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A facile synthesis of N,3-disubstituted indoles and 3-hydroxyl indolines via an intramolecular S_NAr of fluorinated amino alcohols

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ABSTRACT

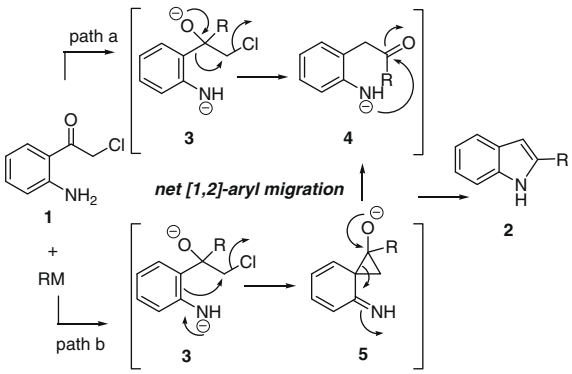
In this Letter, we describe a practical and highly versatile method for the preparation of N,3-disubstituted indoles and 3-hydroxyl indolines. This synthetic strategy relies on an epoxide-opening followed by an intramolecular S_NAr of the resulting fluoroaryl amino alcohols. The reaction afforded 3-hydroxyl indolines when carried out at lower temperature for the derivatives bearing multi-fluorine substituents at the aromatic ring.

The indole and indoline scaffolds are prevalent substructures of many natural products and biologically active compounds.[1] The need for efficient and practical syntheses of indoles and indolines bearing a variety of substitution patterns provides a continual challenge to organic chemists. Despite many diverse and creative approaches that have been used to assemble these heterocycles,[2] a general and efficient synthesis providing control over the regioselective introduction of substituents at C-2 and C-3 is of tantamount importance. We recently reported a synthesis of 2-substituted indoles **2** from readily accessible chloroacetophenones of the type **1** and commercially available organometallic reagents (Scheme 1).[3a]

Of particular significance is the regioselectivity and generality attained under mild reaction conditions, making this method viable for the preparation of many structurally diverse indoles. This efficient synthesis of indoles relies on a unique [1,2]-aryl migration mechanism and serves as a valuable tool for the modular synthesis of C-2 substituted indoles.[3b] In an effort to develop a complimentary method for the synthesis of C-3-substituted indoles and indolines, we became interested in readily available chloroacetophenones of the type **6** (Scheme 2).

As illustrated in Scheme 2, we envisioned that addition of organometallic agents to the *ortho*-F-substituted chloroketones would afford carbinol, which could be further converted to epoxide in situ. Epoxide opening via various amines would give amino alcohols bearing *ortho*-fluoroaryl groups. An intramolecular S_NAr reaction would in turn lead to the formation of either hydroxyl indolines or indoles by in situ dehydration. The regioselective synthesis of the C-3-substituted indole takes advantage of the unique electronic properties of the fluorine substituent. The presence of a fluorine substituent instead of an aniline moiety in the aromatic ring was expected to prevent the facile [1,2] aryl migration of the alkoxide intermediates. The fact that a wide range of fluorinated aromatic chloroketones are commercially available or these can be readily prepared[4] certainly enhances the synthetic potential of the S_NAr approach for the preparation of functionalized indoles and hydroxylindolines. Furthermore, the planned indole synthesis allows for the flexible, sequential introduction of R groups and various amines with potential extension to different substitution patterns on the aromatic ring. In this Letter, we describe such a practical and highly versatile method for the preparation of polysubstituted indoles and 3-hydroxyl indolines.

The synthetic strategy that is outlined in Scheme 2 relies on an epoxide opening followed by intramolecular S_NAr[5] of substituted fluorobenzenes with various amines. A survey of the literature showed that a single example based on this approach was on a penta-F-substituted aromatic amino alkoxide.[6] Apparently, the generality of this transformation has not been well established, especially in the case of mono-fluorinated derivatives of the type **6**. Recently, Schirok reported the microwave-assisted syntheses



Scheme 1. Synthesis of 2-substituted indoles via [1,2]-aryl migration.

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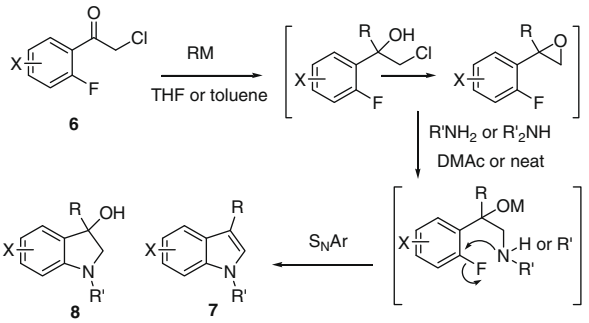
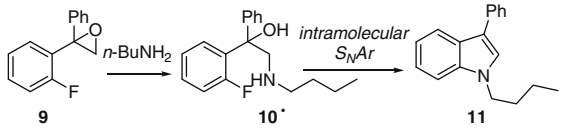


Scheme 2. Synthesis of indole and indolines via intramolecular S_NAr.

of 7-azaindoles and N-alkylated indoles from mono-fluorinated epoxides.[7] However, further extensions to hydroxyl indolines have not been disclosed.

