Regiospecific synthesis of polysubstituted furans and their application in organic synthesis

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Abstract: The role played by 3,4-bis(trimethylsilyl)furan, 2,4-bis(trimethylsilyl)furan and 3,4-bis(tri-n-butylstannyl)furan as building blocks in the preparation of 2,3-disubstituted furans, 3,4-disubstituted furans, as well as 2,3,5-trisubstituted furans will be summarized. The synthetic potential of furan and its polysubstituted derivatives will be illustrated by our Diels-Alder reaction-deoxygenation route for the realization of several theoretically interesting benzenoid molecules, as well as by the preparation of 2-butenolides which are precursors of the naturally occurring prehispanolone, sphydrofuran and secosyrins.

INTRODUCTION

Though not found in animal metabolism, furan ring systems are abundantly available in secondary plant metabolites. Many of these furan natural products show inspiring biological activities, such as cytotoxic and antitumor properties, antispasmodic, and antifeeding activities. More natural furan-containing molecules continue to be uncovered at a rapid speed. Due to their remarkable properties, many synthetic furans are utilized as pharmaceuticals. In addition to being building blocks found in natural molecules, polysubstituted furans are important precursors for the synthesis of natural and non-natural products. The synthetic efforts towards polysubstituted furans belong therefore to an exceedingly active research domain. In this presentation, our own progress in the regiospecific construction of 3,4-disubstituted furans, 2,3-disubstituted furans as well as 2,3,5-trisubstituted furans will be briefly delineated. The second part of this article will then deal with the use of furan and other polysubstituted furans in the synthesis of non-natural and natural molecules.

SYNTHESIS OF POLYSUBSTITUTED FURANS

(a) 3,4-Disubstituted Furans

The inclination of furans to endure lithiation and electrophilic reactions at C-2 or C-5 makes the synthesis of 3,4-disubstituted furans a rather demanding task. Although many approaches are available, they are generally not suitable for furans with elaborate substituents. In our own search of a genuine access to 3,4-disubstituted furans, we reasoned that 3,4-bis(trimethylsilyl)furan (1) could be established as a building block. Because of the well-known overlap of a silyl group with its carbocation, an ipso-substitution (10) is expected to direct substituents to C-3 and/or C-4 of 1. Some typical conversions of 1 to 3,4-disubstituted furans are depicted in Scheme 1. As can be seen, boroxine 2 (14) was obtained in a regiospecific manner and in quantitative yield from 1. Suzuki coupling (15) of 2 with a benzyl bromide afforded 3, which underwent successive boroxine formation and Suzuki coupling to generate the 3,4-unsymmetrically substituted furan 4. The successful preparation of a P-C-H containing alkylfuran was demonstrated by the nickel-catalyzed reaction of iodide 5 with n-butylmagnesium bromide, which gave the n-butyl substituted furan 10. Subsequent boroxine formation and Suzuki coupling of 10 then afforded 11.
Under the Suzuki reaction condition in the presence of 2,3-bis(bromomethyl)quinoxaline, boroxine unexpectedly provided a self-coupling product, namely bifuran 12 in excellent yield (Scheme 2). Interestingly, 12 underwent a regiospecific boroxine formation to give 13, which supplied a cross-coupling product terfuran 14, as well as the self-coupling product quarterfuran 15. A variety of symmetrical and unsymmetrical furan-3,4-diyl oligomers were synthesized in this manner. It is likely that these routes will also deliver quinquefurans, sexifurans and septifurans. To put such suggestion to test, 15 was successfully transformed via a boroxine to octifuran 16, which is the longest furan-3,4-diyl oligomer known.
One shortcoming of the classical Suzuki reaction is that acid halides cannot be employed for the coupling purpose, because of the alkaline condition involved. However, Stille-type reactions (16,19) have successfully converted organostannyl compounds to acyl-substituted products. In order to widen the scope of our boroxine protocol, displacement of the C-B bond of boroxines with a tin functionality was sought. The reaction sequence presented in Scheme 3 is a typical example (20,21). As shown, boroxine 2, on treatment with tri-n-butylstannyl chloride under palladium-catalyzed condition, furnished the key intermediate stannane 17. With 17 in hand, the Stille-type coupling finally gave 18, albeit in an inferior yield (Scheme 3). (20,21) Peroxide oxidation of trimethylsilyl-substituted furans generally produced the corresponding ketones with concomitant cleavage of the C-Si bond. However, our own experience with 2 demonstrated that the reactivity of the C-B bond towards peroxide oxidation was more rapid than that of the C-Si bond, and as a result 19 was produced in an acceptable yield (Scheme 3). (20,21)

