A Novel and Convenient Synthesis of 3-MethylfurAn-2(5H)-one

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3-MethylfurAn-2(5H)-one (1a), a precursor of strigol and its analogues, is prepared in a highly efficient manner by a regiocontrolled alcoholysis of citraconic anhydride and subsequent reduction via the mixed anhydride 5c.

The 3-methylfurAn-2(5H)-one moiety 1a is a common structural feature of all known “strigolactones”, such as (+)-strigol, which are naturally occurring germination stimulants of seeds of the parasitic weeds Striga and Orobanche sp.1-4 Moreover, structure-activity relationship studies revealed that the presence of this structural unit is essential to retain full biological activity, results of which will be published separately.5

In view of our interest in the synthesis of simple, biologically active analogues of strigol, which are suitable for weed control purposes,6,7 a convenient multigram preparation of 1a is required, using cheap chemicals. This compound can readily be transformed into the corresponding 5-bromo derivative 1b, which is the D-ring precursor in the synthesis of the strigolactones and their analogues.8 Several procedures for the synthesis of 1a have been reported, but none of them fulfils these criteria satisfactorily.7,9-15 The present paper deals with an improved procedure for the preparation of 3-methylfurAn-2(5H)-one (1a).

An attractive cheap, commercially available starting material is citraconic anhydride (2), as it only requires a minimal amount of the corresponding ethyl ester of citraconic anhydride (DCA) with either methanol or 4-methoxybenzyl alcohol. The DCA salt is more stable than the corresponding ester of citraconic anhydride (DCA) with either methanol or 4-methoxybenzyl alcohol. After conventional workup, butenolide 1a was isolated in a high overall yield (~80 % from crude 3a, b) after purification by fractional distillation under reduced pressure. The choice of the 4-methoxybenzyl ester was advantageous because carboxylic acid 4a, b by acidification with citric acid or potassium hydrogen sulfate, followed by treatment with ethyl chloroformate in the presence of triethylamine to give the mixed anhydride 5c, which avoids a laborious extractive workup. Crude butenolide 1a could advantageously be used to accomplish the reduction in the desired regiocontrolled fashion in an indirect manner, as is outlined in the Scheme.

Alcoholysis of 2 in the presence of dicyclohexylamine (DCA) with either methanol or 4-methoxybenzyl alcohol gave the esters 3a and 3b, respectively, isolated as the DCA salts, in high yield (80 %) and with high regioselectivity (>90 %). In our first approach the DCA salts 3a, b were converted into the corresponding carboxylic acids 4a, b by acidification with citric acid or potassium hydrogen sulfate, followed by treatment with ethyl chloroformate in the presence of triethylamine to give the mixed anhydride 5c, which circumvented the need to isolate carboxylic acid 4a. However, the formation of 4-methoxybenzyl ester was much more stable than 4a. The 4-methoxybenzyl alcohol during the reduction process severely complicated the purification of 1a by distillation. A considerable improvement of the above procedure is the direct formation of mixed anhydride 5c from 3a (Scheme). This could be accomplished by treatment of 3a with isobutyl chloroformate, which circumvented the need to isolate carboxylic acid 4a. In this experimental setup ethyl chloroformate is not a suitable reagent, as a considerable amount of the corresponding ethyl ester of 4a was formed under these conditions. The mixed anhydride 5c was then immediately subjected to reduction with NaBH₄, using a reversed addition procedure, i.e. addition of a saturated aqueous solution of NaBH₄ to 5c, which avoids a laborious extractive workup. Crude butenolide

Scheme
1a contained a small amount (ca. 1%) of two byproducts, viz. 3-methylfuran-2(5H)-one and an as yet unidentified polar product. It is essential to remove this polar by-product as it substantially suppressed the radical bromination reaction to give 1b (vide supra). This can be achieved by a quick filtration over silica gel. Pure butenolide 1a was thus obtained in a high overall yield (>80% from 3a) after fractional distillation.

In conclusion, a convenient and simple preparation of 3-methylfuran-2(5H)-one (1a), starting from citraconic anhydride (2), has been accomplished by making use of the intrinsic difference in reactivity of both carbonyl groups in citraconic anhydride (2). The procedure has been performed on at least a 0.2 mole scale using inexpensive ingredients and standard laboratory equipment. This method is therefore superior to all previously reported syntheses.

IR spectra were measured on a Unical Mattson 5000 FT-IR spectrometer. 100 MHz. 1H NMR spectra were recorded on a Bruker AC 100 spectrometer. 100 MHz, *HNMR spectra were recorded on a Bruker AC 100 spectrometer (TMS as internal standard). All coupling constants are given as J in Hz, unless indicated otherwise. GC was conducted with a Hewlett-Packard HP 5890 gas chromatograph, using a capillary column (25 m) of HP-1, and N2 (2 mL/min, 0.5 atm) as the carrier gas. Mps were measured with a Reichert Thermopan microscope and are uncorrected. Elemental analyses were performed at the Department of Microanalysis of this laboratory.

