Notes

Reaction of Allylzinc Bromides with Carbonyl Compounds in a Continuous Flow System. An Efficient Synthesis of Homoallyl Alcohols Including Artemisia Alcohol

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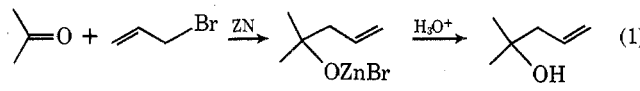
Recently we described a procedure in which the Reformatsky reaction is carried out by passing a mixture of an α-bromo ester and an aldehyde or ketone through a heated column of granular zinc.[1] This continuous-flow adaptation of the conventional synthesis of β-hydroxy esters[2] was shown to give substantially improved yields. We have now found that a similar procedure is applicable to the synthesis of alcohols from an allylic bromide and an aldehyde or ketone (eq 1).

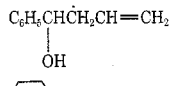
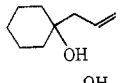
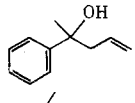
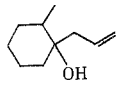
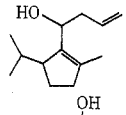
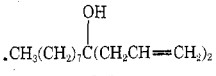
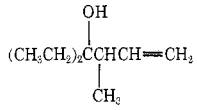
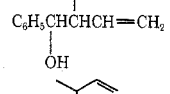
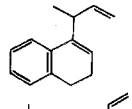
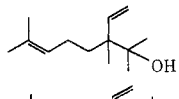
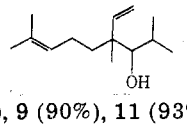


1 2 3 4 (1)

Optimized conditions require the slow addition of a 1:1.5 molar mixture of the carbonyl component (**1**) and allylic bromide (**2**) in tetrahydrofuran to a column of granular zinc, heated to just above the reflux temperature of the solvent. The apparatus is identical with that described previously.[1] After addition is complete, the column is flushed with tetrahydrofuran and the collected zinc alkoxide (**3**) is hydrolyzed with dilute sulfuric acid to yield homoallylic alcohol **4**.

The results are summarized in Table I. Yields of alcohols (**5–15**) are consistently higher than those obtained from allylzinc bromides and aldehydes or ketones under conventional reaction conditions,[3] and are also superior to those obtained in the Barbier–Grignard reaction using allylmag-

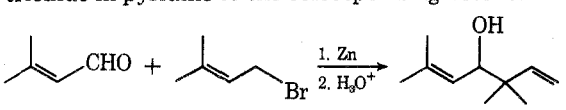
Table I
Reaction of Allylzinc Bromides with Carbonyl Compounds

Carbonyl compd	Registry no.	Bromide	Registry no.	Product		Registry no.	Bp, °C (mm)[a]	Yield, %[b]
Benzaldehyde	100-52-7	Allyl	18925-10-5		(5)	936-58-3	50–54 (0.05)	96
Cyclohexanone	108-94-1	Allyl			(6)	1123-34-8	32–34 (0.05)	97
Acetophenone	98-86-2	Allyl			(7)	4743-74-2	54–56 (0.05)	97
2-Methylcyclohexanone	583-60-8	Allyl			(8)	24580-51-6	40–42 (0.05)	93
2-Methyl-5-isopropyl-cyclopent-1-enecarboxaldehyde	54043-82-2	Allyl			(9)	57256-47-0	65–67 (0.05)	90
Ethyl pelargonate	123-29-5	Allyl			(10)	57256-48-1	75–79 (0.03)	94
3-Pentanone	96-22-0	Crotyl	14735-44-5		(11)	25201-42-7	70–73 (16)	96
Benzaldehyde		Crotyl			(12)	25201-44-9	65–67 (0.05)	95
α-Tetralone	529-34-0	Crotyl			(13)	57256-49-2	79–83 (0.05)	93
Acetone	67-64-1	Geranyl	57256-46-9		(14)	57256-50-5	63–67 (0.05)	80
Isobutyraldehyde	78-84-2	Geranyl			(15)	57256-51-6	71–75 (0.03)	74

[a] Purity as determined by GLC was >95% except for 5 (92%), 9 (90%), 11 (93%), and 15 (93%). [b] Isolated yield following distillation.

nesium halides.[4] A noteworthy feature of the zinc column method is the absence of Wurtz coupling product derived from the allylic halide. Successive addition to the column of different mixtures of carbonyl components with allylic bromides gave, in each case, a product with no detectable contamination from preceding alcohols. Thus, the zinc in the column can simply be replenished as it is consumed. The method is especially well suited to the large-scale preparation of homoallylic alcohols and, as judged from **10**, is applicable to esters as well as aldehydes and ketones. However, the method is ineffective with allylic chlorides and with saturated bromides.

