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The Newman−Kwart Rearrangement Revisited: Continuous Process under Supercritical Conditions†

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Abstract:

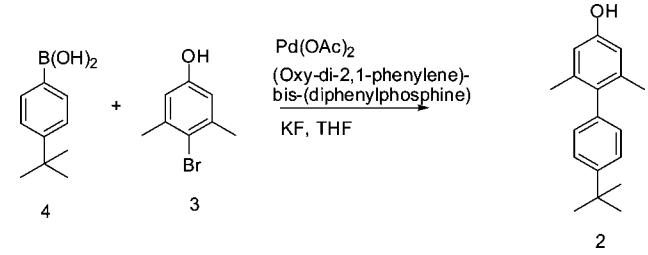
A continuous process that is suitable for large-scale manufacture of the biphenylthiol 1 using dimethoxyethane as solvent at 320 °C and 1000 psi under supercritical conditions has been developed. Due to the use of the low-boiling solvent, the workup through a solvent switch to heptane makes the process suitable for continuous production.

Introduction

The Newman−Kwart rearrangement (NKR) is a valuable synthetic method for the transformation of phenols to thiophenols via their *O*- and *S*-thiocarbamates.[1,2] From this transformation various other sulfur-containing functional groups are readily accessible including thioethers, [3] (homochiral) sulfoxides, [4] sulfones, and sulfonic acids. This approach has also been used to access particular aromatic substitution patterns without a phenol or thiophenol function starting from the common phenol, doing the S_NAr followed by the NKR and desulfurization of the hydrolyzed thiol. Consequently, the NKR has seen a widespread use in medicinal, materials, agrochemicals, and supramolecular chemistry.[5,6−8]

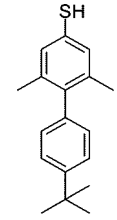
The NKR proceeds via an *O*- to *S*-aryl migration which has a high activation energy requiring high reaction temperatures (200−300 °C). Electron-withdrawing groups are known to accelerate the rearrangement, resulting in reduced reaction time or lowered reaction temperature; on the other hand electron-donating groups slow the reaction down and require higher activation temperatures. Continuous NKRs have also been developed utilizing either microreactors[9] or plug flow reactors.[10,11]

Scheme 1



Results and Discussion

For an early development project we needed quick access to the thiophenolic biaryl compound **1**.



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From an earlier project we had the corresponding biaryl-phenol **2** available in large amounts. The biaryl-phenol **2** is easily obtained through a well-established Suzuki cross-coupling between 3,5-dimethyl-4-bromo phenol **4** and 4-*tert*-butyl phenyl boronic acid **3**. The bisaryl-phenol **2** is easily converted into the *O*-thiocarbamate **5** through a two-step sequence. First, reaction with dimethylthiocarbamoyl chloride in refluxing dioxane in the presence of triethylamine and a catalytic amount of dimethylaminopyridine. After workup and solvent switch, the *O*-thiocarbamate **5** is crystallized from cyclohexane to obtain highly pure material in 79% yield (Scheme 1). In early phase discovery the NKR was performed in a 1:4 (w/v) *O*-thiocarbamate **4**/tetradecane mixture for 6 h at 250 °C. Subsequently,

† This paper is in memory of Chris Schmid.

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(1) Newman, M.; Karnes, H. *J. Org. Chem.* **1966**, *31*, 3980.
(2) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 3410.
(3) Kim, S.; Wu, J. Y.; Zhang, Z.; Tang, W.; Doss, G. A.; Dean, J. B.; DiNinno, F.; Hammond, M. L. *Org. Lett.* **2005**, *7*, 411.
(4) (a) Bowden, S. A.; Burke, J. N.; Gray, F.; McKown, S.; Moseley, J. D.; Moss, W. O.; Murray, P. M.; Welham, M. J.; Young, M. J. *Org. Process Res. Dev.*, **2003**, *7*, 33. (b) Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.*, **1993**, *58*, 1748.
(5) Moseley, J. D; Moss, W. O. *Org. Process Res. Dev.*, **2003**, *7*, 53.
(6) Garcia, C.; Andraud, C.; Collet, A. *Supramol. Chem.* **1992**, *1*, 31.
(7) Kajino, M.; Mizuno, K.; Tawada, H.; Shibouta, Y.; Nishikawa, K.; Meguro, K. *Chem. Pharm. Bull.* **1991**, *39*, 2888.
(8) Ting, Y.; Verboom, W; Groenen, L. C.; Van Loon, J. D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432.
(9) Zhang, X.; Stefanick, S.; Villani, F. J. *Org. Process Res. Dev.* **2004**, *8*, 455.
(10) Lin, S.; Moon, B.; Porter, K. T.; Rossman, C. A.; Zennie, T.; Wemple, J. *Org. Prep. Proced. Int.* **2000**, *32*, 547.
(11) Anderson, N. G. *Org. Process Res. Dev.* **2001**, *5*, 613.

