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Tetrabutylammonium Nitrite - Acetic Anhydride System, Tetrabutylammonium Nitrite, Tetrabutylammonium Acetate, and Cesium Acetate - 18-Crown-6 for Efficient Unmasking of Alkyl *N*-Phenylcarbamates

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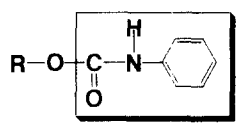
Abstract: Novel unmasking procedures for alkyl *N*-phenylcarbamates are established by the use of a tetrabutylammonium nitrite (Bu_4NNO_2) - acetic anhydride system, Bu_4NNO_2, Bu_4NOAc, and CsOAc - 18-crown-6 towards variously functionalized sugar derivatives.

Keyword: Carbohydrates, Carbamates, Protecting groups, Cleavage reactions.

The *N*-Phenylcarbamoyl protecting group is characterized by its facile introduction to an alcohol through the treatment with phenyl isocyanate in pyridine,[1] but the conditions for its removal hitherto used are rather drastic, i.e., treatment with alkoxide in an alcohol at reflux,[2a] with lithium aluminum hydride in THF or in diglyme at reflux,[2b] and with trichlorosilane - triethylamine in dichloromethane;[3] the protecting group is stable from pH 1 to pH 12 in aqueous solution.[4] Therefore, the protecting group has not been used conveniently for the synthesis of a complex natural product which necessitates delicate chemical differentiation of a variety of protecting groups under mild conditions.



Phenylcarbamoyl (Ph-Car)

Incidentally, a tetrabutylammonium nitrite (Bu_4NNO_2) - acetic anhydride (Ac_2O) system was demonstrated to be remarkably efficient for the deanilidation of phosphoranilidates in an oligonucleotide synthesis, i.e., the reaction is over almost instantly, within 1 min, so far as the authors use adenosine and cytidine derivatives whose exocyclic amino groups are protected with succinyl or phthaloyl groups.[5] The efficiency of the Bu_4NNO_2 - Ac_2O system was deduced to be potentially brought about by the *in-situ* formation of acetic nitrous anhydride (AcON=O). The anhydride might behave as a strong electrophile toward the nitrogen atom of phosphoranilidates to give the corresponding *N*-nitrosophosphoranilidate which is considered to be susceptible to the nucleophilic attack by the acetate ion concomitantly formed.

The efficiency of such a system in the deanilidation reaction, and nitrosation of an amide with $NaNO_2$ - Ac_2O system (15 h at 0 °C)[6] led us to an assumption that utility of the *N*-phenylcarbamoyl protecting group

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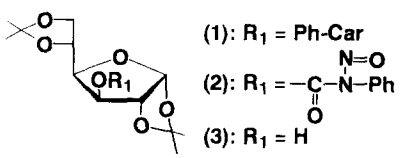
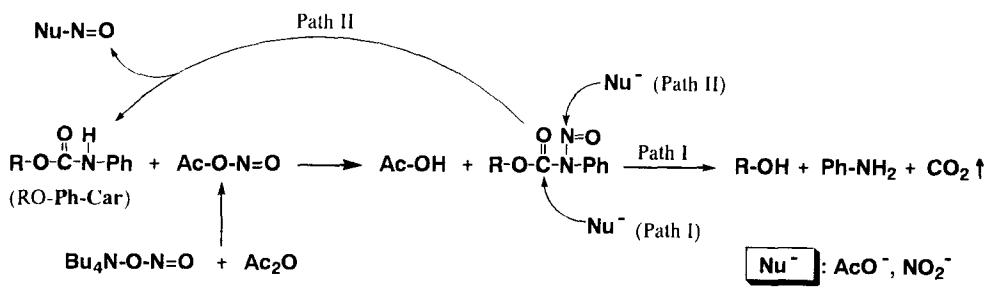
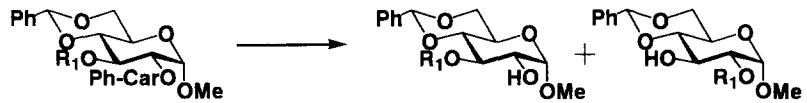
would be tremendously expanded in the field of synthetic organic chemistry if the system is feasible in unmasking of alkyl *N*-phenylcarbamates. Therefore, we undertook the present investigation on the basis of such an assumption, and, as expected, alkyl *N*-phenylcarbamates were found to be easily susceptible to the *N*-nitrosation reaction at 0 °C and easily unmasked at 40 °C by the use of the Bu_4NNO_2 - Ac_2O system (Procedure A). Further investigation was undertaken, assuming the possibility of nucleophilic attack of the counteranions, nitrite and/or acetate, toward the carbonyl carbon of an alkyl *N*-phenylcarbamate without *N*-nitrosation, and it was proved that Bu_4NNO_2 (Procedure B), Bu_4NOAc, and CsOAc - 18-Crown-6 (Procedure C) are also efficient for the unmasking at a higher temperature. We wish to communicate the results herein, using a carbohydrate derivative as a model compound of alkyl *N*-phenylcarbamates.



