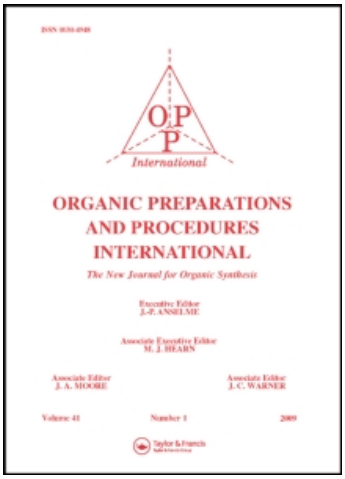


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# A SUPERIOR METHOD FOR THE SYNTHESIS OF 7a-METHYL-2,3,7,7a-TETRAHYDRINDEN-5(6H)-ONE

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## A SUPERIOR METHOD FOR THE SYNTHESIS OF 7a-METHYL-2,3,7,7a-TETRAHYDRINDEN-5(6H)-ONE

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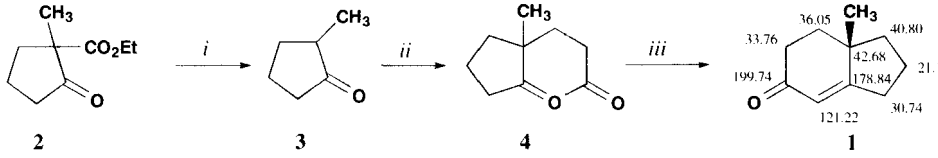
7a-Methyl-2,3,7,7a-tetrahydrinden-5(6H)-one (**1**) is an important synthetic intermediate in the steroid and terpenoid fields.[1] In the course of other work, we required large quantities of this compound. A literature search indicated that the reported Robinson annulations on 2-methylcyclopentanone gave low yields (35%)[2] or used expensive reagents.[3] We report herein a higher yielding method for the synthesis of hydrindenone **1** (Eq. 1).

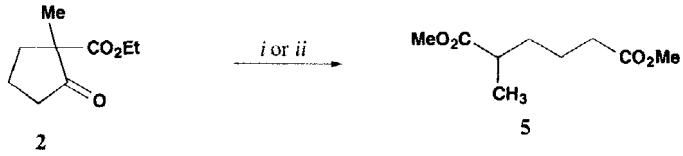



2 3 4 1 (1)

(*i*) conc. HCl, reflux; (*ii*) MVK, conc. $H_2SO_4$ (cat) benzene, reflux; (*iii*) 10% ethanolic KOH, reflux

2-Methylcyclopentanone (**3**) is commercially available, but expensive. As this compound was required in large quantities, we had initially tried the reported procedure[4] which involved hydrolysis of ethyl 1-methyl-2-oxocyclopentanecarboxylate (**2**) under basic conditions (aqueous ethanolic

KOH) and subsequent decarboxylation. In our hands this procedure did not work and the ring opened product, dimethyl 2-methyladipate (**5**) was the only compound obtained (Eq. 2), which had possibly formed *via* a retro-Dieckmann reaction.[5] Reaction with relatively mild base, $K_2CO_3$ also led to the




**2** **5** (2)

(*i*) a) KOH, $CH_3OH$, $H_2O$, reflux, b) dil. HCl; (*ii*) $K_2CO_3$, $CH_3OH$, reflux

formation of the ring opened product **5**. A thorough literature search revealed that 2-methylcyclopentanone had been obtained by acid-catalyzed hydrolysis and decarboxylation of the β-ketoester **2**.[6] This procedure worked quite well to afford 2-methylcyclopentanone (**3**) from the β-ketoester **2** in quantitative yield when the reaction was conducted at reflux temperature of conc. HCl.

Next, we found that the two-step Robinson annulation on 2-methylcyclopentanone (**3**) with methyl vinyl ketone, i. e. the conjugate addition (Michael Reaction) under acidic conditions[7] and intramolecular aldol condensation and dehydration under basic conditions, resulted in a better yield of the desired enone **1**. Thus, acid ($H_2SO_4$) catalyzed Michael addition of methyl vinyl ketone to 2-methylcyclopentanone (**3**) resulted in dione **4** in quantitative yield. Dione **4** was then subjected to aldol condensation under basic conditions (ethanolic KOH) resulting in 7a-methyl-2,3,7,7a-tetrahydrinden-5(6H)-one (**1**) in over 88% overall yield. Details of $^{13}C$ NMR spectral assignments for the enone **1** are given in structure **1** (Eq. 1). The assignments are based on the literature data for similar compounds[8] and SEFT experiments.