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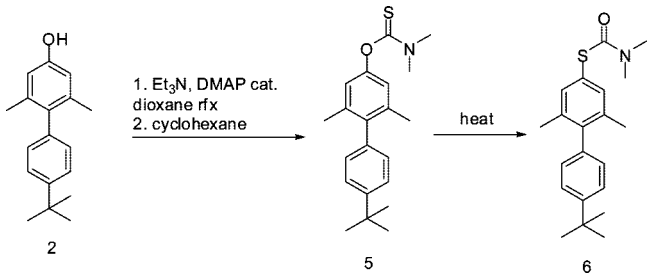
Scheme 2



the mixture was cooled down to 60 °C, and hexane was added as *anti* solvent. Finally *S*-thiocarbamate **6** was obtained in 69% yield.

For the further development it became necessary to prepare 1 kg of *S*-thiocarbamate **6**. As this would not be possible with the existing method, due to the lack of an appropriate high temperature reactor, optimization was done by performing the NKR at a higher concentration. The rearrangement was first tested in neat conditions at 250 °C. Under these conditions the reaction is complete within 1 h. During the cooling, tetradecane is added at 180 °C to have a 1:1 (w/v) *S*-thiocarbamate **6**/tetradecane ratio. The crystallization onset is observed at 150 °C, and after addition of hexane, *S*-thiocarbamate **6** is finally obtained after filtration as a highly pure compound in 83% yield. During this development work the NKR was also tested in 1:1 (w/v) *S*-thiocarbamate **6**/tetradecane at 250 °C. In this case, the rearrangement needs 5 h at 250 °C to go to completion (Scheme 2). The *S*-thiocarbamate **6** was obtained in the same yield and quality from this procedure as when the reaction was run neat (yield 83%, 92% purity).

To avoid any safety issues on larger scale as the project was moving towards phase I clinical material delivery, it was decided to re-evaluate the rearrangement under continuous reaction conditions. A Newman−Kwart rearrangement utilizing a continuous flow reactor has already been reported.[10] The authors used the high-boiling solvent tetraglyme for the rearrangement. The solubility of *O*-thiocarbamate **5** in tetradecane is too low at room temperature for a continuous reaction; the solubility in tetraglyme, on the contrary, is good. At room temperature a clear solution of the *O*-thiocarbamate **5** is obtained in 15 volumes of tetraglyme. The solubility of the product **5**, however, is too high, and the addition of heptane results in a very low yield of crystalline material. We then turned our attention to diglyme (bp 162 °C) and chlorobenzene (bp 131 °C). We thought that it might be possible to use solvents with a lower boiling point if the mixture is cooled to room temperature before it comes out of the reactor. We built a continuous reactor from 1/8 in. stainless steel tubing, 23 m long, coiled, in an oven, a preparative HPLC pump, a coiled 1/8 in. stainless steel tubing outside of the oven (6 m long to function as the cooling zone) prior to a section of short tubing 1/16 in. with one needle valve to function as a back-pressure regulator. The first experiments were run in 10 volumes of diglyme at 250, 280, 300, and 320 °C with a flow rate of 2 mL/min. We estimated that at this flow rate the residence time in the reactor would be approximately 30 min. To start up a reaction screen we filled the reactor with pure solvent, stopped the flow, and started to heat the reactor to 250 °C. During the heating period, solvent continued to come out of the reactor due to the expansion of the solvent volume above the boiling point.