Procedure A: Initially, the *N*-nitrosation reaction toward alkyl *N*-phenylcarbamates was examined by treatment of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*N*-phenylcarbamoyl)-α-D-glucofuranose (**1**) (100 mg) with Bu_4NNO_2 (4 mol equiv.) and Ac_2O (3 mol equiv.) in pyridine (2 mL) at 0 °C, which afforded the corresponding *N*-nitroso derivative (**2**) quantitatively. The structure of **2** was confirmed by ^1H, ^{13}C, and ^{15}N NMR spectroscopy.[7] Treating this reaction mixture up to 40 °C gave unchanged **1** in addition to 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) (63% yield).[8] Therefore, the way of addition of Ac_2O was changed by dividing it into 3 parts and adding them portionwise at intervals, i.e., **1** (100 mg) was treated with Bu_4NNO_2 (4 mol equiv.) and Ac_2O (1.5 mol equiv.) in pyridine (2 mL) at 0 °C for 10 min, and warmed up to 40 °C and kept at that temperature for 2 h. The resulting mixture was cooled down to 0 °C again, Ac_2O was added (1.2 mol equiv.), warmed up to 40°C again, and kept at 40 °C for 2 h. This procedure was repeated once more with the use of Ac_2O (1.0 mol equiv.). Subsequent work-up, involving column chromatographic purification after quenching the mixture with a saturated aqueous solution of sodium hydrogencarbonate, gave **3** in an improved yield of 80%.[9] Such an improvement might be attributed to the potential instability of AcON=O produced *in situ* and the reverse reaction of *N*-denitrosation from **2** to **1** involved therein. Procedure A thus conceivably involves a two-step reaction mechanism as shown in Scheme 1, i.e., 1) quantitative *N*-nitrosation reaction of an alkyl *N*-phenylcarbamate **1** into **2** by AcO-N=O at 0 °C, and, subsequently, 2) the nucleophilic attack of a nucleophile (Ac-O$^-$ and/or O=N-O$^-$) onto the carbonyl carbon (unmasking reaction from **2** to **3**; Path I) or to the nitrogen of the nitroso function (reverse reaction from **2** to **1**; Path II) at 40 °C. Procedure A was then applied to the unmasking of methyl 4,6-*O*-benzylidene-2-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranoside derivatives [3-*O*-benzyl (**4a**, R_1 = Bn; Entry 1), -methoxymethyl (**4b**, R_1 = MOM; Entry 2), -acetyl (**4c**, R_1 = Ac; Entry 3),



Scheme 1



(4a): R_1 = Bn (4d): R_1 = Bz
(4b): R_1 = MOM (4e): R_1 = TBDMS
(4c): R_1 = Ac (4f): R_1 = Piv

Table 1. Unmasking of *N*-Phenylcarbamates of Sugar Derivatives

Entry	Substrate	Procedure	Yield (%) [a] Product	
1	(4a)	A	(5a): quant.	
2	(4b)	A	(5b): quant.	
3	(4c)	A	(5c): 93	(5c'): –
4	(4d)	A	(5d): 83	(5d'): –
5	(4e)	A	(5e): 79	(5e'): –
6	(4f)	A	(5f): 93	(5f'): –
7	(4a)	B	(5a): 88	
8	(4b)	B	(5b): 91	
9	(4c)	B	(5c): 46	5(c'): 36
10	(4d)	B	(5d): 44	5(d'): 39
11	(4e)	B[b]	(5e): 52	(5e'): 19
12	(4f)	B	(5f): 44	(5f'): 31

Procedure A:
Bu_4NNO_2 (4.0 mol eq.) / Ac_2O [(1.5 + 1.2 + 1.0) mol eq.] / Py. / 0 ° → 40 °C.

Procedure B:
Bu_4NNO_2 (3.0 mol eq.) / DMF / 80 °C.

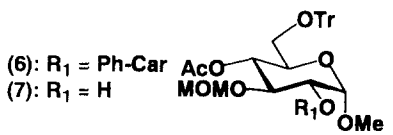
a) Isolated Yield.
b) The reaction was carried out at 110 °C.
c) All reactions were performed until the disappearance of the corresponding starting materials on TLC (ca. 4 -12h).

-benzoyl (**4d**, R_1 = Bz; Entry 4), -*t*-butyldimethylsilyl (**4e**, R_1 = TBDMS; Entry 5), and -pivaloyl (**4f**, R_1 = Piv; Entry 6)]; the results thus obtained are summarized in Entries 1 - 6 in Table 1. It is of particular interest that, during the unmasking, no acyl and silyl migration was observed in the cases of the 3-*O*-acylates and -silylate, and the *O*-(*N*-phenylcarbamoyl) protecting group could thus be discriminated chemically from the *O*-acetyl and *O*-benzoyl groups through *Procedure A*.

