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EFFICIENT SYNTHESIS OF SECONDARY CARBOXAMIDES WITH ω-SUBSTITUTED ETHYL AND PROPYL GROUPS ON NITROGEN ATOM BY NUCLEOPHILIC RING OPENING OF CYCLIC IMIDATES

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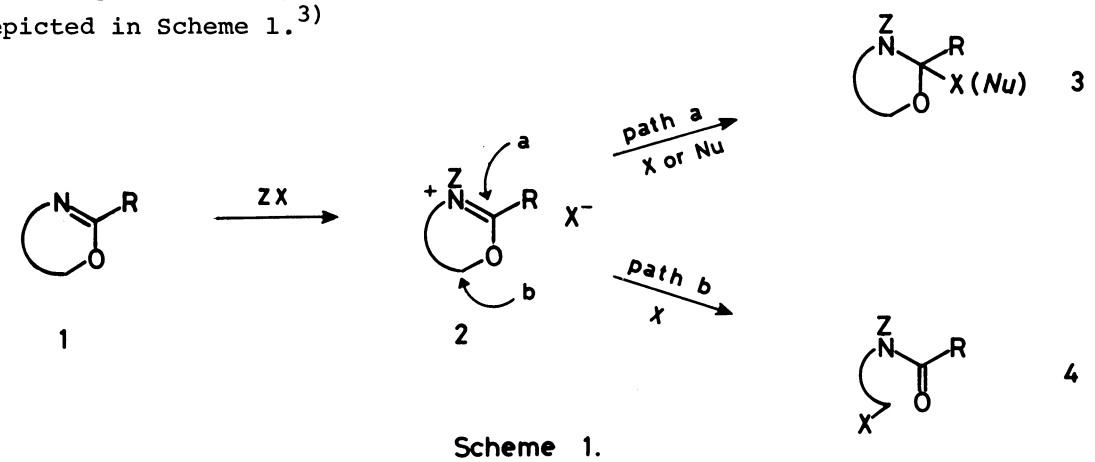
An efficient synthesis of secondary carboxamides carrying ω-substituted ethyl and propyl groups on nitrogen atom has been developed which highlights nucleophilic ring opening of 2-methyl-2-oxazoline, 2-methyl-2-oxazine, and their derivatives with $(CH_3)_3SiX$ and HX (X= Cl, N_3, SeC_6H_5, SC_6H_5) type reagents.

The cyclic imidates such as 2-oxazoline and 2-oxazine derivatives have proven promising as a masked formyl or carboxyl equivalent in the synthesis of a myriad of organic compounds both in chiral and achiral forms.[1] Synthetic application of them as a carboxamide synthon, however, has not been explored yet so far with a few exceptions[2] in spite of its potential utility as a non-condensative route to carboxamides. In principle, cyclic imidates (1) are susceptible to nucleophilic attack via path (a) or path (b), if it is converted to imidatonium ion stage (2) as depicted in Scheme 1.[3]



Scheme 1.

In connection with our research programs concerned with the total synthesis of amide alkaloids or macrocyclic lactam antibiotics, we have intrigued the realization of an efficient carboxamide synthesis relying on the path (b) which, at the same time, realizes a direct introduction of an appropriate activating group into ω-carbon of *N*-substituent. Because of the well-established azaenolate chemistry of these cyclic imidates,[1] it would be possible to elaborate R group in 1 suitable not only for macrocyclization with *N*-substituent functionalized at ω-position

through the path (b) but also for acyclic amide alkaloids. Described herein is our execution which discloses a simple and efficient transformation of 1 to 4 under mild conditions. The method for the conversion of cyclic imidates into carboxamides is highly simple and selective, and seems to serve as a general application in organic synthesis.

The results for the reaction of 2-methyl-2-oxazoline, its 4- and 5-methyl analogues, and 2-methyl-2-oxazine with various HX and $(CH_3)_3SiX$ type reagents are summarized in Table 1. The following experimental procedure for trimethylsilyl azide with 2-methyl-2-oxazine is illustrative. To a mixture of 2-methyl-2-oxazine (1 mmol) and $(CH_3)_3SiN_3$ (1.2 mmol), placed in an ampoule, was added dry methanol (0.5 ml) at 0 °C (exothermic). Then the ampoule was sealed after flashing with nitrogen stream and heated at 70 °C for 5 h. The content of the ampoule was concentrated to give colorless oil which, on column chromatography over silica gel, afforded pure *N*-(3-azidopropyl)acetamide in 99% yield.

Table 1. Conversion of Simple Cyclic Imidates to Carboxamide Derivatives

Entry	Imidate[a]	X (equiv.) in Me_3SiX[b]	X (equiv.) in HX[c]	Solv.	Temp °C	Time h	Product R in RNHCOMe	Yield/%[d]
1		Cl (1.2)		DMF	20	48	$Cl(CH_2)_2$	62
2		Cl (1.2)		MeOH	20	20	$Cl(CH_2)_2$	87
3		N_3 (1.3)		DMF	95	48	$N_3(CH_2)_2$	57
4		N_3 (1.3)		MeOH	70	3	$N_3(CH_2)_2$	93
5		SPh (1)		——	20	60	$PhS(CH_2)_2$	95
6			SPh (1.3)	——	80	5	$PhS(CH_2)_2$	94
7		SePh (1)		——	20	60	$PhSe(CH_2)_2$	95
8		SePh (1)		——	80	2	$PhSe(CH_2)_2$	78
9			SePh (1)	——	80	5	$PhSe(CH_2)_2$	99
10[e]	5-Me	SePh (1)		DMF	80	3	$PhSeCH(CH_3)CH_2$	95
11[f]	4-Me	SePh (1)		DMF	80	55	$PhSeCH_2CH(CH_3)$	85
12		Cl (1)		MeOH	75	2	$Cl(CH_2)_3$	90
13			SePh (1.3)	DMF	80	40	$PhSe(CH_2)_3$	99
14			SPh (1.3)	DMF	80	39	$PhS(CH_2)_3$	69
15		N_3 (1.2)		DMF	100	48	$N_3(CH_2)_3$	57
16		N_3 (1.2)		MeOH	90	5	$N_3(CH_2)_3$	99

