Electrophilic Vinylation of Thiols under Mild and Transition Metal-Free Conditions
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In memory of Professor Kilian Muñiz

Abstract: The iodine(III) reagents vinylbenziodoxolones (VBX) were employed to vinylate a series of aliphatic and aromatic thiols, providing E-alkenyl sulfides with complete chemo- and regioselectivity, as well as excellent stereoselectivity. The methodology displays high functional group tolerance and proceeds under mild and transition metal-free conditions without the need for excess substrate or reagents. Mercaptothiazoles could be vinylated under modified conditions, resulting in opposite stereoselectivity compared to previous reactions with vinyliodonium salts. Novel VBX reagents with substituted benziodoxolone cores were prepared, and improved reactivity was discovered with a dimethyl-substituted core.

Hypervalent iodine compounds have emerged as sustainable alternatives to metal-based oxidants and organometallic catalysts. Most iodine(III) reagents are nontoxic, easily synthesized, and reactive under mild conditions.[1] Iodonium salts have a unique ability to form C–C and C-heteroatom bonds through transfer of one carbon ligand to a variety of nucleophiles.[2] Although vinyl(aryl)iodonium salts can be employed to vinylate nucleophiles,[3] their reactivity is difficult to control under metal-free conditions, often leading to product mixtures.[4] Benziodoxolones have enhanced stability and more controllable reactivity compared to iodonium salts. This feature has been demonstrated by the Togni trifluoromethylation reagents and Waser’s alkynylation using alkynybenziodoxolones (EBX).[5] While the corresponding vinylbenziodoxolones were reported as products from the addition of azide to EBX already in 1996,[6] they have remained unexplored as synthetic reagents. In 2016, we reported a one-pot synthesis of vinylbenziodoxolones from 2-iodobenzoic acid and abbreviated these novel reagents VBX (Scheme 1a).[7] Their unique reactivity was demonstrated in the vinylation of nitrocyclohexane, with opposite regioselectivity to the corresponding vinyliodonium salt[6] (Scheme 1b).[7] In parallel, Yoshikai and co-workers developed the synthesis of β-oxygen-functionalized VBX reagents through Pd-catalyzed hydrocarboxylation of EBX-type reagents (Scheme 1c).[9] The scope of VBX has since increased further by addition of heteroatom nucleophiles to various iodine(III) precursors,[10] and the reagent class has been employed in metal-catalyzed cross couplings and C–H vinylations, as well as in metal-free reactions.[9–11]

Vinyl sulfides are important building blocks in organic synthesis,[12] natural products and biologically active compounds.[13] Their reactivity is interesting since they can be considered as enolate equivalents[14] and Michael acceptors.[15] Most synthetic routes to vinyl sulfides involve the use of transition metals, such as Ru-catalyzed hydrothiolation of terminal alkynes,[16] and Cu-catalyzed cross coupling reactions at elevated temperature.[17] Whereas metal-free additions to alkynes proceed under mild conditions, other synthetic routes require strong base, and often give diastereo- or regioisomeric mixtures.[18] Ochiai and co-workers reported a single vinylation of PhSNa with a phenyl(4-tert-butylcyclohexenyl)iodonium under mild conditions,[19] which has not been further explored.

Intrigued by the different regiochemical outcome with VBX and vinyliodonium salts (Scheme 1b), and inspired by Waser’s EBX-alkynylation of thiols,[20] we have investigated the reactivity of VBX with thiols, and herein report our

Scheme 1. Preparation of vinylbenziodoxol(on)es and vinylations with VBX.
Influence of substituents on the benziodoxolone core. [a]

Table 1: Optimization on thiophenol. [a]

| Entry | Solvent | Base | I [%] | Yield of 3a [%][b] | E/Z Ratio | Yield of 4a [%][c] |
|-------|---------|------|-------|-------------------|-----------|-------------------|
| 1     | THF     | TMG  | 15     | 68                | 15:1      | 18                |
| 2     | Toluene | TMG  | 15     | 53                | >20:1     | 34                |
| 3     | THF     | –    | 15     | 54                | 20:1      | 30                |
| 4     | THF     | NaHCO₃ | 15   | 36                | 9:1       | 30                |
| 5     | THF     | BuOK | 15     | 78                | 10:1      | 18                |
| 6     | THF     | BuOK | 2      | 76[a]             | >20:1     | 13                |
| 7     | THF     | BuOK | 2      | 87[b,d]           | >20:1     | 7                 |
| 8[a]  | THF     | –    | 2      | 79[b]             | >20:1     | 12                |

[a] Reaction conditions: 1a (0.3 mmol) and base were stirred in solvent for 5 min before addition of 2a. [b] 1H NMR yield using trimethoxybenzene as internal standard. [c] Addition of VBX, then base. [d] Anhydrous and degassed solvent.

