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NEW SYNTHESIS OF SECONDARY CARBOXAMIDE BY USING 2-METHYL-2-OXAZOLINE AS A BUILDING BLOCK

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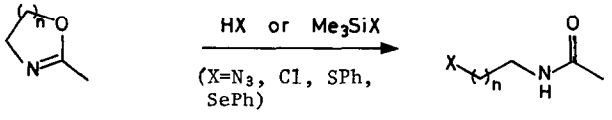
Summary: New method for the synthesis of secondary carboxamides of type, R^2NHCOR^1, which utilizes 2-methyl-2-oxazoline as a carboxamide building block and various halides, R^2X, has been developed.

Embarking in an investigation to develope a general method for carboxamide synthesis using cyclic imidates such as 2-methyl-2-oxazoline (**1**) or 2-methyl-5,6-dihydro-4H-1,3-oxazine (**2**) as a carboxamide synthon, we have recently recorded the basic idea[1] and its application to the total synthesis of kukoamine A[2] and (±)-celacinnine[3], one of spermine and spermidine alkaloids, respectively. Although it provided for novel facet of imidate chemistry, a structural variation accessible through this chemistry is unfortunately limited to those which bear ω-functionalized ethyl or propyl group on the nitrogen atom (Scheme 1), that seems to be a deficiency of this transformation. Accordingly, when we contemplate the manipulation of more complex carboxamide framework as witnessed in the streptogramine antibiotics,[4] the kirromycin antibiotics,[5] or some of the macrocyclic spermidine or spermine alkaloids,[6] further exploitation of the methodology for introducing an appropriate substituent on nitrogen atom has been required, keeping the central basis for the synthetic strategy laying in Scheme 1. We now record such a method for executing the synthesis of various secondary carboxamide, which is capable of introducing methyl, benzyl, crotyl, prenyl, or 2,4-hexadienyl substituent on the nitrogen atom.

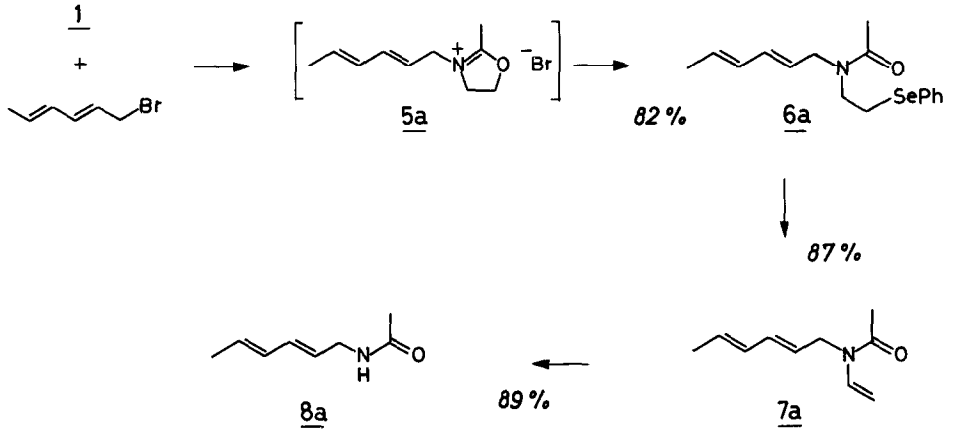


1 n = 1
2 n = 2

3 n = 1
4 n = 2

Scheme 1

The present strategy is illustrated in Scheme 2 as exemplified in the synthesis of *N*-(2,4-hexadienyl)acetamide (**8a**). This involves three basic transformations: i) initial carbon-nitrogen bond forming reaction between **1** and an appropriate halide, ii) nucleophilic ring opening of the oxazine moiety by the use of sodium benzeneselenolate to effect the construction of carboxamide framework, and iii) final splitting off of the 2-phenylselenoethyl substituent on the nitrogen atom.



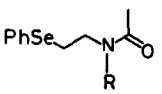
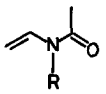
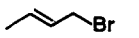
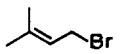
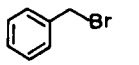
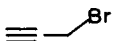
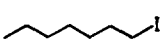
Scheme 2

