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HEXAMETHYLDISILAZANE−PROMOTED SONOGASHIRA REACTION OF POLYFUNCTIONALIZED *N*-CONTAINING HETEROCYCLES

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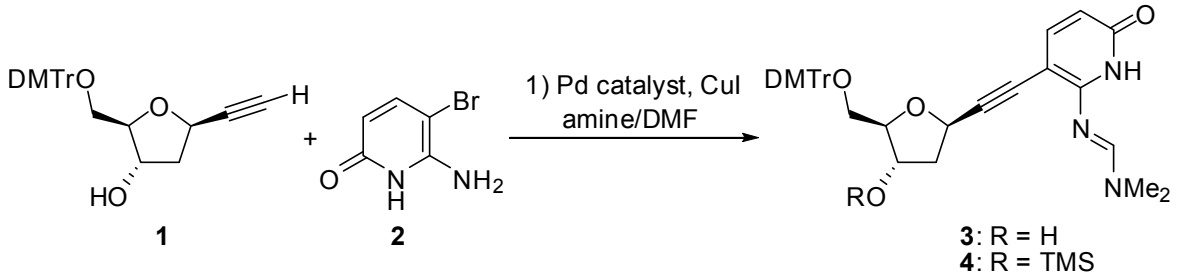
Abstract – 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) was found to be an efficient solvent for Sonogashira reaction. For the synthesis of *C*-nucleosides, Sonogashira reaction of ethynyldeoxyriboside with halogenated pyrimidine or pyridine derivatives could be improved by the use of an HMDS−DMF mixed solvent. In situ protection of hydroxy and amino groups by the solvent system may play an important role for the improvement.

Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

When one would like to assemble two organic moieties by an acetylene bond, Sonogashira reaction is one of the most versatile strategies.[1] However, sometimes undesirable side reactions accompany with the coupling reaction, such as nucleophilic addition to triple bonds and deprotonation of substituents on substrates. Common solvents for Sonogashira reaction are organic amines, which can behave as a nucleophile. When the acidic substituent is deprotonated, its conjugated base may be nucleophilic. It is also troublesome that the substrates may be labile to bases at long reaction time. Recently, our group has developed artificial DNAs, in which two kinds of heterocyclic moieties are linked by acetylene bonds: one is an *N*-containing heterocycle and the other is a deoxyribose.[2,3] During the course of this study, we sometimes have faced low yields in Sonogashira reaction, and the improvement had to be required. In this communication, we describe the use of HMDS as an effective promoter as well as a solvent for Sonogashira reaction of polyfunctionalized *N*-containing heterocycles. The key to our success is that in situ protection of the polar substituents took place in this solvent and that the protective group could be removed during the work-up.

As mentioned above, our object was to bind *N*-containing heterocycles and deoxyribose moieties by an acetylene bond to form novel *C*-nucleosides. The ethynyldeoxyribose is represented as 4,4'-dimethoxytrityl- (DMTr-) protected ethynyl 2-deoxy-β-D-ribofuranoside **1**.[4,5] A bromopyridone derivative, 6-amino-5-bromo-2(1*H*)-pyridone **2** was attempted to couple with this terminal acetylene. The optimization of reaction conditions is described in Table 1. In triethylamine, no or little coupled product could be observed (entries 1, 2). On the other hand, when HMDS was used as the solvent, *C*-nucleotide **3** and its TMS-protected derivative **4** was obtained (entry 3). The TMS group of **4** was transferred from HMDS.[3c,6,7] Through the optimization, a higher reaction temperature and Pd(0) catalysts were found to give **3** in a better yield after desilylation (entries 7, 8).[8] It is remarkable that the amino group on the pyridone ring of **3** was protected by dimethylaminomethylene group, which was transferred from DMF. Products with free NH_2 group were not detected, and the DMTr groups were preserved.

Table 1. Optimization of Sonogashira reaction between **1** and bromopyridone **2**

