

# Concise Two-Step Synthesis of $\gamma$ -Pyrone from Acetone

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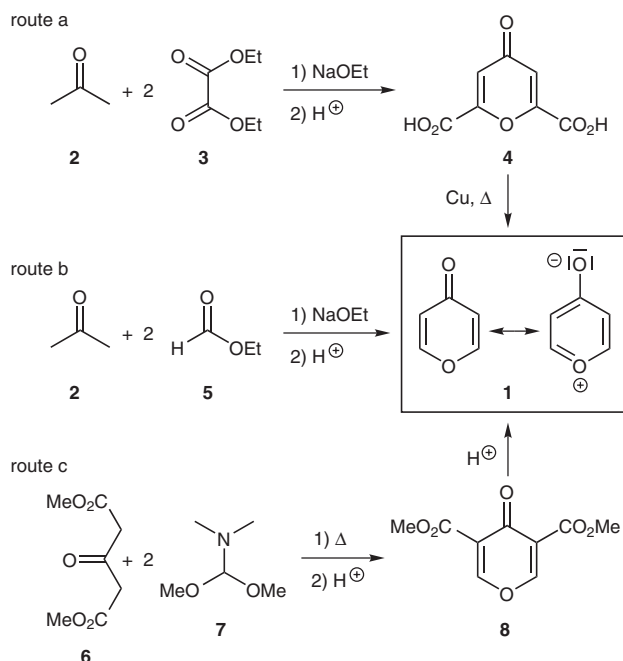
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**Abstract:**  $\gamma$ -Pyrone (**1**) is readily accessible in 59% overall yield via 1,1,5,5-tetraethoxy-3-pentanone (**10b**) and subsequent acidic hydrolysis. The synthesis enables an easy scale up, as demonstrated for intermediate **10b**.

**Key words:** diethoxymethylation, formylation,  $\gamma$ -pyrone, tetraethoxypentanone

In contrast to other heterocyclic compounds the tedious synthetic access to unsubstituted  $\gamma$ -pyrone (**1**) restricted severely its application as a heterocyclic building block.<sup>1</sup> Some known synthetic approaches to **1** are depicted in Scheme 1. Among the earliest procedures is the copper-promoted decarboxylation of chelidonic acid **4** developed by Willstätter and Pummerer (route a).<sup>2</sup> Although starting material **4** is available from acetone **2** and diethyl oxalate **3** via ester condensation,<sup>3</sup> the final decarboxylation requires temperatures up to 350 °C.<sup>4,5</sup> Neelakantan reported a direct ester condensation of acetone **2** and ethyl formate **5** to form  $\gamma$ -pyrone (**1**, route b),<sup>6</sup> however, no experimental details were given and our re-examination of this

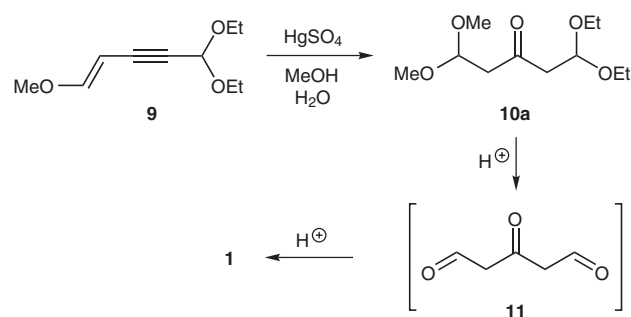


Scheme 1

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reaction did not result in any trace of the desired product **1**. In a patent of Takada and Adachi the synthesis of **1** from methyl acetonedicarboxylate **6** and *N,N*-dimethylformamide dimethylacetal (**7**) via diester **8** as the key intermediate (route c) is described.<sup>7</sup>

After considerable experimentation we found that the above mentioned procedures were not reliable on a gram scale. According to Dornow and Ische  $\gamma$ -pyrone (**1**) is accessible from the mixed acetal **10a** via intermediate bis-aldehyde **11**.<sup>8</sup> The mixed acetal **10a** was generated by oxymercuration of the ene-yne **9** (Scheme 2).



