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Articles

The Rupe Rearrangement: A New Efficient Method for Large-Scale Synthesis of Unsaturated Ketones in the Pilot Plant

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Abstract:
During scale-up studies of a new steroidal drug, the Rupe rearrangement of an intermediate was investigated in detail. As the traditional method for this reaction was not adaptable safely to conditions for the pilot plant, a new procedure had to be developed. It was found that the reaction can be catalyzed by strongly acidic cation-exchange resins in a very economical way. The yield of the reaction product was dramatically increased compared to that in the original method. From an environmental point of view, this method is also superior to traditional approaches as catalyst and solvent can be recycled and the waste streams are greatly reduced. The reaction was run successfully on a scale of 64 kg in the pilot plant. Furthermore, the procedure was applied successfully to several other steroids on a laboratory scale.

Introduction

The acid-catalyzed rearrangement of propargylic hydroxy compounds was invented by Rupe in 1924[1] and is today a well-known method[2] for the preparation of α,β-unsaturated ketones. During scale-up studies of a new steroidal drug, we investigated the Rupe rearrangement of the intermediate **1** to the α,β-unsaturated ketone **2**. Unfortunately, a major drawback of this rearrangement is the rather harsh reaction conditions. Typically, the compound is dissolved in boiling formic acid, and yields of labile reaction products tend to be low. For this reason, several attempts are described in the literature to improve this reaction by using other acids. To the best of our knowledge, there are only three procedures in the literature where polymer-bound acids have been used. M. S. Newman described a Rupe rearrangement catalyzed by the cation-exchange resin Dowex-50 with acetic acid as the solvent.[3] Although acetic acid is not a strong acid, the influence of this solvent on the reaction rate is not clear. Furthermore, the isolation of the product from the acetic acid solution is not convenient, and the disposal of the acidic wastewater or the large amounts of salts produced after neutralization give no advantage compared to the original procedure of Rupe from an environmental point of view. Some years later M. E. McEntee et al. were not able to reproduce this method.[4] For this reason there remains at least some doubt about the general applicability of this method.

In a patent from BASF, a Rupe rearrangement for the production of ingredients for perfumes is described.[5] There the use of Dowex-50 in a listing of different acids as catalysts for this special rearrangement is claimed, but no experimental details are given.

Another procedure for this transformation was introduced by G. A. Olah. He used Nafion-H as the catalyst.[6] Nafion-H is a perfluorinated resin with sulfonic acid groups which is described as superacid because of its extraordinary acidic character. However, the very high price of this resin is a major disadvantage for economical use in larger amounts in industrial processes. Although Amberlyst-type cation-exchange resins were used in several reactions as strongly acidic catalysts,[7] to the best of our knowledge they have not been applied to Rupe rearrangements.

Results and Discussion

In studies connected with the scale-up of the synthesis of a new steroidal drug, we faced the problem of transforming the propargylic alcohol **1** to the unsaturated ketone **2** which is a valuable intermediate in steroid chemistry (Scheme 1). The propargylic alcohol **1,** which was the starting material for our rearrangement studies, can be easily prepared from commercially available estrone-3-methyl ether **3** in a few steps. With this material in our hands, we first checked the original discovery method from medicinal chemistry.[8] According to this procedure, the propargylic alcohol was dissolved portionwise in a boiling mixture of formic acid and water. After 20 min the reaction was quenched with ice water, and extraction with dichloromethane gave **2** in 51% yield. In addition to the moderate yield, this method suffers from several severe drawbacks from a technical, safety, and