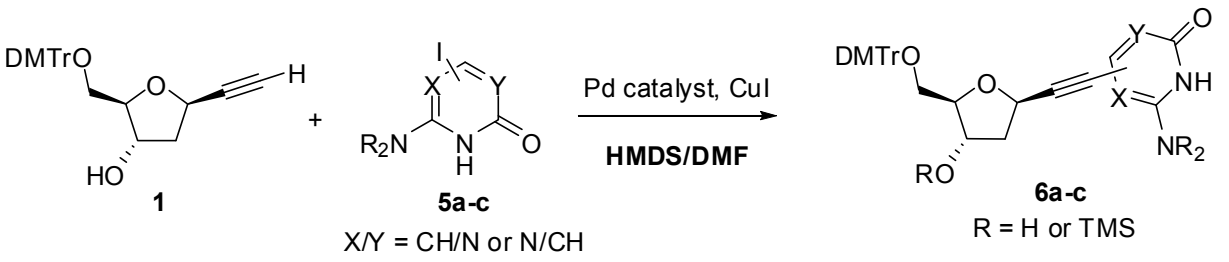


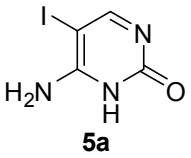
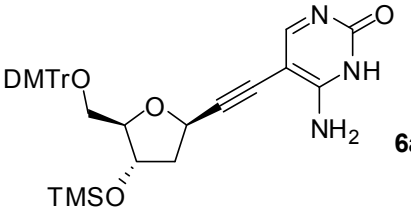
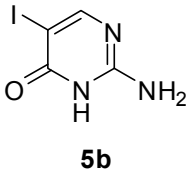
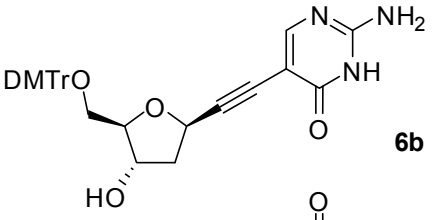
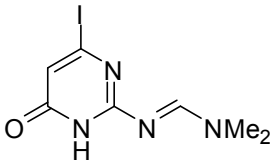
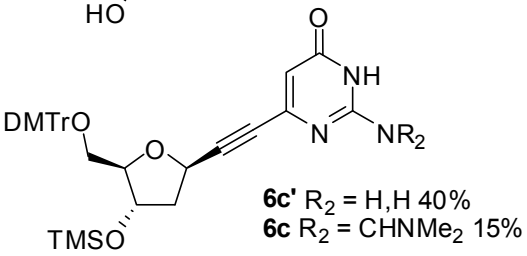
entry	reaction conditions				product [%][a]	
	amine	reagents (mol%)	temp [°C]	time [h]	**3**	**4**
1	Et_3N	$PdCl_2(PPh_3)_2$ (1), CuI (1)	90	4.5	n.d.[b]	n.d.[b]
2	Et_3N	$Pd_2(dba)_3$•$CHCl_3$ (4), PPh_3 (8), CuI (1)	90	3.5	trace	n.d.[b]
3	HMDS	$PdCl_2(PPh_3)_2$ (4), CuI (1)	90	3.5	11	31
4	HMDS	$Pd(PPh_3)_4$ (4), CuI (1)	90	7	37[c]	
5	HMDS	$Pd_2(dba)_3$•$CHCl_3$ (4), PPh_3 (8), CuI (1)	90	6.5	60[c]	
6	HMDS	$PdCl_2(PPh_3)_2$ (4), CuI (1)	120	3.5	30[c]	
7	HMDS	$Pd(PPh_3)_4$ (4), CuI (1)	120	2.5	70[c]	
8	HMDS	$Pd_2(dba)_3$•$CHCl_3$ (4), PPh_3 (8), CuI (1)	120	1	73[c]	

[a] Isolated yields. [b] Not detected. [c] Yields after desilylation by TBAF treatment.

Next, several kinds of iodopyrimidinone derivatives **5a-c** were coupled with **1** by Sonogashira reaction in HMDS/DMF (Table 2).[2]

Table 2. Sonogashira reaction of **1** with iodopyrimidinones **5a-c** in HMDS/DMF



entry	iodopyrimidine	reaction conditions	product[a]
1	 **5a**	$PdCl_2(PPh_3)_2$, CuI, HMDS/DMF, rt, 16 h	 **6a** 79%
2	 **5b**	1) $PdCl_2(PPh_3)_2$, CuI, HMDS/DMF, rt, 15 h 2) NH_4OH, pyridine, rt, 2 h	 **6b** 85%[b]
3	 **5c**	$Pd_2(dba)_3$, PPh_3, CuI HMDS/DMF, rt, 3 h then 60 °C, 2.5 h	 **6c'** R_2 = H,H 40% **6c** R_2 = $CHNMe_2$ 15%

[a] Isolated yields are shown. [b] Yield after desilylation by treatment with NH_4OH.

Iodine atoms could be substituted at a room temperature to give targeted *C*-nucleosides **6a-c** in good yields. The 3'-hydroxy groups on the deoxyribose ring were protected with TMS groups and the DMTr groups were preserved. These TMS groups must be transferred from HMDS and could be removed during the work up with aqueous ammonia.

