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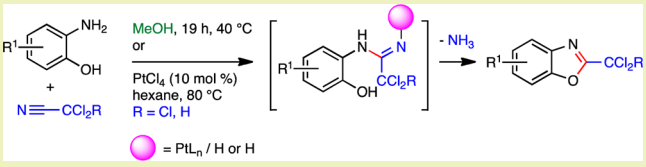
Methods for the Direct Synthesis of Benzoxazoles from Halogenated Nitriles in Alcoholic Solvents

Roy P. Lester and Jason E. Camp*

School of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K.

Supporting Information

ABSTRACT: Two complementary approaches for the direct synthesis of 2-dichloro- and 2-trichlorobenzoxazoles from 2-aminophenols and halogenated nitriles are reported. A green, noncatalyzed method was shown to proceed in an alcoholic solvent without the addition of exogenous acid or base. This method provides a clean and robust synthesis of these important heterocycles, which contain a key functional group handle at the 2-position. A complementary platinum multifaceted catalysis approach was also developed in which the metal can catalyzes multiple mechanistically distinct processes. This method allows for an improved use of the metal catalyst vs stepwise protocols and provides increased flexibility in the choice of reaction conditions.



KEYWORDS: *Green chemistry, Alcoholic solvent, Platinum catalysis, Heterocycle, Multifaceted catalysis*

INTRODUCTION

Benzoxazoles are a useful class of heterocycle that have found prominence in the area of medicinal and agricultural chemistry.[1−5] Due to the preponderance of this motif in biologically active compounds, a number of methods have been developed for their synthesis[6−8] and functionalization.[9] One underutilized method of benzoxazole formation is via the reaction of 2-aminophenols with nitriles.[10] Nitriles have been used extensively in the synthesis of heterocyclic compounds, though they are traditionally activated for nucleophilic addition by the application of strong protic acids[11] or Lewis acids[12] with a small number of alternative methods recently developed.[13−16] Many of these methods though require harsh reaction conditions and toxic additives leading to high levels of waste. Therefore, there remains a demand for increasingly efficient methods for the convergent synthesis of benzoxazoles from simple, readily available starting materials. Encouraged by the potential applications of substituted benzoxazoles, greener approaches to their direct formation from halogenated nitriles were investigated. Herein, is described the development of both a platinum-catalyzed method and a catalysts free method in methanol for the direct synthesis of 2-dichloro and 2-trichloro substituted benzoxazoles from halogenated nitriles.

EXPERIMENTAL SECTION

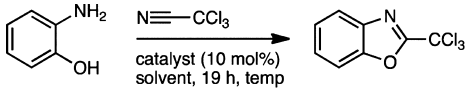
General Procedures. *Platinum-Catalyzed.* To a stirred suspension of $PtCl_4$ (10 mol %) and 2-aminophenol (1 equiv) in *n*-hexane (1 M) at rt was added trichloroacetonitrile (2.2 equiv). The resultant mixture was stirred at 80 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the benzoxazole.

Catalyst Free. To a solution of 2-aminophenol (1 equiv) in methanol (1 M) at rt was added trichloroacetonitrile (1.1 equiv). The resultant mixture was stirred at 40 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the trichlorobenzoxazole.

RESULTS AND DISCUSSION

In search of a suitable transition metal catalyst to facilitate a metal-catalyzed synthesis of benzoxazoles, simple platinum salts were screened[17] in the reaction of 2-aminophenol (**1a**) with trichloroacetonitrile (Table 1, entry 1). Initially, platinum(II) chloride was found to be effective in generating 2-trichlorobenoxazole **2a** from the reaction of 2-aminophenol (**1a**) and trichloroacetonitrile in the nonpolar solvent *n*-hexane. Previously, it had been shown that primary aliphatic amines do

Table 1



1a **2a**

entry	solvent (1 M)	catalyst (10 mol %)	temp (°C)	yield (%)[a]
1	*n*-hexane	$PtCl_2$	80	72
2	*n*-hexane	$PtCl_4$	80	82
3	*n*-hexane		80	0
4	EtOH	$PtCl_4$	80	64
5	EtOH		80	99
6	EtOH		40	98
7	MeOH		40	99

[a]Isolated yield.

