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Directed Lithiation of *N*-Benzenesulfonyl-3-bromopyrrole. Electrophile-Controlled Regioselective Functionalization via Dynamic Equilibrium between C-2 and C-5 Lithio Species

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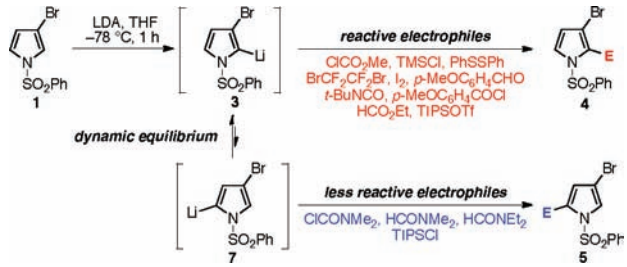
ABSTRACT



Directed lithiation of *N*-benzenesulfonyl-3-bromopyrrole (1) with LDA in THF at −78 °C generated C-2 lithio species 3 selectively. Reactions of 3 with reactive electrophiles produced the corresponding 2-functionalized pyrroles 4. On the other hand, quenching with less reactive electrophiles generated the corresponding 5-substituted pyrroles 5. The latter unusual functionalization at C-5 could be rationalized by dynamic equilibrium between C-2 and C-5 lithio species.

Directed lithiation[1] of N-protected pyrroles followed by reaction with electrophiles has been employed as a reliable way to produce 2-substituted pyrroles. Although a number of N-protecting groups have been developed as the directing groups to facilitate α-lithiation of the pyrrole ring,[2] C-2 versus C-5 regioselectivity in the lithiation of 3-substituted pyrroles has been modestly investigated. In 1985, Iwao and Kuraishi reported for the first time that *N*,*N*-diethyl-1-

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(1) For reviews, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 155–302. (c) Gray, M.; Tinkl, M.; Snieckus, V. *Comprehensive Organometallic Chemistry II*; McKillop, A., Ed.; Pergamon: Oxford, 1995; Vol. 11, Chapter 1. (d) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560. (e) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002. (f) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.

(2) (a) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157–164 (DG = Boc and SO_2Ph). (b) Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3760–3761 (DG = NMe_2). (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630–633 (DG = SEM). (d) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203–205 (DG = SEM). (e) Katritzky, A. R.; Akutagawa, K. *Org. Prep. Proc. Int.* **1988**, *20*, 585–590 (DG = CO_2Li). (f) Gharpure, M.; Stoller, A.; Bellamy, F.; Firnau, G.; Snieckus, V. *Synthesis* **1991**, 1079–1082 (DG = CONLi*t*-Bu). (g) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587–3595 (DG = SO_2NMe_2).

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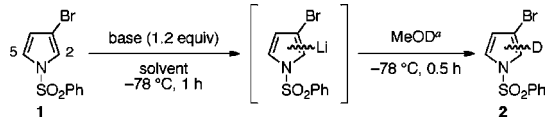
methylpyrrole-3-carboxamide could be lithiated at C-2 with *sec*-BuLi-TMEDA.[3] On the other hand, Meijer and co-workers demonstrated that the lithiation of *N*-Boc-3-hexylpyrrole proceeded at C-5 selectively on treatment with lithium 2,2,6,6-tetramethylpiperidide (LTMP).[4] Demont and co-workers indicated that the regioselectivity of the lithiation of 3-benzenesulfonylpyrroles depended on the nature of the base (LTMP, *n*- or *sec*-BuLi) and the N-protecting group (Boc, SO_2Ph, SEM).[5] Robertson et al. showed that 3-chloro-*N*-(*p*-toluenesulfonyl)pyrrole was lithiated at C-2 with *n*-BuLi.[6] Recently, we have reported that *N*-benzenesulfonyl-3-bromopyrrole (**1**) could also be lithiated at C-2 with lithium diisopropylamide (LDA), and this key reaction has been employed in the synthesis of rationally designed analogues of the antitumor marine alkaloid lamellarin D.[7] In this letter, we describe detailed investigations on the directed lithiation of **1**.