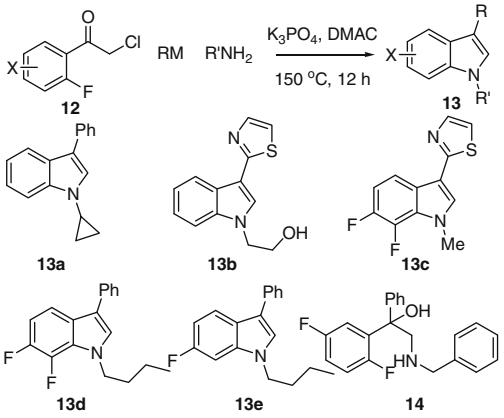
Since the epoxide formation and the ring opening with amines were well precedented in the literature,[7,8] we decided to focus on the study of the proposed intramolecular S_NAr reaction. Instead of using microwave irradiation as reported by Schirok and co-workers, a method that was only shown to afford indoles,[7] we chose to investigate the S_NAr reaction under conventional, thermal conditions. Our investigation into an efficient intramolecular S_NAr reaction began with the ring opening of epoxide **9**[7c] with *n*-butylamine as the nitrogen nucleophile in the presence of inorganic bases. To find the optimal reaction conditions, a number of bases and solvents were evaluated (Table 1). Reaction conditions were initially screened using polar aprotic solvents such as *N*,*N*-dimethylacetamide (DMAc) and either K_2CO_3 or K_3PO_4 as the inorganic bases at 100 °C for 12 h. Under these conditions, no S_NAr occurred to produce the desired indoles. We were pleased to find that simply increasing the reaction temperature to 150 °C allowed us to obtain indole **11** in 78–85% assay yield. Apparently, the choice of polar solvent was not critical as the reactions worked well in DMAc, NMP, and DMSO. More conveniently, the reaction can be run under neat conditions with excess *n*-butylamine serving both as nucleophile for the epoxide opening and as acid scavenger in the intramolecular S_NAr displacement. We noted that the reaction temperature is significantly lower than that in the microwave-assisted conditions, where the internal temperature reaches 240 °C.[7] We believe that using K_3PO_4 as base in DMAc or organic bases under neat conditions at lower temperatures offers advantages in terms of functional group tolerance. More importantly, running the reactions at lower temperature (100 °C, vide infra) allows us to synthesize a number of 3-hydroxylindolines.

Table 1
Optimization of the intramolecular S_NAr



Entry[a]	Base	Solvent	Temperature (°C)	Yield[b] (%)
1	K_2CO_3	DMAc	100	NR
2	K_3PO_4	DMAc	100	NR
3	K_2CO_3	DMAc	150	78
4	K_3PO_4	DMAc	150	85
5	K_3PO_4	DMSO	150	83
6	K_3PO_4	NMP	150	81
7	—	*n*-$BuNH_2$	150	84

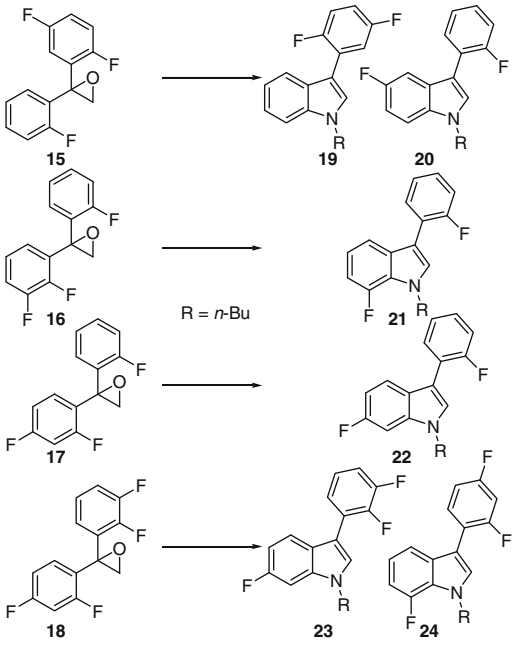
[a] All reactions were run in a sealed tube for 12 h.
[b] Yield of indole (**11**) was assayed by HPLC.



Scheme 3. One-pot process for the synthesis of indoles.

