Pergamon

Tetrahedron Letters 42 (2001) 1069–1072

TETRAHEDRON LETTERS

2-(Azidomethyl)benzoyl as a new protecting group in nucleosides†

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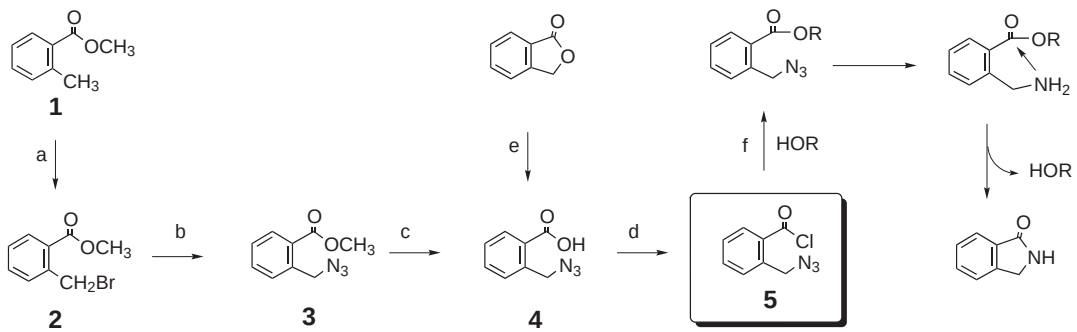
Received 28 September 2000; revised 21 November 2000; accepted 24 November 2000

Abstract—A new protecting group, 2-(azidomethyl)benzoyl (AZMB), which can be easily removed by treatment with $MePPh_2$ in dioxane–H_2O or reduction with $HCOONH_4$–Pd/C in dioxane–MeOH, was developed for protection of the hydroxy and amino functions of deoxyribonucleosides. © 2001 Elsevier Science Ltd. All rights reserved.

A wide variety of protecting groups, which can be removed indirectly via 'assisted cleavage mechanism' by conversion of a stable inside functional group into a reactive nucleophile capable of intramolecular attack on the neighboring genuine protected site, have been developed.[1] The deprotection of these protecting groups depends essentially on the chemical property of the masked auxiliary group. Among the protecting groups of this type, Kusumoto and co-workers reported 4-azidobutyryl as the hydroxy protecting group that can be removed via reduction of the azido group with H_2–Pd/C, H_2S or PPh_3.[2] Complete removal of this protecting group required additional conditions of reflux in EtOH for 1–2 h at the second stage for intramolecular cyclization. It was also expected that the neighboring group participation of the once-generated amino function toward the nearest ester function would be more effective in geometrically locked aromatic ring systems than in conformationally flexible aliphatic systems, as exemplified by 2-substituted benzoyl groups such as 2-(chloroacetoxymethyl)benzoyl,[3] 2-(benzoyloxymethyl)-benzoyl,[4] 2-(acetoxymethyl)benzoyl,[5,6] and 2-[(*t*-butyldiphenylsilyoxy)methyl]benzoyl.[7,8] From these examples, it was expected that 2-azidomethylbenzoyl must be an ideal structure as the protecting group since, once the azido group is reduced to an amino group, rapid ring closure readily occurs because of stronger nucleophilicity of the amino group than that of the hydroxy group, as well as accessibility to a stable five-membered ring system. Actually, Osborn has reported 2-(azidomethyl)-5-methylbenzoyl and related polymer-supported linkers involving the 2-azidomethylbenzoyl



Scheme 1. (a) NBS (1.1 equiv.), $(BzO)_2$ (0.02 equiv.), CCl_4, reflux, 1 h; (b) $TMGN_3$ (1.5 equiv.), CCl_4–MeOH (1:1, v/v), reflux, 1.5 h; (c) 2 M NaOH–MeOH (1:1, v/v), rt, 30 min; (d) $SOCl_2$ (1.5 equiv.), reflux, 1 h (no solvent); (e) $Et(iPr)_2NHN_3$, (3 equiv.), 140°C, 4.5 h (no solvent); (f) see Table 2.