First, we investigated regioselectivity via deuteration experiments (Table 1). Treatment of **1** with 1.2 equiv of LDA in THF at −78 °C for 1 h followed by quenching with MeOD gave the deuterated pyrrole **2** in 91% yield after chromatographic purification. The 400 MHz ^{1}H NMR analysis of the product indicated 72% total deuterium incorporation and excellent C-2 regioselectivity[8] (entry 1). A longer lithiation time (3 h) did not improve the total deuterium incorporation (entry 2). Utilization of LTMP instead of LDA resulted in preferential deuteration at C-5 rather than C-2 (entry 3). More bulky LTMP might deprotonate at the less congested C-5 preferentially. Lithium isopropylcyclohexylamide (LICA) displayed a selectivity similar to that of LDA (entry 4). Lithium hexamethyldisilazide (LHMDS) was totally ineffective for the lithiation of **1** apparently due to its lower basicity[9] (entry 5). Utilization of diethyl ether or toluene instead of THF increased C-5 selectivity (entries 6−9). These results might be accounted for by higher aggregation of the amide bases in the less polar solvents.[10] The bulky aggregates might deprotonate at the less congested C-5 preferentially. Although deuterium incorporation was quite modest,[11] selective C-5 lithiation was achieved using LTMP as a base in toluene (entry 9). Unfortunately, however, use of more base (2.4 equiv) or a longer reaction time (12 h) resulted in the loss of high C-5 selectivity (entries 10 and 11). Further attempts to effect selective C-5 lithiation were not performed because we discovered a practical Br−Li exchange route to generate the C-5 lithio species (vide infra).

Table 1. Survey of Reaction Conditions for Regioselective Lithiation of **1**



				deuterium incorporation[c]			
entry	base	solvent	**2** yield (%)[b]	C-2 (%)	C-5 (%)	total (%)	ratio (C-2:C-5)
1	LDA	THF	91	70	2	72	97:3
2[d]	LDA	THF	92	70	3	73	96:4
3	LTMP	THF	95	27	58	85	32:68
4	LICA	THF	95	65	4	69	94:6
5	LHMDS	THF	94	0	0	0	–
6	LDA	Et_2O	97	17	31	48	35:65
7	LDA	toluene	99	32	25	57	56:44
8	LTMP	Et_2O	96	15	39	54	28:72
9	LTMP	toluene	98	∼0	11	11	1:>99
10[e]	LTMP	toluene	98	3	18	21	14:86
11[f]	LTMP	toluene	94	15	36	51	29:71

[a] MeOD (3.0 equiv) was added as a THF solution. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis (400 MHz). [d] Lithiation for 3 h. [e] 2.4 equiv of LTMP. [f] Lithiation for 12 h.

Having established the conditions for efficient and selective C-2 lithiation, we next examined the functionalization of the lithiated **1**. Thus, **1** was treated with 1.2 equiv of LDA in THF at −78 °C for 1 h, and the resulting C-2 lithio species **3** was reacted with 1.8 equiv of an appropriate electrophile under the conditions A (−78 °C, 1 h) or B (−78 °C, 1 h → 0 °C, 3 h). After the usual workup, products were isolated by column chromatography. As shown in Table 2, in the reactions with methyl chloroformate, chlorotrimethylsilane, diphenyl disulfide, 1,2-dibromo-1,1,2,2-tetrafluoroethane, iodine, *p*-methoxybenzaldehyde, and *tert*-butyl isocyanate, the corresponding 2-functionalized pyrroles **4a**−**g** were obtained exclusively in excellent yields (entries 1−8). In the reactions with *p*-methoxybenzoyl chloride, however, the unexpected 5-acylated pyrrole **5h** was detected as a minor product by ^{1}H NMR analysis (entries 9 and 10). More surprisingly, when dimethylcarbamoyl chloride was used as an electrophile, 5-functionalized pyrrole **5i** was generated as the major product (entry 11). Similar C-5-preferred formylation was also observed in the reaction with *N*,*N*-dimethylformamide (entry 12). Especially when *N*,*N*-diethylformamide was reacted under the conditions B, **5j** was isolated as the sole product (entry 14). In contrast, the reaction with ethyl formate, a more reactive formylating agent for organolithiums, gave the normal 2-formylated isomer **4j** exclusively (entry 15). This striking change of regioselectivity dependent on the reactivity of electrophiles was also observed in the silylation reactions with sterically demanding triisopropylsilyl chloride and triisopropylsilyl triflate (entries 16−19). The less reactive

