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C–H Activation of Methyl Arenes in the MnO_2-Mediated Aroylation of *N*-Chlorosulfoximines

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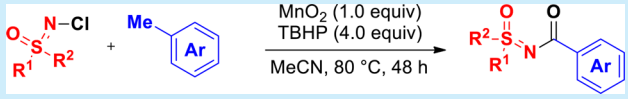
Supporting Information

ABSTRACT: An investigation into the reactivity profile of *N*-halogenated sulfoximines has led to the development of a new method for the synthesis of *N*-aroylated sulfoximines. This protocol involves the manganese oxide promoted C–H activation of methyl arenes to form an aroyl intermediate which then reacts readily with *N*-chlorosulfoximines to form a series of valuable aroyl sulfoximine derivatives in high yields.



In recent decades, sulfoximines have found extensive application in asymmetric synthesis as both chiral auxiliaries and ligands.[1,2] More recently, the sulfoximidoyl moiety has been successfully incorporated into molecules developed for use in a clinical setting; however to date, there are no commercially available pharmaceutical treatments containing this fascinating functional group.[3]

Of particular interest, the exchange of a sulfonamide for a sulfoximidoyl group in the optimization of the pan-CDK inhibitor developed by Bayer (BAY 1000394 - now well into clinical trials), had a significant impact on the success of this medicinal chemistry program.[4] More specifically, the sulfoximidoyl moiety incorporated into the drug candidate not only facilitated retention of the high level of desired bioactivity but also improved drug solubility and dramatically minimized off-target activity against carbonic anhydrases (CAs), often observed for other sulfonamide-based drugs.[4]

Following on from this exciting application of sulfoximine derivatives in a medicinal chemistry setting, we envisage that the sulfoximidoyl moiety will become a very important functional group in drug discovery programs in years to come. To facilitate this progress, our group, among others, has undertaken an intensive research program to thoroughly explore the properties of sulfoximines and to develop efficient and practical methods for both the synthesis and derivatization of sulfoximines.[5]

In recent years, *N*-chloroamines have been widely applied as electrophilic amination reagents in numerous synthetic transformations due to their enhanced reactivity when compared to *NH*-amines.[6] The analogous *N*-chlorosulfoximines were first reported in 1968 by Cram and co-workers;[7] however, since that time few additional reports regarding either the synthesis or application of *N*-halosulfoximines have appeared.[8] As such, we set out to further explore the synthetic potential of *N*-halogenated sulfoximine derivatives as both reactants and chiral reagents in numerous synthetic transformations. To this end, we herein report the development of a new method to access *N*-aroylated sulfoximines from *N*-chlorosulfoximines by the C–H activation of methyl arenes.

The C–H activation and subsequent oxidative functionalization of methyl arenes has recently emerged as an efficient approach to access a range of valuable synthetic intermediates.[9] This strategy for the formation of new carbon–heteroatom bonds has been successfully applied to the oxidative cyanation, esterification, and amidation of methyl arenes.[9] Advantageously, when the readily available methyl arenes are utilized as precursors to the activated carbonyl coupling partner required for amide bond formation, the use of more traditional carbonyl coupling partners that require preactivation, including carboxylic acids and acyl chlorides, is avoided.

Singh and co-workers recently disclosed a protocol for amide bond formation through reaction of methyl arene derivatives with *N*-chloroamines.[9e] After screening several plausible oxidants, the *in situ* oxidation of the methyl arene to form an activated carbonyl species was found to be best promoted by manganese salts.[10] In addition, the use of *N*-chloroamines offered enhanced reactivity over the *NH*-amines trialed and greatly increased the yields obtained for amide bond formation.[6,11] Inspired by these recent developments we then turned our attention to exploring the *N*-aroylation of sulfoximine derivatives using methyl arenes as the source of the carbonyl coupling partner.

To initially explore this reaction process, *N*-choro-*S*-methyl-*S*-phenylsulfoximine (**1**) was readily prepared by reaction of the *NH*-sulfoximine with NCS in MeCN. Following isolation of the *N*-chlorosulfoximine, it was subjected to the aroylation conditions reported by Singh,[9e] using toluene as the methyl arene in the presence of MnO_2 and *tert*-butylhydroperoxide (70% aqueous solution). To our delight, after 48 h of reaction time at elevated temperatures, the *N*-benzoyl sulfoximine **3a** was formed in a yield of 81% (Scheme 1). To further investigate this process, a range of methyl arenes were then applied under the standard conditions (Scheme 1).

