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Synthesis of Bicyclic Adduct through Regioselective Baeyer-Villager oxidation

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ABSTRACT

Baeyer-Villager oxidation reaction has become accepted as a right approach in the ring expansions for the preparation of both bicyclic and tricyclic lacotnes; however, successful application of the regioselective Bayer-Villager oxidation protocol to the synthesis of particularly congested scaffolds remains distinctly tricky. Herein the Baeyer–Villiger oxidation of Bicyclo[3.2.0]hept-3-ene-6-one is studied with oxygen insertion leading to the functionalized oxabicyclic adduct with complete regioselectivity.

Keywords: bicyclic adduct, regioselectivity, Bayer Villager oxidation, synthesis

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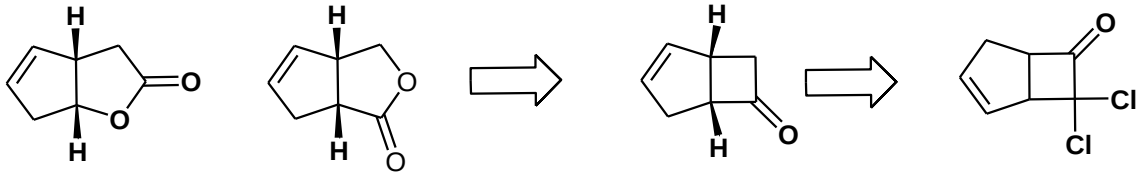
Introduction

In our previous report[1,2], we have shown the versatility of thermal cycloaddition to form cyclobutanones. We have also demonstrated the efficiency of the Baeyer-Villager oxidation protocol in the formation of the resulting AB-ring systems[2]. In order to pursue our research plan, an efficient way of assembling a suitably substituted AB-ring system was required. What appeared to be a very facile route was a method developed by Grieco[4,5,6,7] in which the AB-ring could be generated by a [2+2] cyclo-addition between an alkene and dichloroketene. This strategy was chosen as a route to prepare the model cyclobutanone (3a). It was also decided to repeat the method developed by Grieco with slight modification involving a change in the solvent. With this in mind, cyclopentadiene (1) and dichloroacetyl chloride (2) was investigated, anticipating the correct product structure (6) and (7) at the end of Baeyer-Villager oxidation.

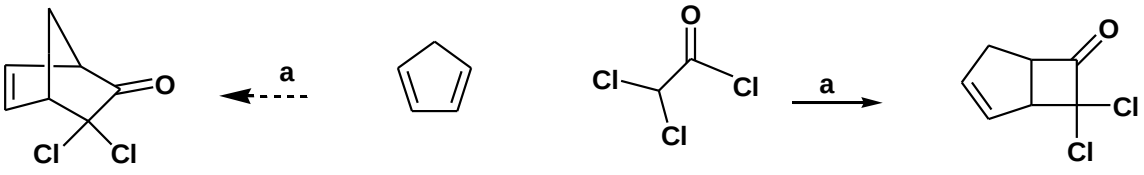


(6) **(5)** **(4)** **(3a)**

Scheme 1.1

Result and Discussion

A mixture of cyclopentadiene (1) and dichloroacetyl chloride (2) in DCM was treated with a solution of triethylamine at room temperature to furnish (3) as the predominant product in the moderate yield of 41%. The IR spectrum of this product showed absorption frequencies at 1806 cm^{-1} and at 1608 cm^{-1} representative of the ketone and alkene respectively and this was consistent with that expected for structure of adduct (3). The ^{1}H NMR spectrum amongst other things, showed a one proton multiplet at δ 6.07-6.02 ppm, a one proton resonance at δ 5.82-5.78 ppm, the bridgehead proton resonace as a double doublet centred at δ 4.27 ppm (*J* 6.4 Hz) and a multiplet centred at δ 4.09-4.05 ppm. These data, together with characteristic molecular ion of *m/z* 155 in the mass spectrum confirmed the successful preparation of ketene-diene adduct (3a). Based on the IR stretching regions for the carbonyl and alkene, the possibility of a Diels-Alder adduct (3b), been formed was discarded Scheme 2.1.



