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An Improved Synthesis of Pyran-3,5-dione: Application to the Synthesis of ABT-598, a Potassium Channel Opener, via Hantzsch Reaction

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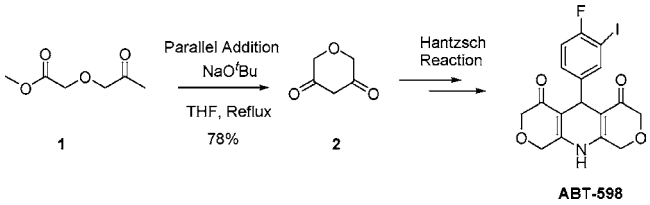
Received October 26, 2005



Ketoester **1** is cyclized to give pyran-3,5-dione **2** in 78% yield using a parallel addition of ketoester **1** and base NaO^{t}Bu in refluxing THF. Compared to the previously reported procedures, these optimized conditions have significantly increased the yield of this transformation and the quality of pyran **2** and prove to be suitable for large-scale preparation. An application of **2** to the synthesis of ABT-598, a potassium channel opener, is demonstrated.

Pyran-1,3-dione **2** is an important building block which has been incorporated into compounds of pharmaceutical interest such as potassium channel opener ABT-598 for overactive bladder[1] (Figure 1) and quinolizinecarboxylic acid for antibacterial agent.[2] Compound **2** also found valuable utility in exploring biological activities of steroid natural products as their 16-oxa-homoanalogues.[3] During the course of development of ABT-598, we needed to prepare multi-kilograms of **2**. Several syntheses of diketone **2** were reported in the literature.[4−6] However, these procedures utilized transformations and reagents which were not suitable for our multi-kilogram scale, such as hydromercuration and organocadmium reagents. Therefore, we developed a synthetic approach that was both efficient and scalable (Scheme 1).

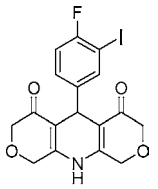
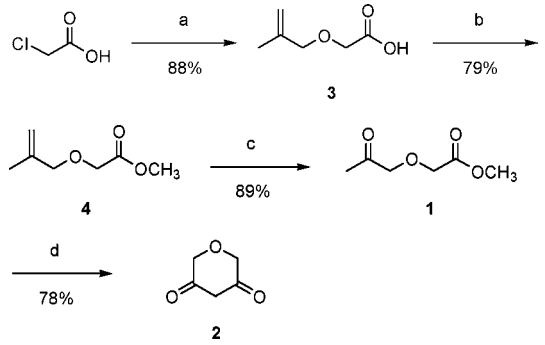


FIGURE 1. Structure of ABT-598.

SCHEME 1. Synthesis of Pyran-3,5-dione[a]



[a] Reagents and conditions: (a) β-methallyl alcohol, KO^{t}Bu (2.2 equiv), rt, 16 h; (b) 5 wt % Amberlyst-15 resin, MeOH, 60 °C, 8 h; (c) K_2OsO_4 (0.1 wt %), $NaIO_4$ (2.3 equiv), THF/H_2O, rt, 11 h; (d) NaO^{t}Bu (1.3 equiv), THF, 65 °C.

The synthesis began with coupling of chloroacetic acid and methallyl alcohol. The use of chloroacetic acid as a substrate allowed an acid−base workup to be utilized and enabled the effective removal of excess methallyl alcohol. The major impurity was 2-*tert*-butyloxyacetic acid, resulting from the reaction between chloroacetic acid and potassium *tert*-butoxide. This impurity was minimized by the use of an excess of methallyl alcohol and by addition of the base to a solution of the two substrates. The coupling product **3** was obtained as a MTBE solution in 88% yield.

To avoid product loss during an aqueous workup due to the relatively high water solubility of **4**, the esterification reaction was carried out under anhydrous conditions (MeOH, 5 wt % of Amberlyst-15 resin). Once the reaction was complete (8 h, 60 °C), the resin was filtered off and the methanol removed by distillation. Unfortunately, some product was lost due to co-distillation with methanol, resulting in an assay yield of 80%. A coupling of chloroacetic acid methyl ester and methallyl alcohol could afford **4** directly. However the reaction was low yielding and not clean. The two-step sequence we employed provided methyl ester **4** in good yield and high purity without requiring additional purification.

