

SYNTHETIC CONNECTIONS TO THE AROMATIC DIRECTED METALATION REACTION.

RADICAL-INDUCED CYCLIZATION TO SUBSTITUTED BENZOFURANS, BENZOPYRANS, AND FUROPYRIDINES

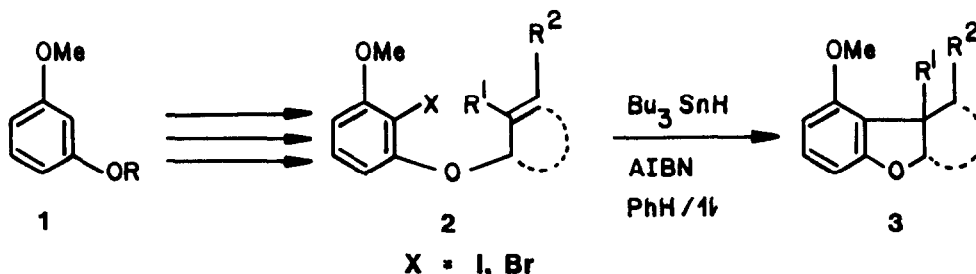
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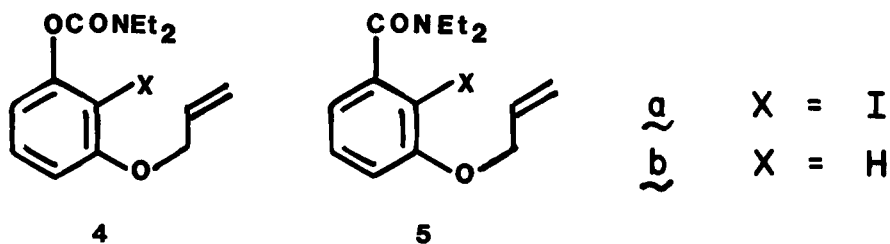
Abstract: The *ortho*-iodoaryl allyl ethers **2**, derived from **1** via the aromatic directed metalation protocol, undergo tributyl tin hydride-induced heteroring annelation to lead to unusually substituted benzofuran (**3**) and benzopyran, and furopyridine derivatives (**Table**).

In spite of their extensive mechanistic background¹ and promising early synthetic applications,² free radical-mediated C-C bond-forming cyclizations are only recently becoming recognized as highly useful preparative reactions.³ Major emphasis has been given to the construction of stereochemically rich alicyclic frameworks,^{3,4} and little effort has been devoted to synthetic exploration of radical-mediated annelations to aromatic rings.⁵ We report on a general radical-induced method for the preparation of benzofurans, **2** → **3** and selected benzopyran and furopyridine systems (**Table**) whose regiospecific bias is based on the availability of iodoaromatic precursors **2** from **1** via the directed *ortho* metalation strategy.⁶ This synthetic connection allows the preparation of substituted systems **3** which are difficult to achieve by classical methodology.⁷



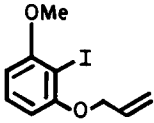
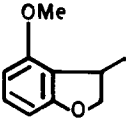
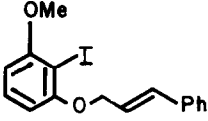
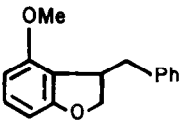
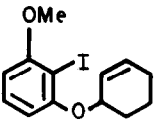
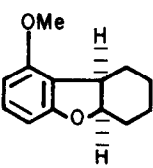
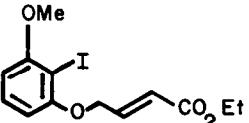
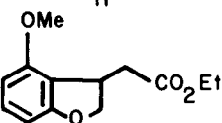
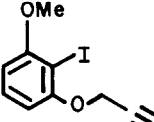
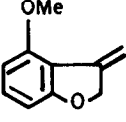
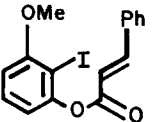
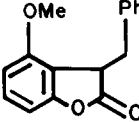
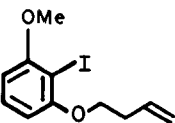
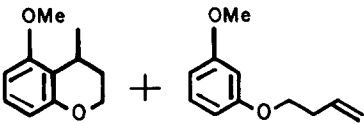
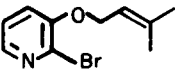
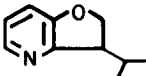
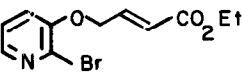
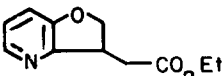
The contiguously trisubstituted iodoaryl allyl ether⁸ (**Table**, entry 1) was treated with 2 equiv of tributyltin hydride in the presence of AIBN in refluxing benzene (0.02 M concentration of Bu₃SnH)^{5a} under nitrogen for 18 h to give the expected benzofuran in high yield. In contrast to the observations of Ueno,^{5a} variation of Bu₃SnH concentration did not

