N-HYDROXYAMIDE-CONTAINING HETEROCYCLES. PART 6. APPLICATION OF 1-HYDROXY-4,6-DIMETHYL-2(1*H*)-PYRIMIDINONE TO A NEW BENZYLOXYCARBONYLATING AGENT

Akira Katoh,* Syoichi Kondoh, and Junko Ohkanda
Department of Industrial Chemistry, Faculty of Engineering, Seikei University,
Musashino-shi, Tokyo 180, Japan

Abstract: An *N*-hydroxyamide-containing heterocycle, 1-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone **1** was allowed to react with benzyl chloroformate (Z-Cl) in the presence of pyridine to give the corresponding *O*-benzyloxycarbonyl-2(1*H*)-pyrimidinone **2**. Compound **2** was treated *in situ* with amines, amino acids, and alcohols under mild conditions to afford Z-protecting products in high yields. Judging from these experimental results, compound **2** was found to be a new convenient benzyloxycarbonylating agent.

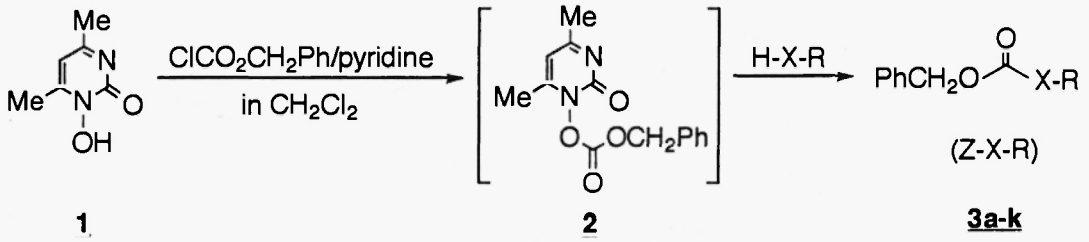
Introduction

The benzyloxycarbonyl (Z) group is one of the most convenient amine protecting group along with *tert*-butoxycarbonyl (Boc) one, because these urethane-type protection of amino acids is resistant to racemization during peptide syntheses (1,2). The Z-protecting group is easily removed by the catalytic hydrogenation with palladium on carbon. Recently the application of heterocycles to organic synthesis has received considerable attention. For example, pyridine (3), pyrimidine (4), and pyrazine (5-7) have been demonstrated to be useful *tert*-butoxycarbonylating agents. The utilization of 2-hydroxy- and 2-mercaptopyrazines as benzyloxycarbonylating agents has been reported by Ohta and co-workers (8), while no paper concerning 1-hydroxy-2(1*H*)-pyrimidinone has been reported, to the best of our knowledge. Since the pKa value of 1-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone **1** was estimated to be 6.1 (9), its *O*-acyl derivative is regarded as a kind of the active ester and should be applicable as the new mild acylating agent. As a part of our studies on the application of *N*-hydroxyamide-containing heterocycles to organic synthesis (10a), we describe here the utilization of 1-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone **1** as a new benzyloxycarbonyl carrier.

Results and Discussion

1-Hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone **1** was prepared by condensation of pentane-2,4-dione and *N*-benzyloxyurea and subsequent catalytic hydrogenation of 1-benzyloxy-4,6-dimethyl-2(1*H*)-pyrimidinone (10b). Compound **1** was treated with benzyl chloroformate in the presence of pyridine in CH_2Cl_2 at 0 °C to give the corresponding *O*-benzyloxycarbonyl-2(1*H*)-pyrimidinone **2**. In IR spectrum, compound **2** showed two absorption bands at 1810 and 1755 cm^{-1} characteristic of the active ester. Since the partial decomposition of compound **2** was observed during isolation, the one-

Table 1 : The Benzyloxycarbonylation of Amines, Amino Acids, and Alcohols[a]