The result from this first screen showed that the conversion at 250 °C, with a flow of 2 mL/min, was only 50%; at 280 °C it was 80%; at 300 °C, 87%; and at 320 °C, full conversion but with 10% impurities. Encouraged by these results we investigated the reaction in chlorobenzene as this could be run more concentrated due to a higher solubility of the starting material. The reaction was performed in the same reactor with a solution of the *O*-thiocarbamate **6** in 3 volumes of chlorobenzene at 280 °C using a flow rate of 2 mL/min. From this experiment we obtained complete conversion but 15% of different impurities. Lowering the temperature to 250 °C did not have much of an effect on the impurity profile, so chlorobenzene was ruled out as solvent. As we obtained 80% conversion at 280 °C with almost no impurities in diglyme we decided to investigate these conditions in more detail. Due to the volume expansion of the solvent at temperatures above the boiling point, we had no data on the residence time in the reactor. The volume expansion of diglyme at 280 °C with a backpressure of 20 bar was found to be 2. This cuts the estimated residence time in the reactor by half, giving a true residence time of 15 min. at this temperature. As we lowered the flow rate of the reaction to 1 mL/ min, we obtained 98% conversion. The isolated yield on 10-g scale was 90% of 97% pure *S*-thiocarbamate **6**.

The removal of diglyme on large scale, unfortunately, is also not straightforward, and without removal the yield from the reaction is very low. But, as we can control solvents at high temperatures above the boiling point with back-pressure regulation, we could use an ether solvent that is easily removed for the reaction. Our decision fell on dimethoxy ethane (DME). The *O*-thiocarbamate **5** is soluble in 5 volumes of DME.

To develop this reaction under more controlled conditions a new reactor setup was built, consisting of an ISCO high-pressure syringe pump, 60 m of stainless steel tubing coiled in the GC oven, and at the outlet five backpressure valves each controlling 250 psi to be able to run the reaction under controlled conditions at 1000−1100 psi (70−77 bar).

Under the setup conditions DME would be in the supercritical zone (536 K, 3.87 MPa, $V_c = 271$ mol/cm^3). Prior to evaluating the chemical reaction we measured the thermal expansion for DME at 300 °C. The reactor was filled with 205 mL of DME, and the pump was stopped prior to heating. To estimate the expansion coefficient for the solvent between room temperature and the reaction temperature, the volume of DME that leaves the reactor during heatup was collected in a measuring flask. During heatup a pressure of 983 psi was measured in the reactor. *During heatup it is extremely important not to close the reactor as the volume expansion will build a very large overpressure >2000 psi.* From the heatup we were able to collect 145 mL of DME corresponding to a thermal expansion of 3.4. This translated into a residence time in the reactor of 7.6 min at a flow rate of 7.5 mL/min. As the reactor temperature lined out at 300 °C, the reaction could be started. *At higher flow rates is it important to have an efficient cooling prior to the outlet as the supercritical DME will ruin the backpressure regulator.* After the setup was completed, a test

