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Facile Dearomatizing Radical Arylation of Furan and Thiophene

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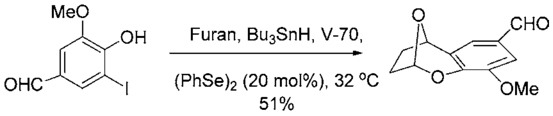
ABSTRACT

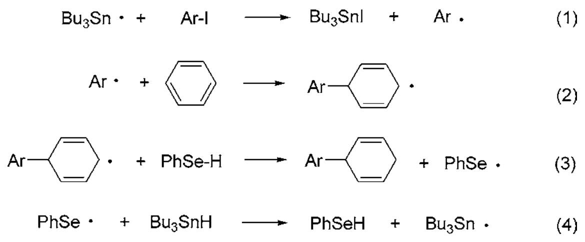


In the presence of catalytic diphenyl diselenide, reduced in situ to benzeneselenol, tributyltin hydride and V-70 promote the addition of aryl iodides to furan and thiophene. The adduct radicals are trapped by the selenol to give the 2-aryl-2,3-dihydro and 2-aryl-2,5-dihydro heterocyclic products. When the iodide is an *o*-iodophenol, a cyclization follows the radical addition and provides bridged bicyclic acetals.

Some time ago we showed how benzeneselenol, produced in situ stoichiometrically by the reduction of diphenyl diselenide with tributyltin hydride,[1] facilitates the propagation of stannane-mediated radical chain reactions.[2] Although the Sn−H and Se−H bond dissociation energies are very similar,[3] the selenol traps alkyl radicals some 500 times faster than the stannane[4] because of the operation of a polarity effect.[5] The quenching of aryl or vinyl radicals, on the other hand, is barely accelerated by the presence of the selenol, as trapping of such σ-type radicals by the stannane alone already approaches the diffusion controlled limit.[6] The selenol-accelerated process offers significant advantages in chain sequences involving allyl and benzyl radicals when it effectively increases the propagation efficiency leading to higher substrate conversion, less formation of byproducts through chain-terminating dimerization of radicals, and a significant reduction in the amount of initiator required.[2a,b]

We also have found the selenol catalysis trick to be applicable to the trapping of cyclohexadienyl radicals arising from the addition of aryl radicals to benzene, when a four propagation step chain sequence (Scheme 1, eqs 1−4) takes place.[7] In the absence of the selenol, as is well-known for the cyclization of aryl radicals onto arenes, the cyclohexadienyl radical does not propagate the chain and suffers rearomatization, perhaps at the hands of the initiator.[8] The failed propagation step inevitably results in the need for greater quantities of initiator if high conversion is to be achieved.[9]

Scheme 1. Mechanism of Dearomatizing Aryl Radical Addition to Arenes



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[1] (a) Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84−88. (b) Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem.* **1996**, *61*, 2368−2373. (c) Crich, D.; Hwang, J.-T.; Gastaldi, S.; Recupero, F.; Wink, D. J. *J. Org. Chem.* **1999**, *64*, 2877−2882.

[2] (a) Crich, D.; Mo, X.-S. *J. Org. Chem.* **1997**, *62*, 8624−8625. (b) Crich, D.; Mo, X.-S. *J. Am. Chem. Soc.* **1998**, *120*, 8298−8304.

[3] BDE Me$_3$Sn-H, 78 kcal mol^{-1}; BDE PhSe-H, 78 ± 4 kcal mol^{-1}. (a) Laarhoven, L. J. J.; Mulder, P.; Wayner, D. D. M. *Acc. Chem. Res.* **1999**, *32*, 342−349. (b) Leeck, D. T.; Li, D. T.; Chyall, L. J.; Kenttamaa, H. I. *J. Phys. Chem.* **1996**, *100*, 6608−6611.

[4] The rate constants for trapping for primary alkyl radicals by Bu$_3$SnH and PhSeH at 25 °C are, respectively, 2×10^6 and 1×10^9 M^{-1} s^{-1}. (a) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742. (b) Newcomb, M.; Choi, S.-Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225−1231.