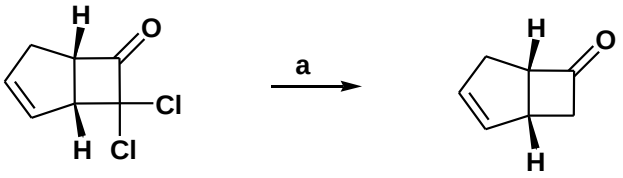
(3b) **(1)** **(2)** **(3a)**

(a) DCM, Et_3N, 0 ^{o}C, 41%

Scheme 2.1

The chlorine atoms in ketene-diene adduct (3a) were readily removed and the compound was efficiently converted to α-methylene-keto adduct (4) by treatment with excess zinc dust in glacial

acetic acid at 70 ^{o}C. It was hoped that the bicyclic compound (4) would be a suitable partner with aqueous acetic acid and H_2O_2 for regioselective Baeyer-Villager oxidation especially considering the two sites available to for oxygen insertion. In any case, the product was characterized using analytical techniques. The IR spectrum of (4) disclosed a strong carbonyl stretching absorption at 1805 cm^{-1} and the stretching of the double bond gave rise to an absorption at 1614 cm^{-1}. The ^{1}H NMR spectrum revealed the appearance of the methylene protons alpha to the ketone group as a two set of resonances centered at δ 3.89-3.87 ppm and at 3.31 ppm (1H, dddd, *J* 17.0 Hz, *J* 8.9 Hz, *J* 2.9 Hz, *J* 0.6 Hz, $CHCH_2C{=}O$), and a pair of one proton multiplets typical of the alkene at δ 5.87-5.81 ppm and at δ 5.80-5.79 ppm confirmed the product to be the desired α-methylene-keto adduct (4) Scheme 2.2.



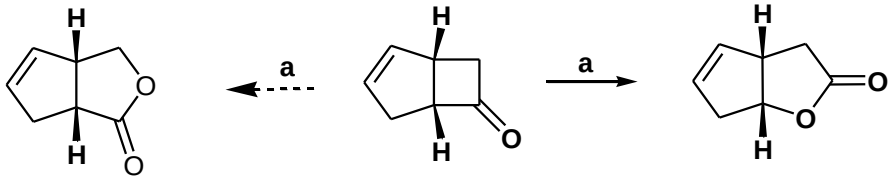
(3a) **(4)**

(a) acetic acid, zinc dust, 70 ^{o}C

Scheme 2.2

Ring expansion of cycobutanones by Baeyer-Villager oxidation

The availability of the ketene-adducts opened the pathway towards Baeyer-Villager oxidation and such a reaction was carried out in a solution of (4) and glacial acetic acid at 0 ^{o}C with 27.5% H_2O_2 for approximately 24 h. Gratifyingly, the bicyclic adduct system (5a) was obtained in almost quantitative yield and as a single regioisomer. That (5a) was the only product formed, was also confirmed by spectroscopic analysis. The IR spectrum of (5a) showed the carbonyl group of the cyclic ester at 1769 cm^{-1} and the high frequency cyclobutanone carbonyl stretching band was absent. There was also a stretching at 1639 cm^{-1} which corresponded to the double bond. The ^{1}H NMR spectrum not only revealed the disappearance of the methine resonance adjacent to ketone group in the cyclobutanone of (4), but also showed a downfield shift of the methine adjacent to the oxygen in the lactone, which now centered at δ 5.15 ppm. The diastreotopic CH_2 protons adjacent to the ester showed as a double doublet centred at δ 2.81 ppm (*J* 18.0 Hz and *J* 5.6 Hz) and at 2.47 ppm (*J* 18.0 Hz and *J* 5.9 Hz). These data excluded (5b) and confirmed (5a) Scheme 2.3.



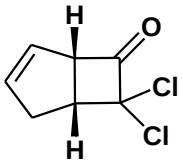
(5b) **(4)** **(5a)**

(a) glacial acetic acid, 27.5% H_2O_2 , 70%

Scheme 2.3

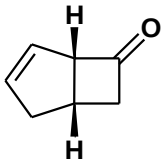
3.0 Experimental

7, 7-Dichlorobicyclo [3.2.0] hept-3-en-6-one (3a)



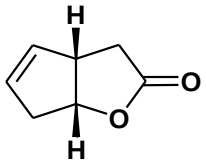
To a vigorously stirred solution of freshly distilled cyclopentadiene (220) (3.4 g, 0.05 mmol, 1.00 equiv) and of dichloroacetyl chloride (248) (3.8 g, 0.03 mmol, 0.50 equiv) in dry DCM (25 mL) was added (2.7 g, 0.3 mmol, 0.50 equiv) of dry triethylamine in DCM (25 mL) over a period of 1 h. After stirring for 13 h under an atmosphere of nitrogen, the reaction mixture was filtered and the filter cake was washed with hexane (30 mL). The solvent was removed *in vacuo*, yielding a brown liquid weighing (4.1 g). Vacuum distillation afforded a colourless oil (3.6 g, 41%); υ_{max} (thin film/cm^{-1}), 2924, 2855, 1806, 1608, 1028, 754, 632; δ_H (250 MHz, $CDCl_3$), 6.07-6.02 (1H, m, CH=CH), 5.82-5.78 (1H, m, CH=CH), 4.27 (1H, dd, J_{cis} 6.4 Hz, *J* 1.2 Hz, CHC=O, bridgehead), 4.09-4.05 (1H, m, $CHCl_2$, bridgehead), 2.55-2.84 (2H, m, CH_2); δ_C (62.5 MHz, $CDCl_3$) 198.2, 137.3, 128.8, 88.5, 59.9, 58.9, 36.5; $^m/_z$ (C.I) 175 (MH^+, 3.82%), 178 (100%), 148, (8.4%), 141, (50.8%) $C_7H_7OCl_2$, requires 175.9796, found, 175.9794.

