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On the use of 2-(trimethylsilyl)iodobenzene as a benzyne precursor

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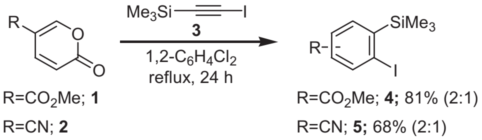
ABSTRACT

A mild method for the generation of benzynes from 2-(trimethylsilyl)iodobenzene derivatives is reported. The employment of silver fluoride in conjunction with caesium fluoride is key for promoting useful levels of elimination and providing benzyne derived products in good yields. Moreover, the substrates are accessed by a novel alkynyl iodide cycloaddition.

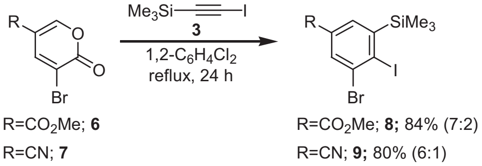
Kobayashi's discovery that 2-(trimethylsilyl)phenyl trifluoromethanesulfonate behaves as a competent benzyne precursor in the presence of a fluoride source has revolutionised the application of benzynes in organic synthesis.[1] This is largely attributable to the mild conditions under which the benzyne can be unmasked, thereby allowing substrates and reagents bearing sensitive functionality to participate in efficient reaction processes.[2] However, a potentially limiting factor is associated with this useful precursor. Although a handful of 2-(trimethylsilyl)phenyl trifluoromethanesulfonates are commercially available, if a more complex benzyne precursor is required the synthesis can become rather lengthy. Typical preparative routes involve a three-step method consisting of the treatment of a silylated phenol with a strong base followed by O–Si bond cleavage and triflation of the resulting phenol. Several efforts have been made to improve this strategy.[3] Moreover, we recently reported an alternative protocol which involves the oxidation and subsequent triflation of a trimethylsilyl alkynylboronate cycloadduct.[4] Herein we report some useful and general conditions for the in situ generation of benzyne from 2-(trimethylsilyl)iodobenzenes; substrates which offer the potential to be obtained in fewer synthetic steps than their triflate congeners.

In 1973, Cunico reported that 2-(trimethylsilyl)halobenzenes could be utilised for the generation of benzynes.[5] For example, they found that treatment of 2-(chloro)trimethylsilylbenzene with KO^{t}Bu in hexamethylphosphoramide and furan afforded the corresponding cycloadduct in 18% yield. However, products arising from desilylation were also isolated along with *tert*-butyl phenyl ether (18% and 4%, respectively). Similar results were also observed when the bromo- and iodo-analogues were employed. Since this pioneering work, these potential precursors have largely been ignored. Given the advances since these investigations, specifically within the area of mild fluoride sources for the activation of silyl groups, we decided to reassess this timely problem.

For the purposes of these studies we chose to prepare our benzyne precursors via a novel alkynyl iodide cycloaddition; our results are depicted in Eqs. 1 and 2. Pleasingly, treatment of methyl coumalate (**1**) with trimethylsilyl iodoacetylene (**3**) afforded the desired product in excellent yield and as a 2:1 mixture of regioisomers. The presence of regioisomers should prove inconsequential as they were expected to converge to a single benzyne intermediate. The reaction could also be conducted in a microwave reactor (200 °C, 2 h) to provide **4** in 87% yield with an identical regioisomer ratio. Pyranone **2** reacted similarly, whereas substrates **6** and **7** gave marginally improved regioselectivities [Eq. 2; only one regioisomer was shown for clarity)].[6] Notably, this synthesis represents the first reported cycloaddition of alkynyl iodides with pyranones and extends the utility and potential application of such alkynes in organic synthesis.[7,8]



(1)



(2)

We next turned our attention to uncovering conditions to generate the appropriate benzynes in situ. We decided to use compound **4** for our optimisation studies in conjunction with furan as a benzyne trap. For the iodide precursor to be deemed useful, we stipulated that any such conditions should be mild in nature and comparable to those used for the analogous 2-(trimethylsilyl)phenyl trifluoromethanesulfonate. Accordingly, when **4** was treated with 2 equiv of TBAF in the presence of 5 equiv of furan the desired adduct **10** was isolated in 32% yield along with 54% of desilylated product **11** (Scheme 1). We considered that the

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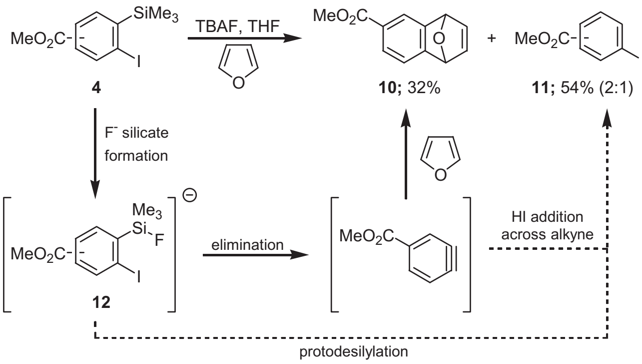
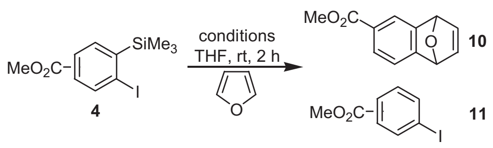


