



## Convenient indole synthesis from ethynylanilines with a polymer-supported fluoride

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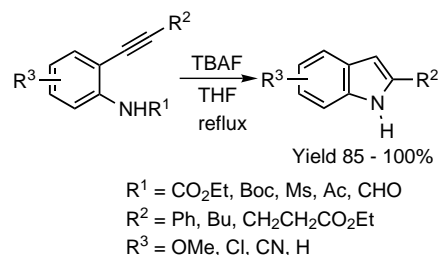
**Abstract**—The cyclization reaction of ethynylanilines having phenyl, alkyl, methoxy, cyano, chloro, and ethoxycarbonyl groups with (polystyrylmethyl)trimethylammonium fluoride in dry MeCN under an argon atmosphere at 100°C proceeded in good yields to give the corresponding indoles without affecting these functional groups. Moreover, the polymer-supported fluoride could be reused for the cyclization reaction when the deprotection reaction of the *N*-substituted indole with the fluoride ion on resin did not occur under the cyclization conditions. © 2002 Elsevier Science Ltd. All rights reserved.

Polymer-supported reagents have been employed in organic synthesis in recent years.<sup>1</sup> There are some major benefits associated with the use of polymer-supported reagents. Excess immobilized reagents can be used to complete the reaction, because any unreacted materials can be simply removed by filtration. The polymer-bound catalytic reagents can be easily removed and recycled. Polymer-bound toxic or hazardous compounds can thus be handled safely. Since Cainelli and Manescalchi reported the transformation from alkyl halides to alkyl fluorides with a polymer-supported fluoride in 1976,<sup>2</sup> the resin has been used as a fluorination reagent of alkyl halides,<sup>2,3</sup> a desilylation reagent,<sup>4</sup> and a base for  $\beta$ -elimination,<sup>5</sup> *C*-alkylation,<sup>6</sup> *O*-alkylation,<sup>6</sup> sulfonylation,<sup>6</sup> and a Michael addition reaction.<sup>6</sup>

On the other hand, we reported that tetrabutylammonium fluoride (TBAF) is a good reagent for the cyclization reaction of 2-ethynylanilines, 2-alkynyl- and 2-alkenylbenzylamines.<sup>7,8</sup> The cyclization reaction of 2-ethynylanilines with TBAF proceeds at refluxing or room temperature to give 2-substituted indoles in excellent yields without affecting the bromo, chloro, cyano, ethoxycarbonyl and ethynyl groups (Scheme 1).<sup>7</sup> When describing the usefulness of this cyclization reaction,<sup>9</sup> we have also reported the syntheses of natural products using the indole synthesis with TBAF as a key step.

Based on the above background concerning the use of polymer-supported fluoride and the cyclization reaction of ethynylanilines with TBAF, we now report the convenient synthesis of 2-substituted indoles by the cyclization reaction of ethynylanilines with commercially available fluoride on resin, (polystyrylmethyl)trimethylammonium fluoride (3 mmol F<sup>-</sup>/g).

First, based on the liquid phase reaction conditions of the cyclization reaction with TBAF, the cyclization reaction of *N*-[2-(1-hexynyl)phenyl]methanesulfonamide (**1a**) with the polymer-supported fluoride refluxed for 5 h in THF gave the *N*-methylsulfonyl-2-butylindole (**2a**) in quantitative yield, but the reaction of ethyl 2-(1-hexynyl)phenylcarbamate (**1b**) did not occur at all (Table 1). In a previous paper,<sup>7</sup> we reported that THF and acetonitrile are good solvents for the cyclization reaction with TBAF, so we tried the reaction of **1b** in acetonitrile with a polymer-supported fluoride and obtained **2b** in 22% yield. Moreover, the cyclization reaction in acetonitrile using a sealed apparatus at 100°C gave **2b**, 2-butylindole (**3b**), and



Scheme 1.