With the optimal set of conditions for the epoxide opening-S_NAr sequence selected, we were then poised to test the one-pot process and to evaluate the substrate scope of this reaction. Gratifyingly, addition of organometallics (RM) to ketone **12** followed by aging at ambient temperature afforded crude epoxide smoothly. The epoxide was isolated by extraction and subjected to the ring-opening intramolecular S_NAr sequence.

To investigate the scope of the process, reactions using various organometallics and amines (3–5 equiv) were carried out using K_3PO_4 (1.5 equiv) in DMAc at 150 °C for 12 h to afford a wide variety of N,3-disubstituted indoles (**13a**–**e**) as summarized in Scheme 3. All reactions proceed in good yields using primary amines such as *n*-butylamine, methylamine, and aminoethanol. Extension of the reaction to the poly-fluorinated aromatic ketones provides access to fluorinated indoles. For example, running the reaction with *n*-butylamine afforded the indoles **13d** and **13e** in 81% and 77% yield, respectively. Running the reactions with aminoethanol and 40% methylamine solution afforded indole **13b** (70%) and **13c** (73%). Importantly, an *N*-cyclopropyl group can be readily incorporated onto the indole using cyclopropyl amine as shown in **13a** (65% yield). It should be noted that introduction of an *N*-cyclo-



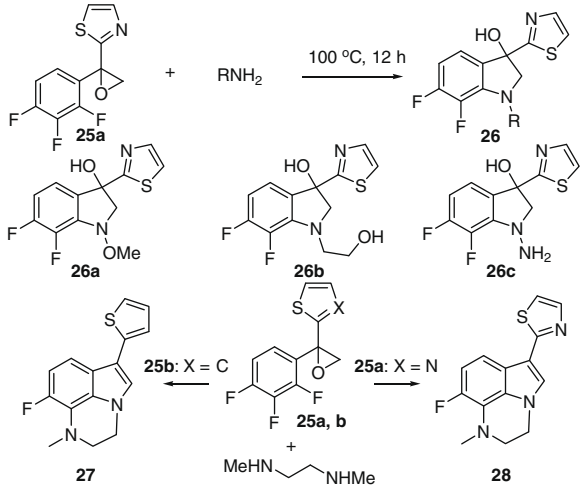
Scheme 4. Competitive S_NAr reactions in neat *n*-$BuNH_2$.

propyl group to an indole is a difficult task, which calls for the copper-mediated cyclopropanation using an excess amount of an expensive cyclopropyl boronic acid or a bismuth derivative.[9]

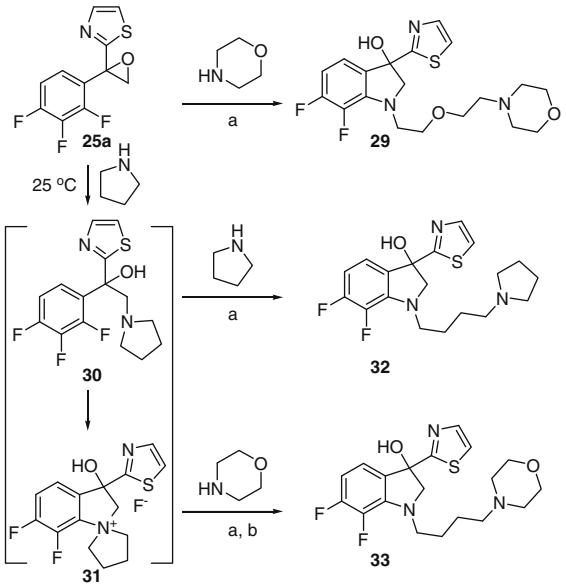
The S_NAr reaction failed for the *para*-F-substituted ketone such that amino alcohol **14** was recovered completely (Scheme 3). Perplexed by the deactivating effect of *para*-F substitution, we decided to perform some competition experiments to understand the effects of additional fluorine atom substitution. Four compounds (**15**–**18**) were independently prepared using conventional methods,[10] and were subjected to the S_NAr reaction. As shown in Scheme 4, substrate **15** afforded a 3:1 mixture of two compounds **19** and **20** in 67% yield, favoring substitution at less substituted aromatic ring. This result clearly supports the fact that the *para*-F substituent disfavors the S_NAr, presumably due to the π-donor capacity of fluorine.[11] Conversely, for both substrates **16** and **17**, in which two regioisomers are possible, the S_NAr reaction is completely regioselective, providing only indole **21** (70%) and **22** (73%), respectively. The S_NAr reaction of **18** afforded a 3.3:1 mixture of two readily separable compounds, **23** (53%) and **24** (16%), favoring substitution at *meta*-substituted aromatic ring. These competition experiments suggest that fluorine substitution activates the S_NAr in the order: *meta*-F > *ortho*-F > H > *para*-F.

