ORGANIC LETTERS

2010
Vol. 12, No. 1
120−122

Tetramethylsuccinimide as a Directing/ Protecting Group in Purine Glycosylations

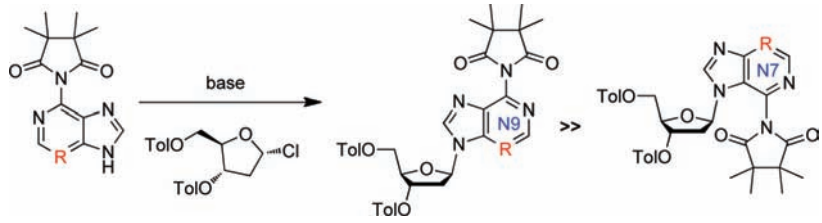
Joseph W. Arico, Amy K. Calhoun, Kerry J. Salandria, and Larry W. McLaughlin*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

mclaughl@bc.edu

Received October 29, 2009

ABSTRACT



Tetramethylsuccinic anhydride can be used to protect the exocyclic amine of 6-aminopurine derivatives by forming the corresponding tetramethysuccinimide. X-ray crystallography confirms that the imide carbonyl and the methyl groups are positioned to sterically block the N7 nitrogen so that glycosylations occur with very high regiochemical control at N9. This approach is particularly effective for 3-substituted purines where the substituent tends to block access to N9 and inhibit glycosylation at that site.

Syntheses of purine 2′-deoxynucleosides are challenging, particularly because the glycosylation step must be both regioselective and diasterioselective. Reaction yields of the naturally occurring β-N9 products are often low to moderate. Most preparations of purine 2′-deoxynucleosides employ the sodium salt method,[1] which typically uses a 6-chloropurine heterocycle and 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride.[2,3] For example 6-chloropurine (**1a**, Table 1) reacts to form 57% β-N9 nucleoside and 13% β-N7 with no α-isomers detected.[1] Treatment with NH_3/MeOH deprotects the sugar and displaces the 6-chlorine to form 2′-deoxyadenosine. Small changes in the sterics or electronics of the heterocycle can impact the ratio of coupling products. The favorable coupling ratio for **1a** (N9:N7 = 4.7:1) largely reverses itself for the 6-chloropurine derivative **2a** containing a 3-deaza-3-methyl substituent (N9:N7 = 1.0:2.2).[4] The products of **1a** and **2a** can be separated by flash chromatography, but this is not always the case. Many substrates produce significant amounts of α-nucleoside products, further complicating purification and lowering yields.

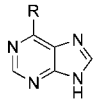
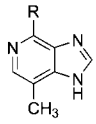
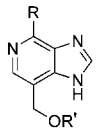
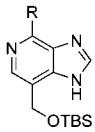
Robins has described the use of purines bearing a 2-alkylimidazole[5,6] or triazole[6] in the 6-position to achieve highly regio- and diastereoselective glycosylations using the sodium salt method. However, the purine coupling partners must be prepared from the corresponding oxopurines or the often expensive chloropurines. In addition, removal of the 2-alkylimidazole was reported to be difficult with most purines.[6] Related studies include the regioselective N9 arylation of purines.[7]

We attempted to use the Robins method in our work with **2a** and other 3-deaza-3-substituted purines, but the 6-(2-alkylimidazolyl) derivatives of **2a** and **3a** could not be prepared, largely because displacement of the 6-chlorine of 3-deazapurines requires harsh conditions (i.e., refluxing

(1) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379–6382.
(2) Rolland, V.; Kotera, M.; Lhomme, J. *Synth. Commun.* **1997**, *27*, 3505–3511.
(3) Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777–2780.
(4) Irani, R. J.; Santalucia, J. *Nucleosides, Nucleotides Nucleic Acids* **2002**, *21*, 737–751.
(5) Zhong, M.; Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 4216–4221.
(6) Zhong, M.; Nowak, I.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 7773–7779.
(7) Bakkestuen, A. K.; Gundersen, L. L. *Tetrahedron Lett.* **2003**, 3359–3362.

10.1021/ol9025028
Published on Web 12/04/2009

Table 1. Regioselective Purine Glycosylations

heterocycle		β-N9:β-N7	%yield (β-N9)	%yield (β-N7)	%yield (α-N9/α-N7)
	**1a** R = Cl[a]	4.7:1	57	13	0
	1b R = Phthalimide[b]	>99:1	36	0	0
	1c R = M_4SI[c]	>99:1	71	0	6/0
	**2a** R = Cl[d]	1:2.2	39	61	0
	2b R = Phthalimide[b]	1:1.1	15	16	15/16
	2c R = M_4SI	6.4:1	59	9	14/4
	**3a** R = Cl, R' = Ac[b]	1:2.3	26	59	0
	3b R = Phthalimide, R' = Ac[b]	1.2:1	28	23	5/5
	**4a** R = M_4SI	7.6:1	76	11	12/1

[a] See ref 1. [b] Unpublished results. [c] A procedure with KOH and cryptand catalyst TDA-1[4] was used instead of the sodium salt method. [d] See ref 4.

hydrazine followed by Raney nickel reduction[4,8]). Furthermore, the glycosylation products of **3a** could not be separated easily, leading us to seek an alternative procedure.

