The Reformatsky–Claisen Reaction, a New Synthetically Useful Sigmatropic Process

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Summary Reaction of α-bromo-esters derived from allylic and acetylenic alcohols with zinc dust provides a useful synthesis of γδ-unsaturated acids, *via* [3,3]-sigmatropic rearrangement of the intermediate zinc enolate, the efficiency depending upon substitution and solvent.

The [3,3]-sigmatropic rearrangement of 3-oxa-1,5-diene species, as (**1**), to γδ-unsaturated carbonyl compounds (**2**), originally demonstrated by Claisen,[1] is an important tool for the stereospecific construction of unsaturated systems, *e.g.* the rearrangements of vinyl ethers (**1**; R = H or alkyl),[2] amide acetals (**1**; R = NR_2),[3] and orthoesters (**1**; R = OR).[4] In view of a report on the rearrangement of lithium enolates (**1**; R = OLi and $OSiMe_3$)[5] we report the results of our studies on [3,3]-sigmatropic rearrangements of zinc enolates (**1**; R = OZnBr) and enol phosphates [**1**; R = OP(O)-$(OR)_2$].

Zinc enolates, *e.g.* (**4**), generated by Reformatsky-type reaction of α-halogeno-esters (**3**) with zinc dust, under suitable temperature conditions, provide an economic and ready route to the corresponding zinc carboxylates (**5**) of γδ-unsaturated acids. Thus, allylic alcohols were esterified with the readily available α-bromo-acid bromides[6] to provide the esters (**3**) in high yield (>90%).† When these esters were added to a refluxing suspension of an excess of zinc dust in an aromatic hydrocarbon solvent they were smoothly converted into the carboxylates (**5**). Examples are in the Table.

Table

	Ester (3)				Solvent	Temp. (t/°C)	Yield of (5) (%)
	R^1	R^2	R^3	R^4			
a	Me	Me	H	H	Benzene	80	100
b	Me	H	H	Me	Toluene	110	96
c	H	H	H	H	Xylene	140	<15
d	Me	H	Ph	H	Toluene	110	16

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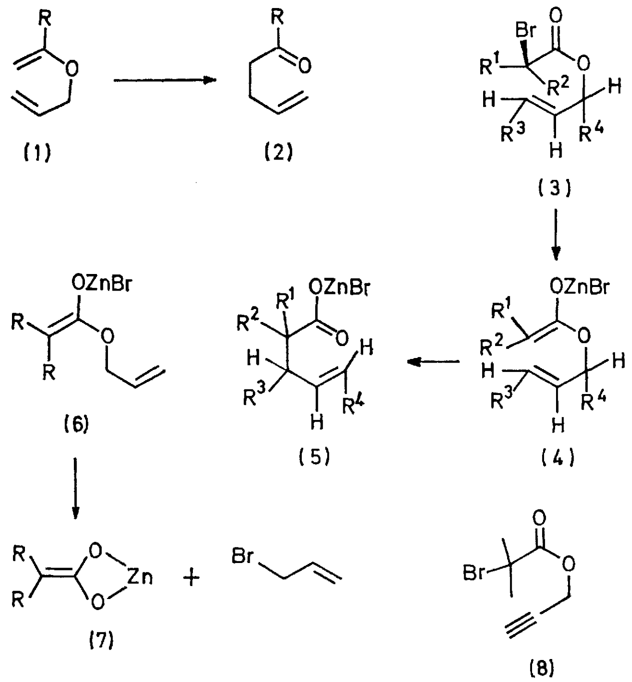
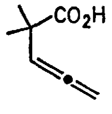
† All new compounds were characterised by analytical and spectral data.

The results in the Table, together with knowledge of the other products isolated from these and other reactions, indicates two side reactions, whose contributions depend on substitution and solvent. Firstly, we find the condensation of the zinc enolates derived from acetic esters to yield 1,3-dicarbonyl compounds, a known byproduct of classical Reformatsky reactions.[7] This process is depressed by α-alkyl substitution of the ester and is illustrated here by the decreasing yield, from 100 to 15%, in passing from the isobutyrate (**3a**) to the acetate (**3c**). Substitution in the allyl portion, on the other hand, favours an alternative side reaction: the decomposition of the zinc enolate to allylic halide, (**6**) to (**7**). This halide undergoes Friedel–Crafts condensation with the aromatic solvent, catalysed by zinc bromide present in the reaction, *e.g.* (**3d**). Attempts to reduce this side reaction by complexation of the intermediate (**4**) with difunctional ether solvents, *e.g.* diglyme, thereby lowering the Lewis acidity of the zinc atom, did provide increased yields in some cases, *e.g.* (**3d**, 48%); however, in other examples the opposite effect was observed. At present the origin of this variation is not clear.