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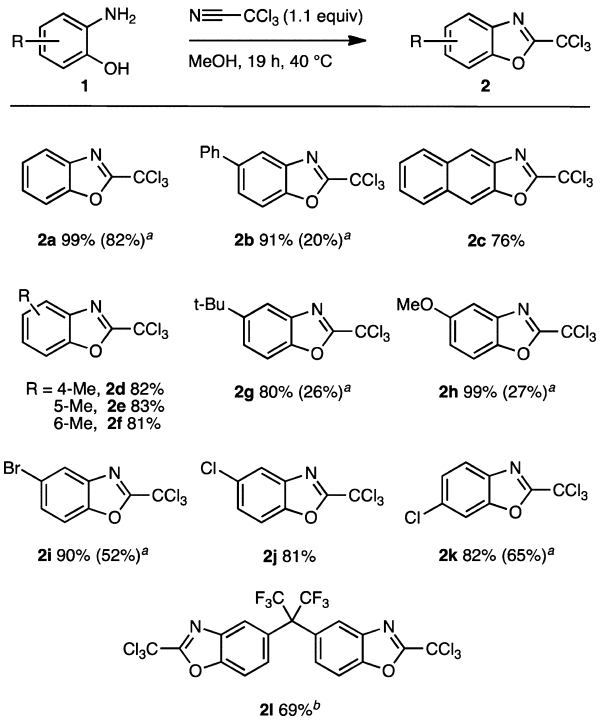
no react with trichloroacetonitrile in nonpolar solvents in the absence of a catalyst.[18] After minimal experimentation,[19] it was found that the reaction proceeded in the highest yield when run in *n*-hexane at 80 °C in the presence of 10 mol % platinum(IV) chloride (Table 1, entry 2). Importantly, none of the desired benzoxazole **2a** was observed in the absence of the catalysts (Table 1, entry 3). As part of a screen utilizing more environmentally friendly solvents,[20,21] it was found that the protic solvent ethanol was also a viable solvent for the platinum-catalyzed process.[19] Interestingly, when the control reaction was run in the absence of the platinum species a near quantitative yield of benzoxazole **2a** was isolated (Table 1, entry 4 vs 5).[22] Subsequently, it was found that after 19 h the reaction between aminophenol (**1a**) and trichloroacetonitrile to give benzoxazole **2a** at temperatures down to 40 °C in either ethanol or methanol proceeded in good yield. Decreased yields were observed when the time of the reaction was reduced. Thus, two viable methods for the direct synthesis of 2-trichlorobenzoxazoles were developed. Importantly, these methods are complementary and allow for flexibility with regards to polar protic or nonpolar aprotic solvents, which have implications on both downstream processing and the potential for further tandem transformations.

Due to the high price and limited amounts of transitions metals for catalysis[23] and issues surrounding the use of hydrocarbon solvents,[24] we decided to focus on the more sustainable noncatalyzed process in alcoholic solvents. Owing to its high yield of product as well as increased workers'/process safety and decreased environmental impact verses traditional organic solvents,[20,21] methanol was chosen as the solvent for the direct formation of benzoxazoles from halogenated nitriles. With the choice of solvent in hand, the scope of the catalyst free method for the direct formation of benzoxazoles was investigated. It was found that aryl-substituted and fused aminophenols gave the corresponding benzoxazoles **2b**,**c** in good yields when reacted with trichloroacetonitrile at 40 °C in methanol (Scheme 1). Additionally, alkyl substituted aminophenols and electron rich methoxy derivatives gave the expected benzoxazoles **2d**–**g** in good yield. Importantly, halogenated aminophenols formed the corresponding benzoxazoles **2i**–**k**, which contain a functional group handle for further cross-coupling transformations.[25,26] Finally, it was found that bis-benzoxazole **2l** could be formed from the corresponding bis-aminophenol in good yield by increasing the amount of trichloroacetonitrile to 2.2 equiv. Unfortunately, aminophenols with strongly electron withdrawing groups, such as nitro and carboxylic acids moieties did not afford any of the desired benzoxazoles and only the starting materials were recovered. A number of the aminophenol substrates were also subjected to the platinum-catalyzed conditions. For example, the platinum-catalyzed reaction of aminophenol **1b** with Cl_3CCN in *n*-hexane at 80 °C afforded the desired benzoxazole **2b** in 20% yield. In all of the cases examined, a lower isolated yield of the benzoxazole products was observed in comparison to the methanol conditions. The platinum-catalyzed process though may be applicable to systems that require aprotic conditions or in which further tandem processes facilitated by the platinum are desired.[27] Additionally, the product trichlorobenzoxazoles are useful substrates for further functionalization as the trichloro moiety can be converted into a variety of other functional groups[28−30] or directly displaced by a nucleophile.[31,32]