significantly affect the yields of products. Under similar treatment (reflux times 2 - 18 h), a variety of aryl ethers underwent cyclization to provide the corresponding benzofurans (Table, entries 2 - 6). Cases proceeding via stabilized radical intermediates underwent smooth cyclization (entries 2 and 4) while that presenting a modest steric requirement proceeded in less favorable yields (entry 3). That analogous aryl propargyl ethers participate in the radical-induced cyclization was also demonstrated (entry 5).⁹ An ortho-iodophenyl cinnamate ester was cyclized to also give a benzofuranone derivative (entry 6). Products in entries, 4, 5, and 6 represent functionalized benzofuran derivatives amenable to further synthetic manipulations. Extension to a 6-exo-trig ring closure (entry 7) was less successful leading to lower yields and comparable amounts of deiodinated material resulting from competitive hydrogen transfer. On the other hand, 2-bromo-3-pyridyl allyl ethers¹⁰ underwent efficient cyclization to give furopyridines (entries 8 and 9), representing a relatively unknown ring system.¹¹



Attempts to extend the regioselective tin hydride-induced cyclization to the ortho-iodoaryl allyl ethers **4a** and **5a**, derived from the corresponding meta-methoxy O-phenyl carbamate and meta-methoxybenzamide¹² resulted in the formation of dehalogenated products **4b** (80%) and **5b** (70%) respectively. The steric and electronic effects of various directed metalation groups influencing the ring closure are under further study.

Table Synthesis of Benzofurans, Benzopyrans, and Furopyridines

Entry	Starting Material	Product ^a	Yield, % ^b	Bp °C ^c
1			80	73-76/ 0.5 mm
2			88	166-167/ 0.5 mm
3			46	115-119/ 0.5 mm
4			75	156-160/ 0.5 mm
5			52	82-86/ 0.5 mm ^d
6			54	101-102/ (Et ₂ O)
7			41 ^e	-
8			88	80-84/ 0.5 mm
9			75	131-134/ 0.6 mm

Footnotes to Table

^a All new compounds show analytical and spectral (IR, ¹H NMR, MS) data fully consistent with the assigned structures. ^b Yields correspond to chromatographically pure materials. ^c Bps correspond to Kugelrohr bath temperatures. ^d Bp of 3-methyl-4-methoxyfuran, see text. ^e The two inseparable products were obtained in a 1:1 ratio as established by ¹H NMR.

In summary, the synthetic link established between the radical-induced heteroannulation and the directed ortho metalation tactic allows the construction of substituted benzofurans, benzopyrans, and furopyridines which are not easily accessed by classical methodology. Furthermore, this method complements, in part, our recent anionic epoxy-cyclization route.¹³ Such interactive strategies may have broader synthetic utility and application.¹⁴

References and Footnotes

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2. Julia, M. *Acct. Chem. Res.* **1971**, *4*, 386; Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553.
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8. All starting materials shown in the Table were prepared in 70-80% yields from *m*-methoxy methoxymethoxybenzene as follows: 1. a) *t*-BuLi/TMEDA/Et₂O/-78°C; b) I₂; 2. TFA/CH₂Cl₂/RT/10 h; 3. RBr/K₂CO₃/Me₂CO/reflux.
9. The structure of this unstable product was secured by its isomerization into the known 3-methyl-4-methoxybenzofuran (Demerseman, P.; Lechartier, J.-P.; Pene, C.; Cheutin, A.; Royer, R. *Bull. Soc. Chim. Fr.* **1965**, 1473.
10. Prepared from commercially available 2-bromo-3-hydroxypyridine (Aldrich Chemical Co.) by the method described in ref. 8.
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12. Directed metalation (Sibi, M.P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935 and ref. 6) followed by iodination (I₂), BBr₃ demethylation, and allylation as described in ref. 8 gave compounds **4a** and **5a** in 50-70% overall yields.
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14. We are grateful to NSERC Canada and Merck Frosst Canada for financial support of our synthetic programs.

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