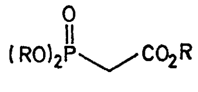


(1) (2) (3) (4) (5) (6) (7) (8)

This new reaction appears to exhibit a similar stereospecificity to that observed in the related [3,3]-sigmatropic processes.[8] Thus, the α-bromopropionate (**3b**) gave a *trans* to *cis* ratio of 93:7 for the product 2-methylhex-4-enoic acid. Finally, this method is also applicable to acetylenic esters as was shown by the smooth quantitative conversion, in refluxing benzene, of (**8**) into the allenic acid (**9**). In summary the Reformatsky–Claisen reaction provides an alternative to the earlier described methods of effecting the change (**1**) to (**2**), which avoids both strongly acidic and basic conditions.



(9)



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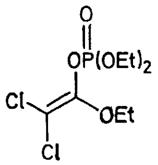

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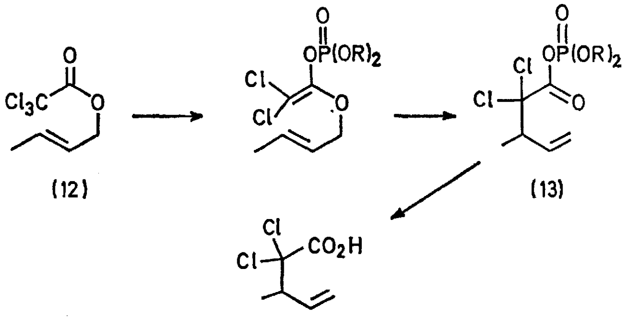

(12) (13) (14)

As an alternative reagent for the reductive formation of enols we have examined derivatives of trivalent phosphorus. As is well known[9] α-bromo-esters react with phosphites through the Arbusov pathway to yield the phosphonate (**10**). However, Kharasch showed[10] that trichloracetyl esters yield mainly enol phosphate, *e.g.* as (**11**), from ethyl trichloracetate and triethyl phosphite. This was readily applied to the [3,3]-sigmatropic rearrangement. *E.g.*, the ester (**12**), when mixed in ether with tri-isopropyl phosphite was converted directly into the mixed anhydride (**13**; R = Pr^i) which on mild basic hydrolysis gave the acid (**14**) (70%). The intermediate enol phosphate could not be isolated and rearranged immediately under the reaction conditions. This procedure is so far restricted to trichloracetyl esters of allylic alcohols and provides an extremely mild preparative route to the rearranged dichloro-acids.

We thank the National Science Foundation and Eli Lilly and Co., Indianapolis, for support.

(*Received*, 18*th October* 1972; *Com.* 1779.)

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[1] Reviewed by D. S. Tarbell, 'Organic Reactions,' ed. R. Adams, Wiley, New York, 1944, vol. II, p. 1; S. J. Rhoads, 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, vol. I, p. 655; A Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, **22**, 391.

[2] A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, 1961, **83**, 198; G. Saucy and R. Marbet, *Helv. Chim. Acta*, 1967, **50**, 2091; K. Saki, J. Ide, O. Oda, and N. Nakamura, *Tetrahedron Letters*, 1972, 1287.

[3] A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425; J. Ficini and C. Barbara, *Tetrahedron Letters*, 1966, 6425.

[4] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, 1970, **92**, 741.

[5] R. E. Ireland and R. H. Mueller, *J. Amer. Chem. Soc.*, 1972, **94**, 5898.

[6] C. W. Smith and D. G. Norton, *Org. Syn.*, 1963, *Coll. Vol.* 4, 348.

[7] R. L. Shriner, *Org. Reactions*, 1942, **1**, 4.

[8] C. L. Perrin and D. J. Faulkner, *Tetrahedron Letters*, 1969, 2783; D. J. Faulkner and M. R. Peterson, *ibid.*, 1969, 3243.

[9] R. Hudson, 'Structure and Mechanism in Organo-Phosphorus Chemistry,' Academic Press, New York, 1965, p. 149.

[10] M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, 1955, **20**, 1356.