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USE OF THE ELECTROPHILIC C-ARYLATION BY ARYLLEAD TRIACETATES IN THE CONSTRUCTION OF SYNTHONS FOR AIZOACEAE AND AMARYLLIDACEAE ALKALOID SYNTHESIS

Darren J. Ackland and John T. Pinhey*

Department of Organic Chemistry, University of Sydney, Sydney 2006, Australia

The vinylogous β-keto esters, ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's Ester) (4), ethyl 4-oxocyclohex-1-enecarboxylate (7a) and its double bond isomer (7b), undergo regiospecific arylation with aryllead triacetates at C1; reaction of the mixture of isomers (7a) and (7b) with aryllead compounds (5a), (5c) and (5d) provides intermediates for the synthesis of (±)-*o*-methyljoubertiamine (1), (±)-mesembrine (2) and (±)-lycoramine (3) respectively.

Recently we have shown that aryllead triacetates are particularly useful reagents for the electrophilic arylation of CH-acids such as β-dicarbonyl compounds[1] and nitroalkanes.[2] The development of this particularly mild method of C-arylation as a synthetic tool, and the study of the mechanism of the reaction, has led us to explore the reactions of these reagents with vinylogous β-keto esters. Our initial investigations of such substrates have led to highly efficient routes to intermediates for the synthesis of the alkaloids, (±)-*o*-methyljourbertiamine (1), (±)-mesembrine (2) and (±)-lycoramine (3), and we now wish to report this aspect of the work.

The first compound of this type which we investigated was ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's Ester) (4); when reacted with *p*-methoxyphenyllead triacetate (5a) in chloroform containing pyridine under our previously established conditions[1] (Table 1), regiospecific arylation at C1 occurred to give ethyl 1-(*p*-methoxyphenyl)-2-methyl-4-oxocyclohex-2-enecarboxylate (6a) as the only isolable product. A similar reaction occurred with (4) and phenyllead triacetate (5b) (Table 1); however, in this case the reaction was found to be faster and higher yielding if carried out in dimethyl sulfoxide without added base, which were the conditions developed for the arylation of nitroalkanes[2] by these reagents.

The above reactions offered the prospect of a new convergent approach to the synthesis of the keto ester (6c), a useful intermediate in the synthesis of (±)-*o*-methyljourbertiamine.[3] The required starting material in this case is a 5:2 mixture of isomers (7a) and (7b),[4] which may be obtained by Diels-Alder reaction of 2-ethoxy-1,3-butadiene and ethyl propiolate, followed by hydrolysis.[5] In the present work we found it more convenient to use 2-trimethylsilyloxy-1,3-butadiene[6] in the cycloaddition reaction, and the overall yield of the mixture of (7a) and (7b) was 77%. Reaction of this isomeric mixture with the aryllead

compound (5a) under the chloroform/pyridine conditions resulted in slow formation of the desired product (6c) in moderate yield; however, as with the formation of (6b) above, use of dimethyl sulfoxide as solvent led to a faster reaction and a good yield of (6c) (Table 1). This is a considerably shorter and higher yielding route to (6c) than that of Pearson,[3] which involves the use of an organoiron complex as a *p*-methoxyphenyl cation equivalent to achieve a synthesis of the methyl ester analogue of (6c).

The corresponding (±)-mesembrine synthon (6d) is readily obtained in a similar reaction of (7a, 7b) with 3,4-dimethoxyphenyllead triacetate (5c) (Table 1), which is available by our recently reported tin-lead exchange route.[7] The transformations required for the conversion of (6d) into (±)-mesembrine (2) have been carried out on related compounds.[3,8]

2,3-Dimethoxyphenyllead triacetate (5d), which was required for a similar synthesis of an intermediate (6e) potentially useful for the construction of (±)-lycoramine (3) and related alkaloids, was also prepared by tin-lead exchange. This was simply achieved in good yield by stirring the stannane (8)[9] with lead tetraacetate and a catalytic amount of mercury(II) acetate in chloroform. Unlike the above two examples, reaction of (7a, 7b) with lead compound (5d) in dimethyl sulfoxide led to a very poor yield of desired keto ester (6e); however, by use of the chloroform/pyridine system and a higher temperature, an acceptable yield of (6e) was eventually achieved (Table 1). The use to which this compound could be put as an advanced intermediate in the synthesis of (±)-lycoramine can be gauged from a recently developed route to the alkaloid.[10]

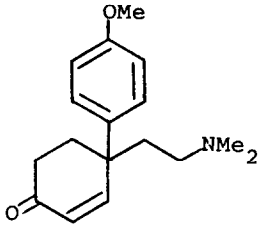
Table 1. Reaction of keto esters (4) and (7a, 7b) with aryllead triacetates.[a]

Keto ester	$ArPb(OAc)_3$	Base	Solvent	Temp./ °C	Time/ h	Product,%[b]
(4)	(5a)	py	$CHCl_3$	40	72	(6a) 53
(4)	(5b)		DMSO	40	24	(6b) 59
(7a, 7b)	(5a)	py	$CHCl_3$	40	66	(6c) 26
(7a, 7b)	(5a)		DMSO	40	48	(6c) 68
(7a, 7b)	(5c)[c]		DMSO	40	48	(6d) 53
(7a, 7b)	(5d)[c]	py	$CHCl_3$	60	42	(6e) 54

[a] For reactions in chloroform the ratio of keto ester : $ArPb(OAc)_3$: pyridine was 1:1.5:3 unless otherwise indicated.

[b] All new compounds were characterised fully by microanalytical and spectroscopic methods; yields were for purified material.

[c] 2 equiv. of $ArPb(OAc)_3$ used.



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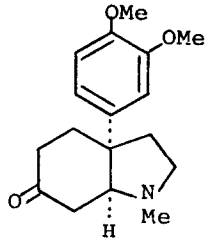
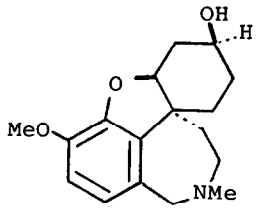


(2)



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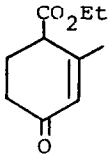

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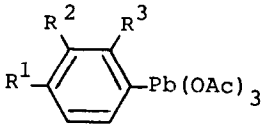

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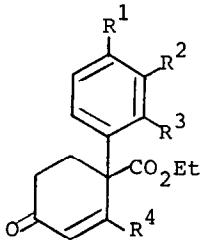
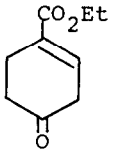


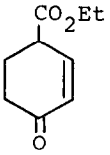
(6)

a; R^1 = OMe, R^2 = R^3 = H
b; R^1 = R^2 = R^3 = H
c; R^1 = R^2 = OMe, R^3 = H
d; R^1 = H, R^2 = R^3 = OMe

a; R^1 = OMe, R^2 = R^3 = H, R^4 = Me
b; R^1 = R^2 = R^3 = H, R^4 = Me
c; R^1 = OMe, R^2 = R^3 = R^4 = H
d; R^1 = R^2 = OMe, R^3 = R^4 = H
e; R^1 = R^4 = H, R^2 = R^3 = OMe



(7a)



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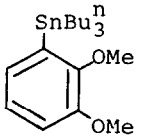

(8)

Acknowledgements

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