THE SYNTHESIS OF β-LACTONES AND β-LACTAMS FROM MALONATES AND MALONAMIDES

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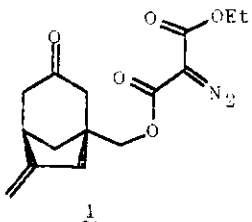
Abstract - The rhodium diacetate induced insertion reactions of some simple esters and amides of diazomalonic acid result in the formation of β-lactones and β-lactams.

During our investigations of methods for the preparation of substituted bicyclo-[3.2.1]octanes, we attempted to transform the compound (1) by the intramolecular insertion of the rhodium diacetate generated carbenoid centre on the malonate group into one of the nearby methylene groups. Rhodium diacetate carbenoid insertion reactions are known to favour the formation of five-membered rings (ref. 1). With suitable substrates, these reactions also yield six-membered (ref. 2) and four-membered (ref. 3) rings, although less readily. Diazomalonates have been transformed into γ-lactones by the copper catalyzed insertion procedure, but these reactions did not produce β-lactones (ref. 4). It is also significant that the reactions of the diazoacetoacetates (ref. 5) did not produce β-lactones.
The compound (1) was prepared in 95% yield by the esterification of the alcohol (2) (ref. 6) with ethyl malonoyl chloride in pyridine, followed by the reaction of this malonate ester with tosyl azide (ref. 7) and triethylamine in acetonitrile for 8 h (95% yield). The solutions of the compound (1) in dichloromethane were quite stable at room temperature, but when they were treated with rhodium diacetate (1% by weight), nitrogen was evolved and the sole isolable product of cyclization was the trans-substituted lactone (3), in 34% yield, after 45 min. None of the



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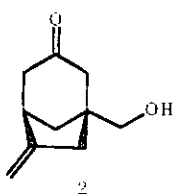

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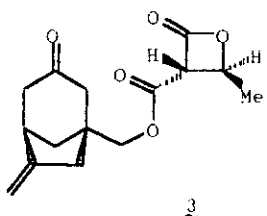

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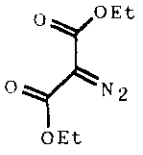
cis-isomer was detected in the nmr spectra, neither were products containing four-, or six-membered rings detected.

Consistent with previous observations (refs. 8 and 9), the methylene groups flanked by π-bonded moieties did not participate in the reaction and the insertion into the methylene group of the ethyl group, rather than that of C-9, might be the consequence of the hindered, neopentyl-like nature of the C-9 methylene group. Using identical concentrations of reagents as above, we ascertained that the diazo compound (4), derived from diethyl malonate was rapidly, 45 min, and quantitatively transformed into the trans-substituted lactone (5). However, the diazo compound (6), derived from dimethyl malonate was transformed very slowly, only 25% of the staring material had reacted after 24 h, producing only the lactone (7), in 24% yield.



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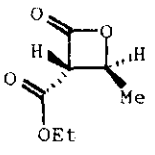

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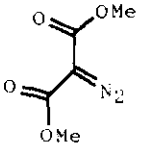

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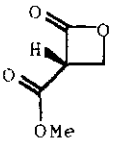

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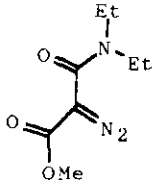
We were intrigued by the possibility of preparing β-lactams by this process. Exotic amines are usually quite expensive and if a symmetrical malonamide was used, then insertion would occur on only one of the two amine moieties, resulting in the unproductive use of the other amine moiety. On the other hand, β-lactam formation utilizing a suitable mixed malonate-malonamide, which could be forced to react at the amide center and not at the ester, would be more expedient.

Our results above showed that methyl groups and neopentyl-like methylene groups participated very reluctantly in these insertion reactions, and so we decided to perform this insertion reaction on the mixed malonate-malonamide derived diazo compound (8) in an attempt to force the insertion to occur into the amidic methylene group. The resulting, slow reaction, only 40% of the starting material had reacted after 12 h, provided only the trans-substituted β-lactam (9), in 40% yield, with no detectable amounts of any lactone. Thus, methylene groups attached to nitrogen are significantly more favorable sites for these insertion reactions



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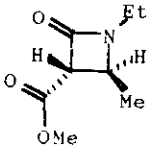

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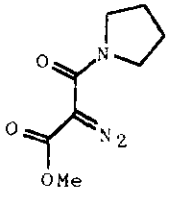

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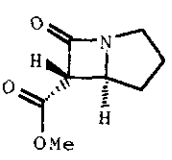

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than methyl groups attached to oxygen. To our surprize, the diazo compound (10) did not react as was expected and was recovered from attempts to convert it into the bicyclic β-lactam (11).

We have not attempted to optimize the yields of the reactions described above, however it is clear that these insertion reactions can be developed into a valuable procedure for the selective preparation of more complex β-lactones and β-lactams (ref. 10).

