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Oxidation of *p*-Aminophenols and Formal Radical Cyclization onto Benzene Rings: Formation of Benzo-Fused Nitrogen Heterocycles†

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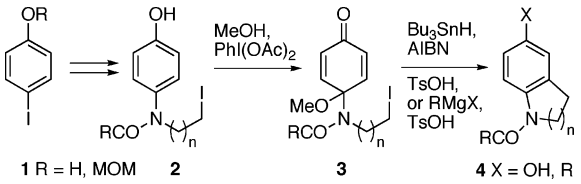
ABSTRACT

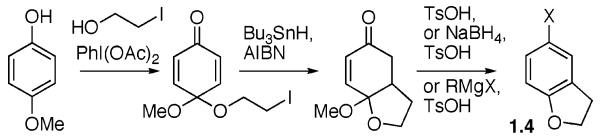


1 R = H, MOM **2** **3** **4** X = OH, R

***p*-Iodophenol and its *O*-MOM-protected ether can be converted into iodoamines 2. These give cross-conjugated ketones 3 on oxidation with hypervalent iodides in the presence of methanol, and the ketones undergo radical cyclization. Exposure of the products to acid or sequential treatment with a Grignard reagent and acid effects rearomatization to produce benzo-fused nitrogen heterocycles 4.**

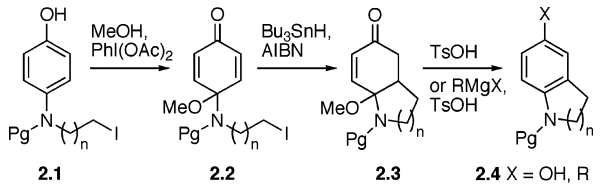
Radical cyclizations onto benzene rings represent an undeveloped but potentially useful process, although, at present, such reactions are often difficult and the mechanism is not fully understood.[1] The most reliable procedure appears to involve the use of xanthates with stoichiometric amounts of a diacyl peroxide.[2,3] A previous publication[4] from this laboratory has described a method for making benzo-fused oxygen heterocycles by a process that is formally equivalent to a radical cyclization onto a benzene ring (Scheme 1). This method was limited to oxygen heterocycles, as it relies on the oxidative dearomatization of a *p*-alkoxy phenol. The formation of other types of benzo-fused heterocycles by radical closure would be useful and, in particular, synthesis of 2,3-dihydrindoles and 1,2,3,4-tetrahydroquinolines, especially those with chiral centers, could give access to a broad range of biologically significant compounds.

Scheme 1



We now report synthetic methodology that allows the same principle to be applied to nitrogen heterocycles conforming to the general structure **2.4** (Scheme 2). These compound classes include many substances reported in recent pharmaceutical patents[5] as having important biological properties.

Scheme 2



The key intermediates of our method are the cross-conjugated ketones **2.2**, and we first evaluated a number of synthetic routes in order to identify a preparative sequence

† Dedicated to Professor E. Piers in recognition of his contributions to Chemistry and to the Canadian Chemical Community.

