

Base-Promoted Domino Reaction of 5-Substituted 2-Nitrosophenols with Bromomethyl Aryl Ketones: A Transition-Metal-Free Approach to 2-Aroylbenzoxazoles

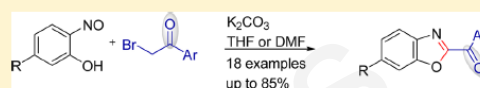
Nayyef Aljaar,^{†,‡} Chandi C. Malakar,[†] Jürgen Conrad,[†] and Uwe Beifuss^{*,†}

[†]Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstraße 30, D-70599 Stuttgart, Germany

[‡]Faculty of Pharmacy and Medical Sciences, Al-Ahliyya Amman University, Amman 19328, Jordan

Supporting Information

ABSTRACT: The reaction of 5-substituted 2-nitrosophenols with bromomethyl aryl ketones and related compounds employing K_2CO_3 as a base in refluxing THF and DMF at 80 °C, respectively, delivers 2-aroilybenzoxazoles in a single step with yields up to 85%. The new method involves an intermolecular nucleophilic substitution followed by intramolecular 1,2-addition and elimination. It allows an efficient and practical access to 2-aroilybenzoxazoles under transition-metal-free conditions.



INTRODUCTION

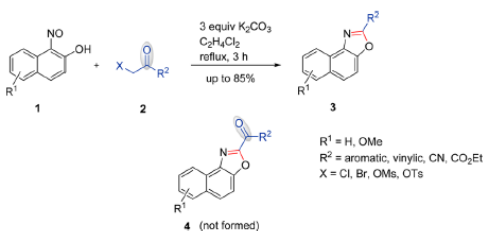
Natural as well as unnatural benzoxazoles are heterocyclic compounds with a wide range of interesting biological and pharmacological properties.^{1,2} In addition, they are important building blocks and intermediates in organic synthesis. Of particular interest are α -ketobenzoxazoles, which are well-known in drug discovery due to their significant biological activities such as the inhibition of fatty acid amide hydrolase inhibitors,³ cysteine protease inhibitors,⁴ and channel-activating protease inhibitors.⁵

This is the reason why a number of methods have been developed for the preparation of α -ketobenzoxazoles. Some of them are based on the modification of the benzoxazoles skeleton, such as the functionalization at C-2. Among them are the deprotonation/metalation of benzoxazoles followed by transition-metal-catalyzed acylation,^{3c,d,6} the Pd-catalyzed carbonylative coupling of benzoxazoles with aryl halides,⁷ and the Pd,⁸ and Ni-catalyzed⁹ decarbonylative coupling of benzoxazoles with α -oxocarboxylic acids. Another method is the NHC-catalyzed C–H arylation of benzoxazole-2-carboxaldehydes.¹⁰ In addition, some methods have been reported that are based on the formation of the benzoxazole moiety as the key step. They include the Ru-catalyzed reaction between 2-aminophenols and 1,2-dibromoethenes,¹¹ the Fe-catalyzed reaction of 2-aminophenols with alkynyl bromides,¹² and the hypiodite-catalyzed oxidative cycloetherification of *N*-(2-hydroxyphenyl)-4-methyl-*N*-(phenacyl)benzenesulfonamides.¹³ Our intention was to develop a method for the selective preparation of 2-aroilybenzoxazoles in a single step that uses cheap and easily available starting materials and reagents and can be performed under transition-metal-free conditions. Here, we disclose the formation of 2-aroilybenzoxazoles from the reaction of 5-substituted 2-nitrosophenols with α -bromo acetophenones and related compounds.

RESULTS AND DISCUSSION

Recently, we have reported on the reaction between 1-nitroso-2-naphthols **1** and α -functionalized ketones, such as α -bromo, α -chloro, α -mesyloxy, α -tosyloxy, and α -hydroxy ketones **2**, under basic conditions to deliver 2-substituted naphtho[1,2-*d*][1,3]oxazoles **3** in a single synthetic operation with yields up to 85% (Scheme 1).¹⁴ The formation of the naphtho[1,2-

Scheme 1. Unexpected Formation of 2-Substituted Naphtho[1,2-*d*][1,3]oxazoles **3**



d][1,3]oxazoles **3** was accompanied by the unexpected loss of the C=O group from the α -functionalized ketones. The expected α -ketonaphtho[1,2-*d*][1,3]oxazoles **4** could not be detected even in trace amounts. In this context, it should be mentioned that 2-aryl-annulated oxazoles can be obtained by reaction of 2-nitrosophenols and 1-nitroso-2-naphthols with benzyl halides.¹⁵

We wondered whether the reaction between 2-nitrosophenols **5** and bromomethyl aryl ketones **6** delivers the required 2-aroilybenzoxazoles **7** or whether this transformation

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