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Communications

Barbier-type Reactions in Proton Media: Carbonyl Allylation in Formamide Solution

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Formamide as a proton source is proposed for carbonyl allylation by Zn–allyl bromide in THF or diethyl ether solutions.

The formation of allyl carbinols when allyl halogenides and metallic zinc react with aldehydes or ketones in aqueous media is an interesting reaction from both a practical and a mechanistic point of view. Aqueous ammonium chloride–THF or aqueous acetic acid were shown to be effective for saturated[1] and unsaturated[2] carbonyl compounds, respectively. However, in attempts to apply this aqueous procedure to some other carbonyl compounds, *e.g.* acetone, we encountered the problem of low yields of allyl carbinols and excessive reduction of allyl halogenide. In fact, the latter process dominated.

This communication describes the results of our efforts to eliminate the reductive pathway in the reaction by experimenting with aqueous systems and a non-aqueous protic solvent – formamide. It may be inferred that in aqueous solvent the acidity is the controlling factor in protolysis. For us, however, attempts to suppress extensive propene evolution by using alcoholic solvents (MeOH, Bu^tOH), triethylamine hydrochloride as a proton source or reducing acidity by addition of sodium hydroxide were of little success: again, the metal was consumed mainly on reduction of allyl bromide. Incomparably more rewarding were results with the solvent systems THF–formamide (homogeneous) and diethyl ether–formamide (heterogeneous).

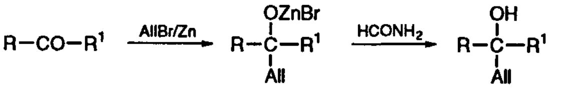
We report here that carbonyl allylation with the reagent Zn dust–allyl bromide may be successfully run in the solvent system formamide–THF (or dithyl ether for low boiling ketones or aldehydes). With formamide the reduction of allyl bromide to propene is suppressed completely and when THF is a co-solvent the resulting Zn complexes and reactions products form a homogeneous mixture which is turned into a two-phase system by adding ammonium hydroxide–ammonium chloride where THF forms the upper layer. When ethyl ether is used as a co-solvent the reaction mixture remains heterogeneous with all Zn complexes in the lower layer and resulting allyl carbinols in the ether solution. No special treatment is required here and the product is obtained by decanting the upper layer followed by distillation.

Of special interest is the function of formamide. Quite obviously, it serves not only as a proton source, reaction (1), but in some way as a Zn surface activator or a general catalyst for the reaction. Instructive is the following experiment: when a mixture of allyl bromide, crotonaldehyde, THF and Zn dust is

Table 1 Carbonyl allylation by Zn/allyl bromide/$HCONH_2$.

Carbonyl compound /mol	Method	Allyl bromide /mol	Zn (g at)	$HCONH_2$ /ml	Solvent /ml	Yield (%)
Crotonaldehyde	A	0.3	0.3	30	Et_2O[50]	62
"	A	0.3	0.3	30	THF[50]	75
"	B	0.3	0.3	30	THF[50]	82
Cyclohexanone	A	0.3	0.3	30	Et_2O[50]	78
"	A	0.3	0.3	30	THF[50]	85
Isobutyraldehyde	B	0.3	0.3	30	Et_2O[50]	79
Acetone	A	0.5	0.3	30	Et_2O[50]	76

stirred at room temperature no reaction occurs. But when some formamide is added an uncontrollable explosion-like reaction occurs. Therefore, in experiments (denoted as method A), Zn dust was added gradually with cooling and stirring to the rest of the reagents and solvents. Another approach (method B) to controlling the reaction is the addition of allyl bromide to a mixture of carbonyl component, formamide and co-solvent. Here the induction period is somewhat longer than in method A and therefore the portion of initially-added bromide should be carefully controlled. In both methods the end of the reaction is marked by complete dissolution of Zn and temperature drop.



