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AN IMPROVED SYNTHESIS OF α,β METHYLENIC CYCLIC KETONES

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ABSTRACT: This communication describes a convenient two steps procedure for the preparation of α,β methylenic cyclic ketones from arylmethyl ketones involving a preformed Mannich reagent.

Although a variety of approaches for the synthesis of α,β unsaturated carbonyl compounds [1,2,3]have hitherto been reported, considerable attention to new methods for the building of this system is still being paid from the view point of the medicinal activity of these compounds based on their chemical reactivity towards various enzymes. Effectively, α,β unsaturated carbonyl compounds are of great biological importance because of their behaviour to act as substrates in Michael type reaction with sulfhydryl groups of enzymes or proteins. For example, both α methylene lactone or α,β unsaturated ketones can alkylate the sulfhydryl groups of cysteine[4]. The diuretic Ethacrynic acid, which contains a similar α methylenic ketone group, is thought to act as binding thiol group by conjugate addition[5].

α methylenation of carbonyl compounds is often achieved by reaction with formaldehyde to give the intermediate α hydroxymethylene carbonyl compounds undergoing an acid or base induced β elimination.[6] Others methods involve an initial Mannich aminoalkylation of the α acidic proton, followed by quaternization and β elimination of the alkylamino group[7] or a Mannich reaction in high boiling solvents such as

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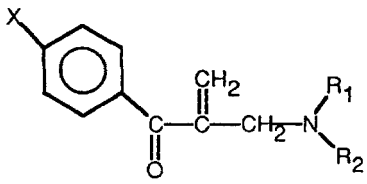
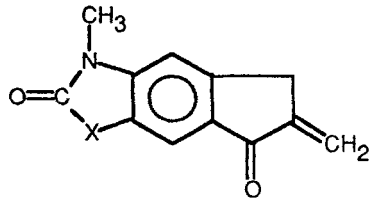
dimethylformamide or acetic acid [8]. Modifications of the Mannich reagent may consist, by the use of s.trioxanne and N-méthylanilinium trifluoroacetate [9] or by the use of preformed Mannich salts such as N,N-dialkyl (methylene) ammonium iodide [10] or acetate [11] obtained by iodotrimethylsilane or acetic anhydride cleavage of tertiary geminal diamines such as N,N,N',N' tetramethyldiaminomethane.

Some of us, have earlier synthesized [12] acrylophenones derivatives (Scheme 1 ; Structure [A]) and showed that their antimicrotubular and antifungal properties were related to the α, β unsaturated carbonyl group. Based on the antihelmintic activity of some antimicrotubular benzimidazolic carbamates [13], some of these acrylophenones were tested against Echinococcus multilocularis and showed interesting activity [14]. Thus, in continuation of our program on potential therapeutic benzoxazolyl and benzoxazinyl compounds, it seemed us of interest, for a latter antiparasitic evaluation, to study the synthesis of α,β methylenic cyclic ketones of structure [B] or [C] (Scheme 1).



Structure [A]



X: O Structure [B]

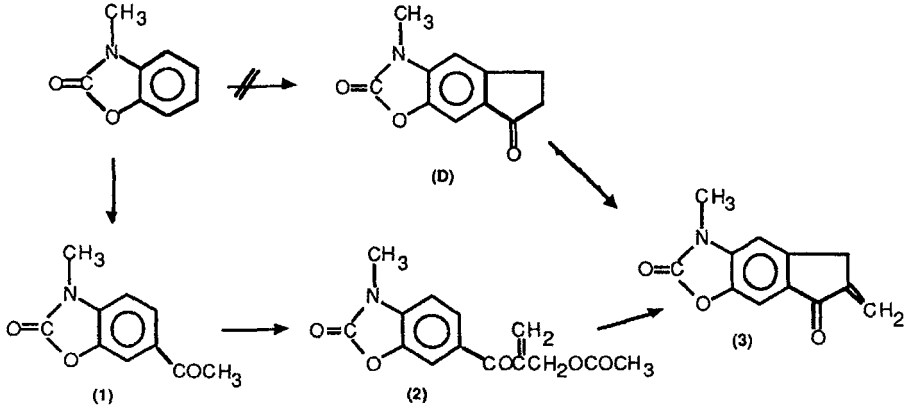
X: $OC(CH_3)_2$ Structure [C]

Scheme 1

An obvious route (Scheme 2) to compounds [B] would be the direct α methylenation of the indanone [D]. However, in our hands, the synthesis of this precursor failed and this paper describes an alternative indirect method for introducing a methylenic moiety α to a cyclic carbonyl group.This method involves a novel and easy two steps conversion of an arylmethyl ketone to the corresponding α,β methylenic cyclic ketone , using readily available reagents(Scheme 2).

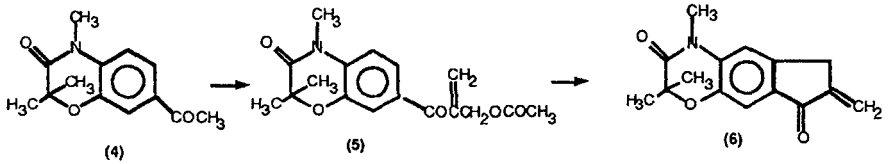
Acetylation of 2-oxo-2,3-dihydro benzoxazole with acetic acid in polyphosphoric acid[15] gave the methyl ketone(1). This was reacted with an excess of N,N,N',N'-tetramethyldiaminomethane (preformed Mannich

salt: dimethylmethyleneammonium acetate) to give (60% yield) the acetyloxymethyl compound (2) containing a vinyl ketonic moiety.This reaction probably involves two Mannich condensation of the arylmethyl ketone followed by deamination [7] and acetolysis[16] steps because of the presence of acetate ion and acetic anhydride in the reaction medium. Heating (2) with concentrated sulfuric acid at 40°C led to hydrolysis of the ester group and cyclization (80% yield) to the ketone (3) .



