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Formal radical cyclization onto benzene rings—a general method proceeding *via* cross-conjugated dienones

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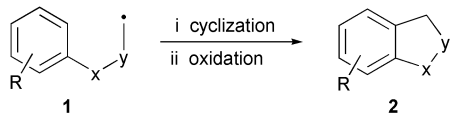
Cross-conjugated dienones of type 5 (X = I), which are readily available from phenols, undergo radical cyclization (5 → 6 → 7), and the products are easily aromatized (7 → 8), giving substances that are formally derived by radical cyclization onto a benzene ring (*cf.* eqn. (1)).

Cyclization of an alkyl radical onto a benzene ring in the sense of eqn. (1) (*x*, *y* = linking chain) would offer a useful route to benzo-fused compounds. Although examples related to eqn. (1) are known,[1,2] there is need for a mild general procedure that



(1)

operates under standard radical cyclization conditions.[3,4] We report an indirect method that satisfies this requirement. Our approach (Scheme 1) involves converting the starting benzenoid compound into a cross-conjugated dienone (**3** → **5**); this readily undergoes radical cyclization (**5** → **6** → **7**), affording a product which is easily aromatized (**7** → **8**).

The cross-conjugated enones **5** are available by reaction of *p*-methoxyphenols **3** with α,ω-halo alcohols in the presence of $PhI(OAc)_2$ and K_2CO_3.[5] We have examined halo alcohols **4** (Scheme 1, X = Cl, I); the reaction **3** → **5** does not appear to work with α,ω-(phenylseleno) alcohols, at least as judged by experiments with **4** (*n* = 1, 3, X = SePh). Compounds of type **5** can, of course, also be made from phenols already bearing a halo alkoxy unit (see Table 1, entry iv, compound **12a** and entry v, compound **13a**); in these cases, the oxidation with $PhI(OAc)_2$ is done in the presence of MeOH. Enones **5** undergo radical cyclization under standard conditions[6] and, when the products **7** are exposed to the action of $TsOH{\cdot}H_2O$, they are converted into the phenols **8**. Table 1 lists our results. Phenols **3**, **12a**,[7] **13a** [8] and **14** were converted into enones **9a**, **10a**, **11a** (from **3**), **12b** (from **12a**), **13b** (from **13a**) and **14a** [9] (from **14**), by oxidation in the presence of the indicated alcohols. Our optimized conditions involve adding a solution of the starting phenol (0.40 mmol) in the appropriate alcohol[10] (2 mL) to a stirred mixture of $PhI(OAc)_2$ (0.44 mmol), K_2CO_3 (0.87 mmol) and the alcohol (1 mL); the excess of alcohol is removed *in vacuo* and the products are chromatographed using a small amount of Et_3N in the eluant. In the case of the transformation **13a** → **13b**, the starting phenol (**13a**) must contain a trace of EtOAc.[11] In most cases iodo alcohols can be used, but in order to make **11a′** we had to use an indirect method *via* the chloro alcohol, as the iodo alcohol was not stable to $PhI(OAc)_2$. Chloride **13a** (as opposed to the iodide) was used simply because it was an easily accessible known[8] starting material.

In all cases the radical cyclization step proceeded without incident,[12] except for a homolog of **11a′** with five carbons in the halo alkoxy chain; this gave a complex mixture when heated with Bu_3SnH in the presence of AIBN. The cyclization products, which were all single isomers, were aromatized by acid treatment. In the case of **13c** and **14c** we were unable to obtain the derived phenols but could easily make the corresponding acetates by including Ac_2O in the acid hydrolysis medium.

Our method can be modified in a number of synthetically useful ways, and three possibilities were examined. The first is shown in Table 1, entry vi, and the others are summarized in Scheme 2. Reduction ($NaBH_4$, $CeCl_3{\cdot}7H_2O$) of ketone **12c** (Scheme 2) gave a single alcohol **12e**; on aromatization ($TsOH{\cdot}H_2O$) a product (**12f**) was obtained (85%) lacking the phenolic hydroxyl group, as expected. When dienone **12b** was cyclized in the presence of allyltributyltin (Scheme 2), the intermediate radical was captured to afford **12g** as a mixture of isomers, and acid-catalyzed aromatization then gave **12h** (72% from **12b**).

Compounds **14b** and **12e** contained slight impurities (^{1}H NMR), but the derived aromatization products were obtained pure (^{1}H NMR) in the yields indicated.