Further, extending this methodology to a trisubstituted fluoroketone would allow the preparation of hydroxyl indolines and indoles in excellent yields with an even wider scope of the substrates. We speculated that the additional fluorine substituents would further accelerate the S_NAr resulting in lower reaction temperature. As highlighted in Scheme 5, ring opening of epoxide **25** and S_NAr reaction using $MeONH_2$, ethanolamine, and hydrazine at 100 °C efficiently afforded the hydroxyl indolines (**26a**–**c**) in 89%, 92%, and 85% yield, respectively. Using dimethyl ethylene diamine, structurally interesting indoles such as **27** and **28** were obtained smoothly in 84% and 98% yield, respectively.[12] In these two cases, a second S_NAr displacement occurred to form the six-membered ring. In addition to the lower reaction temperatures, we believed that the presence of additional fluorine atoms disfavors dehydration to form the corresponding indoles due to the inductive effect[11] of the fluorine substituents. Scheme 6 These indoles (**27** and **28**) cannot be easily prepared via other means, but are readily accessible using this strategy.

Realizing that a secondary amine such as dimethyl ethylene diamine can be applied to the S_NAr reaction as shown in cases **27** and **28**, we next explored the reaction using cyclic amine such as pyrrolidine and morpholine. Surprisingly, reaction of epoxide **25a** with excess pyrrolidine gave hydroxylindoline **32** in 79% yield as the sole product. This structurally distinct indole bearing an amine containing side chain clearly incorporated 2 equiv of pyrrolidine. Apparently, the S_NAr reaction occurs to from cyclic ammonium species such as **31** which upon reacting with excess amine resulted in ring opening to form indoline **32**. Similar process was observed using morpholine to afford indoline **29** in 74% yield. More interestingly, combination of pyrrolidine and morpholine allowed for the preparation of hydroxylindoline **33** in 71% yield. These examples clearly indicate that a wide variety of N-substituents can be introduced by judicious combination of amines. The isolation of the indolines rather than the indoles further supports our hypothesis that additional fluorine substitution on the aromatic ring in combination with milder conditions (100 °C) prevents the dehydration process.



Scheme 5. Synthesis of indoles and hydroxylindolines at 100 °C.



a. Reactions were run in neat amines (10 eq) at 100 °C in a sealed tube for 12 h.
b. Crude product **30** was isolated and subjected to the reaction with morpholine.

Scheme 6. Synthesis of hydroxylindolines from cyclic amines.

In summary, we have developed a highly versatile protocol for the preparation of a wide variety of indole and hydroxylindolines from commercially available chloroketones, organometallics, and amines. The success of the transformation relies on the facile intramolecular S_NAr reaction. The method constitutes a practical and modular strategy to access both indoles and hydroxylindolines, which are useful motifs in a variety of interesting, biologically active compounds. We believe that such strategy will find wide applications in the synthesis of indole and hydroxylindolines.

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10. Compounds **15**–**17** were prepared by addition of 2-fluorophenyl lithium to the corresponding di-fluorinated α-chloroketones, whereas **18** was prepared from 2,3-difluorophenyl lithium and the 2',4'-difluoro α-chloroacetophenone. These crude epoxides were directly subjected to the S_NAr reaction in neat *n*-butyl amine at 150 °C for 12 h.
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12. Procedure for the preparation of indole **28** follows: A mixture of **25a** (0.13 g, 0.5 mmol) and *N*,*N*-dimethylethylene diamine (0.44 g, 5 mmol, 10 equiv) was heated in a sealed tube at 100 °C for 12 h. The mixture was cooled to ambient temperature, concentrated and partitioned between 5 mL of MTBE and 5 mL of water. Separation of the organic layer followed by concentration in vacuo afforded indole **28** (0.13 g, 98% yield) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, 1H, J = 3.3 Hz), 7.67 (s, 1H), 7.48 (dd, 1H, J = 7.7, 3.6 Hz), 7.20 (d, 1H, J = 3.3 Hz), 6.97 (dd, 1H, J = 13.8, 8.7 Hz), 4.28 (m, 2H), 3.45 (m, 2H), 3.21 (d, 3H, J = 2.8 Hz ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.5, 146.5 (d, J = 234.1 Hz), 142.7, 128.2 (d, J = 9.2 Hz), 125.2 (d, J = 2.5 Hz), 121.9 (d, J = 11.7 Hz), 120.4, 115.8, 112.7 (d, J = 24.7 Hz), 112.2, 111.3 (d, J = 9.0 Hz), 51.1, 43.9, 41.6 (d, J = 9.8 Hz). ^{19}F NMR ($CDCl_3$, 470.5 MHz): δ −139.07.