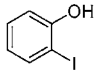
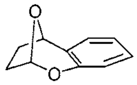
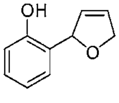
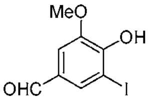
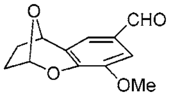
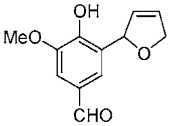
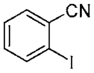
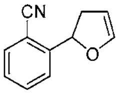
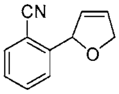
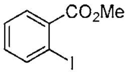
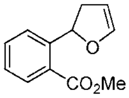
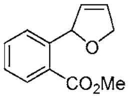
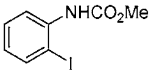
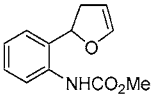
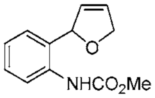
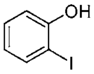
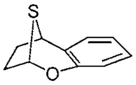
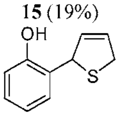
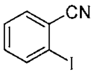
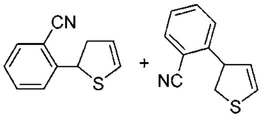
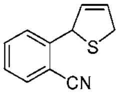
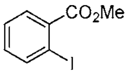
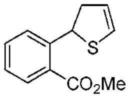
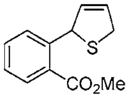
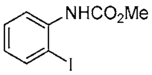
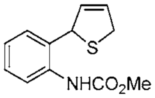
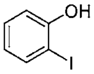
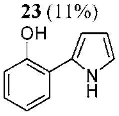
[5] Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25−36.

[6] Garden, S. J.; Avila, D. V.; Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 805−809.

[7] Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770.

10.1021/ol051027w CCC: $30.25

Table 1. Aryl Radical Addition to Furan, Thiophene, and Pyrrole

entry	heterocycle	substrate	2,3-dihydro derived products (yield)	2,5-dihydro derived products (yield)
1	furan	 1	 **2** (45%)	 **3** (14%)
2	furan	 **4**	 **5** (51%)	 **6** (14%)
3	furan	 **7**	 **8** (45%)	 **9** (22%)
4	furan	 **10**	 **11** (32%)	 **12** (10%)
5	furan	 **13**	 **14** (43%)	 **15** (19%)
6	thiophene	 1	 **16** (4%)	 17 (32%)
7	thiophene	 **7**	 **18** + **19** (13%; 2-/3-: 1.4/1)	 **20** (25%)
8	thiophene	 **10**	 **21** (15%)	 **22** (35%)
9	thiophene	 **13**	 **23** (11%)	 **24** (31%)
10	pyrrole	 1	 **25** (17%)	

When the aryl radical employed in eqs 1−4 (Scheme 1) is substituted at the *ortho*-position by a suitable functional group, such as a phenol, the chain sequence may be followed up by a cyclization reaction providing a very facile entry into tetrahydrodibenzofurans and the like.[10] Indeed, we have successfully applied this chemistry in syntheses of carbazomycin B[11] and of a dibenzofuran peptide β-sheet initiator,[12] with the two key building blocks in each case being an *o*-functionalized iodobenzene and benzene itself. We now report that this chemistry is also effective with the simple

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(8) (a) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98. (b) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343−7366. (c) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. (d) Engel, P. S.; Wu, W.-X. *J. Am. Chem. Soc.* **1989**, *111*, 1830−1835.

(9) A recent study on the intermolecular addition of aryl radicals to benzene with isolation of fully aromatic biaryls. Martínez-Barrasa, V.; Garcia de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933−3935.

(10) Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319−3322.

(11) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513−1516.

(12) Crich, D.; Grant, D. *J. Org. Chem.* **2005**, *70*, 2384−2386.

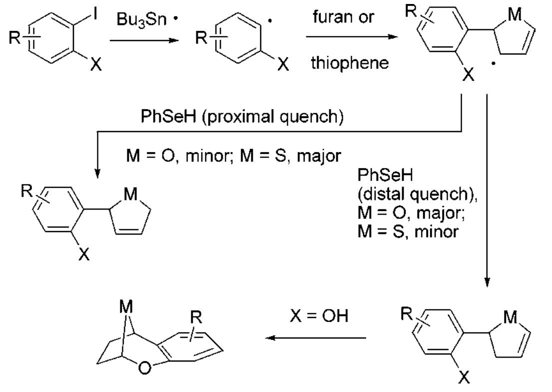
aromatic heterocycles furan and thiophene, thereby permitting the very straightforward synthesis of 2-aryl 2,3-dihydrofurans and thiophenes and their 2,5-dihydro isomers.

