Reaction of *N*-Benzoyl Amino Acids with Oxalyl Chloride: a Facile Route to 4-Substituted 2-Phenyloxazole-5-carboxylates

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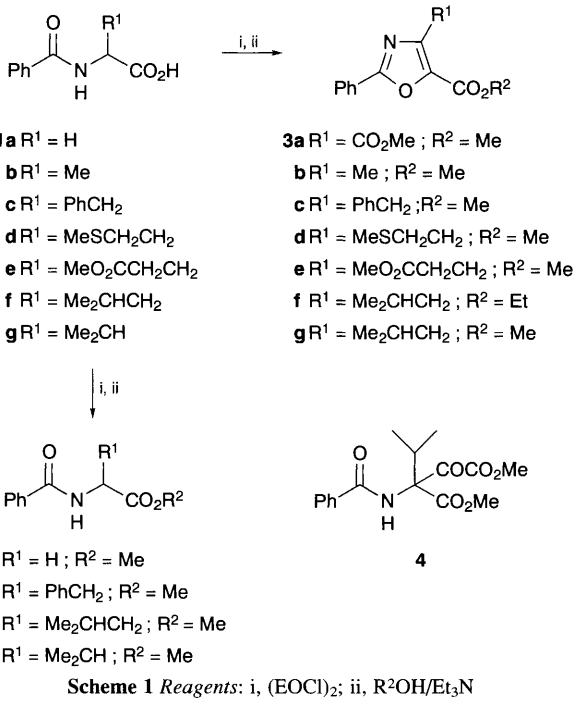
N-benzoyl amino acids **1a–g** react with excess oxalyl chloride at room temperature followed by addition of alcohols to afford 4-substituted 2-phenyloxazole-5-carboxylates **3a–g**.

In an attempt to prepare esters of *N*-benzoyl protected amino acids, *via* their reaction with oxalyl chloride followed by treatment with alcohols, an unexpected product was obtained. Under these conditions, when *N*-benzoylalanine **1b** was treated with oxalyl chloride followed by methanol, methyl 2-phenyl-4-methyloxazole-5-carboxylate **3b** was formed; none of the expected *N*-benzoylalanyl methyl ester was detected in the reaction mixture. The following procedure is representative: to a stirred slurry of *N*-benzoyl-L-alanine **1b**, (386 mg, 2 mmol) in either a mixture of benzene (8 ml) and dichloromethane (3 ml), or in dry THF (10 ml), was added oxalyl chloride (1.74 ml, 20 mmol). The mixture was stirred at room temperature overnight and then the solvent(s) were evaporated *in vacuo*. The oily residue was treated with toluene and evaporated to remove traces of oxalyl chloride. The residue was then cooled in an ice bath and triethylamine (1.5 equiv.) was added followed by methanol (15 ml). The resulting homogenous solution was stirred at room temperature for 3 h. The residue, after solvent evaporation, was chromatographed on silica gel (hexane–ethyl acetate, 11 : 1) to yield **3b** as a white solid (221 mg, 51%) mp 49–50 °C, (lit.,[1] 45–47 °C).



Scheme 1 *Reagents*: i, $(EOCl)_2$; ii, R^2OH/Et_3N

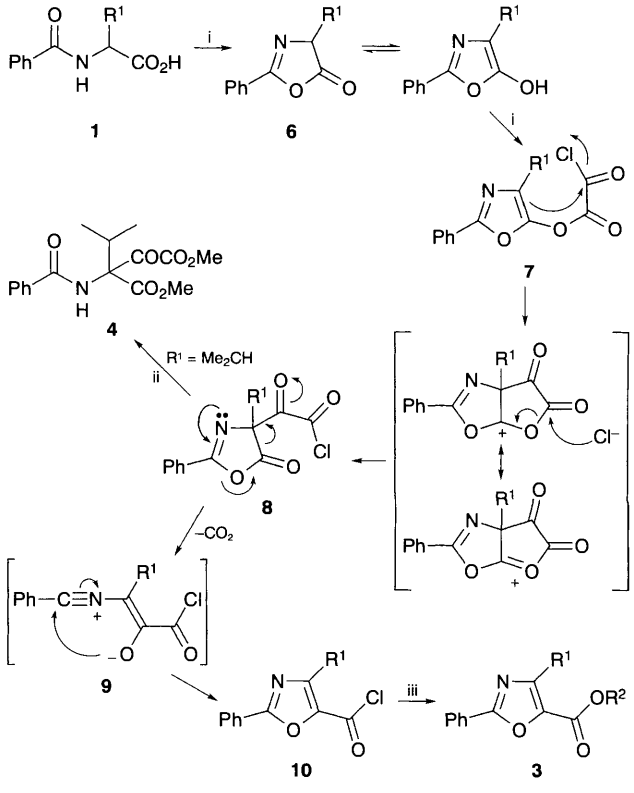
Table 1 Synthesis of 2-phenyloxazole-5-carboxylate esters from *N*-benzoylamino acids and alcohols

N-benzoylamino acid	Alcohol	Product	Conditions[a]	Yield (%)[a]
1a	MeOH	**3a**	$PhH–CH_2Cl_2$	21[b]
1b	MeOH	**3b**[5]	$PhH–CH_2Cl_2$	51
1c	MeOH	**3c**	$PhH–CH_2Cl_2$	29[c]
1d	MeOH	**3d**	THF	52
1e	MeOH	**3e**	$PhH–CH_2Cl_2$	51
1e	EtOH	**3f**	$PhH–CH_2Cl_2$	52
1e	**11**	**12**	$PhH–CH_2Cl_2$	54
1f	MeOH	**3g**	THF	30[d]
1g	MeOH	**4**	THF	11[e]
5a	MeOH	**5b**	$PhH–CH_2Cl_2$	98

[a] Yields and conditions were not optimised. All at room temp. [b] 47% of **2a** was also formed. [c] 42% of **2b** was also formed. [d] 50% of **2c** was also formed. [e] 50% of **2d** was also formed.

