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Cycloaddition of benzynes and nitrile oxides: synthesis of benzisoxazoles

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ABSTRACT

A mild and efficient process has been developed for the synthesis of benzisoxazoles through the cycloaddition of benzynes and nitrile oxides. This method allows access to both (hetero)aromatic and alkenyl-substituted benzisoxazoles. Preliminary studies concerning regioselectivity are also reported.

The development of new reactions featuring the employment of benzynes has received increasing attention over recent years. Although arynes have been known since the 1950s,[1] a recent surge in this research area can be partly attributed to the realisation of a mild method for the generation of these reactive intermediates. A plethora of recent literature employs the tactic developed by Kobayashi and co-workers[2] whereby, the treatment of easily prepared or commercially available *o*-(trimethylsilyl)aryl triflates with a mild fluoride source leads to the in situ release of arynes through *ortho*-elimination. Such generated benzynes have been successfully employed in, for example, inter-[3] and intra-molecular cycloaddition-,[4] domino-,[5] copper-mediated-,[6] palladium-mediated-[7] and rearrangement-processes.[8] Arynes derived in this manner have also found utility in a number of recent elegant total syntheses.[9] Complementary but less mild methods for the generation and employment of benzynes have also been the subject of widespread attention in the literature.[10] Considering the popularity of this chemistry we were rather surprised to find scant coverage of the reactivity of benzynes with nitrile oxides. We thought that this could reflect the potential difficulties of bringing together two highly reactive intermediates to participate in the desired cycloaddition event (Fig. 1). Indeed, when we started this work only two isolated reports existed, both of which offered one example which proceeded in poor yield and started from anthranilic acid (a potentially explosive benzyne precursor).[11] However, during the course of our studies, Moses and co-workers reported their preliminary work in this area,[12] prompting us to detail our own efforts towards this goal. Herein we describe our differing optimisation process, the synthesis of heteroaromatic and alkenyl-substituted benzisoxazoles as well as initial studies on the regioselectivity of the cycloaddition.

Nitrile oxides are reactive intermediates, commonly generated in situ from the treatment of their chloro-oxime counterparts with base. Such intermediates are known to undergo an irreversible homodimerisation process, to give furoxan products.[13] For the purposes of our studies we simplified our initial investigations by employing mesityl *N*-oxide, which is known to participate reluctantly in furoxan synthesis.[14] Given the consistency of fluoride source/solvent combination seen in the literature, our first conditions featured CsF and MeCN. Pleasingly, on subjecting 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) and mesityl *N*-oxide (**2**) to CsF in MeCN the desired benzisoxazole product **3** could be isolated in quantitative yield (Table 1, entry 1). However, the reaction was extremely sluggish, requiring 3 days at room temperature for complete conversion. Attempts to increase the rate of reaction by increasing the temperature resulted in the observation of an oxadiazole byproduct **4**, derived from the cycloaddition of *N*-oxide

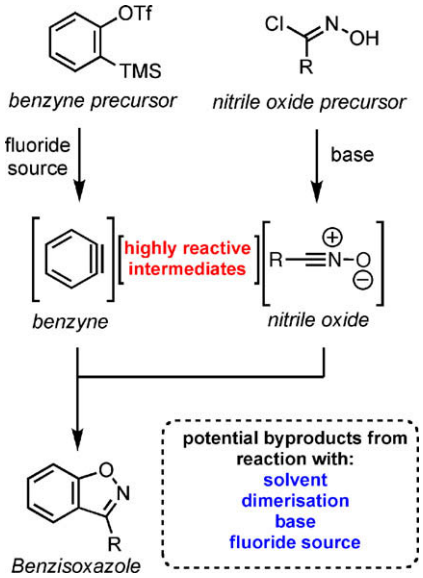

Figure 1.

