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Syntheses of 3,5-Dimethylspiro[5.5]undeca-2,4-diene-1,8-dione and 7,11-Dimethylspiro[5.5]undeca-7,10-diene-2,9-dione

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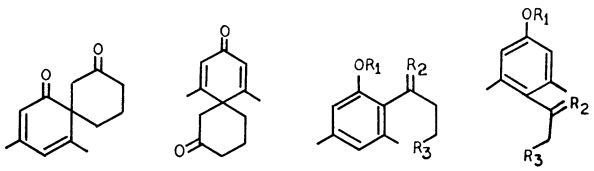
Synopsis. Syntheses of 1-diazo-5-(2-hydroxy-4,6-dimethylphenyl)-2-pentanone and 1-diazo-5-(4-hydroxy-2,6-dimethylphenyl)-2-pentanone and their acid catalysed spiroannulation to 3,5-dimethylspiro[5.5]undeca-2,4-diene-1,8-dione and 7,11-dimethylspiro[5.5]undeca-7,10-diene-2,9-dione respectively *via* Ar_1-6 participation are described. Succinylation of 3,5-dimethylanisole is also discussed.

Aryl participation of phenolic diazo ketones toward the formation of spirodienone have recently been developed. Mander and Beams[1] reported a spectral indication of the formation of spirodienone *via* Ar_1-6 participation route in connection with their study on intramolecular alkylation of phenolic diazo ketones. Here we report the syntheses of two intermediate phenolic diazo ketones, 1-diazo-5-(2-hydroxy-4,6-dimethylphenyl)-2-pentanone (**8**) and 1-diazo-5-(4-hydroxy-2,6-dimethylphenyl)-2-pentanone (**18**) and their conversion into the spirodienones, 3,5-dimethylspiro[5.5]undeca-2,4-diene-1,8-dione (**1**) and 7,11-dimethylspiro[5.5]undeca-7,10-diene-2,9-dione (**2**), respectively. The spirodienones were isolated and characterized by spectral analyses.

Succinylation of 3,5-dimethylanisole at −5 °C in 1,1,2,2-tetrachloroethane–nitrobenzene mixture afforded the ortho-isomer, 3-(2-methoxy-4,6-dimethylbenzoyl) propanoic acid (**3**), mp 101 °C, in an excellent yield. The NMR spectrum of the keto acid **3** showed two sets of distinct singlets at δ 2.08, 2.25 (aromatic methyls) and at δ 6.61, 6.71 (aromatic protons). Clemmensen reduction of **3** and subsequent demethylation gave the hydroxy acid **5**, mp 130 °C. The same compound was synthesised by Brown and McCall[2] from a different route, mp 130—132 °C. The hydroxy acid was converted into the hydroxy diazo ketone **8** *via* acetylation, diazo ketone formation and deacetylation. Consistency in spectral data due to non-equivalent aromatic protons and methyls has also been observed in each step reaction product in the synthesis of **7** starting from the succinylated product **3** (*vide* Experimental). Aryl participation of the phenolic diazo ketone **8** was carried out in thoroughly dried nitromethane in presence of boron trifluoride etherate catalyst in an atmosphere of dry nitrogen at room temperature. Two products **1** and **9** were isolated by column chromatography from the crude reaction mixture. The formation of **9** during spiroannulation can be explained simply by SN_2 attack of ambident nitromethane on protonated[3] diazo ketone **8**.

Uneyama *et al.*[4] succinylated 3,5-dimethylanisole under almost identical conditions, but they reported the formation of the para-isomer, 4-(4-methoxy-2,6-dimethylbenzoyl) propanoic acid (**20**), mp 102—102.5 °C, and further converted it into **14**. Their claim for the above para products is untenable on the ground of non-equivalent aromatic protons and methyls shown in their NMR spectra. Moreover, we have synthesised the para-isomer **14** independently from authentic 3-(4-methoxy-2,6-dimethylphenyl) propanoic acid[5] (**12**) by the Arndt-Eistert reaction. The product gave a singlet (δ 2.28) for two aromatic methyls and a singlet (δ 6.46) for two aromatic protons in the NMR spectrum suggesting the para structure. The mp and NMR data reported by Uneyama *et al.* for the same compound **14** are different. Following exactly their method we also succinylated 3,5-dimethylanisole and obtained the same ortho acid **3** (undepressed mixed mp and identical NMR spectra). We presume that Uneyama *et al.* also obtained the ortho-isomer **3** by succinylation of 3,5-dimethylanisole but reported it as the para-isomer **20**.