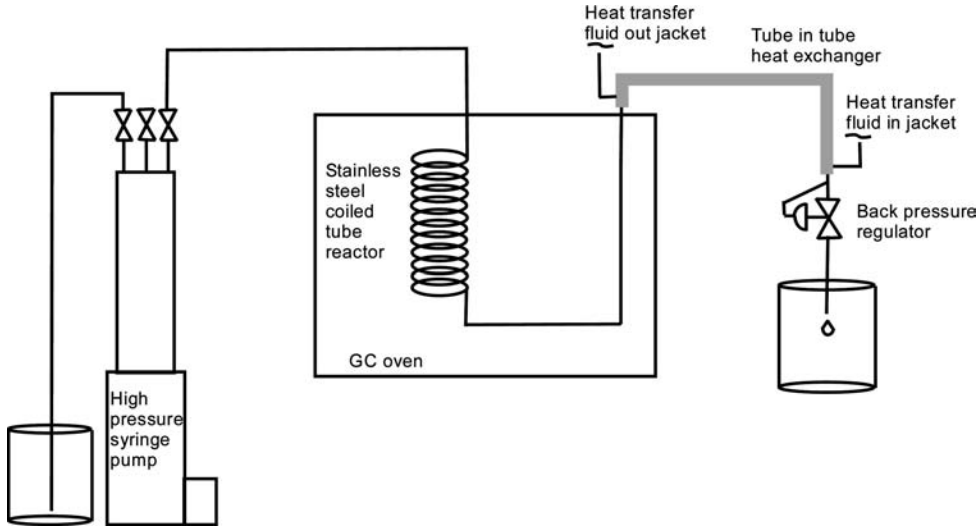


Figure 1

run of the reaction was done prior to scale-up for phase I delivery (see Figure 1). For the test run 250 g of *O*-thiocarbamate **6** was dissolved in 1250 mL of DME. The reactor, with a backpressure of 983 psi, was filled with DME at 300 °C. The pump was started with a flow rate of 7.5 mL/min. (The pump can hold 266 mL of solution.) During the refill of the pump, product solution continued to come out of the back end of the reactor at a constant flow, and the pressure in the reactor dropped down to 840 psi. A total of five refills was necessary to pump the entire reaction volume through the reactor. To ascertain that the whole reaction volume had passed the reactor, two refills (70 and 140 mL) of DME were done. After reaction completion a sample was taken for analysis. The sample showed a 99.1% conversion with 0.6% starting material and 0.3% of an unknown impurity.

The product isolation is easy under this protocol; the DME is removed under distillation, and *n*-heptane is added as an *anti*-solvent to initiate the product crystallization. After removal of the DME, the heptane product slurry is cooled to 25 °C, and the product is filtered off. This procedure gives a product with a 99.2% quality in a yield of 93%.

With this laboratory-scale reactor it would be possible to produce 1.5 kg of pure product from this process per 24 h. For the delivery of the material for the phase I study a somewhat larger reactor would be needed. A reactor that could deliver 6 kg per day would be easily installed using the same pump and oven. In this case the combination with a continuous distillation would be beneficial. However, since the project was terminated, the setup of this system had to be set aside.

Conclusion

In conclusion we have been able to develop, through thoughtful chemical engineering and organic chemistry process development, a completely new protocol for the Newman−Kwart rearrangement that combines a highly efficient and fast reaction with a very simple workup. The development of this new protocol was only possible due to the use of a new small-scale laboratory reactor that can handle pressures above 2000 psi and temperatures above 300 °C. Through this protocol we have been able to show that in some cases it is possible to reduce the reaction time for standard organic reactions that normally take a long time even in high-boiling solvents. The use of low-boiling solvents even under supercritical conditions does not have an influence on the reaction performance, as far as we have seen, but does simplify the workup of the reaction mixture. We have also found that in this case the yield and the purity from the continuous process is much higher than from the batch process due to the very fast heatup and cooldown times.

Experimental Section

Dissolve 250 g of *O*-thiocarbamate **5** in 1250 mL of dimethoxyethane in a 1500 mL flask with a screwcap with an outlet tubing for the syringe pump refill and a nitrogen gas inlet. Set up the reactor through filling with solvent; after stopping the pump start to heat the reactor to 300 °C. During heatup collect the immersing solvent for waste. After the reactor reaches 300 °C, start pumping the *O*-thiocarbamate **6** solution in a flow rate of 7.5 mL/min. It is important during the whole reaction to control the pressure in the reactor. The pressure should be between 800−1100 psi, depending on whether the pump is running. The residence time in the reactor is at this flow rate approximately 7.6 min. After the starting material is completely used up, the feed flask is rinsed first with 70 mL of DME and then with 140 mL to ascertain that the whole reaction mixture is flushed out of the reactor. Analyze the reaction for conversion. When the conversion is complete, strip off the solvent under vacuum and add *n*-heptane (500 mL) as an *anti* solvent. After complete removal of DME cool the slurry to room temperature and filter. Wash the product twice with 100 mL of *n*-heptane. Dry in a vacuum oven at 40 °C for 4 h. Yield 93% of *S*-thiocarbamate **6**. Quality 99.2%, t_R 12.41 min. Zorbax SB-C18 4.6 mm × 50 mm 1.8 μm, 1.5 mL/min at 40 °C, Solvent A 0.1% TFA in water; solvent B 0.1% TFA in CAN; time: 0 min, 95% A, 5% B; 12 min, 15 % A, 85% B; 13 min, 95% A, 5% B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.05 (s, 6H), 3.08 bs, 6H), 7.07 (d, 2H, J = 8.5 Hz), 7.26 (s, 2H), 7.43 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.910, 31.457, 34.539, 36.914, 125.261, 126.298, 128.418, 134.436, 137.227, 137.254, 143.035, 149.494, 167.501.

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