Pergamon

Tetrahedron Letters 42 (2001) 2887–2889

TETRAHEDRON LETTERS

Novel acid-free cleavage of *N*-(2-hydroxyarylidene) protected amines

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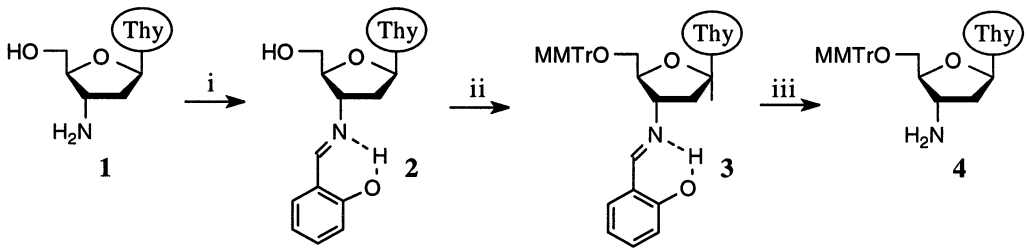
Received 3 January 2001; revised 15 February 2001; accepted 21 February 2001

Abstract—A novel, mild, neutral and selective procedure for deprotection of salicylaldehyde protected primary amines has been developed. Examples in nucleoside, polyamine and amino acid chemistry are given in which *N*-salicylidene derivatives were selectively deprotected with methoxyamine in the presence of other typical protecting groups for these compounds.

Several protecting groups have been developed for the amino group. Common protecting functionalities are imines, which are prepared under mild conditions from amines and aldehydes and cleaved by acid hydrolysis.[1] The stability of these Schiff bases can be increased if the free electron pair from the nitrogen is hydrogen bonded, typically with an adjacent hydroxyl group bound to an aromatic ring. One example of utilising this approach is the carbodiimide synthesis of dipeptides from 5-chlorosalicylaldehyde and 2-hydroxy-1-naphthaldehyde protected amino acids.[2] Hydrolysis of these derivatives proceeds in moderately acidic media and requires treatment with an equivalent amount of HCl[2] or boric acid[3] in aqueous media. This causes limitations in the use of these protecting groups in combination with other acid-sensitive groups.

In this paper, three examples are given in which an amino group is deblocked from a 2-hydroxyarylidene derivative under mild and neutral conditions by using $MeONH_2$ as the deprotecting agent, resulting in the required primary amine and the corresponding, easily separated, *O*-methyl oxime. The use of $MeONH_2$ (pK_a 4.8, bp 43°C) instead of the readily available NH_2OH (pK_a 5.9) has several advantages, including easy removal of the excess reagent and the lower nucleophility of $MeONH_2$ compared with NH_2OH, which is known to convert carboxylic acid esters into the corresponding hydroxamates. The deprotection conditions distinguish the *N*-(2-hydroxyarylidene) functionality from the protecting groups currently used in polyamine, nucleoside, amino acid and carbohydrate chemistry.

Selective monomethoxytritylation of amino alcohols on the hydroxyl group. An example of the *N*-salicylidene strategy for the selective protection of an OH group in the presence of an NH_2 group is the three-step synthesis of 5′-MMTr-3′-deoxy-3′-aminothymidine with a total



Scheme 1. (i) Salicylaldehyde/MeOH; (ii) MMTr-Cl/pyridine; (iii) $MeONH_2$/MeOH/$CHCl_3$.

Keywords: amines; protecting groups; hydroxylamines.
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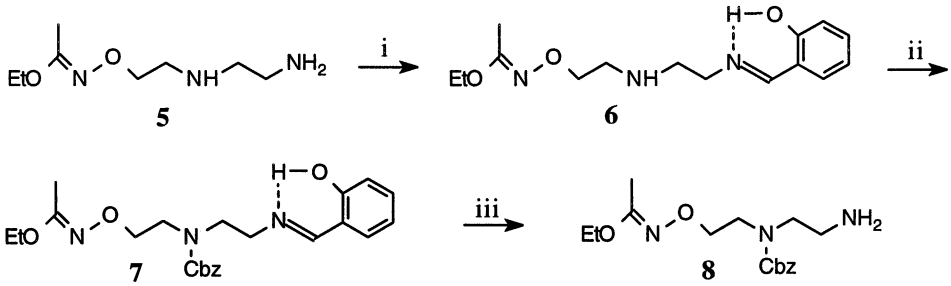
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00315-X