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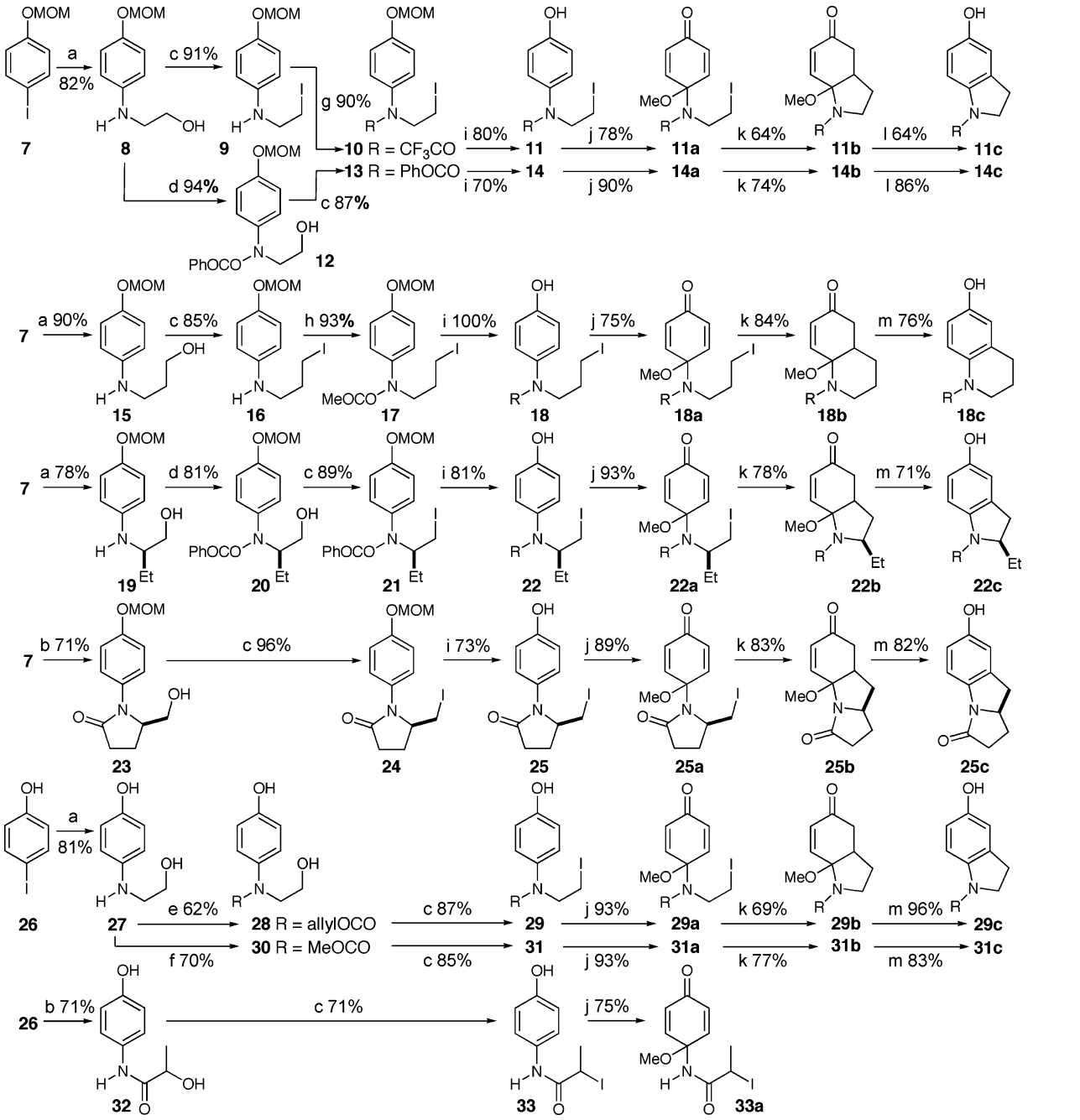
Scheme 3[a]



[a] Reagents and conditions: (a) CuI (cat.), L-proline (cat.), K_2CO_3, DMSO, amino alcohol, heat. (b) CuI (cat.), *N*,*N*′-dimethylethylenediamine (cat.), Cs_2CO_3, DMF, amido alcohol, heat. (c) I_2, Ph_3P, imidazole. (d) PhOCOCl, *i*-Pr_2NEt, CH_2Cl_2. (e) (i) allylOCOCl (0.6 equiv), −40 °C; (ii) *i*-Pr_2NEt (0.6 equiv); (iii) allylOCOCl (0.6 equiv), MeCN. (f) (i) MeOCOCl (0.6 equiv), −30 °C; (ii) *i*-Pr_2NEt (0.6 equiv); (iii) MeOCOCl (0.6 equiv), MeCN. (g) $(CF_3CO)_2O$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C. (h) MeOCOCl, *i*-Pr_2NEt, CH_2Cl_2. (i) Me_3SiBr, CH_2Cl_2. (j) $PhI(OAc)_2$, MeOH. (k) Bu_3SnH, AIBN, PhMe. (l) TsOH·H_2O (cat.), $CHCl_3$. (m) TsOH·H_2O (cat.), 4 Å molecular sieves.

in which several closely linked requirements are each satisfied in a mutually compatible way. Access to these ketones requires preparation and oxidation of the *p*-aminophenols **2.1** carrying a protecting group on nitrogen and also an alkyl chain terminating in an iodine atom. Homolysis of the carbon−iodine bond serves to trigger radical cyclization (**2.2** → **2.3**), and the length of the alkyl chain determines the size of the newly formed ring.

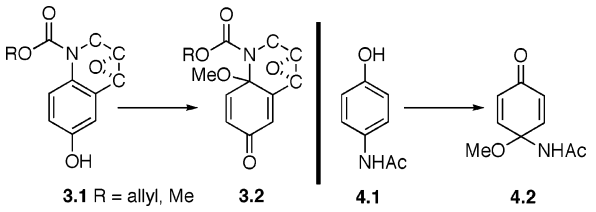
The starting amino or amido alcohols (Scheme 3, column 2) were best made by copper-mediated coupling of an O-protected *p*-iodophenol, although in some cases the

(1) (a) For mechanistic discussion, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Story, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98. (b) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977−978. (c) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770. (d) Cf. Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319−3322.

