

A General Synthesis of Substituted Indoles from Cyclic Enol Ethers and Enol Lactones

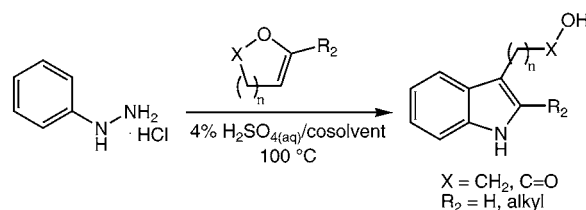
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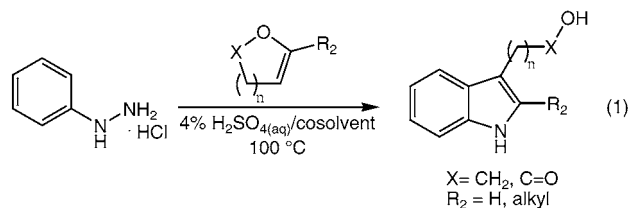
ABSTRACT



A general method was developed for the one-pot synthesis of highly functionalized indoles from simple, commercially available aryl hydrazines and cyclic enol ethers. Enol lactones were also used as substrates, affording substituted indole acetic acid or indole propionic acid derivatives. This procedure affords 2,3-disubstituted indoles as single regioisomers from the appropriately substituted enol ether or enol lactone. This method was highlighted in the efficient synthesis of the antimigraine drug sumatriptan and the antiinflammatory drug indomethacin.

The prevalence of indoles in natural products and biologically active compounds has led to a continued strong interest in the practical synthesis of the indole nucleus.¹ Among the diverse and creative approaches that have been discovered,² the Fischer indole reaction remains the benchmark to which other methods are compared.³ Despite being quite versatile, the Fischer indole reaction with aldehydes often suffers from low yields and involves a two-step process (i.e., hydrazone formation, [3 + 3] rearrangement).⁴ We herein wish to report a convenient and practical one-pot synthesis of 3-substituted indoles from commercially available cyclic enol ethers and

enol lactones and the extension of this procedure to the regioselective synthesis of 2,3-disubstituted indoles (eq 1). This methodology is highlighted in the synthesis of several structurally diverse pharmaceutical agents, including the commercial drugs sumatriptan and indomethacin.



(1) (a) Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1995**, 277. (b) Saxton, J. E. *Nat. Prod. Rep.* **1994**, 493. (c) Saxton, J. E. *Indoles*; Wiley-Interscience: New York, 1983.

(2) For a review of recent developments in the synthesis of indoles, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1.* **2000**, 1045–1075 and references therein.

(3) (a) Gribble, G. W. *Contemp. Org. Synth.* **1994**, 1, 1. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, 25, 607–632. (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

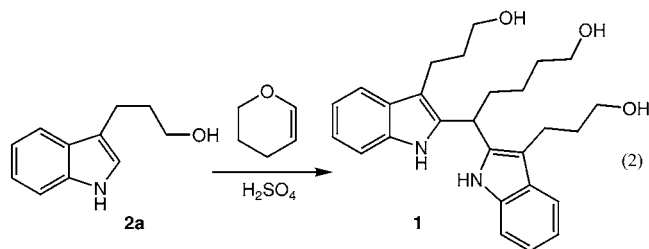
(4) (a) Zepeda, L. G.; Morales-Rios, M. S.; Joseph, Nathan, P. *Synth. Commun.* **1992**, 22, 3243–3256. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Org. Chem.* **1984**, 49, 3711–3716. (c) Fischer, G. W. *J. Heterocycl. Chem.* **1995**, 32, 1557–1561. (d) Pete, B.; Bitter, I.; Szantay, C. J.; Schon, I.; Toke, L. *Heterocycles* **1998**, 48, 1139–1149.

In our pursuit of an efficient synthesis of tryptophol homologs, we were intrigued with the possibility of using dihydropyran as an aldehyde equivalent in the Fischer indole reaction.⁵ We suspected that suitable conditions could be

(5) This method has been attempted, resulting in low yields as a two-step process. (a) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1994**, 116, 1831–1838. (b) McKittrick, B.; Failli, A.; Steffan, R. J.; Soll, R. M.; Hughes, R.; Schmid, J.; Asselin, A. A.; Shaw, C. C.; Noureldin, R.; Gavin, G. *J. Heterocycl. Chem.* **1990**, 27, 2151–2163.

developed that would not only generate the hydrazone from the aryl hydrazine and dihydropyran *in situ* but also catalyze the [3 + 3] rearrangement in the same pot.

We chose 4% aqueous sulfuric acid as the solvent because of its documented success in promoting the Fischer indole reaction involving the *in situ* hydrolysis of an aldehyde protected as its dimethyl acetal.⁶ When dihydropyran was added to a solution of phenylhydrazine hydrochloride in 4% aqueous sulfuric acid at 100 °C, indole **2a** was obtained in 50% isolated yield. The major byproduct of the reaction was triol **1**, resulting from further reaction of **2a** with dihydropyran (eq 2).