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(1) Rupe, H.; Glenz, K. *Justus Liebigs Ann. Chem.* **1924**, *436*, 195.
(2) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.
(3) Newman, M. S. *J. Am. Chem. Soc.* **1953**, *75*, 4740.
(4) McEntee, M. E.; Pinder, A. R.; Smith, H.; Thornton, R. E. *J. Am. Chem. Soc.* **1956**, *78*, 4699.
(5) Hoffmann, W.; von Fraunberg, K.; Baumann, M. PI: U.S. Patent 4,301,303 A 811117; AI: U.S. Patent 77 812153 770701.
(6) Olah, G. A.; Fung, P. A. *Synthesis* **1981**, 473.
(7) (a) Chakrabarti, A.; Sharma, M. M. *React. Polym.* **1993**, *20*, 1. (b) Sharma, M. M. *React. Polym.* **1995**, *26*, 3.
(8) Schoellkopf, K.; Halfbrodt, W.; Kuhnke, J.; Schwede, W.; Fritzemeier, K.-H.; Krattenmacher, R.; Muhn, H.-P. WO 96 20 209, April 7, 1996.

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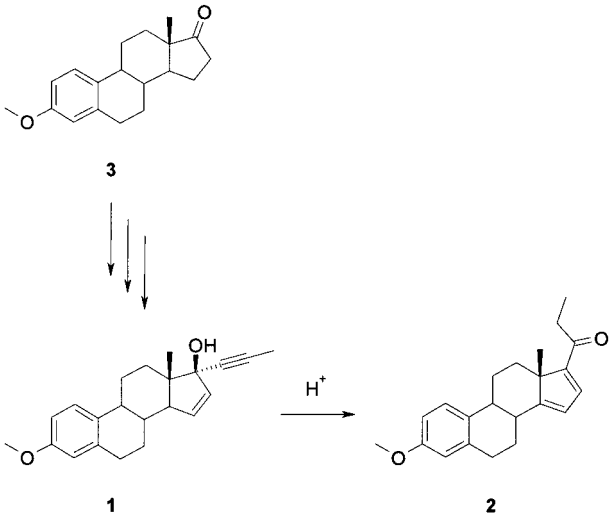
Table 1. **Comparison of the different methods for the Rupe rearrangement of 1 to 2**

method	batch size (kg)	water content (mol equiv)	yield (%)	purity (HPLC)
formic acid	0.400		51	
formic acid diluted with ethyl acetate	0.005		84	87.4
Dowex 50X2 200/ethyl acetate	0.001		46	96.7
Amberlite IR 120 H	0.001		incomplete and slow reaction	
A-252C/toluene	0.5	2 mol equiv	78.6	97.3
A-252C/ethyl acetate	0.5	1.42 mol equiv	84.4	97.4
A-252/ethyl acetate (pilot-plant scale)	64	2 mol equiv	77.8	98.1

Scheme 1. **Rupe rearrangement of a steroidal propargylic alcohol**



environmental point of view because the addition of the solid steroid to the boiling reaction mixture in the vessel can be dangerous on a larger scale and because large amounts of salt-containing or acidic wastewaters are produced during the work-up process. Therefore, it was highly desirable to improve this method.

The first attempts to add the steroid in an ethyl acetate solution to the formic acid were successful, but the product was of relatively poor quality, and the work-up was tedious. Therefore, we abandoned these efforts to work with diluted acids and turned our interest to polymer-bound acids as catalysts for this rearrangement. Dowex 50X2 100−200 mesh beads in ethyl acetate catalyzed the reaction, and the yield of 46% obtained under these heterogeneous reaction conditions was in the range of the originally used homogeneous method with formic acid as catalyst and solvent. This was already a step forward, but as Dowex 50 is relatively expensive, other types of cheaper Amberlyst catalysts were tested. At first, the Amberlite IR 120 H gave only slow and incomplete transformation. The macroporous Amberlyst-type resin A-252 C gave also incomplete reaction initially. A dramatic increase in the reaction rate with A-252 C was detected when the excess water, which comes from the aqueous activation of the polymeric catalyst, was distilled off by azeotropic distillation of the reaction mixture. A water content of 1−2 mol equiv was found to be the optimum[9] because there is enough water for the hydration of the alkyne but not so much that the contact between the hydrophilic catalyst surface (sulfonic acid groups) and the hydrophobic solution is disturbed. Ethyl acetate and toluene were found to be the solvents of choice at the reaction temperature of 80 °C.

