# Ethyl 5-[(4-Methylphenyl)sulfonyl]-3-Oxopentanoate: A Bench-Stable Synthon for Ethyl 3-Oxopent-4-enoate (Nazarov's Reagent)

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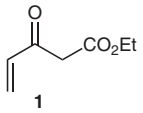
**Abstract:** The easily available adducts of sodium *p*-toluenesulfinate to both acrylonitrile or acrylic acid were efficiently transformed through a two-step, high-yielding sequence into ethyl 5-[(4-methylphenyl)sulfonyl]-3-oxopentanoate, a convenient source for the popular Nazarov's reagent, ethyl 3-oxopent-4-enoate, which could be generated in situ by base-induced β-elimination and used for annulation reactions.

**Key words:** Nazarov's reagent, annulations, tandem reactions, bicyclic compounds, carbocycles

Ethyl 3-oxopent-4-enoate (**1**, Nazarov's reagent, Figure 1)[1] is a well-known annulating agent extensively used for several transformations, including Robinson annulation of cyclic β-diketones,[2] cycloalkanones[3] or the corresponding enamines,[4] and cyclic imidates.[5] Moreover, its versatility has been further extended to the synthesis of 4-piperidones[6] and carbocyclic β-keto esters.[7]




**1**

**Figure 1**

A number of preparations of **1** and its analogues has been developed since the original work of Nazarov and Zav'yalov in 1953,[1a] including β-elimination from latent enone precursors,[2b,4b,5a,8] pyrolysis,[9a] and rhodium(II)acetate-catalyzed transformations of suitable α-diazo-β-hydroxy esters,[9b,c] as well as retro Diels–Alder reaction of formal cyclopentadiene adducts.[2c,10] The applicability of most of these protocols has been hampered either by poor yields, difficulty accessible starting materials, and/or requirement of special apparatus.

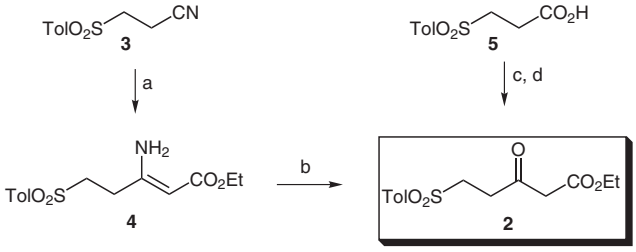
The most reliable procedure for the synthesis of **1** and its analogues[11] entailed on the oxidation of the β-hydroxy esters derived by 1,2-addition of a lithioalkyl acetate to acrolein and the red-written warning 'the product is volatile and will be lost by evaporation if care is not taken' highlighted the main drawback of the checked protocol.[11b]

Consequently, the development of suitable precursors allowing the in situ generation of Nazarov's reagents, thereby eliminating the need for their isolation, may be particularly useful.

In connection with our continuous interest in the synthesis of new reagents acting as latent enone precursors,[12] we envisaged the hitherto unknown ethyl 5-[(4-methylphenyl)sulfonyl]-3-oxopentanoate (**2**) as a new synthon for **1**, a base-induced elimination of the γ-keto sulfone moiety being required for the introduction of the unsaturation conjugated to the carbonyl group.

The preparation of **2** has been efficiently achieved by two different synthetic routes[13] starting from easily available adducts **3**[14] and **5**[15] of sodium *p*-toluenesulfinate to acrylonitrile or acrylic acid, respectively (Scheme 1).

The required two-carbon elongation has been accomplished through Blaise reaction of **3** with ethyl bromoacetate and in situ activated zinc by action of a catalytic amount of methanesulfonic acid.[16] The intermediate β-aminoacrylate **4** was then hydrolyzed by aqueous HCl solution to afford β-ketoester **2** in 75% overall yield.




