NOVEL ONE-POT PREPARATION OF 5-METHOXYLATED INDOLINE AND INDOLE DERIVATIVES USING A HYPERVALENT IODINE(III) REAGENT

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Abstract –A novel and efficient one-pot preparation of 1-tosylindoline and indole derivatives from *N*-tosylaniline derivatives (**1**) and activated olefin derivatives (**2**) using a hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), is described.

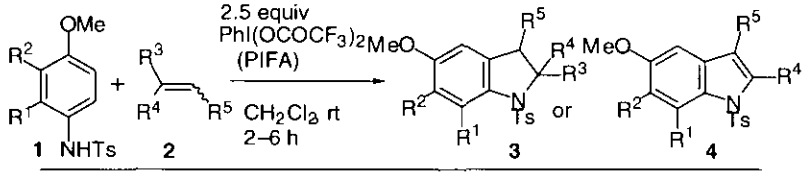
Hypervalent iodine reagents have been used extensively in organic syntheses due to their low toxicity, ready availability and easy handling.[1] In particular, phenolic oxidation reactions using (diacyloxyiodo)benzenes such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have provided a variety of useful transformations in organic synthesis and have been applied to total syntheses of biologically active natural products by our group and others.[2] In contrast to the phenolic oxidations, there have been relatively few reports concerning hypervalent iodine oxidation of aniline derivatives. These include the well-known diazo coupling of anilines,[3,4] acetoxylation of *N*-acetylaniline derivative,[5] recently developed azidation,[6,7] amidation[8] and cyanation[9] reactions of *N,N*-dialkylanilines and the oxidation of *N*-protected aniline derivatives to quinone-imine derivatives.[10] Recently, much attention has been paid to facile and efficient syntheses of heterocyclic compounds using hypervalent iodine reagents because of their mild and versatile reactivities.[11] Since indole core is especially important in many pharmacologically active compounds, we planned to investigate a new facile methodology for synthesizing useful indole derivatives from aniline derivatives using a hypervalent iodine reagent.

Prior to our research, the few reported preparative methods for indoline derivatives were stepwise procedures *via* the oxidation of aniline derivatives. Dalidowicz and Swenton reported the anodic oxidation of *N*-acylaniline derivatives to quinone imine ketals followed by treatment with β-methylstyrene derivatives under acidic conditions to give indoline derivatives only in low yields with several by-products.[12] Similarly, Lewis acid catalyzed preparation of indoline derivatives from 4-(*N*-phenylsulfonyl)-2-alkoxy-1,4-benzoquinone monoimine was reported by Engler *et al.*[13] In the latter reaction, the quinone carbonyl group of the substrates requires an adjacent alkoxy group for a bidentate coordination to the Lewis acid center, leading to higher yields of indolines at the expense of substrate generality. On the other hand, the only intermolecular approach to indole derivatives using hypervalent iodine species was reported by Feldman *et al.* They developed an efficient route to pyrrole and indole derivatives by intermolecular

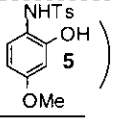
addition/cyclizations of sulfonamide anions with alkynyliodonium salts.[14] However, this method still has room for improvement with regioselectivity of the products. As a continuation of our studies concerning hypervalent iodine(III) chemistry, we have developed several preparative methods to synthesize heterocyclic compounds from phenol and phenol ether derivatives.[15] We report herein a novel and facile one-pot preparation of indoline or indole derivatives by intermolecular addition followed by cyclization between *N*-tosylaniline derivative (**1**) (*N*-tosyl 4-anisidine)[16] and activated olefin derivative (**2**) using PIFA.

It is well-known that olefins as well as *N*-protected aniline derivatives are very reactive toward hypervalent iodine species.[1] However, the slightly higher reactivity of **1** than that of **2** enabled **2** to be used as a suitable carbon nucleophile for this reaction.[17] The present method is applicable to preparations of a variety of 2,3-disubstituted indoline and indole derivatives (Table 1).[18]

Table 1. One-pot Preparation of 5-Methoxy-1-tosylated Indoline and Indole Derivatives



entry	1 R1	1 R2	2 R3	2 R4	2 R5	3 or 4 Yield (%)
1	H	H (**1a**)	Ph	Me	H (**2a**)	**3a**: 65
2	//	//	4-MeOC$_6$H$_4$	H	Me (**2b**)	**3b**: 83
3	H	H (**1a**)	SPh	H	H (**2d**)	**4a**: 76
4	//	//	//	H	Me (**2e**)	**4b**: 50 (94)[a]
5	//	//	//	Me	H (**2f**)	**4c**: 42 (75)[a]
6	//	//	//	H	CH$_2$OAc (**2g**)	**4d**: 53
7	H	OMe (**1b**)	//	H	H (**2d**)	**4e**: 54
8	//	Cl (**1c**)	//	//	//	**4f**: 50
9	Me	H (**1d**)	//	//	//	**4g**: 44
10	H	H (**1a**)	3-NO$_2$C$_6$H$_4$	H	H (**2h**)	**5**: 50[b]
11	//	//	CH$_2$Br	//	// (**2i**)	**5**: 52[b]
12	//	//	O^{n}Bu	//	// (**2j**)	**5**: 42[b]