Radical addition of aryl radicals to both furan and thiophene has been studied previously. However, under the non-chain conditions applied the isolated products were either fully aromatic aryl furans and thiophenes or dihydro systems carrying a triphenylmethyl substituent resulting from combination of the adduct radical with the triphenylmethyl radical.[13] Nevertheless it was determined, using phenyl radicals derived from the benzenediazonium ion, that the relative rates of addition to furan, thiophene, and benzene are 11.5:2.6:1.[13a]

In the chemistry described in eqs 1−4, benzene functions as reagent and solvent and the reactions are run at reflux. Under these conditions azobisisobutyronitrile (AIBN) with $t_{1/2} = 2$ h at 80 °C[14] is a suitable initiator. Not surprisingly, when we attempted to conduct a similar reaction in furan (bp 32 °C) at reflux, little or no reaction was observed. Switching, however, to 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) as initiator, with a lower decomposition temperature ($t_{1/2}$ 30 °C = 10 h in toluene for the commercial ±/*meso* isomer mixture)[15] brought immediate results. Thus, a 0.01 M solution of *o*-iodophenol in furan containing 20 mol % of diphenyl diselenide was heated to reflux under argon and treated with a solution of 175 mol % tributylstannane (0.05 M) and 20mol % of initiator V-70[16] in furan dropwise over 16 h. After heating to reflux for a further 1 h, the furan was stripped off, and after partitioning between hexanes and acetonitrile, the products **2** and **3** were isolated by chromatography over silica gel (Table 1, entry 1). Examination of the crude reaction mixture by ^{1}H NMR spectroscopy revealed that the 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepin **2** is formed directly in the reaction mixture and not on passage over silica gel. Presumably, the phenol itself or the catalytic benzeneselenol promotes cyclization of the initial 2-(2,3-dihydro-2-furanyl)phenol. When *o*-iodovanillin was employed as substrate a more highly functionalized epoxybenzoxepin **5** was obtained in 51% yield together with the 2,5-dihydrofuran **6** in 14% yield (Table 1, entry 2). Other iodoarenes lacking the phenolic hydroxyl group in the *o*-position also underwent smooth addition to furan giving mixtures of the 2,3- and 2,5-dihydro-2-arylfurans (Table 1, entries 3−5).

All additions to furan (Table 1, entries 1−5) were clean and showed no indication of the alternative mode of addition at the furan C3-position, an observation that is in keeping with the previous work in the area.[13a] The additions to furan show a preference of between 2/1 and 3.6/1 for quenching of the intermediate 1-oxyallyl radicals distal to the ring oxygen leading to preferential formation of the 2,3-dihydro product (Scheme 2).

Scheme 2. Aryl Radical Addition to Furan and Thiophene



When thiophene (bp 84 °C) was employed as solvent and the reactions conducted at an oil bath temperature of 50 °C using V-70 as initiator, comparable adducts were obtained, albeit with reduced yield and a reversed selectivity in the quenching step favoring the formation of the 2,5-dihydro rather than the 2,3-dihydro system (Table 1, entries 6−9). The difference in the regioselectivity of the hydrogen atom transfer step between the furan and thiophene series is consistent with a change in spin delocalization in the intermediate heteroatom-substituted allyl radicals as the heteroatom is changed from oxygen to sulfur. Indeed, it has previously been found from the magnitudes of the electron spin resonance hyperfine splitting constants in the 1-*tert*-butylthioallyl and the 1-*tert*-butoxyallyl radicals that alkylthio groups are much more effective at localizing spin than the corresponding alkoxy groups.[17,18] Minor products arising from aryl attack at the thiophene 3-position also were discernible in the crude reaction mixture of all thiophene additions, even if only isolated in one case (Table 1, entry 7). Again, the formation of minor amounts of the 3-aryl addition product in the thiophene series is consistent with the results of an earlier study in which phenylazotriphenylmethane was employed as aryl radical source.[13b] In the addition of the 2-hydroxyphenyl radical to thiophene (Table 1, entry 6) the ^{1}H NMR spectrum of the crude reaction mixture revealed two significant products in a ratio of 2.6:1 favoring the 2,5-dihydro system **17**. The second product was the corresponding 2,3-dihydro system, but this could not be isolated pure and underwent slow decomposition on standing to the 2,3,4,5-tetrahydro-2,5-epithio-1-benzoxepin **16** isolated, the fully aromatic 2-(2-thienyl)phenol, and a number of unidentified substances. This observation stands in contrast

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[13] (a) Benati, L.; La Barba, N.; Tiecco, M.; Tundo, A. *J. Chem. Soc. B* **1969**, 1253−1256. (b) Camaggi, C. M.; Leardini, R.; Tiecco, M.; Tundo, A. *J. Chem. Soc. B* **1969**, 1251−1253 and references therein.

[14] Walling, C. *Tetrahedron* **1985**, *41*, 3887−3900.