**Scheme 1** *Reagents and conditions*: (a) Zn, $BrCH_2CO_2Et$, MsOH, THF, reflux, 3 h; (b) HCl, THF, r.t., 2 h, 75% from **3**; (c) 1,1′-carbonyldiimidazole, THF, r.t., 4 h; (d) $HO_2C(CH_2)CO_2Et$, $Mg(OEt)_2$, THF, r.t., 12 h, 80% from **5**.

Alternatively, the β-ketoester **2** was obtained in 80% yield through chain elongation of the acid derivative **5** via activation of the carboxyl group as imidazolide followed by reaction with the neutral magnesium salt of monoethyl malonate according to the procedure developed by Masamune et al.[17]

The new reagent **2** is a white powder, bench-stable, that can be stored indefinitely at room temperature without special precautions.[18]

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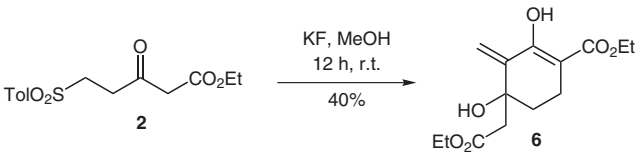
A preliminary investigation of its chemical behavior in the presence of different bases led us to discover that a smooth transformation took place by treatment with potassium fluoride in MeOH at room temperature,[19] leading to the formation of the cyclic β-ketoester **6**, other basic reagents being ineffective or causing polymerization (Scheme 2).




**Scheme 2**

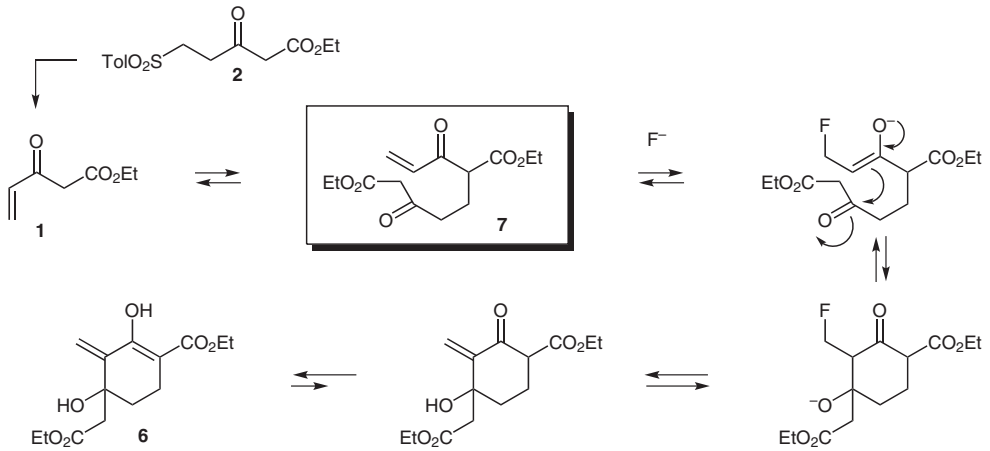
Interestingly, the highly functionalized cyclohexane derivative **6** was also formed submitting freshly prepared **1** to identical reaction conditions.

A plausible mechanism to explain the formation of **6** is likely to involve elimination of *p*-toluenesulfinic acid as the first event leading to the formation of **1**, which underwent an intermolecular base-induced Michael reaction producing the nonisolated intermediate **7** (Scheme 3). This was eventually converted into **6** through an intramolecular Morita–Baylis–Hillman reaction[20] promoted by fluoride-ion activation of the double bond.[21]