Analogous oxazole products were obtained when other *N*-benzoylamino acids were utilised in place of **1b** (Scheme 1 and Table 1). When *N*-benzoyl derivatives of amino acids possessing a bulky α-alkyl substituent were reacted with methanol under the above conditions, the expected *N*- benzoylamino acid methyl ester was obtained in low yield (Table 1), along with the oxazole product. Interestingly, when **1g** was reacted with oxalyl chloride in THF, followed by addition of methanol–triethylamine, the oxazole product was not formed, but in addition to the expected methyl ester, a major byproduct was the dicarboxylate ester **4**. Compound **1f**, under similar conditions, afforded the oxazole product **3g** along with the expected *N*-benzoylamino acid ester **2c**. Also, reaction of the α,α-dimethyl analogue of *N*-benzoylglycine **5a** under identical conditions, gave only the *N*-benzoylamino acid methyl ester **5b** in almost quantitative yield.

In order to determine the mechanism of formation of the above 2-phenyloxazole-5-carboxylate esters, we reacted [1-^{13}C]-*N*-benzoylalanine with oxalyl chloride in THF, followed by treatment with methanol–triethylamine, and obtained

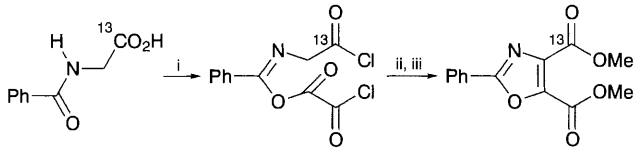


Scheme 2 *Reagents*: i, $(COCl)_2$; ii, MeOH; iii, R^2OH

the oxazole **3b**. The ^{13}C NMR spectrum of this product showed the absence of any ^{13}C enrichment in the molecule, indicating that loss of the α-carboxyl group of the amino acid had occurred during the formation of **3b** from **1b**.

We were also able to form **3b** from **1b** *via* initial formation of the azlactone **6**, followed by treatment with oxalyl chloride and methanol (Scheme 2).

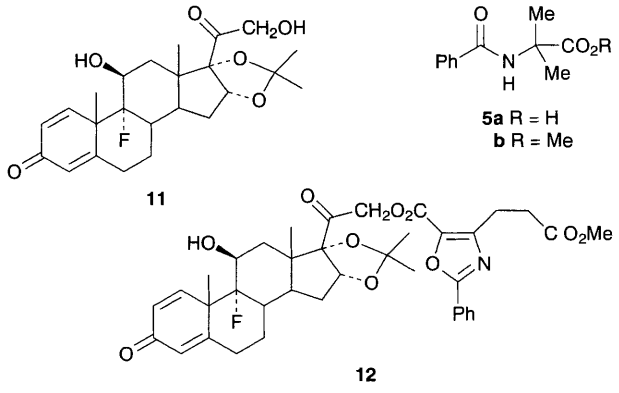
These data support a mechanism of formation of the 4-substituted-2-phenyloxazole-5-carboxylate esters from their respective *N*-benzoylamino acids that is outlined in Scheme 2. Reaction of the *N*-benzoylamino acid with oxalyl chloride initially affords as expected the corresponding azlactone **6**,[1] which can then react further to afford the enolate ester **7**, followed by rearrangement to **8**, and subsequent decarboxylation to give the dipolar intermediate **9**. A similar dipolar intermediate has been suggested in the formation of trisubstituted oxazoles from the thermolytic cycloelimination of CO_2 from 4-acyl-Δ^2-oxazolin-5-ones.[2,3] Cyclisation of **9** to **10** followed by reaction with an alcohol affords the oxazole product **3**. The formation of **4** from **1g** can be explained by reaction of the intermediate **8** (R = Me_2CH) with methanol. Presumably, the presence of the bulky α-isopropyl group in **1g** prevents the normal decarboxylation of **8** to **9**, most likely through steric inhibition in the formation of the required transition state.



Scheme 3 *Reagents*: i, $(COCl)_2$; ii, $-H_2O$; iii, MeOH

In one particular case, *i.e.* with *N*-benzoylglycine **1a**, the regular ester **2a** was formed together with the oxazole dicarboxylate product **3a**. Formation of this product cannot be explained by the mechanism presented in Scheme 3. When [1-^{13}C]-*N*-benzoylglycine was utilised in the reaction to determine the fate of the carboxyl group, it was found that the ^{13}C label was retained in the oxazole product, which is presumably formed *via* the pathway presented in Scheme 3.

We conclude from these observations that the use of oxalyl chloride in the preparation of *N*-benzoyl protected amino acid esters *via* intermediate formation of the corresponding acyl chloride, is not recommended, except in those cases where α,α-disubstituted amino acids are utilised. On the other hand, the reactions described above may provide a general and facile route to variously substituted 2-phenyloxazole-5-carboxylic acid esters from readily available L-amino acid precursors. Such esters have previously been investigated for antineoplastic activity, and are normally obtained *via* multistep synthetic sequences.[4] In this manner, for example, we were able to synthesise in one step from triamcinolone acetonide **11** and *N*-benzoylglutamic acid monomethyl ester **1e** the steroidal analogue **12**. In view of the accessibility of starting materials, the present method may find useful application in the synthesis of a wide variety of these types of potential medicinal agents.



This research was supported by a grant from Control Delivery Systems, Inc.

Received, 24th July 1995; Com. 5/04840K

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