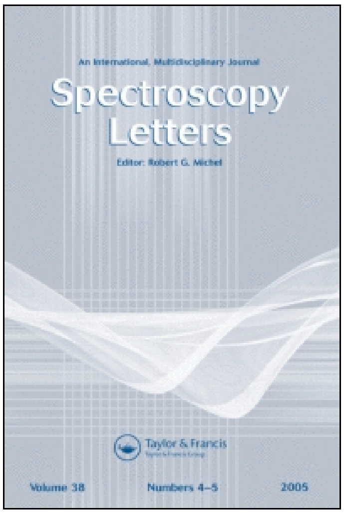

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Assignment of the ^{1}H and ^{13}C NMR Chemical Shifts of (3,4-Dihydro-2*H*-pyran-5-yl)-oxo-acetic Acid Methyl Ester Using the Two Dimensional HMBC Technique

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To cite this Article Lamarque, Laurent , Méou, Alain , Brun, Pierre and Chauvet, Frederic(1996) 'Assignment of the ^{1}H and ^{13}C NMR Chemical Shifts of (3,4-Dihydro-2*H*-pyran-5-yl)-oxo-acetic Acid Methyl Ester Using the Two Dimensional HMBC Technique', Spectroscopy Letters, 29: 1, 159 — 167

To link to this Article: DOI: 10.1080/00387019608001591

URL: http://dx.doi.org/10.1080/00387019608001591

SPECTROSCOPY LETTERS, 29(1), 159–167 (1996)

ASSIGNMENT OF THE ^{1}H AND ^{13}C NMR CHEMICAL SHIFTS OF (3,4-DIHYDRO-2*H*-PYRAN-5-YL)-OXO-ACETIC ACID METHYL ESTER USING THE TWO DIMENSIONAL HMBC TECHNIQUE

Key words: (3,4-dihydro-2*H*-pyran-5-yl)-oxo-acetic acid methyl ester, ^{1}H NMR, ^{13} C NMR, HETCOR, HMBC.

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ABSTRACT: The identification of (3,4-dihydro-2*H*-pyran-5-yl)-oxo-acetic acid methyl ester has been realized by combination of two dimensional HETCOR and HMBC techniques. ^{13}C and ^{1}H chemical shifts asignements are described.

INTRODUCTION:

The synthesis of γ-butyrolactones by Mn^{III}-mediated addition of acetic acid derivatives on double bonds is a well known reaction (1).

Among these acetic acid derivatives, the monomethyl ester of malonic acid is particularly interesting as it leads to α-carbomethoxy-γ-butyrolactones which are useful precursors for the synthesis of α-methylene-γ-butyrolactones (2) (FIG. 1). These α-methylene-γ-butyrolactones are important building blocks and can be found as substructures in numerous natural products (3).

During the course of a study of this reaction applied to 3,4-dihydro-2*H*-pyran, we have observed that if the γ-lactone **1** is indeed obtained, it is always accompanied by an unknown product **2** which is formed in variable amounts depending on the reaction conditions (FIG. 2).

In order to obtain a better control of the product distribution we have run several experiments under different conditions and we have noticed that the reaction course was very sensitive to oxygen. When the reaction was performed in degassed acetic acid under an argon or a nitrogen atmosphere, the yield of the lactone **1** was 70% as estimated by gas chromatography while the yield of the unknown product **2** was only 4%. In the same conditions but under an air atmosphere, **1** and **2** were obtained in respectively 50 and 23% yield. The same reaction run in acetic acid previously saturated with oxygen and under an oxygen atmosphere leads to **1** and **2** in 11.8 and 62.5 % yield. Clearly **2** is formed by a competitive oxidation process at the expense of **1**.

It should be noted that such a behavior has not been observed in our previous studies using non-heterocyclic unsaturated substrates. We describe in this work how the combination of HETCOR and HMBC techniques was used in order to elucidate the structure of **2**.

