A New Synthesis of 5,7-Dicarboxy-2,1-benzisoxazolin-3-one

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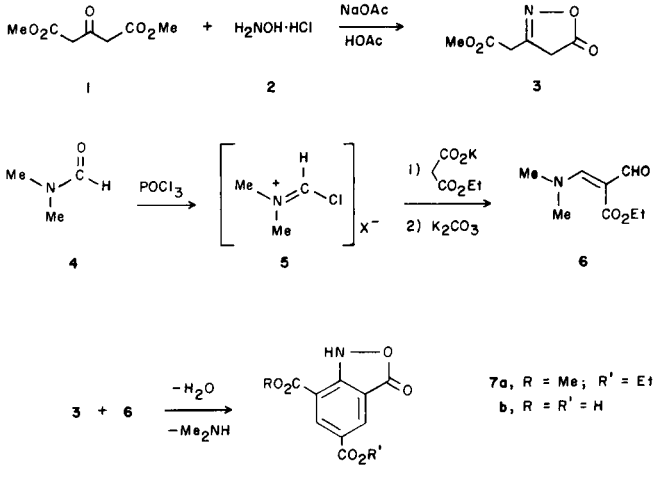
Received May 17, 1984

Condensation of methyl 2-isoxazolin-5-on-3-yl acetate (**3**) and 3-(*N,N*-dimethylamino)-2-ethoxycarbonylacrolein (**6**) gave 5-ethoxycarbonyl-7-methoxycarbonyl-2,1-benzisoxazolin-3-one (**7a**). Simple hydrolysis of the diester **7a** afforded 5,7-dicarboxy-2,1-benzisoxazolin-3-one (**7b**).

J. Heterocyclic Chem., **22**, 127 (1985).

5,7-Dicarboxy-2,1-benzisoxazolin-3-one (**7b**) is a key building block of positive-working photographic dye releasers [1]. This compound was prepared by reductive cyclization of nitrotrimesic acid which was obtained from nitromesitylene by a difficult potassium permanganate oxidation process [1-3]. We report herewith a novel synthesis of benzisoxazolinone **7b** without using the nitrotrimesic acid precursor.

Our new synthesis consists of (a) preparation of an isoxazolinone **3**, which corresponds to the upper half part of the molecule **7**; (b) preparation of a malondialdehyde derivative **6**, which corresponds to the lower half part of the molecule **7**; and (c) condensation of those two parts, **3** and **6**, to give the benzisoxazolinone derivative **7a** which, upon hydrolysis, would afford the desired 5,7-dicarboxy-2,1-benzisoxazolin-3-one (**7b**).



The reaction of commercially available dimethyl acetone-dicarboxylate (**1**) with hydroxylamine hydrochloride (**2**) and sodium acetate in acetic acid gave the isoxazolinone **3** in 77% yield. The isoxazolinone **3** is a low melting colorless solid which slowly turns to dark brown oil upon standing at room temperature. However, it can be stored in a refrigerator for a long period of time without any significant change in color and physical state.

The preparation of the malondialdehyde derivative **6** was reported by Arnold [4], and involved the reaction of a Vilsmeier complex **5**, derived from *N,N*-dimethylformamide (**4**) and phosphorus oxychloride, with potassium ethyl malonate [5]. The aldehyde **6** is a fairly stable viscous oil.

For the condensation of isoxazolinone **3** and malondialdehyde derivative **6**, piperidinium acetate is a typical catalyst for the Knoevenagel condensation reaction of active methylene compounds with aldehydes and ketones [6] was first employed. However, the reaction mixture turned to dark brown and gave a multiple product mixture from which the desired benzisoxazolinone **7a** was isolated in only about 25% yield. It was believed that water and dimethylamine formed during the condensation reaction reacted with starting materials as well as products and led to the formation of multiple products. Thus, we attempted to use sodium acetate in acetic acid in the presence of acetic anhydride for the condensation reaction. It was hoped that the acetic anhydride may generate inert species such as acetic acid and *N,N*-dimethylacetamide instead of reactive species such as water and dimethylamine during the condensation reaction. Indeed, the condensation of **3** and **6** using sodium acetate in acetic acid with an excess of acetic anhydride proceeded very smoothly and much more cleanly, and gave mainly a new product which seemed to be *N*-acetyl derivative of benzisoxazolinone **7a**. This new product was not isolated and instead treated briefly with hydrochloric acid in methanol to give the desired benzisoxazolinone **7a** in 56% yield.

Simple hydrolysis of the diester **7a** with sodium hydroxide and subsequent acidification afforded the 5,7-dicarboxy-2,1-benzisoxazolin-3-one (**7b**).

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4220 Spectrophotometer. A Varian EM 360 NMR Spectrometer was used for ^{1}H-nmr spectra with tetramethylsilane as an inernal standard. Precoated silica gel 60F-254 plates made by EM Reagents were used for thin layer chromatography (tlc). Elemental analyses were performed by Research Laboratories, Kodak Park, Eastman Kodak Company.

Methyl 2-Isoxazolin-5-on-3-ylacetate (**3**).

