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Technical Notes

Process Development and Pilot Plant Scale Synthesis of Spiro[3.5]nonane-6,8-dione

Thomas E. Lehmann, Oliver Kuhn, and Jochen Krüger*

Chemical Development Pharma, Bayer Health Care, Building 64, 42096 Wuppertal, Germany

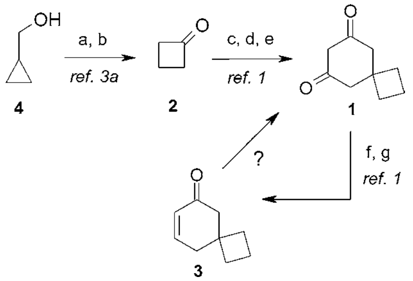
Abstract:

A two step synthesis of spiro[3.5]nonane-6,8-dione is reported which allows the production of the target molecule on a pilot plant scale. The first step of the process comprises the epoxidation of spiro[3.5]non-7-en-6-one mediated by sodium perborate. Here, the use of sodium perborate proved beneficial over the standard protocols employing hydrogen peroxide since a much safer process was accomplished. The resulting crude epoxide was subsequently submitted to a palladium-catalyzed rearrangement to afford spiro[3.5]nonane-6,8-dione in 26% overall yield.

Introduction

The compound spiro[3.5]nonane-6, 8-dione (**1**) was required as a key intermediate in the synthesis of a pharmaceutical development product. The synthesis of **1** has been detailed before, and kilogram quantities are accessible via the published route in a three step protocol.[1] The approach to **1** commences from rather costly cyclobutanone (**2**) (Scheme 1)[2] which can be synthesized from inexpensive cyclopropylmethanol (**4**) by acid-catalyzed rearrangement to cyclobutanol followed by oxidation to the ketone **2**[3]. Thus, the synthesis of diketone **1** amounts to a five step procedure with an overall yield of 16%.

Scheme 1. **Synthetic routes to spiro[3.5]nonane-6,8-dione (1)**[a]



[a] Reagents and conditions: (a) aq. HCl, 42%; (b) NaOCl, H_2O, AcOH, 65%; (c) $Ph_3P{=}CHCOCH_3$, 87%; (d) $CH_2(CO_2Me)_2$, NaOMe, MeOH; (e) aq. KOH and then aq. HCl, 99%; (f) *p*-TsOH, isobutanol, toluene; (g) RedAl, toluene, 77%.

Our initial task was to produce about 40 kg of the key intermediate **1** on a quick time frame, which would subsequently enable us to supply the first multikilogram quantities of drug substance. As a potentially faster and economical alternative to the five step process starting from cyclopropylmethanol (**4**), we envisioned a short synthetic access starting from cyclohexenone **3** (Scheme 1). The latter has been synthesized in a related project from diketone **1** in a two step procedure (cf. Scheme 1),[1] and hexenone **3** was available from internal stock in quantities of about 200 kg. Under these circumstances, the recycling of **3** into **1** appeared to be the most economical and fastest access to diketone **1**.

In this communication, we summarize our endeavors to transform hexenone **3** into diketone **1** on a pilot plant scale.

Results and Discussion

The conversion of **3** to **1** corresponds to a simple oxidation process. Accordingly, we scrutinized a typical Wacker-type oxidation protocol employing $Na_2PdCl_4-t\text{BuOOH}$ in aqueous acetic acid as reported in the literature.[4] Furthermore, we conducted a methodical screening using catalytic amounts of different palladium salts (Na_2PdCl_4, $PdCl_2$, $Pd(OAc)_2$) in combination with stoichiometric amounts of oxidation reagents (MnO_2, *t*BuOOH, H_2O_2, $CuCl_2$) and different solvent systems (NMP, acetic acid, 2-propanol, and 1:1 mixtures of these solvents with water) at a range of temperatures (50−100 °C). To our dismay, all of these conditions failed in our hands to afford satisfying conversion of the α,β-unsaturated hexenone **3** to the target molecule **1**. In all cases, only traces of the product were detected.

