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Regioselective, nucleophilic carbon–carbon bond formation at the C4-position of indoles initiated by the aromatic Pummerer-type reaction

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Abstract—The treatment of the 5-(phenylsulfinyl)indoles with trifluoroacetic anhydride in the presence of carbon nucleophiles achieved the title reactions with complete regioselectivity.

Indole derivatives are one of the most abundant components of natural products as well as synthetic compounds possessing a variety of biologically important activities. Therefore, the synthesis of the indole framework and the installation of substituents thereon have undergone considerable advancement over a century.[1] However, the preparation of indoles having a carbon-substituent at the C4-position such as ergot alkaloids and hapalindoles has still been a challenging subject. The most common method for preparing the indoles having carbon-substituents at the C4-position is based on the construction of the pyrrole ring from suitably functionalized benzene derivatives.[1a,b,d] On the other hand, although the direct installation of a carbon-substituent at the C4-position of the indole skeleton must be more effective and convenient, such approaches have not extensively been developed. The existing methods include electrophilic reactions such as the Mannich reaction of the 5-hydroxyindole derivatives[2] and the generation of metalated intermediates by either the halogen–metal exchange reaction[3] or the directed *ortho*-metalation (D*o*M)[4] followed by the reaction with carbon electrophiles. The Claisen rearrangement reactions of the 5-allyloxyindoles[5] and the transition metal-catalyzed reactions of the C4-halogenated indoles have also been reported recently.[6] On the other hand, the direct nucleophilic substitution reactions at the C4-position of indoles have been limited to the specific combination of either the substrates having a nitro group at the C5-position[7] or the indole-chromium complex[8] with highly reactive carbanions. We present here novel nucleophilic and regioselective carbon–carbon bond forming reactions at the C4-position of indoles under mild conditions which were initiated by the aromatic Pummerer-type reaction of 5-sulfinylindoles (**6**).

As a background of this work, we have recently disclosed the preparation of indoles (**3**) via the aromatic Pummerer-type reaction[9] of *p*-sulfinylanilines (**1**). In this reaction, the treatment of **1** with trifluoroacetic anhydride caused the successive *O*-acylation of the sulfinyl group and the elimination of the acyloxy group, both of which were accelerated by the electron donation of the *p*-amino group, to generate *p*-iminoquinone sulfonium intermediates (**A**). The regioselective nucleophilic conjugate addition of external olefins (**2**) to **A** took place followed by cyclization to give **3** (Scheme 1).[10]

We also developed the regioselective carbon–carbon bond forming reactions on furans and thiophenes using the Pummerer-type reaction (Scheme 2).[11,12] The latter reactions similarly generated the sulfonium intermediates (**B**), to which carbon nucleophiles were added with perfect regioselectivity to give the products (**5**).

Keywords: Aromatic Pummerer-type reaction; Indole; Carbon–carbon bond formation; Nucleophilic reaction.

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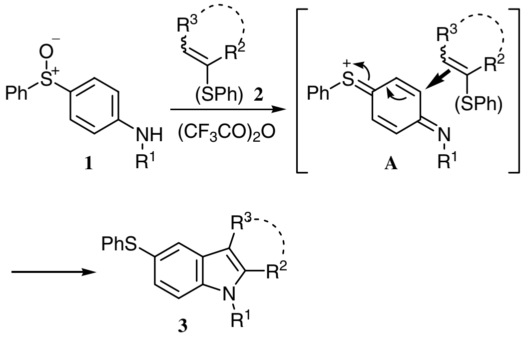
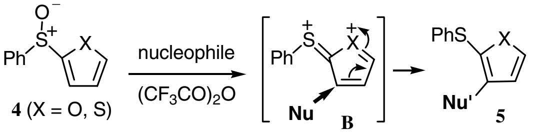