It was observed that methyl arenes containing halide substituents worked exceptionally well in this reaction process

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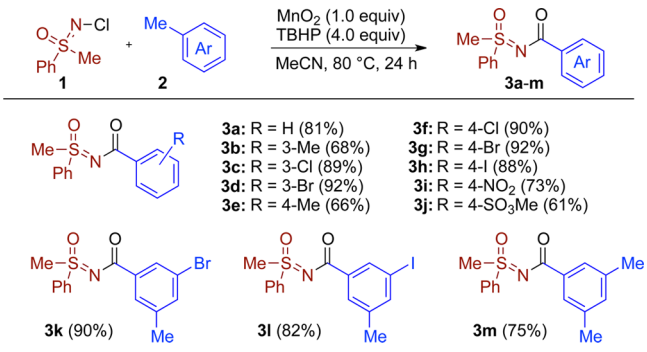
Scheme 1. Synthesis of *N*-Aroylated Sulfoximines by the C–H Activation of Methyl Arenes

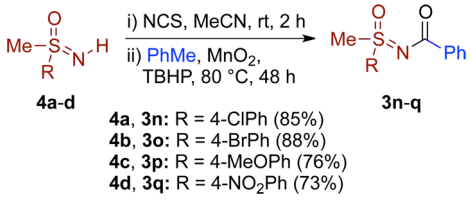


affording the corresponding sulfoximine derivatives in excellent yield (82–92%, **3c,d,f–h,k,l**). Other aryl substrates containing methyl, nitro, or sulfonate groups also gave products in good yields (61–75%, **3b,e,i,j,m**). Methyl arenes containing two or more methyl groups including mesitylene and halogenated xylene derivatives also reacted well (**3k–m**), and none of the polysulfoximine products that might arise for these substrates were observed.

As reported for other reaction processes with the relatively non-nucleophilic sulfoximines,[5f] electron-rich substrates including 4-methyl anisole and 2-methyl furan failed to react under the standard conditions. In regards to steric factors, substituents at the 3- or 4-position of the aryl ring were well tolerated; however, toluene derivatives containing a methyl or halo substituent at the 2-position failed to afford synthetically useful yields of the corresponding *N*-aroyl sulfoximine.

To investigate variation in the sulfoximidoyl moiety, a one-pot, two-step procedure was utilized. Initially, the nitrogen of the sulfoximidoyl moiety was halogenated using NCS, and after stirring for 2 h at room temperature, the additional reagents were added and the reaction mixture was heated to 80 °C for 48 h (Scheme 2). Under these conditions, employing toluene

Scheme 2. Variation of the Sulfoximine Moiety in the Aroylation of *N*H-Sulfoximines via *N*Cl-Sulfoximines

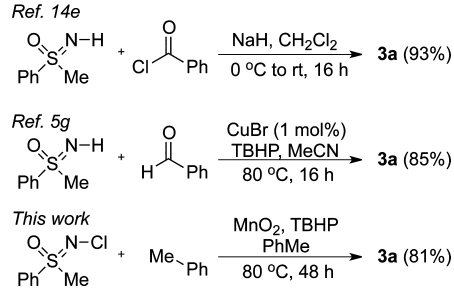


as the methyl arene source, the *S*-methyl-*S*-arylsulfoximines containing a chloro-, bromo-, methoxy-, or nitro-substituent (**4a–d**) were all aroylated in good yield (73–88%, **3n–q**).

Mechanistically, this process is proposed to proceed through a radical intermediate, in analogy to previous reports on the aroylation of both amines and sulfoximines.[5g,9e,12] Following the manganese promoted oxidation of the Ar–CH_3 to the corresponding aldehyde (Ar–CHO), in the presence of TBHP an aroyl radical is generated.[9e,12,13] This aroyl radical then reacts with the sulfoximine to form the *N*-aroylated sulfoximine adduct. Attempts to perform the same reaction using the *N*H-sulfoximine only afforded trace amounts of the desired product. As such, it is proposed that this amidative reaction process also involves a nitrogen-based radical formed following cleavage of the *N*-Cl bond,[11a] as recently proposed by Singh and co-workers.[9e]

Traditionally, aroyl-functionalized sulfoximines have been prepared by the reaction of aroyl chlorides with *N*H-sulfoximines (Scheme 3, top).[14] In addition, we recently

Scheme 3. Methodology Available for the *N*-Aroylation of Sulfoximines



disclosed a new strategy for the preparation of aroylated sulfoximines through the copper-catalyzed oxidative coupling of *N*H-sulfoximines and aldehydes (Scheme 3, middle).[5g] The novel method reported herein provides an alternative approach to these syntheses of *N*-aroylated sulfoximine derivatives through the reaction of *N*-chlorosulfoximines with methyl arenes (Scheme 3, bottom). This protocol employs readily available methyl arenes as substrates, instead of the more commonly applied acyl chloride or carboxylic acid coupling partners, and provides access to a range of functionalized *N*-aroyl sulfoximines.

In summary, an investigation into the properties of *N*-halosulfoximines has led to the development of a new method for the *N*-aroylation of sulfoximines. Further exploration into the potential of *N*-halosulfoximines as both reactants and (chiral) reagents in chemical synthesis remain underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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