The olefinic double bond of methyl ester **4** was converted to the corresponding carbonyl functionality affording ketoester **1** by oxidative cleavage with catalytic K_2OsO_4 (0.1 wt %) and $NaIO_4$ (2.3 equiv) in THF/H_2O. The active catalyst OsO_4 was generated by in situ oxidation of K_2OsO_4 with $NaIO_4$. The use of K_2OsO_4 as a precatalyst minimized the exposure to toxic OsO_4. Reducing the catalyst loading from 0.5 to 0.1 wt % did

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10.1021/jo052226w CCC: $33.50
Published on Web 01/20/2006

TABLE 1. Effect of Base on Cyclization[a]

entry	base	yield[b] (%)
1	LiHMDS	23
2	KHMDS	35
3	NaHMDS	44
4	LiOMe	<1[c]
5	KOMe	45
6	NaOMe	68
7	KO^{t}Bu	50
8	NaO^{t}Bu	64

[a] The reaction was conducted in THF at 65 °C. [b] Yields were determined by HPLC assay of the quenched reaction mixture versus a working standard. [c] Some **1** remained.

TABLE 2. Effect of Temperature on Cyclization[a]

entry	*T* (°C)	yield (%)
1	−20	19
2	−5	28
3	23	29
4	45	39
5	65	50

[a] The reaction was conducted in THF using KO^{t}Bu as base.

not affect reaction yield but slightly increased reaction time (12 h). After the reaction was complete, the precipitated salts were removed by filtration and the aqueous filtrate was washed with MTBE to remove nonpolar impurities and residual osmium. The ketoester **1** was extracted three times with dichloromethane, and after dichloromethane was removed in vacuo, ketoester **1** was dissolved in THF. The yield of the oxidative cleavage was 89%.

The key step is the cyclization of **1** to form diketone **2**. In the literature, this was achieved by the addition of a ketoester **1** THF solution to NaH in THF at 0 °C with a 48% isolated yield.[6] For safety reasons, we replaced NaH with KO^{t}Bu. This change resulted in a low yield (~30%) and required chromatographic purification. To identify a robust process for this conversion, a detailed study of the cyclization conditions (base, solvent, temperature, etc.) was initiated.

The majority of the screening experiments was conducted in THF with ketoester **1** solution being added to a base solution. The initial results showed that sodium methoxide provided the highest yield (68%) among eight bases screened, and sodium *tert*-butoxide gave the second highest (64%) (Table 1, entries 6 and 8). However, the sodium methoxide results were variable, presumably due to its low solubility in THF.[7] Meanwhile, the NaO^{t}Bu reaction constantly produced high yields. A trend of counterion (Li, Na, K) effect on yield was also observed with Na^+ superior to K^+ and to Li^+ (Table 1). As a result, NaO^{t}Bu was chosen as the base for cyclization reaction.

Temperature has a big effect on the reaction. When the reaction was conducted at different temperatures using KO^{t}Bu in THF, the reaction yield increased steadily from 19% at −20 °C to 50% at 65 °C (Table 2). The effect of solvent on the cyclization reaction was examined among THF,1,4-dioxane and toluene. THF stood out as the solvent of choice achieving 64% yield and was subsequently selected for scale-up (Table 3).

The addition mode was critical to achieving high yield. Earlier experiments showed that ketoester-to-base protocol gave a much

TABLE 3. Solvent Effect on Cyclization[a]

entry	solvent	yield (%)
1	THF	64
2	1,4-dioxane	38
3	toluene	32

[a] Reaction was conducted at 65 °C using NaO^{t}Bu as base.

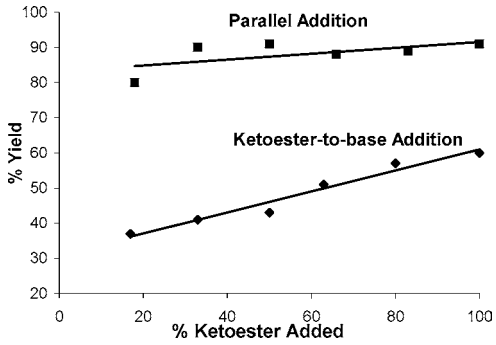


FIGURE 2. Effect of addition modes on % yield of cyclization.

higher yield than the base-to-ketoester protocol (64% versus 20%). Using this addition protocol (THF, NaO^{t}Bu, 65 °C) we prepared **2** in 55% solution assay yield on kilogram scale. The modest yield prompted us to identify further improved cyclization conditions. After analyzing the ketoester-to-base addition mode we found that a critical drawback in this addition mode was the varying concentration of base relative to ketoester **1**. At the beginning of the addition there is a large excess of base, which decreases over time with the addition of ketoester **1**. To gain insight into how the reaction progressed, yields of the reaction were determined over time during the addition of ketoester **1**.[8] The results (Figure 2, Ketoester-to-base Addition) indicated that the yield increased with the addition of the ketoester (or with the decreased excess of base), suggesting a large excess of base had an adverse effect on the reaction. To circumvent this problem, a parallel addition method was developed by which separate base and substrate solutions were added simultaneously to refluxing THF. As shown in Figure 2 (Parallel Addition), constant high yields over the addition span were achieved with this addition mode. Upon scaling up to multi-kilogram scale, the new process averaged 75% assay yield versus the 55% yield obtained with the ketoester-to-base addition protocol. The quality of the product was also improved significantly as a result of a cleaner reaction. The product can be isolated using recrystallization from ethyl acetate without resorting to column chromatography.