R^1 = *p*-toluenesulfonyl, 2,4-dinitrobenzenesulfonyl

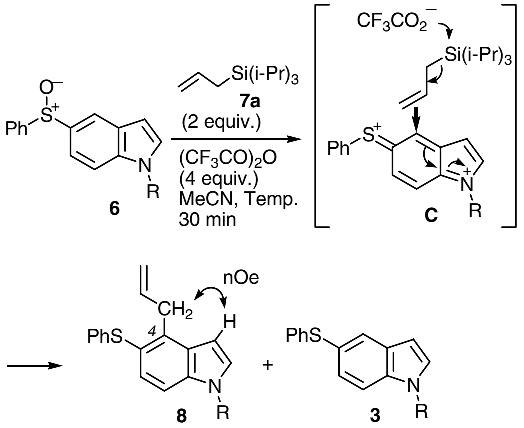
Scheme 1.



Scheme 2.

These two methods feature the umpolung of the electron sufficient aromatics (**1** and **4**) under non-oxidative conditions to achieve the nucleophilic carbon–carbon bond forming reactions. Based on this concept, we envisioned

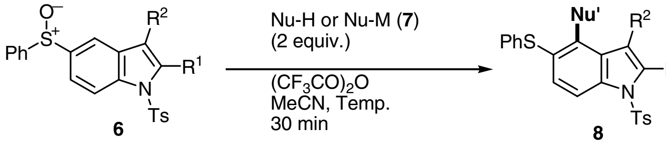
Table 1. Effect of the *N*-protecting group of **6**

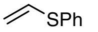
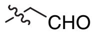
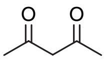
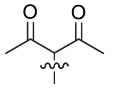
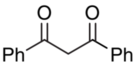
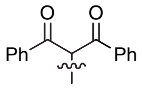
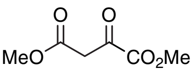
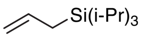
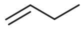
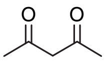
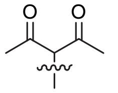
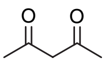
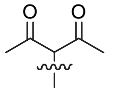
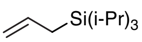
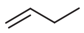


Entry	6, R	Temp.	Yield (%)[a]	
			8	3
1	H	rt	Complex mixture	
2	Me	rt	Complex mixture	
3	TBS	rt	Complex mixture	
4	Cbz	rt	5	48
5	Bz	rt	5	45
6	Ts (**6a**)	rt	**8a** 30	60
7	Ts (**6a**)	80 °C	**8a** 60	30

[a] Isolated yield after column chromatography on SiO$_2$.

Table 2. Nucleophilic carbon–carbon bond forming reaction on the 5-sulfinylindoles **6**



Entry	6	R^1	R^2	Nu-H or Nu-M (7)		Temp.	8	Nu′	Yield (%)[a]
1	**6a**	H	H		**7b**	80 °C	**8b**		29
2	**6a**	H	H		**7c**	rt	**8c**		68
3	**6a**	H	H		**7d**	rt	**8d**		90
4	**6a**	H	H		**7e**	rt	**8e**		48
5	**6b**	H	*n*-C$_6$H$_{13}$		**7a**	80 °C	**8f**		20
6	**6c**	H	Bn		**7c**	rt	**8g**		79
7	**6d**	–(CH$_2$)$_4$–			**7c**	rt	**8h**		74
8	**6e**	*p*-MeOC$_6$H$_4$	Me		**7a**	rt	**8i**		21

[a] Isolated yield after column chromatography on SiO$_2$.

the generation of the cation intermediates (**C**) from the 5-sulfinylindoles (**6**) followed by the conjugate addition of carbon nucleophiles to them.