EXPERIMENTAL

All of the new compounds described above were gums or oils. High resolution mass spectrometry, measured on an AEI M5-9025 double focusing high resolution mass spectrometer and on Finnigan CHS single focusing mass spectrometer, was therefore used to ascertain elemental composition. Infrared spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton magnetic resonance spectra were determined on a Varian EM-360A, or on a IBM NR/300 FT NMR, or on a IBM WP/200-5Y, and/or on a JEOL/JNM/GX-400 FT NMR spectrometer. Chemical shifts are reported in parts per million (ppm, δ values) downfield from internal tetramethylsilane (TMS). Thin-layer chromatography was performed with 13181 silica gel with fluorescent indicator (Kodak) as the adsorbent in 0.2 mm thick, plastic-backed plates. All of the compounds described below were purified by column chromatography on silica gel 60 mesh, unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Preparation of Ethyl Potassium Malonate.

Potassium hydroxide (5.6 g, 100 mmol) was dissolved in 100 ml of absolute ethanol and this solution was added dropwise to a stirred solution of diethylmalonate (20.225 g, 100 mmol) in 100 ml of absolute ethanol, at 0°C, during 1 h. The reaction mixture was then allowed to warm up to room temperature and the stirring was continued for an additional 1 h. The white crystals of the salt were separated by vacuum filtration and dried under vacuum for 3 h.

Preparation of Ethyl Malonoyl Chloride.

Oxaloyl chloride (3.18 g, 25 mmol) in 10 ml of dried benzene was added dropwise to

a stirring suspension of ethyl potassium malonate (2.42 g, 20 mmol) in dried benzene (50 ml) at 0°C during 1 h. After the solution had been stirred at room temperature for 1 h, the solid residue was removed by filtration and the filtrate, was concentrated by rotary evaporation of the benzene and excess oxalyl chloride to give the desired compound (3.61 g, 90%). This acid chloride, which was shown by nmr to be almost pure, was used without further purification. Methyl malonoyl chloride was also prepared by an analogous procedure.

Preparation of Diazomalonate (1).

To a stirred solution of the hydroxy ketone (2) (1.66 g, 10.0 mmol) in methylene chloride (40 ml), in a 100 ml three-necked round bottom flask, was added, dropwise and simultaneously, pyridine (1.19 g, 15.0 mmol) dissolved in methylene chloride (15 ml) and ethyl malonoyl chloride (1.66 g, 11.0 mmol) dissolved in methylene chloride (20 ml), at 0°C, during 1 h. After an additional 1 h, the resulting precipitate was removed by filtration; the filtrate was extracted with methylene chloride; the extract was washed with water and then dried over sodium sulfate. The solvent was removed by a rotary evaporator to give the colorless oily mixed malonate ester (2.58 g, 92%): Ir (neat, cm^{-1}) 3060 (w), 2970 (s), 2935 (s), 1745 (s), 1720 (s), 1655 (w); ^1H nmr (60 MHz, $CDCl_3$, ppm) 5.10-4.85 (m, 2H), 4.15 (q, J = 6 Hz, 2H), 4.10 (s, 2H), 3.40 (s, 2H), 3.00 (m, 1H), 2.45-2.25 (m, 6H), 1.85-1.65 (m, 2H), 1.25 (t, J = 6 Hz, 3H); mass spectrum, exact mass calcd for $C_{15}H_{20}O_5$ m/z 280.1311, obsd m/z 280.1313.

The ester above (2.80 g, 10.0 mmol) was dissolved in dry acetonitrile (30 ml), triethylamine (1.22 g, 12.0 mmol) and tosyl azide (2.37 g, 12.0 mmol) were each added to the solution. The mixture was stirred for 12 h at room temperature. After evaporating the solvent, the reaction product was suspended in ether (50 ml) and the insoluble material was removed by filtration. The filtrate was washed with 1M sodium hydroxide, water and brine, and dried over magnesium sulfate. After filtration and concentration of the filtrate, the residue was purified by column chromatography (hexane:ethyl acetate, 3:1) to provide the diazo compound (1) (3.00 g, 98%) as a greenish liquid: Ir (neat, cm^{-1}) 3050 (w), 2960 (m, sh) 2925 (s), 2120 (s), 1750 (s), 1725 (s), 1710 (s), 1680 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 5.15-4.85 (m, 2H), 4.30 (q, J = 6 Hz, 2H), 2.25 (s, 2H), 3.05 (m, 1H), 2.55-2.25 (m, 6H), 1.85-1.65 (m, 2H), 1.35 (t, J = 6 Hz, 3H); mass spectrum, exact mass calcd for $C_{15}H_{18}N_2O_5$ m/z 306.1216, obsd m/z 306.1212.

Preparation of Mixed Ester/Amide Precursors of Compounds (8) and (10).

Under the previously described conditions for the preparation of the mixed malonate precursor of compound (1), the following compounds were prepared.

