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A simple and efficient method for synthesis of 5-substituted 2′-deoxyuridine nucleosides using metal–halogen exchange reaction of 5-iodo-2′-deoxyuridine sodium salt

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Treatment of the sodium salt of 2′-deoxy-3′, 5′-bis-*O*-(*tert*-butyldimethylsilyl)-5-iodouridine (3) with *n*-BuLi effected regioselective lithiation at the 5-position and the following reaction with various electrophiles afforded 5-substituted 2′-deoxyuridines including 1b, the precursor of stable spin-labeled 1a, in good yields.

5-Substituted pyrimidines are an important class of nucleoside and their broad spectrum of biological activity such as antiviral and anticancer activities has received considerable attention. The introduction of substituents with specific functions and reporter groups into the 5-position of uracil is also important for the development of antisense agents and DNA probes.[1] A variety of methods for synthesis of 5-substituted 2′-deoxyuridines have been reported including the reaction of 5-lithiated species formed from **2**[2] or 5-halo-2′-deoxyuridine derivatives[3] and palladium-catalysed reaction with 5-halo 2′-deoxyuridine derivatives.[4] 5-Lithiated 2′-deoxyuridine is a useful intermediate for reacting with various electrophiles, *e.g.* alkyl halides, carbonyl compounds, disulfides and so on, however its formation is less effective compared to the corresponding ribonucleosides. Lithiation of **2** with *sec*-BuLi in the presence of TMEDA gave 5-lithiated species[2a] and this procedure was applied to the synthesis of ^{13}C-methyl-labeled thymidine.[2b] Lithium–halogen exchange reaction of 5-halo 2′-deoxyuridine derivatives with *n*-BuLi was also used for regioselective formation of 5-lithiated species. However, this method gave 5-substituted products in lower yields especially in the use of 5-iodo derivatives as a substrate and a considerable amount of dehalogenated uridine formed.[3c,d] In these lithiation strategies, excess bases were used due to the presence of the unprotected imide moiety. In the course of our work on the synthesis of *N*-*tert*-butylaminoxyl nucleosides,[5] we planned to synthesise 5-*N*-*tert*-butylhydroxylamino-2′-deoxyuridine (**1b**), the precursor of 5-*N*-*tert*-butylaminoxyl 2′-deoxyuridine (**1a**), by the reaction of 5-lithiated 2′-deoxyuridine with 2-methyl-2-nitrosopropane (MNP) (Fig. 1). We found that lithiation of sodium salt of **3** and successive reactions with MNP and several electrophiles afforded **1a** in good yield and 5-substituted 2′-deoxyuridines in improved yields compared to previous reports. We here report this simple and efficient method for synthesis of 5-substituted 2′-deoxyuridines.

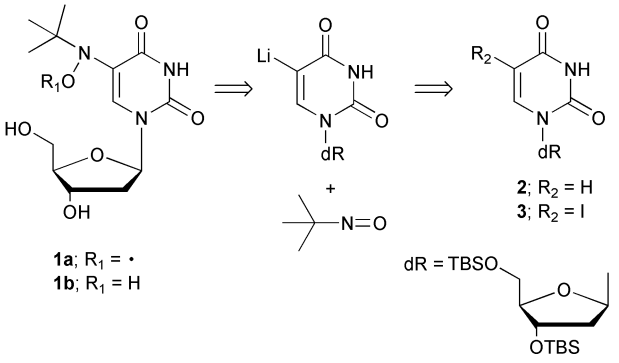
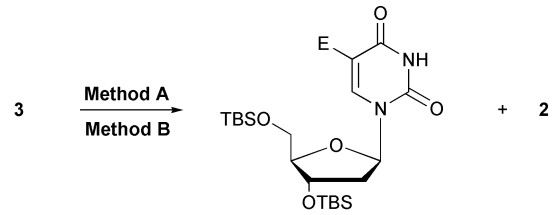


