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Reaction of Ethyl Acetoacetate with *p*-Toluenesulfonic Acid: Formation of Ethyl Isodehydroacetate and/or Ethyl *p*-Toluenesulfonate

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Treatment of ethyl acetoacetate with anhydrous *p*-toluenesulfonic acid at room temperature led to ethyl isodehydroacetate (1) in high yield by acid-catalyzed condensation. On the other hand, in refluxing toluene, the unexpected ethyl ester of *p*-toluenesulfonic acid (2) was formed in moderate yield. This constitutes a new direct esterification of arenesulfonic acids.

Keywords——ethyl acetoacetate; *p*-toluenesulfonic acid; ethyl isodehydroacetate; ethyl *p*-toluenesulfonate; condensation; direct esterification

Ethyl isodehydroacetate (1) is important as an intermediate in the synthesis of polysubstituted aromatic compounds.[1] This compound has been prepared by condensation of ethyl acetoacetate in the presence of an acidic condensing agent such as concentrated sulfuric acid[2] or dry hydrogen chloride.[3] However, these methods do not appear to be of general utility for large-scale preparation, because of difficulty in the disposal of large amounts of mineral acids after the reaction and because of the corrosive action of the condensing agents on the reaction vessel and associated equipment. The present work was undertaken in order to establish an effective means of preparing **1** from ethyl acetoacetate by using *p*-toluenesulfonic acid, which can be readily recovered as a solid from the reaction mixture and is convenient to handle. However, during the course of studying the influence of reaction temperature, we have encountered a novel sulfonic ester-forming reaction. We now wish to report our results on this reaction.

First, the condensation of ethyl acetoacetate to **1** in the presence of anhydrous *p*-toluenesulfonic acid which was prepared by dehydration of commercial monohydrate at 130°C (4 mmHg) was examined at ambient temperature (Chart 1). We found that the desired cyclic compound (1) was obtained in good yields, as shown in Table I. The structure of the product was identified as **1** by comparison of the infrared (IR) and nuclear magnetic resonance (NMR) spectra with those of an authentic sample which was prepared according to the literature method.[2] *p*-Toluenesulfonic acid was recovered quantitatively in all cases.

The best yield of **1** was obtained when, after pre-warming a mixture of ethyl acetoacetate with only[4] 0.76 eq of the sulfonic acid at 30°C for 5 h, the solution was then allowed to stand at room temperature for 3 d. Similar treatment using commercial monohydrate instead of anhydrous acid resulted in recovery of the starting materials. These results may be ascribed to the solubility of the acidic reagent in the substrate: the anhydrous acid is soluble in ethyl acetoacetate, while the hydrate is relatively insoluble.

TABLE I. Reaction of Ethyl Acetoacetate with *p*-Toluenesulfonic Acid at Room Temperature: Formation of **1**

Run	Molar eq of TsOH	Time (h)	Yield of **1** (%)
1	0.76	24	35 (29)[a]
2	0.76	72	61 (48)
3	0.76	96	60 (50)
4	1.10	50	Trace[b]
5	1.50	50	62 (51)

[a] ( ): yield after redistillation.
[b] The reaction was carried out at 5—10 °C. Thin layer chromatography of the reaction mixture showed the presence of a small amount of **1**, which could not be isolated.
Ethyl acetoacetate was recovered nearly quantitatively.

