

Fluorous Synthesis of Yuehchukene by α -Lithiation of Perfluoroalkyl-Tagged 1-(Arylsulfonyl)indole with Mesityllithium

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Lithiation chemistry has not been well explored in fluorous synthesis because of the lack of appropriate base-resistant fluorous tags; we recently developed a perfluoroalkylated arylsulfonyl tag for the protection of the indole ring nitrogen atom. Mesityllithium was found to be a suitable reagent for

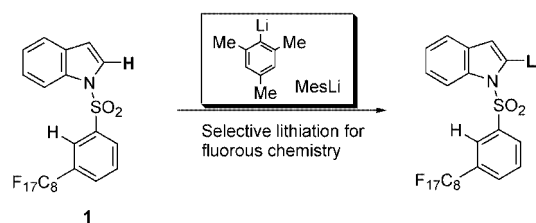
the α -lithiation of perfluoroalkyl-tagged 1-(arylsulfonyl)-indole, and the fluorous synthesis of yuehchukene was accomplished efficiently using this method as a key step. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

Fluorous synthesis^[1] has been widely utilized in organic synthesis since the pioneering works of Horváth^[2] and Curran.^[3] Fluorous-tagged molecules are easily separated from non-fluorous molecules by a fluorous liquid-liquid extraction (F-LLE) using fluorous solvents or a fluorous solid-phase extraction (F-SPE) using perfluorinated silica gel. From the viewpoint of a high-throughput synthesis oriented toward drug discovery, the fluorous synthesis of heterocyclic compounds has been extensively investigated.^[4] In connection to our recent studies on the synthesis of indole derivatives,^[5] we have focused our interest on the use of fluorous-tagged indoles for the synthesis of biologically attractive molecules.^[5c] Lithiated indoles are important synthetic intermediates for the selective functionalization of indole derivatives, and deprotonating lithiation at 2-position has been widely used.^[6] However, lithiation chemistry has not been well explored in fluorous synthesis because of the lack of appropriate base-resistant fluorous tags.^[7] We recently developed a perfluoroalkylated arylsulfonyl tag^[8] for the protection of the indole ring nitrogen atom,^[5c] and now we wish to report the lithiation of a fluorous-tagged indole and the subsequent application to the synthesis of the bis(indole) alkaloid yuehchukene.^[9]

Results and Discussion

It has been reported that mesityllithium (MesLi) can be used as a deprotonating lithiation agent for methoxypyrr-



idines,^[10a] and we have also reported the use as a chemoselective agent for halogen/lithium exchange.^[10b] Encouraged by these discoveries, the lithiation of (phenylsulfonyl)indole was preliminarily examined using mesityllithium (Table 1). The performance of the deprotonation was examined by converting the lithio species into iodo derivatives by treatment with 1,2-diiodoethane. When (phenylsulfonyl)indole **2a** was treated with mesityllithium at -78°C , the 2-iodo derivative **3a** was obtained in 90% yield, whereas the lithiation using *t*BuLi gave the 2-iodo derivative **3a** in 36% yield together with the diiodo derivative **A**. The lithiation using

Table 1. α -Lithiation of (phenylsulfonyl)indole derivatives.

				Yield (%)
Entry	R	RLi	Product	
1	H (2a)	MesLi	3a	90
2	H (2a)	<i>t</i> BuLi	3a	36 (38) ^[a]
3	COOMe (2b)	MesLi	3b	45 ^[b]
4	COOMe (2b)	<i>t</i> BuLi	3b	0
5	CN (2c)	MesLi	3c	65 ^[b]

A

[a] Yield of diiodo compound **A** in parentheses.

[b] Yields of desulfonylated iodoindoles.

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Supporting information for this article is available on the WWW under <http://www.eurjoc.org/> or from the author.

MesLi was found to be compatible with the existence of functional groups such as alkoxycarbonyl and cyano (Table 1, Entries 3, 5), whereas *t*BuLi is not suitable for the chemoselective lithiation (Table 1, Entry 4). The use of *n*BuLi gave a similar result as *t*BuLi.

