DOI: 10.1002/ejoc.200700525

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

Hiroshi Naka,[a] Yusuke Akagi,[a] Kyoko Yamada,[a] Tatsushi Imahori,[a] Takahiro Kasahara,[a] and Yoshinori Kondo*[a]

Keywords: Fluorous tags / Indole alkaloids / Lithiation / Fluorous solid-phase extraction / Yuehchukene

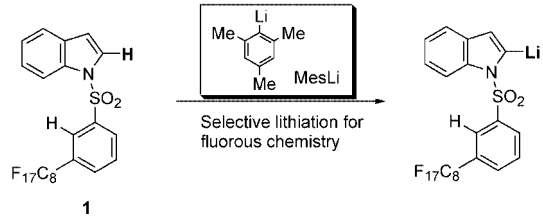
Lithiation chemistry has not been well explored in fluorous synthesis because of the lack of appropriate base-resistant fluorous tags; we recently developed a perfluoroalkylated arylsulfonyl tag for the protection of the indole ring nitrogen atom. Mesityllithium was found to be a suitable reagent for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

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]

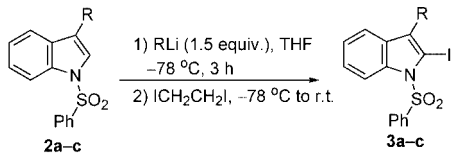
Results and Discussion

It has been reported that mesityllithium (MesLi) can be used as a deprotonating lithiation agent for methoxypyridines,[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



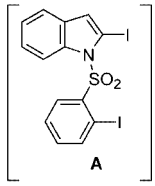
1

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



2a–c **3a–c**

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



A

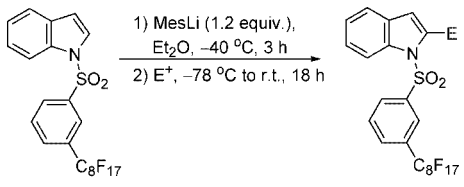
[a] Yield of diiodo compound **A** in parentheses.
[b] Yields of desulfonylated iodoindoles.

[a] Graduate School of Pharmaceutical Sciences, Tohoku University,
Aramaki Aza Aoba 6-3, Sendai 980-8578, Japan
Fax: +81-22-795-6804
E-mail: ykondo@mail.pharm.tohoku.ac.jp
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 fluorous-tagged indoles was carried out using MesLi.[11] The *m*-perfluoroalkylated (phenylsulfonyl)indole **1** was selectively lithiated at the 2-position using mesityllithium in Et_2O, 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, Et_2O was chosen as a solvent for the fluorous-tagged substrate.

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



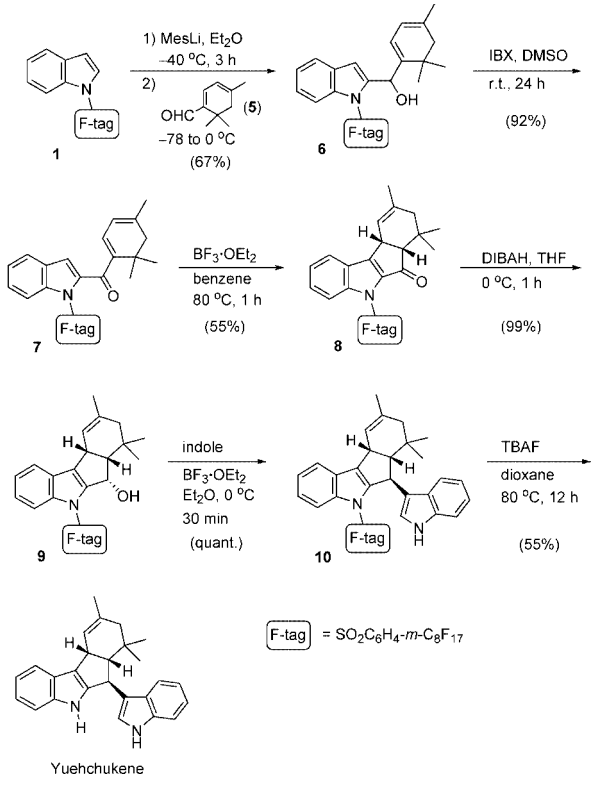
1 4a–f

Entry	E^+	E	Product	Yield (%)
1	ICH_2CH_2I	I	**4a**	65
2	D_2O	D	**4b**	98 (92% D)
3	*t*BuCHO	*t*BuCH(OH)	**4c**	72
4	*n*-C_5H_{11}CHO	*n*-C_5H_{11}CH(OH)	**4d**	52
5	*i*PrCHO	*i*PrCH(OH)	**4e**	67
6	PhCHO	PhCH(OH)	**4f**	76

Next, the lithio species was quenched with D_2O and the D-incoorporated 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 fluorous-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 fluorous synthesis of yuehchukene, Bergman's approach[12c,12g] was modified and the fluorous-tagged indole **1** was employed as a starting material (Scheme 1). The lithiation of **1** using mesityllithium followed by the reaction with the monoterpenoid 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 $BF_3{\cdot}OEt_2$-catalyzed cyclization of the ketone **7** gave the fluorous-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 DIBAH in THF to give the desired α-alcohol **9** in 99% yield with excellent stereoselectivity. The condensation with indole in the presence of $BF_3{\cdot}OEt_2$ gave fluorous-tagged yuehchukene **10** quantitatively. The fluorous 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 ($MeOH/H_2O$) followed by a fluorophilic solvent system (EtOAc).



Scheme 1.

