Organic Process Research & Development

Communication

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A Unique Synthesis of 5,8-Difluoro-2*H*-chromene Using Silicone Oil as a Solvent

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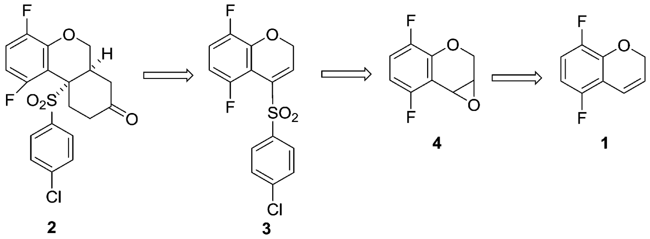
Supporting Information

ABSTRACT: A significantly improved synthesis of 5,8-difluoro-2*H*-chromene **1** using silicone oil as the reaction solvent is described. The new method eliminated the tedious workup and large quantity of waste produced via conventional methods. To our best knowledge, this is the first report of conducting an organic reaction using silicone oil as an organic solvent.

The chromene (benzopyran) ring structure is one of the fundamental scaffolds that are found frequently in natural products. Such natural products have been shown to possess diverse biological activities, such as antiviral, antifungal, anticoagulant, and anticancer.[1] The synthesis of chromenes from phenol propargyl ether was first reported by Iwai and Ide in 1963.[2,3] Subsequently, Zsindely and Schmid proposed that this reaction went through the [3,3] Claisen rearrangement.[4] This reaction was later widely accepted for the synthesis of the chromene skeleton in the synthetic community.[5] In recent years, new methods have been developed for the synthesis of the chromene ring.[6] For example, Wulff et al. reported the synthesis of a highly functionalized chromene scaffold using a benzannulation/*o*-quinone methide formation/electrocyclization cascade.[7] de Bruin et al. reported the synthesis of 2-substituted 2*H*-chromenes via a radical addition reaction.[8] Despite such synthetic advances, the original method of Iwai and Ide remains as a very useful method as it can provide the simplest 2*H*-chromene ring from an easily accessible phenol in just two steps. The caveats are that the post reaction workup is quite tedious, and it produces significant amount of environmentally unfriendly waste besides the poor yield. In this communication, we report a novel solution to address these issues.

In our γ-secretase inhibitor (GSI) program, there was a need to access several hundred gram quantities of 5,8-difluoro-2*H*-chromene **1**, which could be transformed into a tricyclic sulfone **2** for further SAR exploration (Figure 1).[9] Initially, the synthesis of **1** in multigram quantity was done based on the original condition reported by Iwai and Ide.[2,10] The 2,4-difluorophenol **5** was converted to the alkylation product **6** in quantitative yield (Scheme 1). Then compound **6** was dissolved in *N*,*N*-diethylaniline and heated to 195 °C for 15 h. After washing away the *N*,*N*-diethylaniline with aqueous HCl followed by purification via flash chromatography, the desired product **1** was obtained in typically 30–35% yield with the rest of the material having decomposed during the reaction. There were two challenges for this reaction on large scale: the poor yield and, in particular, substantial amounts of waste produced post reaction. To produce 1 kg of compound **1**, we estimated the use of 25 L of *N*,*N*-diethylaniline as solvent, 40 L of 4 N HCl to wash away the basic solvent. Combined with the silica gel needed, such a reaction would create roughly 300 kg of solid and liquid waste. This would become a significant burden to the environment, and it forced us to think about an alternative synthetic method.[11]



2

3

4

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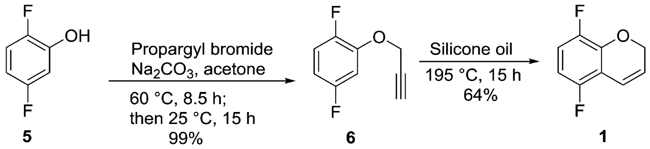
Figure 1. Tricyclic sulfone **2** and its retrosynthetic analysis leading to chromene **1**.

Scheme 1. Synthesis of Chromene 1



5

6

1

The major cause of the poor yield was the polymerization of the substrate **6** at high temperature, leading to a black mixture after heating for just 1 h. Iwai and Ide tried different solvents in efforts to improve the yield and observed that weakly basic solvent such as *N*,*N*-dimethylaniline or *N*,*N*-diethylaniline actually led to less polymerization products than hydrocarbon solvents.[3,12] We turned our attention to the reaction temperature and time. It was found that the reaction was much slower when temperature dropped below 180 °C. Prolonged heating at this temperature only led to more degradation of the starting material. When the reaction temperature was raised to 200–210 °C, rates of both the formation of the desired product and the degradation of the starting material were faster, with no improvement of the isolated yield.