Fig. 1

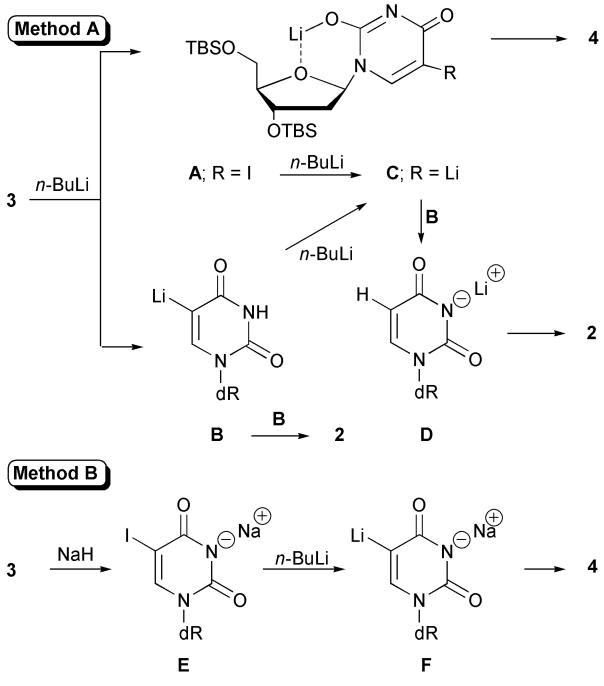
First, direct lithiation of **2** with *sec*-BuLi in the presence of TMEDA followed by the reaction with MNP was attempted for the synthesis of **4**. However, **4** was not obtained and **2** was recovered. As an alternative, we studied a lithium–halogen exchange reaction using 5-iodo-2′-deoxyuridine (**3**) to prepare 5-lithiated species. Treatment of **3** with 2 equiv. of *n*-BuLi followed by the reaction with MNP gave **4**† in 19% and deiodinated **2** was formed in 80% (Scheme 1; Method A).



Method A: 1) *n*-BuLi (2 equiv.), THF, -78°C. 2) MNP (6 equiv.) . **4**; 19%, **2**; 80%
Method B: 1) NaH (1.5 equiv.), THF, 0°C. 2) *n*-BuLi (1.2 equiv.), -78°C. 3) MNP (6 equiv.) **4**; 72%. **2**; 10%

Scheme 1

Unreacted dilithio compound (intermediate **C** in Scheme 2) could be converted to **2** by aqueous workup.[3d] We reasoned that abstraction of imide proton and lithium–iodo exchange could be competitive (formation of intermediates **A** and **B**) at the early stage of the reaction. If the imide proton of **B** was abstracted by



Scheme 2

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B itself and coexisting **C** at 5-position, **2** and **D** formed, which could not be converted to reactive **C** with *n*-BuLi. In fact, treatment of **3** with 1 equiv. of *n*-BuLi followed by aqueous workup gave **2** (62%) and recovered **3** (35%), which suggests that lithiation and deprotonation are competitive. Thus, **3** was treated with 1.5 equiv. of NaH in THF at rt in order to remove the imide proton (*in situ* imide protection). After concentration of the solvent, ^{1}H NMR spectrum was measured.† Disappearance of the imide proton and upfield shift of H6 (8.09 to 7.69 ppm) were observed to indicate formation of intermediate **E**. Its treatment with H_2O resulted in quantitative recovery of **3**. Finally, successive treatment of **3** with 1.5 equiv. of NaH then 1.2 equiv. of *n*-BuLi followed by reaction with MNP gave **4** in 72% yield presumably *via* intermediate **F** (Scheme 1; Method B). Deiodinated **2** formed in 10%, however 6-substituted product was not formed. Treatment of **4** with TBAF in THF afforded **1b** in 85% yield.

Next, we synthesised 5-substituted 2′-deoxyuridines *via* Method B to investigate the scope and limitations of this method.‡ Reactions with MeI, CD_3OD, TMSCl, PhCHO, and MeSSMe proceeded with ease to give 5-substituted **5–9** in improved yields, respectively (Table 1).[2] In all cases, regioselectivity of reactions was controlled and 6-substituted products were not obtained. Deiodinated **2** formed in reactions with MeI, CD_3OD, and TMSCl, but its yield and ratio to 5-substituted products decreased. Reactions with more reactive PhCHO and MeSSMe gave products in higher yields and did not give **2**.

We showed that competitive imide proton abstraction and lithium–iodo exchange took place by treatment of **3** with *n*-BuLi, which led to decreased yield of product due to the concomitant formation of deiodinated **2** as a major product. *In situ* protection of imide moiety with NaH effected the subsequent lithium–iodo exchange reaction of **3** with *n*-BuLi to give 5-lithiated 2′-deoxyuridine derivatives regioselectively. The method we report here, though previously untried, is easy and provides a general, regioselective and efficient synthetic method of 5-substituted 2′-deoxyuridines.

