synthetic variability of the 2-(halomethyl)oxazoles by reaction with suitable amine derivatives under a variety of conditions (Compounds **3-9, Table 1**). While nucleophilic substitution of amines on various halogenated centers are well-known reactions,[7] we find that the 2-halomethylene unit of the title reactants (**1**, X=Cl; **2**, X=Br) offers reactivity characteristic of a benzylic chloromethyl group. Primary alkyl-/aromatic amines such as ethanolamine, cyclohexylamine and aniline are capable of providing the corresponding *N*-substituted (2-aminomethyl) oxazoles (**3**,**4** and **5, Table 1**), while diethylamine, morpholine, *N*-methyl piperazine, and imidazole easily form the corresonding *N*,*N*-disubstituted products (**6-9, Table 1**). We further demonstrate the synthetic utility of the 4,5-diphenyl-2-(halomethyl)oxazoles by reaction with various alkoxides or otherwise in situ-generated phenoxide in affording the corresponding alkyl or phenyl ethers (**10-12, Table 1**). The resulting 2-(alkoxymethyl)- or 2-(phenoxymethyl)-oxazoles have been of interest as anti-inflammatory and analgesic agents whose mechanism of action depends on the modulation of cyclooxygenase activity.[8] Sulfur nucleophiles such as thiocyanate and thiophenoxide afford the corresponding 2-(methylthio) cyanate **13** or the 2-(phenylthiomethyl) oxazole **14** in high yield (**Table 1**). During the formation and purification of **13**, no isomerization to the corresponding isothiocyanate was observed.[9] With respect to the 2-(phenylthiomethyl) oxazole **14** (thiophenol/NaH**)**, we find that this compound is easily oxidized to the corresponding sulfone,[10] a compound which exhibits excellent stabilized anion reactivity for carbon-carbon bond formation. The preparation of triphenylphosphonium salt **15**

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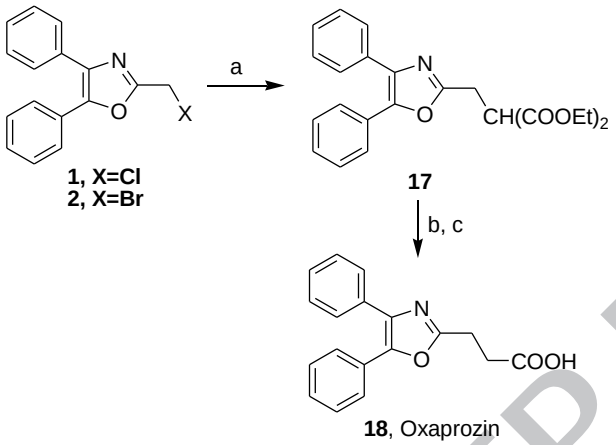
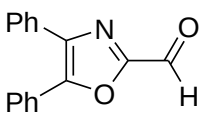
(PPh_3/toluene/heat) was the result of another heterocyclic scaffold modification whereby the potential for carbon-carbon bond formation and oxazole extension exists through Wittig chemistry.[11] The 2-(cyanomethyl)oxazole **16** was prepared by cyanide (NaCN/DMF) substitution of **1**.[12] The nitrile group of **15** should offer excellent potential for carbon-carbon bond formation at the 2-methylene position, through carbanion formation, as well as providing a reactive acceptor for alkyllithiums toward gaining carbonyl products. We demonstrate the usefulness of the 2-halomethyloxazoles **1** and **2** in carbon-carbon bond formation by a synthesis of the non-steroidal anti-inflammatory Oxaprozin (**Scheme 2**).[13] Chloromethyloxazole **1** is reacted with the anion of diethylmalonate (NaH/THF) which affords the diester **17** in 40% isolated yield. Under the same conditions, alkylation with the more reactive bromomethyloxazole **2** provides the diester **17** in 90% isolated yield. Saponification of **17** (aq. NaOH) followed by acidification (dil. HCl/reflux) then gives Oxaprozin in 47% yield.

Scheme 2. Synthesis of Oxaprozin:

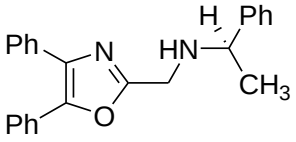


Reagents and conditions:(a) NaH/diethyl malonate/THF/ 5°C to rt/16h (40%, X=Cl; 90%, X=Br). (b) 20% aq. NaOH/ rt/16h. (c) 10% aq. HCl, pH 3-5/reflux/3h (47% for b,c).

Within the realm of amine substitution at the 2-methylene position of the 4,5-diaryloxazoles, we note that in preliminary experiments, our previously-reported 4,5-diphenyloxazole aldehyde **19**[5a,11] reacts as a convenient partner in a Schiff base formation/reduction sequence to give secondary amines. Therefore the employment of the oxazole aldehyde will provide a useful alternative to the halomethyl intermediates in providing 2-aminomethyl-substituted oxazole scaffolds.[14] For example, the reaction of **19** with (+)-*R*-α-methylbenzylamine (methanol/ reflux/16 h) gave the expected intermediate Schiff base (73%) which was directly reduced with sodium borohydride (methanol/rt/1h) to provide the chiral amine **20** (76%).



19



20

In summary we have shown that 2-(chloromethyl)-4,5-diphenyloxazoles, which are readily available from the corresponding chloroacetyl esters of benzoin or substituted benzoins, are excellent reactive scaffolds for synthetic elaboration at the 2-(methylene) position. The 2-(bromomethyl)oxazole analogue is best suited for a concise synthesis of Oxaprozin using malonate alkylation as the key step. A number of diverse amine nucleophiles may be used to prepare 2-methyloxazole-derived primary or secondary amines. Similarly, the halomethyloxazoles react well with alkoxides or phenoxides to give the corresponding ethers which have anti-inflammatory or analgesic activity. Sulfur nucleophiles such as thiocyanates and thiophenoxides react in high yield to give the corresponding carbon-sulfur bond motif whereby the 2-phenylthiomethyl analogue will show promise in further reaction scenarios.

Acknowledgments

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Supplementary Material

Supplementary data (^{1}H NMR, FTIR) for compounds **2-18, 20;** and additional ^{13}C NMR data for new compounds **5**, **9**, **12-15**, **17**, **18**, **20**. HRMS data are included for compounds **9, 10-16, 20**; along with experimental procedures associated with this article can be found, in the online version at http://dx.doi.org/j.tetlet.

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Graphical Abstract

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Pravin C. Patil and Frederick A. Luzzio*

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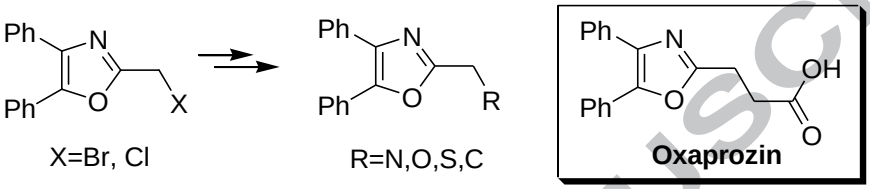

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