1 **2** **3a-k**

Substrate (H-X-R)	Reaction conditions	Product (Z-X-R)		Yield (%)
H_2NCH_2Ph	room temp./3 h	**3a**	Z-$NHCH_2Ph$	85
H_2NPh	room temp./3 h	**3b**	Z-NHPh	63
pyrrolidine	room temp./3 h	**3c**	Z-pyrrolidine	84
morpholine	room temp./3 h	**3d**	Z-morpholine	97
H-L-Ala-OH	room temp./24 h	**3e**	Z-L-Ala-OH	87
H-L-Ala-OMe	room temp./3 h	**3f**	Z-L-Ala-OMe	78
H-L-Phe-OMe	room temp./3 h	**3g**	Z-L-Phe-OMe	75
$HOCH_2Ph$	room temp./20 h	**3h**	Z-OCH_2Ph	44
$HOCH_2Ph$	reflux/4 h[b]	**3h**	Z-OCH_2Ph	56
$HOCH_2Ph$	reflux/20 h[b]	**3h**	Z-OCH_2Ph	85
$HOPr^n$	reflux/20 h[b]	**3i**	Z-OPr^n	73
$HOCH(Et)_2$	reflux/ 48 h[b]	**3j**	Z-$OCH(Et)_2$	0
HOPh[c]	NaH, reflux/ 48 h[b]	**3k**	Z-OPh	0

[a]Ref. 16. [b]In benzene. [c]Attempts to prepare Z-OPh in the presence / absence of Et_3N were also unsuccessful, and the starting material was completely recovered.

pot reaction was carried out as follows. To a solution of compound **1** (280 mg, 2 mmol) and pyridine (175 mg, 2.2 mmol) in CH_2Cl_2 (10 ml) was added dropwise a solution of benzyl chloroformate (360 mg, 2.1 mmol) in CH_2Cl_2 (5 ml) at 0 °C, and then the solution was stirred for 1h (the reaction was checked by monitoring TLC). To the mixture was added a solution of benzylamine (215 mg, 2 mmol) in CH_2Cl_2 (5 ml), and the reaction mixture was stirred for another 3 h at room temperature. The CH_2Cl_2 layer was successively washed with 10% KOH (10 ml), 10% HCl (10 ml), H_2O (10 ml), and then dried over anhydrous Na_2SO_4. Column chromatography on silica gel with $CHCl_3$ afforded *N*-benzyloxycarbonylbenzylamine **3a** in a 85% yield. Similarly the benzyloxycarbonylation of other aliphatic and aromatic amines proceeded in good to high yields as shown in Table 1. In contrast to 2-hydroxy- and 2-mercaptopyrazines (8), the treatment of aniline with the active ester **2** gave *N*-benzyloxycarbonylaniline **3b** in a 63% yield. The one-pot benzyloxycarbonylation of L-alanine was

carried out as follows. To a solution of compound **2** (1 mmol) in MeCN (5 ml) was added a solution of L-alanine (98 mg, 1.1 mmol) and Et_3N (222 mg, 2.2 mmol) in H_2O (5 ml). The mixture was stirred for 24 h at room temperature, diluted with H_2O (25 ml), and then washed with AcOEt (10 ml). The aqueous layer was acidified to pH 2 with 5N HCl and extracted with AcOEt (50 ml). The organic layer was washed with H_2O (20 ml), brine (20 ml), and then dried over anhydrous $MgSO_4$. Evaporation and subsequent purification by recrystallization from AcOEt-petroleum ether afforded the product **3e** in a 87% yield. The specific rotation of the product **3e** was identical with the reported value (14), indicating that a measurable racemization did not occur during this reaction. Similarly two amino acids were also subjected to the one-pot benzyloxycarbonylation to give the corresponding Z-amino acids in good yields. The benzyloxycarbonylation of benzylalcohol was carried out at room temperature in a similar fashion to amines, but the desired cabonate **3h** was obtained only in 44% yield. Refluxing the reaction mixture in benzene for 20 h improved the yield of the product **3h** up to 85%. Propanol gave the corresponding carbonate **3i** in a 73% yield. Neither secondary alcohol, 3-pentanol, nor aromatic phenol gave the desired carbonates even under more forced conditions.

In conclusion, 1-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone was shown to be a new efficient benzyloxycarbonylating reagent for amines, amino acids, and alcohols.