![Scheme 3](image)

Lithiation of 3-iodo-4-trimethylsilylfuran (5) as expected generated the lithio intermediate, which, upon quenching with sulfur, (22) dimethyl sulfide (23) and phenylselenyl bromide, (24) afforded thiol 20, thioether 21 and selenide 22, respectively (Scheme 4). (25) Nitrile 23 was also obtained from 5 via a palladium-catalyzed reaction (Scheme 4). (25,26) The syntheses of fluorine-, nitrogen- and phosphorus-substituted furans from 5 and/or 2 are in progress. (25)

![Scheme 4](image)

Alternatively, the 3,4-bis(tri-n-butylstannyl)furan (24) (27-29) could also lead to 3,4-disubstituted furans, due primarily to an even larger kinetic β-effect exhibited by the stannyl groups. (30) Similar to 1, furan 24 was also prepared via the oxazole route. (27,29) The initial palladium-catalyzed cross-coupling of 24 with p-bromonitrobenzene gave only the symmetrical furan 25 (Scheme 5). (27,29) However, similar reactions of 24 with benzoyl chloride yielded the monoacyl furan 26. This partial acylation therefore provided a direct entry to 3,4-un symmetrically substituted furans. Befitting examples to illustrate such an application were the conversion of 26 to 27 and 28. (27,29) Another pathway from which 3,4-un symmetrically substituted furans could be made was by soliciting a tin-lithium exchange reaction, (28,29) as shown in Scheme 5. In order to accomplish a complete replacement of one stannyl group in 24 with lithium, 2.2 equivalents of n-butyllithium were necessary. One of the transformations for the monolithiated furan was effected with cyclohex-2-enone, which furnished alcohol 29. Finally, a palladium-catalyzed reaction converted 29 to 30. (28,29)

![Scheme 5](image)
(b) 2,3-Disubstituted Furans and 2,3,5-Trisubstituted Furans

Furan 1 was unexpectedly found to undergo a smooth rearrangement to form 2,4-bis(trimethylsilyl)furan (31) (Scheme 6), the mechanism of which being presumably acid-catalyzed because of the trace amount of water needed. The driving force of this intriguing reaction is believed to be derived from the steric congestion of the two vicinal trimethylsilyl groups. The synthesis of 2,3-disubstituted furans(33) and 2,3,5-trisubstituted furans(34) is displayed in Scheme 6.(31) As can be seen, the trimethylsilyl at C-2 of 31 serves to block this reactive site and allows the lithiation and subsequent alkylation to occur only at C-5. Benzyl furan 32 prepared in this way was iodinated regiospecifically, generating iodide 33, which was reduced to provide 34. 2,3-Disubstituted furan 35 was then realized from 34 via our regular boroxine formation-Suzuki coupling approach. Alternatively, iodide 33 was also converted via 36 to the 2,3,5-trisubstituted furan 37 through consecutive nickel-catalyzed coupling as well as the boroxine formation-Suzuki coupling procedure.(31) The advantages of our methodology over those reported in the literature are its stepwise manner and its prospect of diverse substitution variety.

SYNTHETIC APPLICATION OF FURAN AND POLYSUBSTITUTED FURANS

(a) Synthesis of Non-natural Molecules

Examination of the recent literature revealed that there was no shortage of reports involving the use of furan and its derivatives as synthetic precursors.(7,35) Indeed, furans are extremely adaptable since they are able to serve as latent functionalities of hydropyrans,(36) 2-butene-1,4-diols,(37) carboxylic acids,(38) 2-butenolides,(39) and 1,4-dicarbonyls.(40) Notwithstanding their aromatic character, furans also behave as reactive dienes for Diels-Alder cycloaddition.(41)

