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A NEW ROUTE TO 1,4-DIKETONES AND ITS APPLICATION TO (Z)-JASMONE AND DIHYDROJASMONE SYNTHESIS.

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Abstract: (Z)-Jasmone ,dihydrojasmone and other 3-methylcyclopent-2-en-1-ones are easily synthesized starting from aldehydes and 1-(2-methyl-1,3-dioxolane-2-yl)-2-nitroethane as reagent for 3-ketobutyl anion synthon. Nitro-aldol condensation is the chainlegthening reaction followed by oxidation and denitration via p-toluenesulfonylhydrazones of the corresponding α-nitroketones. Removal of protecting groups gives 1,4-diketones which are then cyclized with alkali.

The efficient preparation of 1,4-diketones[1,2] is a fascinating subject because they can be converted into substituted 3-oxocyclopentenones[2-4] by base catalyzed cyclization. A large number of biologically active natural products possess this mojety as structural feature; among them dihydrojasmone (7c) and (Z)-jasmone (7d) are naturally occurring substrates widely used as important perfume ingredients.

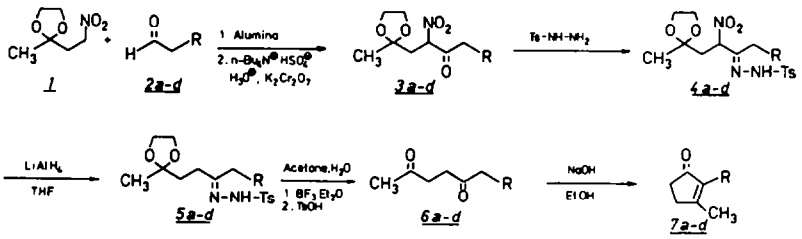
A variety of synthetic approaches for the preparation of 1,4-diketones[1,2] have been developed but several of the existing methods follow lengthy procedures and/or involve expensive chemicals.The recently disclosed procedures[5,6] for denitration of α-nitroketones are of interest in that they provide the possibility for the construction of a wide range of functionalized carbon chains which can be further elaborated.

This paper describes a simple synthesis of 1,4-diketones in which this reaction can be considered the key step of the sequence (Scheme 1).

The starting point for the present synthetic scheme is the nitro-aldol condensation (Henry reaction) on alumina surface[7] without solvent between aldehydes 2a-d and 1-(2-methyl-1,3-dioxolane-2-yl)-2-nitroethane (1) followed by *in situ* oxidation with potassium dichromate under phase-transfer conditions using tetrabutylammonium hydrogen sulphate as catalyst.

Compound 1 can be considered as reagent for 3-ketobutyl anion synthon and was easily prepared from 3-buten-2-one by reaction with sodium nitrite-acetic acid in tetrahydrofuran at room tempera-

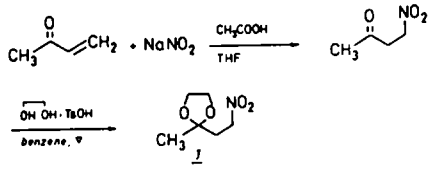
Scheme 1



	R	yield of 3	4	5	6	7
a	H	72%	90%	80%	72%	68%
b	CH_2Ph	85%	80%	88%	68%	84%
c	$CH_2[CH_2]_3CH_3$	75%	93%	90%	82%	89%
d	CH_2–CH=CH–CH_3	84%	90%	94%	84%	78%

ture[8] and successive acid catalyzed (TsOH) ketalization with ethylene glycol in refluxing benzene (Scheme 2).