Cyanoethylation of 3,5-dimethylanisole gave a mixture of propionitriles where the para-isomer **10** predominated. The hydroxy propanoic acid **11** was prepared from the crude propionitrile by refluxing with hydrobromic acid–acetic acid mixture and subsequent separation from the δ-lactone produced from the ortho-isomer. Methylation, homologation by the Arndt-Eistert method, demethylation, acetylation, diazo ketone formation, deacetylation and finally acid-catalysed Ar_1-6 participation starting from **11** afforded **2** and **19** (*vide* Experimental).



1 **2** **3—9** **10—20**

	R_1	R_2	R_3
3	CH_3	O	CO_2H
4	CH_3	H_2	CO_2H
5	H	H_2	CO_2H
6	Ac	H_2	CO_2H
7	Ac	H_2	$COCHN_2$
8	H	H_2	$COCHN_2$
9	H	H_2	$COCH_2OH$
10	CH_3	H_2	CN
11	H	H_2	CO_2H

	R_1	R_2	R_3
12	CH_3	H_2	CO_2H
13	CH_3	H_2	CO_2H
14	CH_3	H_2	$COCHN_2$
15	H	H_2	CH_2CO_2H
16	Ac	H_2	CH_2CO_2H
17	Ac	H_2	CH_2COCHN_2
18	H	H_2	CH_2COCHN_2
19	H	H_2	CH_2COCH_2OH
20	CH_3	O	CH_2CO_2H

Experimental

Light petrol and petroleum refer to the fraction of bp 40—60 °C and 60—80 °C, respectively. NMR spectra were recorded with a Varian EM 390 instrument.

3-(2-Methoxy-4,6-dimethylbenzoyl)propanoic Acid (3). Friedel-Crafts reaction of 3,5-dimethylanisole (2.7 g) with succinic anhydride (2.1 g) and anhydrous aluminium chloride (5.6 g) in dry 1,1,2,2-tetrachloroethane (23 ml) and nitrobenzene (6 ml) at −5 °C for 3 days yielded **3** (3.9 g, 84%) as

colorless cubes, mp 101 °C (ethanol–water); IR(KBr) 1710—1695 cm^{-1}; NMR [$(CD_3)_2SO$] δ 2.08 (s, 3H), 2.25 (s, 3H), 2.48 (t, 2H), 2.93 (t, 2H), 3.72 (s, 3H), 6.61 (s, 1H), 6.71 (s, 1H). Found: C, 65.91; H, 6.90%. Calcd for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78%.

4-(2-Methoxy-4,6-dimethylphenyl)butanoic Acid (4). Clemmensen reduction of **3** (2.3 g) gave **4** (2 g, 90%) as colorless crystals, mp 99 °C (petroleum–benzene): IR(KBr) 1705 cm^{-1}; NMR($CDCl_3$) δ 1.74—1.96 (m, 2H), 2.26 (s, 3H), 2.28 (s, 3H), 2.40—2.76 (m, 4H), 3.76 (s, 3H), 6.54 (s, 1H), 6.61 (s, 1H). Found: C, 70.13; H, 7.94%. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.11%.

4-(2-Hydroxy-4,6-dimethylphenyl)butanoic Acid (5). Demethylation of **4** (2.2 g) with pyridine hydrochloride (7 g) at 210 °C under dry nitrogen gave **5** (1.9 g, 90%) as colorless crystals, mp 130 °C (benzene) (lit,[2] mp 130—132 °C): IR-(KBr) 3250, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.75—1.96 (m, 2H), 2.20 (s, 3H), 2.22 (s, 3H), 2.32—2.78 (m, 4H), 6.46 (s, 1H), 6.52 (s, 1H). Found: C, 69.37; H, 7.48%. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69%.

