Arylation of 4-Ethoxycarbonyl-2-phenyloxazol-5-one by Aryllead Triacetates: A Convenient Route to α-Arylglycines

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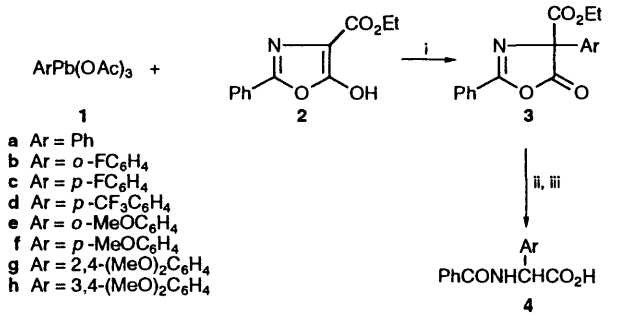
4-Ethoxycarbonyl-2-phenyloxazol-5-one, which exists in chloroform as the enol **2**, undergoes rapid arylation under very mild conditions with aryllead(IV) triacetates to give almost quantitative yields of 4-aryl-4-ethoxycarbonyl-2-phenyloxazol-5-ones **3**, which in alkali undergo hydrolysis and decarboxylation to provide a simple high-yielding route to a wide range of *N*-benzoyl-α-arylglycines **4**.

The growing interest in the antimicrobial and enzyme inhibitory properties of various natural and unnatural glycines has resulted in considerable activity in the synthesis of α-aryl,[1-3] α-vinyl[4,5] and α-alk-1-ynyl[4,6,7] substituted glycines. For some time, we have been exploring the possibility of employing organolead(IV) triacetates to introduce the above groups into a glycine precursor, since these reagents have been shown by us to act as efficient aryl, vinyl and alkynyl cation equivalents.[8] For example, these lead(IV) reagents have been used for the introduction of the above groups in high yield, and under mild conditions, into a range of 'soft' carbon nucleophiles such as β-dicarbonyls,[8-10] nitroalkanes[8,11] and phenols.[8,12]

In our initial attempts to achieve the synthesis of an α-arylglycine by this approach we examined, among others, the reaction of phenyllead triacetate **1a** with diethyl acetamidomalonate in the presence of various tertiary amines, and as the enolate salt; however, unlike our previous experience with α-substituted malonates,[10] no arylation occurred. A search for a more acidic dicarbonyl precursor led us to examine 4-ethoxycarbonyl-2-phenyloxazol-5-one,[13] which exists in the enol form **2** in $CDCl_3$. This compound can be obtained readily from diethyl benzamidomalonate in 78% yield by a modification of the reported partial hydrolysis–cyclodehydration procedure.[13]

When the enol **2** was treated with phenyllead triacetate **1a** in chloroform containing pyridine at 40 °C, a rapid reaction occurred to give the arylated oxazolone **3a** in very high yield (^1H NMR spectroscopic analysis). Compound **3a**, being susceptible to ring opening in the presence of water, was not purified; it was treated directly with sodium hydroxide in a water–ethanol mixture to yield the product of ring opening and decarboxylation, *N*-benzoyl-α-phenylglycine **4a** in high overall yield (entry 1, column 1, Table 1).

As can be seen from the first column of yields in Table 1, the procedure of arylation of the enol **2** by an aryllead triacetate followed by hydrolysis–decarboxylation, as outlined in Scheme 1, proved to be a general, high-yielding route to *N*-benzoyl derivatives of α-arylglycines. As found in our previous work,[8]



Scheme 1 *Reagents and conditions:* i, $CHCl_3$, pyridine, 40 °C; ii, NaOH, EtOH, H_2O, steam bath; iii, H_3O^+

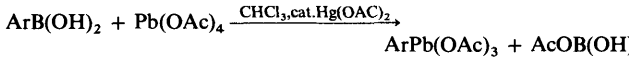
Table 1 Yields of *N*-benzoyl-α-arylglycines obtained by reaction of the enol **2** with aryllead(IV) triacetates and subsequent hydrolysis of the 4-aryl-4-ethoxycarbonyl-2-phenyloxazol-5-one produced[a]

		Yield (%) of compound **4**[b]	
Entry	$ArPb(OAc)_3$	With isolated $ArPb(OAc)_3$[c]	With $ArPb(OAc)_3$ formed *in situ*[d]
1	**1a**	87	94
2	**1b**	—	93[e]
3	**1c**	88	—
4	**1d**	75	70
5	**1e**	—	83[e]
6	**1f**	87	—
7	**1g**	90	—
8	**1h**	89	75

[a] All new compounds were characterised fully by microanalytical and spectroscopic methods. [b] Yields were for pure material based on compound **2**. [c] Oxazolone **2** (2.5 mmol) added over 5 min to $ArPb(OAc)_3$ (3.0 mmol) in chloroform (4 cm^3) and pyridine (9.0 mmol) at 40 °C and stirred for 1 h. Compound **3** was hydrolysed as indicated in Scheme 1. [d] $ArB(OH)_2$ (3.5 mmol), $Pb(OAc)_4$ (3.0 mmol) and $Hg(OAc)_2$ (0.3 mmol) were stirred in $CHCl_3$ (4 cm^3) at 40 °C for 2 h, except for entry 2 where $ArB(OH)_2$ (3.75 mmol) and 24 h exchange time were used, and then as in footnote *c*. [e] Formic acid (2 drops) added at completion of boron–lead exchange.

substituents in the aryllead compound had little effect on the reaction. *p*-Fluorophenyllead triacetate **1c** and the *p*-methoxy compound **1f** reacted similarly with the oxazolone **2** to give almost identical yields of *N*-benzoyl-α-arylglycines **4c** and **f**, respectively (entries 3 and 6), while the 2,4-dimethoxy- and 3,4-dimethoxyphenyllead reagents, **1g** and **h**, afforded similarly high yields of the α-arylglycine derivatives **4g** and **h**, respectively (entries 7 and 8). The lower yield (75%) of *N*-benzoyl-α-(*p*-trifluoromethylphenyl)glycine **4d**, obtained from the reaction of compound **2** with the lead compound **1a** (entry 4), would suggest that strongly electron withdrawing groups lower the reactivity of the aryllead triacetate.

