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The Wacker-type oxidation of allylamine *

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Abstract

Wacker-type oxidation of allylamine in acid solution can be used to produce 1-aminopropan-2-one hydrochloride, **1**, in yields ranging from 26 to 42% depending on reaction conditions. However, the difficulty of its separation from the byproducts limits the scope of this reaction.

Introduction

The cyclization reaction of aminoalkenes to produce nitrogen heterocycles is of major significance for synthetic organic chemistry [1]. As coordinated alkenes are readily attacked by nucleophiles, including amines, transition metal assisted or catalysed cyclization reactions have been much studied [2]. One of the most frequently used metal centers for reactions of this type has been palladium. Although in most cases heterocycle formation is stoicheiometric, many significant catalytic reactions have been developed [3].

Recently another type of metal-catalysed reaction has been used to synthesize nitrogen heterocycles, namely the Wacker oxidation of suitable aminoalkenes, in acid solution, since the resulting aminoketones undergo cyclization reactions with formation of cyclic imines [4]. Thus a 75% yield of 2-methyl-1-pyrroline was obtained by reacting an acidic solution of pent-4-enylamine with the "classical" Wacker reagent mixture, i.e., $Pd^{II}/Cu^{II}/H^{+}/Cl^{-}/O_2$. As expected, heterocycle formation is dependent on the chain-length of the aminoalkene, optimal being five-membered ring-formation although six-membered heterocycles have also been obtained by this reaction. However, when but-3-enylamine was used no cyclization occurred and protonated 1-aminobutan-3-one was formed in 80% yield [4].

1-Aminopropan-2-one is an interesting and potentially useful building block and its hydrochloride, **1**, has been synthesized in a variety of ways the most convenient of them being Hepworths' [5] two-step synthesis which uses glycine as a starting material and produces **1** in a 75% yield.

* Dedicated to the memory of Professor P. Pino.

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The smooth Wacker-type oxidation of but-3-enylamine led us to examine the reaction of allylamine despite an earlier report that treatment of aqueous solutions of allylamine, with palladium chloride in 1 : 1 or 1 : 2 ratios gave only low yields of acetaldehyde, propionaldehyde and methylglyoxal [6]. We report here that, under more typical Wacker-type conditions, 1-aminopropan-2-one, **1**, can be obtained in yields of up to 42%. However, the difficulty of its isolation from the reaction mixture limits the scope of the route.

Experimental section

As the course of the reaction was followed by ^{1}H NMR spectroscopy most of the reactions were carried out using deuterated solvents and reagents. For the isolation experiments, however, normal solvents and reagents were used.

The reaction conditions chosen for the initial studies were those used for the oxidation of pent-4-enylamine, i.e., D_2O (1–2 ml), $PdCl_2$, 0.005 *M*; $CuCl_2 \cdot 2H_2O$, 0.01 *M*; DCl, 0.2 *M* and NaCl, 0.1 *M*, to bring the total Cl^- concentration up to 0.33 *M*, and a temperature of 60 °C. These were then varied to optimize the yield of **1**.

A solution containing all the above reagents was repeatedly degassed and saturated with oxygen to maximize the latter's concentration. The flask was then connected to a balloon filled with oxygen, the solution was warmed to the required temperature and allylamine was *slowly* added to the stirred solution. Addition was stopped when a palladium : amine ratio of 1 : 20 had been reached. Faster addition resulted in the formation of metallic palladium which, however, could be brought back into solution by adding chloride to the suspension. Stirring was continued for various periods of time, usually 20 h. The solution was then cooled to room temperature if necessary and examined by ^{1}H NMR at 250 MHz. The following main resonances were observed: 9.45 (s, br), 8.02 (s, br), 4.95 (s), 3.85 (s, $-CH_2-$, **1** · HCl), 3.03 (s), 2.85 (s), 2.57 (t), 2.02 (s, CH_3- aminoacetone · HCl, CH_3-, methylglyoxal). The yield of **1** formed was determined by comparing the integrals of the resonance at $\delta = 3.85$ ppm with that of the signal from a known amount of TMS placed in a capillary.