Compared to the original reaction method, these conditions were much more efficient, and the product was isolated in yields between 70 and 85% with very good purity (>97%). The isolation of the product is straightforward because the resin only has to be filtered off and the solution has to be concentrated and cooled to 5 °C to effect crystallization of the product. Upon the basis of these promising results on laboratory scale, we transferred the procedure to the pilot plant. We were extremely pleased to find that our new method also worked smoothly at a scale of 64 kg steroid **1** in a 500-L vessel. It was possible to fully reproduce the laboratory yields (77.8%) and product purity (98.3%). As the reaction is very clean, in theory the mother liquors could be reworked to get an additional second crop. Due to extreme time constraints in this project, this was not undertaken in this particular pilot-plant reaction. The different methods for this transformation are summarized in Table 1.

With this new process, the waste stream for this transformation is reduced greatly because the catalyst can be recycled at least five times without significant loss in activity. The solvent also can be recycled, and no wastewater is produced as the aqueous work-up is avoided. This and the cheap Amberlyst cation-exchange resin make this process very favorable not only from an environmental but also from an economic point of view. The recycling of the catalyst is very simple. The resin was filtered off, washed with ethyl acetate, and reusedin a new batch reaction without any further activation.

The generality of this new method for the Rupe rearrangement was tested successfully with two other substrates, and the results are summarized in Table 2.

After we had found that a defined water content of the reaction mixture is essential for the success of the reaction, we rechecked the results with the Amberlite IR 120 H catalyst. Unfortunately the rearrangement was still not catalyzed very efficiently at 80 °C in ethyl acetate or toluene with 2 mol equiv of water; however, the elimination product was formed selectively in good yields. This is an interesting synthetic method because the resulting diene−yne intermediate is very reactive and therefore difficult to prepare and isolate by other reaction methods. Once again, isolation is

(9) Weinmann, H.; Skoetsch, C.; Harre, M. DE 19848305 C 1, May 25, 2000.

Table 2. **Rupe rearrangements of other substrates under standard conditions with Amb 252 C as the catalyst**

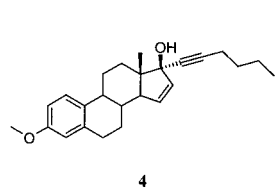
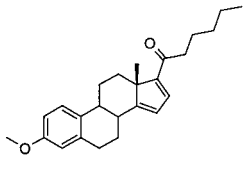
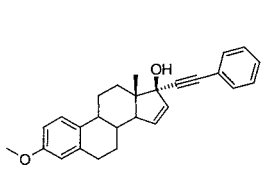
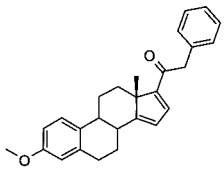
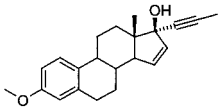
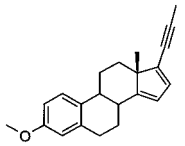
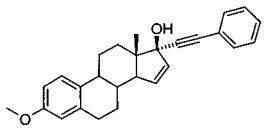
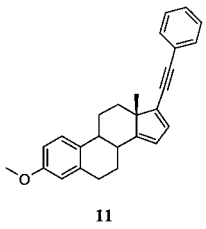
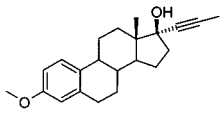
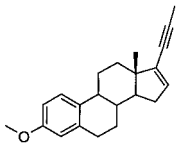
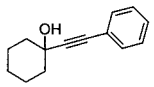
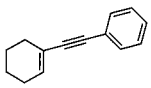
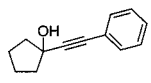
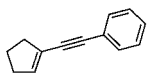
Starting material	Product	Yield
 **4**	 **5**	91 %
 **6**	 **7**	69 %

Table 3. **Elimination reactions catalyzed by IR-120 H**

Starting material	Product	Yield
 **8**	 **9**	41 %
 **10**	 **11**	64 %
 **12**	 **13**	56 %
 **14**	 **15**	90 %
 **16**	 **17**	87 %

very straightforward by just filtering off the resin, and no aqueous work-up is needed. As diene−yne derivatives are useful building blocks for example in natural product syntheses and can be used in a lot of different transformations,[10] we studied several other substrates. The results of these experiments are summarized in Table 3.