The treatment of methyl malonoyl chloride with two equivalents of diethylamine gave the mixed methyl ester, diethyl amide (98% yield): Ir (neat, cm^{-1}) 2970 (m), 2875 (m), 1710 (s), 1620 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 3.90 (s, 3H), 3.60 (s, 2H), 3.55 (q, J = 6 Hz, 4H), 1.50 (t, J = 6 Hz, 6H); mass spectrum, exact mass calcd for $C_8H_{15}NO_3$ m/z 173.1052, obsd m/z 173.1052.

The treatment of methyl malonoyl chloride with two equivalents of pyrrolidine gave the mixed methyl ester, pyrrolidinyl amide (98% yield): Ir (neat, cm^{-1}) 2955 (m), 2880 (m), 1715 (s), 1615 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 3.90 (s, 3H), 3.65 (m, 4H), 3.60 (s, 2H), 2.00 (m, 4H); mass spectrum, exact mass calcd for $C_8H_{13}NO_3$ m/z 171.0895, obsd m/z 171.0897.

The following diazo compounds were prepared from the respective malonates, or malonamides, using the same conditions described for the preparation of the diazo compound (1). All of these reactions produced almost quantitative yields (>98%).

Compound (4): Ir (neat, cm^{-1}) 2985 (s), 2940 (m), 2810 (w), 2140 (s), 1730 (s), 1680 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 3.95 (q, J = 6 Hz, 4H), 1.20 (t, J = 6 Hz, 6H); mass spectrum, exact mass calcd for $C_7H_{10}N_2O_4$ m/z 186.0641, obsd m/z 186.0637.

Compound (8): Ir (neat, cm^{-1}) 2960 (m), 2870 (w), 2110 (s), 1710 (s), 1620 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 3.90 (s, 3H), 3.60 (q, J = 6 Hz, 4H), 1.45 (t, J = 6 Hz, 6H); mass spectrum, exact mass calcd for $C_8H_{13}N_3O_3$ m/z 199.0957, obsd m/z 199.0961.

Compound (10): Ir (neat, cm^{-1}) 2950 (m), 2870 (w), 2105 (s), 1705 (s), 1605 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 3.95 (s, 3H), 3.50 (m, 4H), 2.10 (m, 4H); mass spectrum, exact mass calcd for $C_8H_{11}N_3O_3$ m/z 197.0800, obsd m/z 197.0804.

Reactions of The Diazocompounds With Rhodium Diacetate.

Preparation of (3).

The diazo compound (1) (1.53 g, 5.0 mmol) was dissolved in dried methylene chloride (15 ml), under nitrogen, and then rhodium diacetate (10 mg) was added. The solution was stirred at room temperature for 1.5 h. Gas evolution was observed and the mixture turned brown. At the end of the reaction, 45 min, the reaction mixture was diluted with 4% aqueous HCl (20 ml) and the mixture was extracted with two 30 ml portions of methylene chloride. The combined organic extracts was washed with

saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated by rotary evaporator. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate, 2:1) to give compound (3) (0.47 g, 34%): Ir (neat, cm^{-1}) 1840 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 5.17-4.75 (m, 2H), 4.40-4.00 (m, 4H), 3.18-2.87 (m, 1H), 2.55-2.15 (m, 6H), 1.75 (d, J = 6.0 Hz, 3H).

Preparation of (5).

Compound (4) was treated with rhodium diacetate, as was described in the preparation of (3), to give the β-lactone (5) in 99% yield: Ir (neat, cm^{-1}) 2970 (s), 2925 (m), 1835 (s), 1730 (s); ^1H nmr (60 MHz, $CDCl_3$, ppm) 4.90 (dq, J = 4 and 6 Hz, 1H), 4.30 (q, J = 7 Hz, 2H), 4.15 (d, J = 4 Hz, 1H), 1.65 (d, J = 6 Hz, 3H), 1.35 (t, J = 7 Hz, 3H); ^{13}C nmr (200 MHz, $CDCl_3$, ppm) 164.18, 162.52, 71.13, 62.21, 61.54, 19.49, 13.88; mass spectrum, exact mass calcd for $C_7H_{10}O_4$ m/z 158.0579, obsd m/z 158.0575.

Preparation of (9).

Similarly β-lactam (9) was formed from compound (8) by treatment with rhodium diacetate in methylene chloride at room temperature for 12 h. About 40% of the starting material was converted quantitatively into compound (9) and the remaining 60% of the starting material was recovered. Ir (neat, cm^{-1}) 2960 (m), 2930 (m), 2870 (w), 1755 (s), 1725 (s); ^1H nmr (200 MHz, $CDCl_3$, ppm) 3.94 (dq, J = 2.25 and 6.17 Hz, 1H), 3.34 (s, 3H), 3.52 (d, J = 2.25 Hz, 1H), 3.37 (dt, J = 21.54 and 7.26 Hz, 1H), 3.08 (dt, J = 21.17 and 6.92 Hz, 1H), 1.36 (d, J = 6.17 Hz, 3H), 1.18 (t, J = 7.32 Hz, 3H); mass spectrum, exact mass calcd for $C_8H_{13}NO_3$ m/z 171.0895, obsd m/z 171.0896.

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