

Liquid and solid acids as catalysts for the Thiele–Winter reaction of menadione†

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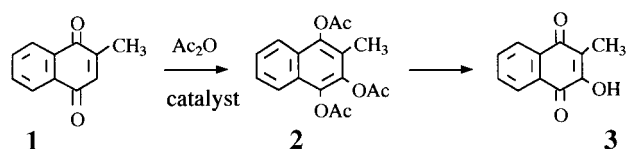
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Liquid acid such as perchloric acid, chlorosulfonic or triflic acid can effectively replace sulfuric acid as a catalyst in Thiele–Winter reaction of menadione. Solid acids like zeolites and heteropolyacids are described for the first time as catalysts in Thiele–Winter reaction. The two step sequence (Thiele–Winter), saponification–oxidation) constitutes a new synthesis of the antibiotic phthiocol from menadione.

The Thiele–Winter reaction is the acetoxylation of quinone in acetic anhydride catalysed by acid.^{1–3} As presently described the reaction uses sulfuric acid under homogeneous conditions as the catalyst. We describe here the use of different acids and particularly acids that are more acidic than sulfuric acid (super acid) under homogeneous conditions and also for the first time the use of solid acids under heterogeneous conditions.

We have been interested in the synthesis of phthiocol (2-hydroxy-3-methyl-1,4-naphthoquinone) (**3**), an antibiotic substance produced by *Mycobacterium tuberculosis* and some plants⁴. Our synthesis of phthiocol involves the transformation of methyl naphthoquinone (menadione) (**1**) into 1,2,4-triacetoxy-3-methyl naphthalene (**2**) by a Thiele–Winter reaction, and then the saponification of (**2**) followed by its catalytic oxidation into phthiocol (**3**) (Scheme 1).



Scheme 1 Synthesis of phthiocol (**3**) from menadione (**1**)

Other acids such as zinc chloride, tetrafluoroboric acid, have been proposed in place of sulfuric acid³ and sometimes the yields are better especially with boron trifluoride⁵. Unfortunately quinones with an electron-donating group like 2-methyl naphthoquinone (**1**) (menadione) do not produce a triacetate in the presence of boron trifluoride or sulfuric acid as a catalyst⁶ (Scheme 2).

In the case of menadione (**1**), we thought that sulfuric acid was not acidic enough to catalyse the Thiele–Winter reaction. We have studied this reaction with strong acids, especially close to superacids (acids that inhibits acid strength greater than that of 100% of H₂SO₄)⁷. We have used different acids in solution in acetic anhydride. Perchloric acid ($H_0 = -10.31$) led to the desired product (**2**) in fair yield (43%, 25°C, 20h). As expected, trifluoromethanesulfonic acid (triflic acid $H_0 = -13.1$) has given a very interesting result⁹ whereas, the reaction with trifluoroacetic acid has been very slow. Surprisingly, in spite of its great acidity, chlorosulfonic acid ($H_0 = -13.8$) only gave a yield of 31% of (**2**).

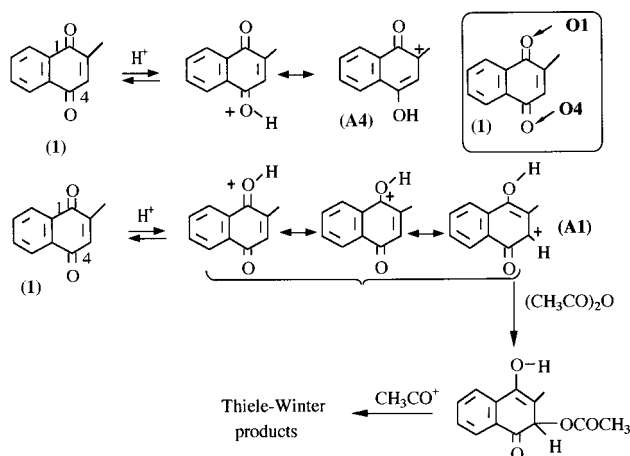
We have studied the bleaching of a menadione: acetic anhy-

dride solution. This bleaching can be related to Thiele–Winter reaction although other reactions can occur (e.g. sulfuric acid, oxidation). Menadione (**1**) shows a maximum absorption at 333 nm whereas the produce of Thiele–Winter reaction (**2**) does not absorb at this wavelength. The relative kinetic first order constants for the bleaching of menadione obtained at 330 nm are reported in Table 1. Triflic acid seems the most effective liquid acid catalyst tested.

