Unusual aluminum chloride-assisted conversion of isopropenyl acetate into 3-acetyl- and 3,5-diacetyl-2,6-dimethyl-4*H*-pyran-4-ones

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Reflux of isopropenyl acetate with an excess of $AlCl_3$ in 1,2-dichloroethane affords 3,5-diacetyl-2,6-dimethyl-4*H*-pyran-4-one in 17% yield. The mild acidic cleavage of the latter (2% HCl, 20 °C, 16 h) gives 3-acetyl-2,6-dimethyl-4*H*-pyran-4-one in 87% yield, whereas this reaction under more drastic conditions (17% HCl, reflux, 3 h) gives 2,6-dimethyl-4*H*-pyran-4-one in 61% yield.

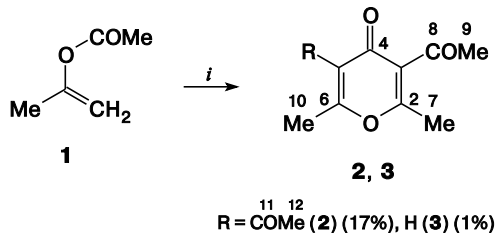
Key words: isopropenyl acetate, aluminum chloride, acetylacetone, γ-pyrones, heterocyclization.

3,5-Diacyl-2,6-dialkyl-γ-pyrones are of interest as polyfunctional synthons for the synthesis of various biologically active compounds.[1—3] Syntheses of γ-pyrones of this type based on reactions of copper salts of 1,3-diketones (for instance, acetylacetone or benzoylacetone) with phosgene[4] and disodium salt of heptane-2,4,6-trione (diacetylacetone) with acid halides (for example, with acetyl chloride or benzoyl chloride)[5] have been known very long ago. Later a simple synthesis through the electrophilic substitution of hydrogen atoms in positions 3 and 5 of 2,6-dialkyl-γ-pyrones for acyl groups under the action of acid anhydrides or halides was elaborated.[6] The simplest method for the synthesis of the initial 2,6-dialkyl-γ-pyrones with identical or different lower alkyl substituents is the cyclocondensation of two molecules of aliphatic acid (or a mixture of such acids) or its anhydride in polyphosphoric acid at 200 °C.[7] The yields of γ-pyrones are 60—70%. A more efficient and universal method for the preparation of 2,6-dialkyl-γ-pyrones is the cyclization of the dienol form of 1,3,5-triketones, whose synthesis proceeds by the acylation of the acetylacetone dianion generated by a strong base.[8] Cyclodehydration of these triketones usually occurs under mild conditions.

We found that the reflux of 1 mole of isopropenyl acetate (**1**) with 2 moles of anhydrous $AlCl_3$ in anhydrous 1,2-dichloroethane for 1 h unexpectedly resulted in poorly accessible γ-pyrone **2** in 17% yield (Scheme 1).

An insignificant amount (~1%) of known γ-pyrone **3** was also detected in the reaction products. No formation of γ-pyrones **2** and **3** was observed in the absence of $AlCl_3$. An increase in the reaction duration to 8 h decreases the yield of γ-pyrone **2** by two times. At room temperature the reaction proceeds slowly, and after 24 h the yield of γ-pyrone **2** does not exceed 4%. Under these conditions, γ-pyrone **3** (~0.4%), acetylacetone, triacetylmethane, and diacetylacetone were formed. The structures of these compounds were established based on the IR and ^{1}H NMR spectroscopic data. According to the ^{1}H NMR spectra ($CDCl_3$), acetylacetone is a mixture of diketo and enol forms (18 and 82%, respectively); diacetylacetone represents a mixture of triketo, monoenol, and dienol forms (14, 62, and 24%, respectively); triacetylmethane exists in solution only as enol (*cf.* Refs 9 and 10). No traces of its triketo form were observed in the spectrum. It should be noted that the earlier published data on the ^{1}H NMR spectrum of diacetylacetone[11] differ by the mistaken assignment of signals of several ^{1}H nuclei.

Scheme 1



i. 2 $AlCl_3$, $C_2H_4Cl_2$, Δ, 1 h.

The structures of γ-pyrones **2** and **3** were determined based on the IR spectroscopy, 1D and 2D ^{1}H and ^{13}C NMR, and mass spectrometry data.

