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Free radical addition of haloalkanes to polymer bound olefins and its application to the solid-phase synthesis of pyrethroids†

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Abstract—Polymer bound olefins undergo free radical initiated 1,2-addition when reacted with a variety of haloalkanes. The strategy could be applied successfully to the solid-phase synthesis of dihaloethenylcyclopropane carboxylic acids which are the key fragments of synthetic pyrethroids. © 2002 Published by Elsevier Science Ltd.

Pyrethroids are photostable and highly effective analogs of natural insecticides, pyrethrins, which are widely used for the control of a broad spectrum of domestic and agricultural pests.[1] Ever since the discovery of Permethrin and Cypermethrin by Elliot et al., dihaloethenylcyclopropane carboxylic acids (the key structural moiety of most of the pyrethroids including Cyhalothrin and Deltamethrin) have occupied prominence in the pesticide industry and major efforts towards the synthesis of pyrethroids have essentially focused on the construction of this moiety itself. Different approaches have been developed by various research groups and multinational companies for the cost-effective production of these economically important molecules. Important among these routes which have gone into large scale commercial production are (i) the prenol route[2] which involve Johnson Claisen orthoester rearrangements starting from prenol followed by haloalkane addition to the ensuing olefin and concomitant cyclization/side chain dehydrohalogenation to get the required cyclopropane carboxylates, (ii) the halocyclobutanone route developed by Ciba Geigy,[3a] which employs haloalkane addition to acrylic acid derivatives and ketene–isobutene cycloaddition followed by Favorski rearrangement of the halo-substituted cyclobutanone to get the required dihaloethenylcyclopropane carboxylic acids.

Thus, the radical initiated 1,2-addition[3b] of haloalkanes to terminal olefins is employed in both commercial routes as an important reaction for the construction of the dihaloethenyl–cyclopropane carboxylic acid moiety required for the synthesis of pyrethroids.

The importance of solid-phase synthesis is reflected by the surge of publications recently.[4a] Even though a few 1,2-addition reactions have been reported on solid phase,[4b] to our knowledge, there has not been any report on the addition of haloalkanes to polymer bound olefins. In connection with our continuing interest on the development of new solid-phase reactions with a view to the generation of small molecule libraries required for the high through put screening of the bioactive molecules,[5] together with our ongoing activity on the development of pyrethroid insecticides, we present here for the first time, free-radical addition of haloalkanes to polymer bound olefins and the successful implementation of this strategy for the synthesis of synthetic pyrethroids.

Olefinic acids were anchored to Merrifield resin[7] by heating (70°C, 12 h) the corresponding sodium salts with Merrifield resin in DMF, whereas carbodiimide coupling (DCC–HOBt, 4 equiv. each in DMF, 18 h) was employed for the Wang[7] resin. The initial loading levels were determined by weight gain after coupling and also by cleavage (TFA) of a known quantity of resin bound olefins and quantitative GC analysis. Free-radical addition reactions of various haloalkanes to resin bound olefins were conducted at elevated temperatures (70–90°C, see Table 1) with butyronitrile as the co-solvent except in case of CCl_4. Benzoyl peroxide (catalytic quantities) was added in two batches with an 8 h interval. Formation of the addition products on

Keywords: solid phase; radical addition; pyrethroids.

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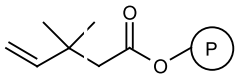
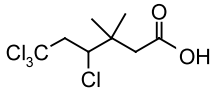
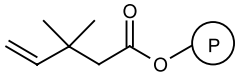
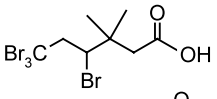
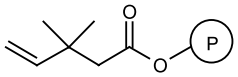
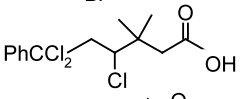
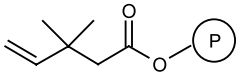
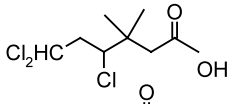
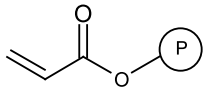
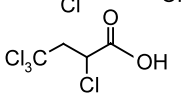
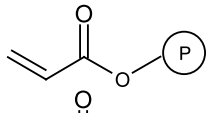
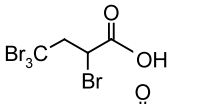
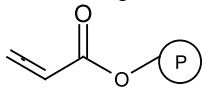
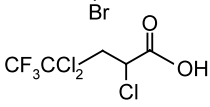
Table 1. Solid-phase telomerization of olefins

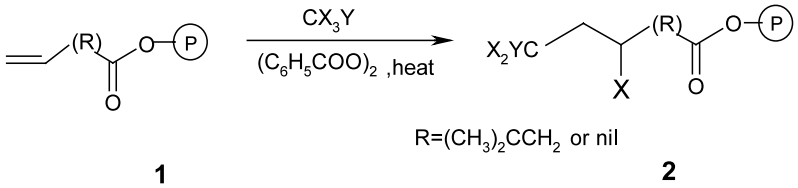
Entry	Olefins	Halo alkanes	conditions [a]	Products [d]	Yield (Purity) % [e]
a.		CCl_4 [b]	78 °C, 48h		92(96)
b.		CBr_4	90 °C,40h		91(90)
c.		$PhCCl_3$	90 °C, 35h		75(80)
d.		$CHCl_3$	60 °C, 48h		62(86)
e.		CCl_4 [b]	76 °C, 24h		94(92)
f.		CBr_4	85 °C, 40h		96(95)
g.		CF_3CCl_3 [c]	80 °C, 48h		78(89)

a. Butyronitrile was used as solvent unless otherwise mentioned. **b.** Reactions were run without any co-solvent. **c.** Reactions were conducted adiabatically in a sealed tube. **d.** All products were characterized by IR (on resin) and ^1H NMR, mass spectra (after cleavage). **e.** Purity based on the GC analysis of the crude product (after cleavage), yields calculated based on initial loading level.