A mixture of 34.8 g (0.5 mole) of hydroxylamine hydrochloride, 41.0 g (0.5 mole) of sodium acetate, and 250 ml of acetic acid was stirred at room temperature for 15 minutes. The mixture was cooled to 15° and

87.1 g (0.5 mole) of dimethyl acetone-dicarboxylate (**1**) was added dropwise over a 20 minute period. The reaction mixture was stirred at room temperature for 1 hour an then heated to 80 ~ 90° on a steam bath for 30 minutes. The mixture was treated with decolorizing carbon, filtered, and the acetic acid was removed by distillation under a reduced pressure. To the residual oil was added 25 ml of water and the oily product was extracted with dichloromethane. The dichloromethane solution was dried over anhydrous magnesium sulfate and concentrated to an oil which was dissolved in 75 ml of toluene and chilled to −5° ~ −10°. The resulting crystalline solid was collected, washed with cold toluene and hexane, and dried in a vacuum oven at room temperature. There was obtained 60.5 g (77%) of **3** as colorless solid, mp 37-39°; ir (potassium bromide): 1790, 1730, and 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 (s, 2H, $-CH_2CO_2CH_3$), 3.68 (s, 2H, $-CH_2-$ at ring C-4), and 3.80 (s, 3H, CO_2CH_3).

Anal. Calcd. for $C_6H_7NO_4$: C, 45.9; H, 4.5; N, 8.9. Found: C, 45.5; H, 4.4; N, 8.8.

This compound turned to yellow solid and then to brown oil upon standing at room temperature for a long period of time. It should be stored in a refrigerator.

3-(*N,N*-Dimethylamino)-2-ethoxycarbonylacrolein (**6**).

This compound was prepared by following the procedure described by Arnold [4], bp 110 ~ 112° (uncorrected)/0.05 mm Hg; ir (neat film): 1680, 1650, 1630, and 1575 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (t, 3H, $-OCH_2CH_3$), 3.19 and 3.38 (two s, 3H, each, $-N(CH_3)_2$), 4.23 (q, 2H, $-OCH_2CH_3$), 7.80 (s, 1H, $-CH=$), and 9.79 (s, 1H, $-CHO$).

5-Ethoxycarbonyl-7-methoxycarbonyl-2,1-benzisoxazolin-3-one (**7a**).

(a) Using Piperidinium Acetate.

A mixture of 1.57 g (10 mmoles) of **3**, 1.71 g (10 mmoles) of **6**, 0.85 g of piperidine, and 0.5 g of acetic acid in 20 ml of pyridine was heated under gentle reflux (105°) for 30 minutes. The color of the reaction mixture was turned to dark brown during this heating period. The pyridine was removed by distillation under a reduced pressure and the residue was taken up into 100 ml of ethyl acetate. The dark brown ethyl acetate solution was treated with carbon, filtered, and washed with water, dilute hydrochloric acid, and water again. The solution was dried over anhydrous magnesium sulfate, concentrated to about 10 ml under a reduced pressure, and allowed to stand at room temperature for 1 hour. There was obtained 0.65 g (25%) of **7a** as yellow solid, mp 149-150° dec; ir (potassium bromide): 3260, 1780, 1760, 1700, 1680, and 1610 cm^{-1}; ^1H nmr (hexadeuteriodimethylsulfoxide): δ 1.40 (t, 3H, $-OCH_2CH_3$), 4.00 (s, 3H, OCH_3), 4.38 (q, 2H, $-OCH_2CH_3$), 8.37 and 8.51 (d and d, J = 1.0 Hz, 2H, aromatic C-4 and C-6*H*).

Anal. Calcd. for $C_{12}H_{11}NO_6$: C, 54.3; H, 4.2; N, 5.3. Found: C, 54.3; H, 4.4; N, 5.2.

The filtrate from **7a** contained at least seven unknown products in addition to a small amount of desired product according to tlc.

(b) Using Sodium Acetate and Acetic Anhydride.

A mixture of 3.14 g (20 mmoles) of **3**, 3.42 g (20 mmoles) of **6**, and 1 g of sodium acetate in 10 ml of acetic anhydride and 20 ml of acetic acid was heated under reflux for 1 hour. The reaction mixture was cooled to room temperature, drowned-out into 100 ml of water, and the mixture was stirred for 30 minutes. The resulting mixture was extracted with toluene. The toluene solution was dried over anhydrous magnesium sulfate and evaporated to dryness on a rotary evaporator. The resulting brown gummy residue whose tlc showed one new major spot, probably *N*-acetyl derivative of **7a**, was dissolved in 40 ml of methanol containing 2 ml of concentrated hydrochloric acid. The solution was warmed briefly to 40° and stirred at room temperature for 1 hour. After cooling in an ice bath for 30 minutes, the product was collected, washed with chilled methanol and ethyl acetate, and dried. There was obtained 2.95 g (56%) of **7a** as yellow solid, whose mp, ir and ^1H nmr spectra were identical with that obtained in (a) above.

5,7-Dicarboxy-2,1-benzisoxazolin-5-one (**7b**).

A mixture of 2.65 g (10 mmoles) of **7a**, 20 ml of methanol, 30 ml of water, and 2 g of 50% sodium hydroxide was heated under reflux for 30 minutes. The methanol was removed by distillation under a reduced pressure and the aqueous mixture was acidified with 6*N* sulfuric acid. The mixture was stirred for 1 hour and extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous magnesium sulfate, treated with carbon, and evaporated to dryness. The residue was recrystallized from *n*-butanol to give 1.6 g (72%) of **7b** as pale yellow solid, whose mp, ir and ^1H nmr spectra were identical with those of an authentic sample prepared by the existing procedure [1].

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