Product alcohols were purified by short-path distillation and were identified by means of infrared, NMR, and mass spectral data (Table II). (See paragraph at end of paper regarding supplementary material.) In the case of the alcohol derived from crotyl bromide and tetralone, dehydration occurred upon distillation, leading to diene **13**. The structures of products **11–15** from crotyl and geranyl halides reveal that attack on the allylic moiety takes place solely at the β carbon in this reaction, in agreement with similar observations made with allylmagnesium[5] and allylzinc halides.[6] This feature ("allylic transposition") lends itself to an efficient, one-step synthesis of (±)-artemisia alcohol (**16**)[7]. Thus, passage through a heated zinc column of a mixture of 3-methyl-2-butenal[8] and 1-bromo-3-methyl-2-butene[9] gave, after hydrolysis, a 91% yield of **16**. The structure of artemisia alcohol was confirmed by oxidation with chromium trioxide in pyridine to the corresponding ketone.[10]



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The continuous-flow, zinc column procedure appears to be a generally useful method for allylation at carbonyl functions where mild reaction conditions are necessary. The operational simplicity and high efficiency of the method afford significant advantages over the Grignard reaction in certain cases.

Experimental Section

Materials. Geranyl bromide was prepared by the method of Eschenmoser.[11] 1-Bromo-3-methyl-2-butene was prepared by addition of hydrogen bromide to isoprene.[9] 3-Methyl-2-butenal was prepared by oxidation of 3-methyl-2-buten-1-ol with manganese dioxide in petroleum ether. 2-Methyl-5-isopropylcyclopent-1-enecarboxaldehyde was prepared by the method of van Tamelen.[12] All other materials were obtained from commercial sources. Granular zinc (10 mesh) was activated prior to use by the method described previously.[1] GLC analysis was carried out using (1) a 10 ft × 0.375 in. column of 30% Carbowax 20M on Chromosorb W, or (2) a 5 ft × 0.25 in. column of 20% SE-30 on Chromosorb W with an Aerograph Autoprep 700 instrument. Infrared spectra were measured on neat liquids using a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were measured on $CDCl_3$ solutions using a Varian EM-360 spectrometer.

Reactions Using Zinc Column. The following procedure for the reaction of 3-pentanone with crotyl bromide to yield **11** is representative. To a heated column charged with activated zinc (10 mesh)[1] was added dropwise 25 ml of anhydrous tetrahydrofuran followed by a mixture of 3.05 g (35.4 mmol) of 3-pentanone and 7.16 g (53.0 mmol) of 1-bromo-2-butene in 50 ml of tetrahydrofuran. A low reflux was maintained at the head of the column during addition, which took 1 hr. The column was then flushed with 25 ml of tetrahydrofuran and the combined eluate, after dilution with 50 ml of ether, was treated with ice-cold 5% sulfuric acid, followed by sodium bicarbonate solution and saturated brine. The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was purified by short-path distillation to give 4.81 g (95.6%) of **11**, bp 70–73° (16 mm).

Artemisia Alcohol (16). A mixture of 1.15 g (13.6 mmol) of 3-methylbut-2-enal and 3.05 g (20.4 mmol) of 1-bromo-3-methylbut-2-ene in 20 ml of tetrahydrofuran was passed through the heated column of granular zinc. After flushing the column, the eluate was diluted with 50 ml of ether and washed with 30 ml of cold 5% sulfuric acid, sodium bicarbonate solution, and brine. After drying and removal of the solvent in vacuo, distillation afforded 1.68 g (91.3%) of artemisia alcohol (**16**).

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Registry No.—**16**, 29887-38-5; 3-methylbut-2-enal, 107-86-8; 1-bromo-3-methylbut-2-ene, 870-63-3.

Supplementary Material Available. Table II (2 pages). Ordering information is given on any current masthead page.

References and Notes

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Crystal and Molecular Structure of Cephalotaxine

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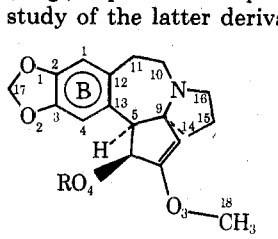
The natural antileukemic esters of caphalotaxine (**1**) include homoharringtonine (**2**), which is undergoing preclinical testing.[1] As these esters are unfortunately noncrystalline, x-ray studies to reveal the conformational preferences of the cephalotaxine portion are limited to other derivatives, e.g., cephalotaxine *p*-bromobenzoate (**3**).[2] Prior to our study of the latter derivative (**3**), we had initiated an



	R
1	H
2	$C_9H_{17}O_4$
3	*p*-BrC_6H_4