reaction was successful even without masking the phenolic hydroxyl. The modern procedures developed by the groups of Ma[6] and Buchwald[7] were tried. It was found that Ma's method is very convenient for coupling with amines (**7** → **8**, **15**, **19**; **26** → **27**), while Buchwald's procedure was excellent for coupling with amides (**7** → **23**; **26** → **32**). Under Ma's conditions (CuI, L-proline, DMSO, K_2CO_2, 55−85 °C), the iodophenol or its MOM ether was converted smoothly into the corresponding secondary amine, which was then processed either by N-acylation and formation of the iodide, or by the reverse sequence, formation of the iodide followed by N-acylation. Use of Buchwald's method gave **23** and **32**, which were directly converted into iodides **24** and **33**, respectively. Our experiments demonstrate the compatibility of these copper-mediated reactions[6,7] with unprotected alcohols and, in some cases, free phenols, a characteristic that is clearly a useful feature.

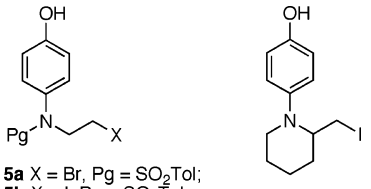
Unlike the oxidation of *p*-alkoxyphenols to quinone acetals (cf. **1.1** → **1.2**, Scheme 1), the corresponding transformation of *p*-aminophenols (cf. **2.1** → **2.2**, Scheme 2) is not well-known, the only relevant examples being found in synthetic work on dynemicin A (Scheme 4, **3.1** → **3.2**)[8] and in a report

Scheme 4



3.1 R = allyl, Me **3.2** **4.1** **4.2**

that **4.1** is convertible into **4.2** on treatment with $PhI(OAc)_2$ (Scheme 4).[9,10] We evaluated a number of nitrogen protecting groups and found that not all of them allow the chemical oxidation **2.1** → **2.2**: *p*-toluenesulfonyl, *t*-butoxycarbonyl, and alkyl groups appear to be unsuitable in this regard, at least as judged by experiments with **5a**−**c** and **6**. However, MeOCO−, allylOCO−, CF_3CO−, and PhOCO− are satisfactory, and oxidation was easily achieved also in the case of **25** (Scheme 3), which is equivalent to an intramolecularly protected amine.



5a X = Br, Pg = SO_2Tol;
5b X = I, Pg = SO_2Tol
5c X = I, Pg = *t*-BuOCO

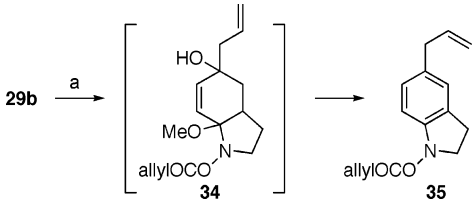
6

The oxidations were done using $PhI(OAc)_2$, $PhI(OCOCF_3)_2$, or PhIO and were also successful with the amides **33** (see Scheme 3) and **4.1** (Scheme 4).[11]

Iodides **2.1** were prepared from the corresponding alcohols using the Ph_3P-I_2-imidazole combination,[12] and we have carried out the alcohol → iodide conversion either before (**8** → **9**, **15** → **16**) or after N-acylation (**12** → **13**, **20** → **21**, **28** → **29**, **30** → **31**). In the case of the conversion **20** → **21**, generation of the iodide was successful only with phenyl carbamate protection. Where appropriate, MOM protecting groups were removed with Me_3SiBr prior to oxidation. Radical cyclization under standard high-dilution conditions[13] worked well in all cases, except for **33a**, which, like **4.2**, was stable only in the solid state or in acidic MeOH but decomposed under other conditions.

The aromatization step (cf. **2.3** → **2.4**) can, in principle, proceed in two ways, depending on whether the methoxy group (**2.3** → **2.4**, Scheme 2) or the amino unit is expelled; fortunately, the desired loss of the methoxy group is the only pathway we observe under our optimized conditions.[14]

Scheme 5[a]



[a] Reagents and conditions: (a) (i) Allyl-magnesium bromide, THF; (ii) $TsOH·H_2O$, 4 Å molecular sieves, CH_2Cl_2, 71%.

As in the formation of benzo-fused oxygen heterocycles (Scheme 1), the present method can be modified to generate compounds carrying hydrogen or a carbon substituent instead

(2) (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett*. **1994**, *35*, 1719−1722. (b) Liard, A.; Quiclet-Sire, B.; Saicic, R.; Zard, S. Z. *Tetrahedron Lett*. **1997**, *38*, 1759−1762. (c) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett*. **1998**, *39*, 7295−7298. (d) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 2125−2126. (e) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 2533−2536. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed*. **2000**, *39*, 731−733. (g) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 1692−1693. (h) Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 2306−2307. (i) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672−685.