Scheme 2



On the other hand the (Z)-double bond in the main chain of (Z)-jasmone was derived from (Z)-3-hexen-1-ol, known as "leaf alcohol" and commercially available with more than 97% stereochemical purity; its conversion into (Z)-4-heptanal (2d) was accomplished according the procedure of Stetter and Kuhlmann.[9]

Reaction of α-nitroketones 3a-d with p-toluenesulfonylhydrazine in methanol furnished compounds 4a-d as solid derivatives, easily purified by crystallization. Denitration of compounds 4a-d proceeded smoothly by reaction with lithium aluminium hydride in tetrahydrofuran[5] to give solid p-toluenesulfonylhydrazones 5a-d in excellent yields. Regeneration of the two differently protected carbonyl groups of compounds 5a-d was accomplished in an one-pot reaction using boron trifluoride etherate and p-toluesulfonic acid in acetone. 1,4-Diketones 6a-d were subsequently cyclized to cyclopentenone derivatives 7a-d via an intramolecular aldolization-dehydration.[10] This compound was shown to be identical with authentic specimens of 3-methylcyclopent-2-en-1-one, 3-methyl-2-(2-phenylethyl)cyclopent-2-en-1-one, dihydrojasmone and (Z)-jasmone by spectroscopy (IR, ^{1}H NMR) and chromatography (TLC, GLC).

We think the present method has some merits since the starting materials are easily accessible and relatively enexpensive.Compared to organometallic reagents frequently used in the chainlenghtening reaction to obtain 1,4-diketones, nitroalkane derivative 1 is easy to handle also in scale process. Furthermore reactions give crude products suitable for the next process or products which are easy to purify by crystallization.

We hope that our findings may encourage a much greater use of nitroalkane derivatives as functionalized alkyl anionic synthon.

EXPERIMENTAL

Proton NMR spectra were recorded at 90 MHz on a Varian EM390 instrument and at 100MHz

on a Varian XL-100 operating in the CW mode. ^{1}H NMR shifts are given in parts per milion from Me_4Si in $CDCl_3$ solvent. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Microanalyses were performed by using C,H,N Analyzer Model 185 from Hewlett-Packard Co. Vapor-phase chromatographic analyses were performed on a Carlo Erba FRACTOVAP 4160 HRGC instrument using capillary column of fused silica (0.40÷45nmx25mt) with Carbowax 20M. Buten-3-one, aledhydes 2a-c, ethylene glycol, alumina, tetrabutyl ammonium hydrogensulphate and p-toluenesulphonylhydrazine are commercial materials. (Z)-4-Heptenal(2d) was prepared in good yield according the procedure of Stetter and Kuhlmann[9] starting from commercial (Z)-3-hexen-1-ol through its bromide and (Z)-1,1-diethoxy-4-hepten. Tetrahydrofuran (THF) was obtained anhydrous by distillation over lithium aluminium hydride under argon.

1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitroethane(1). Nitrobutan-3-one (4.26 g,36.4 mmol) prepared in 80% yield according the procedure of Miyakoshi and coworkers[8], was placed in a dried, nitrogen flushed, 100 ml three-necked flask equipped with a Dean Stark apparatus and condenser. Benzene (50 ml), ethylene glycol (17.0 g,274 mmol) and p-toluenesulfonic acid (0.085 g, 0.5 mmol) were added and the solution was refluxed for 24 h removing water. The mixture was cooled and $NaHCO_3$ saturated aqueous solution (30 ml) added. The organic layer was separated and washed with NaCl saturated aqueous solution (3x30 ml). The inorganic phase was extracted with chloroform (3x30 ml) and the combined organic layers dried ($MgSO_4$). The solvent was removed at reduced pressure to leave an oil. Vacuum distillation afforded 14.6 g of product (87% yield): bp 83-89° C (0.8 mm_{Hg}); IR(neat) 1550(NO_2) cm^{-1}; ^{1}H NMR δ 4.45(t,2H,J=7.3Hz); 3.93(s,4H); 2.42(t,3H,J=7.3Hz); 1.33(s,3H).Anal.Calcd for $C_6H_{11}O_4N$: C,44.71; H,6.88; N,8.69. Found:: C,44.80; H,6.75; N,8.54.