4-(2-Acetoxy-4,6-dimethylphenyl)butanoic Acid (6). Acetylation of the phenolic acid **5** with acetic anhydride in aqueous sodium hydroxide at −5 °C gave **6** (65%) as colorless crystals, mp 93 °C (petroleum–benzene): IR(KBr) 1750, 1705 cm^{-1}; NMR (CCl_4) δ 1.56—1.88 (m, 2H), 2.20 (s, 3H), 2.26 (s, 6H), 2.32—2.68 (m, 4H), 6.60 (s, 1H) 6.80 (s, 1H), 11.26 (s, 1H). Found: C, 66.97; H, 7.31%. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.22%.

1-Diazo-5-(2-acetoxy-4,6-dimethylphenyl)-2-pentanone (7). Acid chloride was prepared from **6** by the oxalyl chloride method. It was transformed into **7** (80%) by diazomethane as a light yellow oil: IR(neat) 2110, 1750, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.64—1.92 (m, 2H), 2.20 (s, 3H), 2.28 (s, 6H), 2.32—2.70 (m, 4H), 5.24 (s, 1H), 6.60 (s, 1H), 6.80 (s, 1H).

1-Diazo-5-(2-hydroxy-4,6-dimethylphenyl)-2-pentanone (8). Deacetylation of **7** by Na_2CO_3–$NaHCO_3$ solution gave **8** (75 %) as a pale yellow oil: IR (neat) 3300, 2110, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.70—1.98 (m, 2H), 2.26 (s, 6H), 2.34—2.70 (m, 4H), 5.30 (s, 1H), 6.56 (s, 2H).

3,5-Dimethylspiro[5.5]undeca-2,4-diene-1,8-dione (1). A mixture of **8** (500 mg) and BF_3–etherate (5 drops) in thoroughly dried nitromethane (40 ml) was stirred for 15 min at 20 °C to afford a red oil after the usual work-up. It was purified by column chromatography. Petroleum eluted **7** (85 mg) as semi-solid mass: UV (MeOH) 232 (log ε 4.31), 280 (log ε 3.52), 312 nm (log ε 4.28); IR ($CHCl_3$) 1710, 1660, 1620, 1575 cm^{-1}; NMR ($CDCl_3$) δ 1.70—2.04 (m, 2H), 2.22 (s, 6H), 2.62—2.96 (m, 4H), 4.40 (s, 2H), 6.78 (s, 2H). Benzene eluted **9** (130 mg) as colorless crystals, mp 95 °C (light petrol–ether): IR(KBr) 3350—3250, 1715, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.64—1.96 (m, 2H), 2.16 (s, 3H), 2.18 (s, 3H), 2.36—2.62 (m, 4H), 2.98 (t, 1H, J 5 Hz), 4.20 (d, 2H, J 5 Hz), 5.36 (s, 1H), 6.42 (s, 1H), 6.50 (s, 1H). Found: C, 70.41; H, 8.02%. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.11%.

3-(4-Hydroxy-2,6-dimethylphenyl)propanoic Acid (11). Cyanoethylation of dimethylanisole with acrylonitrile in 1,1,2, 2-tetrachloroethane by use of anhydrous $AlCl_3$ and dry HCl gas gave **10** (62%), contaminated with a trace of ortho-isomer. Reaction of crude propionitrile **10** with HOAc–HBr mixture gave **11** (68%) as colorless needles, mp 125 °C (benzene) (lit,[5] mp 126—127 °C): IR (Nujol) 3450, 1705 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.50 (t, 2H), 3.0 (t, 2H), 6.50 (s, 2H) 8.50 (s, 2H). Found: C, 67.75; H, 6.86%. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22%.

