Communications to the Editor

Polymeric Protecting Groups. 6.† Synthesis of a Novel *N*-Ethenoxyamino-Modified *tert*-Butoxycarbonyl-Type Amino Protecting Group

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Introduction. The classical *tert*-butoxycarbonyl (BOC) protecting group is still one of the most important amino protecting groups[2–4] and has enriched peptide chemistry since its discovery by Carpino, McKay, and Albertson in 1957.[5,6] The *tert*-butyl rest offers advantages of resistance against strong alkali, catalytic hydrogenation, and reduction by Na. Therefore, the BOC group, for example, is the ideal partner of the Z group in peptide chemistry. In the field of solid-phase peptide synthesis the classical BOC group, for example, is used as a side group of a polystyrene resin known as the commercially available "*Merrifield Hydrazide Resin*".[7]

Trifluoroacetic acid is often a convenient reagent for the removal of the classical BOC group, but much more acidic reagents are used under the formation of isobutene and carbon dioxide.[4,8]

Our interest in the chemistry of the BOC group led to the development of *N*-acylamino-modified BOC-type protecting groups.[1,9–11] They show a peculiar cleavage mechanism under the formation of 4,5-dihydrooxazole derivatives according to Scheme 1.

In our previous papers[1,9–11] we described the synthesis and the behavior of some low-molecular, monomeric and polymeric *N*-acylamino-modified BOC derivatives. The reactivities relative to the acid-induced cleavage and the solubilities of these derivatives are controlled by the *N*-acyl moiety.

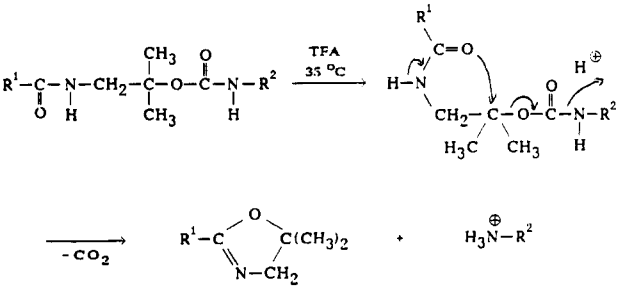
For extension of our concept to modify the BOC group, the present paper deals with the synthesis of the vinyl compound 1,1-dimethyl-2-(ethoxymethanamido)ethyl [*N*-(4-chlorophenyl)amino]methanoate (**5**) and its behavior as a polymeric protecting group. Kinetic measurements of the deprotection of this model compound are followed by means of ^{1}H NMR spectroscopy.

Results and Discussion. The reaction of vinyl chloroformate (**1**) with 3-amino-2-methyl-2-propanol (**2**)[12] was carried out in THF in the presence of triethylamine to give *N*-(2-hydroxy-2-methylpropyl)vinylcarbamate (**3**)[13] (Scheme 2).

In order to obtain the desired monomer 1,1-dimethyl-2-(ethenoxymethanamido)ethyl [*N*-(4-chlorophenyl)-amino]methanoate (**5**), the urethane-modified *tert*-butyl alcohol **3** was reacted with 4-chlorophenyl isocyanate (**4**) as a model amino compound in boiling benzene in the presence of DMAP as catalyst[14] (Scheme 3).

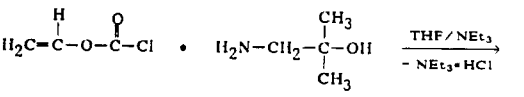
Furthermore, monomer **5** was homo- and copolymerized with 2,2′-azobis(isobutyronitrile) (AIBN) as a radical initiator with methyl acrylate yielding polymers **6**[15] and **7**[16] (Chart 1), that are soluble in many organic solvents like benzene, chloroform, THF, and DMF. The composition of the copolymer was determined by means of ^{1}H NMR spectroscopy and elemental analysis.

Scheme 1[a]

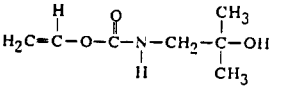


[a] R^1 = *N*-acyl-modification, e.g., alkyl, methacryl; R^2 = protected amine

Scheme 2



1 **2**



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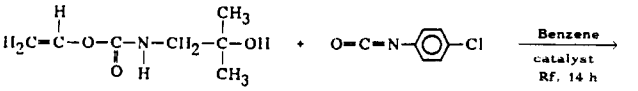
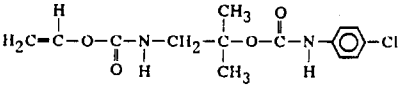
Scheme 3

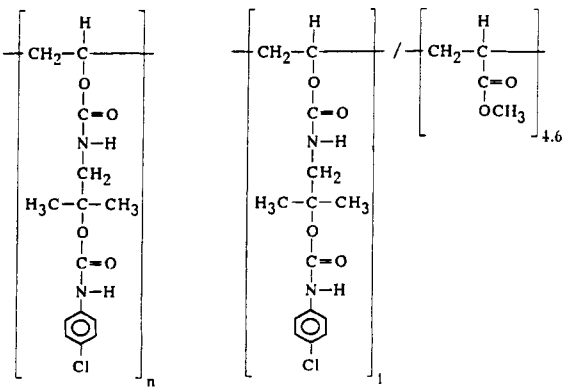


3 **4**



5

Chart 1



6 **7**

† Part 5: cf. ref 1.