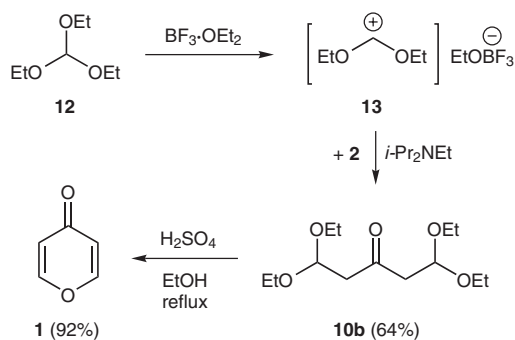
Scheme 2

On the basis of this method we developed an alternative route shown in Scheme 3. In an attempt to simplify the approach to **1** the symmetrical acetal **10b** was prepared following a method by Mock.<sup>9</sup> Triethyl orthoformate **12** was treated with  $\text{BF}_3 \cdot \text{OEt}_2$  to give the carbenium ion **13** which in situ underwent a formylation reaction with acetone **2** in the presence of the Hünig base, yielding bisacetal **10b** on a preparative scale in 64% after distillation.<sup>10</sup> The procedure of Antus<sup>11</sup> was modified for the hydrolysis of **10b**. Bisacetal **10b** was refluxed in the presence of sulfuric acid in EtOH to give  $\gamma$ -pyrone (**1**) in 92% yield after simple aqueous workup and evaporation of the solvent.<sup>12</sup>

In conclusion, a reliable synthesis of  $\gamma$ -pyrone (**1**) has been developed starting from inexpensive starting materials triethyl orthoformate and acetone, which allows an easy scale up. Tetraethoxypentanone **10b** could be isolated already on a multi-gram scale (10 g).

## Acknowledgment

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Scheme 3

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- (10) **Preparation of 1,1,5,5-Tetraethoxy-3-pentanone (10b) on a Multi-Gram Scale.**  
A solution of  $\text{BF}_3 \cdot \text{OEt}_2$  (46.60 mL, 0.36 mol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was added dropwise over 15 min to **12** (44.46 g, 0.30 mol) at  $-30$  °C. The stirred reaction mixture was warmed up to  $0$  °C for 20 min, and then cooled to  $-78$  °C. After addition of absolute acetone (4.41 mL, 0.06 mol),  $i\text{-Pr}_2\text{NEt}$  (55.5 mL, 0.36 mol) was added dropwise over 20 min. The reaction mixture was stirred at  $-78$  °C for 2.5 h, poured into concd  $\text{NaHCO}_3$  solution (500 mL), stirred for 10 min, and was then extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 100$  mL). The combined organic layers were washed successively with ice cold 2 N  $\text{H}_2\text{SO}_4$  (75 mL) and  $\text{H}_2\text{O}$  ( $2 \times 100$  mL), and dried ( $\text{MgSO}_4$ ). The solvent was removed under vacuum and the residue was distilled through a Vigreux column to give **10b** (10.10 g, 64%) as a light yellow liquid, bp  $105$  °C/0.18 mbar (bp  $71$ – $71.5$  °C/0.025 mm).<sup>9</sup>  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  = 1.19 (t,  $J$  = 7.0 Hz, 12 H, 7-H), 2.79 (d,  $J$  = 5.6 Hz, 4 H, 2-H, 4-H), 3.60 (m, 8 H, 6-H), 4.91 (t,  $J$  = 5.6 Hz, 2 H, 1-H, 5-H) ppm.  $^{13}\text{C}$  NMR (62 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  = 15.2 (C-7), 48.5 (C-6), 62.3 (C-2, C-4), 99.6 (C-1, C-5), 204.8 (C-3) ppm.
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- (12) **Preparation of  $\gamma$ -Pyrone (1) from Tetraethoxy-3-pentanone (10b).** In a sealed Schlenk flask a solution of **10b** (2.62 g, 10.0 mmol) in EtOH (50 mL) and 10%  $\text{H}_2\text{SO}_4$ – $\text{H}_2\text{O}$  (5 mL) was heated at  $80$  °C for 24 h. The reaction mixture was then neutralized with  $\text{NaHCO}_3$  (1.60 g), and the solvents were removed under vacuum. The residue was extracted with absolute benzene. Concentration of the combined extracts gave **1** (881 mg, 9.2 mmol, 92%) as a light yellow oil, which crystallized rapidly under vacuum. The crystals liquefy at r.t. (mp  $32.5$  °C).<sup>2</sup>  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  = 5.88 (d,  $J$  = 6.4 Hz, 2 H, 3-H, 5-H), 6.58 (d,  $J$  = 6.3 Hz, 2 H, 2-H, 6-H) ppm.  $^{13}\text{C}$  NMR (62 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  = 118.6 (C-2, C-5), 154.6 (C-3, C-6), 176.5 (C-4) ppm.