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PII: S0040-4039(16)30016-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.01.016
Reference: TETL 47180

To appear in: *Tetrahedron Letters*

Received Date: 14 November 2015
Revised Date: 5 January 2016
Accepted Date: 6 January 2016

Please cite this article as: Patil, P.C., Luzzio, F.A., Synthesis of extended oxazoles II: Reaction manifold of 2-(halomethyl)-4,5-diaryloxazoles, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.01.016

Tetrahedron Letters
journal homepage: www.elsevier.com

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

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
heterocycles
oxazoles
click chemistry
ligands
Oxaprozin

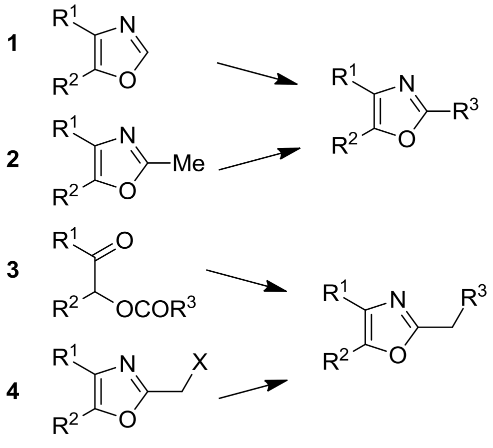
ABSTRACT

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.

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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