Thus, we abandoned the Wacker-type approach and focused on a two step protocol including the epoxidation of hexenone **3** to the epoxyhexanone **5** followed by a palladium-catalyzed rearrangement to the diketone **1** (Scheme 2).

In laboratory scale, the epoxidation was first carried out using H_2O_2 in aq. NaOH.[5] The reaction was run at a

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* Corresponding author. E-mail: Joachim.Krueger.jk2@bayer-ag.de. Telephone: +49-202-362554. Fax: +49-202-362566.

(1) Paulsen, H.; Antons, S.; Brandes, A.; Lögers, M.; Müller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuss, J. *Angew. Chem.* **1999**, *111*, 3574−3576; *Angew. Chem. Int. Ed.* **1999**, *38*, 3373−3375.

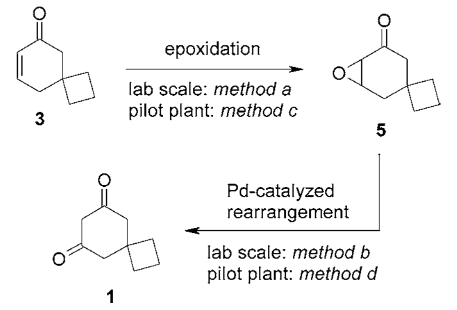
(2) A typical offer from a commercial vendor is 20 000 Euros for 10 kg cyclobutanone.

(3) for the synthesis of **2** see: (a) Knops, H.-J.; Gallenkamp, B.; Mulder, L.; Antons, S. PCT Int. Appl. WO 0053553, 2000. (b) Krumpolc, M.; Rocek, J. *J. Org. Synth.* **1981**, *60*, 20−25. (c) Caserio, M. C.; Graham, W. H.; Roberts, J. D. *Tetrahedron* **1960**, *11*, 171.

(4) for Wacker oxidation of α, β-unsaturated ketones see: (a) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257−260. (b) Fellmann, J. D.; Saxton, R. J.; Tung, P. U.S. Patent 486,921, 1989.

10.1021/op0340560 CCC: $25.00

Scheme 2. **Synthesis of diketone 1**[a]



[a] Reagents and conditions: (a) H_2O_2, aq. NaOH and then $Na_2S_2O_3$, toluene, 88%; (b) $Pd(OAc)_2$, rac-BINAP, 3 M in toluene, 90 °C; (c) $NaBO_3 \cdot 4H_2O$, H_2O and then Na_2SO_3, toluene; (d) $Pd(OAc)_2$, PPh_3, rac-BINAP, Et_3N, 90 °C, 0.8 M in toluene.

Table 1. **Selected results of the primary screening for the conversion of 5 to 1**[a,c]

	BINAP	DPPE	$P(OPh)_3$[b]	PPh_3[b]	DBDP
$Pd(OAc)_2$	++	−	−	+	−
$Pd(dba)_2$	++	−	−	−	n.d.
$Pd(PPh_3)_4$	++	+	n.d.	n.d.	n.d.

[a] All experiments were conducted in refluxing toluene for 24 h using 3 mol % of the Pd source and 3.3 mol % of the ligand. [b] 12 mol % of the ligand were used. [c] Range of conversion: − = 0%−5%, + = 5%−50%, ++ = 60%−100%, n.d. = not determined. HPLC analysis focused on area % of epoxyhexanone **5** and spiro[3.5]nonane-6,8-dione (**1**); byproducts were not quantified.

concentration of 5 M, and it proceeded smoothly at 0 °C to give epoxide **5** after reductive workup ($Na_2S_2O_3$) and extraction with toluene in 88% yield with a purity of 98% (GC). Subsequently, the resulting epoxide solution was used without further purification.