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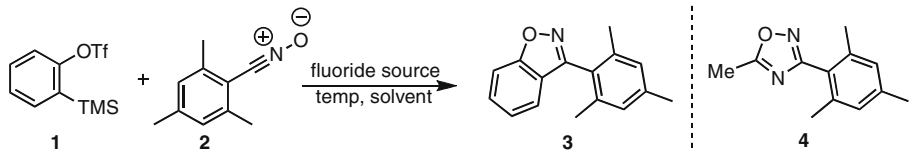
Table 1

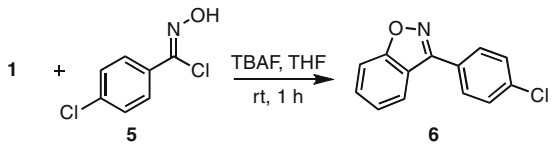


Entry	Solvent	Fluoride source	Time	Temperature (°C)	Yield (%)
1	MeCN	CsF	72 h	22	99
2	MeCN	CsF	20 min	120	99 (1:1, **3**:**4**)
3	MeCN	CsF	24 h	80	99 (7:3, **3**:**4**)
4	1,4-Dioxane	CsF	24 h	101	Complex mixture
5	DME	CsF	36 h	85	Complex mixture
6	Acetone	CsF	24 h	57	Complex mixture
7	DMF	CsF	24 h	153	Complex mixture
8	THF	CsF	24 h	66	Trace
9	***THF***	***TBAF***	***1 h***	***22***	***99***

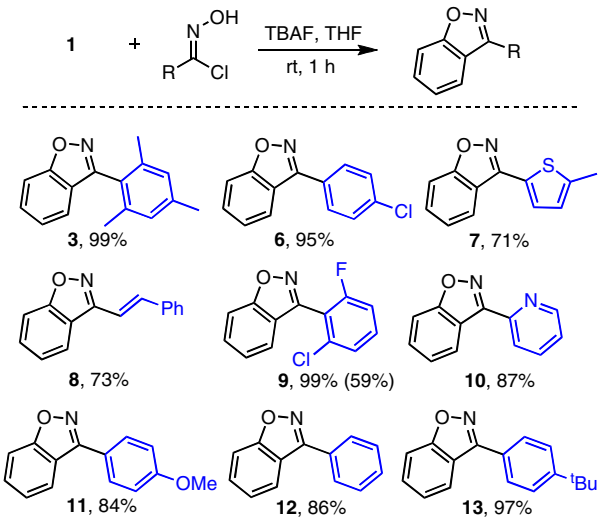
2 with MeCN (Table 1, entries 2 and 3). We therefore tested a range of alternative polar solvents (Table 1, entries 4–8). Disappointingly, all of those assessed delivered complex mixtures.[15] This was presumed to be due to the poor solubility of CsF in this selection of solvents.[16] Gratifyingly, treatment of benzyne precursor **1** and nitrile oxide **2** with a solution of TBAF in THF furnished the desired benzisoxazole within 1 h at room temperature (Table 1, entry 9). From the outset we appreciated that a useful protocol would require both the in situ generation of the benzyne and nitrile oxide species simultaneously. Moreover, this could be further complicated if the rate of furoxan synthesis was competitive with the rate of benzisoxazole formation. We hoped to harness the basic properties of TBAF to our advantage and see if this reagent could initiate the unveiling of both reactive intermediates.[17] Proof that TBAF could function in this way was discovered upon the treatment of chloro-oxime **5** and benzyne precursor **1** with TBAF in THF (using the ratios employed for the mesityl *N*-oxide chemistry). However, conducting the reaction under these conditions delivered poor yields of the desired product. Carrying out the reaction with a 2:1 excess of aldoxime **5** to benzyne precursor **1** resulted in only a trace amount of product (Table 2, entry 1). Reversal of this ratio appeared to overcome this shortfall, furnishing the product **6** in 59% yield (Table 2, entry 2). Probing this a little further highlighted that indeed an excess in the concentration of benzyne was required for a successful cycloaddition. A ratio of 3:1 (**1**:**5**) appeared to suffice, delivering benzisoxazole **6** in 95% yield (Table 2, entry 3).

We next turned our attention to the scope of the reaction with respect to the nitrile oxide partner. As shown in Scheme 1, a selection of both substituted and unsubstituted benzaldehyde derived chloro-oximes underwent smooth cycloaddition to afford the benzisoxazole products in excellent yields. Furthermore, 5-methyl-2-carboxythiophene and 2-carboxypyridyl-derived chloro-aldoximes also gave rise to some interesting bis-heterocyclic scaffolds in good effect (**7** and **10**). A preliminary effort with a primary substituted alkyl chloro-oxime failed to provide any benzisoxazole product. However, cinnamaldehyde-based chloro-oxime did undergo smooth cycloaddition to afford the styrene-substituted benzisoxazole **8**.

