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Reaction of Organolead Triacetates with 4-Ethoxycarbonyl-2-methyloxazol-5-one. The Synthesis of α-Aryl and α-Vinyl N-Acetylglycine Ethyl Esters and Their Enzymic Resolution.

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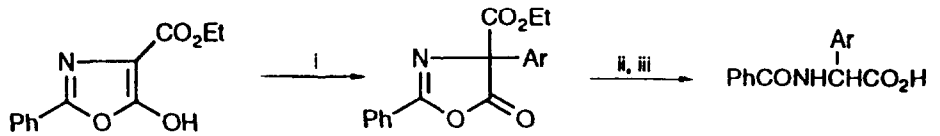
Abstract: An efficient synthesis of the moisture-sensitive compound, 4-ethoxycarbonyl-2-methyloxazol-5-one, has been achieved. This compound undergoes high-yielding arylation and vinylation at the 4-position with organolead triacetates to give compounds which in water are converted to α-aryl and α-vinyl N-acetylglycine ethyl esters. These α-substituted glycine derivatives may be kinetically resolved in very good yield and high enantiomeric excess by enzymic hydrolysis of either the ester group or the amide function of the corresponding carboxylic acids.

The great interest being shown in the development of useful syntheses of α-aryl,[1-3] α-vinyl[4,5] and α-alk-1-ynyl[4,6,7] substituted glycines, compounds of potential therapeutic usefulness, has prompted us to explore their synthesis by the use of organolead(IV) triacetates. These compounds have been developed by us[8] as unique reagents for the arylation, vinylation and alkynylation of soft carbon nucleophiles, and we recently reported preliminary results of the arylation of 4-ethoxycarbonyl-2-phenyloxazol-5-one by aryllead triacetates.[9] These high-yielding reactions provide an efficient route to racemic N-benzoyl α-arylglycines (Scheme 1).



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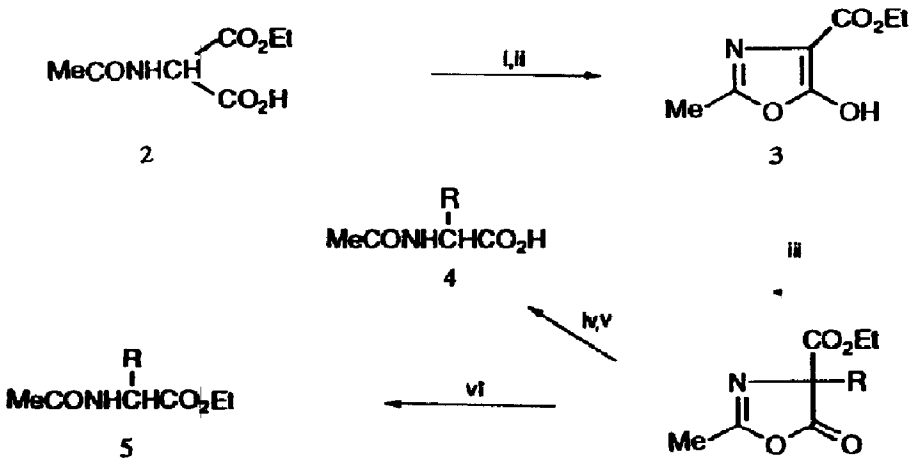
Scheme 1 *Reagents and conditions:* i, $ArPb(OAc)_3$; ii, NaOH, $EtOH/H_2O$, Δ; iii, H_3O^+

Since the enantioselective hydrolysis of a wide range of N-acetyl α-substituted glycines may be effected with acylase 1 enzymes isolated from porcine kidney (PKA) and *Aspergillus* fungi (AA),[10,11] we explored the possibility of extending the method shown in Scheme 1 to produce N-acetylglycine derivatives. We now wish to report the synthesis of the required oxazolone, which exists in chloroform/pyridine as the enol **3**, and its use in place of the phenyloxazolone **1** in the sequence depicted in Scheme 1 to give N-acetyl α-arylglycines.

