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3-ACYL- AND 3-ALKOXYCARBONYL-2-OXAZOLONES AND THEIR HOMOPOLYMERS AS AMINO-PROTECTING REAGENTS

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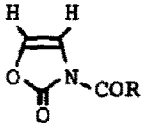
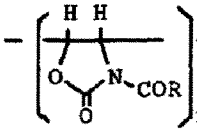
[Summary] 3-Acyl- and 3-alkoxycarbonyl-2-oxazolones as well as their homopolymers serve as practically useful N-protecting reagents of amines including α-amino acids.

The successful use of the five-membered heterocycles such as N-substituted thiazolidines[1] and imidazoles[2] in a wide aspects of synthetic chemistry has prompted us to explore the potential applications of N-acyl-2-oxazolones and the derived-polymers in acylation reactions.

In the course of study on the 2-oxazolone telomers[3], it was noticed that 3-acetyl-2-oxazolone showed remarkably high reactivity toward nucleophiles such as amines and thiols, and 2-oxazolone moiety could play a role as a pertinent leaving group in amino-protection as well as carboxyl-activation, particularly in peptide synthesis[4]. This paper describes the utility of 3-acyl-[5], 3-benzyloxycarbonyl(Cbz)- and 3-tert-butoxycarbonyl(Boc)-2-oxazolones (1~3) and their homopolymers (4, 5) as stable but highly reactive acylating agents.



1 : R=CH_3
2 : R=$OCH_2C_6H_5$
3 : R=O-t-Bu



4 : R=CH_3
5 : R=$OCH_2C_6H_5$

Treatment of 2-oxazolone with benzyloxycarbonyl chloride or with phosgene followed by tert-butanol gave the "ready-to-use" type reagents 2 (Cbz-Ox)[6], mp 85° and 3 (Boc-Ox)[6], mp 83.5°, both of which could be stored in the air at room temperature for months without any practical decompositions. Homopolymers 4[3] and 5[6] (mp 180-90°) were readily obtained as a colorless powder by radical polymerization of the corresponding monomers, except for the highly crowded N-Boc derivative 3.

Reagents 1 and even 4 were found to be much more reactive toward amines than 3-acetyl-2-oxazolidone 6 and thus, acetylation of benzyl-amine (and -mercaptane) with 1 and 4 in DMF or CH_3CN went to above 95% completion within 0.1-1 hr at ambient temperature, while 6 gave only 10% yield of the acetate after 10hr. Reagent 4 was sufficiently reactive in suspensions (THF) as well. By-products, 2-oxazolone (readily water-soluble) and poly-2-oxazolone (insoluble in most solvents) could be easily removed from the reaction mixture. The acetylation of alcohols required a tertiary amine and more drastic conditions (at 55° for 17hr for benzylalcohol). Thus, type 1 compounds were shown to be the advantageous reagents for both selective

Table I. Isolated Yields(%) in N-Benzyloxy- and N-Butoxy-carbonylation of amines[a]

Reagent	Benzylamine	Piperidine	Gly	L-Ala	L-Pro	L-Phe	L-Trp
Cbz-Ox(2)	85[b] (82)[c]	93[d] (80)[e]	98	90	93	87(97)[f]	81
Boc-Ox(3)	80[g]	82[g]	86	96[h]	92	93[h]	60(96)[h]

a: The materials were treated with the reagents(1.1-1.5 equiv. mol) in 30% aqueous acetone(Cbz-Ox) or 50% aqueous dioxane (Boc-Ox) in the presence of Et_3N(1.5 eq)(for amino acids) at room temperature overnight, unless otherwise cited. b: In benzene for 2hr. c: With 5(1.5 eq) dissolved in CH_3CN. d: In DMF for 1hr. e: With 5(1.5 eq) suspended in benzene for 2hr. f: With 2(2 eq). g: In DMF for 4hr. h: With 4-dimethylaminopyridine as a base.

N-acylation and N,O-diacylation of amino-alcohols in the absence and presence of triethylamine, respectively.

In alkoxycarbonylation of amines including α-amino acids with reagents 2 and 3, good to excellent yields were obtained under mild conditions, as indicated in Table I. Polymeric agent 5 was also effective in either soluble (DMF, THF and CH_3CN) or insoluble (benzene) media at room temperature. Compound 3 butoxycarbonylated amino acids ten times faster than N-tert-butoxycarbonyl-2-benzoxazolone (mp 81°) in methanol at 20°.

Highly preservable reagents 2 and 3 may be the competitors for currently available reagents[7] widely used for amino-protection.

The preparation of N-Boc-L-proline provides the typical experimental procedure: A solution of L-proline (1mmol), Boc-Ox (1.5mmol) and Et_3N (or DBU)(1.5mmol) in 50% aqueous dioxane (3ml) was kept at room temperature overnight. To the mixture were added water (20ml) and ethyl acetate (15ml), and the aqueous layer separated was acidified with citric acid followed by usual work-up to give N-Boc-L-proline as a solid (0.20g), mp 133°, $[\alpha]_D^{22}$ -59.8°(c=2, AcOH).

References and Notes

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2. E. J. Corey and D. J. Brunelle, Tetrahedron Lett., 3409 (1976); D. W. Brooks, L. D. L. Lu and S. Masamune, Angew. Chem. int. Ed., 18, 72 (1979) etc.
3. Y. Abe and T. Kunieda, Tetrahedron Lett., 5007 (1979).
4. Diphenyl 2-oxo-3-oxazolylphosphate(i) derived from 2-oxazolone and $(PhO)_2POCl$ served satisfactorily as a condensing agent in peptide in peptide synthesis (ex. N-Cbz-L-Phe-Gly-OEt : 83%, $[\alpha]_D^{25}$-16.8°(EtOH). This will be the subject in a separate paper.
5. cf. K. H. Scholz, H. G. Heine and W. Hartmann, Ann., 1319 (1976). 3-Acyl-2-oxazolones were conveniently prepared from carboxylic acids by phospho-oxazolide (i) and smoothly reduced to aldehydes with $LiAlH(O\text{-}t\text{-}Bu)_3$ at -20° (ex. benzaldehyde : 61%).
6. 2(83%) : IR 1815, 1730 cm^{-1}, NMR($CDCl_3$) δ5.32(2H,s), 6.75(1H,d,J=2.0Hz), 7.02(1H,d,J=2.0Hz), 7.40(5H,s). 3(60%) : IR 1815, 1730 cm^{-1}, NMR($CDCl_3$) δ1.50(9H,s), 6.86(1H,d,J=2.0Hz), 7.08(1H,d,J=2.0Hz). 5(75%) : IR 1820, 1730 cm^{-1}, NMR(CH_3CN) δ4.94(2H,b.s), 5.14(2H,b.s), 7.25(5H,b.s), MW 10300(by GPC method).
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