We suspected that **1** was produced due to the high concentration of dihydropyran relative to indole product during the reaction; however, slow addition of dihydropyran did not decrease the level of **1** (49%).⁷ After considerable study, it was discovered that addition of a cosolvent to the reaction significantly improved the reaction profile, producing less than 5% of byproduct **1**.⁸ Of the solvents investigated, acetonitrile (MeCN) and *N,N*-dimethylacetamide (DMAc) were optimal, affording indole **2a** in 85 and 90% yields, respectively.⁹

The generality of the process was demonstrated with a wide variety of functionalized hydrazines bearing *ortho*, *meta*, and *para* substituents (Table 1).¹⁰ In the case of *m*-tolyl hydrazine, a 1:1 mixture of regioisomeric indoles (**2c:2d**) was obtained. Aryl hydrazines bearing more than one substituent led to the formation of substituted indoles such as **2k** in good yield.

The utility of this method was highlighted in the synthesis of Glaxo's antimigraine drug, sumatriptan (Scheme 1). Despite the documented difficulty of Fischer indole reactions with hydrazine **3** due to the instability of the product under

(6) (a) Chen, C.-Y.; Senanyake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738–3741. (b) Klaver, W. H.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588–2595.

(7) Excess hydrazine (2 equiv) slightly reduced the amount of **1** (40%).

(8) Importance of the cosolvent is due to the homogenization of the reaction mixture. In purely aqueous systems, the product and dihydropyran are insoluble, creating a highly concentrated "organic layer" that leads to increased formation of **1**.

(9) Performing the reaction at 100 °C was optimal. Lower temperatures gave significantly lower yields of **2a** (50 °C, 33% yield; 25 °C, 18% yield). However, in the case of more electron-rich hydrazines such as *p*-methoxyphenylhydrazine, lower temperatures (55 °C) were needed to prevent the formation of the methoxy-substituted analogue of **1**.

(10) **Typical Procedure.** To a solution of phenylhydrazine-HCl (1 g, 6.92 mmol) in 4% H₂SO₄ (aq) (10 mL) and DMAc (10 mL) at 100 °C was added dihydropyran (630 μ L, 6.92 mmol) dropwise over 2 min. The reaction was aged for 2 h and then cooled to room temperature, extracted with isopropyl acetate, and washed with water three times. The crude material was purified by flash chromatography.

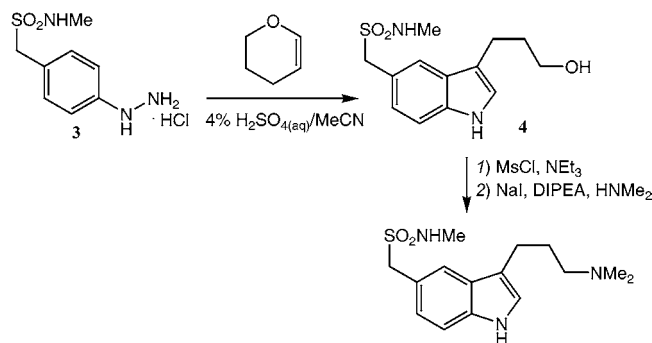
Table 1. Synthesis of 3-Substituted Indoles from Dihydropyran

entry	hydrazine	product	% yield ^a
1			90
2			95
3			75 1:1 (2c:2d)
4			71
5			90
6			70 ^b
7			72 ^b
8			75 ^c
9			60
10			73

^a All reactions were run in 4% H₂SO₄/DMAc (20 mL/g substrate) at 100 °C unless otherwise noted. All reported yields are after isolation by chromatography. ^b Reaction was run in 4% H₂SO₄/MeCN (20 mL/g) at reflux. ^c Reaction was run at 55 °C.

acidic conditions,¹¹ the one-pot reaction could be accomplished to cleanly afford the desired hydroxyindole **4**. Activation of the hydroxyl group as the mesylate followed by displacement in the presence of excess dimethylamine according to previously disclosed methodology^{11b} afforded sumatriptan in three steps and 45% overall yield (unoptimized) from dihydropyran.

Scheme 1. Synthesis of Sumitriptan



To expand the scope of the methodology, the reaction of phenylhydrazine with other cyclic enol ethers was investigated (Table 2). For example, reaction of phenylhydrazine with dihydrofuran (**5**) afforded tryptophol (**6**) in 72% yield. Interestingly, reaction of 1-methyldihydrofuran (**7**) afforded the 2,3-disubstituted indole **8** in 83% isolated yield as a single regioisomer.¹²

Enol lactones also readily participate in this reaction. For example, reaction of enol lactone **11** with phenylhydrazine produced 2-methyl indole propionic acid (**12**) in 75% yield as a single regioisomer (Table 2, entry 4).¹³ In contrast, when the procedure was attempted on angelicalactone (**13**), the cyclic acyl hydrazone **14** was the only observed product.¹⁴ This side reaction could be circumvented by installation of an *N*-benzyl substituent on the hydrazine. Subjection of *N*-benzyl phenylhydrazine to the same conditions cleanly afforded *N*-benzyl-2-methylindole acetic acid (**16**) in 70% yield.