Preparation of α-Nitroketones 3a-d. General Procedure. A 100 ml, two necked flask was equipped with mechanical stirrer, charged with compound 1 (8.05 g, 0.05 mol) and cooled with an ice-water bath. Aldehyde 2a-d (0.05 mol) was added and the mixture stirred during 2-3 min. Chromatographic alumina (Carlo Erba RS, activity I according Brokman) (10 g) was added and stirring continued for one h at room temperature and then allowed to stand for 23 h. Dichloromethane (100 ml) and tetrabutylammonium hydrogen sulphate (0.1 mol x mol of substrate) were added under stirring. The mixture was cooled (-5°C) and then a solution of potassium dichromate (9.70 g, 0.033 mol) in 30% sulphuric acid (60 ml) was added dropwise keeping the inner temperature at -5°C to 0°C. After 3 h 10% $FeSO_4$ solution (50 ml) was added and layers were separated. The organic phase was washed with 10% sodium hydroxide (2x20 ml) solution and water. The solvent was removed at reduced pressure and the crude product dissolved with diethyl ether (30 ml) and eluted through a bed of Florisil. Elimination of the solvent afforded α-nitroketones 3a-d.

1-(2-Methyl-1,3-dioxolan-2yl)-2-nitrobutan-3-one (3a). Compound 1 and acetaldehyde (2a) gave compound 3a in 72 % yield: mp 59-60°C ; IR(kBr) 1730(CO),1558(NO_2) cm^{-1}. ^{1}H NMR δ 5.45-5.23(m,1H);4.05-3.82(m,4H); 2.80-2.50(m,2H); 2.30(s,3H); 1.33(s,3H).Anal.Calcd for $C_8H_{13}NO_5$: C,41.29; H,6.45; N,6.89. Found: C,47.38; H,6.35; N,6.77.

1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitro-5-phenylpentan-3-one (3b). Compound 1 and 3-phenylpropionaldehyde (2b) gave

compound 3b in 85% yield as an oil: IR (neat) 1725(CO),1550(NO_2) cm^{-1}. ^1H NMR δ 7.43-7.05(m,5H); 5.40-5.20(m,1H); 4.05-3.75(m,4H); 2.90(s,4H); 2.75-2.40(m,2H); 1.30(s,3H).Anal.Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H,6.53; N,4.78. Found: C,61.50; H, 6.62; N,4.70.

1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitrononan-3-one (3c). Compound 1 and heptaldehyde (2c) gave compound 3c in 75 % yield as an oil: IR(neat) 1730(CO),1550(NO_2) cm^{-1}. ^1H NMR δ 5.48-5.25(m,1H);4.05-3.80(m,4H); 2.85-2.35(m,4H); 1.80-1.10((m+s,1H); 0.87(t,3H,J=6.0Hz). Anal.Calcd for $C_{13}H_{23}NO_5$: C,57.12; H,8.48; N,5.13. Found: C,57.22; H,8.57; N,5.22.

(Z)-1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitronon-6-en-3-one (3d). Compound 1 and (Z)-4-heptenal (2d) gave compound 3d in 84% yield as an oil: IR(neat) 1730(CO), 1550(NO_2) cm^{-1}. ^1H NMR δ 5.75-5.05(m,3H) 3.97(s,4H); 2.85-1.85(m,8H); 1.38(s,3H); 0.98(t,3H,J=7.5Hz). Anal.Calcd for $C_{13}H_{21}NO_5$: C,57.55; H,7.80; N,5.16. Found: C,57.50; H,7.90; N,5.20.

Preparation of α-Nitroketones p-Toluenesulfonylhydrazones (4a-d). General Procedure: A solution of p-toluenesulfonylhydrazine (0.05 mol) in methanol (50 ml) was added to a solution of equimolar amount of α-nitroketone 3a-d, in methanol (50 ml) and the mixture was allowed to stand at room temperature for 8-10 h. The crystalline p-toluenesulfonylhydrazones 4a-d , which crystallize upon cooling of the solution is isolated by suction, dried in vacuo, and used in the reduction step without further purification. An analytical sample may be prepared by recrystallization from methanol or ethanol.