We reasoned that decomposition of the solvents may also occur even though their boiling points are high (*N*,*N*-

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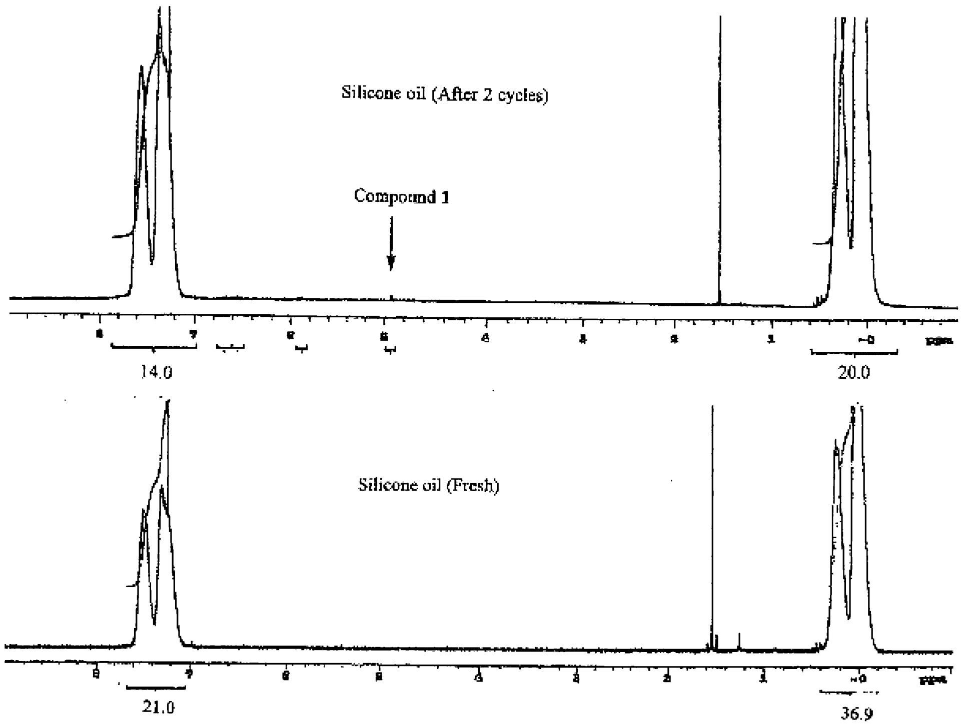

Figure 2. ^{1}H NMR comparison of fresh and recycled silicone oil.

dimethylaniline: 194 °C; *N*,*N*-diethylaniline: 216 °C). Such decomposition might accelerate the polymerization of the compound **6**. Therefore, an inert solvent with even higher boiling point would help improve the reaction yield. Among several choices such as diphenyl ether, silicone oil, and syltherm, we chose silicone oil as the solvent since it is widely commercially available.

With excellent thermal stability and good heat transfer characteristics, silicone oil has long been used for oil baths in laboratories as well as refrigerants. It is also highly soluble in hydrocarbon solvents such as toluene and xylene as well as chlorinated hydrocarbons, and therefore, it should be a good solvent for nonpolar compounds such as **6** and **1**. With the boiling point of 300 °C for silicone oil vs 220 °C for the desired product **1**, it should also be possible to obtain compound **1** by distillation, eliminating the workup step and waste production.

To test the hypothesis, 34 g of compound **6** was mixed with 500 mL of high-temperature silicone oil (Aldrich, Cat. No. 175633) and heated to 190 °C (internal temperature) under nitrogen atmosphere for 15 h. After cooling, direct distillation under reduced pressure afforded 22 g of a light yellow oil. The ^{1}H NMR spectrum revealed a clean compound as the desired product **1** with <2% of the starting material, suggesting a yield of 62%. There was no obvious color change in the silicone oil residue which was filtered through a small silica gel pad. About ~450 mL of silicone oil was recovered. The absence of color or other physical change indicated that the recycled oil could be reused.

We were very encouraged by this initial attempt. To ensure the reaction reproducibility and to check whether the silicone oil could be recycled, the reaction was repeated (33 g of compound **6**, 400 mL of recycled silicone oil) at 195 °C under otherwise identical conditions. Distillation provided the desired product **1** (24.5 g, 96% pure along with 4% starting material) in 71% yield. There was no color change in the silicone oil which was filtered through a small pad of silica gel pad before NMR measurement. The ^{1}H NMR spectra of the silicone oil (fresh sample, after two-cycle use, respectively) were collected with no indication of major changes (Figure 2). Some other modifications of the reaction conditions were tried. Reducing the amount of silicone oil by half led to a lower yield of 50%, which was consistent with the low concentration requirement for an intramolecular reaction. Raising the temperature to 205 °C in efforts to drive the reaction to completion did not help. Instead, the silicone oil started to become darker which indicated possible decomposition and could make the recycling more difficult.