Scheme 2. (i) Salicylaldehyde/THF; (ii) Cbz-Cl, THF, H_2O, $NaHCO_3$; (iii) $MeONH_2$/THF.

yield of 75% (Scheme 1). Treatment of 3′-deoxy-3′-aminothymidine **1** with salicylaldehyde in MeOH gave the stable derivative **2**. The synthesis was continued, without isolation, to the monomethoxytritylated derivative **3**, which was purified by flash chromatography and selectively deprotected by $MeONH_2$ to give **4**.[4]

Selective acylation of secondary amino group in the presence of an NH_2 group. Salicylaldehyde is known to react exclusively with an NH_2 group in the presence of a secondary amine.[5,6] In a one-pot procedure, diamine **5**, containing both NH and NH_2 groups, was protected selectively to give **6**, which was then, without isolation, carbobenzyloxylated to give **7** (Scheme 2). After deprotection with $MeONH_2$, the isolated yield of **8** was 81%.

Deprotection of N-(2-hydroxyarylidene) amino acids. Both naphthylidene and salicylidene derivatives of valine react smoothly with $MeONH_2$ in an organic solvent to give valine, which precipitates from the reaction mixture in almost quantitative yield.

5′-Monomethoxytrityl-3′-deoxy-3′-amino-thymidine **4**. Amine **1**[6] (48 mg, 0.2 mmol) in MeOH (5 mL) was added to salicylaldehyde in MeOH (0.22 mL of a 1 M solution) at 20°C. After 2 h a yellow solution containing practically pure **2** was evaporated to dryness and co-evaporated with pyridine (4×3 mL). The residue was dissolved in pyridine (2 mL) and MMTr-Cl (77 mg, 0.25 mmol) was added and the reaction was stirred for 3 days at 20°C. After being evaporated to dryness, the residue was chromatographed on silica gel using first $CHCl_3$ as an eluent and then $CHCl_3$–MeOH (9.5: 0.5, *v*/*v*) to afford **3**[7] (100 mg, 83%) as a yellow solid. Deprotection of **3** (62 mg, 0.1 mmol, in MeOH–$CHCl_3$ (1 mL, 1:1)) was performed with $MeONH_2$ (47 mg, 1 mmol) for 60 min at 20°C resulting in a colourless solution. After evaporating to dryness, the residue was chromatographed on silica gel using $CHCl_3$–MeOH (9:1, *v*/*v*) as eluent to give **4**[7] (45 mg, 90%).

5-[[(1′-Ethoxyethylidene)amino]oxy]-3-[[N-(benzyl)oxy]-carbonyl]-aza-1-aminopentane **8**. Amine **5**[8] (2.89 g, 15.3 mmol) in THF (10 mL) was added to salicylaldehyde (1.86 g, 15.3 mmol) and the reaction was maintained at 20°C for 30 min. To the resulting yellow solution, THF (20 mL), water (5 mL) and $NaHCO_3$ (2.57 g, 30 mmol) were added followed by benzyl chloroformate (2.73 g, 16 mmol) at 4°C in three portions over a 90 min period. Stirring was continued for 1 h at 4°C, followed by 3 h at 20°C, and the precipitate was filtered off. The THF phase, containing **7**, was treated with $MeONH_2$ (1.44 g, 30.6 mmol) and after 2 h at 20°C the colourless solution was evaporated to dryness. The resulting oil was chromatographed on silica gel using first $CHCl_3$ as eluent and then $CHCl_3$–MeOH (9:1, *v*/*v*) to afforded pure **8** (4 g, 81%).[7]

Acknowledgements

The authors would like to thank Dr. A. Guzaev, ISIS Pharmaceuticals Inc., Carlsbad, CA, for critical remarks and helpful discussion. This work was supported by Grants from the Russian Fundamental Research Foundation (97-04-48708) and NATO LST.CLG.976.270.

