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SELECTIVE ALLYLATION OF CARBONYL COMPOUNDS IN AQUEOUS MEDIA

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Summary

The use of aqueous neutral media leads to excellent yields of homoallylic alcohols from reactions of allyl halides with carbonyl compounds in the presence of tin or zinc. The stereochemical course and range of application of this reaction have been investigated.

Introduction

Allylations of aldehydes and ketones to give homoallylic alcohols are attracting renewed interest [1]. The addition of allylic residues to open chain substrates has been examined from a stereochemical point of view [2] with the aim of preparing useful intermediates for the synthesis of some natural products [3]. The reaction can be achieved by use of conventional organometallics (of Li, Mg, Zn, Al, Cu), or in the presence with catalysts of allyl-boranes, -silanes, -stannanes, or -titanium compounds. New selective reactions involving mild conditions have recently been developed, and appear to be promising, in that they enable the allylations to be carried out under unusual conditions, namely in aqueous media [4], electrochemically [5], or in the presence of metallic salts in a lower valence state [6]. We recently reported that this very useful synthetic procedure can be achieved with great ease and efficiency in aqueous solvents [7], without the help of acidic coreagents (e.g. HBr, AcOH) which are needed in the case of several recent methods [4]. Two different pathways are depicted in eq. A and B. In the first, the condensing agent is metallic zinc, employed in a mixture of THF with saturated aqueous ammonium chloride (1/1 v/v). The second involves use of zinc, or preferably tin, in THF/water (1/1 v/v) and requires ultrasonic irradiation to ensure convenient reaction times and satisfactory yields. In view of the synthetic potential of these two processes, further investigations have been undertaken in order to determine the scope and selectivities.

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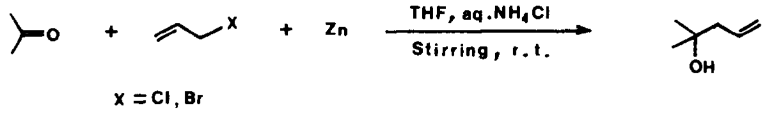
TABLE 1

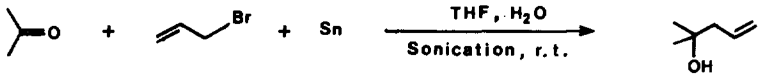
REACTION OF ALLYL BROMIDE WITH CARBONYL COMPOUNDS IN THE PRESENCE OF Sn OR Zn

Carbonyl compound	Method (metal)	Equiv. of reagent [a]	Yield [b] (%)	% *axial(erythro)* alcohol	
				this work	lit.
4-t-BuC$_6$H$_9$O	A(Zn)	4	89	72	84 [c]
	B(Zn)	4	97	70	
	B(Sn)	2	85	94	92 [d]
2-MeC$_6$H$_9$O	A(Zn)	4	60	87	88 [c]
	B(Zn)	4	10	85	
	B(Sn)	4	55	85	94 [d]
	B(Sn) [e]	4	55	86	
PhCH(CH$_3$)CHO	A(Zn)	2	80	79	
	A(Zn) [g]	2	80	78	
	B(Sn)	2	80	73	84 [f]

[a] See experimental section. [b] Isolated yield of purified compound. [c] From use of diallylzinc. See ref. 11. [d] From addition of allyltrimethyltin in the presence of boron trifluoride etherate. See ref. 12. [e] In ethanol solution. [f] From addition of allyltrimethyltin in the presence of aluminium trichloride. See ref. 2b. [g] In the presence of 0.2 equiv. of MgCl$_2$.



(A)

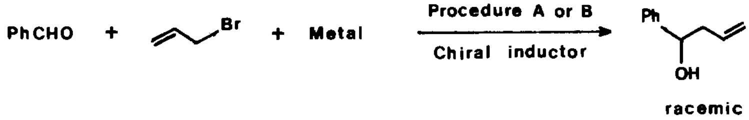


(B)

A stereochemical study was judged of especial interest because all the many studies of this aspect were all concerned with reactions under the usual anhydrous conditions used for organometallic syntheses. For such reactions, several mechanisms, involving 6-membered cyclic or acyclic processes according to the organometallic used, have been proposed to account of the stereoselectivity [2]. In our systems, the presence of water probably precludes the presence of organometallic species, and so the transition state must be different. Although no direct evidence has yet been obtained for a free radical intermediate in solution or absorbed on the metal surface [8], it can be regarded as highly probable. Since the additions of free radical species to carbon–heteroatom double bonds are reported to be rare [10] the stereochemical study also was of interest because it could provide useful data on such processes. To facilitate comparison with established methods, the experiments were carried out with 4-t-butylcyclohexanone, 2-methylcyclohexanone, and 2-phenylpropanal.