The IR spectra ($CHCl_3$) of γ-pyrones **2** and **3** are consistent with the known IR spectra (KBr) of γ-pyrone **2**

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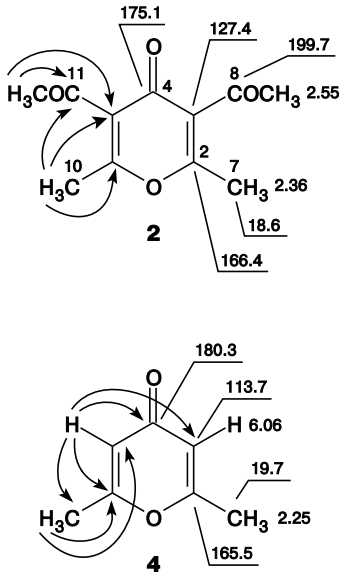


Fig. 1. The $^1H—^{13}C$ nuclear correlations in the HMBC spectra of γ-pyrones **2** and **4**; δ values are presented.

(see Ref. 1) and IR spectra (KBr) of relative γ-pyrones with benzoyl and cinnamoyl substituents in positions 3 and 5.[6]

The $^1H—^{13}C$ nuclear correlations corresponding to the intense cross-peaks in the HMBC spectrum of γ-pyrone **2** are shown in Fig. 1.

One of specific features of the HMBC spectrum of γ-pyrone **2** is the very weak cross-peak of protons of the C(8)- and C(11)-Me groups and C(7) and C(10) atoms with a chemical shift (CS) of 18.6 ppm, which appears only when the experiment is optimized by a value of the constant of 1 Hz. Another feature is the absence of a correlation of the ^1H nuclei of the Me groups at C(2) and C(8) with the nucleus of the C(4) atom lying in the symmetry plane of a molecule of γ-pyrone **2**.

The mild acidic cleavage of γ-pyrone **2** (2% hydrochloric acid, 20 °C, 16 h) gave γ-pyrone **3** in 87% yield, whereas known γ-pyrone **4** is formed in 61% yield under the drastic conditions (17% hydrochloric acid, reflux, 3 h, Scheme 2). As γ-pyrone **2**, γ-pyrone **4** possesses a high synthetic potential.[12—16]

The structure of γ-pyrone **4** was confirmed by the data of IR spectroscopy, ^1H and ^{13}C NMR, and mass spectrometry. The $^1H—^{13}C$ nuclear correlations in the HMBC spectrum of γ-pyrone **4** are shown in Fig. 1. Note that in the ^1H NMR spectrum ($CDCl_3$) of γ-pyrone **4** the spin interaction between the H(3) and H(5) protons (δ 6.06, s, 2 H) and protons of the C(2)- and C(6)-Me groups (δ 2.25, s, 6 H), respectively, do not appear. Attempts to find the signal splitting of these protons with the linewidth 0.5 Hz at the half-height by using special procedures (Gaussian multiplication of the free induction response before the Fourier transform) were unsuccessful.

γ-Pyrone **2** has been obtained for the first time[4,5] in 15 and 20% yields and later on[12] in 16% yield by the acylation of γ-pyrone **4** with acetic anhydride in a solution of CS_2 in the presence of anhydrous $AlCl_3$, but the structure of the product was mistakenly ascribed as γ-pyrone **3**. Since Ref. 12 contains no spectral data, this conclusion was made on the basis of coincidence of the melting points of γ-pyrone **2** and its 2,4-dinitrophenylhydrazone synthesized in the present work with the corresponding characteristics of the compounds described previously.[12]

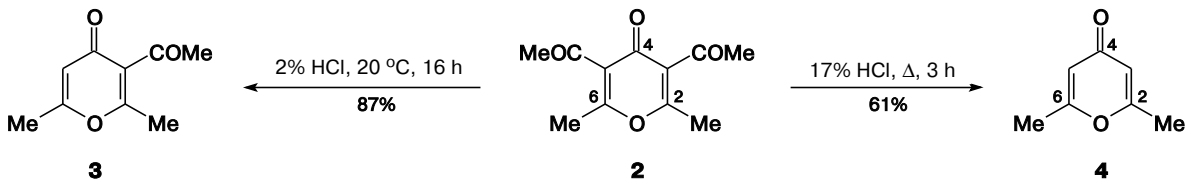
γ-Pyrone **3** was synthesized later[17] by the reaction of acetylacetone with diketene in the presence of H_2SO_4 at 90 °C.