**Keywords:** polymer-supported fluoride; indole synthesis; cyclization reaction; ethynylanilines.

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2-(1-hexynyl)aniline (**4b**) in 61, 18, and 11% yields, respectively (Table 2, entry 2).<sup>10</sup> We then investigated the influence of the reaction solvent on the yields of the cyclization reaction and the swelling rate of the resin in each solvent (Table 2). We surmised that THF and acetonitrile are good solvents for this cyclization reaction in the liquid-phase, but the fluoride on resin was not fully used during the reaction, because of the low swelling rate of the resin in THF. As a result, THF is not a good solvent for the reaction with the polymer-supported fluoride despite being a good solvent for the liquid-phase reaction. Furthermore, the reaction of **1b** with the polymer-supported fluoride in dry acetonitrile under an argon atmosphere gave **2b** and **3b** in 79 and 10% yields, respectively, and we used these conditions for following reactions (entry 6).

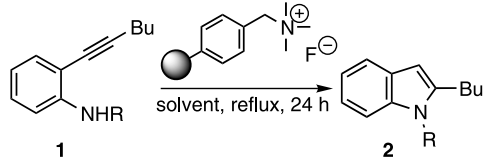
As shown in Table 3, the cyclization of the *N*-ethoxycarbonyl- (**1b**, **f**, **g**, **i**), *N*-formyl- (**1d**), and *N*-*tert*-butoxycarbonyl-2-ethynylanilines (**1e**, **h**) proceeded in good yields, and the reaction of *N*-acetyl-2-phenylethynylaniline (**1c**) for 72 h gave 2-phenylindole (**3c**) in 53% yield. The cyclization reaction of the ethynylanilines having a methoxy (**1f**), chloro (**1i**), and

methoxycarbonyl group (**1h**), also proceeded in 68–95% yields to give the *N*-protected and/or *N*-unprotected indoles. In some of the cyclization reactions with the polymer-supported fluoride, the corresponding *N*-protected indoles were obtained in good yields. We previously reported the deprotection of *N*-methylsulfonylindoles with TBAF. The deprotection reaction requires a stoichiometric amount of TBAF.<sup>11</sup> In contrast, the cyclization reaction of ethynylanilines is a catalytic reaction with TBAF.<sup>7</sup> In some of the cyclization reactions with the polymer-supported fluoride, deprotection of the *N*-substituted indole did not occur, and the resin was easily separated from the reaction mixture by filtration. Therefore, we next tried to reuse the resin for the cyclization reaction of **1b**.

The resin was used five times for the cyclization reaction of **1b** to give **2b**, **3b**, and **4b**. As the number of times increased, the yields of **3b** and **4b** decreased. After seven times, the reaction gave only **2b** and was not completely finish until 24 h (Table 4). The cyclization reaction of **1b** for 48 h in the ninth experiment gave **2b** in 85% yield. We supposed that the differences of the yields between each cycle and the decrease in reactivity of this reaction depended on the decrease in the fluoride anion on the resin, because the fluoride anion was consumed for the deprotection of the ethoxycarbonyl group in the indole.

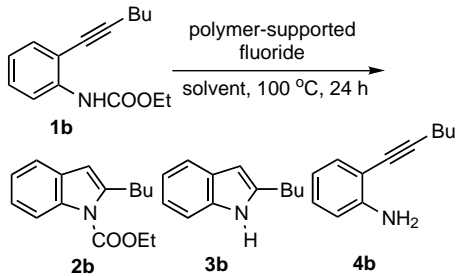
In conclusion, the cyclization reaction of 2-ethynylanilines with a polymer-supported fluoride to produce indoles proceeded in good yields. The cyclization reaction of ethynylanilines having a methoxy, chloro, or cyano group on the benzene also produced good yields to give the corresponding indoles without affecting these functional groups. The polymer-supported fluoride could be reused for the cyclization reaction of ethyl 2-(1-hexynyl)phenylcarbamate depending upon one of the polymer-supported reagent's features, which