Results and discussion

The results which are listed in Table 1, were somewhat disappointing in one sense, there were no important differences from those obtained under anhydrous conditions. Addition of a salt, $MgCl_2$ which is known normally to have some influence on the stereoselectivity [13], also had no effect. However, the results reveal positive information that the reaction medium has no marked influence on the steric course of the addition, revealing that the medium can not be directly involved in the transition state. Whereas in the usual procedures solvation of the organometallic or formation of clusters with itself or with added metallic salts affect the energies of the transition states, the stereoselectivities observed in the present cases must reflect the intrinsic features of the reacting species and of their steric and electronic interactions. Moreover, it can also be concluded that the reacting species is probably absorbed on the metal surface, since this is the simplest way of accounting for the lack of influence of the medium. This view is supported by the complete absence of asymmetric induction in reaction (C) when it is carried out in the presence of hydrophilic (mannitol, starch) or lipophilic (camphoric acid) chiral auxiliaries, even when they are used in very high concentrations.



(C)

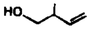
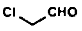
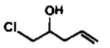
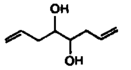
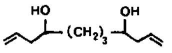
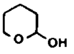
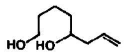
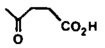
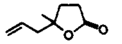
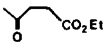
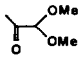
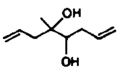
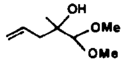
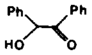
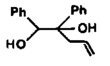
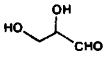
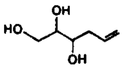
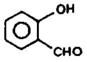
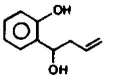
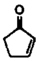
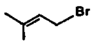
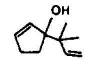
In this case the reaction would proceed stepwise in the immediate neighbourhood of the metal by radical addition to the carbonyl group [14], followed by reduction of the highly reactive alkoxy radical to the alkoxide. In an aqueous medium the latter is immediately hydrolyzed, and a change of pH should be observed; that this is not the case is probably the result of the very low solubility of tin hydroxides (a thick whitish precipitate is formed during the reaction), or in the case of reactions involving zinc, the buffering effect of ammonium chloride which forms soluble ammino complexes with zinc cations. Thus, even though no stereochemical advantages result from the use of aqueous conditions, some interesting mechanistic features can be discussed.

Important improvements could, however, be expected from these processes when water soluble species have to be used. It is well known that some low molecular weight substances, including C_1 and C_2 aldehydes, give rise to difficulties in organometallic synthesis because the aqueous solutions in which they are commercially supplied are obviously inappropriate for direct use. A second aspect is that species bearing functional groups incompatible with organometallic reagents, such as a hydroxyl function, have to be modified, either for protection or to ensure a satisfactory solubility in the commonly used solvents (polyhydroxylated compounds). As these inconveniences do not apply in our systems, several reactions were examined and the results are shown in Table 2.

It will be seen that in many cases, the tin mediated reaction gives better yields and purer products. Reactions involving use of aqueous formaldehyde give satisfactory yields, which compare favourably with those obtained by established methods [15]. As expected, the presence of free hydroxyl groups in the substrate does not affect the general course of the reaction, satisfactory results are also obtained in the presence of acid. In contrast, in the presence of a base (ephedrine) reactions that usually go to completion are completely inhibited. Excellent selectivity was observed using chloroacetaldehyde, but complex mixtures were obtained from trichloroacetaldehyde. Noteworthy is the dependence of the behaviour of pyruvaldehyde

TABLE 2

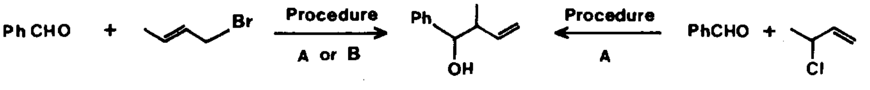
REACTIONS OF ORGANIC HALIDES WITH CARBONYL COMPOUNDS IN THE PRESENCE OF Sn OR Zn

Carbonyl Compound	Halide	Metal (equiv)	Product	Yield(%)
CH_2O		Zn (1.2)		30
		Sn (1.2)		60
		Sn (1.2) Zn (2)		54 30
CHO CHO		Sn (2.4)		51
CHO(CH$_2$)$_3$CHO		Sn (2 4)		80
		Sn (1.2)		79
		Sn (1.2) Sn (2)		52 71
		Sn (2)		86
		Sn (2)		73
		Zn (2)		60
		Sn (1.2) Zn (2)		90 82
		Sn (2)		55
		Zn (2)		75
		Zn (2)		65

dimethyl ketal on the metal; whereas the protecting group is left unchanged when zinc is used, a double allylation is observed in the presence of tin. However, reactions involving free pyruvaldehyde gave only polymers.