To examine the feasibility of this plan, we preliminarily investigated the Pummerer-type reaction of various *N*-protected 5-sulfinylindoles (**6**) with the allylsilane (**7a**) (2 equiv) in the presence of trifluoroacetic anhydride (4 equiv). The *N*-*p*-toluenesulfonyl (Ts) indole (**6a**) gave the expected 4-allylindole (**8a**) in 30% yield (Table 1, entry 6) and the formation of other regioisomers was not observed at all. The structure of **8a** was determined based on ^{1}H NMR data and the nuclear Overhauser effect (NOE) experiment. The use of the *N*-H, the *N*-Me and the *N*-*tert*-butyldimethylsilyl (TBS) indoles gave complex mixtures (entries 1–3), and the *N*-benzoyl (Bz) and the *N*-benzyloxycarbonyl (Cbz) derivatives afforded small amounts of **8** (entries 4 and 5). In the latter cases, the corresponding sulfides (**3**) were isolated as the major side product. After intensive studies by changing the solvents, the reaction temperature and the activating reagents, we discovered that the reaction of **6** with trifluoroacetic anhydride in refluxing MeCN significantly reduced the formation of **3** to give **8a** in 60% yield (entry 7).[13]

Next, we examined various carbon nucleophiles (**7**) (Table 2). The use of the vinylsulfide (**7b**) gave the indole-4-acetaldehyde (**8b**) after aqueous workup (entry 1). The β-diketones (**7c**,**d**) were found to be good nucleophiles to afford the products (**8c**,**d**) in 68% and 90% yields, respectively (entries 2 and 3). A similar reaction using **7e** gave the indole-4-acetate (**8e**) as a single product (entry 5). Similar reactions of indoles (**6b–e**) having substituents at the 2- and/or 3-position with some nucleophiles (**7a**,**c**) gave the corresponding 4-substituted indoles (**8f–i**) (entries 5–8). It is worth noting that the nucleophilic substitution exclusively occurred at the C4-position in all cases. Because **6b–e** were prepared by the aromatic Pummerer-type reaction of the aniline derivatives (**1**) shown in Scheme 1 followed by the oxidation,[10a] the iterative use of the aromatic Pummerer-type reaction has been proved to open a new route to the regioselective preparation of biologically important 3,4-di- and 2,3,4-tri-substituted indole derivatives.

In conclusion, we have developed a novel regioselective, carbon–carbon bond-forming reactions at the C4-position of the indole skeleton. This method features nucleophilic substitution on electron sufficient indoles that was attained via their umpolung initiated by the aromatic Pummerer-type reaction. The iterative application of the single sulfinyl group of the aniline derivatives (**1**) to two types of the aromatic Pummerer-type reactions has attained an efficient construction of the multi-substituted indoles (**8**). The application of this method is under study in our laboratory.

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13. A typical experimental procedure: under a nitrogen atmosphere, trifluoroacetic anhydride (92 μL, 0.65 mmol) was added to a solution of **6a** (65 mg, 0.16 mmol) and **7a** (110 mg, 0.33 mmol) in anhydrous MeCN at 80 °C. The

reaction mixture was stirred for 30 min at 80 °C. After cooling to the ambient temperature, the reaction was quenched with aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic layer was successively washed with water and brine, dried over Na_2SO_4, and purified by flash column chromatography on SiO_2 (EtOAc/hexanes = 1:10) to give **8a** (36 mg, 60% yield) and **3a** (29 mg, 30% yield). Compound **8a**: A colorless oil. IR (KBr) 1636, 1597, 1582 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 2.37 (3H, s), 3.80 (2H, d, $J = 6.5$ Hz), 4.94 (1H, d, $J = 15.5$ Hz), 4.95 (1H, d, $J = 11.5$ Hz), 5.76–5.91 (1H, m), 6.72 (1H, d, $J = 3.5$ Hz), 7.06–7.27 (8H, m), 7.43 (1H, d, $J = 9.0$ Hz), 7.58 (1H, d, $J = 3.5$ Hz), 7.83 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 21.6, 35.5, 107.4, 112.4, 115.7, 125.5, 126.3, 126.7, 127.9, 128.7, 129.8, 131.6, 135.5. Anal. Calcd for $C_{24}H_{21}NO_2S_2$: C, 68.70; H, 5.04; N, 3.34; S, 15.29. Found: C, 68.59; H, 5.22; N, 3.26; S, 14.91.