The experimental confirmation of the presence of such compounds as acetylacetone, triacetylmethane, and diacetylacetone among the products of the reaction of isopropenyl acetate (**1**) with aluminum chloride suggests that the mechanism of this reaction can be presented by Scheme 3.

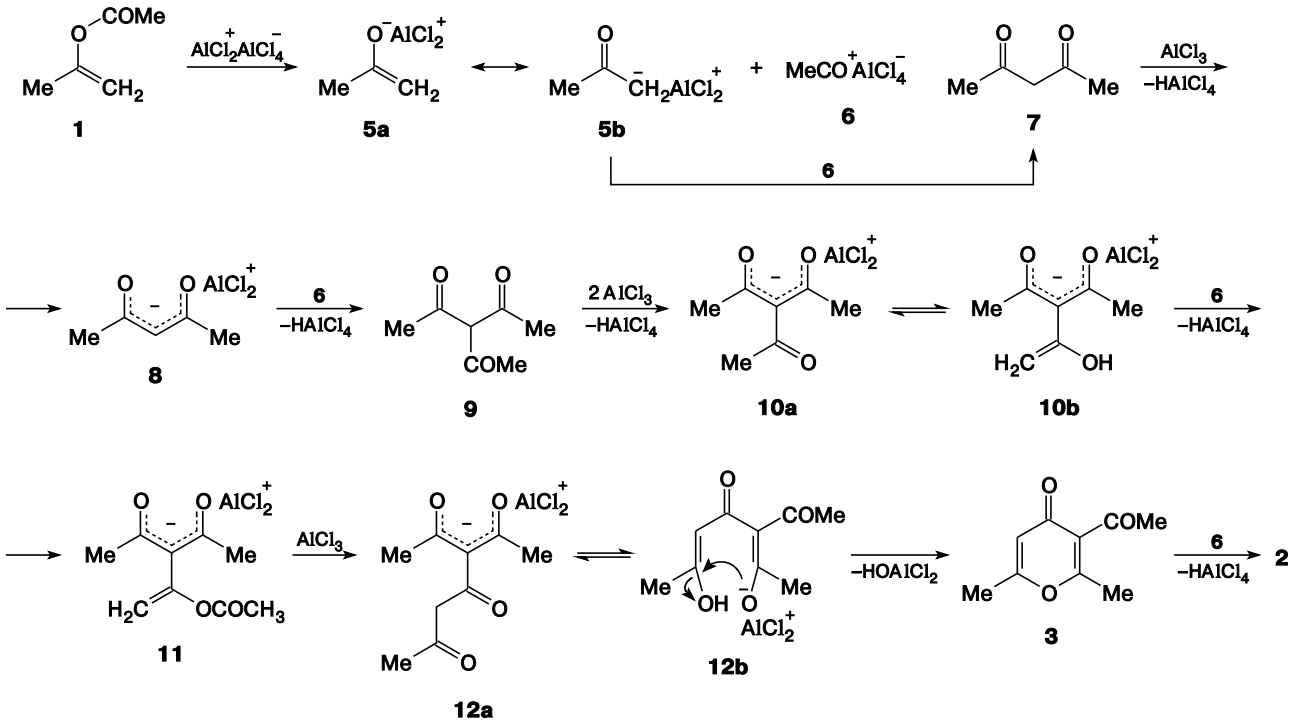
As known, aluminum chloride exists in a 1,2-dichloroethane solution as a dimer,[18] which is probably an ion pair $AlCl_2^+AlCl_4^-$. Under the reaction conditions, the Lewis acid induces the conversion of isopropenyl acetate (**1**) to acetylacetone **7** due to the attack of acyl **6** to form **5b** of intermediate **5**. The interaction of $AlCl_3$ with acetylacetone enol results in its transformation into salt **8**, the attack to which by acyl **6** gives triacetylmethane **9**. The latter, similarly to 1,3-diketone **7**, with $AlCl_3$ forms salt **10a**. The attack of acyl **6** to the enol form **10b** of this ketone affords enol acetate **11**, which in the presence of $AlCl_3$ can undergo O—C-isomerization[19] to heptane-2,4,6-trione derivative **12a**. The cyclization of tautomeric form **12b** of the latter completes the formation of the major reaction product, namely, γ-pyrone **2**.