The scope of the allylation processes thus appears to be rather wide in respect of the carbonyl component, but is more restricted in respect of the allyl halide.

Allyl bromide or chloride can be used in the reaction in presence of zinc, but only the bromides react in the presence of tin. Substituted allyl bromides, such as crotyl or prenyl, always react at the more substituted carbon [7], as does 3-chloro-1-butene. In this case a poor (1/1.5) stereoselectivity is obtained starting from both halides



(D)

(eq. D). Cinnamyl bromide yielded phenylpropene, and the aldehydic coreactants (benzaldehyde, isobutanal) remained unchanged under all the conditions examined. 3-Bromocyclohexene decomposed readily to numerous unidentified products without formation of the expected adducts.

Notwithstanding these limitations, the new methods should find many synthetic applications, as they give satisfactory or excellent yields in the most important cases involving addition of allyl, mono- and dimethyl-allyl groups. Rapidity, experimental convenience and the possibility of using inexpensive aqueous commercial solutions of some substrates constitute important advantages for possible industrial applications.

Experimental

Tetrahydrofuran (THF) (reagent grade) was used as received. Zinc and tin powders were purchased from Merck and Fluka, respectively. Other reagents were obtained from Aldrich, and generally used as received. Products were identified by the usual techniques, viz. IR (Perkin–Elmer 397 spectrometer) and NMR (WP 80 Bruker spectrometer) spectroscopy and mass spectrometry (VG Micromass 7070F), comparison being made with literature data. Purifications were by column chromatography (Merck, silicagel). Microanalyses of new compounds were performed by the Service Central d'Analyse du CNRS (Lyon).

Standard procedures

The allylic halides and the metal were always used in equimolecular amounts. (A) A mixture of 2 mmol of the carbonyl compound and the specified amounts (see Tables 1 and 2) of the allylic halide and zinc in 1 ml of THF and 1–4 ml saturated aqueous NH_4Cl was stirred at room temperature. Usually the exothermal reaction proceeded readily and the metal disappeared within 10–20 min for reaction with an allylic bromide and 40–60 min for that with an allylic chloride. The product mixture was extracted with ether and the organic layer is worked-up as usual. The crude material was purified by column chromatography. Yields are based on the isolated product.

(B) The same reagents and amounts as in A were used, but with tin as the metal in a THF/water mixture (1 ml of each). The mixture was sonicated in a laboratory cleaning bath (Sonoclean^R 50 kHz, 15–18°C) until the metal had disappeared and a thick suspension had formed (30–60 min). The mixture was then diluted with THF and filtered through Celite (The solid being washed with THF), and the filtrate worked-up as above.

1-(2-Propenyl)-4-t-butyl-1-cyclochexanol, 1-(2-propenyl)-2-methyl-1-cyclohexanol, and 5-phenyl-1-hexene-4-ol gave satisfactory analyses and data consistent with those in the literature.

2-Methyl-3-butene-1-ol [16]. Liquid. IR (neat): 3350, 3070, 1640, 1440, 1040, 1000, 970, 920 cm^{-1}. NMR ($CDCl_3$): 6.1–5.4(m, 1H), 5.2–4.9(m, 2H), 3.4(d, 2H), 2.3(m, 1H), 1.8(br.s, 1H), 1.0(d, 3H) ppm.

1-Chloro-4-pentene-2-ol [17]. Oil. IR (neat): 3450, 3060, 1640, 1420, 1040, 990, 920, 740 cm^{-1}. NMR ($CDCl_3$): 6.2–5.5(m, 1H), 5.4–4.9(m, 2H), 4.1–3.7(m, 1H), 3.7–3.4(m, 2H), 2.7(br.s, 1H), 2.2(t, 2H) ppm.

1,7-Octadiene-4,5-diol. Oil. IR (neat): 3450, 1635, 1420, 1040, 990, 910 cm^{-1}.