Here we describe 2,2,3,3-tetramethylsuccinimide (M_4SI) as a new directing/protecting group for the synthesis of β-N9 nucleosides with high regio- and diastereoselectivity.

We reasoned that 6-aminopurines protected with a cyclic imide might perform well as glycosylation partners. The cyclic imide would (i) protect the amino group from side reactions, (ii) permit direct glycosylation to N9, and (iii) be removed by mild base to expose the amino group, with or without deprotection of the sugar, as needed. We first examined phthaloyl protection of adenine using phthalic anhydride. Phthalimide has been reported as a protecting group in DNA synthesis[9,10] and ^{15}N-phthalimide has been used for the introduction of isotopic nitrogen into nucleosides.[11,12] The N^6-phthalimide derivative of adenine could be prepared (**1b**), although the yield was poor (~40%) under all conditions examined. It participated in glycosylation reactions to give almost exclusively the N9 regioisomer but in only 36% isolated yield. Deprotection with NH_3/MeOH removed the phthalimide in less than 15 min and the sugar toluoyl esters after several hours at room temperature. The amine could be reprotected as needed for DNA synthesis, but that approach was less than ideal.

We then considered aliphatic anhydrides that might exhibit better hydrolytic stability, beginning with 1,4-*cis*-cyclohexanedicarboxylic anhydride.[13] Unfortunately this compound polymerizes easily and attempts to prepare simple imides from ammonia or methyl amine have failed. Attempts to prepare the cyclic imide from adenine in this work also failed.

The third compound we considered was tetramethylsuccinic anhydride (M_4SA). Upon formation of the imide with adenine (Figure 1) the methyl groups should partially shield

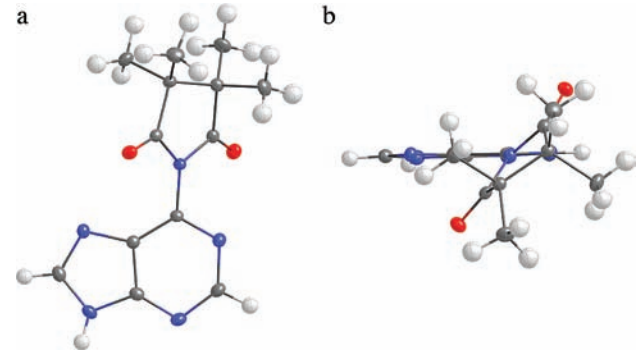
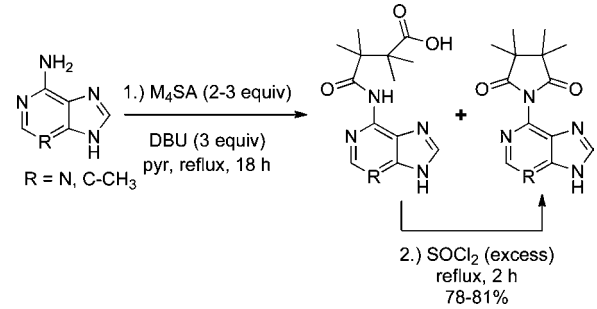


Figure 1. Structure of adenyl-N^6-tetramethylsuccinimide from X-ray diffraction methods: (a) face view and (b) edge view.

the N7 nitrogen from glycosylation. The cyclic anhydride M_4SA is readily obtained in two steps[14] from AIBN.

M_4SA reacted smoothly with adenine and other purines in refluxing pyridine in the presence of DBU (Scheme 1).

Scheme 1. Synthesis of M_4SI-Protected Purines



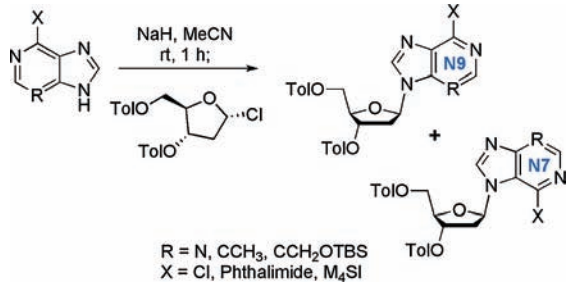
Surprisingly, no reaction took place without base, and other bases such as triethylamine and proton sponge failed to promote the reaction. A small amount of the amide was always present due to incomplete cyclization, but this could be converted to the cyclic imide with refluxing $SOCl_2$, resulting in 78−81% yields of the purine-N^6-tetramethylsuccinimide. It is important to convert the residual amide