Because the yields achieved in the arylation reaction were practically quantitative, the purification of the moisture-sensitive oxazolones **3** proved to be unnecessary; however, one of them, 4-(2,4-dimethoxyphenyl)-4-ethoxycarbonyl-2-phenyloxazol-5-one **3g**, which was more stable than the others, was fully characterised.



Scheme 2

In those cases where the required aryllead triacetate is produced by metal–metal exchange,[8,14,15] it has been shown in

our laboratories that the *in situ* generation of the aryllead reagent from the arylboronic acid or a derivative[15,16] (Scheme 2) is a more efficient procedure. We have demonstrated the use of this method here with a number of two-pot conversions of arylboronic acids into *N*-benzoyl-α-arylglycines (see Table 1). The procedure involved the treatment of the arylboronic acid with lead tetraacetate and a catalytic amount of mercury(II) acetate in chloroform at 40 °C. The enol **2** was then added to the mixture,* and the method outlined above employing the isolated aryllead reagent was followed. The yields obtained for the glycine derivatives **4a**, **d** and **h** (column 2, Table 1) were comparable to those produced with purified aryllead triacetates, and this very simple procedure is our preferred route to such α-arylglycine derivatives. The *in situ* formation of the aryllead reagent is especially useful for the synthesis of *N*-benzoyl-α-arylglycines such as **4b** and **e**, where direct lithiation of fluorobenzene and anisole provides a short route to the *o*-substituted boronic acid.

We are presently exploring enzymic hydrolytic approaches in order to achieve syntheses of the optically active α-arylglycines.

Experimental

Preparation of N-*Benzoyl-α-phenylglycine* **4a**.—(a) Phenyllead triacetate **1a** (1.383 g, 3.0 mmol, 1.2 mol equiv.) and dry pyridine (0.712 g, 9.0 mmol, 3.6 mol equiv.) were dissolved in dry chloroform (4 cm^3) and 4-ethoxycarbonyl-2-phenyloxazol-5-one **2** (0.583 g, 2.5 mmol) was added over 5 min at 40 °C with stirring. The mixture was stirred in a stoppered flask for 1 h at 40 °C and then diluted with chloroform (25 cm^3) and washed with sulfuric acid (3 mol dm^{-3}; 15 cm^3). The aqueous layer was washed with chloroform (25 cm^3) and the chloroform extracts were combined and washed with saturated sodium hydrogencarbonate (25 cm^3). The chloroform solution was filtered and evaporated at 40 °C and then finally subjected to high vacuum to yield a pale yellow oil. Ethanol (12 cm^3) and aq. sodium hydroxide (1.25 mol dm^{-3}, 4 cm^3, 2 mol equiv.) were added to the oil and the mixture was heated at reflux for 0.5 h. The mixture was cooled, diluted with water (20 cm^3) and the ethanol was evaporated at 40 °C. The aqueous mixture was washed with ethyl acetate (2 × 20 cm^3), acidified with an excess of hydrochloric acid (3 mol dm^{-3}), and extracted with ethyl acetate (3 × 40 cm^3). The combined extracts were dried (Na_2SO_4), filtered and evaporated at 40 °C. Carbon tetrachloride (20 cm^3) was added to the residue for azeotropic removal of water and the solvent was evaporated at high vacuum to yield *N*-benzoyl-α-phenylglycine as a colourless crystalline solid (0.557 g, 87%), m.p. 168–169 °C (chloroform–light petroleum) (lit.,[17] 172–173 °C); δ_H(200 MHz, [$^2H_6$]DMSO) 5.71 (1 H, d, *J* 7.5, CH), 7.24–7.62 (8 H, m, α-phenyl and benzoyl 3-, 4- and 5-H), 7.86–8.05 (2 H, m, benzoyl 2- and 6-H) and 8.86 (1 H, d, *J* 7.5, NH).

(b) Phenyllead triacetate was generated *in situ* by adding phenylboronic acid (0.427 g, 3.5 mmol, 1.4 mol equiv.) over 15 min at 40 °C to a stirred mixture of dry lead tetraacetate (LTA) (1.33 g, 3.0 mmol, 1.2 mol equiv.) and mercury(II) acetate (0.0956 g, 0.3 mmol, 0.12 mol equiv.) in dry chloroform (4 cm^3). The mixture was stirred for 1 h at 40 °C, after which a test for residual LTA was negative. Pyridine (0.712 g, 9.0 mmol, 3.6 mol equiv.) was added to the mixture followed by the oxazolone **2** (0.583 g, 2.5 mmol) added over 5 min at 40 °C. The mixture was stirred for 1 h at 40 °C, after which the work-up and hydrolysis were carried out as in method (a).

* If unchanged $Pb(OAc)_4$ was present at this stage, some of the enol **2** was oxidised, to yield a symmetrical dimer resulting from C–C coupling at the 4-position. This possibility can be avoided by adding a small amount of formic acid to destroy excess $Pb(OAc)_4$ prior to addition of the substrate.

Acknowledgements

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