Selective 5-exo-*trig* Iodocyclization of *N*-tosyl-2-allylanilines in Water

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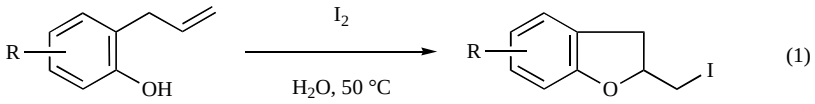
Abstract: Various 2-iodomethyl-*N*-tosylindolines are obtained in high yields from the reaction of *N*-tosyl-2-allylanilines with iodine in water at 50 °C.

Keywords: Iodocyclization, indolines, iodine, water.

The indoline core is a prevalent structural component found in a variety of natural products and synthetic compounds with diverse biological activities [1]. Because of their promising pharmacological applications, indolines serve as attractive synthetic targets and a number of methodologies based on cyclization of aniline derivatives [2,3] or radical-mediated additions [4] have been reported. Also, domino Pd-catalyzed *ortho*-alkylation/amination [5] or Cu-catalyzed amidation/nucleophilic substitution reactions of substituted iodoarenes [6], Pd^{II}-catalyzed C-H activation reactions of arylethylamines [7], and intramolecular cyclizations of 2-*p*-tolylsulfinyl alkylbenzene derivatives [8] have been referred. Additional functionalization of the indoline core remains an open challenge for synthetic chemists on the way to the construction of more complex compounds [9].

Recently, we disclosed the water-promoted iodocyclization of 2-allylphenols (Eq. **1**) [10]. The interest of this procedure has been highlighted by Tripathi and co-workers who have synthesized a range of 2-methylbenzofurans [11]. This urges us to exploit this methodology to synthesize 2-iodomethyl-indolines. The iodocyclization of *N*-alkenyl-amides has been reported using MeCN as the solvent and excess of both *t*-BuOCl and NaI [12], I_2 under basic or acidic conditions [13], or a mixture of Chloramine T and I_2 [14], but, to the best of our knowledge, these methods have not been used with 2-allylaniline type compounds as substrates.



(1)

Equation 1.

In contrast, Pd^{II}-catalysis has been used with excesses of K_2CO_3 and CuX_2 (X = Cl or Br) to mediate the halocyclization of *N*-substituted-2-allylanilines [15]. These catalytic conditions led however to a mixture of 5-*endo* and 6-*exo* cyclisation products.

Preliminary experiments carried out with 2-allylaniline as substrate and various amounts of iodine led to complex mixtures containing low amounts of the expected 2-iodomethyl-indoline. Strong improvements of the results have been obtained with the substitution of the nitrogen atom of the substrate by a tosyl group [16]. Indeed, heating 4-methoxy-*N*-tosyl-2-allylaniline (**1a**) with 4 equiv. of iodine in water (2 mL/mmol of **1a**) at 50 °C for 2 h afforded 2-(iodomethyl)-5-methoxy-1-tosylindoline [17] (**2a**) that has been isolated in 81% yield after column chromatography (Eq. **2**; Table **1**, run 1). Lowering the amount of I_2 to 1.2 equiv. and increasing the reaction time to 3 h led to a similar yield (Run 2) while the decrease to 1 equiv. resulted in 72% yield (Run 3). Performing the iodocyclization in a 1:1 mixture of H_2O/MeCN, with or without $NaHCO_3$ as basic additive, was not beneficial to the process (Runs 4 and 5). A high yield can be obtained in the absence of water but an extended reaction time is thus required (Runs 6 and 7).

Encouraged by these results, the iodocyclization of *N*-tosyl-2-allylanilines **1b-1f** has been carried out using 1.2 and 4 equiv. of I_2 in water at 50 °C (Eq. **3**) [18]. As shown in Table **2**, the corresponding 2-iodomethyl-indolines (**2b-2f**) have been obtained, in up to 90% yield [19], with efficiency and a reaction rate depending on both the structure of the substrate and the amount of iodide. It should be noted that, in all aforementioned experiments, the alternative 6-*exo* cyclisation was never detected.