The Pd-catalyzed rearrangement of epoxides to β-diketones was first introduced by Noyori et al.[6] In a typical reaction, catalytic amounts of $Pd(PPh_3)_4$ and 1,2-bis(diphenylphosphino)ethane (DPPE) were used in toluene−water (50:50 v/v) at 80 °C under argon atmosphere. However, in our hands these conditions failed to deliver the desired product **1**.

This negative result prompted us to conduct a broader reaction screening using an automated parallel synthesizer.[7] The experimental setup allowed us to rapidly screen a variety of phosphine ligands, palladium sources, solvents, and reaction parameters (cf. Table 1). From this screening, we learned that the nature of the palladium source ($Pd(PPh_3)_4$, $Pd(dba)_2$, or $Pd(OAc)_2$) was not crucial for the success of the transformation. We assume that palladium acetate as a source for palladium(II) is being reduced in situ by the phosphine ligand to give the catalytic active palladium(0) complex.

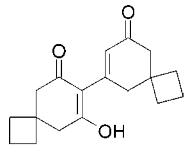


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Figure 1. **Self-condensation product of diketone1.**

In contrast, it turned out that the reaction proved very sensitive to the nature of the phosphine ligand. Accordingly, we found that the reaction worked well in the presence of rac-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) while other ligands such as DPPE, triphenyl phosphite, triphenylphosphine, or 2-(di-*tert*-butylphosphino)biphenyl (DBDP) failed to promote the desired rearrangement (cf. Table 1).

An extended screening program revealed that best conversions were achieved in toluene, in toluene/water (1:1), or NMP as solvent. Finally, optimized reaction conditions in laboratory scale included the use of 3 mol % $Pd(OAc)_2$ and 3 mol % of rac-BINAP in toluene at 75 °C for 9 h (Scheme 2, method b). As the major byproduct in this reaction, we identified the deeply red-colored dimer **6** (Figure 1) arising from self-condensation of diketone **1**.

Product isolation was conveniently accomplished exploiting the acidic nature of the β-diketone **1**. Thus, the crude diketone was extracted into a dilute aqueous NaOH solution at pH 8.6, and the toluene phase containing catalyst residues was disposed. Subsequently, byproduct **6** was separated by extraction of the aqueous layer at pH 7 with ethyl acetate, while product **1** remained in the aqueous phase. The spiroanellated diketone **1** was finally precipitated from the aqueous layer upon further acidification with aqueous HCl to pH 2, and diketone **1** was obtained in yields ranging from 35% to 53%. The product **1** was slightly contaminated by the dimer **6**; however, further synthetic studies revealed that **6** did not interfere in the following transformations and it could conveniently be separated in the next step of the synthesis by a single crystallization step.[8]

Since the two step protocol as outlined in Scheme 2 worked reliably on a 50 g scale, we considered a scale-up and a transfer of this sequence to the pilot plant.

Differential scanning calorimeter (DSC) analysis of the epoxidation step employing H_2O_2 (Scheme 2, method a) revealed a strongly exothermic reaction with a heat of reaction of about 900 kJ/kg with an onset temperature of 150 °C. This would amount to a calculated adiabatic temperature rise of up to 262 K in case of a runaway reaction. Additionally, we were concerned about the free oxygen being liberated in the process due to the decomposition of H_2O_2 in basic media.[9] Both aspects clearly raise notable safety issues in the setting of a pilot plant. In total, these adverse

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(5) For the epoxidation of cyclohexenone derivatives using H_2O_2−NaOH, see: (a) Wasson, R. L.; House, H. O. *Org. Synth.* **1963**, *4*, 552. (b) Felix, D.; Winter, C.; Eschenmoser, A. *Org. Synth. Coll. Vol VI* **1988**, 679−682.

(6) (a) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095−2096. (b) Suzuki, M.; Watanabe, A.; Noyori, R. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 230−236.