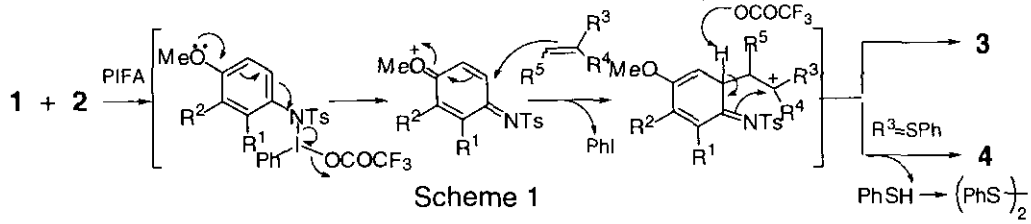


[a]Yields in the parenthesis indicate the conversion yields based upon the consumed starting material. [b]No indoline derivative (**3**) was obtained.

Interestingly, the reaction of **1** with phenyl vinyl sulfides (**2d-g**) predominantly and directly yielded indole derivatives (**4**). This reaction was accompanied by the spontaneous elimination of thiophenol, which was then readily oxidized to diphenyl disulfide by excess PIFA (Table 1; entries 3-9). On the other hand, when olefins such as allyl bromide, an electron-deficient 3-nitrophenylstyrene, or an electron-rich *n*-butyl vinyl ether were used, coupling to component (**1**) was not observed, but rather, the hydroxylated product (**5**) was mainly formed.

A plausible mechanism of the present reaction is depicted in Scheme 1. That is, PIFA initially reacts with *N*-tosylaniline (**1**), then nucleophilic attack by olefin (**2**) followed by cyclization reaction to give 1-tosyl-indoline (**3**)[19] or 1-tosylindole (**4**). Another mechanism involving the iodine-olefin complex also seems

possible. However, on the basis of the high reactivity of **1** toward PIFA even in the presence of excess amount of **2**, the mechanism described in Scheme 1 seems more likely.



Scheme 1

In summary, we developed a novel and efficient one-pot preparation of indoline and indole derivatives using *N*-tosylaniline, activated olefin, and PIFA. This method provides a facile preparative method for a variety of substituted indoles because all starting materials are readily available.[20] The optimization of this reaction and its application to the total syntheses of biologically active indole alkaloids are now underway.

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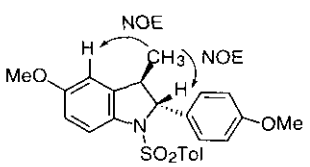
16. *N*-Tosylaniline was found to proceed more efficiently than *N*-acetylaniline; the reaction of *N*-acetyl-4-anisidine with **2d** yielded the corresponding indole (36%) and 3-hydroxy-4-anisidine (33%). Thus, the choice of protective group plays an important role for the yield of products.
17. We examined the reactions of **1a** and **2d** respectively with PIFA. *N*-Tosyl-2-hydroxyanisidine (35%) and *N*-tosyl-4-hydroxyaniline (28%) were obtained immediately by the reaction of **1a** with PIFA. On the other hand, the oxidation of **2d** with PIFA gave predominantly phenylthioacetaldehyde (58%) *via* the iodine-olefin complex.
18. Typical experimental procedure is as follows; To a stirred solution of **1a** (27.7 mg, 0.10 mmol) and **2b** (48.9 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of PIFA (107.3 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) over 2 h by the syringe pump at rt, and then, the reaction mixture was stirred for another 1 h. The mixture was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel to give indoline (**3b**) (35.0 mg, 83%) as a colorless oil. **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.68 (d, 1H, *J*=8.9 Hz), 7.59 (d, 2H, *J*=8.2 Hz), 7.18-7.25 (m, 4H), 6.78-6.84 (m, 3H), 6.56 (d, 1H, *J*=2.4 Hz), 4.60 (d, 1H, *J*=3.7 Hz), 3.78 (s, 3H), 3.77 (s, 3H), 3.00-3.04 (m, 1H), 2.36 (s, 3H), 0.78 (d, 3H, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.0, 157.1, 143.8, 137.6, 134.9, 134.6, 134.5, 129.4, 127.3, 127.0, 116.8, 113.9, 113.1, 110.1, 72.6, 55.6, 55.3, 46.1, 21.6, 21.5; HRMS calcd for $C_{24}H_{25}NO_4S$ 423.1504, found 423.1501.
19. Structural assignment for **3b** is supported by NOE experiment; strong ^{1}H-^{1}H NOE's are observed between the C-3 methyl and both H-2 and H-4 in **3b**, supporting a cis stereo chemistry between CH_3 and H-2.



20. *N*-Tosylaniline was prepared from commercially available anilines. A variety of phenyl vinyl sulfide derivatives except for commercially available **2d** were readily prepared by literature's procedures; see: (a) P. A. Magriotis, T. J. Doyle, and K. D. Kim, *Tetrahedron Lett.*, 1990, **31**, 2541; (b) P. A. Magriotis, J. T. Brown, and M. E. Scott, *Tetrahedron Lett.*, 1991, **32**, 5047.

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