The route to the 4-methyloxazolone **3** was based on that which we used to obtain the 4-phenyl analogue in high yield;[9] this involved treatment of monoethyl acetamidomalonate **2** with trifluoroacetic anhydride (2.2 mol

equiv.) in ether, followed by the slow addition of water (1.1 mol equiv.) at 0°C. The oxazolone **3**, which precipitated from the ether solution, was obtained in 70-75% yield.[12]



Scheme 2 *Reagents and conditions:* i, $(CF_3CO)_2O$, Et_2O, ii, H_2O; iii, $RPb(OAc)_3$, $CHCl_3$, pyridine; iv, NaOH, $EtOH/H_2O$, Δ; v, H_3O^+; vi, H_2O, Δ

Reaction of the methyloxazolone **3** with aryllead triacetates in chloroform/pyridine under conditions employed for the 2-phenyl derivative **1**[9] resulted in practically quantitative arylation at the 4-position; however, the products were again moisture-sensitive and were therefore hydrolysed (with decarboxylation) either in alkali to the racemic N-acetyl α-arylglycines **4** or in water to the corresponding racemic N-acetylglycine ethyl esters **5** (Scheme 2). As can be seen from Table 1, yields were unaffected by the nature of substituents in the aromatic ring; the phenyl (entry 1), *o*-methoxyphenyl (entry 2), *p*-methoxyphenyl (entry 3), 2,4-dimethoxyphenyl (entry 4), *o*-fluorophenyl (entry 5), *p*-fluorophenyl (entry 6), and *p*-trifluoromethylphenyl (entry 7) lead(IV) compounds all gave similar high overall yields of the racemic acids **4a** - **4g**, respectively. Hydrolysis of the intermediate arylated oxazolones in water to the corresponding esters proceeded in similar high yield as illustrated for the preparations of the compounds **5a** and **5d** (entries 1 and 4).

The method outlined in Scheme 2 is also applicable to the synthesis of N-acetyl α-vinylglycines and their esters. Reaction of the oxazolone **3** with (*E*)-styryllead triacetate and (*E*)-*p*-methoxystyryllead triacetate followed by hydrolysis of the vinylated oxazolones gave useful yields of N-acetyl-α-(*E*)-styrylglycine **4h** and its ethyl ester derivative **5h** (entry 8), and N-acetyl- α–(*E*)-*p*-methoxystyrylglycine ethyl ester **5i**(entry 9).

As indicated previously, the overall strategy included the kinetic resolution of the α-substituted N-acetylglycines by the acylase 1 enzymes PKA or AA. Such resolutions have previously been achieved for the α-phenyl[13] and α-*p*-methoxyphenyl[14] derivatives **4a** and **4c**, and the α-*p*-hydroxyphenyl derivative;[13] however, we are unaware of any reports of the enzymic resolution of the other acid derivatives of Table 1. Our initial rate

studies indicated that PKA was generally more active than AA towards the acidic substrates of Table 1 but in our hands neither enzyme preparation was active towards the *o*-methoxyphenyl derivative **4b**, the 2,4-dimethoxyphenyl substituted compound **4d**, and only slightly active towards N-acetyl-α-(*E*)-styrylglycine **4h**. It seems reasonable to assume that, from the initial rate studies[11] and the excellent results obtained (isolated yield and high % ee) for N-acetyl-α-phenylglycine **4a** and N-acetyl-α-*p*-trifluoromethylphenylglycine **4g** (see Table 2), the resolution of all acidic compounds of Table 1, except **4b**, **4d** and possibly **4h**, should be achievable.