3-(4-Methoxy-2,6-dimethylphenyl)propanoic Acid (12). Methylation of **11** with $(CH_3)_2SO_4$ gave **12** (82%) as colorless needles, mp 95 °C (petroleum): NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.50 (t, 2H), 3.0 (t, 2H), 3.80 (s, 3H), 6.50 (s, 2H), 11.50 (s, 1H). Found: C, 68.94; H, 7.46%. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69%.

4-(4-Methoxy-2,6-dimethylphenyl)butanoic Acid (14). Diazo ketone **13** was prepared from **12** and the crude product was treated with Ag_2O in methanol. After saponification of the intermediate ester, methoxy acid **14** (75%) was obtained as colorless crystals, mp 108 °C (petroleum–benzene): NMR (CCl_4) δ 1.62—1.90 (m, 2H), 2.28 (s, 6H), 2.37—2.68 (m, 4H), 3.68 (s, 3H), 6.46 (s, 2H), 11.54 (s, 1H). Found: C, 70.39; H, 7.99%. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.11%.

4-(4-Hydroxy-2,6-dimethylphenyl)butanoic Acid (15). Demethylation of **14** gave **15** (90%) as colorless crystals, mp 125 °C (benzene): IR ($CHCl_3$) 3250, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.60—1.92 (m, 2H), 2.32 (s, 6H), 2.38—2.70 (m, 4H), 6.50 (s, 2H). Found: C, 69.10; H, 7.51%. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69%.

4-(4-Acetoxy-2,6-dimethylphenyl)butanoic Acid (16). Acetylation of **15** gave **16** (60%) as colorless crystals, mp 96 °C (petroleum–benzene): IR ($CHCl_3$) 1750, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.62—1.90 (m, 2H), 2.25 (s, 3H), 2.32 (s, 6H), 2.38—2.72 (m, 4H), 6.72 (s, 2H), 11.30 (s, 1H). Found: C, 66.91; H, 7.08%. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20%.

1-Diazo-5-(4-acetoxy-2,6-dimethylphenyl)-2-pentanone (17). Diazo ketone **17** (91%) was prepared from **16** following the usual procedure as a pale yellow oil: IR ($CHCl_3$) 2100, 1750, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.62—1.90 (m, 2H), 2.26 (s, 3H), 2.32 (s, 6H), 2.40—2.82 (m, 4H), 5.20 (s, 1H), 6.75 (s, 1H).

1-Diazo-5-(4-hydroxy-2,6-dimethylphenyl)-2-pentanone (18). Deacetylation of **17** afforded **18** (90%) as a light yellow oil: IR ($CHCl_3$) 3300, 2100, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.62—1.92 (m, 2H), 2.32 (s, 6H) 2.40—2.78 (m, 4H), 5.20 (s, 1H), 6.48 (s, 2H).

7,11-Dimethylspiro[5.5]undeca-7,10-diene-2,9-dione (2). Ar_1-6 participation of **18** (500 mg) with BF_3–etherate gave a red oil. Dienone **2** (90 mg) was obtained from benzene elute as colorless needles, mp 128 °C (light petrol–ether): UV (MeOH) 246 nm (logε 4.40); IR ($CHCl_3$) 1710, 1660, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.67—1.87 (m, 4H), 2.06 (s, 6H), 2.23—2.48 (m, 4H), 6.05 (s, 2H); MS (50 eV) 204 (M^+), 176 (M−CO), 161 (M−CH_2CO), 134 [M−(C_2H_4, CH_2CO)], 91 [M−(C_2H_4, CH_2CO, CO, CH_3)] (100%). Found: C, 76.29; H, 7.96%. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84%. The hydroxy ketone **19** (120 mg) was obtained from benzene–ethyl acetate elute as colorless crystals, mp 100 °C (ether–light petrol): IR ($CHCl_3$) 3340—3250, 1715, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.64—1.90 (m, 2H), 2.30 (s, 6H), 2.36—2.64 (m, 4H), 4.20 (d, 2H), 5.0 (t, 1H), 6.50 (s, 2H). Found: C, 70.06; H, 8.10%. Calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.11%.

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