The preparative experiments were carried out using 250 ml of H_2O with the reagents in the concentrations stated above. The following attempts were made to isolate 1-aminopropan-2-one from these solutions after oxidation:

(1) The solvent was evaporated to dryness under reduced pressure at 60 °C. The residue was dissolved in a small amount of anhydrous EtOH and anhydrous Et_2O was added. The yellow powder thus formed was filtered off but it immediately turned into a brown oil on exposure to air. Furthermore, difficulties were encountered in removing the copper ions present.

(2) The yellow powder obtained as described above (0.3 g) was dissolved in EtOH (10 ml) and this solution treated with semicarbazide hydrochloride (0.5 g) in H_2O (1 ml). The copper(II) semicarbazide complex formed was precipitated by adding Et_2O (3 ml) and filtered off. After standing at room temperature for 5 days some brownish crystals had formed. These were filtered off and dried, m. p. 212–213 °C. Yield 0.1 g. Their microanalytical and NMR data indicated that they were aminoacetonesemicarbazone hydrochloride. Found: C, 28.26; H, 6.60; N, 31.73. $C_4H_{11}N_4ClO$ calc.: C, 28.84; H, 6.65; N, 33.63%. IR (KBr): 3400,

3320, 3250, 2950, 1660, 1590, 1520, 1160 cm^{-1}. ^1H NMR (250 MHz, D_2O); δ (ppm): 3.67 (s, $-CH_2-$, 2H), 2.73 (s, $-CH_3$, 3H).

For comparison purposes **1** was prepared as described by Hepworth [5]. ^1H NMR (250 MHz, D_2O) δ (ppm): 4.01 (s, $-CH_2-$, 2H), 2.20 (s, $-CH_3$, 3H). The position of these resonances is pH dependent.

Tests for the presence of methylglyoxal in the reaction mixture obtained from the Wacker oxidation using either with phosphomolybdic acid [7] or α-methylindole [8] showed the presence of significant amounts of this byproduct. Blank tests showed that the presence of **1** did not interfere with these reactions.

Basic work-up. Samples of the solution obtained from a standard NMR experiment described above were neutralized with 40% NaOD in D_2O and extracted with $CDCl_3$. In the ^1H NMR spectrum of the organic phase only the signals due to 2,5-dimethylpyrazine could be clearly identified ($\delta = 8.35$ (s, 2H); 2.53 (s, 6H)). Extraction of the alkaline D_2O solution with Et_2O and GLC examination of the extract, using a Carbonax 3% KOH column, showed six peaks, one of them corresponding to 2,5-dimethylpyrazine.

Results and discussion

A representative selection of the experiments carried out is presented in Table 1. As can be seen there, when the reaction was carried out at 60 °C, allylamine has completely reacted within 20 h (Entry No. 1) but prolonging the reaction up to 100 h caused a modest increase in the yield of **1** (cf. Experiments Nos. 1 and 2 as well as 3 and 4).

It was also observed that an increase in the acid concentration from 0.2 to 0.3 *M*, with the other reagent concentration and conditions kept constant, resulted in a significant increase in the yield of **1** (cf. Experiments Nos. 1 and 3 as well as 2 and 4). The conditions used in Experiment No. 4 gave the highest yield of **1** recorded in

Table 1

Yield of 1-aminopropan-2-one hydrochloride, **1**, as a function of oxidant, reaction temperature and time and proton and chloride concentration

Experiment [a]	Oxidant [b]	T (°C)	t (h)	$[H^+]$	$[Cl^-]$	Conversion (%) [c] of allylamine	Yield (%) [c] of **1**
1	$CuCl_2$	60	20	0.2	0.33	100	28
2	$CuCl_2$	60	100	0.2	0.33	100	33
3	$CuCl_2$	60	20	0.3	0.33	100	38
4	$CuCl_2$	60	100	0.3	0.33	100	42
5	$CuCl_2$	60	20	0.3	0.43	100	31
6	$CuCl_2$	60	20	1.0	1.03	100	37
7	$CuCl_2$	60	100	1.0	1.03	100	26
8	$CuCl_2$	25	20	0.2	0.33	93	29
9	$CuCl_2$	25	100	0.2	0.33	100	28
10	$CuCl_2$	25	20	0.3	0.33	64	20
11	$CuCl_2$	25	100	0.3	0.33	100	30
12	$FeCl_3$	60	20	0.2	0.34	93	32
13	$FeCl_3$	60	20	0.3	0.44	95	38

[a] The following concentrations were used: allylamine = 0.1 *M*, $PdCl_2 = 5\times10^{-3}$ *M*. [b] Used in 1×10^{-2} *M* concentration. [c] Calculated on the basis of the allylamine used.

this study. However, an increase in chloride concentration, at constant pH, caused a marked decrease in yield of product (cf. Experiments Nos. 4 and 5). This loss of product could be partially compensated by increasing both the pH and chloride concentration (cf. Experiments Nos. 5 and 6). However, under these conditions, longer reaction time led to loss of product (cf. Experiments Nos. 6 and 7).