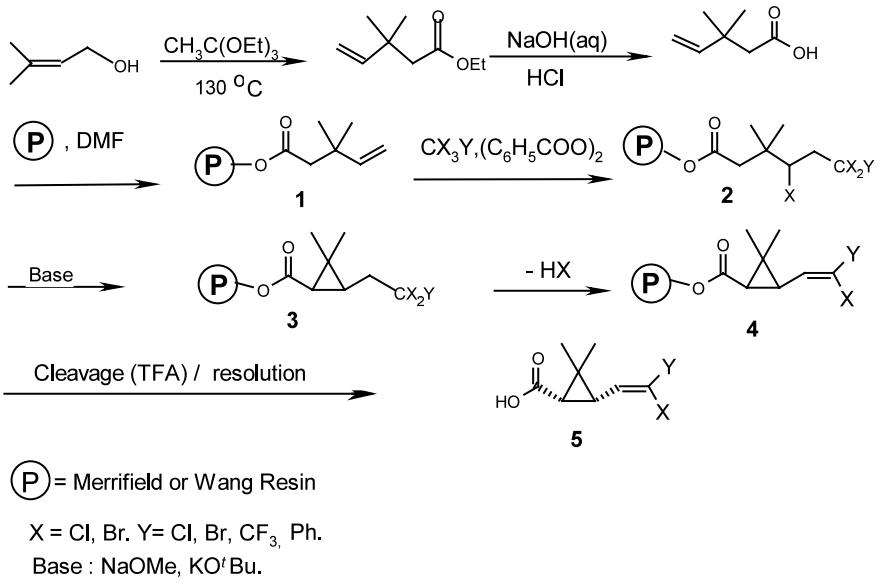
solid-phase could be confirmed by IR (Scheme 1) and by cleavage of a small quantity of the resin with TFA and analysis of the residue by ^1H NMR and MS. Different halo compounds viz., CCl_4, CBr_4, CF_3CCl_3, $PhCCl_3$ could be added successfully to different terminal resin bound olefins. The conversion was complete as no olefin could be detected in the ^1H NMR of the crude product obtained after resin cleavage. Interestingly, perhaps due to a pseudo dilution effect exerted by the polymeric backbone, no telomeric products could be detected in the residue obtained after cleavage. It is important to mention here that our efforts to convert the resin bound olefin using a Cu(I)Cl complex with TMEDA or ethanolamine did not give fruitful results.[3] Cyclization on the resin was carried out by vortexing the resin bound halo compound **2** with bases such as NaOMe and KO′Bu (3.5 equiv.) in DMF at 0°C–rt (6–12 h).

The resin bound addition products could be successfully cyclized and the cyclopropane carboxylate **3** thus formed underwent simultaneous side chain dehydrohalogenation at rt to afford the required dihaloethenylcyclopropane carboxylate **4**. Mixtures of *cis*- and *trans*-acids were isolated in ratios (ca. 75:25) as encountered in solution-phase cyclization. However, cyclization on solid-phase often associated with partial release of the product which could be isolated after acidification of the filtrate and aqueous work-up and solvent extraction. The remainder of the resin bound dihaloethenylcyclopropane carboxylates could be effectively released by routine TFA cleavage (TFA–DCM, 1:1, 4–6 h) (Scheme 2).

Most pyrethroids are chiral molecules with many having three stereogenic centers. The biological activity of the pyrethroids is mainly attributed to a set of



Scheme 1.



Scheme 2.

diastereomeric pairs. There has been a marked trend towards marketing these molecules in optically pure form. It has been established in our laboratory[6] that vinylcyclopropane carboxylates can be cleaved selectively from the resin enzymatically to get optically pure esters or acids. Thus, resin bound dihaloethenylcyclopropane carboxylates prepared using the present strategy can be conveniently subjected to kinetic resolution.

In conclusion, we have developed a methodology for the free-radical initiated 1,2-addition of a variety of haloalkanes to resin bound olefins and the successful implementation of this strategy for the solid-phase synthesis of various dihaloethenylcyclopropane carboxylates of commercial and biological significance.

Acknowledgements

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6. Nanda, S.; Rao, A. B.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 5905–5908.
7. (a) Merrifield resin (Advanced ChemTech, USA); 100–200 mesh; substitution 0.8–1.5 mmol/g; cross linking, 1% DVB; (b) Wang resin (Advanced ChemTech, USA); 100–200 mesh; substitution 0.8 mmol/g; cross linking, 1% DVB.