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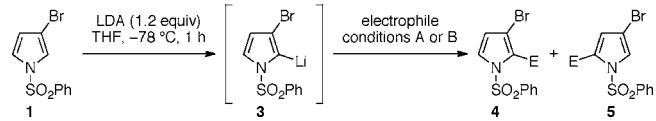
(4) Groenendaal, L.; Van Loo, M. E.; Vekemans, J. A. J. M.; Meijer, E. W. *Synth. Commun.* **1995**, *25*, 1589–1600.
(5) Bailey, N.; Demont, E.; Garton, N.; Seow, H.-X. *Synlett* **2008**, 185–188.
(6) Robertson, J.; Kuhnert, N.; Zhao, Y. *Heterocycles* **2000**, *53*, 2415–2420.
(7) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143–8153.
(8) *Ortho*-directing effect of bromine has been reported, see: (a) Arroyo, Y.; Rodríguez, J. F.; Sanz-Tejedor, M. A.; Santos, M. *Tetrahedron Lett.* **2002**, *43*, 9129–9132. (b) Mongin, F.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2771–2777. (c) Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 5384–5387.
(9) The pK_a values of LTMP, LDA, and LHMDS are 37.3, 35.7, and 29.5, respectively. See: ref 1c.
(10) Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 199–202, and references cited therein.
(11) LTMP was precipitated as white crystalline solid at −78 °C. This might be the reason for inefficient lithiation of **1** with LTMP in toluene.

Table 2. Selective C-2 Lithiation of **1** Followed by Reactions with Electrophiles



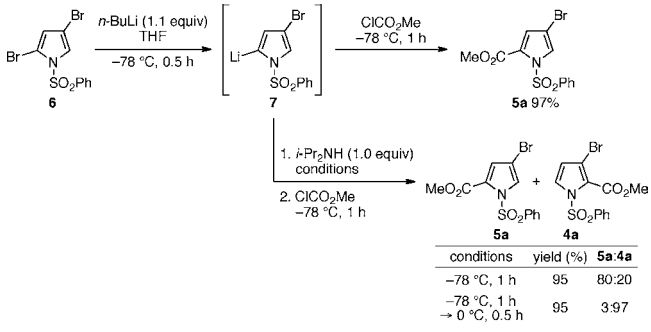
entry	electrophile[a]	conditions[b]	products	E	yield (%)[c]	ratio (**4**:**5**)[d]
1	$ClCO_2Me$	A	**4a**,**5a**	CO_2Me	86	>99:1
2	TMSCl	A	**4b**,**5b**	TMS	84	>99:1
3	PhSSPh	A	**4c**,**5c**	SPh	99	>99:1
4	$BrCF_2CF_2Br$	A	**4d**,**5d**	Br	90	>99:1
5	I_2	A	**4e**,**5e**	I	99	>99:1
6	*p*-$MeOC_6H_4CHO$	A	**4f**, **5f**	CH(OH)(C_6H_4OMe-*p*)	86	>99:1
7	*t*-BuNCO	A	**4g**,**5g**	CONH*t*-Bu	24	>99:1
8	*t*-BuNCO	B	**4g**,**5g**	CONH*t*-Bu	95	>99:1
9	*p*-$MeOC_6H_4COCl$	A	**4h**,**5h**	COC_6H_4OMe-*p*	15	86:14
10	*p*-$MeOC_6H_4COCl$	B	**4h**,**5h**	COC_6H_4OMe-*p*	70	97:3
11	$ClCONMe_2$	B	**4i**, **5i**	$CONMe_2$	22	16:84
12	$HCONMe_2$	A	**4j**, **5j**	CHO	76	35:65
13	$HCONEt_2$	A	**4j**, **5j**	CHO	4	28:72
14	$HCONEt_2$	B	**4j**, **5j**	CHO	24	1:>99
15	HCO_2Et	A	**4j**, **5j**	CHO	71	>99:1
16	TIPSCl	A	**4k**,**5k**	TIPS	1	1:>99
17	TIPSCl	B	**4k**,**5k**	TIPS	45	1:>99
18	TIPSOTf	A	**4k**,**5k**	TIPS	59	86:14
19	TIPSOTf	B	**4k**,**5k**	TIPS	82	95:5

[a] Electrophile (1.8 equiv) was added as a THF solution. [b] A: −78 °C, 1 h. B: −78 °C, 1 h → 0 °C, 3 h. [c] Isolated yield. [d] Determined by ^1H NMR analysis (400 MHz).

chloride was reacted at C-5 exclusively, whereas the more reactive triflate was combined at C-2 selectively.