In a typical experiment, a mixture of **1** and 2,4-hexadienyl bromide[7] (1.2 eq) in CH_2Cl_2 (3 ml/g of **1**) was stirred at room temperature for two days. The reaction mixture was treated under vacuum to evaporate the volatile and dissolved in dry DMF (6 ml/g of **1**). To this DMF solution was added an aliquot of sodium benzeneselenolate suspension in THF[8] (1.4 eq) at room temperature and the resulting mixture was stirred at that temperature for 4 hours. After usual aqueous workup and silicagel chromatographical purification, the desired *N*-(2-phenylseleno-ethyl)-*N*-(2',4'-hexadienyl)acetamide (**6a**) was furnished in 82% yield: IR (film) 1650 (N-C=O), 1590, 1490, 1445-20 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (3H, d, J=5.0 Hz, CH_3-C=), 1.99 (3H, s, $COCH_3$), 2.70-3.75 (4H, m, NCH_2CH_2Se), 3.75-4.25 (2H, m, =C-CH_2-N), 5.00-6.35 (4H, m, olefinic-H), 7.05-7.70 (5H, m, aryl-H). An oxidative *syn*-elimination of phenylseleno-group[9] in **6a** [$NaIO_4$/MeOH[10] followed by gentle heating in the presense of Et_2NH[11]] gave *N*-vinyl derivative (**7a**) in 87% yield after chromatographical purification (SiO_2): IR (film) 1679 (N-C=O), 1630 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.72 (3H, d, J=6.0 Hz, CH_3-C=), 2.19 (3H, s, CH_3CO), 3.95-4.40 (2H, m, N-C=CH_2), 4.50 (2H, d, J=10.6 Hz, =C-CH_2N), 5.09-6.38 (4H, m, CH=CH-CH=CH), and 6.76 (1H, q, J=9.2 and 14.6 Hz, N-CH=C).

The stage was set for final devinylation leading to desired product. An attempted hydro-

lysis under acidic conditions to remove the *N*-vinyl group resulted in the formation of complex mixture which denied any structural elucidation. However, it turned out that oxymercuration-demercuration protocol[12] served as the best available solution to this problem, at the time, in terms of yield, chemoselectivity, and operational simplicity. Thus, to a solution of **7a** in THF, cooled to 0° C, was added a solution of mercuric acetate (1 eq) in THF-H_2O (1:1), and, after 15 minutes, the reaction was treated sequentially with 3-N NaOH and $NaBH_4$ to give the secondary amide (**8a**) in 89% yield (silicagel chromatography): IR (KBr) 3310 (NH), 1642 (C=O), 1548 (C-N-H), 1285, 894 cm^{-1}; NMR ($CDCl_3$) δ 1.74 (3H, d, J=5.6 Hz, CH_3C=), 1.97 (3H, s, CH_3-C=O), 3.69-4.20 (2H, m, NCH_2C=), 4.90-6.90 (4H, m, olefinic-H, CONH). To our delight, neither undesired oxymercuration reaction at other olefinic linkage nor hydrolysis of the amide function took place under the given reaction conditions.[13] This essentially three-step sequence was applied to other systems and the whole results are summarized in the Table.

Table. Synthesis of Secondary Carboxamides from **1** and RX[a]

RX		Yield/%[b] **6**: 	**7**: 	**8**: 
	a	82	87	89
	b	83	69	66
	c	87	84	87
	d	62	88	97
CH_3I	e	81[c]	55	65
	f	31[d]	73	N.R.[e]
	g	8[f]	no exam.	no exam.

a) Conducted under the same reaction conditions as indicated in the text, unless otherwise noted; b) For chromatographically homogeneous product which showed satisfactory spectral data (IR, ^1H and ^{13}C NMR); c) no solvent, 55°, 1 h (CH_3I in excess); d) N-allenyl derivative (16%) was obtained (for related reaction, see S. Saito, S. Hamano, M. Inaba, and T. Moriwake, Synth. Commun., 14, 1105 (1984); e) **7f**, recovered (59%); f) no solvent, 100°, 3 h.

As indicated in the Table, the overall efficiency of a series of transformations with allylic and benzylic halides is quite acceptable, whereas the reaction of **1** with rather long-chain alkyl iodide is extremely sluggish and resulted in an unacceptable yield of the product (**6g**).[14] However, the potential utility of the present method for the synthesis of secondary carboxamides should be emphasized in the light of the fact that 2-methyl group of **1** can be a cite for deprotonation and, thereby, for electrophilic attack, which allows to elaborate this methyl group readily to lead to a specific structure before conducting the present sequence of reactions. Moreover, in view of the simplicity and mild reaction conditions of our method, and the ease with which halides can be prepared as compared with corresponding amines, it has great synthetic utility. Thus, in relation to our recent effort on the total synthesis of (+)-griseoviridine,[4] the present method seems to be obvious choice for constructing *N*-2,4-hexadienyl amide moiety embedded in this natural product, which is currently under active investigation in our laboratory.

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13) It has been reported that enamines can be attacked at β-carbon by mercuric ion to produce iminium salt, which, on treatment with $NaBH_4$, is smoothly reduced, giving rise to corresponding tertiary amines in an aprotic solvent as DMF (R. D. Bach and D. K. Mitra, Chem. Commun., 1433 (1971). In our enamide case under protic conditions, such iminium-type intermediate is considered not to be involved.
14) Because of a general trend that oxazolinium salt plays a role of cationic catalyst for polymerization of **1** (E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W, Thier, and H. Hellmann, Angew. Chem. Internat. Edit., 5, 875 (1966)), initially-formed *N*-heptyl-oxazolinium salt catalyzed such reaction to leave significant amount of polymerized product.

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