Table 2

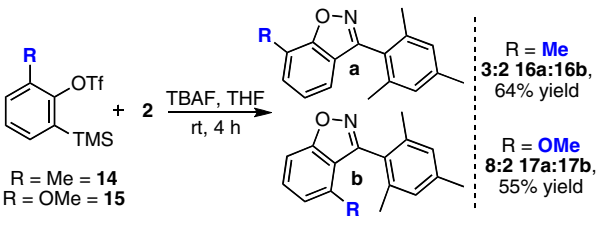


Entry	Equiv **1**	Equiv **5**	Equiv TBAF	Yield (%)
1	1	2	3	Trace
2	2	1	3	59
3	***3***	***1***	***4***	***95***



Scheme 1. Number in parentheses represents the yield when the reaction was conducted under the molar ratios in Table 2, entry 2.

Previous studies on benzyne cycloadditions have offered mixed outcomes with regard to regioselectivity.[18] Prior work from Larock and co-workers demonstrated that a 1,3-dipolar cycloaddition of an azide with an *ortho*-MeO-substituted benzyne precursor could give rise to a regioselective cycloaddition.[3c] We therefore next endeavoured to see if simple *ortho* substituents could affect regio-



Scheme 2.

control over this process. Treatment of 2-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (**14**) with mesityl *N*-oxide and TBAF provided some interesting findings (Scheme 2). Firstly, the reaction was notably slower, with 4 h required for complete consumption of the *N*-oxide starting material, resulting in the isolation of an inferior yield (64%, combined yield). Secondly, the methyl substituent appeared to offer poor control over regioselectivity, delivering a 3:2 mixture in favour of the sterically less congested system **16a**.[19]

Conversely, although the same reduced reactivity was observed with the methoxy-substituted congener **15** an improvement in selectivity was apparent, delivering the desired products **17a**,**b** in an 8:2 ratio These findings suggest that a moderate improvement in regioselectivity can be imparted to this cycloaddition by the presence of a σ-withdrawing group.

In conclusion we have designed and optimised a mild method for the synthesis of benzisoxazoles.[20] Aromatic, heteroaromatic and alkenyl-substituted chloro-oximes are all competent 1,3-dipole precursors and provide the products in good to excellent yields. We have also shown, and in line with previous findings on dipolar cycloadditions of benzynes, that methoxy benzyne offers improved regiocontrol over simple alkyl analogues.

Acknowledgements

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15. As determined by ^{1}H NMR spectroscopy and TLC analysis of the crude reaction mixture.
16. Notwithstanding the possibility of the solvent reacting with the benzyne intermediate.
17. For the use of TBAF as a base, see: Li, H.-Y.. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; vol. 7, p 4728.
18. For some interesting work on this topic, see: Matsumoto, T.; Sohma, T.; Hatazaki, S.; Suzuki, K. *Synlett* **1993**, 843.
19. Regiochemical assignment of **16a** and **16b** was deduced by nOe analysis after preparative TLC isolation of the individual isomers. The regiochemistry of **17a**,**b** is made by inference.
20. *Representative experimental procedure as applied to the synthesis of benzisoxazole* **7**: To a stirring solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (150 mg, 0.500 mmol) and 5-methylthiophene-2-hydroximoyl chloride (**5**) (29 mg, 0.167 mmol) in THF (3 mL) was added TBAF (1 M solution in THF, 0.67 mL, 0.67 mmol). After 1 h the reaction mixture was evaporated to dryness and purified by flash column chromatography (stepwise gradient: starting with petroleum ether, finishing with 10% EtOAc in petroleum ether) to give the product **7** as a colourless solid, 26 mg, 71% yield; mp 75–78 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.60 (s, 3H), 6.88–6.92 (m, 1H), 7.35–7.44 (m, 1H), 7.55–7.65 (m, 3H), 7.99 (d, J = 8.0 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 15.4, 110.2, 120.1, 122.0, 123.9, 126.2, 127.6, 128.2, 129.9, 143.3, 152.3, 163.7 ppm. FT-IR 3104 (w), 1611 (m), 1558 (m), 1506 (m), 1463 (m), 1375 (m) cm^{-1}. HRMS (EI$^+$): calcd for $C_{12}H_{10}NOS$ $[M+H]^+$ 216.0483, found: 216.0481.