With all the information in mind, a 20-fold scaleup reaction with 690 g of compound **6** was carried out in 8 L of fresh silicone oil at 195 °C for 18 h. The crude was cooled down, and vacuum distillation (4−5 mmHg) was initiated. After the first fraction was collected (a total of 40 g of compound **1** with 10% starting material based on ^{1}H NMR spectrum), the major fraction containing compound **1** was collected (404 g with 6% starting material) followed by the third fraction at (41 g of compound **1** with 2% starting material). Excluding the first fraction (which was recycled for the next round reaction), this reaction provided the desired product in 64% yield with 90% purity. The silicone oil was clear and colorless. It was filtered through 1 kg silica gel pad and recycled for the next 710 g scale reaction without further treatment.

With no further modification of the reaction conditions, this reaction was repeated on a scale of 710 g of compound **6**. A portion of 484 g of compound **1** (94% pure) was obtained in 64% yield, demonstrating the reproducibility of this reaction. Combining these two runs, a total of ~900 g of compound **1** was delivered for further SAR exploration. Due to the time sensitivity, the further purification of the chromene **1** was not carried out as the remaining starting material **6**/impurity had no impact on the next reaction (epoxidation of the chromene **1** to give compound **4**). However, we were confident that a higher purity would be possible by carefully monitoring the distillation fractions.[13]

We were very pleased to report that the use of silicone oil as a solvent for this reaction not only improved the reaction yield dramatically but also obviated the tedious workup and massive waste production. Just for an estimate, producing 1 kg of the compound **1** using the original method would generate ~300 kg of solid and liquid waste, whereas the new method required only 1 kg of silica gel for filtration. The silicone oil could still be recycled for further use. To our best knowledge, this is the first report of conducting an organic reaction using silicone oil as an organic solvent, and it sets a great example for green chemistry. The method should be applicable to the synthesis of many other chromenes[10] and chromans via such an intramolecular reaction which generates no other product(s). It can also be potentially used for intermolecular reactions such as the Diels—Alder reaction as long as the reagents and products have reasonable solubility in silicone oil and do not have a negative impact on it. Such a reaction would have wide application in pharmaceutical as well as chemical industry with tremendously positive impact on the environment.

In summary, we have reported for the first time the use of silicone oil as an organic solvent for an organic reaction as well as a novel method to produce chromene **1** in a significantly improved yield with minimum waste production. This novel synthetic procedure would serve as a general method to produce simple chromenes in large quantities. We certainly hope that our example will lead to the discovery of many more green chemistry examples in the future.

EXPERIMENTAL SECTION

710 g of compound **6** (prepared according to refs 2 and 10, 4.22 mol) was dissolved in 7.5 L of silicon oil (recycled from the previous 690 g scale reaction) in a 12 L three-neck flask equipped with a mechanic stirrer under nitrogen atmosphere. The solution was heated to 195 °C (internal temperature) using a heating mantle for 18 h. The crude was cooled down, and a sample was taken directly for ^{1}H NMR. The NMR spectrum indicated the presence of 8% of starting material. Distillation of the crude through a 15 cm Vigreux column at 3—4 mmHg into a room temperature-cooled receiver was initiated. The first fraction was collected at 75 °C (internal temperature, external temperature 115 °C, 4 mmHg) to afford 61 g of compound **1** (91% pure, with 9% starting material based on ^{1}H NMR).[14] A major fraction of **1** was obtained at the same temperature (444 g, 94% pure with 6% starting material). The third and last fraction (40 g of **1**, 97% pure with 3% starting material) was collected and combined with the major fraction. Excluding the first fraction (which was recycled for the next round reaction), this process provide 484 g of the desired product **1** as colorless oil in 68% yield with 94% purity. The silicone oil was filtered through a 1 kg silica gel pad.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.92 (dd, 2 H, J = 3.4, 1.9 Hz, C2 CH_2) 5.89 (dt, 1 H, J = 10.1, 3.4 Hz, C3 CH), 6.55 (ddd, 1H, J = 9.2, 8.6, 3.8 Hz, C6 CH), 6.67 (ddt, 1 H, J = 10.1, 3.8, 1.9 Hz, C4 CH), 6.89 (ddd, 1 H, J = 10.1, 9.2, 5.1 Hz, C7 CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.10 (dd, J = 245.0, 2.4 Hz), 147.46 (dd, J = 240.6, 3.1 Hz), 141.99 (dd, J = 12.6, 7.3 Hz), 122.80 (d, J = 2.6 Hz), 117.59—117.42 (m), 115.83 (dd, J = 20.8, 10.0 Hz), 112.81 (dd, J = 20.7, 2.4 Hz), 107.06 (dd, J = 23.8, 7.1 Hz), 65.85.

^{19}F NMR (500 MHz, $CDCl_3$): δ −142.8, −127.8.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of compound **1**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00126.

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Notes

The authors declare no competing financial interest.

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(13) The difficulty of completely separating the starting material from the desired product by fractional distillation under our conditions was likely due to the high saturation pressure requirement for distillation vs the large volume of the reaction flask. It is therefore conceivable to gain better separation by using smaller reaction flask and longer Vigreux column for distillation.

(14) We observed internal boiling point variation ranging from 75 to 120 °C in different runs. This was due to the challenge of keeping the three-neck system tightly sealed while operating.

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