Table 1 Relative kinetic first order constants of bleaching of Thiele–Winter reaction of menadione (**1**) at 25°C

Catalyst	H_0	Yield of 2 (%)	k
Sulphuric acid	-11.93	00	1.00
Chlorosulfonic acid	-13.80	31	1.74
Perchloric acid	-10.31	43	3.70
Trifluoroacetic acid	0.23	00	0.26
Triflic acid	-14.1	53	16.86

The kinetic of menadione transformation (bleaching) depends on acidity of catalyst. It seems that the limiting step of the Thiele–Winter reaction is the protonation of the quinone⁶. In the case of menadione the oxygen bear by the carbon 4 (O4) is more basic than the oxygen bear by the carbon 1 (O1). (O4) has a higher charge density and a higher coefficient of HOMO than (O1).⁸ The protonation of quinone leads, in the case of menadione, to the formation of two cations. The cation (A4) is more stable than the cation (A1). The enthalpies of forma-



Scheme 2 Probable first steps of Thiele–Winter reaction

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tion calculated by AM1 are respectively 176.337 kcal/mol for A1 and 143.444 kcal/mol for A4. (O4) is more easily protonated than (O1) and the formation of A4 is easier than A1, but A4 is an unproductive cation. We consider that poor results of Thiele–Winter reaction were due to the lack of protonation of menadione on oxygen (O1) when the catalyst used was not acidic enough.

However, we could not really use the Hammett acidity functions for correlation in solution, because they were defined in aqueous solutions, whereas the Thiele–Winter reactions are carried out in acetic anhydride.

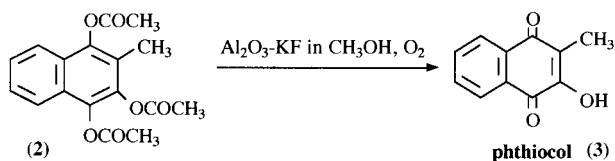
To the best of our knowledge, the Thiele–Winter reaction with solid acids has not been reported in the literature. Solid acids show a lot of advantages: they are not too expensive, not toxic, environmentally acceptable and easier to handle than mineral acids like sulfuric acid^{10,11}. The yield of isolated product formed with solid acids under heterogeneous conditions of Thiele–Winter reaction are reported in Table 2.

We have used superacid Nafion-H (NR50) which is a perfluorinated ion-exchange polymer known to catalyse various reactions in organic synthesis.¹² With Nafion-H (NR50), uncoloured Nafion-H balls were surrounded with a fine brown layer of tars, that seemed to make the catalyst inefficient. The reaction was carried out under different conditions (room temperature, reflux, ultrasounds), however, the Nafion-H always became brown and ineffective.

Zeolites with high Si–Al ration (15–20) are known to possess strongly acidic sites.¹⁰ Two acid zeolites (H-ZSM5 and H-DAY) were also tested successfully. Zeolites can be reused without loss of activity when the reaction is carried out at room temperature. Unlike Nafion, no poisoning by tar formation was observed with ZSM-5 or DAY. With solid catalysts like zeolite, the menadione is too wide to enter the pores of ZSM-5, and, the reaction took place on the surface of zeolite.

Heteropolyacids (HPAs also called polyoxometalates) are catalysts of very great interest^{10–15}. They display a very high Bronsted acidity, close to superacids. We have decided to test 3 Keggin-type HPAs: $H_3PW_{12}O_{40}$ (noted PW), $H_4SiW_{12}O_{40}$ (SiW) and $H_3PMo_{12}O_{40}$ (PMo). The SiW provided the product (B) with a yield of 51% (isolated product) whereas a yield of 40% was achieved with the PW. We have noticed that no product (2) was obtained with the PMo, and the reaction medium colour changed, from green to deep blue, proving the reduction of PMo. 85% starting product was recovered. It has been noticed that the SiW appeared a better catalyst than the PW. This is rather surprising.¹⁴ However, in a few cases the SiW shows better results than the PW in acid catalysis in organic reactions^{15,16}. This fact can be linked to the great softness of the conjugate base $SiW_{12}O_{40}^{4-}$ (great charge and large size of anion), which could stabilise the cationic intermediates¹⁶. Another explanation could be assigned to the higher ratio of number of protons in SiW.¹⁵ Furthermore, the result with $H_3PMo_{12}O_{40}$ (PMo) is not surprising owing to its high redox potential resulting from the presence of molybdenum atom. It is reduced by the organic substrate even at room temperature. In our case, a change of colour from yellow to deep blue is observed.

The reactions with solid acids were generally slower than with homogeneous media and best results were achieved at room temperature for 5 days. This result can be explained by the



Scheme 3 Oxidation of Thiele–Winter product (2) into phthiocol (3)

Bronsted site concentration and the necessity of diffusion phenomena. Some different attempts have been made to improve rates and yields by increasing the temperature without success due to the formation of by-products. But when the medium was refluxed at 140 °C, the formation of coke and dark tar occurred very quickly due probably to tar decomposition reaction.