Table 2: Influence of substituents on the benziodoxolone core. [b]

| Entry | Z R | Yield of 3a [%] | E/Z ratio | Yield of 5 [%] |
|-------|-----|----------------|-----------|---------------|
| 1     | Z   | 87             | >20:1     | 0             |
| 2     | 2a  | 11             | >20:1     | 40            |
| 3     | 2c  | 67             | 11:1      | 0             |
| 4     | 2d  | 75             | >20:1     | 0             |
| 5     | 2e  | 90             | >20:1     | 0             |
| 6     | 2f  | 9              | >20:1     | 18            |
| 7     | 2g  | 68             | >20:1     | 0             |
| 8[a]  | 6   | 20             | 1:1       | 0             |

[a] Reaction conditions: see Table 1 entry 7; NMR yields given.
derivatives of 3x and 3ab were low-yielding, likely due to solubility problems.[21]

A set of substituted VBX reagents was synthesized to demonstrate the feasibility to transfer other vinyl groups (Scheme 3). Indeed, reactions with E-VBX reagents 2h–2l, having different electronic properties, resulted in thioethers 3a c–3a g in good yields. High E-selectivities were obtained in all cases except 3a e. Vinylations with cyclohexyl-substituted VBX 2m proved less reactive and gave a modest yield. [21]

Attempts to synthesize the Z-stereoisomer of 2a were in vain due to isomerization to E-2a under the reaction conditions. [26]

Waser and co-workers recently reported a vinylation of thiophenol with a Z-configured sulfonamide-substituted VBX to provide a thioenamide with moderate Z-selectivity.[10d] Considering the excellent stereoselectivity of our methodology, we were intrigued to investigate the reactivity of such reagents under our conditions. Indeed, trisubstituted thioenamide 3a h and thioenol ether 3a i were obtained in excellent yields with good to complete Z-selectivity.[27] However, the corresponding disubstituted thioenamide 3a j only formed in modest yield with 1,2-bis(phenylthio)ethene[11e] as the main byproduct, and attempts to optimize the reaction conditions were in vain. Pleasingly, the corresponding Me 2-substituted VBX reagent 2p (cf. 2e in Table 2) proved more efficient, delivering thioenamide 3a j in 59% yield with complete Z-selectivity and suppressed byproduct formation.

Me 2-VBX reagent 2e was thus investigated in selected E-selective vinylations as alternative to 2a, and indeed provided product 3l in increased yield (97 vs. 77%). While vinyl sulfide 3i formed in similar yields with 2a and 2e, reactions with Me 2-VBX are more convenient as column chromatography is not needed. We are currently investigating the Me 2-VBX backbone in other transformations, and will report the results in due time. The formed iodobenzoic acid can be recovered and reused in formation of VBX, thus increasing the sustainability and economy of the process.[21]

Ochiai and co-workers have demonstrated that metal-free vinylation of various nucleophiles with E-alkylvinyl(phenyl)iodonium salts result in Z-vinylated products through a vinylic S N2 mechanism. [3a] In this fashion, vinylation of mercaptobenzothiazole in the absence of base resulted in selective formation of the corresponding Z-vinylsulfide.[3a] To compare the reactivity of VBX with vinyliodonium salts, the vinylation of a small series of mercaptothiazoles 8 (X = S) was investigated. This substrate class could indeed be vinylated in moderate yields and high stereoselectivity (E/Z 10:1 to 20:1) under modified reaction conditions (Scheme 4). [21] Interestingly, we observed opposite stereochemistry compared to previous results with the vinyliodonium salt. The methodology was also applied to mercaptooxazole (X = O) to give 9d.

The observed regioselectivity of the S-vinylation is intriguing, as the C-vinylation of nitrocyclohexane with VBX 2a gave a terminal alkene as the main product (see Scheme 1b). [21] Furthermore, the high E-stereoselectivity is opposite to reactions with vinylidonium salts and shows that
VBX does not react through a vinylic S$_2$2 mechanism.\textsuperscript{[3a]} While preliminary radical trap experiments were inconclusive,\textsuperscript{[21]} isomerization of $\text{3e}$ was observed upon purification on column chromatography (from $E/Z > 20:1$ to $16:1$), and we hence propose that the main reaction pathway gives the $E$-product, while the $Z$-product is formed by isomerization. We are currently investigating the mechanisms of VBX vinylations with various nucleophiles by DFT calculations and $^{13}$C-labelling studies to detect any carbene pathways, and will report the results in due time.

To conclude, we have reported a high-yielding method for vinylation of aromatic and aliphatic thiols with the recently discovered hypervalent iodine(III) reagents VBX. This transition metal-free methodology uses equimolar amounts of reagents and proceeds under mild conditions with complete chemo- and regioselectivity, as well as high stereoselectivity. Mercaptoheterocycles could be vinylated under modified conditions. Moreover, the synthesis and reactivity of several novel, substituted VBX reagents was described to illustrate the influences of steric and electronic factors on the vinylation. The Me$_2$-V BX backbone proved superior to the parent VBX, a discovery that could have impact on reactions with other benziodoxolone reagents too, such as alkynylation and trifluoromethylation. Results from our ongoing mechanistic studies of metal-free vinylations with VBX and various nucleophiles will be reported in due time.

Experimental Section

General Procedure for Vinylation of Thiols: Thiol 1 (1.0 equiv, 0.3 mmol) was placed in an oven-dried microwave vial with magnetic stirring bar under argon, followed by the addition of anhydrous and degassed THF (2.0 mL). Subsequently, VBX 2 (1.0 equiv) and rBuOK (1.0 equiv) were sequentially added and the vial was rinsed with THF (1.0 mL). The mixture rapidly turns yellow and it was stirred at RT for 2 h. The reaction was quenched with water (2.0 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 /C148 10 mL) and the combined organic phases were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude reaction was purified via column chromatography to provide product $\text{3}$. The authors declare no conflict of interest.

Keywords: alkenyl sulfides · benziodoxolones · hypervalent compounds · synthetic methods · vinylbenziodoxolones

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