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## Heterocyclic analogs of o-xylylene

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

1990

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

van den Berg, K. J. (1990). *Heterocyclic analogs of o-xylylene: a study of the synthesis and reactivity of dimethylene derivatives of thiophene and pyrrole*. s.n.

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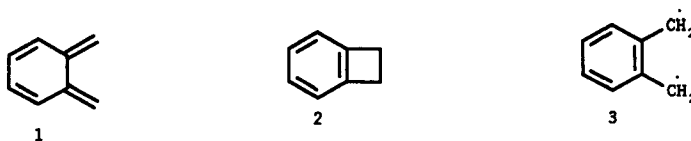
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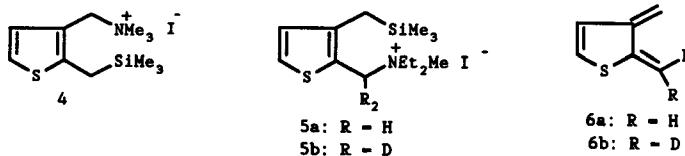
## SUMMARY

This Thesis describes the chemistry of heterocyclic analogs of *o*-xylylene (**1**). *o*-Xylylenes are intermediates which has been used often in the synthesis of polycyclic compounds, such as steroids.

Chapter I briefly reviews the use of *o*-xylylene and derivatives in organic synthesis. The methods available for the *in situ* generation of *o*-xylylene are described. The valence tautomers of *o*-xylylene *i.e.* the diene form **1**, the closed cyclobutene **2** and the biradical **3** are discussed. Our choice to use the "Saegusa" procedure for the generation of heterocyclic dienes **6** and **12** is argued. Furthermore Chapter I contains an overview of the known heterocyclic analogs of **1**.

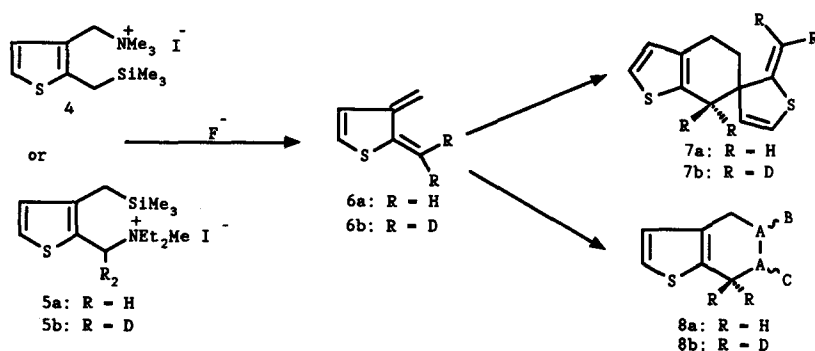


Chapter II describes the synthesis of the precursors **4** and **5a** that were necessary for the "Saegusa" type generation of 2,3-dimethylene-2,3-dihydrothiophene (**6a**), one of the two conceivable thiophene analogs of *o*-xylylene. The synthesis of compound **5b**, which is a precursor of dideutero derivative **6b** of diene **6a**, is described also in this Chapter. Chapter II gives a short literature review of *o*-lithiation reactions influenced by  $-\text{CH}_2\text{NMe}_2$  and by tertiary carboxamide groups. Furthermore a review is given of the use of  $\text{XCH}_2\text{SiMe}_3$  ( $\text{X} =$  leaving group) in substitution reactions to introduce  $-\text{CH}_2\text{SiMe}_3$  groups. Unsuccessful attempts not leading to compounds **4** or **5** are also discussed in Chapter II.

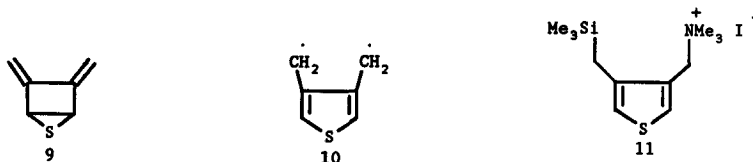


Chapter III describes the results of the generation of dienes **6a** and **6b** by fluoride-induced 1,4-eliminations of the  $\text{Me}_3\text{Si}$  and  $\text{NR}_3$  groups of the precursors **4**

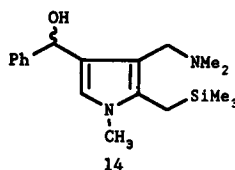
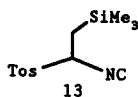
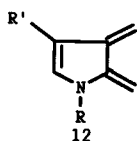
or 5 according to the Scheme given below. Dienes **6a** and **6b** are not stable. They dimerize spontaneously at the temperatures at which they are generated ( $-10^{\circ}\text{C}$  and higher) to spiro compounds **7a** and **7b**, respectively. Dienes **6a** and **6b** have been trapped with several added dienophiles in [4+2] cycloaddition reactions. Scope and limitations of these [4+2] cycloadditions are discussed. A significant difference in the rate of reaction of **6a** towards dimethyl maleate (cis) and dimethyl fumarate (trans) has been observed. Reactions of diene **6a** with unsymmetrical dienophiles give mixtures of C-5 and C-6 substituted tetrahydrobenzo[*b*]thiophenes. The ratio of the isomers is independent of the precursor **4** or **5**, which proves that diene **6a** is indeed formed as such. Diene **6a** has been used for the synthesis of a thiophene analog of N-0437 (a dopamine agonist), as is described in Chapter III also.



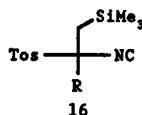
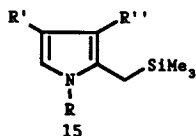
Chapter IV describes results on the research of the 3,4-substituted analog **9** (or its valence tautomer **10**) of thiophene diene **6a**. The synthesis of precursor **11** is described. Attempted syntheses to *c*-fused bicyclic thiophene systems are described.



Chapter V describes the research to (4-substituted) pyrrole analogs **12** of *o*-xylylene. The best method for the synthesis of the precursor is discussed. The synthesis of  $\alpha$ -(trimethylsilylmethyl)tosylmethyl isocyanide ( $\text{Me}_3\text{SiCH}_2\text{-TosMIC}$ , **13**) is described, as well its use in the synthesis of pyrrole **14**.



Reactions of isocyanide **13** with several Michael acceptors leading to pyrroles of type **15**, and with several alkyl halides to isocyanides **16** are described in Chapter V.



The formation of an anion at the 2-methyl group of some pyrroles has been accomplished by treatment of two 3,4-substituted-2-Me<sub>3</sub>SiCH<sub>2</sub>-pyrroles of type **15** with TASF. Reactions of the so formed anions with a Michael acceptor and with aldehydes are described in Chapter V.