Keywords: protecting group; AZMB; nucleosides; $HCOONH_4$–Pd/C.

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† This paper is dedicated to Professor Jan Michalsky on the occasion of his 80th birthday.

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PII: S0040-4039(00)02183-3

skeleton, especially designed for the oligopeptide synthesis.[9] Nonetheless, the simplest mother structure of 2-(azidomethyl)benzoyl has not yet been reported to date.

Here, we report 2-(azidomethyl)benzoyl (AZMB) as a new protecting group of the hydroxy and amino functions in deoxyribonucleosides. It was found that 2-(azidomethyl)benzoic acid (**4**)[10] could be easily synthesized by a three-step reaction from commercially available methyl 2-methylbenzoate (**1**), as shown in Scheme 1. The transformation of the bromomethyl group of **2** into the azidomethyl group was achieved in situ by treatment with tetramethylguanidinium azide ($TMGN_3$) in CCl_4–MeOH (1:1, v/v). Heating of a mixture of benzolactone and 3 equiv. of diisopropylethylammonium azide at 140°C for 4.5 h gave **4** (mp 74°C) but in only 18% yield. In this reaction, the use of other ammonium azide salts such as $TMGN_3$, Bu_4NN_3, and $DBUHN_3$ resulted in poorer yields of **4**.

For introduction of the AZMB group into the hydroxy or amino functions of nucleosides, the acid chloride **5** was prepared quantitatively by reaction of **3** with thionyl chloride in neat under reflux for 1.5 h, followed by evaporation under reduced pressure. The acid chloride **5** was used in situ since all attempts to purify **5** by distillation caused considerable decomposition. Reaction of 5′-*O*-dimethoxytritylthymidine **6** with **5** in pyridine at room temperature for 2 h gave the 3′-*O*-acylated product **7** in 81% yield, as shown in Table 1. Reaction of 3′-*O*-benzoylthymidine **8** with **5** gave the 5′-*O*-acylated product **9** in 98% yield. It was observed that these *O*-acylations required more than 2.5 equiv. of the reagent for smooth reactions. It is likely that the steric hindrance of the 2-azidomethyl group influenced significantly the *O*-acylation. When compound **4** was used in the presence of CIP[11] or Bop-Cl,[12] the acylated products were obtained in somewhat lower yields, as shown in Table 1.

Reaction of thymidine (**10**) with 1.5 equiv. of **4** in pyridine in the presence of 1.5 equiv. Bop-Cl and 0.02 equiv. of 4-methoxypyridine *N*-oxide (NPO) at room temperature for 14 h gave the 5′-*O*-acyalted product **11** (mp 150–152°C from MeOH) in 75% yield (Scheme 2).

The *exo*-amino groups of deoxyribonucleosides **12a–c** could be monoacylated by the transient protection method via trimethylsilylation.[13] Thus, the *N*-AZMB-deoxyribonucleosides **13a–c** were obtained in good overall yields, as summarized in Table 1. In these reactions, 5 equiv. of **5** was required. Compounds **13a–c** were tritylated with 1.1 equiv. of DMTrCl in pyridine at room temperature for 2.5 h in the usual manner to give the 5′-*O*-protected products **14a–c** in 80, 80, and 83% yields, respectively.