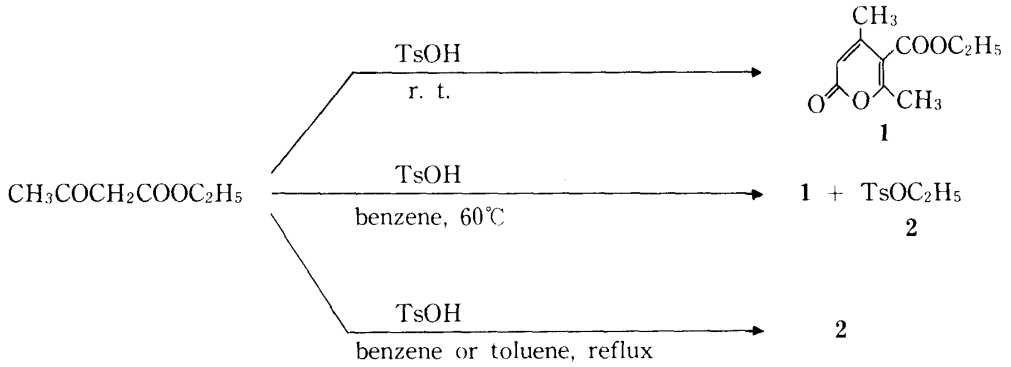

Chart 1

It has been reported that the condensation of ethyl acetoacetate in the presence of concentrated sulfuric acid resulted in the formation of free isodehydroacetic acid as well as the ethyl ester (**1**).[4] However, in our hands, the free acid, which can only be esterified with difficulty,[2] was not obtained from the reaction mixture and the ester (**1**) was produced in higher yield as compared to the reported procedure. This suggests that under our conditions using the anhydrous acid ethyl acetoacetate is not hydrolyzed and affords only the ester (**1**) by condensation. Accordingly, *p*-toluenesulfonic acid is an effective and convenient reagent for this condensation.

A study of the influence of temperature indicated that the yields were poor at lower temperature (run 4). Increasing the ratio of the sulfonic acid to the ester did not significantly increase the yields. In conclusion, our procedure is greatly superior to the literature procedures for the preparation of **1** in terms of yiled of the desired ester and recovery of condensing agent.

Next, while carrying out the reaction at further elevated temperature in refluxing benzene, we found a novel synthetic reaction yielding an unusual product which was identified as ethyl *p*-toluenesulfonate (**2**) by comparison of its IR and NMR spectra with those of an authentic sample. Thus, when a solution of ethyl acetoacetate and one molar eq of anhydrous sulfonic acid in dry benzene was refluxed under standard azeotropic conditions for 24 h, **2** was obtained in 15% yield, though it was contaminated by small amounts of **1**. The use of *p*-toluenesulfonic acid obtained by refluxing a solution of commercial monohydrate in dry benzene through a Dean–Stark trap for 3 h until no more water was collected gave similar results. Accordingly, further examination of the reaction under various reaction conditions was carried out by employing the sulfonic acid described above.

Interestingly, attempts to examine the reaction of ethyl acetoacetate with one molar eq of sulfonic acid at lower temperature (60°C) for 2 d led to **1** as the major product in 28% yield, along with **2** in 5% yield. This result demonstrated that the yield of **2** depended on the reaction temperature and also that the condensation of ethyl acetoacetate proceeded at elevated temperature even with the sulfonic acid obtained from the monohydrate by azeotropic removal of water. The temperature dependence of the product ratio (**1**: **2**) was further established when it was found that the use of toluene led to a noticeable increase of yield and no formation of **1**, as shown in Table II (run 5).

The yield of **2** also depended on the amount of the sulfonic acid. Better yields were obtained in the presence of 3 molar eq (runs 4, 5). These results suggest that the sulfonic acid can serve as a source of nucleophile which attacks the ethyl group of the protonated carboxylic acid ester to lead to the formation of the ethyl ester of the sulfonic acid, and a large excess of the sulfonic acid was used to induce a higher concentration of protonated acid ester, which favored the nucleophilic displacement.

This new finding appears to be the first example of the direct esterification of an arenesulfo-

Table II. Reaction of Ethyl Acetoacetate with *p*-Toluenesulfonic Acid at ElevatedTemperature: Formation of **1** and **2**

Run	Molar eq of TsOH	Solvent	Reaction conditions	Yield (%) **1**	Yield (%) **2**
1	1	Benzene	Reflux, 24 h	Trace	15
2	1	Benzene	60 °C, 72 h	28	5
3	2	Benzene	Reflux, 24 h	—	26
4	3	Benzene	Reflux, 24 h	—	37
5	3	Toluene	Reflux, 24 h	—	50
6	4	Benzene	Reflux, 24 h	—	38

nic acid with a common carboxylic acid ester. The novel reaction of *p*-toluenesulfonic acid prompted us to initiate a further study on its scope and mechanism, and this is in progress.

