Tetrahedron Letters No. 21 pp 1679-1682, 1975. Pergamon Press. Printed in Great Britain.

γ-HALOTIGLATES, II. A HIGH YIELD, STEREOSELECTIVE PREPARATION AND THE CONVERSION TO USEFUL TRISUBSTITUTED OLEFIN SYNTHONS

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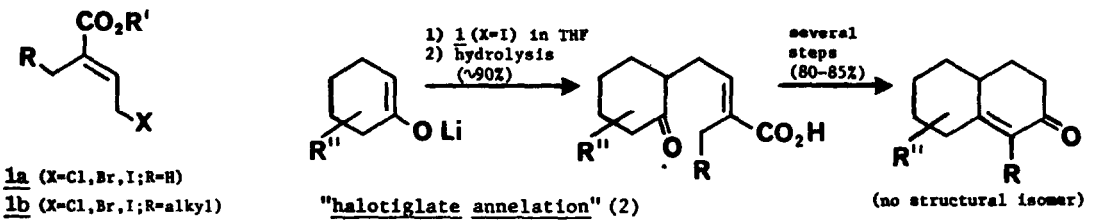
(Received in USA 9 December 1974; received in UK for publication 7 April 1975)

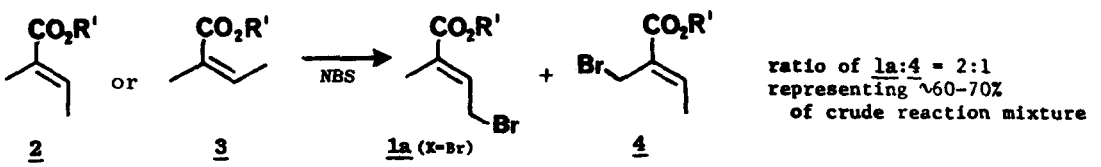
We have, for some time, been interested in γ-halotiglates 1 as synthetic intermediates for a variety of purposes (1) and have recently reported (2) the use of these versatile reagents in a high-yield, position-specific annelation of unsymmetrically substituted cyclohexanones.



"halotiglate annelation" (2)

In this letter, we wish to report a viable stereoselective preparation of 1, which makes these synthetic intermediates readily available as annelating agents and as precursors to selectively functionalized trisubstituted olefin synthons. In a subsequent letter (3), we will detail further synthetic utility of γ-halotiglates as annelating agents.

To function as useful and effective synthetic intermediates, both 1a and 1b must be readily available; but the literature records no efficient preparations of these compounds. For example, Dreiding and co-workers(4) provided a definitive correction of some earlier reports(5) which had suggested that γ-bromotiglates could be easily prepared by the action of NBS on the parent tiglates. Dreiding's reinvestigation demonstrated that this bromination produces, either from tiglates 2 or from isomeric angelates 3, essentially the same complex product mixture; from this mixture, a 2:1 ratio of γ- and β'-bromotiglates (1a and 4) can be isolated only in modest yield and purified only with difficulty. Consequently, we sought an efficient and viable synthetic alternative for the preparation of compounds 1.



2 3 1a (X=Br) 4

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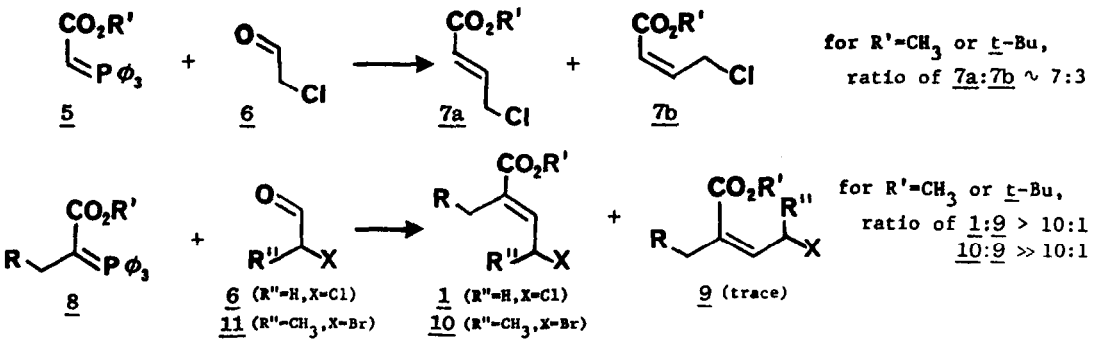
House and co-workers (6) have reported that the Wittig reaction of carbomethoxymethylidene triphenylphosphorane 5 and chloroacetaldehyde 6(7) produces methyl 4-chlorobutenoates 7a and 7b, as an isomeric mixture in excellent yield. On reexamining this reaction, we have found that it can be extended to the preparation of γ-halotiglates 1 in excellent yield; but, even more interesting is the high stereoselectivity we observed in this preparation of 1 which makes isomerically pure γ-halotiglate acids readily available, for use as precursors to differentiably functionalized trisubstituted olefin synthons of known double bond geometry.