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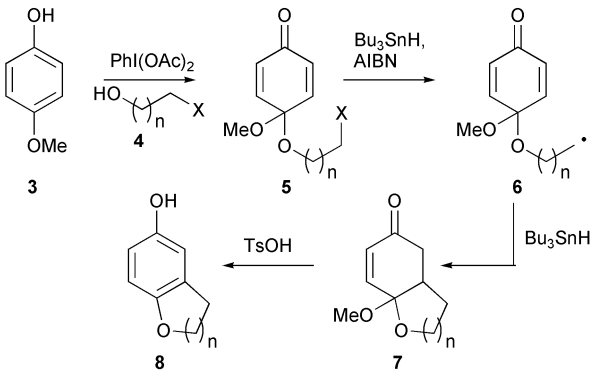
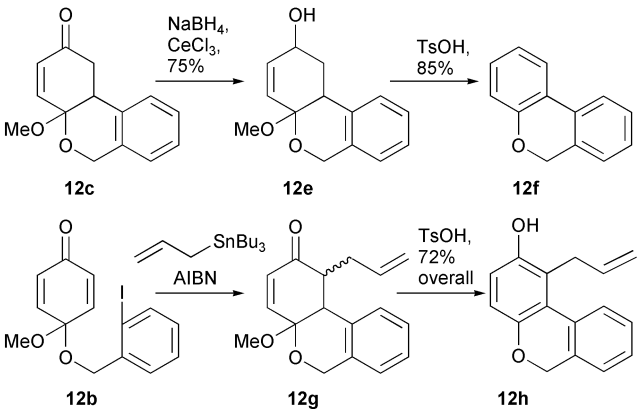


Scheme 1



Scheme 2

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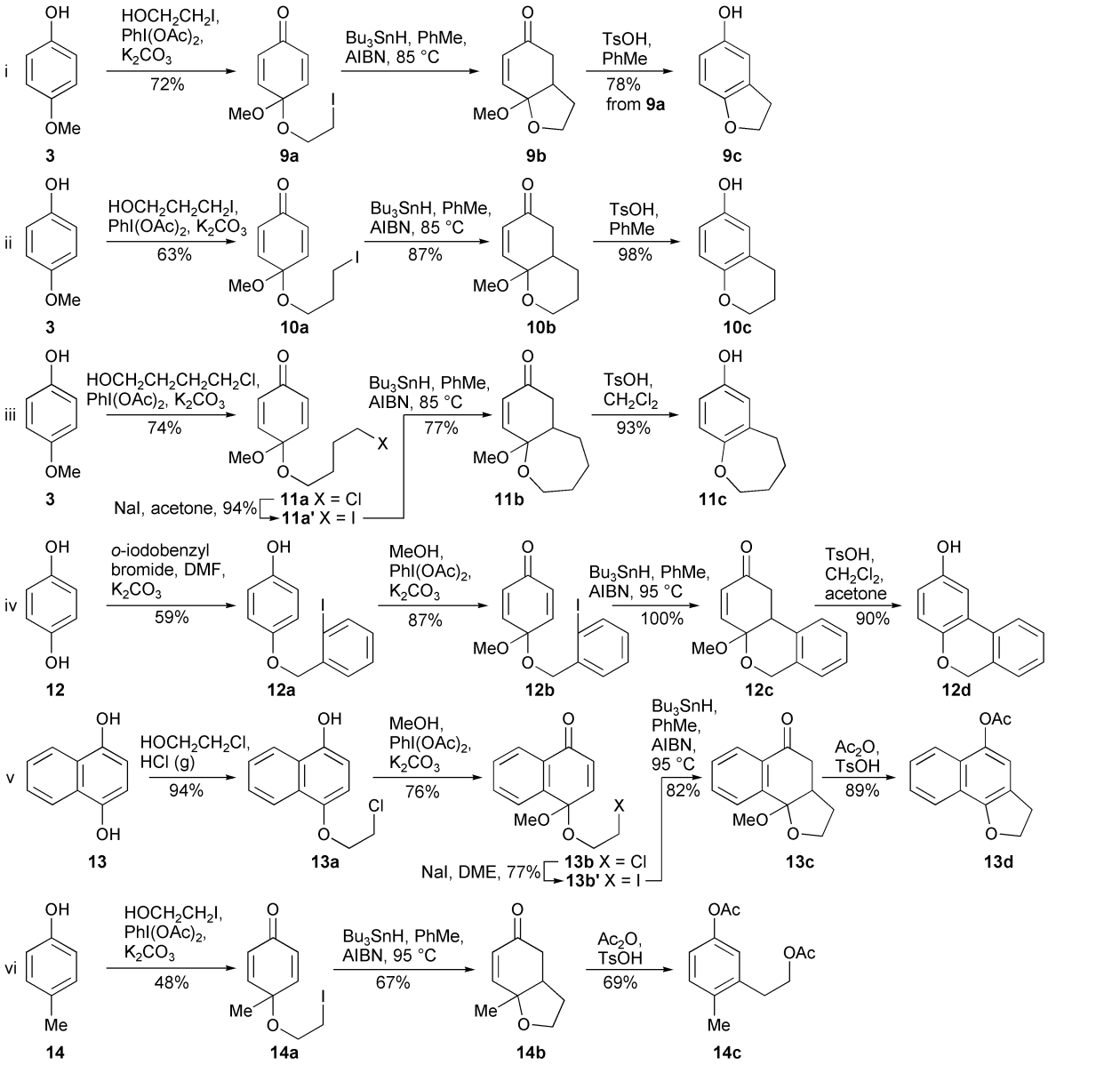
Table 1 Cyclization and aromatization of dienones