$$R{-}CO{-}R^1 \xrightarrow{AllBr/Zn} R{-}\overset{OZnBr}{\underset{All}{C}}{-}R^1 \xrightarrow{HCONH_2} R{-}\overset{OH}{\underset{All}{C}}{-}R^1 \quad (1)$$

Another experiment which sheds some light on the reaction mechanism of carbonyl allylation in formamide is the following. When allyl bromide was added to a formamide–THF–Zn dust mixture with no carbonyl component (or some other reactive electrophile) present, evolution of propene starts immediately and proceeds to completion. It follows that the Zn surface should contain in its double electric layer not only formamide-coordinated Zn cations but also a carbonyl component to intercept radical or ionic species arising from electron transfer to allyl bromide.

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An Unusual Selectivity Change in the Acetylation of 1,8-Dihydroxy-3,7-dimethyl-9-(2′,6′6′-trimethylcyclohexen-1′-yl)nona-2,4,6-triene under Phase-transfer Catalysis

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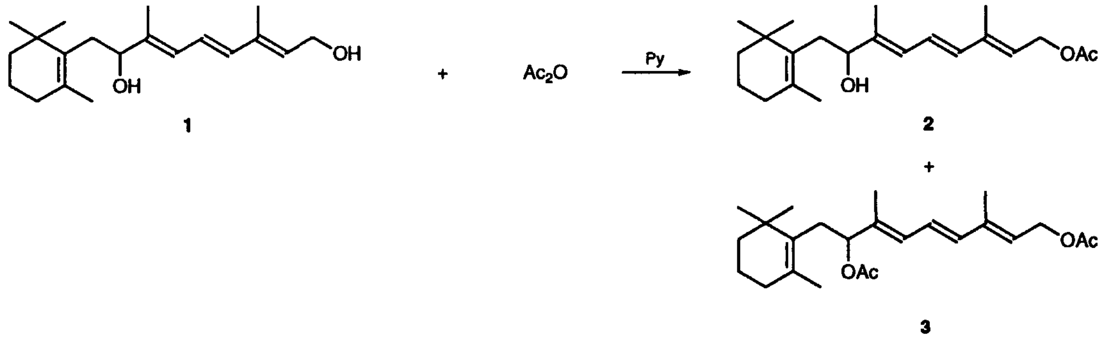
During acetylation of an intermediate in vitamin A synthesis under phase-transfer catalysis in the solid-liquid system, only monosubstitution occurs in contrast to acetylation in the homogeneous system.



One of the stages of vitamin A synthesis by the method of Preobrazhensky and Samokhvalov is the acetylation of 1,8-dihydroxy-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohexen-1′-yl)-nona-2,4,6-triene **1** with acetic anhydride.[1]

Usually the ratio of products of di- and monoacetylation in this reaction is 3:2 = 4:1. However, this method has certain disadvantages, such as the use of a toxic reagent, pyridine, as a catalyst. The method of solid-liquid phase-transfer catalysis (PTC) has been widely used in the last few years.[2] We have studied the possibility of acetylation of compound **1** in such a system. As a solid base Na_2CO_3, K_2CO_3, $NaHCO_3$, NaOH, KOH and $CaCO_3$ were used. A commercially-available quaternary ammonium salt dimethylbenzylalkyl (C_{12}–C_{16}) ammonium chloride was used as a catalyst, and methylene dichloride or hexane as solvents. In a typical run 150 ml of hexane, 11 g of **1**, 5–8 g of solid base and 0.8 g of the catalyst were placed in a reactor and 0.004–0.008 ml of acetic anhydride was added over 30 min at 28–35 °C and the mixture was stirred for 3–4 h. The reaction mixture was analysed by HPLC (eluent, 3% Pr^iOH in hexane; column, Silasorb C 600; wavelength, 230 nm).

Acetylation of **1** under PTC conditions proceeds nearly quantitatively just as with pyridine, but the ratio of products **2** and **3** changes drastically. The dominant product with any solid

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