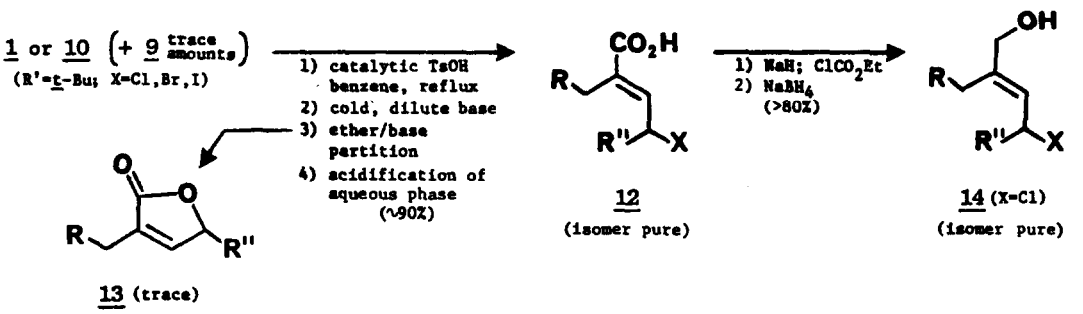
When phosphoranes 8 (8,9) were exposed to one equivalent of chloroacetaldehyde in refluxing methylene chloride for 20 hours, γ-chlorotiglates 1 were produced in high yield (see Table 1). Refluxing methylene chloride appears to be the solvent of choice, since other solvent systems at reflux afforded lower yields of isolated products or less desirable trans:cis product ratios. Synthetically, it is significant that the trans:cis product ratio observed in this preparation of 1 is greater than that observed by House for the simpler system 7, cited above. Under conditions which produce a 7:3 mixture of 7a and 7b, the γ-chlorotiglate esters 1 were produced almost to the exclusion of their angelate isomers 9 (see Table 1). Perhaps, this high double bond isomer selectivity is rationalizable with hindsight (10a), in view of diverse observations (10b) concerning the stereochemistry of related Wittig reactions.

TABLE I

phosphorane +	α-halo-aldehyde	CH_2Cl_2 reflux 20 hours → product	% yield (distilled)	% trans isomer in product mixture (11)
5 (R'=Me) mp 162-3 (6)	6	7 methyl 4-chloro-2-butenoate	84 [67-95 (6)]	71
5 (R'=t-Bu) mp 151-2 (12)	6	7 t-butyl 4-chloro-2-butenoate	85	72
8 (R=H, R'=Me) mp 152-4 (6,13)	6	1 methyl 4-chloro-2-methyl-2-butenoate	84	92
8 (R=H, R'=t-Bu) mp 168-9 (12)	6	1 t-butyl 4-chloro-2-methyl-2-butenoate	86	94-95
	11	10 t-butyl 4-bromo-2-methyl-2-pentenoate	86	>96
8 (R=CH_3, R'=t-Bu) mp 169-70 (12)	6	1 t-butyl 4-chloro-2-ethyl-2-butenoate	86	>96
8 (R=C_2H_5, R'=Me) mp 105 (14)	6	1 methyl 4-chloro-2-propyl-2-butenoate	84	>96

Apparently, this preparation of γ-halotiglates is quite general and can also be used for the direct preparation of γ-alkyl-γ-bromotiglates. For instance, phosphorane 8 (R=H, R'=t-Bu) readily gives 10, t-butyl trans-4-bromo-2-methyl-2-pentenoate, on exposure to α-bromopropionaldehyde 11 in refluxing methylene chloride. Bromo ester 10 was isolated in 86% yield and showed no detectable amounts of the cis isomer (by nmr).

When compounds 1 and 10 were prepared as t-butyl esters, these esters could easily be converted to the corresponding γ-halo unsaturated acids 12 in high yield without double bond isomerization (catalytic toluenesulfonic acid in refluxing anhydrous benzene). Furthermore, a simple aqueous base work-up allowed direct isolation of isomerically pure γ-halotiglic acids 12 (under the influence of base, any small amounts of isomeric angelates cyclize to base-insoluble lactones 13, which are easily separated). Isomerically pure γ-chlorotiglic acids 12 (X=Cl) were converted to trisubstituted olefin synthons 14 (15), using Perron's two-step sequence (16): conversion to the mixed anhydride (sodium hydride followed by ethyl chloroformate in THF at 0°C) and subsequent reduction ($NaBH_4$ in THF at 0°C). Products 14 were isolated in greater than 80% yield and proved to be trans-4-chloro-2-alkyl-2-alken-1-ols, uncontaminated with by-products derived from overreduction or double bond isomerization.



Finally, since γ-chloro and γ-bromotiglic esters and acids undergo very rapid halogen exchange (usually >95% yield) (using LiBr or NaI in tetrahydrofuran, ethylene glycol, or acetone at room temperature) without double bond isomerization (12b), it should be apparent that these simple procedures make a variety (12b) of γ-halotiglate esters and acids readily and easily available for use as synthetic intermediates.

