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Reductive iodonio-Claisen rearrangement of iodothiophene diacetates with allylsilanes: formal synthesis of Plavix®

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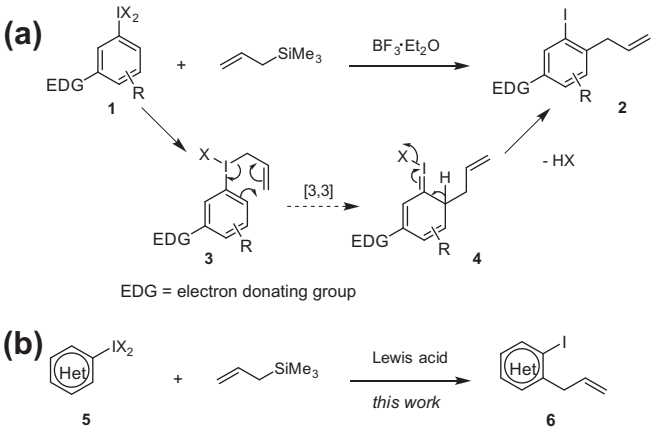
ABSTRACT

Iodothiophene diacetates react with allyltrimethylsilanes in the presence of boron trifluoride diethyl etherate to afford corresponding *ortho*-allyliodothiophenes via reductive iodonio-Claisen rearrangement. This method has been successfully applied to the synthesis of Plavix®, a blood clot inhibitor used to reduce the risk of heart attack and stroke.

Hypervalent iodine compounds, including both λ^3-iodanes[1] and λ^5-iodanes,[2,3] have been extensively employed as oxidants for oxidative transformations due to their unique chemical reactivity and environmentally benign character.[4] In addition to serving as general oxidants in organic synthesis, hypervalent iodine(III) compounds (λ^3-iodanes) were also investigated in reductive iodonio-Claisen rearrangement (RICR) for preparation of various synthetically useful building blocks bearing versatile aryliodide functionality. Studies of RICR were pioneered by Ochiai et al., and they found *ortho*-propargyliodoarenes can be obtained via RICR from λ^3-iodanes and propargyl silanes, germanes, or stannanes in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$).[5] Their observations were later reaffirmed by Norton and co-workers.[6] Additional evidences were also previously reported on the occurrence of RICR involving reactions between λ^3-iodanes and allyltrimethylsilane[7] or resorcinol derivatives.[8,9]

Recently, our laboratory has reported efficient synthesis of complex *ortho*-allyliodoarenes (**2**) via reductive iodonio-Claisen rearrangement from allylsilane and hypervalent iodine(III) compounds bearing electron-donating groups in the *meta*-position (**1**) (**a**, Scheme 1).[10] The desired products, *ortho*-allyliodoarenes (**2**), are likely formed via re-aromatization of intermediate **4** which were in turn obtained by RICR of hypervalent allyl(aryl)iodinanes **3**. An electron-donating group at the *meta*-position was found to be indispensable in order to favor the [3,3]-sigmatropic rearrangement over reductive elimination.[10] Based on this success, we speculated that heteroaromatic hypervalent iodine(III) compounds (**5**),[11] especially those electron-rich heteroaromatic λ^3-iodanes, may be suitable substrates for this type of pericyclic reaction to give rise to synthetically useful *o*-allyl iodoheteroarenes (**6**) (**b**, Scheme 1). Herein, we report the synthesis of *o*-allyl iodoheteroarenes via RICR and their application in the synthesis of a therapeutic agent.

Initially, 2-iodothiophene diacetate (**7**) was prepared[11] and studied in this type of pericyclic transformation. To our delight, 2-iodothiophene diacetate (**7**) reacted with allyltrimethylsilane in



Scheme 1. Reductive iodonio-Claisen rearrangement.

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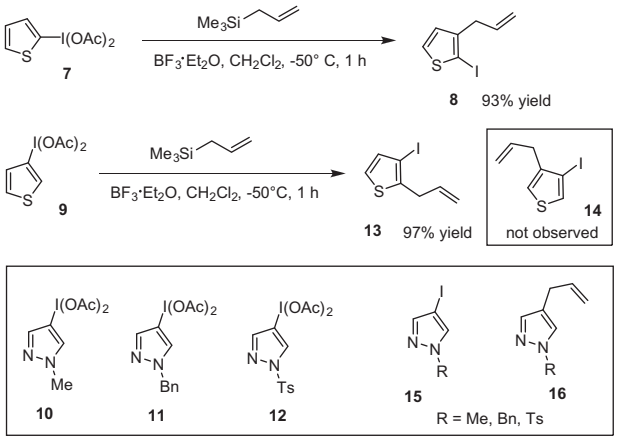
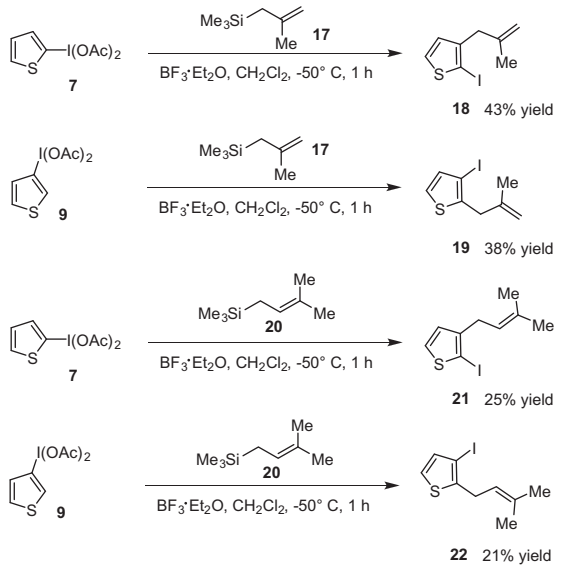
the presence of $BF_3{\cdot}Et_2O$ at −50 °C to afford the desired 3-allyl-2-iodothiophene (**8**) in 93% yield (Scheme 2). Given this encouraging result, we prepared several heteroaromatic hypervalent iodine(III) compounds, such as 3-iodothiophene diacetate (**9**), *N*-methyl-4-iodopyrazole diacetate (**10**), *N*-benzyl-4-iodopyrazole diacetate (**11**), and *N*-tosyl-4-iodopyrazole diacetate (**12**).[11,12] Subsequent studies revealed that 3-iodothiophene diacetate (**9**) reacted with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ at −50 °C to afford the desired 2-allyl-3-iodothiophene **13** in 97% yield, while its regioisomeric product, 3-allyl-4-iodothiophene **14**, was not observed in the reaction mixture. This is probably because C2 position of **9** is more electron-rich and nucleophilic than C4, which results in the selective allylation at C2.[10] However, less electron-rich pyrazole-derived hypervalent iodine(III) compounds (**10**–**12**) only afforded a trace amount of corresponding desired *o*-allyliodoheteroarenes. Major side products including corresponding 4-iodopyrazoles **15** and 4-allylpyrazoles **16** were formed presumably via reductive elimination[10] and *ipso*-substitution,[5] respectively.