The question how diacetylacetone is formed under the reaction conditions remains unanswered. It is most likely

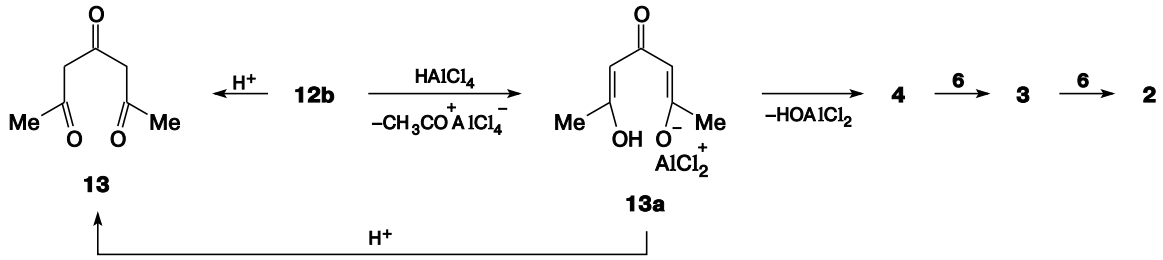
Scheme 2



Scheme 3



Scheme 4



that this is the result of the partial acidic cleavage of intermediate **12** under the action of $HAlCl_4$, which is present in the reaction medium (Scheme 4).

Intermediate **13a** can further undergo cyclization to γ-pyrone **4**, whose fast acylation gives γ-pyrone **2**. It should be mentioned that no γ-pyrone **4** itself was observed among the reaction products. Of course, it cannot be excluded that diacetylacetone **13** is formed as a by-product of the acidic treatment of the reaction mixture, which is accompanied by the cleavage of intermediate **12b**.

To conclude, the here reported conversion of isopropenyl acetate (**1**) to γ-pyrone **2** under the action of anhydrous $AlCl_3$ is the simplest of all known methods of its synthesis and is not inferior to them in efficiency.

Experimental

Melting points were determined on a Boetius heating stage and were not corrected. IR spectra were recorded on a Bruker Vector 22 spectrophotometer in a $CHCl_3$ solution. ^1H and ^{13}C NMR spectra were measured on a Bruker AVANCE-700 spectrometer (^1H, 700.13 MHz; ^{13}C, 176.05 MHz) in a $CDCl_3$ solution using Me_4Si as an internal standard. Mass spectra (EI) were obtained on an AMD 604 S instrument (8 kW) with direct inlet at an ionization energy of 70 eV. Elemental analysis was carried out on a Flash EA1112 C,H,N-analyzer. TLC analysis was carried out on Silufol UV 254 plates in a benzene—acetone (30 : 1) system. Individual compounds were isolated from mixtures of reaction products on columns packed with SiO_2 (Alfa Aesar, 70—230 μm) eluting with acetone—hexane mixtures.

Freshly distilled isopropenyl acetate (Lancaster, b.p. 94 °C (760 Torr), n^{20}_D 1.4011), 1,2-dichloroethane (Lancaster, b.p. 83 °C (760 Torr), n^{20}_D 1.4440), and anhydrous powdered aluminum chloride (Lancaster, m.p. 190 °C (subl.)) were used in the reaction.

3,5-Diacetyl-2,6-dimethyl-4*H*-pyran-4-one (2) and 3-acetyl-2,6-dimethyl-4*H*-pyran-4-one (3). Freshly distilled isopropenyl acetate (1.5 g, 0.015 mol) was added dropwise for 3 min to a vigorously stirred suspension of anhydrous $AlCl_3$ (4.0 g, 0.03 mol) in anhydrous 1,2-dichloroethane (15 mL), cooling the flask with ice-cold water. A transparent light yellow solution that formed was refluxed for 1 h. After cooling to ~20 °C, the solution was poured to a mixture of 20 mL of 15% hydrochloric acid and 10 g of chipped ice. The organic layer was separated and washed with 5% hydrochloric acid (3×10 mL). The aqueous phases were combined, and the reaction products were additionally extracted with chloroform (3×30 mL). The combined organic phases were washed with water (3×15 mL) to the neutral pH in the washings and dried (Na_2SO_4). The solvent was removed, and the residue was chromatographed on a column with SiO_2. Elution with a hexane—acetone (6 : 1) mixture gave 0.133 g (17%) of γ-pyrone **2**, light yellow needles, m.p. 125—126 °C (from hexane) (*cf.* Ref. 1: m.p. 124 °C; Ref. 4: m.p. 120—121 °C; Ref. 12: m.p. 125.5—127 °C). IR, ν_{max}/cm^{-1}: 1697 (C=O), 1649 (C=O), 1626 (C=C), 1403, 1371, 1357, 1150, 1061. ^{1}H NMR, δ: 2.36 (s, 6 H, C(2)Me, C(6)Me); 2.55 (s, 6 H, C(3)COMe, C(5)COMe). ^{13}C NMR, δ: 18.6 (C(7), C(10)); 31.8 (C(9), C(12)); 127.4 (C(3), C(5)); 166.4 (C(2), C(6)); 175.1 (C(4)); 199.7 (C(8), C(11)). MS, m/z (I_{rel} (%)): 209 $[M + 1]^+$ (14), 208 $[M]^+$ (100), 207 $[M - 1]^+$ (3), 193 (2), 192 (4), 166 (6), 165 (18), 162 (3), 152 (5), 151 (48), 148 (9), 138 (4), 127 (6), 125 (21), 123 (6), 111 (5), 109 (31), 85 (8), 67 (33), 44 (49). Found (%): C, 63.29; H, 5.86. $C_{11}H_{12}O_4$. Calculated (%): C, 63.45; H, 5.81.

