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Synthesis of 3-Substituted Furans.

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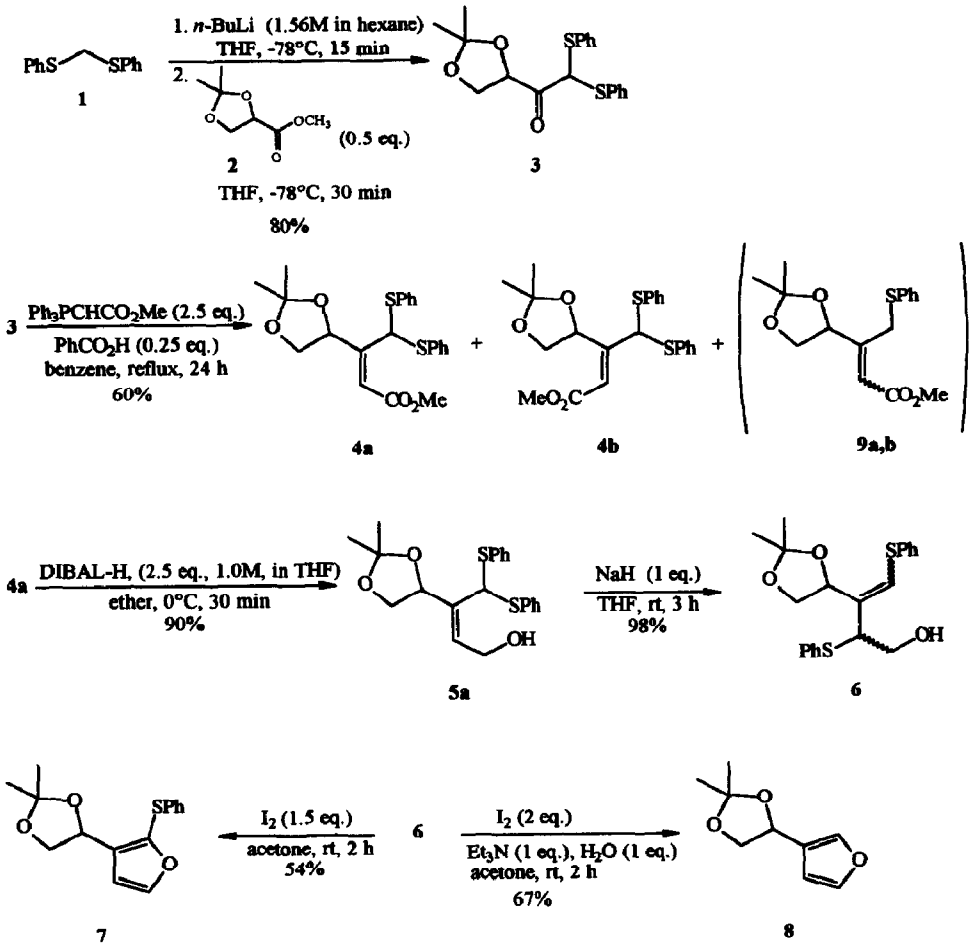
Abstract: *A method for the preparation of 3-substituted furans starting with the addition of bis(phenylthio)methyllithium to an ester, followed by a sequence consisting of a Wittig reaction, a DIBAL-H reduction and an iodine-mediated cyclization is described.*

Natural products containing a furan ring substituted in the 3-position are known since long ago.[1] They are frequently synthesized by addition of 3-furyllithium[2] or lithium di(3-furyl) cuprate[3] to carbonyl compounds or substitution on alkyl halides or epoxides, or by further elaboration of an existing 3-substituent[4] or even by the construction of the furan ring.[5] In some of these methods, the stereochemistry of the C-atom bearing the furan ring is hard to control, and is usually lost during the process while in others the reactions involved lack flexibility or are plagued by low yields.

As part of our studies on the synthesis of natural products we have developed a novel method for furan ring formation that preserves the original configuration of the 3-substituent and thus could be useful for the preparation of chiral compounds.