(3) (a) Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R. Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem*. **2004**, *69*, 4001−4004. (b) For other leading references, see ref 4.

(4) Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem*. **2004**, *69*, 3282−3293.

(5) For example, see the following. Kinase inhibitors: Smithkline Beecham, WO 2004043379, 2004. Histamine H3 receptor antagonists: Eli Lilly, WO 2004026837, 2004. 2,3-Oxidosqualene-lanosterol cyclase inhibitors: Hoffmann-La Roche, WO 2002050041, 2002. Growth hormone release promoters: Sumimoto Pharmaceuticals, JP 11292894, 1999. Treatment for dementia: U.S. Department of Health and Human Services, WO 2002048150, 2002. Dopamine D4 receptors: H. Lundbeck A/S, WO 9828293, 1998. Estrogen receptor modulators: Eli Lilly, WO 2002094788, 2002.

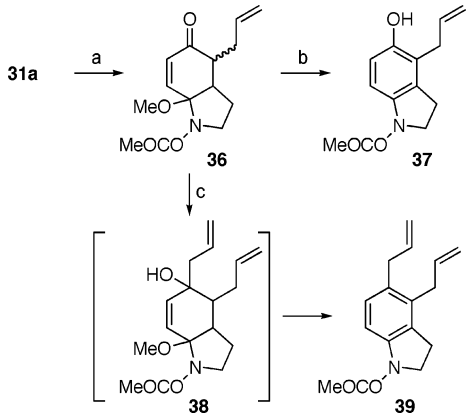
(6) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett*. **2003**, *5*, 2453−2455.

(7) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421−7428.

(8) (a) Yoon, T.; Shair, M. D.; Danishefsky, S. J. *Tetrahedron Lett*. **1994**, *35*, 6259−6262. (b) Shair, M. D., Yoon, T. Y.; Mosnie, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1996**, *118*, 9509−9525. (c) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc*. **1997**, *119*, 6072−6094.

(9) Fleck, A. E.; Hobart, J. A.; Morrow, G. W. *Synth. Commun*. **1992**, *22*, 179−187.

Scheme 6[a]



[a] Reagents and conditions: (a) allyltributyltin, AIBN, PhMe, reflux, 61%. (b) TsOH·H_2O, 4 Å molecular sieves, CH_2Cl_2, 80%. (c) (i) Allylmagnesium bromide (1.2 equiv), THF; (ii) TsOH·H_2O, 4 Å molecular sieves, CH_2Cl_2, **39** (48%) and **37** (35%).

of a phenolic hydroxyl (see Scheme 5, **29b** → **35**), and the intermediate radical can also be intercepted (see Scheme 6, **31a** → **36** → **37**); in addition, both possibilities can be combined for a single substrate (see Scheme 6, **31a** → **36** → **38** → **39**).

The above exploratory studies establish that our indirect method for cyclization onto a benzene rings is not limited to the oxygen series but is also a general and flexible route to a wide range of benzo-fused nitrogen heterocycles. An especially attractive feature is the opportunity to use chiral amino alcohols in the first step so as to afford products with chiral centers, as illustrated by structures **22c** and **25c**, and the possibility of modifying the intermediate enones before rearomatization offers additional synthetic possibilities.

Acknowledgment. We thank NSERC for financial support, a Graduate Fellowship (S.P.F.), and an Undergraduate Student Research Award (D.A.W.).

Supporting Information Available: Characterization data for **11c**, **14c**, **18c**, **22c**, **25c**, **29c**, **31c**, **35**, **37**, **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Reported experimental procedure did not work in our hands. However, we were able to make **4.2** (75%) by a modified workup, while a modified method gave 92% yield: PhIO was added to a solution of **4.1** and then TsOH was added. The mixture was concentrated to a small volume (not to dryness) and then chromatographed over silica gel, using MeOH−EtOAc−hexane (the presence of MeOH was essential).

(11) Oxidation of **4.1** was examined as a model for **33**.

(12) Garegg, P. J.; Samuelson, B. *J. Chem. Soc., Chem. Commun*. **1979**, 978−980.

(13) Toluene solutions of tributyltin hydride (0.07−0.12 M) and AIBN (0.005−0.0110 M, 0.1 equiv) were added over 3−5 h to a hot (85 °C) solution (0.035 M) of the substrate, and heating was continued for an arbitrary period of 1−10 h after the addition.

(14) In the absence of molecular sieves, with compound **11b**, we did observe the undesired pathway as a minor pathway (we have not tested other compounds under the same conditions or attempted to optimize this minor pathway). Conversion of **14b** to **14c** was arbitrarily done without molecular sieves.