**Table 1.** Cyclization reaction of **1a** and **1b** with polymer-supported fluoride at refluxing temperature

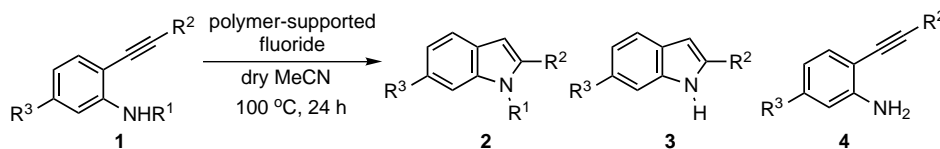


Entry	R	Solvent	Yield (%)	
1	<b>a</b>	Ms	THF	100
2	<b>b</b>	CO <sub>2</sub> Et	THF	0
3	<b>b</b>	CO <sub>2</sub> Et	MeCN	22

**Table 2.** Effect of solvent in cyclization reaction of **1b**

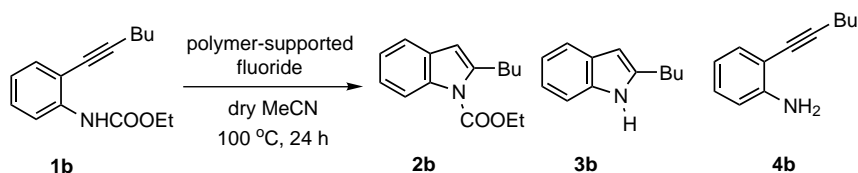


Entry	Solvent	Yield (%)			Recovery	Swelling (ml/g)
		<b>2b</b>	<b>3b</b>	<b>4b</b>		
1	THF	0	0	0	95	0.44
2	MeCN	61	18	11	10	0.71
3	Dioxane	0	0	5	95	0.52
4	Toluene	12	0	0	85	0.50
5	AcOEt	2	0	0	70	0.40
6	Dry MeCN	79	10	3	0	

**Table 3.** The cyclization reaction of various ethynylanilines with polymer-supported fluoride

Entry	<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)			
					<b>2+3</b>	<b>2</b>	<b>3</b>	<b>4</b>
1	<b>b</b>	COOEt	Bu	H	72	61	11	23
2 <sup>a</sup>	<b>c</b>	Ac	Ph	H	53	0	53	0
3	<b>d</b>	CHO	Ph	H	82	0	82	0
4	<b>e</b>	Boc	Bu	H	86	86	0	0
5	<b>f</b>	COOEt	Bu	MeO	68	60	8	10
6	<b>g</b>	COOEt	Ph	CN	90	0	90	0
7	<b>h</b>	Boc		H	95	83	12	0
8	<b>i</b>	COOEt		Cl	85	49	36	0

<sup>a</sup> Cyclization reaction performed for 72 h. Recovery yield: 35%.

**Table 4.** Recycle experiment of polymer-supported fluoride for the cyclization reaction of **1b**

Reuse	Yield (%)									
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th <sup>a</sup>	10th
<b>2</b>	79	81	79	81	92	91	66	42	85	53
<b>3</b>	10	12	7	5	2	6	0	0	0	0
<b>4</b>	3	4	6	4	0.5	2	0	0	0	0
Recovery	0	0	0	0	0	0	32	42	13	45

<sup>a</sup> The reaction was carried out for 48 h.

is the ease of separation from the reaction mixture by filtration.

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10. General procedure for the cyclization reaction of ethynylanilines with polymer-supported fluoride. A mixture of ethynylanilines (1 mmol), polymer-supported fluoride (1.2 mmol, 300 mg), and dry MeCN was heated under an argon atmosphere at 100°C for 24 h in a sealed apparatus. After cooling, the mixture was filtered and the resin was washed with AcOEt. The residue obtained from the filtrate was purified by column chromatography.
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