1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitrobutan-3-one p-toluenesulfonylhydrazone (4a): 94 % yield, mp 139-141°C. IR(KBr) 3240(NH), 1550(NO_2),1340,1160(SO_2) cm^{-1}. ^1H NMR δ 9.45(s,1H); 7.57(AA'BB' pattern 4H, J=8.0Hz); 5.28(t,1H,J=6.7Hz); 3.90-3.58(m,4H); 2.70-2.38(m+s,5H); 1.98(s,3H); 1.38(s,3H).Anal.Calcd for $C_{15}H_{21}N_3O_6S$: C,48.51; H,5.70; N,11.32. Found: C, 48.60; H,5.81; N,11.26.

1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitro-5-phenylpentan-3-one p-toluenesulfonylhydrazone (4b): 80 % yield, mp 113-114 °C. IR(KBr) 3230(NH),1550(NO_2),1340,1160(SO_2) cm^{-1}. ^1H NMR δ 7.80-6.95(m,9H); 5.25-5.05(m,1H); 3.98-3.78(m,4H); 2.95-2.35(m+s,9H); 1.28(s,3H).Anal.Calcd for $C_{22}H_{27}N_3O_6S$: C,57.26; H,5.90; N,9.11. Found: C,57.30; H,6.00; N,9.05.

1-(2-Methyl-1,3-dioxolan-2yl)-2-nitrononan-3-one p-toluenesulfonylhydrazone (4c) 93 % yield, mp 116-118°C. IR(KBr) 3200 (NH) 1538(NO_2), 1340,1160(SO_2) cm^{-1}. ^1H NMR δ 8.3(s,1H); 7.57(AA'BB' pattern,4H, J=8.0Hz);5.35-5.15(m,1H); 4.05-3.80(m,4H) 2.95-2.60(m,2H); 2.45(s,3H); 2.35-2.10 (m,2H); 1.60-1.00(m+s,11H); 0.85(t,3H, J=6.0Hz). Anal.Calcd for $C_{20}H_{31}N_3O_6S$: C, 54.41; H,7.08; N,9.52. Found: C,54.35; H, 7.00; N,9.60.

(Z)-1-(2-Methyl-1,3-dioxolan-2-yl)-2-nitronon-6-en-3-one p-toluenesulfonylhydrazone (4d): 90% yield, mp 98-100°C. IR(KBr 3205(NH),1550(NO_2),13340,1160(SO_2) cm^{-1}. ^1H NMR δ 7.57(AA'BB' pattern, 4H, J=8.0 Hz); 5.60-5.00(m,3H); 3.88(m,4H); 2.95-1.65(m,11H); 1.30(s,3H); 0.90(t,3H,J=7.5 Hz). Anal Calcd for $C_{20}H_{29}N_3O_6S$: C,54.66; H,6.65; N,9.56. Found: C,54.70; H,6.69; N,9.50.

Denitration of p-Toluenesulfonylhydrazones 4a-d. General Procedure: Dry tetrahydrofuran (100 ml) was placed in a dried nitrogen flushed 250 ml flask fitted with a septum inlet and a magnetic stirring bar. Lithium aluminium hydride (1.14 g,30 mmol) was added and the mixture cooled to 0°C. p-Toluenesulfonylhydrazones 4a-d (10 mmol) were dissolved in dry tetrahydrofuran (25 ml) and added dropwise (Caution:hydro

en evolution). The mixture was stirred for 30 min, treated carefully with cold water, acidified with 2N H_2SO_4 and extracted with ether (2x100 ml). The ether layer was dried (Na_2SO_4), passed through a bed of Florisil (30 g) and the solvent was removed at reduced pressure. Crude products 5a-d were crystallized from dichloromethane/cyclohexane.