Scheme 2

Similarly, the 7-acetyl-3-oxo-2,2,4-trimethyl-2,3-dihydro [1,4] benzoxazine (4) was used as starting material [17](Scheme 3) and reacted with the Mannich reagent followed by treatment with sulfuric acid (isolated yield for each steps: 55 and 50%).



Scheme 3

EXPERIMENTAL PART

Melting points were determined on a BUCHI 510 capillary apparatus and are uncorrected. Microanalyses were performed by CNRS laboratories (Vernaison). Infra-red spectra were obtained on a PERKIN-ELMER 297 spectrometer on KBr paths. ^{1}H-NMR spectra were obtained on a WP 80 BRUCKER spectrometer. All NMR spectra were run in

$CDCl_3$ and are reported relative to the internal standard tetramethylsilane as values in parts per million,using the following abbreviations : s, singulet ; d, doublet ; t, triplet ; m, multiplet.

6-(3-acetoxy-2-methylenepropionyl)-2-oxo-3-methyl-2,3-dihydrobenzoxazole (2)

To a stirred suspension of the ketone (1)[17] (19g, 0.1mol) in N,N,N'N'-tetramethyldiaminomethane (50 ml, 0.37 mol)is added dropwise acetic anhydride (100 ml, 1.04 mol). The mixture is heated at 90°C during 3 hours. After cooling, the reaction mixture is poured into cold acidic water (500 ml) and the resulting precipitate collected by filtration is washed with water and purified after drying by recrystallisation from cyclohexane(16.5g, 60% yield). mp 104-106°C; IR: 3040-2820, 1780, 1730, 1640, 1610 cm^{-1}; ^{1}H-NMR δ: 2.20 (s, 3H); 3.50 (s, 3H) ; 4.95 (s, 2H) ; 5.70 (s, 1H) ; 6.10 (s, 1H) ; 7.00 (d, J= 8.2 Hz, 1H) ; 7.70 (d, J=2.75 Hz, 1H) ; 7.8O (dd, J=8.2 and 2.75 Hz, 1H).Anal Calcd for $C_{14}H_{13}NO_5$: C, 61.08 ; H, 4.76 ; N, 5.08 ; O, 29.06. Found : C, 61.02 ; H, 4.62 ; N, 4.96 ; O, 29.08.

7-(3-acetoxy-2-methylenepropionyl)-3-oxo-2,2,4-trimethyl-2,3-dihydro[1,4]benzoxazine(5)

This compound is obtained in a similar manner from the ketone (4)[17] (11.7g, 0.05 mol) , N, N, N', N'-tetramethyldiaminomethane (25ml, 0.185 mol) and acetic anhydride (50 ml, 0.52 mol). Yield: 8.7g from methanol (55%). mp 108-110°C ; IR: 3060-2920, 1720, 1680, 1640, 1600, 910 cm^{-1}; ^{1}H-NMR δ: 1.50(s, 6H) ; 2.10(s, 3H) ; 3.40(s, 3H) ; 5.00(s, 2H) ; 5.80(s, 1H) ; 6.10(s, 1H) ; 7.00(d, J=8.8 Hz, 1H) ; 7.45(d, J=3 Hz, 1H) ; 7.60(dd, J=8.8 and 3 Hz, 1H). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34 ; H, 6.03 ; N, 4.41 ; O, 25.21. Found : C, 64.57 ; H, 6.12 ; N, 4.21 ; O, 25.20.

2,7-dioxo-3-methyl-6-methylenecyclopenta[f]-2,3-dihydrobenzoxazole(3)

A solution of the compound (2) (8g, 0.03 mol) in concentrated sulfuric acid (30 ml) is heated at 40°C for 4 hours. The mixture is then cooled and poured into cold water (150 ml). The separated solid is filtered, washed with water, dried and recrystallised from acetone or acetonitrile (4.3g, 80% yield). mp 210-215°C ; IR: 3060-2900, 1760, 1680, 1610, 920 cm^{-1} ; ^{1}H-NMR δ : 3.45(s, 3H) ; 3.80(s,2H) ; 5.65(s, 1H) ; 6.80(s,1H) ; 7.10(s, 1H) ; 7.60(s, 1H).Anal. Calcd for $C_{12}H_9NO_3$: C,66.97 ; H, 4.28 ; N, 6.50 ; O, 22.30. Found: C, 66.93 ; H, 4.05 ; N, 6.49 ; 22.53.

3,8-dioxo-2,2,4-trimethyl-7-methylenecyclopenta[g]-2,3-dihydro[1,4]benzoxazine(6)

This compound is obtained in a similar manner from the ketone (5) (9.5g ; 0.03 mol) and concentrated sulfuric acid (30 ml). Yield: 3.85g from methanol (50%). mp 182-185°C ; IR: 3040-2840, 1680, 1640, 1600, 940 cm^{-1} ; ^{1}H-NMR δ : 1.50(s, 6H) ; 3.40(s, 3H) ; 3.70(s, 2H) ; 5.60(s, 1H) ; 6.35(s,1H) ; 7.00(s, 1H) ; 7.45(s, 1H).Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02 ; H, 5.88 ; N, 5.44 ; O, 18.65. Found: C, 70.01 ; H, 5.91 ; N, 5.29 ; O, 18.78.

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