Further investigation on the lithiation of fluoros-tagged indoles was carried out using MesLi.^[11] The *m*-perfluoroalkylated (phenylsulfonyl)indole **1** was selectively lithiated at the 2-position using mesityllithium in Et₂O, and the 2-iodo derivative was obtained in 65% yield without formation of the corresponding diiodo side product (Table 2, Entry 1). When THF was used as a solvent, the reaction gave a mixture of many products; therefore, Et₂O was chosen as a solvent for the fluoros-tagged substrate.

Table 2. Electrophile trapping of the α -lithiated fluoros-tagged 1-(arylsulfonyl)indole.

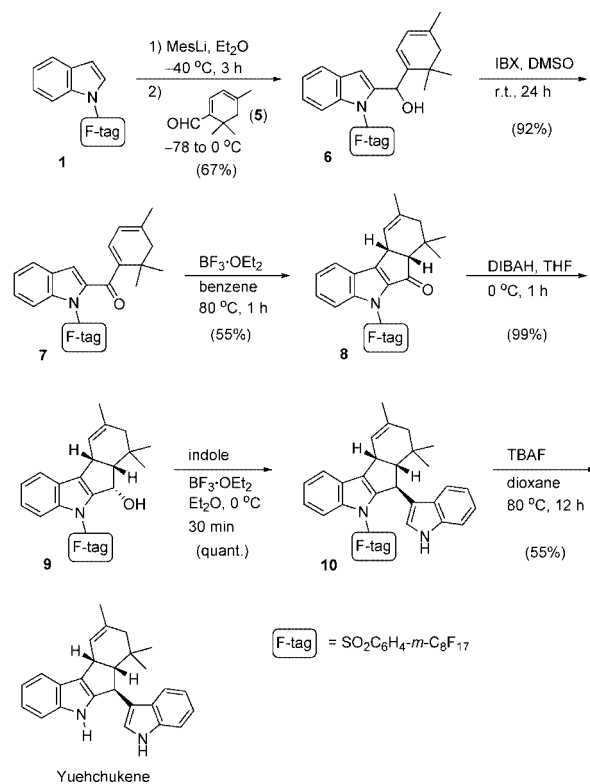
Entry	E ⁺	E	Product	Yield (%)
1	ICH ₂ CH ₂ I	I	4a	65
2	D ₂ O	D	4b	98 (92% D)
3	<i>t</i> BuCHO	<i>t</i> BuCH(OH)	4c	72
4	<i>n</i> -C ₅ H ₁₁ CHO	<i>n</i> -C ₅ H ₁₁ CH(OH)	4d	52
5	<i>i</i> PrCHO	<i>i</i> PrCH(OH)	4e	67
6	PhCHO	PhCH(OH)	4f	76

Next, the lithio species was quenched with D₂O and the D-incorporated indole **4b** was obtained in 98% yield (92% D) (Table 2, Entry 2). Pivaldehyde was used as an electrophile, and the corresponding alcohol **4c** was obtained in 72% yield (Table 2, Entry 3). Other aliphatic aldehydes with an α -hydrogen atom were also used, and the corresponding alcohols **4d**, **4e** were obtained in slightly lower yields (Table 2, Entries 4, 5). The reaction with benzaldehyde gave the alcohol **4f** in 76% yield (Table 2, Entry 6). Thus, mesityllithium was found to be a suitable reagent for the selective functionalization of fluoros-tagged indoles.