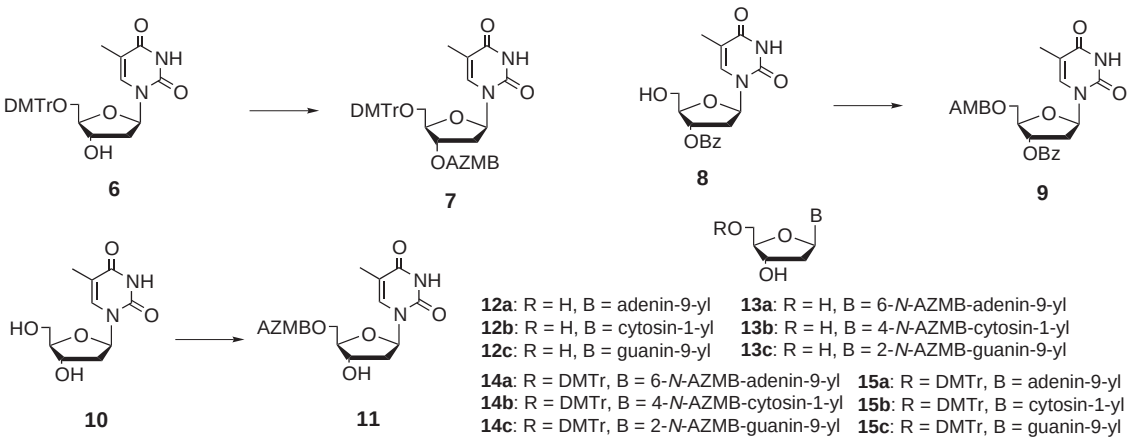
Detailed examination was made of the conditions prescribed for removal of the AZMB group from **7**. Three kinds of phosphines, i.e. PBu_3, PPh_3, and $MePPh_2$, were tested. PBu_3, which has been used for removal of the 2-(azidomethyl)-5-methylbenzoyl group,[9] was less effective than the other two. PPh_3 required 30 min for complete reaction, while use of $MePPh_2$ resulted in a shorter time of 15 min with a $t_{1/2}$ of 2 min. Thus, compound **6** was obtained in 96% yield by treatment of **7** with 4 equiv. of $MePPh_2$ in dioxane–water (9:1, v/v) at room temperature (Method A) for 15 min. When PPh_3 was used as a reducing reagent, no intermediate was observed on TLC. When PBu_3 was used, iminophosphorane intermediates were detected on TLC but gradually converted to the deprotected products. In the case of $MePPh_2$, iminophosphorane intermediates were also observed but more rapidly converted to the products within 15 min. When PPh_3 was employed in anhydrous dioxane, the AZMB group could not be removed.

The AZMB group attached to the 5′-hydroxy group of **9** was more easily removed in 8 min under similar

Table 1. Introduction of the AZMB group into the hydroxy and amino functions of deoxyribonucleoside derivatives

Entry	Compd	Product	Conditions[a]		Yield of product (%)
			Reagent (equiv.)	Time	
1	**6**	**7**	**5** (2.5)	2 h	81
2	**6**	**7**	**4** (2.0) CIP (2.5)	2 h	66
3	**6**	**7**	**4** (1.5) BOP-Cl (2.0) NPO (cat.)	1 day	71
4	**8**	**9**	**5** (2.5)	30 min	98
5	**8**	**9**	**4** (1.5), BOP-Cl (2.0), NPO (cat.)	16 h	87
6	**10**	**11**	**4** (1.5), BOP-Cl (1.5), NPO (cat.)	14 h	75
7	**12a**	**13a**	(1) Me_3SiCl (5.0) (2) **5** (5.0)	(1) 20 min (2) 3 h	70
8	**12b**	**13b**	(1) Me_3SiCl (5.0) (2) **5** (5.0)	(1) 20 min (2) 3 h	89
9	**12c**	**13c**	(1) Me_3SiCl (5.0) (2) **5** (5.0)	(1) 20 min (2) 3 h	75

[a] All the reactions were carried out in pyridine at room temperature.



Scheme 2.

conditions to give **8** in 98% yield. Similarly, it was also found that the AZMB group could be uniformly removed from **14a–c** to the *N*-unprotected deoxynucleoside derivatives **15a–c** in 90, 94, and 91% yields, respectively. Alternatively, 4 equiv. of ammonium formate in MeOH–dioxane (3:1, v/v) in the presence of Pd/C at room temperature (Method B) for 4 and 2 h was also effective for removal of the AZMB group from **7** and **9**, respectively, as shown in Table 2.