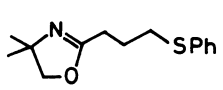
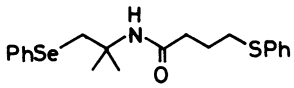
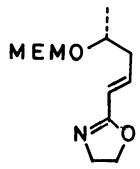
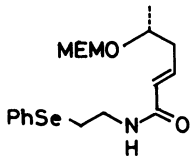
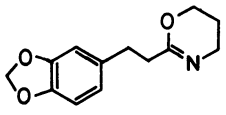
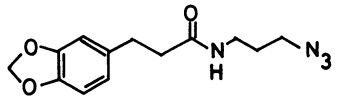
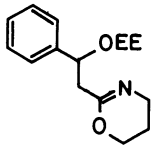
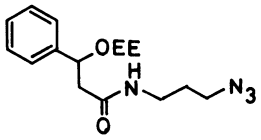
a) Commercial or synthesized; A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, J. Am. Chem. Soc., 97, 6266 (1975). b) Commercial or synthesized; for X= SPh, I. Ojima, M. Nihonyanagi, and T. Nagai, J. Organomet. Chem., 50, C26 (1973) and for X=SePh, N. Miyoshi, H. Ishii, K. Kondo, S. Murai, and N. Sonoda, Synthesis, 1979, 300. c) Commercial or synthesized; X=SePh, H. J. Reigh and M. L. Cohen, J. Org. Chem., 44, 3148 (1979). d) For purified products by column chromatography over silica gel but not optimized. e) 2,5-Dimethyl-2-oxazoline. f) 2,4-Dimethyl-2-oxazoline.

As a general trend, HX type reagents are much more efficient than the corresponding $(CH_3)_3SiX$ type reagents. For example, both $(CH_3)_3SiCl$ and $(CH_3)_3SiN_3$ refused to react with 2-methyl-2-oxazoline in the absence of solvent. In these cases, DMF solvent effected the conversion but the yields were still moderate (entries 1 and 3). The use of methanol gave a quick solution to this problem (entries 2 and 4) and, under these conditions, an actual reacting species should be corresponding HX type reagent generated in situ by the reaction of $(CH_3)_3SiX$ type reagents with methanol. For the six-membered imidate, this was also to be the case (entries 12, 15, and 16).

Both selenium and sulfur reagents required no solvent for the reaction of 2-methyl-2-oxazoline. In every case (entries 5 - 9), the desired acetamide derivatives were furnished in excellent yield. However, the reactions of these reagents with 2,4- or 2,5-dimethyl-2-oxazoline and 2-methyl-2-oxazine were extremely sluggish in the absence of solvent. Again, DMF brought about the desired transformations, though the reactions were somewhat slow (entries 10, 11, 13, and 14).

The informations as mentioned above prompted us to test this transformation of cyclic imidate to carboxamide for more complex molecules, including those which were synthesized in the hope of supplying key intermediates directed toward natural products. These results are indicated in Table 2.

Table 2. Nucleophilic Ring Opening of 2-Oxazoline and 2-Oxazine Derivatives[a)]

Entry	Substrate[b)]	Reaction conditions	Product	Yield/%
17		PhSeH (1 equiv.) DMF, 80 °C, 6 h		82
18		$PhSeSiMe_3$ (1.3 equiv.) THF, 60 °C, 48 h		72
19		N_3SiMe_3 (1 equiv.) MeOH, 60 °C, 6 h		74
20		N_3SiMe_3 (1 equiv.) MeOH, 70 °C, 5 h		72

a) See the footnote in Table 1. b) Synthesized through the reaction of corresponding azaenolates generated from 2-methyl-2-oxazoline or 2-methyl-2-oxazine in the usual way with appropriate halides or aldehydes in excellent yields.

In every case cited in Table 2, the desired carboxamide derivatives were successfully furnished in acceptable yield and purity. The products appeared in the entries 18, 19, and 20 may be promising building blocks for the synthesis of griseoviridin,[4] kukoamine A,[5] and celacinnine,[6] respectively.

It is clear that the method for the transformation of the cyclic imidates to secondary carboxamides disclosed here should make valuable contribution to facile construction of above-mentioned natural products and related molecules possessing carboxamide frameworks.

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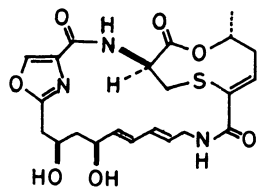
6) S. M. Kupchan, H. P. J. Hintz, R. M. Smith, A. Karim, M. W. Cass, W. A. Court, and M. Yatagai, J. Chem. Soc., Chem. Commun., 1974, 329; J. Org. Chem., 42, 3660 (1977); celacinnine, structure C, see below.



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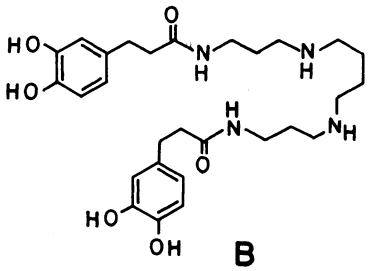

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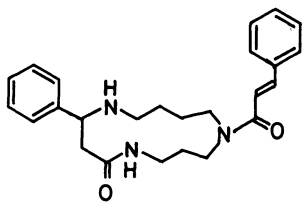

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