(8) Itoh, T.; Yamaguchi, T.; Mizuo, Y. *J. Carbohydr., Nuleosides, Nucleotides* **1981**, *8*, 119–129.
(9) Kume, A.; Sekine, M.; Hata, T. *Tetrahedron Lett.* **1982**, *23*, 4365–4368.
(10) Beier, M.; Pfleiderer, W. *Helv. Chim. Acta* **1999**, *82*, 633–644.
(11) Kamaike, K.; Kinoshita, K.; Niwa, K.; Hirose, K.; Suzuki, K.; Ishido, Y. *Nucleosides, Nucleotides Nucleic Acids* **2001**, *20*, 59–75.
(12) Kamaike, K.; Takahashi, M.; Utsugi, K.; Tomizuka, K.; Ishido, Y. *Tetrahedron Lett.* **1995**, *36*, 91–94.
(13) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 6412–6420.
(14) Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J. P. P. M.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819–1830.

into the cyclic imide since the amide (Scheme 1) does not function well as a blocking group. We obtained the structure of the M_4SI of adenine by X-ray crystallography and two views are shown in Figure 1. In the "face view" (Figure 1a) the four methyl groups can be observed positioned "umbrella-like" above the N7 edge of the adenine ring system. The distance between the imide carbonyl oxygen and the N7 nitrogen is 3.1 Å, and that to C5 is 3.0 Å. These distances likely prevent a coplanar conformation between the imide and heterocycle, and in combination with the four methyl groups seem sufficient to limit access to N7 by the gylcosylation reagent. The "edge view" (Figure 1b) illustrates that the plane of the imide functionality is in fact rotated 52° relative to the plane of the heterocycle, and this rotation is necessary to prevent the steric clash between the imide carbonyls and the N7 nitrogen and C5 carbon.

We next examined a number of adenine-based heterocycles for their ability to undergo glycosylation with M_4SI as a directing/protecting group at the 6-position (Scheme 2) and

Scheme 2. Purine Glycosylations with the Sodium Salt Method



compared these results with those obtained for the corresponding 6-chloropurine, when available (Table 1). Phthalimide-protected heterocycles **1b**, **2b**, and **3b** showed a better directing efffect for N9 than did the 6-Cl derivatives, but only gave low to moderate yields; varying and poorly reproducible amounts of α-nucleosides were always isolated as well. The N7 and N9 regioisomers could be separated but the α and β diasteriosomers could not.

In contrast, glycosylation of M_4SI-protected adenine **1c** yielded only the N9 isomer. The best yield (71%) was obtained with phase transfer conditions using KOH/TDA-1[15] in comparison with NaH (54%). M_4SI performed well with 3-deaza-3-substituted purines. **2c** gave a 6.4:1 ratio of N9 to N7 β-nucleosides, and this ratio increased to 7.59:1 for a 3-deaza analogue bearing a silyl-protected linker (**4a**). Although some coupling reactions generated small amounts of the unwanted regioisomer or diastereomers, with the M_4SI group in place the desired β-N9 products could be resolved from the β-N7 and α-nucleosides by flash chromatography. The α-nucleosides result from anomerization of the chlorosugar (structure illustrated in Scheme 2), which is accelerated in polar solvents.[16] While the M_4SI group is quite effective in blocking access to N7, the 3-substituted purines such as **2c** and **4a** are more hindered nucleophiles; the reaction is then slower to reach completion and larger amounts of α-nucleosides are formed.

The M_4SI group displayed the desired stability that phthalimide lacked. Treatment of the coupling products of **1c** and **2c** with NaOMe/MeOH or 7 M NH_3/MeOH at room temperature removed the two toluoyl esters on the sugar but *not* the M_4SI (64% and 82% yield, respectively), and in 86% yield for the coupling product of **4a** (see the Supporting Information).

Purine nucleosides with substituents at the 3-position are valuable to probe hydration effects in the DNA minor groove. Even a simple methyl substituent at C3 will be directed into the minor groove of duplex DNA where it may disrupt or effect a reorganization of water structure.

As a further example of this protecting group's utility we elaborated M_4SI-protected 2′-deoxy-3-deaza-3-methyladenosine, the coupling product of **2c**, to the DMT-protected phosphoramidite for use in DNA solid-phase synthesis (see the Supporting Information). The M_4SI can be cleanly removed with NH_3/MeOH or concd NH_4OH at 55 °C overnight, both compatible with DNA synthesis protocols. The use of M_4SI-protected phosphoramidites in solid-phase DNA synthesis will be reported elsewhere.

M_4SI is a valuable new directing/protecting group that allows rapid access to β-N9 6-aminopurine-2′-deoxynucleosides and functions as an effective base-labile protecting group. It is especially valuable for 3-substituted purines. It should also serve in other applications where bidentate amine protection is desired.

Acknowledgment. We thank Dr. Bo Li for the crystallographic analysis of **1c** and Dr. Nick Greco for critical discussions. This work was supported by an award from the NSF to L.W.M. (MCB 0451488).

Supporting Information Available: Experimental procedures and characterization of all compounds along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9025028

(15) Seela, F.; Roseyer, H.; S., F. *Helv. Chim. Acta* **1990**, *73*, 1602–1611.

(16) Kotick, M. P.; Szantay, C.; Bardos, T. J. *J. Org. Chem.* **1969**, *34*, 3806–3811.