Notes and references

1 For use of xanthates, see, for example: (*a*) A. Liard, B. Quiclet-Sire, R. N. Saicic and S. Z. Zard, *Tetrahedron Lett*., 1997, **38**, 1759–1762; (*b*) N. Cholleton and S. Z. Zard, *Tetrahedron Lett*., 1998, **39**, 7295–7298; (*c*) T.-M. Ly, B. Quiclet-Sire, B. Sortais and S. Z. Zard, *Tetrahedron Lett*., 1999, **40**, 2533–2536; (*d*) T. Kaoudi, B. Quiclet-Sire, S. Seguin and S. Z. Zard, *Angew. Chem. Int. Ed*., 2000, **39**, 731–733; (*e*) B. Quiclet-Sire, B. Sortais and S. Z. Zard, *J. Chem. Soc., Chem. Commun*., 2002, 1692–1693; (*f*) For oxidative cyclizations initiated by radical formation from β-dicarbonyl compounds, see: B. B. Snider, *Chem. Rev*., 1996, **96**, 339–363.

2 Other closures onto benzene rings: (*a*) J. J. Köhler and W. N. Speckamp, *Tetrahedron Lett*., 1977, 631–634; (*b*) H. Ishibashi, N. Nakamura, K. Ito and S. Kitayama, *Heterocycles*, 1990, **31**, 1781–1784; (*c*) S. Bertrand, N. Hoffmann, J.-P. Pete and V. Bulach, *J. Chem. Soc., Chem. Commun*., 1999, 2291–2292; (*d*) A. L. J. Beckwith and J. M. D. Storey, *J. Chem. Soc., Chem. Commun*., 1995, 977–978.

3 Numerous cyclizations of alkyl radicals onto heteroaromatic rings have been reported: *e.g.* (*a*) L. D. Miranda, R. Cruz-Almanza, M. Pavón, Y. Romero and J. M. Muchowski, *Tetrahedron Lett*., 2000, **41**, 10181–10184; (*b*) C. J. Moody and C. L. Norton, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2639–2643; (*c*) S.-F. Wang, C.-P. Chuang, J.-H. Lee and S.-T. Liu, *Tetrahedron*, 1999, **55**, 2273–2288; (*d*) F. Aldabbagh, W. R. Bowman, E. Mann and A. M. Z. Slawin, *Tetrahedron*, 1999, **55**, 8111–8128; (*e*) S. Araneo, F. Fontana, F. Minisci, F. Recupero and A. Serri, *Tetrahedron Lett*., 1995, **36**, 4307–4310.

4 For important aspects of radical addition to arenes, see: D. Crich and J.-T. Hwang, *J. Org. Chem*., 1998, **63**, 2765–2770.

5 R. M. Moriarty and O. Prakash, *Org. React*., 2001, **57**, 327–415.

6 Toluene solutions of a tin hydride (0.07–0.12 M) and AIBN (0.005–0.0110 M, 0.1 equiv) are added over 3–5 h to a hot solution (0.035 M) of the substrate.

7 R. Imbos, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc*., 2002, **124**, 184–185.

8 H. Laatsch, *Liebigs Ann. Chem*., 1980, 140–157.

9 For a cyclization substrate related to **14a**, see: F. Villar, O. Equey and P. Renaud, *Org. Lett*., 2000, **2**, 1061–1064.

10 We have run the reaction on a 0.40–7.00 mmol scale. THF is unsuitable as a cosolvent.

11 We have not identified the mechanistic basis of this observation.

12 A small amount (1%) of Et_3N should be added to the eluant during chromatographic isolation of the acetal products.