This efficient approach to *N*-protected indole acetic acids prompted us to apply the method to the synthesis of Merck's antiinflammatory drug, indomethacin.¹⁵ Coupling of *N*-acyl hydrazine **17**¹⁶ with angelicalactone under standard condi-

Table 2. Fischer Indole Reaction of Phenylhydrazine with Cyclic Enol Ethers and Enol Lactones^a

entry	substrate	product	% yield ^a
1			72
2			83
3			80
4			75
5			90
6			70 ^{b,c}

^a All reactions were run in 4% H₂SO₄/DMAc (20 mL/g substrate) at 100 °C. All reported yields are after isolation by chromatography. ^b *N*-benzyl phenylhydrazine was used in this coupling instead of phenylhydrazine. ^c Reaction was run in 4% H₂SO₄/MeCN (20 mL/g substrate) at reflux.

(11) Highest yield obtained in a Fischer indole with **3** was 63%. (a) Albinson, F. D.; MacKinnon, J. W. M.; Crookes, D. L. U.S. Patent 5103020, 1992. (b) Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. *J. Org. Chem.* **1997**, *62*, 9192–9202. Much lower yields (20–30%) have been reported in most other cases. (c) Dowles, M. D.; Coates, I. H. U.S. Patent 4816470, 1989. (d) Oxford, A. W. U.S. Patent 5037845.

(12) Reported difficulty of achieving regioselective Fischer indole cyclizations on unsymmetrical ketones makes this result particularly noteworthy. Zhao, D.; Hughes, D. L.; Bender, D. R.; DeMarco, A. M.; Reider, P. J. *J. Org. Chem.* **1991**, *56*, 3001 and references therein.

(13) Structures containing this nucleus have been reported to be human neurokinin-1 receptor antagonists and serve as potential therapeutic agents for emesis, anxiety, and depression. Copper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, 1233–1236. Dinnell, K.; Chicchi, G. G.; Dhar, M. J.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K.-L.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, 1237–1240.

(14) This is a commonly observed intermediate when the *N*-acylhydrazine forms a six-membered heterocycle. Gouault, N.; Cupif, J. F.; Picard, S.; Lecat, A.; David, M. *J. Pharm. Pharmacol.* **2001**, *53*, 981–985.

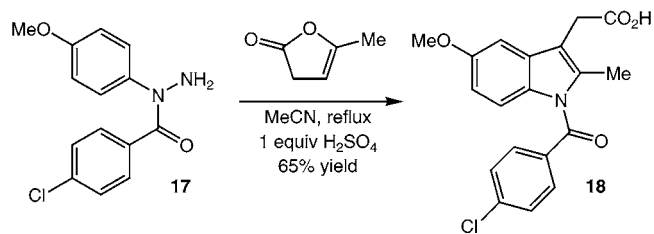
(15) Shen, T. Y.; et al. *J. Am. Chem. Soc.* **1963**, *85*, 8–489. Shen, T. Y. U.S. Patent 3161654.

(16) This hydrazine could be made in one step according to literature precedent in 90% yield from commercially available starting materials. Karady, S.; Ly, M. G.; Pines, S. H.; Chemerda, J. M.; Sletzing, M. *Synthesis* **1973**, 50–51.

tions delivered indomethacin (**18**) along with a significant amount of deacylated product. We discovered that reduction of the amount of water in the reaction suppressed the deacylation reaction. When the reaction was run with a minimal amount of water, using 1 equiv of sulfuric acid, indomethacin was produced in 65% yield (Scheme 2). This procedure represents a one-step approach to the regioselective synthesis of indomethacin from readily available starting materials.

In conclusion, a general, one-pot method for the synthesis of highly functionalized indoles from commercially available cyclic enol ethers and enol lactones has been demonstrated. The procedure is general with respect to both the aryl hydrazine and the enol ether that are used. The method was

Scheme 2. Synthesis of Indomethacin



especially useful for the regioselective synthesis of 2,3-disubstituted indoles. Cyclic enol lactones could be used in this coupling to afford substituted indole propionic acids and indole acetic acid derivatives in an efficient manner. The utility of this method was highlighted in the efficient

synthesis of two commercial drugs: sumatriptan and indomethacin. We are currently investigating the application of this methodology to the preparation of highly functionalized indoles. The results of our findings will be reported in due course.

Acknowledgment. We would like to thank Dr. Jeff Kueth and Dr. Cheng-yi Chen (Merck & Co.) for valuable comments and discussions.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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