In the course of discussion on the mechanistic aspect of the second step in *Procedure A*, we assumed a possibility that the nucleophiles could attack the carbonyl carbon of **1** to give **3**, and, as expected, an alkyl *N*-phenylcarbamate was confirmed to be unmasked at a higher temperature; the results thus obtained are described below in *Procedures B and C*.

Procedure B using Bu_4NNO_2 as the nucleophile: Treatment of **1** with Bu_4NNO_2 (3 mol equiv.) in DMF at 80 °C for 1.5 h was successful to give **3** quantitatively. Similar treatment of **4a-f** with Bu_4NNO_2 (3 mol equiv.) resulted in reasonable yields of **5a-f** as summarized in Entries 7 - 12 in Table 1. In this case, however, the corresponding 3-acetate (**4c**; Entry 9), 3-benzoate (**4d**; Entry 10), 3-pivaloate (**4f**; Entry 12) afforded a mixture of the corresponding 3-acylates (**5c,d,f**) and 2-acylates (**5c',d',f'**), and **4e** (Entry 11) afforded a

mixture of 3- (**5e**) and 2-*O*-TBDMS (**5e'**) derivatives; it was not possible to control the acyl and silyl migration reactions above ca. 60 °C. A similar treatment of methyl 4-*O*-acetyl-3-*O*-methoxymethyl-2-*O*-(*N*-phenylcarbamoyl)-6-*O*-triphenylmethyl-α-D-glucopyranoside (**6**) gave the corresponding 2-hydroxyl derivative (**7**) in 96% yield. It is also of interest that Procedure B could differentiate the *O*-acyl groups from the *O*-(*N*-phenylcarbamoyl) group efficiently. Incidentally, it was confirmed on monitoring by TLC that all the reactions herein involved no *N*-nitrosation reaction.



Procedure C using tetrabutylammonium acetate and cesium acetate - 18-crown-6: On treatment with **1** in DMF at 80 °C for 1.5 h, nucleophiles of Bu_4NOAc (3 mol equiv.) and CsOAc (3 mol equiv.) - 18-crown-6 (3 mol equiv.) system as expected afforded **3** in 92% and 86% yields, respectively.

The corresponding alkyl *N*-*p*-tolylcarbamates and -*N*-*p*-nitrophenylcarbamates showed similar chemical behavior toward the agents under the conditions described above.

REFERENCES AND NOTES

The results described herein have been reported on the occasion of XIXth Japanese Carbohydrate Symposium, Nishinomiya, August 5 - 7, 1997, K. Sato, S. Akai, N. Nishino, J. Hiyama, and Y. Ishido, The Abstracts, D-16, p. 98.

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7. ^1H, ^{13}C, and ^{15}N NMR spectroscopic data of **2** obtained in DMSO-d_6 are as follows: ^1H NMR: δ 7.54 - 7.13 (5H, m, Ph), 5.93 (1H, d, H-1, $J_{1,2}$ = 3.6 Hz), 5.34 (1H, d, H-3, $J_{3,4}$ = 3.0 Hz), 5.00 (1H, d, H-2), 4.33 (1H, dd, H-4, $J_{4,5}$ = 5.6 Hz), 4.04 (1H, ddd, H-5, $J_{5,6a}$ = $J_{5,6b}$ = 6.3 Hz), 3.68 (1H, dd, H-6a, $J_{6a,6b}$ = 8.6 Hz), 3.62 (1H, dd, H-6b), 1.48, 1.33, 1.31, and 1.24 (3H x 4, each s, Me); ^{13}C NMR: δ 152.3 (C=O), 130.2, 129.9, 129.4, 128.1 (Ph), 111.4, 108.2 ($C(CH_3)_2$), 104.6 (C-1), 82.2 (C-2), 79.6 (C-3), 78.7 (C-4), 72.3 (C-5), 65.2 (C-6), 26.5 - 24.8 ($C(CH_3)_2$); ^{15}N NMR ($MeNO_2$ = -5.00): δ +210.9 [CON(*N*O)Ph] and -97.5 [CO*N*(NO)Ph].
8. The result suggests that the reaction might involve a considerable degree of *N*-denitrosation to the starting alkyl *N*-phenylcarbamate other than the objective unmasking reaction.
9. The molar proportion and the way of addition of acetic anhydride to Bu_4NNO_2 in this reaction is crucial as follows: Bu_4NNO_2 to Ac_2O (10 to 8 mol equiv.) gave **3** (60% yield) and its acetate, 4 to 1.5 mol equiv. gave **3** (39% yield), and 4 to (1.5 + 1.2) mol equiv. gave **3** (77% yield).
10. Elemental analyses of the substrates and products gave satisfactory results for their structures assigned.