To explain these unusual electrophile-controlled regioselective functionalizations[12] of **3**, the following experiments were carried out (Scheme 1). Treatment of *N*-benzenesulfonyl-2,4-dibromopyrrole (**6**)[13] with 1.1 equiv of *n*-BuLi in THF at −78 °C for 0.5 h followed by a reaction with methyl chloroformate gave 5-methoxycarbonylated pyrrole **5a** in excellent yield. This result clearly indicated that the C-5 lithio species **7** was generated via regioselective Br−Li exchange, and this species did not isomerize to the corresponding C-2 lithio species **3** under the reaction conditions. On the other hand, quenching the lithio species after reaction with 1.0 equiv of diisopropylamine at −78 °C for 1 h produced a mixture of **5a** and **4a** (80:20) in 95% yield. Moreover, **4a** was obtained in excellent yield and in high purity by warming the mixture of **7** and diisopropylamine in THF to 0 °C and quenching with methyl chloroformate.

Scheme 1. Reactivity of 5-Lithiopyrrole **7** Generated by Regioselective Br−Li Exchange of **6**



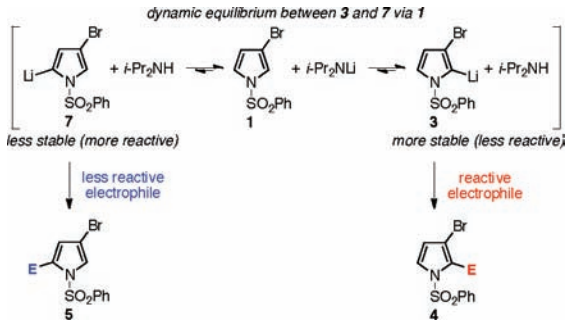
The results shown above suggest that the lithio species **3** and **7** are in dynamic equilibrium[14] via **1** in the presence of diisopropylamine (Scheme 2). The C-2 lithio species **3** is apparently more stable than the C-5 lithio species **7**. However, **3** may be less reactive to electrophiles than **7** owing to the steric and electron-withdrawing effects of the adjacent 3-bromo group. In the reaction with reactive electrophiles such as methyl chloroformate and methyl formate, the reaction rate between **3** and electrophiles may be much faster than the equilibration rate from **3** to **7**. This difference allows the selective functionalization at C-2 to yield **4**. On the other hand, in the reactions with less reactive electrophiles such as *N*,*N*-diethylformamide and triisopro-

(12) Similar electrophile-controlled regioselective functionalization has been reported in the directed lithiation of the 1,3-dimethoxybenzene−$Cr(CO)_3$ complex and related compounds. See: (a) Schmalz, H.-G.; Volk, T.; Bernicke, D.; Huneck, S. *Tetrahedron* **1997**, *53*, 9219–9232. (b) Michon, C.; Murai, M.; Nakatsu, M.; Uenishi, J.; Uemura, M. *Tetrahedron* **2009**, *65*, 752–756.

(13) Compound **6** was readily prepared in two steps from *N*-benzenesulfonylpyrrole. See Supporting Information. We thank Mariko Okamoto for the synthesis of **6**.

(14) Dynamic equilibrium of organolithiums has been observed in sparteine-mediated enantioselective functionalization of benzylic anions. See ref 1d.

Scheme 2. Rationale for Electrophile-Controlled Regioselective Functionalization of **1**



pylsilyl chloride, the equilibration rate may be faster than the reaction rate with the electrophiles. As a result, such electrophiles react with more reactive **7** rather than **3** to give the unusual 5-functionalized pyrrole **5** preferentially.

In conclusion, we have discovered that *N*-benzenesulfonyl-3-bromopyrrole (**1**) can be lithiated at C-2 selectively with LDA in THF at −78 °C. The C-2 lithio species **3** thus generated was trapped with a number of reactive electrophiles to give 2-functionalized pyrrole **4** in good yields. On the other hand, **3** was reacted with less reactive electrophiles to give 5-functionalized pyrrole **5**. The unusual electrophile-controlled regioselective functionalization of **3** was rationalized by assuming dynamic equilibrium between C-2 and C-5 lithio species. The reactions described herein may be useful for the regioselective synthesis of a variety of 2,3- and 2,4-disubstituted pyrroles[15] in view of the further possibility to functionalize the pyrrole ring using specific reactivity bromine.

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Supporting Information Available: Experimental details including analytical and spectroscopic data and ^{1}H NMR and ^{13}C NMR spectra of all compounds synthesized in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For regioselective syntheses of 2,3- and 2,4-disubstituted pyrroles, see: (a) Franc, C.; Denonne, F.; Cuisinier, C.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 4555–4558. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825. (c) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970–5978. (d) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004–3007.