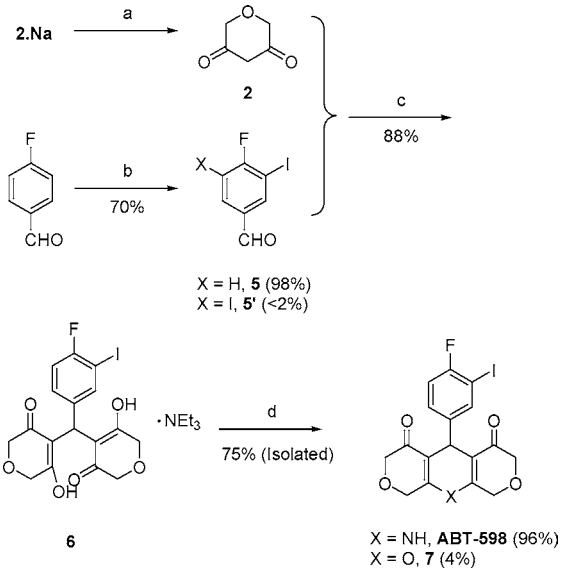
A more efficient way to obtain the product is to isolate the sodium salt of **2** (**2.Na**), which precipitates during the reaction. Thus, after the reaction is complete, the reaction mixture is simply quenched with 1 equiv of water to destroy any excess NaO^{t}Bu and filtered. Later, this salt can be protonated and the freed diketone **2** either isolated by recrystallization from EtOAc or used without isolation.

The synthetic utility of pyran-3,5-dione **2** was demonstrated in the synthesis of ABT-598, a potent potassium channel opener, via Hantzsch reaction (Scheme 2). The required 4-fluoro-3-iodobenzaldehyde (**5**) was synthesized in 55% isolated yield employing a direct iodination approach using *N*-iodosuccinimide

(7) When conducting a 25 g run using NaOMe, the yield dropped abruptly to 31%. We suspected that this might be due to the relatively low solubility of NaOMe in THF. The use of stirbar in screening experiment could help reduce the particle size of NaOMe and hence increase its surface area. This grinding effect was not present when overhead stirring was used on 25 g scale.

(8) The data were collected by analyzing aliquots of the reaction mixture using pyridine as an internal reference.

SCHEME 2. Synthesis of ABT-598[a]



[a] Reagents and conditions: (a) 6 M HCl; (b) NIS (1.2 equiv), AcOH/H_2SO_4, 40 °C, 12 h; (c) NEt_3, EtOAc/HO^{i}Pr, 50 °C, 1 h; (d) NH_4OAc, HOAc, 105 °C, 1 h.

(NIS) in AcOH/H_2SO_4 at 40 °C, a modification of Olah's NIS/triflic acid conditions for substituted benzonitriles.[9] Because of the competitive diiodination reaction, the reaction was allowed to proceed to approximately 78% completion, thereby controlling the level of diiodo byproduct **5′** to < 2%. The sodium salt of **2** was dissolved in a small amount of water and its pH adjusted to 1.2 with 6 M HCl solution. The resulting **2** was extracted into ethyl acetate and condensed with 0.5 equiv of aldehyde **5** to give triethylamine salt **6** in 88% isolated yield with >99% pa purity. This novel Hantszch reaction intermediate is a new synthetic entity.[1b] Since the final product, ABT-598, is very insoluble in most of common solvents for recrystallization, the isolation of triethylamine salt provides an important opportunity for purification. The triethylamine salt then was heated at 105 °C with ammonium acetate in acetic acid to form ABT-598 as a yellow solid with ∼4% of pryan **7**. Purification using 1% KOH in EtOH removed pyran **7** and afforded pure ABT-598 in 75% isolated yield.

In conclusion, we have developed an efficient synthesis for pyran-3,5-dione **2**. Optimized conditions for the key cyclization were established resulting in substantial improvements in both reaction yield and product purity. The synthetically important pyran-3,5-dione was used in the preparation of ABT-598.