The subsequent elution with a hexane—acetone (4 : 1) mixture gave 0.009 g (1%) of γ-pyrone **3**, light yellow prisms, m.p. 56—58 °C (from hexane) (*cf.* Ref. 17: m.p. 58—60 °C; Ref. 1: m.p. 63—64 °C). IR, ν_{max}/cm^{-1}: 1694 (C=O), 1664 (C=O), 1625 (C=C), 1621 (C=C), 1402, 1372, 1356, 1159, 1042. ^{1}H NMR, δ: 2.26 (d, 3 H, C(6)Me, J = 0.6 Hz); 2.36 (s, 3 H, C(2)Me); 2.55 (s, 3 H, C(3)COMe); 6.15 (q, 1 H, H(5), J = 0.6 Hz). ^{13}C NMR, δ: 18.8 C(10)); 19.6 (C(7)); 32.0 (C(9)); 114.9 (C(5)); 126.5 (C(3)); 164.8 (C(6)); 167.3 (C(2)); 177.4 (C(4)); 200.6 (C(8)). MS, m/z (I_{rel} (%)): 167 $[M + 1]^+$ (10), 166 $[M]^+$ (100), 165 $[M - 1]^+$ (7), 152 (3), 151 (42), 149 (8), 148 (50), 125 (9), 124 (18), 123 (6), 110 (5), 109 (35), 85 (16), 69 (9), 67 (86), 44 (49). Found (%): C, 65.17; H, 6.12. $C_9H_{10}O_3$. Calculated (%): C, 65.05; H, 6.07.

Under the conditions described,[12] 0.02 g of γ-pyrone **2** gave 0.017 g of its 2,4-dinitrophenylhydrazone as yellow needles, m.p. 188—190 °C (from EtOH) (*cf.* Ref. 12: m.p. 189—191 °C).

Under the conditions described,[12] 0.02 g of γ-pyrone **3** gave 0.015 g of its 2,4-dinitrophenylhydrazone as orange needles, m.p. 193—195 °C (from EtOH) (*cf.* Ref. 17: m.p. 194—196 °C).

Interaction of isopropenyl acetate with $AlCl_3$ at room temperature. As described above, a transparent solution, which was stored for 24 h at ~20 °C, was obtained from freshly distilled isopropenyl acetate (1.5 g, 0.015 mol), anhydrous $AlCl_3$ (4.0 g, 0.03 mol), and anhydrous 1,2-dichloroethane (15 mL). The treatment analogous to that described above gave a mixture of products, which was separated on a column with SiO_2. Elution with a hexane—acetone (20 : 1) mixture gave 0.011 g of pentane-2,4-dione (acetylacetone), mobile colorless liquid, n^{25}_D = 1.4497. IR, ν_{max}/cm^{-1}: 3320—2180 (OH), 1729 (C=O), 1704 (C=O), 1619 (C=O, C=C), 1606 (C=O, C=C), 1459, 1421, 1361, 1301, 1245, 1172. ^{1}H NMR of the diketo form, δ: 2.24 (s, 6 H, 2 Me); 3.59 (s, 2 H, CH_2). ^{1}H NMR of the enol form, δ: 2.04 (s, 6 H, 2 Me); 5.50 (s, 1 H, H(3)); 15.44 (s, 1 H, OH).