NMR ($CDCl_3$): 6.2–5.5(m, 2H), 5.3–4.9(m, 4H), 3.8–3.2(m, 2H), 2.9(br.s, 2H), 2.4–2.0(m, 4H) ppm.

1,10-Undecadiene-4,8-diol. Oil. IR (neat): 3300, 3060, 1630, 1420, 990, 910 cm^{-1}. NMR ($CDCl_3$): 6.2–5.4(m, 2H), 5.2–4.9(m, 4H), 3.9–3.5(m, 2H), 2.3–2.0(m, 6H), 1.5(br.s, 6H) ppm.

7-Octene-1,5-diol [18]. Oil. IR (neat): 3300, 3070, 1640, 1420, 1050, 1020, 1000, 920 cm^{-1}. NMR ($CDCl_3$): 6.2–5.6(m, 1H), 5.2–5.0(m, 2H), 3.6(m, 3H), 2.4–2.0(m, 2H), 1.7(s, 2H), 1.5(br.s, 6H) ppm.

4-Methyl-4(2-propenyl)-butanolide [3d]. Oil. IR (neat): 3060, 1770, 1640, 1200, 1160, 1000, 940 cm^{-1}. NMR ($CDCl_3$): 6.2–5.5(m, 1H), 5.3–4.9(m, 2H), 2.8–1.8(m, 6H), 1.4(s, 3H) ppm.

4-Methyl-1,7-octadiene-4,5-diol. Oil. IR (neat): 3400, 3050, 1640, 1430, 1370, 1060, 990, 910, 790 cm^{-1}. NMR ($CDCl_3$): 6.2–5.6(m, 2H), 5.3–4.9(m, 4H), 3,5(dd, 1H), 2.6–2.0(m, 4H), 1.15 and 1.20(2 s for the 2 stereoisomers, 3H).

1,1-Dimethoxy-2-methyl-4-pentene-2-ol [19]. Oil. IR (neat): 3450, 3060, 1640, 1440, 1100, 1070, 980, 910 cm^{-1}. NMR ($CDCl_3$): 6.2–5.6(m, 1H), 5.2–4.9(m, 2H), 4.0(s, 1H), 3.6(s, 6H), 2.2(d, 2H), 2.0(br.s, 1H), 1.1(s, 1H) ppm.

1,2-Diphenyl-4-pentene-1,2-diol [20]. Solid, m.p. (hexane) 96–97 °C. IR (nujol): 3450, 3050, 1620, 940, 760, 740, 710, 690 cm^{-1}. NMR ($CDCl_3$): 7.4–6.9(m, 10H), 5.6–4.9(m, 3H), 4.8(br.s, 1H), 3.9–2.5(m, 4H) ppm.

5-Hexene-1,2,3-triol [4c]. Procedure B was used, but with dimethyl formamide in place of THF. After the sonication the mixture was diluted with ethanol and filtered through Celite. Evaporation of the filtrate under vacuum left a thick syrup, which was chromatographed on silica gel (eluent: CH_2Cl_2/EtOH (4/1). Evaporation of the solution gave a glass. IR (neat): 3350, 2900, 1635, 1060, 1020, 910 cm^{-1}. NMR (CD_3COCD_3): 6.2–5.6(m, 1H), 5.2–4.9(m, 2H), 3.7(s, 3H), 4.0–3.5(m, 4H), 2.3(m, 2H) ppm.

1-(2-Hydroxy)phenyl-3-butene-1-ol [12]. Oil. IR (neat): 3350, 3070, 1640, 1590, 1240, 1050, 1000, 920, 760 cm^{-1}. NMR ($CDCl_3$): 8.0(br.s, 1H), 7.3–6.7(m, 4H), 6.1–5.6(m, 1H), 5.3–5.0(m, 2H), 4.8(t, 1H), 3.0(br.s, 1H), 2.6(t, 2H) ppm.

1-(1,1-Dimethyl-3-propenyl)-2-cyclopentene-1-ol. Oil. IR (neat): 3450, 3080, 3050, 2960, 1640, 1360, 1060, 920 cm^{-1}. NMR ($CDCl_3$): 6.2–5.6(m, 3H), 5.2–4.9(m, 2H), 2.5–2.0(m, 3H), 1.7(s, 2H), 1.0(s, 6H) ppm.

Acknowledgements

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8 The formation of organolithium and organomagnesium compounds is thought to involve a single electron transfer from the metal to the carbon–halogen bond [9]. This first step necessarily occurs on the solid surface. It is reasonable to assume that this initial process applies also to other metals.

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