Tetrahedron Letters Vol. 21, pp 965 - 968 0040-4039/80/0301-0965$02.00/0

THE α-ARYLATION OF DERIVATIVES OF MALONIC ACID WITH ARYLLEAD TRIACETATES. NEW SYNTHESES OF IBUPROFEN AND PHENOBARBITAL.

John T. Pinhey and Bruce A. Rowe

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

Derivatives of Meldrum's acid and the sodium salts of substituted malonic esters undergo rapid arylation in high yield when treated with aryllead triacetates. These reactions have been applied to the synthesis of ibuprofen, an analgesic, and in a closely related reaction 5-ethylbarbituric acid has been reacted with phenyllead triacetate to give phenobarbital.

During a study of the chemistry of aryllead(IV) compounds[1-4] we found that aryllead triacetates react with many β-diketones[4] and β-keto esters[5] under particularly mild conditions to give good yields of the corresponding α-aryl β-dicarbonyl compound. Attempts were made[6] to extend this arylation reaction to malonic esters but these compounds proved to be much less reactive, and useful yields of α-aryl malonic esters could not be obtained in this way. We now wish to report that the desired arylation can be achieved by reacting either a substituted Meldrum's acid or an anion of a substituted malonic ester with an aryllead triacetate.

In the first method high yields of arylated products were obtained simply by mixing the Meldrum's acid derivative and aryllead triacetate in a 1:1 ratio in chloroform containing pyridine (3.0 equivalents) at 40° (Table 1). Clearly this reaction provides a very convenient route to a variety of arylated malonic acids and α-arylalkanoic acids. Although the full scope of the reaction remains to be investigated a number of comments can be made at this stage. Whereas the Meldrum's acid derivatives prepared from methylmalonic acid (entry 1), ethylmalonic acid (entry 2), and phenylmalonic acid (entry 3) reacted rapidly with p-methoxyphenyllead triacetate (2a) to give the α-arylated β-dicarbonyl compound in almost quantitative yield, Meldrum's acid itself (1d) gave only a low yield of the diarylated product (3d) when treated as above with (2a) (entries 4 and 5). Even with a 2:1 ratio of (2a) to (1d), the yield of (3d) was poor. The isopropyl derivative (1e) (entries 6 and 7) reacted far more slowly than (1a), (1b), and (1c), presumably due to a steric factor. Nevertheless a fair yield of (3e) could be obtained after a reaction time of 48 h.

We have demonstrated the usefulness of the above reaction in a short high-yielding synthesis of ibuprofen (4), a widely used nonsteroidal antiinflammatory agent. The required aryllead compound (2b) was readily obtained (61%) by the direct plumbylation[1] of isobutylbenzene. This was reacted as above with (1a) to give a quantitative yield of the Meldrum's acid derivative (3f), (entry 8) which afforded (4) on hydrolysis and decarboxylation.

Table 1. Reaction of aryllead triacetates with 2,2-dimethyl-1,3-dioxan-4,6-dione (Meldrum's acid) and it derivatives[a]

Entry	Substrate	$ArPb(OAc)_3$	Time (h)	Product	Yield (%)
1	(1a)	(2a)	1	(3a)	91[b]
2	(1b)	(2a)	24	(3b)	94[b]
3	(1c)	(2a)	1	(3c)	92[b]
4	(1d)	(2a)	1	(3d)	7[b]
5	(1d)	(2a)	24	(3d)	8[b]
6	(1e)	(2a)	24	(3e)	29[b]
7	(1e)	(2a)	48	(3e)	42[b]
8	(1a)	(2b)	1	(3f)	95[c]

[a] The reactions were carried out in chloroform at 40° using the following concentrations: β-dicarbonyl compound (0.6M), aryllead triacetate (0.66M), and pyridine (2M).

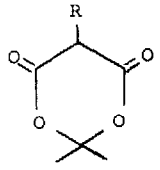
[b] Yield by n.m.r. spectroscopy. [c] Isolated yield.

Table 2. Reaction of aryllead triacetates with the anions of diethyl malonate derivatives[a]

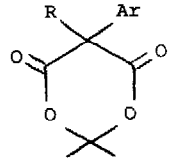
Entry	Substrate	$ArPb(OAc)_3$	Time (h)	Product	Yield (%)
1	(7)	(2a)	1	(10)	85[b]
2	(8)	(2a)	1	(11)	77[b]
3	(9)	(2a)	24	(12)	61[b]
4	(7)	(2b)	1	(13)	80[c]

[a] The sodium salt of the β-dicarbonyl compound (1.0 mmol) in THF (1-2 ml) was added slowly under nitrogen to the aryllead triacetate (1.1 mmol) in pyridine (1.5-3.0 ml) at room temperature, except for entry 2 in which the amounts were (8) (1.5 mmol) and (2a) (1.0 mmol).