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4. The second-order reaction rate constant 0.2 L/mol/min ($\tau_{1/2}$=11.3 min) from **3** to **4** was determined at 20°C by ^{1}H NMR spectroscopy using **3** (0.043 mmol) and $MeONH_2$ (0.187 mmol) in 0.5 mL $CDCl_3$–CD_3OD (1:1).
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7. Spectral data for the final products. Compound **3**:[9] NMR ($CDCl_3$): δ_H 12.52 (1H, s), 8.24 (1H, s), 7.72 (1H, q, $^4J_{HH}$=1.2 Hz), 7.43 (4H, m), 7.35–7.16 (10H, m), 6.96 (1H, d, J=8.3 Hz), 6.89 (1H, td, J=7.4, $^4J_{HH}$=1.1), 6.81 (2H, d, J=9.0 Hz), 6.33 (1H, dd, J=7.1 Hz, 4.1 Hz), 4.26 (1H, m, J=7.8, 7.5 and 6.9 Hz), 4.13 (1H, m, J=6.9, 2.9 and 2.8 Hz), 3.74 (3H, s), 3.63 (dd, $^2J_{HH}$=−11.0 Hz, J=2.8 Hz), 3.25 (dd, $^2J_{HH}$=−11.0 Hz, J=2.9 Hz), 2.68 (1H, m, $^2J_{HH}$=−13.9 Hz, J=7.5 and 7.1 Hz), 2.52 (1H, ddd, $^2J_{HH}$=−13.9 Hz, J=7.8 and 4.1 Hz), 1.60 (3H, bs); δ_C 166.40 d, 164.00 s, 160.76 s, 158.84 s, 150.33 s, 143.96

s, 143.73 s, 135.52 d, 134.80 s, 132.97 d, 131.70 d, 130.37 d, 128.32 d, 128.27 d, 128.06 d, 128.03 d, 127.29 d, 118.93 d, 118.31 s, 117.09 d, 113.33 d, 110.93 s, 87.06 s, 85.19 d, 84.40 d, 67.23 d. 61.67 t, 55.20 q, 40.56 t, 12.20 q. Compound **4**:[9] NMR (D_2O): δ_H 7.57 (1H, q, $^4J_{HH}=1.2$ Hz), 7.43 (4H, m), 7.33–7.22 (8H, m), 6.85 (2H, d, $J=9.0$ Hz), 6.26 (1H, dd, $J=6.8$ Hz, 5.0 Hz), 3.79 (3H, s), 3.78 (1H, m, $J=6.2$, 3.3, 3.1 Hz), 3.74 (1H, m, $J=7.3$, 6.8, 6.3 Hz), 3.50 (1H, dd, $^2J_{HH}=-10.6$ Hz, $J=3.1$ Hz), 3.37 (1H, dd, $^2J_{HH}=-10.6$ Hz, $J=3.3$ Hz), 2.35 (1H, ddd, $^2J_{HH}=-13.6$ Hz, $J=7.3$ and 5.0), 2.23 (1H, m, $^2J_{HH}=-13.6$ Hz, $J=6.8$ and 6.8 Hz), 1.52 (3H, d, $^4J_{HH}=1.2$ Hz); δ_C 163.97 s, 158.81 s, 150.44 s, 143.98 s, 143.93 s, 135.57 d, 135.02 s, 130.40 d, 128.41 d, 128.00 d, 127.23 d, 113.29 d, 110.82 s, 87.02 s, 86.56 d, 84.51 d, 62.99 t, 55.25 q, 51.58 d, 41.72 t, 12.05 q. Compound **8**: NMR (D_2O): δ_H 7.36–7.28 (5H, m), 5.13 (2H, s), 4.02–3.92 (4H, m), 3.54 (2H, m), 3.37 (2H, m), 2.85 (2H, m), 1.90 (3H, s), 1.26 (3H, t, $J=7.0$ Hz); δ_C 162.32 s, 156.55 s, 136.59 s, 128.38 d, 127.86 d, 127.71 d, 71.67 t, 67.03 t, 62.11 t, 51.42[10] t, 46.57[10] t, 40.22[10] t, 14.25 q, 13.58 q.

8. [[(1′-Ethoxyethylidene)amino]oxy]-3-aza-1-aminopentane **5** was prepared by aminooxyethylation of 1,2-diaminoethane, as described earlier for aminooxyethylation of 1,4-diaminobutane;[11] yield 65%; bp 81°C/1 mmHg; n_D^{20} 1.4626; NMR ($CDCl_3$): δ_H 4.03–3.98 (4H, m), 2.88 (2H, m), 2.81 (2H, m), 2.70 (2H, m), 1.94 (3H, s), 1.27 (3H, t, $J=7.1$ Hz); δ_C 162.40 s, 72.84 t, 62.18 t, 52.54 t, 48.70 t, 41.88 t, 14.39 q, 13.66 q.
9. ^{1}H NMR spectra of the sugar rings were analysed using PERCH software. See: Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson. Ser. A* **1996**, *120*, 1–10.
10. Due to hindered rotation of the N–C=O bond on the NMR timescale, these signals exist as doublets.
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