(10) Batey, R. A.; Thadani, A. N.; Lough, A. J. *Chem. Commun.* **1999**, 475.

Conclusions

A new economic method for the efficient large-scale preparation of Rupe rearrangement products was developed and successfully run in the pilot plant.

Experimental Section

Commercial reagent grade solvents were used as obtained. Melting points were measured with a Büchi 510 melting point apparatus and are uncorrected. IR spectra were measured on a Bruker FT-IFS 25 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC 300 (300 MHz), and δ values are given in ppm relative to tetramethylsilane as internal standard. Mass spectra were determined with a Fisons Instruments VG 70-70 E spectrometer at 70 eV ionizing voltage using NH_3 for chemical ionization (CI). TLC analyses were performed on Merck F_{254} silica gel plates. For HPLC measurements Hewlett-Packard HPLC systems were used.Further details of the HPLC method: reversed phase column Kromasil 100 C8; mobile phase water/acetonitrile, 2:3; UV-detector 204 nm; flow rate 1 mL/min.

General Procedure for the Rupe Rearrangement Catalyzed by Strongly Acidic Cation-Exchange Resins. Strongly acidic cation-exchange resin (type AMB 252 C) (500 g) was stirred in 1000 mL of EtOH for 30 min at 20 °C, filtered, washed with water, and stirred for another 30 min in 2 N sulfuric acid. After filtration and washing with water the activated cation-exchange resins together with 500 g of propargylic alcohol **1** (1550 mmol) (3-methoxy-17α-prop-1-ynylestra-1,3,5(10),15-tetraene-17β-ol) were suspended in 2000 mL of ethyl acetate and warmed to 80 °C. Ethyl acetate (1000 mL) was distilled off, and the same amount of fresh ethyl acetate was added. This was repeated once. The water content was measured to be 1.42 mol equiv by Karl Fischer titration. After another hour at 80 °C the TLC control showed that the reaction was complete. The resin was filtered off and washed with 1000 mL of warm ethyl acetate. The solution was cooled to 5 °C and stirred at this temperature for 1 h. The precipitated crystals were filtered off, washed three times with 80 mL of ethyl acetate, and dried at 50 °C. Yield: 432.08 g (1308.99 mmol, 84.4%) colourless crystals of ketone **2**.

Recycling of the strongly acidic cation resin is achieved by simply washing the resin with ethyl acetate and using it again in a new batch reaction. The yield on a 5-g scale was 78% of colourless crystals of ketone **2**.

3-Methoxy-21-methyl-19-nor-pregna-1,3,5(10),14,16-pentaen-20-one (2): fp: 153 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.0−1.1 (m, 1 H), 1.15 (tr, J = 7.5 Hz, 3 H), 1.25 (s, 3 H), 1.55−1.70 (m, 1 H), 1.75−1.95 (m, 1 H), 2.2−2.4 (m, 4 H), 2.55−2.65 (m, 1 H), 2.75 (q, J = 7.5 Hz, 2 H), 2.9−3.1 (m, 2 H), 3.8 (s, 3 H), 6.10 (m, 1 H), 6.6−6.8 (m, 2 H), 7.15−7.35 (m, 2 H).