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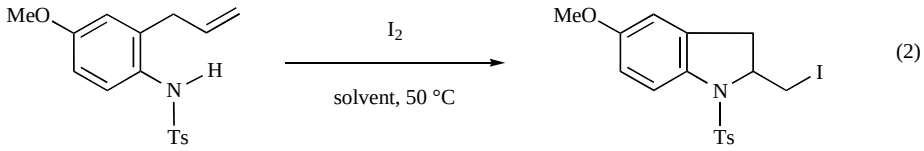


(2)

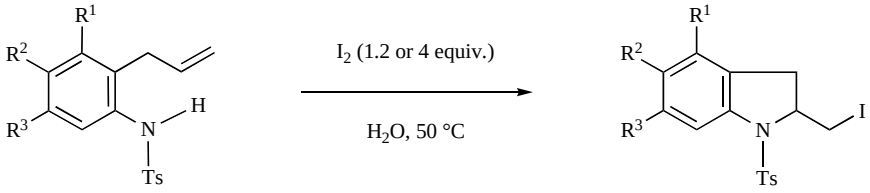
1a **2a**

Equation 2.

Table 1. Iodocyclization of 1a Under Different Conditions

Run	Solvent	I_2 (equiv.)	Time (h)	Yield %
1	H_2O	4	2	81
2	H_2O	1.2	3	82
3	H_2O	1	3	72
4	H_2O/MeCN (1:1)	1.2	3	69
5[a]	H_2O/MeCN (1:1)	1.2	16	70
6	MeCN	1.2	3	62
7	MeCN	1.2	27	81

[a]Reaction carried out in the presence of $NaHCO_3$ (1.2 equiv.).



(3)

1b-1f **2b-2f**

b: $R^1 = R^3 = H$, $R^2 = n$-Bu. **c**: $R^1 = R^3 = H$, $R^2 = Cl$.
d: $R^1 = R^3 = H$, $R^2 = Me$. **e**: $R^1 = R^2 = R^3 = H$.
f: $R^1 = R^3 = Me$, $R^2 = H$.

Equation 3.

Table 2. Iodocyclization of 1b-1f

Substrate	I_2 (equiv.)	Time (h)	Yield (%)
1b	1.2	3	68
"	4	1	90
1c	1.2	2	80
"	4	4	71
1d	1.2	4	79
"	4	1	73
1e	1.2	2.75	79
"	4	1	84
1f	1.2	0.5	88
"	4	0.3	79

In conclusion, 2-iodomethyl-*N*-tosylindolines can be obtained from *N*-tosyl-2-allylanilines using an inexpensive and efficient procedure requiring only iodine as reagent and water as solvent.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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[16] This nitrogen substituent is commonly used for the halocyclization of *N*-alkenylamides [12-15].

[17] Physical data for compound **2a**: Mp: 146.5-147.5 °C. IR (KBr) ν cm^{-1}: 3009, 2920, 2837, 1597, 1487, 1350, 1161, 812, 704, 665, 606, 571, 540. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.36 (s, 3H), 2.73-2.84 (m, 2H), 3.23 (t, J = 10.0 Hz, 1H), 3.62 (dd, J = 9.7, 3.6 Hz, 1H), 3.76 (s, 3H), 4.29-4.35 (m, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.76 (dd, J = 8.8, 2.6 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.8 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 11.1, 21.5, 34.9, 55.6, 62.9, 110.9, 113.2, 118.2, 127.2, 129.7, 132.4, 134.3, 134.6, 144.1, 157.6. GC-MS (EI): t_R = 14.08; 443 (12) [M$^+$], 288 (44), 161 (100), 146 (18), 130 (4), 118 (5), 105, 91

(6). Anal. Calcd. for $C_{17}H_{18}INO_3S$: C, 46.06; H, 4.09; N, 3.16; Found: C, 45.98; H, 4.07; N, 3.14.

[18] Typical procedure for the synthesis of 2-iodomethyl-N-tosyl-indoline derivatives **2a-2f**. A mixture of **1** (0.25 mmol) and iodine (1.2 or 4 mmol) in water (0.5 ml) was stirred at 50 ºC for the indicated time. The reaction mixture was diluted with dichloromethane (10 mL) and aqueous saturated $Na_2S_2O_3$ was added. The phases were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography using hexanes-ethyl acetate mixtures as eluents to afford the corresponding 2-iodomethyl-*N*-tosyl-indoline **2**.

[19] For spectroscopic data of **2b-2f** see Supplementary Material.