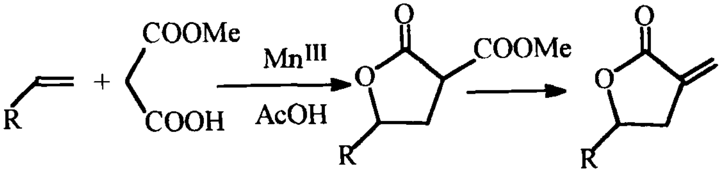
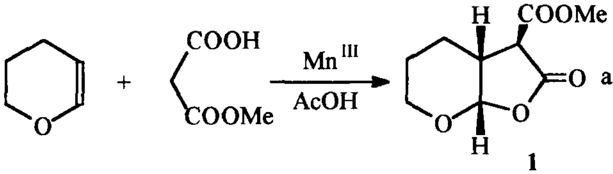


FIG. 1 Mn^{III}-mediated synthesis of α-methylene-γ-butyrolactones



1 and/or 2

FIG. 2 Reaction of dihydropyran in the presence of Mn^{III}

EXPERIMENTAL:

Synthesis of 1 and 2:

To a suspension of 2.4 mmol (640 mg) of $Mn(OAc)_3$, $2H_2O$ and 2.4 mmol (375 mg) of potassium monomethylmalonate in 10 mL of glacial acetic acid saturated with oxygen, 1.2 mmol (100 mg) of freshly deperoxidized dihydropyran was added. The brown reaction mixture was heated at 65°C under an oxygen atmosphere until it turned pale yellow (45 mn). After cooling to room temperature, 20 mL of water were added and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with a 10% $NaHCO_3$ aqueous solution until neutral and dried over $MgSO_4$. The solvent was removed under reduced pressure and compounds 1 and 2 were isolated by column chromatography on silica gel with hexane-ether mixtures as eluent.

NMR spectra:

NMR spectra were recorded on a Bruker AC 250 Fourier transform spectrometer operating at 250.13 MHz for ^1H and 62.896 MHz for ^{13}C in deuterated chloroform with all chemical shifts referred to internal tetramethylsilane (TMS). Carbon and hydrogen spectra were recorded with the respective following parameters: acquisition times of 2.097 and 3.27 s for 32 K data table, spectral widths (SW) of 250 and 13 ppm. Carbon-13 spectra were recorded with broad band decoupling and a digital resolution of 0.477 Hz/pt.

The proton-carbon chemical shift correlation utilized the HETCOR sequence with a pulse length of 6.5 μs for carbon and 19.5 μs for hydrogen. Pulse length for Waltz decoupling was set to 105 μs with a decoupler power of 18H.

The HMBC sequence was recorded on a Bruker AMX 400 spectrometer and was accumulated non-spinning with the standard pulse sequence (INV4LPLRND in the operating Bruker software). The spectral widths were F2= 3500 Hz and F1= 20000 Hz. The delays Δ1 and Δ2 were set to 3.4 ms and 60 ms respectively.

The mass spectrum was recorded using a Delsi-Nermag Automass gas chromatography-coupled spectrometer with sample diluted in diethyl ether (1 mg/ml) on an OV 17 column (50 m) in the splitless mode with programmed temperature (130 to 220°C, 5°C/mn), at 70 eV in the e.i. mode.

RESULTS AND DISCUSSION:

The identification of γ-lactone 1 is straightforward, this compound having been described previously (4). However, although the ^1H and ^{13}C NMR spectra of the unknown product 2 were deceptively simple, they did not allow an unambiguous structure determination. Similarly the ^1H-^{13}C heterocorrelation

(HETCOR) sequence does not provide additional structural information. Therefore, the structure of 2 has been established by using an heteronuclear multiple bond correlation (HMBC) (5).

Compound 2, whose formula is $C_8H_{10}O_4$ as determined by mass spectroscopy and ascertained by microanalysis, displays in its IR spectrum an absorption at 1725 cm^{-1} and two absorptions at 1660 and 1610 cm^{-1}, typical of a conjugated carbonyl group.

