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

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 anhydrides 5a,b. Removal of the Et3N • HCl precipitate by filtration, immediately followed by addition of ethyl chloroformate to 5a,b to a saturated aqueous solution of sodium borohydride, smoothly produced 1a.17 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 4b is much more stable than 4a. However, the formation of 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...
1a contained a small amount (ca. 1%) of two byproducts, viz. 3-methylfurans-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 infra). 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-methylfurans-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 Unicam Mattson 5000 FT-IR spectrometer. 100 MHz. 1H NMR 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 performed on at least a 0.2 mole scale using 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.

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

To a cooled (–15°C) solution of citraconic anhydride (2, 56 g, analytical grade. 85%); mp 121-122°C (propan-2-ol) as colorless crystals. 100 MHz, 1H NMR spectra were recorded on a Bruker AC 100 spectrometer. 100 MHz. All coupling constants are given as Δ in Hz, unless indicated otherwise. GC was performed on at least a 0.2 mole scale using 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.
Alternative convenient procedures involve the use of α-methyl-γ-butyrolactone (ref 13) or α-methylene-γ-butyrolactone (ref 12), which are very expensive starting materials and difficult to prepare.