Scheme 1. TBAF promoted benzyne formation.

iodobenzene byproduct **11** could be derived from two pathways: (1) Addition of hydrogen iodide across the benzyne intermediate. (2) Protodesilylation, resulting in incomplete benzyne formation. The observation that **11** was present as a 2:1 ratio of regioisomers (analogous to the starting material **4**) suggested that it was derived from protodesilylation rather than addition of HI across the triple bond of the benzyne. This observation in conjunction with Cunico's results led us to consider the employment of an additive which could help promote the halide elimination process. Moreover, we also considered the use of alternative fluoride sources; our results are displayed in Table 1.

Whilst experiments showed that increasing the number of equivalents of TBAF increased the observed ratio of **10**:**11** favourably (entries 1–4), we were unable to achieve a ratio reflecting preference for the desired product. The use of TBAF on silica gel offered no improvement over the use of TBAF in THF (cf. entries 2 and 5), whereas the use of TBAT did appear to provide an increase in product formation compared to TBAF (cf. entries 2 and 6). Conducting the reaction in acetonitrile with caesium fluoride as the fluoride source gave no improved ratio, although, in this case the reaction mixture also contained starting material (entry 7). However, we were pleased to find that in the presence of silver fluoride both caesium fluoride and TBAT delivered promising outcomes, resulting in 5:1 and 2.5:1 ratios of **10**:**11**, respectively (entries 8 and 9).

Table 1

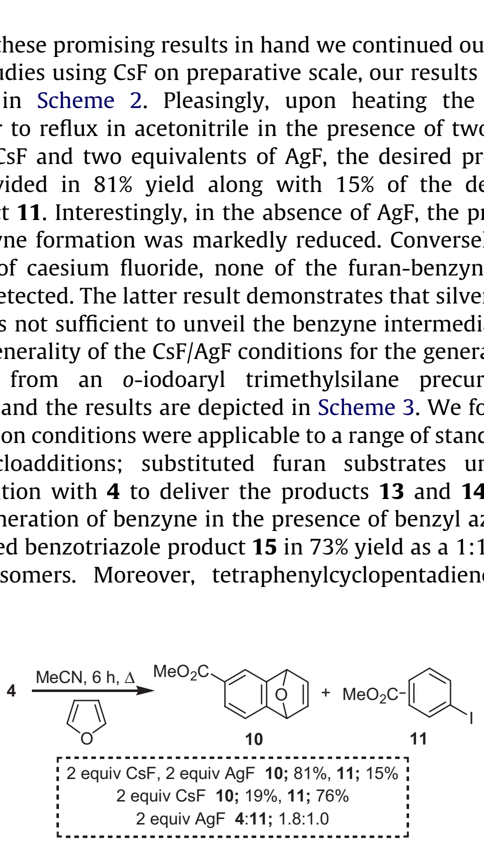


Entry	Fluoride source (equiv)	Additive (equiv)	(**10**:**11**)[a]
1	TBAF (1)	–	1.0:5.2
2	TBAF (2)	–	1.0:2.8
3	TBAF (4)	–	1.0:2.2
4	TBAF (10)	–	1.0:1.1
5	TBAF/Si (2)	–	1.0:4.2
6[b]	TBAT (2)	–	1.0:1.6
7[c,d]	CsF (2)	–	1.0:4.0
8[c,d]	CsF (2)	AgF (2)	5.0:1.0
9	TBAT (2)	AgF (2)	2.5:1.0

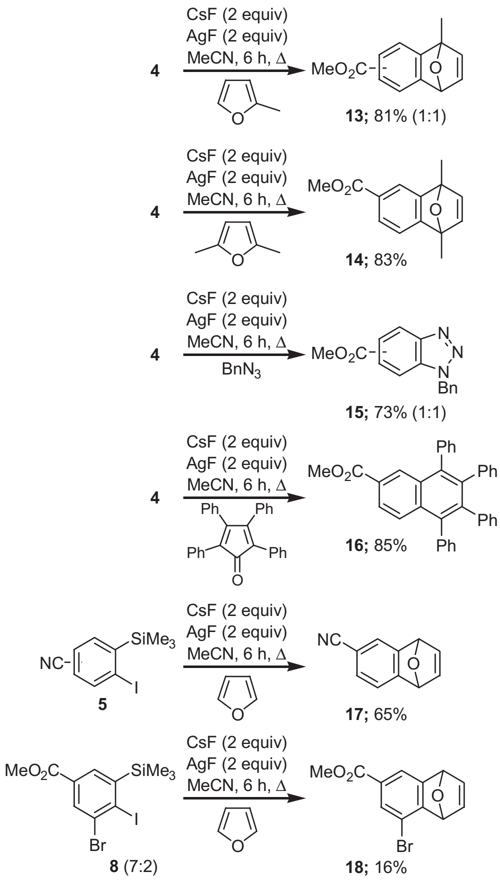
[a] Relative ratios calculated from GC–MS analysis.
[b] TBAT: tetrabutyl-ammonium triphenyldifluorosilicate.
[c] Reaction conducted in acetonitrile.
[d] Starting material also observed by GC–MS analysis.