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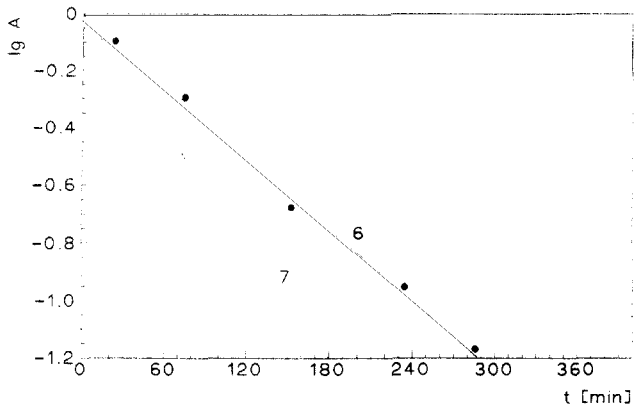

Figure 1. Time/log conversion plot for the TFA-induced cleavage of chloroaniline.

Table 1. Half-time Values τ and Reaction Rate Constants for the Deprotection of Homopolymer 6 and Copolymer 7

	6	7
τ in TFA (min)	70	45
τ in TFA/$CaCl_2$ (min)	30	25
τ in HBr/HOAc (min)	<5	<5
k (in TFA) (s^{-1})	16.2×10^{-5}	26.0×10^{-5}

Under acidic conditions, spontaneous polymerization of monomer **5** was observed. Therefore, only the polymeric derivatives **6** and **7** were used for kinetic measurements.

Time-dependent cleavage of the amine was performed according to our previous paper[1] by measuring the integrals of the ^1H NMR signals at 7.25 ppm (aromatic protons) of the protected amine versus the signals of the released aniline at 7.49 ppm.

TFA, TFA/$CaCl_2$, and HBr/HOAc were used as deprotecting reagents.[17] In this way, half-time values (τ) of the deprotection and the reaction rate constant k in TFA were obtained. In HBr/HOAc as solvent, the reaction rate was too fast to determine the reaction rate constant by this NMR method.

Figure 1 shows the time/log conversion plot for the TFA-induced cleavage of chloroaniline, and Table 1 summarizes the obtained values of τ and k.

The significant difference in the sensitivities of the homo- and copolymers can be explained by lowering the probability of hydrogen-bond formation between neighboring amide groups by copolymerization. Calcium ions cause the destruction of these hydrogen bonds and may activate the urethane functions to enhance the rate of deprotection. Similar copolymer effects have been found also with analogous methacryl polymers.

According to recent observations,[1,11] the cleavage of the polymer-protected amine in HBr/HOAc is much faster with violent CO_2 evolution in comparison with TFA as the deprotecting solvent.

From our results it can be concluded that the presented polymeric [1,1-dimethyl-2-(ethenoxymethanamido)ethoxy]-carbonyl function is a further useful *N*-acylamino modification for the BOC amino protecting group. It shows a peculiar cleavage mechanism, leading to the inert oxazole derivative in contrast to the reactive isobutene in the case of the classical BOC group. Additionally, the new modification opens an interesting application in the area of peptide chemistry because of the rapid cleavage in HBr/HOAc as a deprotection reagent and the good solubility in organic solvents.