[15] (a) Kita, Y.; Gotanda, K.; Sano, A.; Oka, M.; Murata, K.; Suemua, M.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 8345−8348. (b) Kita, Y.; Matsugi, M. In *Radicals in Organic Synthesis*; Sibi, M. P., Renaud, P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 1−10.

[16] Commercial V-70 from Wako Chemicals was employed.

[17] (a) Griller, D.; Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1817−1821. (b) Korth, H.-G.; Sustmann, R. *Tetrahedron Lett.* **1985**, *26*, 2551−2554. (c) Korth, H.-G.; Lommes, P.; Sustmann, R. *J. Am. Chem. Soc.* **1984**, *106*, 663−668. (d) Edge, D. J.; Kochi, J. K. *J. Chem. Soc., Perkin Trans. 2* **1973**, 182−190.

[18] The recommended BDEs of the C−H bonds in methanol, methylamine, and methanethiol are 96.06 ± 0.15, 93.9 ± 2, and 93.9 ± 2 kcal•mol^{-1}, respectively, suggesting that bond strength is not the dominating factor here. Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, 2003.

to entries 1 and 2 of Table 1 in which, as noted above, addition of the phenolic OH bond across the corresponding 2,3-dihydrofuran could not be suppressed and is no doubt indicative of the reduced reactivity of vinyl sulfides as opposed to their ether counterparts.

Finally, we briefly investigated arylation of pyrrole (bp 131 °C) employing a reaction temperature of 50 °C and V-70 as initiator. Unfortunately, complex reaction mixtures were obtained and only a rearomatized product **25** could be isolated pure in low yield (Table 1, entry 10).[19] Our inability to suppress rearomatization in the pyrrole additions parallels our earlier observations on radical addition to pyridine under the benzeneselenol-catalyzed conditions when rearomatized products were also formed, albeit in significantly better yields.[20,21]

In conclusion, 2-aryl-2,3-dihydrofurans, some of which have previously found application in mutlicomponent coupling reactions,[22] can be readily accessed in a single step via a selenol-catalyzed aryl radical addition to furan. The 2,5-dihydroisomers are byproducts of these reactions as they are in the alternative approach employing the Heck reaction of arylmercuric salts and aryl triflates with dihydrofuran.[23,24] When the substrate is an *o*-iodophenol the 2-aryl-2,3-dihydrofuran undergoes addition of the O−H bond across the enol ether in the reaction mixture to provide a very convenient one-pot synthesis of 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepins.[25,26] The analogous chemistry is found with thiophene, although the 2-aryl-2,5-dihydrothiophene is preferred over the 2,3-dihydro-isomer. Unlike furan and thiophene, pyrrole provides complex reaction mixtures from which fully aromatized 2-aryl pyrroles could only be obtained in low yield.[27]

Acknowledgment. We thank the University of Illinois at Chicago for partial support of this work.

Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] We note that the amino group is even better at localizing spin density than the alkylthio group and that 1-aminoallyl radicals are more localized on the heteroatom than the corresponding alkylthio and alkoxyallyl radicals.[17a] Griller, D.; Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1373−1379.

[20] Crich, D.; Patel, M. *Heterocycles* **2004**, *64*, 499−564.

[21] A parallel study of aryl radical addition to pyridine in the absence of selenol. Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217−6224.

[22] Ghosh, A. K.; Xu, C.-X.; Kulkarni, S. S.; Wink, D. *Org. Lett.* **2005**, *7*, 7−10.

[23] (a) Lee, T. D.; Dawes, G. D. *J. Org. Chem.* **1983**, *48*, 399−402. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485−1488. (c) Ozawa, F.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417−1419.

[24] In contrast, we are not aware of any reports of Heck reactions with either 2,3- or 2,5-dihydrothiophene.

[25] The 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepin skeleton is found in Nature at the core of the spiroxins, a series of marine-derived potent antitumor antibiotics, and in averufin, an intermediate in the biosynthesis of aflatoxin B. (a) Miyashita, K.; Saki, T.; Imanishi, T. *Org. Lett.* **2003**, *5*, 2683−2686. (b) Townsend, C. A.; Christensen, S. B.; Davis, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 839−861 and references therein.

[26] Interestingly, the 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepin skeleton is also formed on Heck reaction of *o*-hydroxyarylmercuric salts with dihydrofuran. Holzapfel, C. W.; Williams, D. B. G. *Synth. Commun.* **1994**, *24*, 2139−2146.

[27] 2-Aryl pyrroles may be conveniently accessed by rhodium-catalyzed arylation of pyrrole. Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996−4997.