Acknowledgements

The authors would like to express their thanks to the Robert A. Welch Foundation (Grant F-345) for supporting the bulk of this research, as well as to Research Corporation and to the Petroleum Research Fund administered by the American Chemical Society for supporting this work in its initial stages. The principal author wishes to thank Professor Andre S. Dreiding for several stimulating discussions and for personal communication of interesting and pertinent experimental results prior to their publication (4).

References and Footnotes

1. Preliminary reports of our continuing work with γ-halotiglates were made in the following oral communications: 159th National Meeting of the Amer. Chem. Soc., Houston, Texas (Feb. 1970), Abst. ORGN 117; 161st National Meeting of the Amer. Chem. Soc., Los Angeles, Calif. (March 1971), Abst. ORGN 030, ORGN 138; Second International Symposium on Synthesis in Organic Chemistry, Cambridge, England (July 1971).

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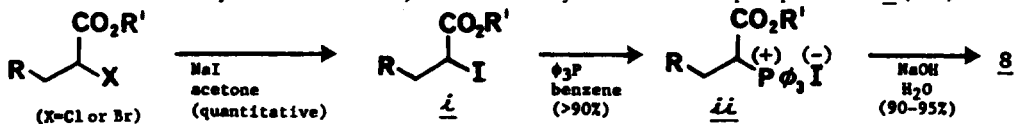
7. (a) Although a lachrymator and skin irritant, chloroacetaldehyde 7 can be easily and safely manipulated for use in carbonyl-stabilized Wittig reactions. Suitable reagent is most easily obtained from commercially available chloroethylene carbonate, as reported by Gross (7b). Alternatively, commercially available chloroacetaldehyde in water can be suspended in excess CH_2Cl_2 over $MgSO_4$; although somewhat unwieldy because of the large amounts of CH_2Cl_2 necessary, such dried solutions of 7 are also suitable for direct use in the preparation of compounds 1.
(b) H. Gross, J. Prakt. Chem., 21, 99 (1963).

8. Phosphoranes 8 were prepared by a slight modification of the standard sequence (6,13), as schematized below. Note that use of α-iodoesters *i* in the preparation of phosphonium iodides *ii* allows much improved overall yields. Crude phosphonium iodides, isolated as somewhat unstable crystalline solids, were directly converted to phosphoranes 8 (12a).



9. Our attempts to use the Emmons-Wadsworth modification of the Wittig reaction for the preparation of 1 were largely unsuccessful. Some γ-chlorotiglate ester 1a was obtained using triethyl phosphonopropionate (with sodium hydride) and chloroacetaldehyde; however, yields were low and less double bond isomer selectivity was observed. With longer chain phosphonoalkanoates, no 1b was observed and starting phosphonate esters were recovered after work-up; the chloroacetaldehyde was, however, destroyed.

10. (a) Apparently, for whatever mechanistic rationalization one prefers, the preferences (10b) of α-carbonyl substituted phosphoranes for forming trans olefins and of α-alkyl substituted phosphoranes for forming cis olefins, in normal Wittig reactions with aldehydes, are additive, at least for reactions with α-haloaldehydes.
(b) H. O. House and G. H. Rasmusson, J. Org. Chem., 26, 4278 (1961); E. J. Corey, et al., J. Amer. Chem. Soc., 88, 5653 (1969); ibid., 89, 2758 (1967); ibid., 91, 5675 (1969); E. Hamanaka, Ph.D. Thesis, Harvard University, Cambridge, Massachusetts, 1967; W. P. Schneider, Chem. Commun., 785 (1969); S. Trippett, Quart. Rev. (London), 17, 406 (1963); H. J. Bestmann and O. Kratzer, Chem. Ber., 95, 1894 (1962).

11. Isomer distributions were determined in all cases by high amplitude nmr examination and were corroborated, when possible, by gas chromatography.

12. (a) Satisfactory chemical analyses were obtained for previously unreported phosphoranes.
(b) Assignments of structure for all new compounds were made from unexceptional spectral data (which compared favorably with those reported for the known members of the series) and from high resolution mass spectral determinations of parent peaks and base fragments. Isomerically pure, crystalline γ-chloro and γ-bromo acids 12 gave satisfactory combustion analyses.

13. O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser, and P. Zeller, Helv. Chim. Acta, 40, 1242 (1957).

14. H. J. Bestmann and H. Schulz, Angew. Chem., 73, 27 (1961).

15. Trisubstituted olefin synthons 14 may be readily O-functionalized before use as "normal" allylic halides in alkylation reactions. However, we have observed that chlorohydrins such as 14 can be "protected" as the lithium alkoxide during alkylation of reactive nucleophiles. See, for example, P. L. Stotter and R. E. Hornish, J. Amer. Chem. Soc., 95, 4444 (1973).

16. Y. G. Perron, et al., J. Med. Chem., 7, 483 (1964).