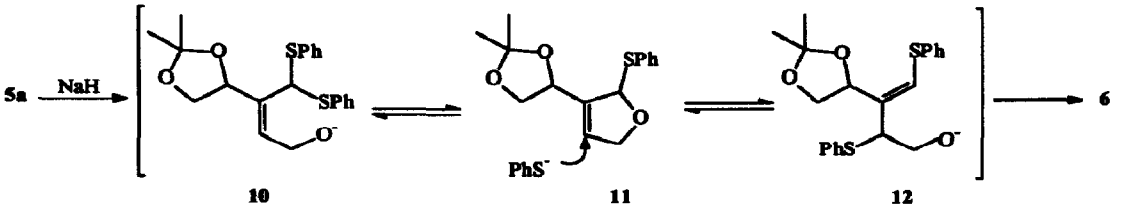
The method is depicted in scheme 1. Treatment of ester **2**[6] with 2 equivalents of bis(phenylthio)methyllithium[7] afforded the thioacetal ester **3**[8] in 80% yield after purification by flash chromatography. Olefination reaction of the stereocongested ketone **3** was carried out with 60% yield by treatment with methyl (triphenylphosphoranylidene)acetate in the presence of benzoic acid[9] leading to a 1:1-mixture of the E, Z-isomeric compounds **4a**[10] and **4b**.[11] The reaction, monitored by TLC, is quenched when the presence of monodesulfurization products **9a** and **9b** is detected; if the reaction time is extended long enough, these compounds will be the main products isolated from the reaction. Compounds **4a** and **4b** are readily separated by flash chromatography. DIBAL-H reduction of ester **4a** afforded alcohol **5a**[12] (90%, based on the unrecovered starting material). Treatment of the allylic alcohol **5a** with NaH in THF resulted in isomerization to the homoallylic alcohol **6**,[13] with 98% yield (a mixture of 4 isomers). Compound **5a** is quite unstable and also isomerizes to **6**, either spontaneously during storage or by extending the reaction time in the DIBAL-H reduction.

Scheme 1



One could expect the alkoxide formed after reduction of ester **4a** to cyclise to a dihydrofuran and by elimination to give the target furan. What is observed however, is a very easy isomerization of the reduction product to the alcohol **6**, which is quite resistant to cyclization. Probably the isomerization reaction goes through a ring closure—ring opening sequence (scheme 2), which can be explained by the Baldwin's rules.[14] Cyclization of **10** to **11** is a *5-exo-tet* process, favoured according to those rules. Then, phenylsulfide ion promotes the ring opening giving the alkoxide **12**. Since the reverse reaction, **12** to **11**, is a *5-endo-trig* process, unfavoured, the equilibrium is shifted towards **12** thus, leading to the formation of **6**.

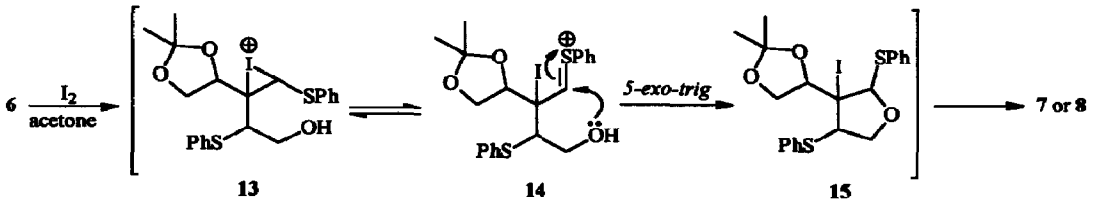
Scheme 2



It was observed later that the alcohol obtained by reduction of ester **4b** also isomerizes slowly to compound **6** (now by an allylic rearrangement). Therefore, the mixture of esters **4a** and **4b** was treated with DIBAL-H and monitored by TLC to afford the rearranged alcohol **6** directly.

Although the ring closure of compound **6** (*5-endo-trig*) is a disfavoured process, this difficulty can be circumvented by a reaction pathway in which an intermediate formed from **6** could undergo a favoured *5-exo-trig* cyclization. This condition can be achieved by an iodine mediated ring closure as illustrated in scheme 3.

Scheme 3



Accordingly, treatment of homoallylic alcohol **6** with iodine in acetone afforded 2-(phenylthio)furan **7**.[15] Raney-nickel mediated desulfurization of **7** to give furan **8** is complicated by the presence of a benzyllic-like C-O bond, also prone to hydrogenolysis. However, treatment of homoallylic alcohol **6** with iodine in the presence of Et_3N and H_2O afforded the desired furan **8** in 67% yield.[16]