With these promising results in hand we continued our optimisation studies using CsF on preparative scale, our results are summarised in Scheme 2. Pleasingly, upon heating the benzyne precursor to reflux in acetonitrile in the presence of two equivalents of CsF and two equivalents of AgF, the desired product **10** was provided in 81% yield along with 15% of the desilylated byproduct **11**. Interestingly, in the absence of AgF, the propensity for benzyne formation was markedly reduced. Conversely, in the absence of caesium fluoride, none of the furan-benzyne adduct **10** was detected. The latter result demonstrates that silver fluoride alone was not sufficient to unveil the benzyne intermediate.[9]

The generality of the CsF/AgF conditions for the generation of a benzyne from an *o*-iodoaryl trimethylsilane precursor was explored and the results are depicted in Scheme 3. We found that the reaction conditions were applicable to a range of standard benzyne cycloadditions; substituted furan substrates underwent cycloaddition with **4** to deliver the products **13** and **14** in good yield. Generation of benzyne in the presence of benzyl azide gave the desired benzotriazole product **15** in 73% yield as a 1:1 mixture of regioisomers. Moreover, tetraphenylcyclopentadienone also



Scheme 2. Cycloaddition optimisation studies.



Scheme 3. Scope of the benzyne cycloaddition method.

participated in a benzyne cycloaddition under these conditions to afford product **16** in 85% yield. Nitrile substituted benzyne was successfully generated and trapped by furan to provide **17** in good yield, unfortunately however, the more heavily substituted substrate **8** was found to be less efficient and only provided **18** in low yield, together with a significant quantity of protodesilylated material.

In conclusion, we have developed conditions that significantly improve the potential for the generation of benzynes from 2-(trimethylsilyl)iodobenzenes. Such benzyne precursors offer the potential to be synthesised in relatively short order compared to their triflate counterparts, for example, via the described alkynyl iodide cycloaddition process.[10,11]

Acknowledgements

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9. We also explored the use of tetrabutylammonium triphenyldifluorosilicate in conjunction with AgF. Whilst we found that these reactions also provided **10**, the yields were slightly lower in comparison and the recovery of side product **11** was hampered by co-elution with fluorotriphenylsilane.
10. Representative experimental procedure for the cycloaddition of alkynyl iodides with methyl coumalate: To methyl coumalate (612 mg, 3.97 mmol), and trimethylsilyliodoacetylene (1.80 g, 8.03 mmol) was added 1,2-dichlorobenzene (10 mL). The mixture was heated to reflux and stirred for 24 h before cooling to room temperature. The crude reaction mixture was purified by flash column chromatography (stepwise gradient: starting with petroleum ether, finishing with 5% EtOAc in petroleum ether) to give the product **4** as a pale orange oil (1.08 g, 81%, 2:1 mixture of regioisomers). ^{1}H NMR (250 MHz, CDCl$_3$): 8.49 (0.67H, d, J = 1.5 Hz), 8.03 (0.33H, d, J = 2.5 Hz), 7.97–7.94 (1H, m), 7.64 (0.33H, dd, J = 8.0, 2.0 Hz), 7.47 (0.67H, d, J = 8.0 Hz), 3.93 (3H, s), 0.47 (3H, s), 0.46 (6H, s); ^{13}C NMR (62.8 MHz, CDCl$_3$): 167.7, 166.7, 142.9, 139.7, 138.9, 133.2, 132.2, 131.2, 130.8, 130.6, 129.9, 101.9, 94.9, 53.5, 53.4. FTIR (CH$_2$Cl$_2$): 2952 (s), 2898 (m), 1732 (s), 1434 (s), 1253 (s), 1192 (m), 1097 (s), 1005 (s) cm^{-1}; HRMS (ES) m/z [MH]$^+$ calcd for $C_{11}H_{16}O_2SiI$: 334.9964, found: 334.9969.
11. Representative experimental procedure for the generation of benzynes: To a microwave vial were added iodobenzene **4** (68 mg, 0.2 mmol), CsF (60 mg, 0.4 mmol), AgF (50 mg, 0.4 mmol) and MeCN (2 mL). After the addition of a stirrer bar, the vial was sealed and furan (72 μL, 1 mmol) was injected through the septum. The vial was then heated at reflux in an oil bath for 6 h before purification by flash column chromatography (product eluted with 10% EtOAc in petroleum ether) to give the desired product **10** as a colourless solid (33 mg, 81%). ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.89 (1H, s), 7.78 (1H, d, J = 7.5 Hz), 7.32 (1H, d, J = 7.5 Hz), 7.05 (2H, m), 5.77 (2H, m), 3.91 (3H, s). ^{13}C NMR (100.6 MHz, CDCl$_3$): 167.4, 154.8, 150.0, 143.8, 142.8, 128.5, 127.7, 121.1, 120.4, 82.6 (×2), 52.5.