The ^1H NMR spectrum shows the presence of a methoxy group at 3.82 ppm (s, 3H), a very deshielded signal at 7.82 ppm (1H) and three multiplets at respectively 4.13 (2H), 2.27 (2H) and 1.90 ppm (2H). These multiplets were analyzed as respectively a triplet (J=5.2 Hz), a triplet (J=6.2 Hz) and a doublet of triplet (J=6.2 Hz, 5.2 Hz), characteristic of an $-O-CH_2-CH_2-CH_2-$ backbone.

The ^{13}C NMR spectrum exhibits the signals corresponding to three quaternary carbons at 184.6, 164.2 and 114.4 ppm, one tertiary sp_2 carbon at 163.6 ppm and three secondary carbons at 68.1, 20.7 and 17.7 ppm.

The data provided by the ^1H-^{13}C heterocorrelation and by the HMBC sequence are summarized in Table 1.

These experiments show that 2 contains a methoxy group (52.7/3.82 ppm), a deshielded tertiary sp_2 carbon atom bearing an hydrogen (163.6/7.82 ppm), three CH_2 (68.1/4.13 ppm, 20.7/1.90 ppm and 17.7/2.27 ppm) whose respective chemical shifts are in agreement with those found in an $-O-CH_2-CH_2-CH_2-$ framework or related sequence and two quaternary carbon atoms with one of them at 184.6 ppm, very deshielded for an ester carbonyl or shielded for a ketone carbonyl. At this stage, the available data do not allow to put forward a single structure for 2.

However, the problem can easily be solved (FIG. 3) by using an HMBC pulse sequence which gives the spectrum depicted in Figure 4.

TABLE 1

^{1}H and ^{13}C assignments for compound 2

Carbon N°	^{1}H, $J^{H,H}$ in Hz, (multiplicity)	^{13}C, δ in ppm	Protons showing HMBC correlation [coupling]
2	4.13 (t, $J^{2,3}$=5.2)	68.0	4,6 [^{3}J (C,H)]; 3 [^{2}J (C,H)]
3	1.90 (dt, J=6.2, 5.2)	20.7	2,4 [^{2}J (C,H)]
4	2.27 (t, $J^{4,5}$=6.2)	17.7	2,6 [^{3}J (C,H)]; 3 [^{2}J (C,H)]
5		114.4	3 [^{3}J C,H)]; 4,6 [^{2}J (C,H)]
6	7.82 (s)	163.6	2,4 [^{3}J (C-H)]
7		184.6	4,6 [^{3}J (C,H)]
8		164.2	9 [^{3}J (C,H)]
9	3.82 (s)	52.7	

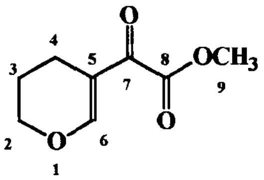


FIG. 3 Structure and numbering system of compound 2

The quaternary carbon C-7 at 184.6 ppm displays clear correlation cross signals for long range ^{13}C-^{1}H couplings (^{3}J) with H-4 and H-6 and can be assigned to a carbonyl group. The ethylenic carbon C-5 at 114.4 ppm is correlated with H-4 and H-6 [^{2}J(C,H)] and H-3 [^{3}J(C,H)] while C-6 is correlated with H-2 and H-4 [^{3}J(C,H)]. C-8 is correlated only with the H-9 protons [^{3}J(C,H)]. It now appears undoubtedly that 2 possesses a dihydropyran ring with an unsubstituted -6