The Following Compounds Were Prepared by the Same Procedure. 21-Butyl-3-methoxy-19-nor-pregna-1,3,5(10),14,16-pentaen-20-one (5): ^{1}H NMR ($CDCl_3$, 300 MHz) 0.9 (tr, J = 7.5 Hz, 3 H), 1.0−1.1 (m, 1 H), 1.25 (s, 3 H), 1.3−1.4 (m, 4 H), 1.55−1.70 (m, 3 H), 1.8−1.95 (m, 1 H), 2.15−2.4 (m, 4 H), 2.55−2.65 (m, 1 H), 2.70 (q, J = 7.5 Hz, 2 H). 2.9−3.1 (m, 2 H), 3.8 (s, 3 H), 6.10 (m, 1 H),

6.6−6.8 (m, 2 H), 7.15−7.35 (m, 2 H). IR (cm^{-1}) 2950 (s), 1650 (s), 1530 (m), 1495 (s), 1250 (s). MS (EI) 364 (85, M^+), 293 (45), 186 (100), 119 (64).

3-Methoxy-21-phenyl-19-nor-pregna-1,3,5(10),14,16-pentaen-20-one (7): ^{1}H NMR ($CDCl_3$, 300 MHz) 1.0−1.15 (m, 1 H), 1.25 (s, 3 H), 1.55−1.70 (m, 1 H), 1.8−1.95 (m, 1 H), 2.15−2.4 (m, 4 H), 2.55−2.65 (m, 1 H), 2.9−3.1 (m, 2 H), 3.8 (s. 3 H), 4.0 (s, 2 H), 6.10 (m, 1 H), 6.6−6.8 (m, 2 H), 7.15−7.4 (m, 7 H). IR (cm^{-1}) 2950 (m), 1650 (s), 1520 (s), 1500 (s), 1250 (s).

Procedure for the Rupe Rearrangement of Steroid 2 in the Pilot Plant. In a 500-L enamelled reaction vessel, 64 kg of cation-exchange resin A-252 C and 128 L of ethanol were charged. The mixture was stirred for 1 h. The resin was filtered off using a 200-L pressure filter and washed with 220 L of deionized water. The resin was taken back into the vessel, and 117 L of deionized water and 6.4 L of concentrated sulfuric acid were added, and the mixture was stirred for 1 h. The resin was filtered off using the pressure filter and washed neutral with deionized water. The activated resin was returned to the vessel. Steroidal derivative **1** (64 kg) and 256 L of ethyl acetate were added. Ethyl acetate/water (130 l) was distilled off and replaced by 130 L of ethyl acetate. This step was repeated once, and then the water content was measured and adjusted to 2 mol equiv by addition of deionized water. The reaction mixture was refluxed for 4 h after which time TLC control showed complete conversion of the starting material. The resin was filtered off using a preheated 200-L pressure filter and was washed four times with 50 L of ethyl acetate; 250 L of the filtrate was distilled off, and then the mixture was cooled to 0 °C and stirred for 1 h. The crystals were isolated with a centrifuge, washed with 50 L of cold ethyl acetate, and dried in a drying cabinet at 50 °C. A total yield of 49.8 kg (77.8%) of colourless crystals was obtained with high purity (98.3%).

General Procedure for the Elimination of Propargylic Alcohols to Diene−Yne Compounds Catalyzed by Strongly Acidic Cation-Exchange Resins. Strongly acidic cation-exchange resin (type IR-120 H) (2 g) was stirred in 10 mL of EtOH for 30 min at 20 °C, filtered, washed with water, and stirred for another 30 min in 2 N sulfuric acid. After filtration and washing with water, the activated cation-exchange resin together with 2 g of propargylic alcohol **14** (*rac*-1-(2-phenylethynyl)-cyclohexane-1-ol) (9.99 mmol) was suspended in 10 mL of ethyl acetate and warmed to 80 °C. Ethyl acetate (10 mL) was distilled off, and the same amount of fresh ethyl acetate was added. This was repeated once. After 9 h at 80 °C, the TLC control showed that the reaction was complete. The resin was filtered off and washed with 10 mL of warm ethyl acetate. Complete evaporation of the solvent gave the product as a colourless oil. Yield: 1.62 g (8.91 mmol, 90%) of diene-yne **15** (Cyclohex-1-enylethynylbenzene). ^{1}H NMR ($CDCl_3$, 300 MHz) 1.55−1.8 (m, 4 H), 2.1−2.2 (m, 2 H), 2.2−2.3 (m, 2 H), 6.15−6.25 (m, 1 H), 7.2−7.3 (m, 3 H), 7.35−7.45 (m, 2 H). IR (cm^{-1}) 2950 (s), 1595 (m), 1495 (s), 760 (s), 695 (s). MS (CI/NH_3) 200 (70, $M^+ + NH_4$+), 183 (100, $M^+ + 1$), 162 (9), 145 (12).