The oxidation reaction could also be carried out at 25 °C. When relatively low H^+ and Cl^- concentrations were used no significant slowing down of the reaction was observed, and the yield of **1** remained unchanged (cf. Experiments Nos. 1 and 8) although longer reaction times proved to be less favourable (cf. Experiments Nos. 2 and 9). However, at the higher acid concentration a significant slowing down of the reaction rate was observed (cf. Experiments Nos. 1 and 10). It is noteworthy that, even after 100 h at 25 °, although complete conversion of allylamine had occurred, the yield of **1** remained slightly lower than in the case of the reaction at higher temperature (cf. Experiments Nos. 2 and 11).

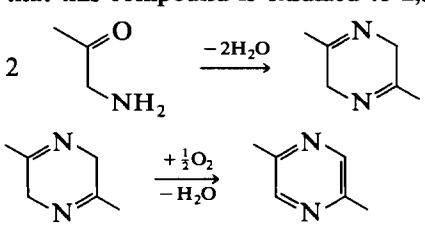
Finally, $FeCl_3$ could be used instead of $CuCl_2$ as catalyst for the re-oxidation of palladium, the yield of **1** being slightly higher (cf. Experiments Nos. 1 and 12 as well as Nos. 5 and 13).

From the above results it appears likely that a more systematic variation of the above parameters, as well as the oxygen pressure, could lead to more acceptable yields of **1**. However, its separation from the significant amounts of by-products could still prove to be quite troublesome.

While there appears to be no reason to suppose that the mechanistic pathway for the Wacker-type oxidation of allylamine hydrochloride would be significantly different from that for non-functionalized alkenes [9], it is clear that the presence of the amine function on the intermediates and products is likely to influence the course of the reaction and thus the yield of product.

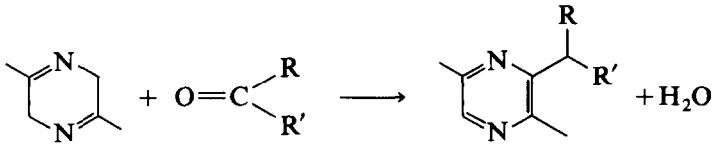
Given the nature of the reaction mixture it would be very time-consuming to analyze quantitatively the by-products formed as a function of the different reaction parameters in order to arrive at plausible mechanistic pathways for their formation. As mentioned in the Introduction, earlier studies showed that acetaldehyde, propionaldehyde, and methylglyoxal are formed. Our investigation confirmed the presence of the latter compound, but showed that the amount of glyoxal formed under the conditions listed in Table 1 are small, and do not exceed 5%.

Finally, it should be mentioned that when the acidic solutions from the oxidation reaction were neutralized before work-up, the formation of a complex mixture of products was observed. Thus preparative GLC of the organic phase after solvent removal showed that no less than six products had formed. Only one of them could be identified, i.e., 2,5-dimethylpyrazine. Further studies [10] using complexes in which the nitrogen atoms of 1-aminopropan-2-one is coordinated to platinum(II) show that the free ketoamine dimerizes to 2,5-dihydro-3,6-dimethylpyrazine and that this compound is oxidized to 2,5-dimethylpyrazine by molecular oxygen.



Furthermore, it is known that 2,5-dihydropyrazines react with organic carbonyl compounds to give substituted pyrazines [11]. Thus, the large number of products observed by GLC is not surprising given the variety of aldehydes and ketones formed during the oxidation reaction.

In conclusion, in contrast to previous reports, allylamine can be oxidized, in acid solution, to 1-aminopropan-2-one hydrochloride, albeit in moderate yield. However, further improvements of this reaction will require extensive analytical and mechanistic studies to identify the byproducts and the pathways by which they are formed. Such studies will be justified only if and when 1-aminopropan-2-one has been shown to be a valuable building block for the synthesis of important products or intermediates.



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