References and Notes

Part 5. J. Ohkanda and A. Katoh, *Tetrahedron* in press

(1) R. Geiger and W. König, "*The Peptides*", Vol. 3, pp.1-88, ed. by E Gross and J. Meienhofer, Academic Press, New York, 1981

(2) T. W. Greene and P. G. M. Wuts,"*Protective Groups in Organic Synthesis*", John Willey & Sons Inc., New York, 1991

(3) S. Kim and J. I. Lee, *Chemistry Lett.* 237(1984)

(4) T. Nagasawa, K. Kuroiwa, K. Narita, and Y. Isowa, *Bull. Chem. Soc. Jpn.* **46**, 1269(1973)

(5) A. Ohta, M. Shimazaki, H. Tamamura, Y. Mamiya, and T. Watanabe, *J. Heterocycl. Chem.* **20**, 951(1983)

(6) A. Ohta, Y. Inagawa, M. Inoue, M. Shimazaki, and Y. Mamiya, *J. Heterocycl. Chem.* **22**, 1173(1985)

(7) Y. Okuwaki, Y. Inagawa, H. Tamamura, T. Suzuki, H. Kuwana, M. Tahara, K. Yuasa, and A. Ohta, *J. Heterocycl. Chem.* **24**, 187(1987)

(8) A. Ohta, Y. Inagawa, and C. Mitsugi, *J. Heterocycl. Chem.* **22**, 1643(1985)

(9) G. Zvilichovsky, *Tetrahedron* **23**, 353(1967)

(10) a) A. Katoh, J. Ohkanda, Y. Itoh, and K. Mitsuhashi, *Chemistry Lett.* 2009(1992); b) J. Ohkanda, T. Tokumitsu, K. Mitsuhashi, and A. Katoh, *Bull. Chem. Soc. Jpn.* **66**, 841(1993)

(11) M. A. Casadei and D. Pletcher, *Synthesis* 1118(1987)

(12) C. Bakhtiar and E. H. Smith, *J. Chem. Soc. Perkin Trans. 1,* 239(1994)

(13) K. Kondo, N. Sonoda, and S. Tsutsumi, *Tetrahedron Lett.*, 4885(1971)

(14) Y. Kita, J. Haruta, K. Fukunaga, Y. Shirouchi, and Y. Tamura, *J. Org. Chem.* **47**, 2697(1982)

(15) M. Selva, C. A. Marques, and P. Tundo, *J. Chem. Soc. Perkin Trans. 1,* 1889(1995)

(16) **3a** (14) IR($CHCl_3$): 3448 and 1718 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 4.38 (2H, d, J=8 Hz), 5.05 (1H, br s), 5.14 (2H, s), and 7.38 ppm (10H, m); **3b** IR($CHCl_3$): 3435 and 1736 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 5.21 (2H, s), 7.05 (1H, br s), and 7.34 ppm (10H, m). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.67; H, 5.79. Found C, 73.99; H, 5.77.; **3c** (5) IR($CHCl_3$): 1720 cm^{-1}; ^1H NMR(δ, $CDCl_3$): 1.86 (4H, m), 3.37 (4H, m), 5.12 (2H, s), and 7.36 ppm (5H, m); **3d** (11) IR($CHCl_3$): 1720 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 3.49 (4H, m), 3.65 (4H, m), 5.12 (2H, s), and 7.31 ppm (5H, m); **3e** (14) IR(neat): 3480-2600, 1720, and 1700 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 1.43 (3H, d, J=7 Hz), 4.40 (1H, m), 5.10 (2H, s), 5.41 (1H, br s), and 7. 34 ppm (5H, m), $[\alpha]_D^{23}$ -17.9° (c 0.23 in AcOH) {lit (14) $[\alpha]_D^{27}$ -14.5° (c 0.21 in AcOH)}; **3f** IR($CHCl_3$): 3435, 1740, and 1720 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 1.20 (3H, d, J=7 Hz), 3.50 (3H, s), 4.2 (1H, quint, J=7 Hz), 4.92 (2H, s), 5.30 (1H, br s), and 7.18 ppm (5H, m). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found C, 60.81; H, 6.52.; **3g** IR($CHCl_3$): 3430, 1740, and 1717 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 3.0-3.2 (2H, m), 3.64 (3H, s), 4.51 (1H, m), 5.10 (2H, s), 5.33 (1H, br s), and 7.25 ppm (10H, m), $[\alpha]_D^{25}$ +6.4° (c 1.0 in AcOH) Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.03; H, 6.26. Found C, 68.09; H, 6.11.; **3h** (12, 13, 15) IR($CHCl_3$): 1709 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 5.14 (4H, s) and 7.38 ppm (10H, m); **3i** (13) IR(neat): 1760 cm^{-1}, ^1H NMR(δ, $CDCl_3$): 0.94 (3H, t, J=7 Hz), 1.67 (2H, q, J=7 Hz), 4.09 (2H, t, J=7 Hz), 5.13 (2H, s), and 7.34 ppm (5H, m).

Received October 9, 1995