Next, we carried out the reductive iodonio-Claisen rearrangement of 2- and 3-iodothiophene diacetates (**7** and **9**) with substituted allylsilanes, such as 2-methallylsilane **17** and prenylsilane **20**. As shown in Scheme 3, 2-iodothiophene diacetate (**7**) reacted with 2-methallyltrimethylsilane **17** to afford desired product 2-iodo-3-methallylthiophene **18** in 43% isolated yield, while 3-iodothiophene diacetate (**9**) reacted with 2-methallyltrimethylsilane **17** to afford desired product 3-iodo-2-methallylthiophene **19** in 38% isolated yield. In addition, 2-iodothiophene diacetate (**7**) reacted with prenyltrimethylsilane **20** to afford desired product 2-iodo-3-prenylthiophene **21** in 25% isolated yield, while 3-iodothiophene diacetate (**9**) reacted with prenyltrimethylsilane **20** to afford desired product 3-iodo-2-prenylthiophene **22** in 21% isolated yield. In all these cases, major side products generated via reductive elimination or *ipso*-substitution were observed. These experimental results indicated that the [3,3] rearrangement pathway may be suppressed by the sterically hindered allylsilanes due to the steric effect.[10]

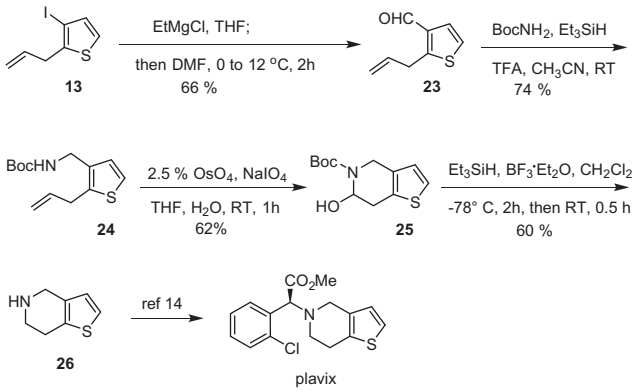
To demonstrate the potential utility of these *o*-allyl iodothiophenes, we carried out a concise formal synthesis of Plavix® (clopidogrel),[13] a blood clot inhibitor used to reduce the risk of heart attack and stroke. As depicted in Scheme 4, 2-allyl-3-iodothiophene **13** underwent magnesium–halogen exchange[14] to provide corresponding heteroaryl magnesium which was subsequently formylated to afford aldehyde **23** (66%). Aldehyde **23** was then subjected to reductive amination with *tert*-butyl carbamate in the presence of triethylsilane and trifluoroacetic acid to afford Boc-protected amine **24** (74%). Next, a one-pot dihydroxylation–



Scheme 2. Reductive iodonio-Claisen rearrangement involving heteroaromatic iodine(III) compounds.



Scheme 3. Reductive iodonio-Claisen rearrangement involving substituted allylsilanes.



Scheme 4. Synthesis of Plavix®.

oxidative cleavage of the terminal olefin of **24** generated the corresponding aldehyde which spontaneously cyclized to afford hemiaminal **25** (62%). Finally, reductive amination of hemiaminal **25** using triethylsilane and $BF_3{\cdot}Et_2O$ followed by in situ deprotection of the Boc-carbamate functionality provided the key intermediate **26** (60%). This thiophene-containing bicycle **26** has been previously utilized to prepare Plavix®.[15] Therefore, our preparation of bicycle **26** constitutes a formal synthesis of Plavix®.

In summary, our studies on the reductive iodonio-Claisen rearrangement using heterocyclic iodine(III) compounds led to the synthesis of various *o*-allyliodothiophenes. It was found that this pericyclic reaction was dramatically influenced by steric and electronic factors, as substituted allylsilanes or electron-poor heteroaromatic hypervalent iodine(III) compounds gave lower yields of the products. In addition, application of one of *o*-allyliodothiophenes in the concise synthesis of blood clot inhibitor Plavix® has been achieved.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.138.

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