It should be noted that no intermediates formed by the reduction of the AZMB group with ammonium formate on Pd/C could be observed throughout this study. This implies that, as expected, the second cyclization occurred much faster than the reduction.

The AZMB group can be removed by treatment with $NaBH_4$ (Method C), as shown in Table 2. It also turned out that the AZMB group was stable under the following conditions: (1) $Ce(NH_4)_2(NO_2)_6$ (1 equiv.) in CH_3CN–H_2O (9:1, v/v) at rt for 24 h. (2) Bu_4NF (1 equiv.) in THF at rt for 24 h. (3) TMSOTf (1 equiv.) in CH_2Cl_2 at rt for 5 h. (4) DDQ (4 equiv.) in CH_2Cl_2–H_2O (1:1, v/v) at rt for 24 h.

As described above, the AZMB group could be introduced into the primary and secondary hydroxy groups as well as the *exo*-amino groups using the in situ generated acid chloride **5** or the 1-Bop-Cl/NPO system. The removal of the AZMB group could be easily carried out by dimethyphenylphosphine or reduction with ammonium formate on Pd/C. The AZMB group could be a useful protecting group for hydroxy and amino functions within the nucleic acid and other fields.

Acknowledgements

This work was supported by a Grant from 'Research for the Future' Program of the Japan Society for the Promotion of Science (JSPS-RFTF97I00301) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

Table 2. Conditions of removal of the AZMB group

Entry	Compd	Product	Conditions[a]		Yield of product (%)
			Method	Time	
1	**7**	**6**	Method A	15 min	96
2	**7**	**6**	Method B	4 h	94
3	**9**	**8**	Method A	8 min	98
4	**9**	**8**	Method B	2 h	98
5	**9**	**8**	Method C	1 h	86
6	**14a**	**15a**	Method A	20 min	90
7	**14b**	**15b**	Method A	20 min	94
8	**14c**	**15c**	Method A	20 min	91

[a] Method A: $MePPh_2$ (4 equiv.) in dioxane–H_2O (9:1, v/v) at rt.
Method B: $HCOONH_4$ (4 equiv.) on Pd/C in dioxane–MeOH (1:3, v/v) at rt.
Method C: $NaBH_4$ (3 equiv.) in EtOH–THF (1:1, v/v) at rt.

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10. Bromination of **1** with 1.1 equiv. of NBS in the presence of 0.02 equiv. of dibenzoyl peroxide in CCl_4 under reflux for 1 h. A solution of 1.5 equiv. of $TMGN_3$ in MeOH was added to the mixture containing the brominated product **2**, and the resulting mixture was refluxed for 1.5 h. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was treated with 10% NaOH–MeOH (1:1, v/v) at rt for 30 min. The mixture was extracted with $CHCl_3$, and the aqueous layer was acidified to pH 1.0 by addition of dilute HCl. The mixture was extracted three times with $CHCl_3$. The extracts were combined, dried over $NaSO_4$, filtered, and condensed. The resulting precipitate was collected and recrystallized from cyclohexane to give the acid **4** as white crystals in 76% yield (mp 73–75°C): ^{1}H NMR ($CDCl_3$) δ 4.90 (2H, s, CH_2N_3), 7.47 (1H, td, J=7.6, 1.3 Hz, H-5), 7.57 (1H, dd, J=7.6 Hz, 1.0 Hz, H-3), 7.65 (1H, td, J=7.6 Hz, 1.3 Hz, H-4), 8.19 (1H, dd, 7.9 Hz, 1.3 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 53.17, 127.31, 128.23, 127.79, 132.15, 133.76, 138.31, 171.55. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 53.93, H, 3.84; N, 23.88.
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