Our first encounter with furans stemmed from our failure in isolating alkyne 38(42) in a stable form. Such setback, nonetheless, directed us to design and to synthesize 39, which was not expected to suffer from the detrimental peri H-H interactions as experienced by 38. It is towards the goal of procuring 39 that an efficient synthesis of tribenzo[a,c,e]cyclooctene derivatives was searched. In this connection, the construction of benzenoid systems via 1,4-endoxide deoxygentaion seemed to be a genuine solution.(43) Indeed, 1,4-dimethyltribenzo[u,c,e]cyclooctene (42) was obtained in this manner as illustrated in Scheme 7.(44) Thus, dehydrobromination of dibromide 40 generated a strained alkyne,(45) which underwent Diels-Alder reaction with 2,5-dimethylfuran to form the 1,4-endoxide 41. Low-valent-titanium deoxygentaion then provided 42.(44,46,47) Functionalization of the two methyl groups was made possible by benzylic bromination to give 43, which was utilized for the formation of methyl ether 44.

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Scheme 7

Hydrogenation of the double bond of 44 to provide 45 was necessary prior to the ruthenium tetroxide oxidation. Eventually, alcohol formation, cyclization, benzylic bromination and dehydrobromination delivered the target 39, via 46 as the key intermediate. As anticipated, 39 was very stable, forming light-yellowish crystals which melted between 203-205°C.

Novel and theoretically interesting benzenoid molecules, whose benzene rings could be constructed via the furan-endoxide-arene procedure, were our next prime targets. In light of this, dibenzo[2.2]paracyclophane (47) stood out as a unique molecule (Scheme 8), because its fixed geometry for orthogonal benzenes should likely be provided by virtue of its rigid molecular framework. In this regard, 47 is an impeccable model for the study of classically conjugated but orbitally unconjugated systems. The tactics for the synthesis of 47 were also applied to the synthesis of dibenzo[2.2]metaparacyclophane (48) (Scheme 9).

As shown in Scheme 8, the dibromide 49 was dehydrobrominated in the usual manner to give presumably the strained alkyne 50. Expectedly, all efforts to isolate 50 as a stable compound were in vain. However, 50 was trapped by furan to form the endoxide 51, which was deoxygenated by low-valent-titanium to give the desired target 47.

Scheme 8

By using exactly the same method as depicted above, dehydrobromination of 52 in the presence of furan yielded endoxide 54. The expectedly elusive cyclopane 53 was presumably an intermediate in this conversion. Our low-valent-titanium reagent was utilized again to transform 54 into the target cyclopane 48 (Scheme 9). The most unusual phenomenon in the proton NMR of 48 was the barely observable appearance at 24°C of a very broad coalesced signal at δ 6.95 for the four benzenoid protons of the para-linked benzene ring. Expectedly, all efforts to isolate 50 as a stable compound were in vain. However, 50 was trapped by furan to form the endoxide 51, which was deoxygenated by low-valent-titanium to give the desired target 47. (49) The distortion of the para-linked benzene rings in 47 into face-to-face boat conformations was revealed by an X-ray crystallographic analysis.

Scheme 9

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In order to prove the latter argument, 55 was also obtained from 53 and 2,5-dimethylfuran. Similar deoxygenation of 55 gave the dimethylcyclophane 56, whose interaction between the C-1 methyl and the meta-bridged benzene ring proton is obviously much more severe than the peri H-H interaction in 48. As a result, the coalescence temperature of 56 was found to be higher than 140°C. (50)

(b) Synthetic Studies of Natural Molecules: Prehispanolone, Sphydrofuran and Secosyrins

We recently isolated two diterpenes prehispanolone (57) (54) and hispanolone (58) (55) from a Chinese herb *Leonurus heterophyllus*. Interestingly, 57 is very acid labile and on treatment with dilute acid can be converted to 58 via a similar mechanism proposed by White. (56) Prehispanolone (57) has been found to be a specific platelet activating factor (PAF) receptor antagonist, and also exhibits some effects on the proliferation of lymphocytes. (57) The structural relationship of sphydrofuran (59) and 60 is strikingly similar to that of 57 and 58. (58) A metabolite isolated from the culture filtrate of *Streptomyces sp.* (Strain GÖ 28 and Tü 3616), sphydrofuran 59 is an anomic and ring-chain tautomeric mixture and can be easily transformed into the stable furan derivative 60 under acidic condition. (58) Of equal interesting nature are secosyrin 1 (61a), secosyrin 2 (61b), syributin 1 (62a) and syributin 2 (62b), which are unusual metabolites produced by Gram-negative bacteria expressing the class I homology group of *avrD* alleles, genes from *Pseudomonas syringae* involved with formation of bacterial signal molecules of elicitors. (59) It is of particular interest to indicate the stereochemistry of 59 and 61, of which the absolute configuration of the spiro carbons is the only disparity. In this Section, the partial synthesis of 57 using 58 as the precursor will first be discussed, and will be followed by the synthetic studies towards 59, 61 and 62 utilizing polysubstituted furans as starting materials.