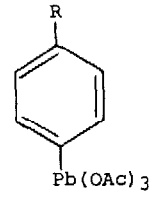
[b] Yield by n.m.r. spectroscopy. [c] Isolated yield.



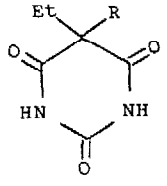
(1a) R = Me
(1b) R = Et
(1c) R = Ph
(1d) R = H
(1e) R = Me_2CH



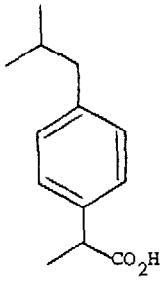
(3a) R = Me, Ar = p-$MeOC_6H_4$
(3b) R = Et, Ar = p-$MeOC_6H_4$
(3c) R = Ph, Ar = p-$MeOC_6H_4$
(3d) R = Ar = p-$MeOC_6H_4$
(3e) R = Me_2CH, Ar = p-$MeOC_6H_4$
(3f) R = Me, Ar = p-$Me_2CHCH_2C_6H_4$



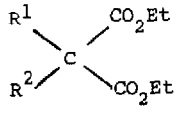
(2a) R = MeO
(2b) R = Me_2CHCH_2



(5) R = Ph
(6) R = H



(4)



(7) R^1 = Me, R^2 = H
(8) R^1 = Ph, R^2 = H
(9) R^1 = Me_2CH, R^2 = H
(10) R^1 = Me, R^2 = p-$MeOC_6H_4$
(11) R^1 = Ph, R^2 = p-$MeOC_6H_4$
(12) R^1 = Me_2CH, R^2 = p-$MeOC_6H_4$
(13) R^1 = Me, R^2 = p-$Me_2CHCH_2C_6H_4$

Since there is a close relationship between Meldrum's acid and barbituric acid, and in view of their similar acidity, it seemed likely that 5-substituted barbituric acids would behave similarly to the above compounds with aryllead triacetates. Early results indicate that this is the case, and the potential of the reaction is illustrated here by the rapid formation of phenobarbital (5) in quantitative yield on treatment of 5-ethylbarbituric acid (6) with phenyllead triacetate under the above conditions.

From the above results and those obtained with other β-dicarbonyl compounds,[4,5] it appeared that the ease of arylation with aryllead triacetates is partially dependent on the acidity of the substrate and we reasoned that the anions of these carbonyl compounds should be more reactive. Indeed this has been found to be the case with malonic ester derivatives (Table 2) thus providing a simple route to α-arylmalonic esters. As with the Meldrum's acid derivatives, the isopropyl derivative (entry 3, Table 2) was less reactive than the methyl and phenyl substituted compounds and the yield of arylated product was lower. Again we attribute this lower reactivity of the sodium salt of (9) to a steric factor. The reaction of diethyl sodiomethylmalonate with (2b) to give (13) (entry 4), followed by hydrolysis and decarboxylation, provides a further high-yielding route to ibuprofen. Unlike the salts listed in Table 2 diethyl sodiomalonate does not undergo arylation with (2a) under these conditions.

This work and a study of the reactions of other carbanions with aryllead triacetates will be reported in detail in the Australian Journal of Chemistry.

Acknowledgements. This work was supported by a grant from the Australian Research Grants Committee. The award of a Commonwealth Postgraduate Award (to B.A.R.) is gratefully acknowledged.

References

1. H.C. Bell, J.R. Kalman, J.T. Pinhey, and S. Sternhell, Austral. J. Chem., 1979, 32, 1521.
2. H.C. Bell, J.R. Kalman, G.L. May, J.T. Pinhey, and S. Sternhell, Austral. J. Chem., 1979, 32, 1531.
3. H.C. Bell, J.T. Pinhey, and S. Sternhell, Austral. J. Chem., 1979, 32, 1551.
4. J.T. Pinhey and B.A. Rowe, Austral. J. Chem., 1979, 32, 1561.
5. J.T. Pinhey and B.A. Rowe, Austral. J. Chem., in press.
6. J.T. Pinhey and B.A. Rowe, unpublished data.

(Received in UK 2 January 1980)