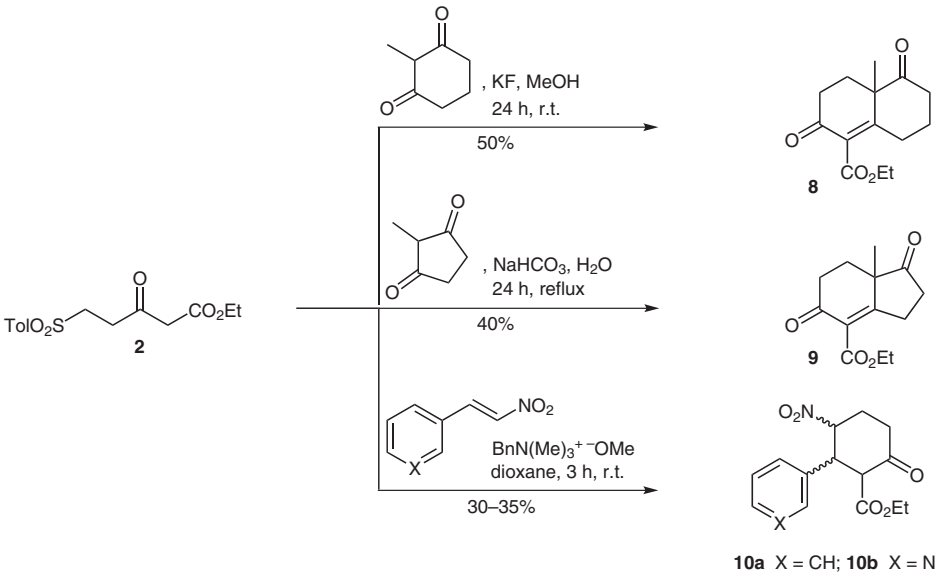
In order to test the utility of **2** as source of **1**, we next examined its behavior in several model reactions described in the literature in which **1** has been directly applied.[2]

Thus, the annulated product **8** could be obtained when **2** was reacted with 2-methylcyclohexane-1,3-dione in MeOH in the presence of potassium fluoride (Scheme 4), the overall 50% yield of isolated product comparing well with the existing data.[2d–2f]

Surprisingly, we were unable to obtain the bicyclic ester **9**[2a–2c] by the reaction of **2** with 2-methylcyclopentane-1,3-dione under the same conditions. However, the expected annulation leading to **9** was successfully accomplished in 40% yield performing the reaction in boiling aqueous 0.1 N $NaHCO_3$ according to a known procedure.[2c]




**Scheme 3**




**Scheme 4**

Moreover, we extended the use of the masked Nazarov's reagent **2** as counterpart of β-nitrostyrenes in a tandem Michael reaction promoted by benzyl trimethylammonium methoxide producing in unoptimized moderate yields diastereomeric mixtures of the completely enolized cyclic β-ketoesters **10**, which could be partially separated by silica gel column chromatography.[22]

Interestingly, Takemoto et al.[23] investigating the bifunctional thiourea-catalyzed enantioselective double Michael addition of **1** to nitroalkenes could not obtain either Michael adducts or the desired cyclized product, the reaction giving rise to a complex mixture owing to the instability of **1**.

In conclusion, solid crystalline and bench-stable 5-[(4-methylphenyl)sulfonyl]-3-oxopentanoate (**2**) was shown to serve as an excellent precursor for Nazarov's reagent **1**. Its facile preparation from easily available chemicals and the mild conditions required for the in situ demasking of the enone moiety make the new reagent an attractive tool for obtaining a wide variety of carbo- and heterocyclic compounds.