Table 1

n-BuLi (equiv.)	Reagent	**E**	Product	Yield (%)	**2** (%)
3	MeI	Me	**5**	81	7
1.2	CD_3OD	D	**6**	64	9
1.2	TMSCl	TMS	**7**	62	12
1.2	PhCHO	PhCH(OH)[a]	**8**	79	0
3	MeSSMe	SMe	**9**	85	0

[a] 1 : 1 diastereo mixture

Notes and references

† Spectroscopic data for **4** and intermediate **E**; **4**; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1H, D_2O exchanged), 7.56 (s, 1H), 6.85 (br s, 1H, D_2O exchanged), 6.27 (dd, J = 8.0, 6.0 Hz, 1H), 4.38 (t, J = 2.8 Hz, 1H), 3.92 (d, J = 2.6 Hz, 1H), 3.72 (dt, J = 11.3, 7.7 Hz, 2H), 2.26 (m, 1H), 2.00 (m, 1H), 1.14 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H); HRMS (FAB) m/z calcd for $C_{25}H_{50}O_6N_3Si_2$ ([M + H]$^+$) 543.3238, found 543.3258. **E**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 6.18 (br s, 1H), 4.32 (br s, 1H), 3.67–3.81 (m, 3H), 2.25 (m, 1H), 1.83 (m, 1H), 0.90 (s, 9H), 085 (s, 9H), 0.08 (s, 6H), 0.04 (s, 6H).

‡ A typical experiment is as follows: to a THF (10 mL) solution of **3** (1.0 g, 1.72 mmol) at rt was added 1.5 equiv. of NaH and the resulting mixture was stirred for 30 min. The reaction mixture was cooled to −78 °C and 1.2–3 equiv. of *n*-BuLi was added. After 15 min, an appropriate electrophile (6 equiv.) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h.

1 (*a*) R. W. Wagner, M. D. Matteucci, D. Grant, T. Huang and B. C. Froehler, *Nat. Biotechnol*., 1996, **14**, 840–844; (*b*) L. E. Heystek, H.–Q. Zhou, P. Dande and B. Gold, *J. Am. Chem. Soc*., 1998, **120**, 12165–12166; (*c*) D. J. Hurley and Y. Tor, *J. Am. Chem. Soc*., 1998, **120**, 2194–2195.

2 (*a*) R. W. Armstrong, S. Gupta and F. Whelihan, *Tetrahedron Lett*., 1989, **30**, 2057–2060; (*b*) M. Ahmadian and D. E. Bergstrom, *Nucleosides Nucleotides*, 1998, **17**, 1183–1190; (*c*) H. Hayakawa, H. Tanaka, K. Obi, M. Itoh and T. Miyasaka, *Tetrahedron Lett*., 1987, **28**, 87–90.

3 (*a*) T. L. V. Ulbricht, *Tetrahedron*, 1959, **6**, 225–231; (*b*) L. Pichat, B. Masse, J. Deshcamps and P. Dufay, *Bull. Soc. Chim. Fr*., 1971, **6**, 2102–2109; (*c*) M. M. Alauddin and P. S. Conti, *Tetrahedron*, 1994, **50**, 1699–1706; (*d*) P. L. Coe, M. R. Harnden, A. S. Jones, S. A. Noble and R. T. Walker, *J. Med. Chem*., 1982, **25**, 1329–1334.

4 (*a*) M. J. Robins and P. J. Barr, *Tetrahedron Lett*, 1981, **22**, 421–424; (*b*) E. De Clercq, J. Descamps, J. Balzarini, J. Giziewicz, P. J. Barr and M. J. Robins, *J. Med. Chem*., 1983, **26**, 661–666; (*c*) F. W. Hobbs, *J. Org. Chem*, 1989, **54**, 3420–3422; (*d*) M. J. Robins and P. J. Barr, *J. Org. Chem*, 1983, **48**, 1854–1862; (*e*) P. Heredewijn, L. Kerremans, P. Wegerinck, F. Vandendiessche and A. Van Aerschot, *Tetrahedron Lett*., 1991, **32**, 4397–4400; (*f*) H. Hirota, Y. Kitade, Y. Kanbe, Y. Isobe and Y. Maki, *Synthesis*, 1993, 213–215.

5 (*a*) M. Aso, K. Norihisa, M. Tanaka, N. Koga and H. Suemune, *J. Chem. Soc., Perkin Trans. 2*, 2000, **8**, 1637–1638; (*b*) M. Aso, T. Ikeno, K. Norihisa, M. Tanaka, N. Koga and H. Suemune, *J. Org. Chem*., 2001, **66**, 3513–3520.