Experimental

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in chloroform-*d* solution on a JEOL JNH-MH-100 spectrometer using tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained in the liquid state on a JASCO IRA-2 spectrophotometer. Microanalyses were performed in the Microanalytical Laboratory of this school by Mrs. R. Igarashi. Column chromatography was performed on Merck silica gel 60 (70—230 mesh).

Ethyl 2,4-Dimethyl-6-oxo-pyran-3-carboxylate (1) (Ethyl Isodehydroacetate)——A mixture of ethyl acetoacetate (17.0 g, 131 mmol) and anhydrous *p*-toluenesulfonic acid (17.2 g, 100 mmol), obtained by dehydration of the commercial monohydrate at 130°C (4 mmHg) for 2 h, was stirred at 30°C for 5 h, then allowed to stand for 3 d at room temperature. Ice water was added and the mixture was extracted with benzene, dried over anhydrous sodium sulfate, and concentrated to a yellow oil under reduced pressure. Distillation of the oil under reduced pressure recovered 4.6 g of ethyl acetoacetate and then yielded 7.8 g (61%) of **1** as a pale yellow oil: bp 118—122°C (2 mmHg) [lit.[2a] bp 185—192°C (35 mmHg), yield 27—36%]. Redistillation of the oil gave 6.2 g (48%) of pure **1** as a colorless oil: bp 119—120°C (2 mmHg). The yield was 65% based on unrecovered starting material. *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.03; H, 6.40. IR ν_{max}^{neat} cm^{-1}: 1730 (CO). NMR ($CDCl_3$) δ: 1.38 (3H, t, $J=7$ Hz, $CH_2\underline{CH_3}$), 2.22 (3H, s, CH_3), 2.40 (3H, s, CH_3), 4.17 (2H, q, $J=7$ Hz, $\underline{CH_2}CH_3$), 6.03 (1H, s, =CH–).

Formation of 1 and 2——A mixture of ethyl acetoacetate (13.0 g, 100 mmol) and *p*-toluenesulfonic acid, obtained by refluxing a solution of commercial monohydrate (19.0 g, 100 mmol) in dry benzene (30 ml) through a Dean-Stark trap for 3 h, was stirred at 60°C for 2 d. Ice water was added to the reaction mixture. The whole was extracted with benzene, and the extract was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting oil was distilled. The fraction with bp 85—125°C (2 mmHg) was purified by column chromatography (silica gel, benzene), affording 2.72 g (28%) of **1** and 1.0 g (5%) of **2**.

Ethyl *p*-Toluenesulfonate (2)——Commercial *p*-toluenesulfonic acid monohydrate (19.1 g, 100 mmol) in dry toluene (30 ml) was refluxed with azeotropic removal of water using a Dean-Stark trap for 3 h. Ethyl acetoacetate (4.4 g, 34 mmol) was added to the solution and the mixture was refluxed for 24 h, then cooled at room temperature. Cold water was added and the mixture was extracted with benzene. The extract was dried over anhydrous sodium sulfate, and concentrated to a pale yellow oil. Distillation of the oil under reduced pressure gave 3.38 g (50%) of **2** as a colorless oil: bp 122—123°C (2 mmHg) [lit.[5] bp 165—166°C (9 mmHg)]. The oil immediately crystallized: mp 32—33°C (lit.[6] mp 33—34°C). *Anal.* Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04. Found: C, 54.08; H, 6.01. IR ν_{max}^{neat} cm^{-1}: 1360 (SO_3), 1180 (SO_3). NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz, CH_3), 2.45 (3H, s, $J=7$ Hz, CH_3), 4.12 (2H, q, $J=7$ Hz, $\underline{CH_2}CH_3$), 7.39 (2H, d, $J=9$ Hz, aromatic H), 7.82 (2H, d, $J=9$ Hz, aromatic H).

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