(7) The automated parallel synthesizer is based on an inhouse-built reaction station. The system consists of a Gilson 222 XL liquid handler, which addresses 24 (50 mL tube) or 48 (20 mL tube) positions with magnetic stirring, heating, or cooling. For the Pd-catalyzed rearrangement, 66 screening experiments were performed under an inert atmosphere on a 4 mmol scale in 20 mL tubes.

(8) Dimeric compound **6** was the only identified byproduct, however, the exact amount of **6** was not determined. Since **6** displays a more intense UV absorption compared to **1**, HPLC analysis based on a UV readout provided no reliable data. Additionally, we had no reference material in hand to undertake a quantification on the basis of a weight % analysis, and ^1H NMR analysis proved difficult since all diagnostic signals of **6** and **1** significantly overlap. Therefore, we focused on a weight % analysis of the desired product **1** which was conducted against a purified standard of **1**. This procedure delivered the most reliable data on the purity of the target molecule **1**.

(9) Temple, R. D. *J. Org. Chem.* **1970**, *35*, 1275.

safety features prompted us to revise the epoxidation conditions. To this end, we replaced H_2O_2 by sodium perborate tetrahydrate ($NaBO_3{\cdot}4H_2O$) which is known to be a safe and cheap source of peroxide and which is reported to react smoothly with α,β-unsaturated ketones without the need of an additional base.[10] Thus, we reacted the enone **3** with 1.6 equiv of $NaBO_3{\cdot}4H_2O$ in an aqueous emulsion at 40 °C, and epoxide **5** was formed quantitatively after 2 h according to GC analyses. The total heat of reaction for this process was 40 kJ/kg as determined by calorimetric measurements corresponding to an adiabatic temperature rise of merely 13 K. Additionally, to further corroborate the safeness of $NaBO_3{\cdot}4H_2O$, we monitored the amount of molecular oxygen being formed in the reaction mixture using an oxygen probe. Indeed, we could not detect significant levels of oxygen throughout the whole reaction. In total, the replacement of hazardous H_2O_2/NaOH by $NaBO_3{\cdot}4H_2O$ proved beneficial for the safety of the process, and the reaction was finally conducted on a 26 kg scale in the pilot plant (see Experimental Section for details). The resulting crude toluene solution of **5** was used in the following rearrangement step. According to DSC analysis, both the pure epoxide as well as its toluene solution were stable up to an onset temperature of 230 °C.

In the laboratory protocol for the Pd-catalyzed rearrangement, we initially used 3 mol % $Pd(OAc)_2$ in combination with 3 mol % BINAP as a source of palladium(0). On larger scale, however, we observed reduced reaction rates which we refer to an incomplete or slow formation of the active palladium(0) catalyst. Thus, we considered to switch to a palladium(0) source such as $Pd(PPh_3)_4$. Since we were concerned about the sensitivity of $Pd(PPh_3)_4$ towards oxidation, we decided to generate $Pd(PPh_3)_4$ in situ from $Pd(OAc)_2$ and PPh_3 in the presence of triethylamine as reducing agent.[11] In practice, this procedure worked well to deliver a Pd(0) precatalyst which formed the active catalytic species upon reaction with rac-BINAP. The catalyst which was formed by this protocol proved highly active, so that we could even reduce the catalyst loading from 3 mol % to 1 mol % (based on Pd and BINAP) without seeing detrimental effects on the reaction rate. From our perspective, this catalyst preparation assured the most reliable process in combination with the best product quality.

On a 50 g scale, the Pd-catalyzed epoxide rearrangement was run in a batch mode at a concentration of 3 M in toluene. However, we could not transfer these conditions to a larger scale since calorimetric measurements revealed a significant exothermic event of 300 kJ/kg with an onset temperature of 90 °C. We addressed this safety issue by diluting the reaction to a concentration of 0.8 M. This measure reduces the maximum heat of reaction to 82 kJ/kg, corresponding to a maximal adiabatic temperature rise of about 45 K. Accordingly, a runaway reaction on a large scale would result in a temperature rise from 90 °C to 135 °C which corresponds to a vapor pressure of toluene of about 2.0 bar, well within the safety margins of the reaction vessels.