Yuehchukene is a bis(indole) alkaloid, isolated as a racemate from *Murraya paniculata* (L.) Jack in 1985, and consists of a unique hexahydroindeno[2,1-*b*]indole structure.^[9a] This compound is known to exhibit a strong anti-implantation activity and a high affinity to the estradiol receptor,^[9] so much interest was focused on the total synthesis of yuehchukene^[12] as well as the synthetic exploration of its derivatives.^[13]

For our fluoros synthesis of yuehchukene, Bergman's approach^[12c,12g] was modified and the fluoros-tagged indole **1** was employed as a starting material (Scheme 1). The lithiation of **1** using mesityllithium followed by the reaction with the monoterpene aldehyde **5** gave the alcohol **6** in 67% yield. The alcohol **6** was oxidized to the ketone **7** using 2-iodoxybenzoic acid (IBX) in DMSO in 92% yield. The

BF₃·OEt₂-catalyzed cyclization of the ketone **7** gave the fluoros-tagged *cis*-hexahydroindeno[2,1-*b*]indol-6-one derivative **8** in 55% yield. The reduction of the cyclized product **8** was carried out by using DIBALH in THF to give the desired α -alcohol **9** in 99% yield with excellent stereoselectivity. The condensation with indole in the presence of BF₃·OEt₂ gave fluoros-tagged yuehchukene **10** quantitatively. The fluoros tag was removed by the treatment with TBAF in dioxane at 80 °C to give yuehchukene in 55% yield. The spectroscopic data of yuehchukene are in good agreement with the reported values. In every step, F-SPE was used effectively for the quick purification of the products by eluting each compound with a fluorophobic solvent system (MeOH/H₂O) followed by a fluorophilic solvent system (EtOAc).



Scheme 1.

Conclusions

A fluoros synthesis of yuehchukene was accomplished by using the selective lithiation of fluoros-tagged indole with mesityllithium as a key coupling step. Lithiation chemistry was proved to be useful in fluoros chemistry if an appropriated base-resistant fluoros tag and a chemoselective lithiating agent are available. Further applications for the fluoros synthesis of other biologically attractive heterocyclic compounds are currently underway.

Experimental Section

{1-[3-(Perfluorooctyl)phenylsulfonyl]-1*H*-indol-2-yl}-(4,6,6-trimethylcyclohexa-1,3-dienyl)methanol (6): Compound **1** (517.3 mg,

0.766 mmol) in Et₂O (3 mL) was added to MesLi (0.92 mmol) in Et₂O at –78 °C under argon. The mixture was stirred at –40 °C for 3 h. Then **5** (308.5 mg, 2.05 mmol) was added to the mixture, and the mixture was stirred at room temp. for 18 h. The reaction was quenched with saturated aqueous NH₄Cl solution (2 mL) and the aqueous layer was extracted with AcOEt (5 mL × 3). The organic layer was washed with brine and dried with MgSO₄. Concentration of the organic phase gave the crude product, which was purified by silica gel column chromatography with *n*-hexane/AcOEt to afford **6** as a solid. ¹H NMR (CDCl₃, 400 MHz): δ = 8.21 (s, 1 H), 8.07–8.11 (m, 2 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 7.31 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 6.80 (s, 1 H), 6.02 (d, *J* = 5.6 Hz, 1 H), 5.95 (br. s, 1 H), 5.70 (d, 1 H), 2.58 (br. s, 1 H), 2.19 (d, *J* = 16.7 Hz, 1 H), 1.83 (d, *J* = 16.7 Hz, 1 H), 1.81 (s, 3 H), 1.06 (s, 3 H), 0.82 (s, 3 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 143.8, 142.5, 139.8, 137.3, 136.0, 131.7, 130.1, 129.8, 128.9, 125.5, 125.1, 121.3, 118.1, 114.5, 112.4, 65.6, 45.7, 33.8, 26.2, 26.0, 23.3 ppm. IR (neat): ν̄ = 2962, 1374, 1198 cm^{–1}. EIMS: *m/z* (%) = 825 (10) [M⁺] 144 (100). HRMS calcd. for C₃₂H₂₄F₁₇NO₃S: 825.1205; found 825.1518.

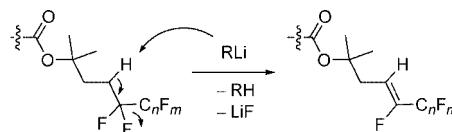
Supporting Information (see also the footnote on the first page of this article): Experimental procedures and spectroscopic data.

Acknowledgments

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