The Following Compounds Were Prepared by the Same Procedure. 3-Methoxy-17-prop-1-ynylestra-1,3,5-(10),14,16-pentaene (9): fp: 93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 0.85−0.95 (m, 1 H), 1.10 (s, 3 H), 1.55−1.70 (m, 2 H), 1.8−1.95 (m, 1 H), 2.05 (s, 3 H), 2.15−2.4 (m, 4 H), 2.9−3.1 (m, 2 H), 3.8 (s, 3 H), 6.0 (m, 1 H), 6.6−6.8 (m, 2 H), 7.4−7.5 (m, 2 H). IR (cm^{-1}) 2950 (s), 1610 (m), 1500 (s), 1250 (s). MS (EI) 304 (100, M^+), 289 (21), 186 (95), 174 (52).

3-Methoxy-17-(2-phenylethynyl)estra-1,3,5(10),14,16-pentaene (11): ^{1}H NMR ($CDCl_3$, 300 MHz) 0.85−0.95 (m, 1 H), 1.20 (s, 3 H), 1.55−1.70 (m, 2 H), 1.8−1.95 (m, 1 H), 2.15−2.4 (m, 4 H), 2.9−3.1 (m, 2 H), 3.8 (s, 3 H), 6.0 (m, 1 H), 6.6−6.8 (m, 2 H), 7.2−7.35 (m, 5 H), 7.4−7.5 (m, 2 H). IR (cm^{-1}) 2950 (s), 2200 (m), 1600 (s), 1500 (s), 1250 (s). MS (CI/NH_3) 368 (45, $M^+ + 1$), 367 (100, M^+).

3-Methoxy-17-prop-1-ynylestra-1,3,5(10),16-tetraene (13): ^{1}H NMR ($CDCl_3$, 300 MHz) 0.87 (s, 3 H), 1.5−2.1 (m, 5 H), 2.0 (s, 3 H), 2.15−2.4 (m, 4 H), 2.8−3.0 (m, 2 H), 3.8 (s, 3 H), 5.9 (br s, 1 H), 6.6−6.8 (m, 2 H), 7.2−7.35 (m, 1 H). MS (CI/NH_3) 324 (19, $M^+ + NH_3$), 308 (25, $M^+ + 1$), 307 (100, M^+).

Cyclohex-1-enylethynylbenzene (15): ^{1}H NMR ($CDCl_3$, 300 MHz) 1.5−1.7 (m, 4 H), 2.4−2.6 (m, 4 H), 6.15−6.2 (m, 1 H), 7.2−7.3 (m, 3 H), 7.4−7.5 (m, 2 H). IR (cm^{-1}) 2950 (s), 2250 (w), 1600 (m), 1495 (s), 1450 (s), 760 (s), 695 (s). MS (EI) 183 (100, $M^+ + 1$), 162 (10), 145 (15).

Cyclopent-1-enylethynylbenzene (17): ^{1}H NMR ($CDCl_3$, 300 MHz) 1.9−2.0 (m, 2 H), 2.4−2.6 (m, 4 H), 6.15−6.2 (m, 1 H), 7.2−7.3 (m, 3 H), 7.4−7,5 (m, 2 H). IR (cm^{-1}) 2950 (s), 2250 (w), 1600 (m), 1495 (s), 1450 (s), 760 (s), 695 (s). MS (EI) 168 (95, M^+), 167 (100), 152 (55), 95 (52).

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