Table 2. **Batch overview**

	batch no.[a]	yield, raw [kg]	purity[8] [weight %]	yield, purity corrected [kg]	yield, purity corrected [%]
	1	6, 9	75	5, 1	18
	2	10, 5	69	7, 3	25
	3	9, 9	81	8, 0	27
	4	9, 5	87	8, 2	28
	5	12, 9	74	9, 4	32
sum		50		38	
average			77		26

[a] For each batch, 26.2 kg of spiro[3.5]non-7-en-6-one (**3**) (192 mol, purity > 98%) were used.

The introduction of a higher dilution eliminated our safety concerns, however, a new problem arose from this change. For the different batches, we observed varying reaction times ranging from 2 to 8 h until conversion was complete. This proved problematic, since prolonged reaction times led to an increase of the formation of side-product **6**. We assume that the varying reaction times arise from deviations of the rate of catalyst formation at the higher dilution. Thus, we incubated the catalyst cocktail at a higher concentration with 5% of the epoxide **5** for 3 h at 90 °C in order to start the catalytic cycle before adding the remaining 95% of the epoxide solution. Under these conditions, the active catalyst was formed quite reproducibly, the reaction was complete within 4.5 h, and the exposure of sensitive diketone **1** to higher temperatures was minimized.

Finally, the whole process was conducted on a pilot plant scale (five batches in total) affording the target molecule **1** in an average yield of 26% (for 2 steps) with an average purity of 77% (see Table 2 and the Experimental Section for details).

In conclusion, we have presented the development of a two step pilot plant process for the production of spiro[3.5]-nonane-6,8-dione (**1**). This process enabled us to produce 50 kg of **1** within 3.5 weeks in five pilot plant batches, thus achieving our initial goal for a quick and, taken into account the 200 kg stock of **3**, economical access to the key intermediate **1**.

Experimental Section

Analytics. NMR spectra were recorded using a Bruker AC500 instrument. All spectra are calibrated against tetramethylsilane as an internal standard ($\delta = 0$) or the signals of the residual protons of deuterated solvent. Coupling constants (J) are given in Hz.

Spiro[3.5]nonane-6,8-dione (**1**) was quantified by HPLC against external reference standard. HPLC analysis was performed on a Phenomenex ODS III RP-18, 3 μm column (150×3 mm^2) at 45 °C with a flow rate of 0.5 mL/min, UV detection at 210 nm, and the following linear gradient (solvent A = 10 mM phosphate buffer pH = 2.4; solvent B = acetonitrile): 0 min, A/B 95:5; 20 min, A/B 20:80; 30 min, A/B 20:80.

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(10) For the use of sodium perborate in epoxidation reactions of α,β-unsaturated esters and ketones, see: (a) Reed, K. L.; Gupton, J. T.; Solarz, T. L. *Synth. Commun.* **1989**, *19* (20), 3579−3588. (b) Straub, T. S. *Tetrahedron Lett.* **1995**, *36*, 663−664.

(11) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3013.

Reactions were monitored by GC on a Hewlett-Packard HP1 fused silica (100% polydimethoxysiloxane) 0.33 μm film capillary column (25 m × 0.2 mm) with hydrogen gas (100 kPa pressure, split 100 mL/min) as eluent, FID detection, and the following temperature program: start 50 °C, heat at 10 °C/min to 300 °C, hold 5 min at 300 °C.