For the resolution of the compounds containing an *o*-methoxyphenyl group or an α-styryl group we turned to the hydrolysis of the corresponding ethyl esters by the proteolytic enzyme subtilisin Carlsberg. This enzyme, which has been previously used for resolution of a number of N-acetyl α-arylglycine esters,[15] gave high yields and very good enantiomeric excesses of the L-amido acids and D-amido esters in the case of N-acetyl -α-phenylglycine ethyl ester **5a**, N-acetyl-α–2,4–dimethoxyphenylglycine ethyl ester **5d** and N-acetyl-α-(*E*)-styrylglycine ethyl ester **5h** (see Table 2). Thus the procedure outlined in Scheme 2 coupled with enzymic resolution by the acylase PKA or the esterase subtilisin Carlsberg should provide an efficient route to a wide variety of D and L α-arylglycines and some D and L α–vinylglycines. Further work is required to determine the range of the latter compounds which may be accesssed by this method, but the limitations previously reported for the vinylation of β-dicarbonyls by vinyllead triacetates[8] will no doubt apply here also.

Table 1. Reaction of 4-ethoxycarbonyl-2-methyloxazol-5-one **3** with organolead triacetates followed by hydrolysis of the 4-substituted oxazolone.[a,b]

Entry	$RPb(OAc)_3$ R=	$MeCONHCH(R)CO_2H$ (Yield %)[c]		$MeCONHCH(R)CO_2Et$ (Yield %)[c]	
1	Ph	**4a**	(93)	**5a**	(93)
2	*o*-$MeOC_6H_4$	**4b**	(81)		
3	*p*-$MeOC_6H_4$	**4c**	(86)		
4	2,4-$(MeO)_2C_6H_3$	**4d**	(82)	**5d**	(87)
5	*o*-FC_6H_4	**4e**	(90)		
6	*p*-FC_6H_4	**4f**	(83)		
7	*p*-$CF_3C_6H_4$	**4g**	(92)		
8	(*E*)-styryl	**4h**	(60)	**5h**	(62)
9	(*E*)-*p*-methoxystyryl			**5i**	(60)

[a] Hydrolyses performed as shown in Scheme 2. [b] New compounds were characterised by analytical and spectroscopic methods. [c]Isolated yields.

Table 2. Enzymic resolution of some α-substituted N-acetylglycines and their ethyl esters by PKA and substilisin Carlsberg.[a,b]

Compound	PKA[c]		subtilisin Carlsberg[d]	
	Yield of L-Amino Acid(%ee)	Yield of D-Amido Acid(%ee)	Yield of L-Amido Acid(%ee)	Yield of D-Amido Ester(%ee)
4a	89 (99)	94 (95)		
4g	86 (94)	100 (95)		
5a			95 (97)	100 (91)
5d			89 (90)	101 (95)
5h			100 (82)	95 (93)

[a] Yields are for isolated material. [b] Percentage ee was determined by GC on a Chirasil-L-V capillary column after derivatisation where necessary, except for compound **5h** where a ^{1}H NMR shift reagent was employed. [c] The method was similar to one previously reported.[11] [d] The method of Berger *et al.*[16] was used.

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12. *4-Ethoxycarbonyl-2-methyloxazol-5-one* **3** is a very moisture-sensitive compound, and must be washed free of CF_3CO_2H with a large volume of dry ether before being stored in an anhydrous atmosphere. It was obtained as pale yellow crystals, m.p. 121-122°C (dec.) (Found: M^+, 171.0532. $C_7H_9NO_4$ requires 171.0532) ν_{max} (Nujol)/cm^{-1} 1777, 1644 and 1629; δ_H ($CDCl_3/C_5D_5N$, 3:1) 1.23 (3 H, t, *J* 7.1 Hz, Me), 2.34 (3 H, s, Me), 4.23 (2 H, q, *J* 7.1 Hz, CH_2), 17.2 (1 H, br, s, OH); δ_C (d_6-DMSO) 13.02 (Me), 14.75 (Me), 58.71 (CH_2), 84.35 (C-4), 151.65 (C-2), 160.47 (C=O or C-5) and 160.69 (C-5 or C=O).
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