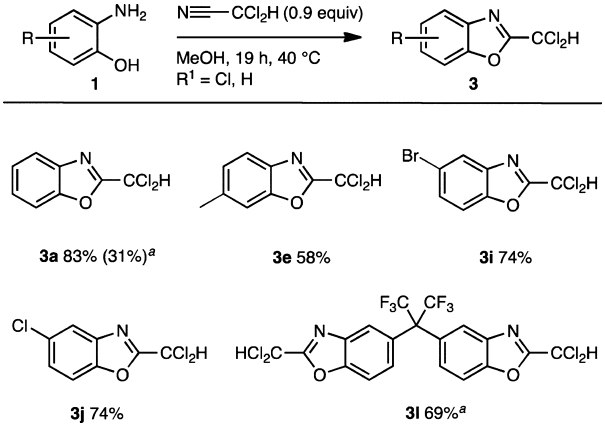
Scheme 1



[a]$PtCl_4$ (10 mol %), *n*-hexane, 80 °C, 19 h. [b]2.2 equiv of Cl_3CCN was used.

Next the reaction between aminophenols **1** and the less activated nitrile, dichloroacetonitrile, to form 2-dichlorobenzoxazoles **3** was investigated. The product dichlorobenzoxazoles **3** are potentially useful compounds as alkylating reagents[33] and as masked aldehydes.[34] Reaction of aminophenol **1a** with dichloroacetonitrile in methanol at 40 °C afforded the desired 2-dichlorobenzonitrile **3a** in good yield (Scheme 2). In

Scheme 2



[a]4.0 equiv of dichloroacetonitrile was used.

contrast, subjection of these reagents to the platinum-catalyzed conditions only afforded 2-dichlorobenzonitrile **3a** in 31% yield. The scope of the methanol reaction was also explored and it was found that methylated **3d**, halogenated **3i**,**j**, and bis-benzoxazole **3l** could be synthesized in good yields. The yields of the 2-dichlorobenzoxazoles **3** were approximately 20% lower than the corresponding 2-trichloro compounds **2**, except in the

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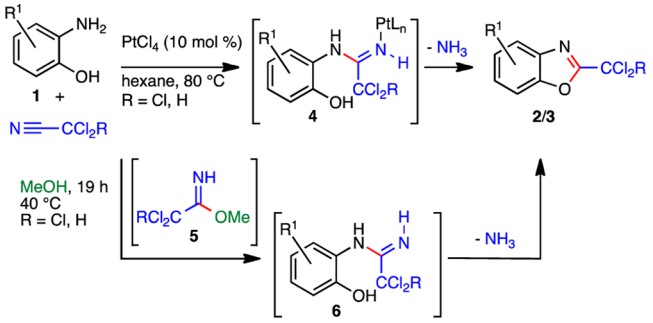
case of bis-benzoxazole **3l**, which was formed in the same isolated yield as **2l**.

Mechanistically, we believe that the both the platinum-catalyzed and the uncatalyzed methanol conditions proceed through similar amidine intermediates **4**/**6** (Scheme 3).[35] Platinum activation of the halogenated nitrile, followed by nucleophilic addition of the aminophenol nitrogen would afford platinum-amidine **4** after proton transfer.[36] Intramolecular addition of the pendant phenol followed by loss of ammonia, facilitated by the platinum, would then afford the desired substituted benzoxazole **2**/**3**. This form of catalysis, in which one metal catalyzes multiple, mechanistically distinct processes is known as multifaceted catalysis[37−46] and allows for a decrease in overall cost in terms of time, waste and to the environment in comparison to a traditional stepwise synthesis. In contrast, the initial step of the uncatalyzed process is most likely formation of imidate **5**, via nucleophilic addition of methanol.[29] The in situ formed imidate can then be attacked by aminophenol **1** to afford amidine **6**. Phenol addition and loss of ammonia would then afford benzoxazoles **2**/**3**.

Scheme 3. Proposed Mechanisms for the Synthesis of Benzoxazoles from Trichloroacetonitrile



In conclusion, a simple, catalyst free method for the direct synthesis of substituted benzoxazoles from di- and trichloroacetonitrile using the green solvent methanol without the addition of exogenous acid or base has been developed. Additionally, a platinum-multifaceted catalysis approach in the aprotic organic solvent *n*-hexane was also developed, which provides increased flexibility in the choice of reaction conditions. We anticipate that these approaches to benzoxazole synthesis will find wide application due to their utility and operational simplicity. Further insights into the mechanisms of these intriguing process and extending these approaches to less activated nitriles are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jason.camp@nottingham.ac.uk.

Notes

The authors declare no competing financial interest.

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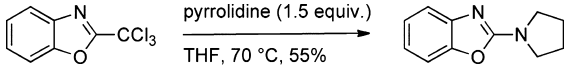

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