References and Notes

(1) Gormanns, M.; Ritter, H. *Makromol. Chem.* **1993**, *194*, 2615.
(2) Barany, G.; Kneib-Cordonier, N.; Mullen, D. G. *Int. J. Peptide Protein Res.* **1987**, *30*, 705.
(3) Wieland, T.; Bodansky, M. *The World of Peptides*; Springer: Berlin, 1991.
(4) Bodansky, M. *The Principles of Peptide Synthesis*; Springer: Berlin, 1993.
(5) Carpino, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 98.
(6) McKay, F. C.; Albertson, N. F. *J. Am. Chem. Soc.* **1957**, *79*, 4686.
(7) Kossmehl, G. A. Polymeric reagents. In *Handbook of polymer synthesis*, part B; Kricheldorf, H., Ed.; Dekker: New York, 1992.
(8) Wünsch, E. *Houben-Weyl*; Müller, E., Eds.; Thieme: Stuttgart, Germany, 1974; Vol. 15/1; pp 46ff.
(9) Rehse, H.; Ritter, H. *Makromol. Chem.* **1989**, *190*, 697.
(10) Rehse, H.; Ritter, H. *Polym. Bull.* **1990**, *23*, 1.
(11) Gormanns, M.; Ritter, H. *Tetrahedron* **1993**, *49*, 6965.
(12) Krassuki, M. K. *C.R. Hebd. Seances Acad. Sci.* **1908**, *46*, 236.
(13) Vinyl chloroformate (1; 1.70 mL, 20 mmol) in absolute THF (20 mL) was added in a small portion to a cold (−10 °C) stirred solution of a mixture of 3-amino-2-methyl-2-propanol (**2**)[11] (1.78 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol) in absolute THF (30 mL). The reaction mixture was stirred at this temperature for 1 h. The reaction temperature was raised up to room temperature and stirred an additional 1 day. The triethylamine hydrochloride was filtered off and the solvent evaporated. The residue was dissolved in chloroform and washed twice with 1 N HCl and water, and finally the organic phase was dried. Evaporation of the solvent led to a slight yellow oil of **3** (51% yield). **3**: IR (film) 1720 (amide I), 1650 (C=C, vinyl), 1530 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ 1.12 (s, 6H), 3.09 (d, ^3J = 6.2 Hz, 2 H), 3.43 (s, 1H), 5.90 (s, 1H), 4.32, 4.64, 7.07 (3H, ν_A, ν_M, ν_X, J_{AM} = 1.46 Hz, J_{AX} = 13.94 Hz, J_{MX} = 622 Hz). Elem anal. Calcd for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 52.4; H, 8.3; N, 8.7.
(14) Compound **3** (0.79 g, 5 mmol) was dissolved together with 4-chlorophenyl isocyanate (**4**; 0.78 g, 5 mmol) and dibutyltin dilaurate (0.02 mL) as catalyst in benzene (20 mL) and heated under reflux for 14 h. After evaporation of the solvent, the resulting oil was diluted with chloroform (10 mL) and washed twice with water. The organic layer was dried, the solvent was evaporated, and the resulting oil was covered with ether to precipitate light brown crystals at −5 °C (68% yield). **5**: mp 43–45 °C; IR (KBr) 1750 and 1720 (amide I), 1640 (C=C, olefin), 1600/1500 (C=C, aromatic), 1540 (amide II) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 6H), 3.51 (d, ^3J = 6.4 Hz, 2H), 5.68 (t, ^3J = 5.2 Hz, 1H), 4.44, 4.75, 7.20 (3H, ν_A, ν_M, ν_X, J_{AM} = 1.46 Hz, J_{AX} = 13.94 Hz, J_{MX} = 6.22 Hz), 7.25 (4H, C_6H_4–); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.05, 49.65, 81.94, 95.18, 119.80, 128.35, 128.88, 136.28, 141.86, 152.38, 153.86. Elem anal. Calcd for $C_{14}H_{17}ClN_2O_4$: C, 53.7; H, 5.4; N, 8.9. Found: C, 53.3; H, 5.3; N, 8.7.
(15) Monomer **5** (312 mg, 1 mmol) and 5 mol % 2,2′-azobis-(isobutyronitrile) (AIBN) (6.7 mg, 0.05 mmol) were dissolved in THF (2 mL). The reaction mixture was heated at 60 °C for 24 h in a nitrogen atmosphere. The solution was poured into ether. The precipitated homopolymer was filtered and dried (89% yield). **6**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–2.00 (9H), 3.40 (3H), 7.15–7.30 (5H). Elem anal. Calcd for $[C_{14}H_{17}ClN_2O_4]_n$: C, 53.7; H, 5.4; N, 8.9. Found: C, 53.4; H, 5.3; N, 8.7. Viscosity: η_{spez}/c = 10.2 [10^{-3} L/g] with c = 4.0 g/L (DMF, 25 °C).
(16) Monomer **5** (156 mg, 0.5 mmol) and acrylic acid methyl ester (215 mg, 2.5 mmol) were copolymerized analogously to **6** with 89% yield. **7**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–2.00 (–CCH_2–, –C(CH_3)$_2$, –CH) 3.40 (OCH_3, NHCH_2–, NH–), 7.15–7.30 (C_6H_4–, NH–). Elem anal. Calcd for $[C_{14}H_{17}O_4N_2Cl]_1[C_4H_6O_2]_{4.6}$: C, 53.7; H, 5.4; N, 8.9. Found: C, 53.3; H, 5.3; N, 8.8. Viscosity: η_{spez}/c = 11.8 [10^{-3} L/g] with c = 4.0 g/L (DMF, 25 °C).
(17) The cleavage of the amine took place as follows: 100 mg of homopolymer **6** or copolymer **7** was dissolved in 350 μL of deprotecting reagent, and the solution was analyzed by NMR spectroscopy at 35 °C. The addition of 50 mg of $CaCl_2$ led to the formation of a sediment.