To our best knowledge, no attempt to construct the dioxaaspiro framework as shown in 57 has been recorded. In view of the relative skeletal simplicity, the readily available 58 appeared to be a handy intermediate *en route* to the realization of 57, whose synthesis is outlined in Schemes 10 and 11. (60) As can be seen, protection of the the keto group of 58 gave 63. Deprotonation and silylation of 63 yielded a mixture of 64a and 64b, which was not separated and was oxidized with peracid to provide a chromatographically separable mixture of 2-butenolides 65a and 65b. Boron trifluoride-promoted desilylation of 65a transformed it to the key compound 66. An intramolecular Michael addition of 66 presumably furnished a pair of diastereomers 67a and 67b, the only stereochemical difference being the 13S or 13R configuration, respectively (Scheme 10). (60)

![Scheme 10](image-url)
Our next step was to verify the configuration of the spiro carbons of 67a and 67b. Fortunately, the 13S configuration of 67a was convincingly established by its DIBAL reduction, from which a mixture of 68 and a crystalline product 69 was obtained (Scheme 11). An X-ray crystallographic analysis of 69 revealed that the spiro C-13 carbon was of S configuration.(60) As such, the R configuration of the spiro carbon in 67b was also indirectly substantiated. Indeed, 67b was converted to 57 via a four step procedure involving DIBAL reduction, thioether formation, sulfoxide generation and thermal elimination (Scheme 11).(60) The physical and NMR spectrometric data of the synthetic 57 were identical with those of the natural 57.(54) In order to complete the formal synthesis of 57, a total synthesis of 64a from the commercially available (S)-(−)-Miescher-Wieland ketone is in progress.

Scheme 11

Our next target molecule was sphydrofuran (59), whose chemo-enzymatic synthesis was reported in 1992.(61) The initial step towards 59 required a large quantity of 3-n-butylstannylfuran (72)(Scheme 12).(62) Despite the fact that 72 has been obtained by other routes,(63) they are not suitable for a large scale preparation. Making use of our general method(9,13) involving Diels-Alder reaction between 4-phenyloxazole and tri-n-butylstannylacetylene and the subsequent extrusion of benzonitrile, 72 was successfully isolated in good yield as well as in multigram scale. With 72 in hand, lithiation and treatment of the resulting 3-lithiofuran with (+)-2,3-O-isopropylidene-D-glyceraldehyde gave a mixture of the syn- and anti-alcohol 73 in an approximately 1:1 ratio. In order to obtain only the syn-form of 73, it was oxidized to ketone 74 and was then reduced with Super-Hydride® to 75, which in syn-form. Protection of 75 gave 76, which was converted to 2-butenolide 78 using a similar procedure as mentioned above. Of special interest was the regiospecific deprotonation step, which provided the butenolide of the desired structure. A mild acid deprotection of 78 gave diol 79 and a base induced intramolecular Michael cyclization transformed it into a chromatographically separable mixture of 80 and 81 (Scheme 12),(62)

Scheme 12
Butenolide 62a was obtained in two steps from 79 (Scheme 13).(62) Further conversions of 79, 80 and 81 into other targets 62b, 59 and 61 respectively are in progress (Scheme 13).(62) An ideal reaction condition for stereospecific Michael cyclization is also being pursued so that either 80 or 81 can be generated as the sole product. (62) Preliminary results revealed that basic amino acids such as arginine and lysine were able to enrich the amount of 81 in the product mixtures. (62)

Scheme 13

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REFERENCES AND NOTES

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32. For the acid-catalyzed rearrangement of 1,2-bis(trimethylsilyl)benzene to 1,3-bis(trimethylsilyl)benzene, see: D. Seyferth and D.L. White, J. Am. Chem. Soc. 94, 3132 (1972). Tungsten group C-3 to C-2 migration in substituted furans has been observed by Professor Rai-Shung Liu (National Tsing Hua University, Hsinchu, Taiwan), private communications.