1-(2-Methyl-1,3-dioxolan-2-yl)butan-3-one p-toluenesulfonylhydrazone (5a): 80 % yield, mp 89-90°C. IR(KBr) 3218(NH),1340 1160(SO_2) cm^{-1}. ^1H NMR δ 7.57(AA'BB' pattern,4H,J=8.0Hz); 3.95-3.78(m,4H);2.40 (s,3H);2.35-1.65(m+s,7H);1.25(s,3H).Anal. Calcd for $C_{15}H_{22}N_2O_4S$: C,55,20; H,6.80; N,8.58. Found: C,55.15; H,6.73; N,8.49.

1-(2-Methyl-1,3-dioxolan-2-yl)-5-phenylpentan-3-one p-toluenesulfonylhydrazone (5b): 88 % yield, mp 55-57°C. IR(KBr)3220 (NH);1340,1160(SO_2) cm^{-1}. ^1H NMR δ 8.60 (s,1H);7.95-6.95(m,9H);3.98-3.78(m,4H); 2.95-2.33(m+s,7H);2.20(t,2H),J=7.5Hz); 1.68(t,2H,J=7.5Hz);1.20(s,3H). Anal.Calcd for $C_{22}H_{28}N_2O_4S$: C,53.44; H,6.78; N,6.73. Found: C,63.40; H,6.85; N,6.64.

1-(2-Methyl-1,3-dioxolan-2-yl)nonan-3-one p-toluenesulfonylhydrazone (5c): 90 % yield, mp 72-73°C. IR(KBr) 3210(NH);1340, 1155(SO_2) cm^{-1}. ^1H NMR δ 8.60(s,1H);7.57 (AA'BB' pattern, 4H,J=8.0Hz);4.00(s,4H); 2.45(s,3H);2.18(t,4H,J=7.5Hz);1.73(t,2H, J=7.5Hz);1.40-1.00(m+s,11H); 0.85(t,3H,J= 6.0Hz). Anal.Calcd for $C_{20}H_{32}N_2C_4S$: C, 60.58; H,8.14; N,7.07. Found: C,60.65; H, 8.10; N,7.00.

(Z)-1-(2-Methyl-1,3-dioxolan-2-yl)non-6-en-3-one p-toluenesulfonylhydrazone (5d): 94 % yield, mp 64-65°C. IR(KBr): 3210(NH) 1340,1160(SO_2) cm^{-1}. ^1H NMR δ 7.57(AA'BB' pattern,4H,J=8.0Hz);5.55-5.05(m,2H);4.00 (s,4H);2.42(s,3H);2.35-1.60(m,10H);1.21 (s,3H);0.95(t,3H,J=7.5Hz). Anal Calcd for $C_{20}H_{30}N_2O_4S$: C,60.89; H,7.67; N,7.10. Found: C,60.79; H,7.72; N,7.00.

Regeneration of 1,4-Diketones 6a-d.General Procedure: p-Toluenesulfonylhydrazone 5a-d (10 mmol) was dissolved in acetone (100 ml) and water (10 ml), distilled boron trifluoride etherate was added and the mixture was stirred at room temperature for 2 h and then p-toluenesulfonic acid (0.43 g, 2.5 mmol) was added. The mixture was stirred at room temperature (12 h) and then evaporated at reduced pressure, diluted with ether (40 ml) and the organic layer dried (Na_2SO_4). Solvent was removed at reduced pressure and the crude product was purified by distillation or by chromatography over a silica gel column (SiO_2, 0.0063-0.200) with EtOAc/n-hexane (20:80) as eluent.

2,5-Hexanedione (6a):72% yield; bp 188-190°C. IR(neat) 1705(CO)cm^{-1}. ^1H NMR δ 2.85-2.65(m,4H);2.18(s,6H).Anal.Calcd for $C_6H_{10}O_2$: C,53.31; H,11.19. Found: C,53.24; H,11.09.