Experimental Section

2-Oxopropoxyacetic Acid Methyl Ester (1). To a solution of chloroacetic acid (794 g, 8.4 mol) in THF (8 L) was added β-methallyl alcohol (720 g, 9.98 mol). The mixture was cooled to −2 °C, and a solution of potassium *tert*-butoxide (1.95 kg, 16.9 mol) in THF (10 L) was added slowly to the mixture. The reaction was stirred at ambient temperature until <3% chloroacetic acid remained by HPLC analysis (∼16 h). The reaction was then quenched slowly with distilled water (5.6 L). The mixture was washed twice with methyl *tert*-butyl ether (MTBE) (2.8 and 5.6 L). After the pH was adjusted to 1.6 with 6 M HCl solution (1.8 kg), the aqueous was extracted twice with MTBE (5.6 L each). The combined organic layer was washed with brine solution (2.7 kg). Analysis of the product solution by HPLC indicated 955 g (87.5%) of **3** present.

The MTBE of **3** solution (6.43 kg, 948 g **3**, 7.29 mol) was removed by distillation, and methanol was added. To the resulting methanol solution of **3** (2 L) was added Amberlyst-15 ion-exchange resin (50 g). The mixture was heated at 60 °C until <2% **3** remained by GC analysis (8 h). The reaction was then cooled to room temperature and filtered. The methanol of the filtrate was removed by distillation and replaced with THF. Analysis of the product solution by HPLC indicated 827 g (79%) of **4** present.

To the above THF solution of **4** (2.47 kg, 814 g **4**, 5.64 mol) were charged potassium osmate dihydrate (0.85 g, 2.30 mmol), distilled water (930 mL), and THF (1.1 L). Then a solution of sodium periodate (2.72 kg, 12.7 mol) in distilled water (23 L) was added over 1 h. The reaction was stirred until <2% **4** remained by HPLC analysis (∼11 h). The reaction mixture was filtered to remove precipitated sodium iodate, and the filter cake was washed with distilled water (3.3 L). The filtrate was washed with MTBE (4.4 L). The aqueous was then extracted four times with dichloromethane (7 L each). Dichloromethane was removed by distillation and replaced with THF. The water content was reduced to less than 0.2% by azeotropic distillation with THF several times. Analysis of the product THF solution by HPLC indicated 738 g (89%) of **1** present. An analytical sample of **1** as a colorless oil was obtained by stripping THF and purifying by column chromatography on silica gel (hexane/ethyl acetate, 7:3): ^{1}H NMR (400 MHz/$CDCl_3$) δ 4.21 (s, 2H), 4.20 (s, 2H), 3.76 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz/$CDCl_3$) δ 205.1, 169.9, 76.5, 68.4, 52.3, 26.8; IR (neat) 1752, 1731, 1217, 1136 cm^{-1}. Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.30; H, 7.12.

Pyran-3,5-dione, Sodium Salt (2.Na). To a 50 L flask containing 10.5 L of THF at reflux were added simultaneously a solution of sodium *tert*-butoxide (0.817 kg, 8.5 mol) in THF (12 L) and a solution of ketoester **1** (1.03 kg, 7.05 mol) in THF (12 L) over 1 h. The addition was carried out using two metering pumps that had been calibrated at 180 g/min. The base solution started first, by about 100 mL. The resulting reaction mixture became heterogeneous with a yellow color. Following the completion of addition, the reaction mixture was stirred at 65 °C for 5 min and then quenched with water (0.13 L). Upon cooling to room temperature, the slurry was filtered. The wet cake was washed with THF (2 L) and was then dried under vacuum with nitrogen bleed at 60 °C to provide 1.066 kg of product (70% potency based on salt; 746 g product **2.Na**; 77.5% yield). An analytical sample of **2** was obtained as a pale yellow solid by converting **2.Na** to **2** and recrystallizing from ethyl acetate: mp 128−129 °C; ^{1}H NMR (400 MHz/$CDCl_3$) δ 5.52 (s, 0.34 H, olefinic 4-H, enol form), 4.22 (s, 4 H, 2-H_2 and 6-H_2), 3.72 (s, 1.21 H, 4-H_2, diketone form); ^{13}C NMR (100 Mz/$CDCl_3$) δ 202.4 (3-C, 5-C, diketone form), 188.2 (3-C, 5-C, enol form), 101.6 (4-C, enol form), 74.0 (2-C, 6-C, diketone form), 68.2 (2-C, 6-C, enol form), 55.9 (4-C, diketone form); IR (KBr) 1644, 1549, 1423, 1231 cm^{-1}. Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.63; H, 5.15.

Acknowledgment. We thank Russell Hertzler for analytical support and Ian Marsden for helpful discussions on NMR issues.

Note Added after ASAP Publication. Author Sou-Jen Chang was added to the version published ASAP January 20, 2006; the corrected version was published ASAP January 27, 2006.

Supporting Information Available: Experimental procedures for compounds **5**, **6**, and **ABT-598** and ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **2**, **5**, **6**, and **ABT-598**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052226W

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