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7. Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097.
8. **Compound 3:** ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.34 (s, 6H), 3.86-4.23 (m, 2H), 4.75 (dd, J=5.8Hz, J=7.4Hz, 1H), 5.40 (s, 1H), 7.17-7.54 (m, 10H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 25.3 (CH_3), 26.0 (CH_3), 60.5 (CH), 66.8 (CH_2), 78.1 (CH), 111.1 (C), 128.6 (CH), 129.1 (CH), 129.3 (CH), 132.0 (C), 132.8 (C), 133.2 (CH), 133.9 (CH), 199.8 (C); MS m/z (relative intensity) 360 (5.8) M^+, 231 (100), 101 (75.2).
9. Rüchart, C.; Eichler, S.; Panse P. *Angew. Chem.* **1963**, *75*, 858.
10. **Compound 4a:** ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.39 (s, 3H), 1.42 (s, 3H), 3.45 (overlap of s and probably dd, 4H), 6.14 (s, 1H), 6.97 (s, 1H), 7.10-7.57 (m, 10H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 26.8 (CH_3), 27.6 (CH_3), 52.6 (CH_3), 54.4 (CH), 73.1 (CH_2), 76.1 (CH), 110.7 (C), 118.2 (CH), 129.0 (CH), 129.8 (CH), 130.3 (CH), 130.4 (CH), 132.5 (CH), 134.4 (C), 135.2 (CH), 156.3 (C), 167.5 (C); IR (neat) ν_{max} cm^{-1} 1713 (C=O), 1642 (C=C); MS m/z (relative intensity) 307 (53.2), 139 (89.9), 109 (97.6), 101 (100), 65 (72.6).
11. **Compound 4b:** ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.38 (s, 6H), 3.46 (dd, J=6.4Hz, J=8.5Hz, 1H), 3.65 (s, 3H), 4.35 (dd, J=8.0Hz, J=8.5Hz, 1H) 5.51 (s, 1H), 5.68 (m, J=2.0Hz, J=6.4Hz, J=8.0Hz, 1H), 6.23 (d, J=2.0Hz, 1H), 7.19-7.54 (m, 10H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 24.4 (CH_3), 25.7 (CH_3), 50.7 (CH_3), 54.6 (CH), 69.1 (CH_2), 73.7 (CH), 109.4 (C), 119.1 (CH), 127.4, (CH), 127.8 (CH), 128.5 (CH), 128.6 (CH), 131.7 (CH), 132.3 (CH), 132.6 (CH), 133.6 (C), 134.0 (C), 156.7 (C), 165.3 (C); MS m/z (relative intensity) 307 (33.2), 139 (86.1), 109 (100), 101 (68.5), 65 (75.8).
12. **Compound 5a:** ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.40 (s, 6H), 3.57 (t, J=8.0Hz, 1H), 4.06 (d, J=6.7Hz, 2H), 4.22 (dd, J=6.0Hz, J=8.0Hz, 1H), 4.77 (br t, 1H), 5.23 (s, 1H), 5.98 (t, J=6.7Hz, 1H), 7.17-7.53 (m, 10H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 25.5 (CH_3), 26.3 (CH_3), 56.5 (CH), 58.6 (CH_2), 70.5 (CH_2), 78.1 (CH), 109.0 (C), 128.2 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 130.0 (CH), 132.6 (CH), 133.8 (CH), 134.0 (C), 134.1 (C), 137.9 (C).
13. The product was purified by flash chromatography. Analysis of the ^{1}H NMR and ^{13}C NMR spectra showed that it is a mixture of isomers. MS m/z (relative intensity) 388 (11.0) M^+, 279 (27.5), 111 (100), 109 (60.7).
14. Baldwin, J. E. *J. C. S. Chem. Comm.* **1976**, 734.
15. **Compound 7:** ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.36 (s, 3H), 1.39 (s, 3H), 3.55-4.21 (m, 3H), 6.40 (d, J=2.1Hz, 1H), 7.06-7.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 25.8 (CH3), 25.9 (CH3), 42.1 (CH), 65.3 (CH_2), 72.7 (C), 109.2 (CH), 114.2 (C), 127.4 (CH), 128.9 (CH), 132.6 (CH), 134.2 (C), 141.1 (CH), 155.6 (C).
16. **Compound 8:** ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.43 (s, 3H), 1.47 (s, 3H), 3.76 (t, J=8.0Hz, 1H), 4.20 (dd, J=5.8Hz, J=8.0Hz, 1H), 5.03 (dd, J=5.8Hz, J=8.0Hz, 1H), 6.39 (m, 1H), 7.34-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 20 Mhz) δ 25.6, 26.7, 70.2, 70.6, 108.6, 109.4, 123.9, 140.1, 143.6.

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