7-Phenyl-2,5-heptanedione(6b): 68% yield; bp 112-115°C/mm_{Hg}. IR(neat) 1705(CO) cm^{-1} ^1H NMR δ 7.35-7.05(m,5H);2.90-2.70(m,4H); 2.60(s,4H);2.10(s,3H).Anal. Calcd for $C_{13}H_{16}O_2$: C,76.44; H,7.90. Found: C,76.30; H,7.79.

Undecane-2,5-dione(6c): 82 % yield: mp 33-34°C; bp 140-42°C/14 mm_{Hg}, lit.,[11] 141°/14mm_{Hg}).IR(KBr) 1700(CO) cm^{-1}. ^1H NMR δ 2.68(s,4H);2.45(t,2H,J=7.5Hz);2.18 (s,3H);1.75-1.15(m,8H);0.85(t,3H,J=6.0Hz). Anal.Calcd for $C_{11}H_{20}O_2$: C,71.70; H,10.95 Found: C,71.69; H,10.89.

(Z)-Undec-8-ene-2,5-dione(6d): 84% yield bp 138-141°C/3mm_{Hg} (lit.,[12] 140°C/2mm_{Hg}) IR(neat) 1710(CO) cm^{-1}.^1H NMR δ 5.70-5.08 (m,2H);2.95-1.85(m+s,13H); 0.92(t,3H,J= 7.5Hz). Anal.Calcd for $C_{11}H_{18}O_2$: C,72.45; H,9.95. Found: C,72.36; H,9.78.

Cyclization of Diketones 6a-d. Preparation of Cyclopentenones 7a-d; General Procedure:According to the procedure of Buchi and Wuest[10] a solution of diketone

6a-d (50 mmol) in ethanol (45 ml) was added with aqueous sodium hydroxide (0.5 N; 90 ml) and refluxed for 6 h. The mixture was cooled, diluted with water, and extracted with ether. The extract was washed with water and brine and dried (Na_2SO_4). Removal of the solvent gave crude Cyclopentenones 7a-d which was purified by distillation.

3-Methyl-2-cyclopenten-1-one (7a): 68% yield; bp 72-74°C/15mm_{Hg} (lit.[13], 74-76/15 mm_{Hg}). IR(neat) 1700(CO),1620(C=C) cm^{-1}. ^1H NMR δ 5.74(m,1H);1.96(d,3H,J=1.OHz); 2.50-2.10(m,4H). Anal.Calcd for C_6H_8O: C, 74.97; H,8.39.Found: C,74.57; H,8.31.

3-Methyl-2-benzyl-2-cyclopenten-1-one(7b): 84 % yield; bp 105-108/0.4 mm_{Hg}. IR(neat) 1690(CO),1640(C=C) cm^{-1}.^1H NMR δ7.4-7.1 (m,5H);3.52(s,2H);2.60-2.25(m,4H);2.03(s, 3H). Anal.Cacd for $C_{13}H_{14}O$: C,83.83; H, 7.58. Found: C,83.27; H,7.71.

Dihydrojasmone(7c): 89% yield; bp 100-102° C/6mm_{Hg},(lit.,[14] 88°C/3mm_{Hg}).IR(neat) 1700 (CO),1645(C=C).^1H NMR δ 2.65-2.00(m+s,9H) 1.60-1.10(m,6H);0.88(t,3H,J=6.OHz).Anal. Calcd for $C_{11}H_{18}O$: C,79.46; H,10.92.Found C,79.04; H,10.54.

(Z)-Jasmone (7d): 78% yield; bp 100-105° C/1mm_{Hg},(lit.,[12] 120-130°C/3mm_{Hg}). IR(neat) 1695(CO),1642(C=C) cm^{-1}.^1H NMR δ 5.65-5.0 m,2H); 3.08-2.70(m,2H);2.68-1.78(m,9H); 0.98(t,3H,J=7.5Hz). Anal.Calcd for $C_{11}H_{16}O$; C,80.44; H,9.83. Found: C,80.86; H,9.65.

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