The subsequent elution with a hexane—acetone (15 : 1) mixture gave 0.013 g of heptane-2,4,6-trione (diacetylacetone), colorless crystals, m.p. 48—49 °C (from hexane) (*cf.* Ref. 1: m.p. 49 °C; Ref. 11: m.p. 45—47 °C). IR, ν_{max}/cm^{-1}: 3390—2320 (OH), 1732 (C=O), 1716 (C=O), 1626 (C=O, C=C), 1615 (C=O, C=C), 1601 (C=O, C=C), 1590, 1583, 1485, 1460, 1415, 1370, 1359, 1300, 1242, 1176. ^{1}H NMR of the triketo form, δ: 2.22 (s, 6 H, 2 Me); 3.70 (s, 4 H, 2 CH_2). ^{1}H NMR of the monoenol form, δ: 1.98 (s, 3 H, C(2)Me); 2.26 (s, 3 H, C(6)Me); 3.40 (s, 2 H, CH_2); 5.56 (s, 1 H, H(3)); 15.20 (s, 1 H, OH). ^{1}H NMR of the dienol form, δ: 2.08 (s, 6 H, 2 Me); 5.14 (s, 2 H, H(3), H(5)); 14.17 (s, 2 H, 2 OH).

The subsequent elution with a hexane—acetone (10 : 1) mixture gave 0.036 g of 3-acetylpentane-2,4-dione (triacetylmethane), poorly mobile light yellow liquid, n^{25}_D = 1.4903, (*cf.* Ref. 9: n^{25}_D = 1.4893; Ref. 10: n^{20}_D = 1.5600). IR, ν_{max}/cm^{-1}: 3370—2190 (OH), 1679 (C=O), 1619 (C=O, C=C), 1598 (C=O, C=C), 1587 (C=O, C=C), 1414, 1359, 1299, 1235, 1154. ^{1}H NMR, δ: 2.24 (s, 6 H, 2 Me); 2.43 (s, 3 H, C(3)COMe); 17.20 (s, 1 H, OH).

The subsequent elution with a hexane—acetone (6 : 1) mixture gave 0.031 g (4%) of γ-pyrone **2** identical to that described above.

The subsequent elution with a hexane—acetone (4 : 1) mixture gave 0.003 g (0.4%) of γ-pyrone **3** identical to that described above.

3-Acetyl-2,6-dimethyl-4*H*-pyran-4-one (3). A solution of γ-pyrone **2** (0.019 g, 0.091 mmol) in 3 mL of 2% hydrochloric acid was stirred for 16 h at ~20 °C, diluted with 10 mL of water, and extracted with chloroform (3×5 mL). The combined organic extract was washed with brine (3×3 mL) and dried (Na_2SO_4). The solvent was removed, and the residue was chromatographed on a column with SiO_2. Elution with a hexane—acetone (4 : 1) mixture gave 0.013 g (87%) of γ-pyrone **3** identical to that described above.

2,6-Dimethyl-4*H*-pyran-4-one (4). A solution of γ-pyrone **2** (0.103 g, 0.493 mmol) in 2 mL of acetone and 20 mL of 17% hydrochloric acid was refluxed for 3 h, then cooled to ~20 °C, diluted with 20 mL of water, and extracted with chloroform (3×20 mL). The combined organic extract was washed with brine (3×10 mL) and dried (Na_2SO_4), the solvent was removed, and the residue was recrystallized from a benzene—acetone (8 : 1) mixture. γ-Pyrone **4** was obtained in a yield of 0.037 g (61%), colorless needles, m.p. 131—132 °C (*cf.* Ref. 7: m.p. 131—132 °C; Ref. 1: m.p. 130—131 °C). IR, ν_{max}/cm^{-1}: 1667 (C=O), 1613 (C=C), 1442, 1398, 1374, 1332, 1194, 1159, 1034. ^{1}H NMR, δ: 2.25 (s, 6 H, C(2)Me, C(6)Me); 6.06 (s, 2 H, H(3), H(5)). ^{13}C NMR, δ: 19.7 (C(7), C(8)); 113.7 (C(3), C(5)); 165.5 (C(2), C(6)); 180.3 (C(4)). MS, m/z (I_{rel} (%)): 125 $[M + 1]^+$ (8), 124 $[M]^+$ (100), 109 (2), 97 (3), 96 (26), 95 (34), 85 (4), 84 (6), 82 (2), 81 (23), 69 (39), 67 (5), 56 (3), 53 (8), 44 (59), 40 (11).

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