A NEW SYNTHESIS OF 4-METHOXYCARBONYLOXAZOLES USING DIETHYL PHOSPHOROCYANIDATE(DEPC) AND ITS APPLICATION TO THE SYNTHESIS OF 3-AMINO-4-HYDROXYTETRONES [1]

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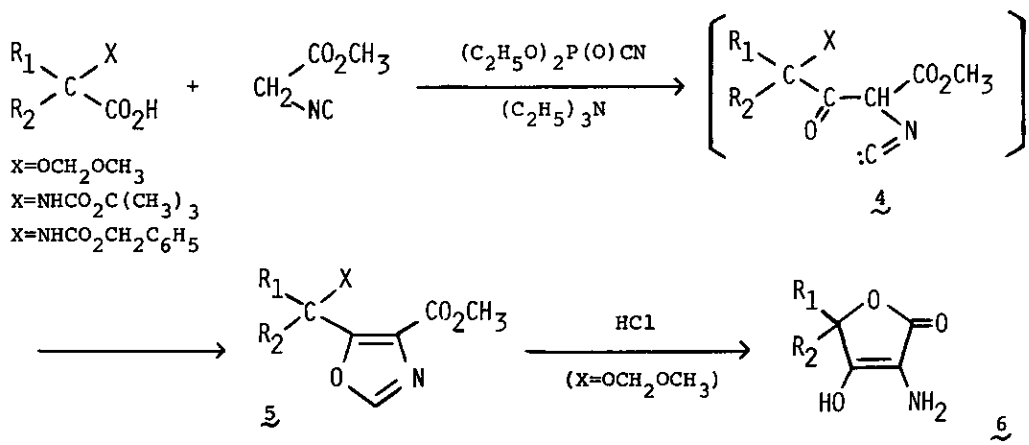
Abstract —— *Diethyl phosphorocyanidate(DEPC) may be used for the direct C-acylation of methyl isocyanoacetate with carboxylic acids. Some of the resulting 4-methoxycarbonyloxazoles have been efficiently converted to 3-amino-4-hydroxytetrones, a class of amino reductones.*

Recent publications from our laboratories[2,3] have demonstrated that diethyl phosphorocyanidate(DEPC, $(C_2H_5O)_2P(O)CN$),[4] in combination with triethylamine, can be used for the direct C-acylation of active methylene or methyl compounds with carboxylic acids. Further investigations along this line have revealed that methyl isocyanoacetate can be acylated with carboxylic acids(1-3) by the use of DEPC and triethylamine to give 4-methoxycarbonyloxazoles(5)[5] via the C-acylated intermediates (4). Oxazoles(5) derived from α-methoxymethyloxycarboxylic acids(1) have been further converted to 3-amino-4-hydroxytetrones(6), a class of amino reductones, by the acid treatment.



1: X=OCH_2OCH_3
2: X=$NHCO_2C(CH_3)_3$
3: X=$NHCO_2CH_2C_6H_5$

Preparation of 4-methoxy or ethoxycarbonyloxazoles has been carried out by the C-acylation of methyl or ethyl isocyanoacetate with acid chlorides,[6,7] acid anhydrides,[7] benzoxazines,[8] or selenol esters.[9] No reports have been concerned with the C-acylation by the direct use of carboxylic acids without prior isolation of active intermediates. DEPC in the presence of triethylamine, however, allows the direct C-acylation of methyl isocyanoacetate with carboxylic acids(1-3) to give 4-methoxycarbonyloxazoles(5).

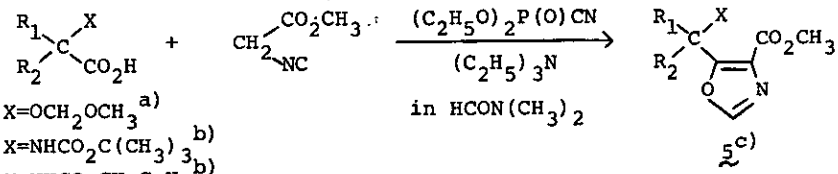
A typical experimental procedure is as follows: To the carboxylic acid(1-3, 6 mM) in dimethylformamide(4 ml) was added DEPC(1.06 g, 6.5 mM) in dimethylformamide(4 ml) at -15° under nitrogen, followed by the addition of triethylamine(0.607 g, 6 mM) in dimethylformamide(4 ml). After the mixture was stirred at -15° for 15 min (45 min for runs 5-10 in Table I), a mixture of methyl isocyanoacetate(0.496 g, 5 mM) and triethylamine(1.52 g, 15 mM) in dimethylformamide(10 ml) was added. The mixture was stirred at -15° for 2 hr and at room temperature for 18 hr(2 hr for runs 5-10). Ethyl acetate(40 ml) and benzene(20 ml) were added, and the mixture was successively washed with water, sat. aq. sodium bicarbonate, water, and sat. aq. sodium chloride, and then dried over sodium sulfate. After evaporation in vacuo, the crude residue was fractionated by silica gel column chromatography with ethyl acetate-hexane(runs 1-5,8) or diethyl ether-hexane(runs 6,7,9,10) and then purified by Kugelrohr distillation or recrystallization.

The results are summarized in Table I. Four equivalents of triethylamine were required to conduct the oxazole synthesis smoothly while 3 equivalents of the base were usually enough for the other direct C-acylation using DEPC.[2,3] This might cause a considerable racemization when N-protected L-amino acids(2 and 3) were used for the oxazole synthesis, and the racemization would occur in the stage of the acylated intermediates(4).