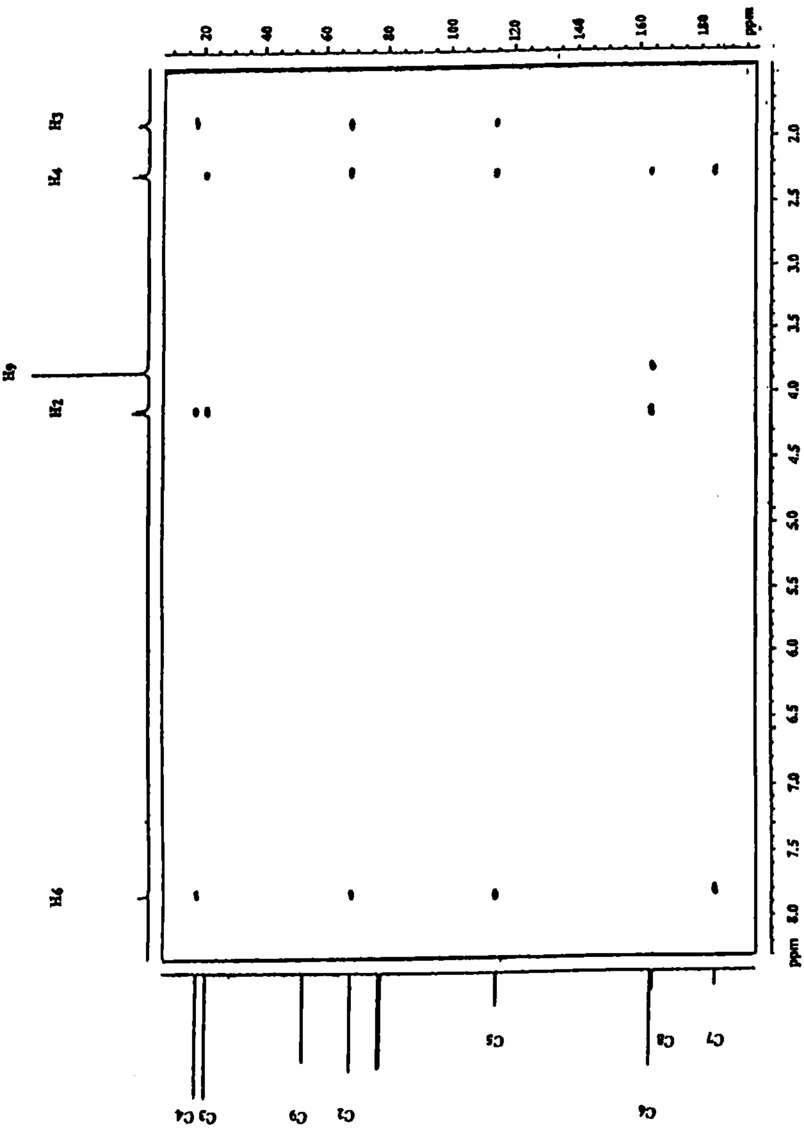


FIG. 4 HMBC spectrum of compound 2

position: ^3J C-6,H-2, ^3J C-6,H-4, ^3J C-2,H-4 and ^3J C-5,H-3. This is in perfect agreement with the chemical shifts observed for C-2, C-3, C-4 and the corresponding hydrogen atoms. The -5 position of this dihydropyran ring is substituted by a carbonyl group (^3J C-7,H-6, ^3J C-7,H-4) while C-8, which is only correlated with H-9, is linked to C-7. Moreover, the chemical shift of C-7 (184.6 ppm) fall within the range of δ reported for such a type of structure (6) and the low field resonance of H-6 is consistently accounted for.

CONCLUSION:

In this study the combination of the two-dimensional NMR techniques HETCOR and HMBC was used in order to elucidate the structure of (3,4-dihydro-2*H*-pyran-5yl)-oxo-acetic acid methyl ester which is formed in the reaction of dihydropyran with potassium monomethylmalonate in the presence of $Mn(OAc)_3,2H_2O$ under an oxygen atmosphere. Such a compound has not been previously detected in this type of reaction and the mechanism of its formation is currently under investigation.

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Received: July 11, 1995
Accepted: August 24, 1995