Conclusions

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

Experimental Section

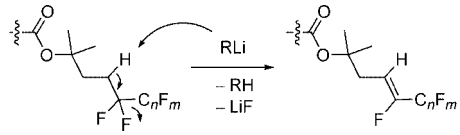
{1-[3-(Perfluoroctyl)phenylsulfonyl]-1*H*-indol-2-yl}-(4,6,6-trimethylcyclohexa-1,3-dienyl)methanol (6): Compound **1** (517.3 mg,

0.766 mmol) in Et_2O (3 mL) was added to MesLi (0.92 mmol) in Et_2O 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 NH_4Cl solution (2 mL) and the aqueous layer was extracted with AcOEt (5 mL × 3). The organic layer was washed with brine and dried with $MgSO_4$. Concentration of the organic phase gave the crude product, which was purified by silica gel column chromatography with *n*-hexane/AcOEt to afford 424.1 mg (67%) of **6** as a solid. ^{1}H NMR ($CDCl_3$, 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. ^{13}C NMR ($CDCl_3$, 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): $\tilde{\nu}$ = 2962, 1374, 1198 cm^{-1}. EIMS: *m*/*z* (%) = 825 (10) [M$^+$] 144 (100). HRMS calcd. for $C_{32}H_{24}F_{17}NO_3S$: 825.1205; found 825.1518.

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

Acknowledgments

This work was partly supported by the Ministry of Education, Science, Sports and Culture, Japan by a Grant-in Aid for Scientific Research (no. 19390002, no. 19790003) and a grant from the Sumitomo Foundation and the Yamada Science Foundation.

[1] J. A. Gladysz, D. P. Curran, I. T. Horváth (Eds.), *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim, **2004**.
[2] a) I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72; b) I. T. Horváth, *Acc. Chem. Res.* **1998**, *31*, 641.
[3] a) A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, D. P. Curran, *Science* **1997**, *275*, 823; b) Q. Zhang, A. Rivkin, D. P. Curran, *J. Am. Chem. Soc.* **2002**, *124*, 5774.
[4] Review: a) W. Zhang, *Chem. Rev.* **2004**, *104*, 2531; b) W. Zhang, D. P. Curran, *Tetrahedron* **2006**, *62*, 11837.
[5] a) K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Org. Chem.* **2003**, *68*, 6011; b) T. Kasahara, Y. Kondo, *Heterocycles* **2006**, *67*, 95; c) T. Kasahara, Y. Kondo, *Chem. Commun.* **2006**, 891.
[6] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) G. W. Rewcastle, A. R. Katritzky, *Adv. Heterocycl. Chem.* **1993**, *56*, 155.
[7] Most of the typical fluorous tags require methylene spacers between the perfluoroalkyl chains and the tagging functionalities to reduce the influence of the perfluorated moieties. When molecules with these tags are exposed to typical lithiation conditions, undesired deprotonation of acidic protons on the methylene spacers occurs as a problematic side reaction.
.


[8] 3-(Perfluorooctyl)benzenesulfonyl chloride: S. Cerezo, J. Cortes, D. Galvan, E. Lago, C. Marchi, E. Molins, M. Moreno-Manas, R. Pleixats, J. Torrejon, A. Vallribera, *Eur. J. Org. Chem.* **2001**, 329.
[9] a) Y.-C. Kong, K.-F. Cheng, R. C. Cambie, P. G. Waterman, *J. Chem. Soc. Chem. Commun.* **1985**, 47; b) T. W. T. Leung, G. Cheng, C. H. Chui, S. K. W. Ho, F. Y. Lau, J. K. J. Tjong, T. C. C. Poon, J. C. O. Tang, W. C. P. Tse, K. F. Cheng, Y. C. Kong, *Chemotherapy* **2000**, *46*, 62.
[10] a) D. L. Comins, D. H. LaMunyon, *Tetrahedron Lett.* **1988**, *29*, 773; b) Y. Kondo, M. Asai, T. Miura, M. Uchiyama, T. Sakamoto, *Org. Lett.* **2001**, *3*, 13.
[11] Other metallic bases were also tested, but MesLi in diethyl ether was proved to be the best reagent for our purpose; see Supporting Information for details.
[12] a) Y.-C. Kong, K.-F. Cheng, T.-Y. Chan, T.-F. Lai, *J. Chem. Soc. Chem. Commun.* **1985**, 48; b) E. Wenkert, P. D. R. Moeller, S. R. Pietter, A. T. McPhail, *J. Org. Chem.* **1988**, *53*, 3170; c) J. Bergman, L. Venemalm, *Tetrahedron Lett.* **1988**, *29*, 2993; d) J. P. Kutney, F. J. Lopez, S.-P. Huang, H. Kurobe, *Heterocycles* **1989**, *28*, 565; e) J. P. Kutney, F. J. Lopez, S.-P. Huang, H. Kurobe, R. Flogaus, K. Piotrowska, *Can. J. Chem.* **1991**, *69*, 2993; f) K.-F. Cheng, Y.-L. V. Hong, *Tetrahedron Lett.* **1991**, *32*, 1045; g) J. Bergman, L. Venemalm, *Tetrahedron* **1992**, *48*, 759; h) K. J. Henry, P. A. Grieco, *J. Chem. Soc. Chem. Commun.* **1993**, 510; i) M. Ishikura, K. Imaizumi, N. Katagiri, *Heterocycles* **2000**, *53*, 553; j) M. Ishikura, K. Imaizumi, N. Katagiri, *Heterocycles* **2000**, *53*, 2201.
[13] a) K.-F. Cheng, T.-Y. Chan, T.-F. Lai, Y.-C. Kong, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3317; b) M. Ishikura, *Heterocycles* **1995**, *41*, 1385.

Received: June 7, 2007
Published Online: August 10, 2007