The combination of HMDS and DMF behaved not only as a reaction solvent but also a protecting agent for polar groups. Probably quite low nucleophilicity of HMDS and in situ protection of reactive groups would suppress side reactions and improved the product yields. Thus, the combination of HMDS and DMF was shown to be an efficient solvent system for Sonogashira reaction of polar substrates. These findings would enlarge the scope of Sonogashira reaction, and the utilization of solvents also as protecting agents would be an interesting maneuver in organic syntheses.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For reviews for Sonogashira reaction, see: K. Sonogashira, 'Metal-catalyzed Cross-coupling Reactions,' ed. by F. Diederich and P. J, Stang, WILEY-VCH, Weinheim, 1998, pp. 203−229; R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874.
2. Y. Doi, J. Chiba, T. Morikawa, and M. Inouye, *J. Am. Chem. Soc.*, 2008, **130**, 8762.
3. For recent synthetic examples of alkynyl *C*-nucleosides by Sonogashira reaction, see: (a) T. Bobula, M. Hocek, and M. Kotora, *Tetrahedron*, 2010, **66**, 530; (b) M. F. A. Adamo and R. Pergoli, *Org. Lett.*, 2007, **9**, 4443; (c) D. Heinrich, T. Wagner, and U. Diederichsen, *Org. Lett.*, 2007, **9**, 5311. In ref. 3c, a two-step procedure (persilylation of 5-iodocytosine in HMDS and Sonogashira reaction in DIPEA/DMF) was reported.
4. M. Takase, T. Morikawa, H. Abe, and M. Inouye, *Org. Lett.*, 2003, **5**, 625.
5. K. Fujimoto, S. Aizawa, I. Oota, J. Chiba, and M. Inouye, *Chem. Eur. J.*, 2010, **16**, 2401; K. Fujimoto, S. Yamada, and M. Inouye *Chem. Commun.*, 2009, 7164; J. Chiba, S. Takeshima, K. Mishima, H. Maeda, Y. Nanai, K. Mizuno, and M. Inouye, *Chem. Eur. J.*, 2007, **13**, 8124.
6. HMDS is known to work as a silylating agent with the presence of acidic catalysts: P. G. M. Wuts and T. W. Greene, 'Protective Groups in Organic Synthesis,' A John Wiley & Sons, Inc., Hoboken, 2007, p. 171.
7. For recent examples of persilylation of thiouracil derivatives in HMDS solutions, see: N. A. Al-Awadi, Y. A. Ibrahim, and M. R. Ibrahim, *Carbohyd. Res.*, 2009, **344**, 2322. M. Carlucci, E. Kierzek, A. Olejnik, D. H. Turner, and R. Kierzek, *Biochemistry*, 2009, **48**, 10882. See also ref. 3c.
8. The preparation of **3**. Typical procedure for Sonogashira reaction in HMDS−DMF (entry 8 in Table 1). A mixture of 2-(4,4'-dimethoxytrityloxymethyl)-3-hydroxytetrahydrofuran **1**[2] (50 mg, 0.11 mmol), 6-amino-5-bromo-2(1*H*)-pyridone **2** (21 mg, 0.11 mmol), $Pd_2(dba)_3$•$CHCl_3$ (4.4 mg, 4.5 μmol), CuI (0.22 mg, 1.1 μmol), PPh_3 (2.4 mg, 9 μmol), HMDS (0.5 mL), DMF (0.5 mL) was stirred at 120 °C for 1 h under an argon atmosphere. The resulting mixture was diluted with THF (50 mL) and AcOEt (50 mL), and subsequently washed with brine × 3, a 1% citric acid solution, a saturated aqueous $NaHCO_3$ solution, and brine once more. The organic layer was concentrated with a rotary evaporator, and the resulting residue was dissolved with THF (2 mL) and water (0.1 mL), and TBAF (1.0 M in THF, 0.12 mL) was added. After stirring at room temperature for 2 h,

the mixture was concentrated with a rotary evaporator. The resulting residue was subjected to silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 20:1) to obtain (2*R*,3*S*,5*R*)-5-(6-(dimethylaminomethyleneamino)-2(1*H*)-pyridinon-5-ylethynyl)-2-(4,4'-dimethoxytrityloxymethyl)-3-hydroxytetrahydrofuran (**3**, 50 mg, 73%) as a brown viscous oil. IR (KBr) ν 3399, 2927, 2223, 1637, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.43 (d, J = 8.7 Hz, 2 H), 7.33−7.14 (m, 8 H), 6.79 (d, J = 8.4 Hz, 4 H), 5.98 (d, J = 9.3 Hz, 1 H), 4.96 (t, J = 8.0 Hz, 1 H), 4.40 (s, 1 H), 3.98 (s, 1 H), 3.75 (s, 6 H), 3.34−3.02 (m, 2 H), 3.11 (s, 3 H), 3.08 (s, 3 H), 2.21−2.18 (m, 2 H); HRMS (ESI) Calcd for $C_{36}H_{37}N_3NaO_6$ ($M + Na^+$): 630.2580; Found: 630.2598.