The triacetate (2) was easily transformed into phthiocol (3)

Table 2 Yield of (2) formed by the Thiele–Winter reaction of menadione (1) with solid acids at 25 °C

Catalyst	H_0	Yield of 2 (%)
Nafion-H NR 50	–12	0
$H_3PW_{12}O_{40}$	–13.6	40
$H_4SiW_{12}O_{40}$		51
$H_3PMo_{12}O_{40}$		0
ZSM5 (H ⁺)		47
DAY (H ⁺)		49

by basic saponification and oxidation with potassium fluoride on alumina¹⁷ in methanol in presence of air at room temperature. The yield of phthiocol from (2) is good (95%).

In conclusion, it appears that triflic acid is the most effective acid catalyst found for the Thiele–Winter reaction of menadione under homogeneous conditions. Zeolites and heteropolyacids can easily catalyse the Thiele–Winter reaction. This work represents the first example of catalysis of this reaction by solid acids. The sequence of the two steps (Thiele–Winter, saponification–oxidation) constitutes a new synthesis of the antibiotic phthiocol (3) from menadione (1).

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, or in $(CD_3)_2SO$ solution on a Bruker AC 250 (250 MHz 1H , 62.6 MHz ^{13}C) spectrometer with Me_3Si as an internal standard. The IR spectra were recorded as KBr pellets on Perkin Elmer 16 PC FT-IR spectrometer UV-visible spectra (λ_{max} log ϵ) were obtained with spectrophotometer Perkin Elmer Lambda 15.

Heteropolyacids were commercially available from Fluka. Nafion (NR-50) was obtained from Aldrich. Zeolites (ZSM-5, DAY) as ammonium form were calcinated at 500 °C under dry air flow before use.

Thiele–Winter reactions under homogeneous conditions (liquid acids): In a typical experiment, 10 mmol of menadione (1.72 g) were dissolved in acetic anhydride (20 ml) and 5 mmol of catalyst was added. The mixture was stirred at room temperature. The solution was poured on ice and after the ice melted the mixture was filtered and the solid 1,2,4-triacetoxy-3-methylnaphthalene, produce (2) was crystallised in ethanol.

Kinetics of menadione bleaching: For the kinetic studies, 10 mmol of menadione (1.72 g) were dissolved in acetic anhydride (20 ml) and 5 mmol of catalyst was added. The mixture was stirred at 20 °C. At intervals, an aliquot of 8 μ l of reaction medium was withdrawn and diluted with acetic anhydride in a 100 ml volumetric flask. A sample of this solution was directly analysed with a UV–visible Perkin-Elmer spectrophotometer lambda 15 and the absorbance was measured at 333 nm. The different acid catalysts used are reported on the Table 1.

Thiele–Winter reactions under heterogeneous conditions (solid acids): In a typical experiment, 2 mmol of menadione (0.34g) were dissolved in acetic anhydride (4 ml). 0.3 g of catalyst was added and the mixture was stirred at room temperature. After 5 days, the products were separated by chromatography on a silica column eluted successfully with ethyl acetate/cyclohexane (10/90) and ethyl acetate/cyclohexane (50/50). The different fractions gave respectively a yellow solid (unreacted quinone) and a white solid [1,2,4-triacetoxy-3-methylnaphthalene (2)]. It must be noted that traces of product of diacetylation could be detected by thin layer chromatography (TLC).

We have used acid solids (procedure see below): Nafion, zeolites and heteropolyacids have been tested¹⁰, the results are reported in Table 2.

1,2,4-Triacetoxy-3-methylnaphthalene (2): White solid, mp 157–158 °C (ethanol); CAS Registry Number 604-86-4; RN 604-86-4. POMR ($CDCl_3$) δ : 2.16 (s, 3H, CH_3); 2.37 (s, 3H, $OCOCH_3$); 2.45

(s, 3 H, OCOCH₃); 2.49 (s, 3 H, OCOCH₃); 7.48–7.76 (m, 4 H, H arom). IR (KBr) cm⁻¹: 3000 (νCH arom), 1774 (νOCOCH₃), 1760. MS. m/z (%): 316 (M⁺, 39.13), 274 (12.50), 233 (17.38), 174 (6.63), 115 (2.88).

Synthesis of phthiocol (3) or 2-hydroxy-3-methyl-1,4-naphthoquinone: The product (2) (1,2,4-triacetoxy-3-methylnaphthalene) (632 mg, 2 mmol), dissolved in methanol (20 ml) was oxidised under airstream in the presence of potassium fluoride on aluminol¹⁷ (2 g). After filtration and evaporation of the methanol, the phthiocol was crystallised (357 mg, 95%).

Phthiocol or 2-hydroxy-3-methyl-1,4-naphthoquinone: Yellow needles (cyclohexane), m.p. 173–174 °C (ether + hexane). CAS REgistry Number 483-55-6; RN 483-55-6. IR (KBr) cm⁻¹: 3330 (νOH), 1655 (νC=O). PMR (CDCl₃) δ: 2.08 (s, 3 H, CH₃); 7.29 (s, 1H, OH), 7.5–8.1 (m 4 H, H arom).

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