Bicyclo[3.2.0]hept-3-ene-6-one (4)



To a vigorously stirred suspension of zinc dust (1.1 g) in of glacial acetic acid (2 mL) at room temperature was added drop wise 7,7-dichlorobicylco[3.2.0] hep-2-en-6-one (249) (500 mg, 2.83 mmol, 1.00 equiv) in glacial acetic acid (2 mL). After the addition was complete, the temperature was raised to 70 ^oC for 40 min. TLC analysis indicated no starting material remaining. The reaction mixture was cooled, treated with ether, and the zinc residue was filtered. The ethereal layer was washed with a saturated solution of Na_2HCO_3 (4 x 10 mL) to remove the acetic acid and dried over ($MgSO_4$). The solvents were removed *in vacuo*. Distillation in a Kugelrohr (100-110 ^oC oven temp., 0.3 mmHg) afforded (215). Further purification using column chromatography on silica, eluting with, ether : light petroleum (1:3) afforded (215) as a colourless oil (234 mg, 77%); υ_{max} (thin film/cm^{-1}), 2800, 1805, 1614, 1466; δ_H (250 MHz, $CDCl_3$) 5.87-5.81 (1H, m, CH=CH), 5.80-5.79 (1H, m, CH=CH), 3.89-3.87 (1H, m, CH=CHCHC=O), 3.52-3.43 (1H, m, $CHCH_2C$=O), 3.31 (1H, dddd, *J* 17.0 Hz, *J* 8.9 Hz, *J* 2.9 Hz, *J* 0.6 Hz, $CHCH_2C$=O), 2.68-2.66 (2H, m, CH_2CH), 2.49 (1H, ddddd, *J* 17.0 Hz, *J* 9.6 Hz, *J* 2.0 Hz, *J* 1.8 Hz, $CHCH_2$); δ_C (62.5 MHz, $CDCl_3$) 211.5, 134.4, 133.2, 66.2, 55.2, 39.5, 37.1; $^m/_z$ (C.I) 108 (MH^+), C_7H_9O, requires 108.1375, found , 108.1355.

Tetrahydrocyclopenta[*b*]furan-2-one (5a)



To a stirred solution of bicyclo [3.2.0] hept-2-ene-6-one (251) (2 g, 18.5 mmol, 1.00 equiv) in of 90% aqueous acetic acid (50 mL) cooled to 0 ^oC was added 27.5% H_2O_2 (5.03 g, 148 mmol, 8.00 equiv) in of 90% aqueous acetic acid (50 mL). The reaction was allowed to warm-up to room temperature for 24 h., after which time TLC analysis indicated a new product has been formed. The product was extracted with ether (4 x 20 mL), washed with 10% aqueous sodium sulfite (2 x 15 mL) and saturated sodium carbonate (2 x 15 mL). The ether layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography, on silica, eluting with hexane : ethyl acetate (2:1) afforded the title compound as a pale green oil (1.6 g, 70%); υ_{max} (thin film/cm^{-1}), 2253, 1769, 1639, 1402, 1256, 1177, 1096; δ_H (400 MHz, $CDCl_3$) 5.82-5.77 (1H, m, CH=CH), 5.81-5.79 (1H, m, CH=CH), 5.15 (1H, ddd, *J* 4.0 Hz, *J* 2.0 Hz, CHCO), 3.55-3.50 (1H, m, CHCH=CH), 2.81 (1H, dd, *J* 18.0 Hz, *J* 5.6 Hz ,CH_2), 2.74-2.71

(2H, m, CH_2), 2.47 (1H, dd, *J* 18.0 Hz, *J* 5.9 Hz, *J* 1.7 Hz CH_2); δ_C (100 MHz, $CDCl_3$) 176.8, 131.7, 130.2, 83.1 45.6, 39.9, 33.3; $^m/_z$ (C.I) 124 (MH^+, 100%), 107 (22%), 103 (8%), 95 (12%), 81 (9%), $C_7H_9O_2$, requires 124.0524, found, 124.0523.

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