Representative Procedure (Batch No. 3 in Table 2) for the Pilot Plant Synthesis of Spiro[3.5]nonane-6,8-dione (1). Spiro[3.5]non-7-en-6-one (**3**) (26.2 kg, 192 mol) was emulsified in water (327 kg) in a 630 L alloy 59 reaction vessel.[12] All operations were carried out under nitrogen. Sodium perborate tetrahydrate (48.0 kg, 312 mol) was added in three portions every 30 min at 40 ± 2 °C. The reaction mixture was stirred at 42 ± 2 °C for 2 h and then cooled to 20 °C. Sodium sulfite (7.3 kg, 58 mol) was added, and stirring was continued at 20 °C for 30 min. Toluene (114 kg) was added, and the organic layer was separated and washed twice with water (2 × 105 kg). Toluene (30 kg) was distilled off (150 mbar, 50 °C) to effect azeotropic water removal. Residual oxygen was removed from the solution by evacuation (200 mbar, 20 °C) followed by ventilation with nitrogen. This procedure was repeated 3 times. The oxygen concentration in the solution dropped below 15 μg/L.

A 250 L alloy 59 reaction vessel[12] was charged with 8.0 kg of the epoxide solution in toluene (approximately 5% of the total amount) and toluene (103 kg). Oxygen was removed as described above. To the solution, triphenylphosphine (3.0 kg, 12 mol), rac-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (1.2 kg, 1.9 mol), palladium(II) acetate (0.43 kg, 1.9 mol), and triethylamine (0.39 kg, 3.9 mol) in toluene (5.0 kg) were added at 20 °C. The catalyst mixture was activated for 3 h at 90−95 °C, the remaining 95% of epoxide solution in toluene was added within 50 min at 90−92 °C, and stirring was continued for 4.5 h at 91−94 °C. After the mixture cooled to 23 °C, Celite (11.7 kg) was added, stirring was continued for 1 h, and the suspension was filtered. The filter cake was washed with toluene (35 kg). Water (175 kg) was added to the combined filtrates, and the pH was adjusted to 8.6 ± 0.1 by the addition of 22.5% aqueous NaOH (13.8 kg) at 20 °C. The layers were separated, and the aqueous phase was washed with toluene (47.0 kg). Ethyl acetate (34.0 kg) was added to the aqueous phase, and the pH was adjusted to 7.0 ± 0.1 by the addition of 20.5% aqueous HCl (1.4 kg). The phases were separated, and the aqueous phase was cooled to 4 ± 2 °C. The pH was adjusted to 2.0 ± 0.2 by the addition of 12% aqueous HCl (21.0 kg), and the precipitated product was isolated on a trailing blade centrifuge (0.55 m^2). After being washed with water (200 kg), the wet product was transferred to a mixing dryer and dried at 45 °C and 50 mbar for 12 h. The spiro[3.5]nonane-6,8-dione (**1**) was obtained as a yellow solid (9.90 kg, 81 weight % purity,[8] 52.7 mol) with an overall yield of 27%.

Melting point (not corrected) = 123 °C; IR (thin film) $\nu = 3426, 2933, 2674, 1623, 1520, 1346, 1297, 1230, 1141$ cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz, mixture of keto- and enol-form) $\delta = 1.92$ (m, 6 H), 2.48 (s, 2 H), 2.73 (s, 2 H), 3.27 (s, 1 H), 5.39 (s, 0.4 H), 6.10 (m, broad, 0.6 H) ppm; ^{13}C NMR (CD_2Cl_2, 125 MHz, mixture of keto- and enol-form) $\delta = 16$ (t), 32 (t), 33 (t), 37 (s), 39 (s), 45 (t), 53 (t), 58 (t), 104 (d), 192 (s), 204 (s) ppm; HPLC $t_R = 10.4$ min; GC $t_R = 9.5$ min; MS (DCI) $m/z = 187$ [$M + N_2H_7$], 170 [$M + NH_4$], 153 [$M + H$].

Acknowledgment

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(12) Alloy 59 (2.4605) is a form of Hastelloy containing approximately 59% Ni, 23% Cr, and 16% Mo.