Dicyclohexylamine Salt of 2-Methylbut-2-enedioic Acid 1-Methyl Ester (3a):

To a cooled (~10°C) solution of DCA salt 3b (15 g, 0.22 mol) in water (30 mL) was added (14 g, 0.4 mol) in methanol (400 mL) was added gradually DCA (1.1 equiv). The reaction mixture was stirred for 30 min at r.t. and then concentrated in vacuo, while keeping the temperature below 25°C. EtOAc was added to the residue and after 1 h the product was isolated by filtration and washed with EtOAc to give 3a (138 g, 85%); mp 121–122°C (propan-2-ol) as colorless crystals.

IR (KBr): ν = 2500–3000 (broad, NH²+), 1733 (C=O, ester), 1665 (C-O, carboxylate) cm⁻¹.

1H NMR (CDCl₃, 100 MHz): δ = 1.0–2.1 (m, 20 H, cyclohexyl), 1.93 (d, 3 H, J = 1.5 Hz, =CH3), 2.8–3.2 (m, 2 H, CH₂N), 3.70 (s, 3 H, OCH₃), 6.05 (q, 1 H, J = 1.5 Hz, =CH), 9.63 (br s, 2 H, NH₂).


Dicyclohexylamine Salt of 2-Methylbut-2-enedioic Acid 1-(4-Methoxybenzyl) Ester (3b):

To a stirred solution of 2 (5.6 g, 0.05 mol) in EtOAc (50 mL) 4-(4-Methoxybenzyl) Ester (3b):

To a cooled (~−20°C), followed by slow addition of DCA (10.0 g, 0.22 mol) in water (30 mL) was added at 0°C, while stirring vigorously, over a 1 h period. Stirring was continued for 2 h at the same temperature and the precipitate was removed by filtration and washed with Et₂O. The filtrate was carefully concentrated in vacuo and the residue was dissolved in t-Pr₂O and dried (MgSO₄). THF was distilled from LiAlH₄ just before use. All other solvents were of analytical grade.

IR (KBr): ν = 2900 (broad, OH), 1734 (C=O, ester), 1661 (C-O, carboxylate) cm⁻¹.

1H NMR (CDCl₃, 100 MHz): δ = 1.0–2.1 (m, 20 H, cyclohexyl), 1.92 (d, 3 H, J = 1.5 Hz, =CH₃), 2.8–3.2 (m, 2 H, CH₂N), 3.79 (3 H, OCH₃), 5.10 (s, 2 H, CH₂), 6.02 (q, 1 H, J = 1.5 Hz, =CH), 6.85 (2 H, arom. H), 7.30 (2 H, arom. H), 9.63 (br s, 2 H, NH₂).

Analysis (C₂₁H₂₃O₄N₂): Calcd C, 69.58; H, 8.64; N, 3.24. Found C, 69.11; H, 8.67; N, 3.36.

2-Methylbut-2-enedioic Acid 1-(4-Methoxybenzyl) Ester (4b):

A suspension of DCA salt 3b (2.0 g, 4.6 mmol) in a mixture of water (10 mL) and EtOAc (25 mL) was acidified by adding KHSO₄ until pH < 3, which resulted in a clear two-phase system. The aqueous phase was separated and the organic layer was dried (MgSO₄), concentrated in vacuo and crystallized from propan-2-ol to give 4b in 80% yield; mp 75–76°C (propan-2-ol) as colorless crystals.

IR (KBr): ν = 2900 (broad, OH), 1734 (C=O, ester), 1661 (C-O, carboxylate) cm⁻¹.

1H NMR (CDCl₃, 100 MHz): δ = 2.08 (d, 3 H, J = 1.6 Hz, =CH₃), 3.79 (3 H, OCH₃), 5.17 (s, 2 H, CH₂), 5.86 (q, 1 H, J = 1.6 Hz, =CH), 6.87 (2 H, arom. H), 7.27 (2 H, arom. H).


3-Methylfuran-2(5H)-one (1a):

To a cooled (~−10°C) solution of DCA salt 3a (65 g, 0.20 mol) in CH₂Cl₂ (150 mL) isobutyl chloroformate (30 g, 0.22 mol) was gradually added with stirring. During the addition a precipitate of dicyclohexylamine chlorohydrate gradually settled. The mixture was stored overnight at ca. −10°C. Then THF (150 mL) was added and the mixture was allowed to stand for 1 h at the same temperature. The precipitate was removed by filtration, while cooling the filtrate (0°C), and washed with THF (150 mL). To the filtrate containing mixed anhydride 5c, a cold solution of NaBH₄ (15 g, 0.4 mol) in water (30 mL) was added at 0°C, while stirring vigorously, over a 1 h period. Stirring was continued for 2 h at the same temperature and the precipitate was removed by filtration and washed with Et₂O. The filtrate was carefully concentrated in vacuo and the residue was dissolved in i-Pr₂O and dried (MgSO₄). The solvent was removed in vacuo to give 1a as a colorless oil, which was purifiable by fractional distillation at low pressure and subsequently passed over a short column of silica gel, using CI₄ as the eluent; yield: 17 g (80%) as a colorless oil; bp 80°C/15 Torr. The 1H NMR data were in full agreement with those reported.

(4) Butler, L.G. ACS Symposium Series 1995, 582, 158.
(15) Alternative convenient procedures involve the use of \( \alpha \)-methyl-\( \gamma \)-butyrolactone (ref 13) or \( \alpha \)-methylene-\( \gamma \)-butyrolactone (ref 12), which are very expensive starting materials and difficult to prepare.