Treatment of 4-methoxycarbonyloxazoles(5), derived from α-methoxymethyloxycarboxylic acids(1), with 10 % methanolic hydrogen chloride at room temperature for several hours afforded 3-amino-4-hydroxytetrones(6), a class of furanose amino reductones, in excellent yields(Table II). Since aminoreductones(6), even in the hydrochloride form, were very susceptible to air oxidation just like ascorbic acid, a representative of reductones,[10] they were immediately converted to stable N-acetyl derivatives(7) with acetic anhydride and sodium bicarbonate.

Using similar reaction sequences, 3-acetamido-4-hydroxycoumarin(10)[11,12] was efficiently prepared from 2-methoxymethyloxybenzoic acid(8)[13] by the C-acylation

Table I. C-Acylation of Methyl Isocyanoacetate

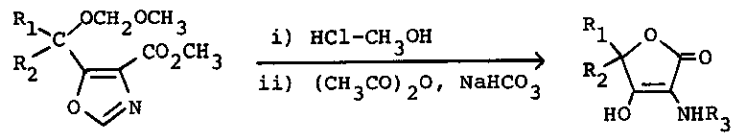


1: X=OCH_2OCH_3 a)
2: X=$NHCO_2C(CH_3)_3$ b)
3: X=$NHCO_2CH_2C_6H_5$ b)

Run	R_1	R_2	X	Yield, %	(Bp/mmHg) d) or Mp(rec. solv.)
1	CH_3	H	OCH_2OCH_3	50	(100°/0.25)
2	CH_3CH_2	H	OCH_2OCH_3	43	(101°/0.14)
3	CH_3	CH_3	OCH_2OCH_3	28	(102°/0.25)
4	C_6H_5	H	OCH_2OCH_3	42	(150°/0.4)
5	H	H	$NHCO_2C(CH_3)_3$	41	72-75°(Et_2O-hexane)
6	CH_3	H	$NHCO_2C(CH_3)_3$	73	75-77°(Et_2O-hexane)
7	$(CH_3)_2CH$	H	$NHCO_2C(CH_3)_3$	76	87-88°(Et_2O)
8	$(CH_3)_2CHCH_2$	H	$NHCO_2C(CH_3)_3$	56	50-59°(Et_2O-hexane)
9	$C_6H_5CH_2$	H	$NHCO_2C(CH_3)_3$	45	106-110°(EtOAc)
10	$C_6H_5CH_2$	H	$NHCO_2CH_2C_6H_5$	35.5	133-133.5°(EtOAc-hexane)

a) Prepared in ca. 80 % overall yields by the treatment of DL-α-hydroxy acid esters with methoxymethyl chloride in the presence of N,N-diethylaniline, followed by alkaline hydrolysis. b) L-Amino acid derivatives were used except run 5. c) Characterized by NMR and IR spectral means and elemental composition. Racemic oxazoles were obtained except runs 3 and 5. d) By Kugelrohr distillation.

Table II. Synthesis of 3-Amino-4-hydroxytetrones



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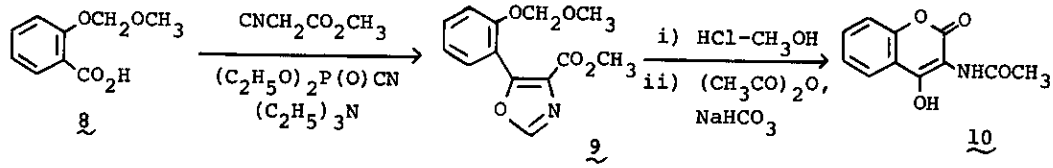
6: R_3=H
7: R_3=$COCH_3$ a)

Run	R_1	R_2	Yield, %, b) of 7	Mp(rec. solv.)
1	CH_3	H	91	153-153.5°(EtOAc-hexane)
2	CH_3CH_2	H	80	159-159.5°(Et_2O-hexane)
3	CH_3	CH_3	96	140°(Et_2O-hexane)
4	C_6H_5	H	90	201-202°(EtOAc-hexane)

a) Characterized by NMR and IR spectral means and elemental composition. b) Overall yield from oxazoles (5).



8 9 10

(81 % yield), acid treatment[14] of the oxazole(9),[15] and then acetylation(95 % yield), as shown above.

Since reductones, in general, are known as physiologically active compounds,[10] we are now examining the physiological activity of amino reductones(6, 7, and 10).

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References and Notes

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9. A.P. Kozikowski and A. Ames, J. Am. Chem. Soc., 102, 860(1980).
10. For reviews on reductones, see K. Schank, Synthesis, 176(1972); H. Omura, Eiyo To Shokuryo, 31, 9(1978); H. Obata, Kagaku(Kyoto), 34, 456(1979).
11. Matsumoto and co-workers reported[7b] a synthesis of 3-amino-4-hydroxycoumarin from acetylsalicylic acid chloride(or acetylsalicylic anhydride) and methyl isocyanoacetate.
12. Mp 224-225°(lit. mp 222-224°, see C.F. Huebner and K.P Link, J. Am. Chem. Soc., 67, 99(1945)).
13. Mp 42-43°(EtOAc-hexane). Prepared from methyl salicylate by the salt formation with sodium hydride, the reaction with methoxymethyl chloride, and then alkaline hydrolysis.
14. Heating at reflux was required in 10 % methanolic hydrogen chloride for 5 hr.
15. Mp 69-71°(EtOAc-hexane).

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