## Acknowledgment

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## References and Notes

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(13) **Typical Procedures for the Preparation of Compound 2**
**Method A**: A stirred suspension of zinc dust (3.8 g, 58.1 mmol) in THF (28 mL) was treated with MsOH (0.14 mL, 2.2 mmol) and heated at reflux for 10 min. Ethyl bromoacetate (1.0 mL, 9.0 mmol) was added dropwise until it turned green, then **3** (4.0 g, 19.1 mmol) was added. Ethyl bromoacetate (4.0 mL, 36.1 mmol) was successively dropped over a period of 30 min. The reaction mixture was refluxed for 3 h, cooled to 0 °C, and treated with 10% HCl (28 mL). The solution was stirred at r.t. for 2 h, then the solvent was concentrated in vacuo. The residue was extracted with EtOAc (3 × 60 mL), the combined organic phases were washed with brine (2 × 100 mL), and dried ($Na_2SO_4$). The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc–PE, 1:2) to afford **2** (4.3 g, 75%).
**Method B**: 1,1′-Carbonyldiimidazole (3.5 g, 21.6 mmol) was added to a solution of the acid **5** (4.0 g, 17.5 mmol) in THF (100 mL). The mixture was stirred at r.t. for 4 h, then the magnesium salt of monoethyl malonate [prepared by stirring monoethyl malonate (4.54 mL, 38.5 mmol) and magnesium ethoxide (2.8 g, 24.5 mmol) in THF (80 mL) for 1 h at r.t.] was added and stirring was continued at r.t. overnight. The solvent was removed at reduced pressure and the residue treated with 1.5 N HCl (80 mL) and extracted with EtOAc (100 mL). The aqueous phase was further extracted with EtOAc (2 × 100 mL), the combined extracts were washed with aq sat. $NaHCO_3$ soln and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the oily residue by flash chromatography (EtOAc–PE, 1:2) gave **2** (4.2 g, 80%).

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(18) **Selected Analytical Data for Compound 2**
White solid, mp 44–45 °C (*n*-hexane). IR: 1740, 1718, 1597 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.04 (t, *J* = 7.2 Hz, 2 H), 3.37 (t, *J* = 7.2 Hz, 2 H), 3.46 (s, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 14.11, 21.72, 35.66, 49.12, 50.52, 61.76, 128.07, 130.13, 135.87, 145.18, 166.56, 198.68. Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.20; H, 6.23.

(19) **Typical Procedure for the Preparation of Compound 6**
A solution of **2** (0.2 g, 0.67 mmol) and KF (0.16 g, 2.75

mmol) in MeOH (10 mL) was stirred at r.t. for 12 h. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography (EtOAc–PE, 1:3) yielding **6** as a colorless oil (76 mg, 40%). IR: 3474, 1697, 1655, 1584 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.72–1.84 (m, 1 H), 1.90–2.00 (m, 1 H), 2.18–2.30 (m, 1 H), 2.48–2.52 (m, 1 H), 2.53–2.58 (m, 2 H), 4.13–4.30 (m, 4 H), 4.47 (s, 1 H), 5.73 (s, 1 H), 6.02 (s, 1 H), 12.09 (s, enol OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 14.13, 14.24, 19.95, 34.02, 42.04, 60.81, 61.06, 71.04, 97.80, 115.83, 143.56, 162.24, 172.52. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.20; H, 7.00.

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(22) **Selected Analytical Data for Compounds 10a and 10b**
**Compound 10a**: colorless oil. IR: 1706, 1650, 1620, 1545 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ (less polar isomer) = 0.95 (t, *J* = 7.2 Hz, 3 H), 2.00–2.12 (m, 1 H), 2.36–2.70 (m, 3 H), 3.96–4.08 (m, 2 H), 4.56–4.63 (m, 1 H), 4.70–4.76 (br, 1 H), 7.17–7.37 (m, 5 H), 12.55 (s, enol OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ (less polar isomer) = 13.70, 20.87, 24.83, 42.46, 60.62, 85.99, 96.79, 127.31, 127.60, 128.77, 141.34, 171.41. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88. Found: C, 61.91; H, 5.80.
**Compound 10b**: colorless oil. IR: 1710, 1660, 1610, 1550 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ (more polar isomer) = 0.96 (t, *J* = 7.2 Hz, 3 H), 2.00–2.13 (m, 1 H), 2.40–2.76 (m, 3 H), 3.93–4.10 (m, 2 H), 4.50–4.60 (m, 1 H), 4.70–4.80 (br, 1 H), 7.20–7.30 (m, 1 H), 7.46–7.53 (m, 1 H), 8.46–8.56 (br, 2 H), 12.56 (s, enol OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ (more polar isomer) = 13.81, 21.24, 25.02, 40.45, 60.94, 85.67, 96.04, 123.66, 135.15, 137.03, 148.89, 149.53, 170.98, 171.98. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52. Found C, 57.50; H, 5.60.

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