## EXPERIMENTAL

IR spectra were recorded on Hitachi FT IR spectrometer. $^1H$ NMR and $^{13}C$ NMR data were obtained using JOEL FT FX90Q NMR spectrometer operating at 90MHz and 22.5MHz respectively, using $CDCl_3$ as solvent and TMS as internal standard. Reactions were routinely monitored by TLC ($SiO_2$, hexane, EtOAc) for completion.

**2-Methylcyclopentanone (3).**- A two-phase reaction mixture of ethyl 1-methyl-2-oxocyclopentanecarboxylate (15.6 g, 0.1 mol)[9] and 30 mL conc. HCl were refluxed for 2 hrs. The cooled reaction mixture was diluted with 150 mL ice-cold water and extracted with ether (30 mL x 6). The combined organic layers were washed with saturated sodium bicarbonate solution (20 mL), water (20 mL), brine (20 mL) and dried ($Na_2SO_4$). After removal of the solvent and distillation, 2-methylcyclopentanone (9.6 g, 98%), bp. 139° was obtained as a colorless liquid. IR (neat): 1742, 1738 $cm^{-1}$. $^1H$ NMR: δ 1.1 (3H, d, J = 10.2Hz, $-CH_3$) 1.2-2.86 (7H, m).

**7a-Methyl-2,3,7,7a-tetrahydrinden-5(6H)-one (1).**- A solution of 2-methylcyclopentanone (**3**), (9.8g, 0.1 mol), methyl vinyl ketone (7g, 0.1 mol) and conc. $H_2SO_4$, 1 drop, in dry benzene (50 mL) was refluxed for 12 hrs. The cooled reaction mixture was washed with ice-cold water (25 mL), satu-

rated sodium bicarbonate solution (20 mL), brine (25 mL x 2), dried ($Na_2SO_4$) and solvent removed under reduced pressure to result in 16.3g (97%) of diketone **4** which was subjected to cyclization without further purification, IR (neat): 1732, 1716 $cm^{-1}$. The diketone (16.3g) was taken in 10% ethanolid KOH (200 mL) and refluxed for 30min. The cooled reaction mixture was neutralized and then acidified (pH = 6) with acetic acid and ethanol was removed under reduced pressure. The residue was partitioned in ether (100 mL) and ice-cold water (100 mL). Aqueous layer was further extracted with ether (20 mL x 3). The combined ethereal layers were washed with ice-cold water (20 mL), saturated sodium bicarbonate solution (20 mL), brine (20 mL), dried ($Na_2SO_4$). and solvent removed under reduced pressure to result in crude hydrindenone **1**. This product on purification by column chromatography ($SiO_2$, 100-200 mesh, hexane:ethyl acetate, 9:1) resulted in 7a-methyl-2,3,7,7a-tetrahydrinden-5(6H)-one (**1**, 13.2g, 88%) as a colorless oil, bp. 141°/15mm, lit.[2] 67°/0.4mm. UV: 238nm; IR (neat): 2976, 1662, 1458 $cm^{-1}$; $^1H$ NMR (270MHz): δ 1.15 (3H, s, C7a-$CH_3$), 1.29-1.56 (2H, m), 2.07-2.08 (6H, m), 2.31-2.8 (4H, m), 5.76 (1H, s); 13C NMR (100MHz): δ 21.12 (C-2), 22.36 (C7a-$CH_3$), 30.74 (C-3), 33.76 (C-6), 36.05 (C7), 40.80 (C-1), 42.68 (C-7a), 121.22 (C-4), 178.84 (C-3a), 199.74 (C-5).

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# A SIMPLE AND SHORT SYNTHESIS OF 2-(2'-AMINOBENZYLAMINO)BENZYL ALCOHOL, A CONSTITUENT OF *JUSTICIA GENDARUSSA* BURM LEAVES

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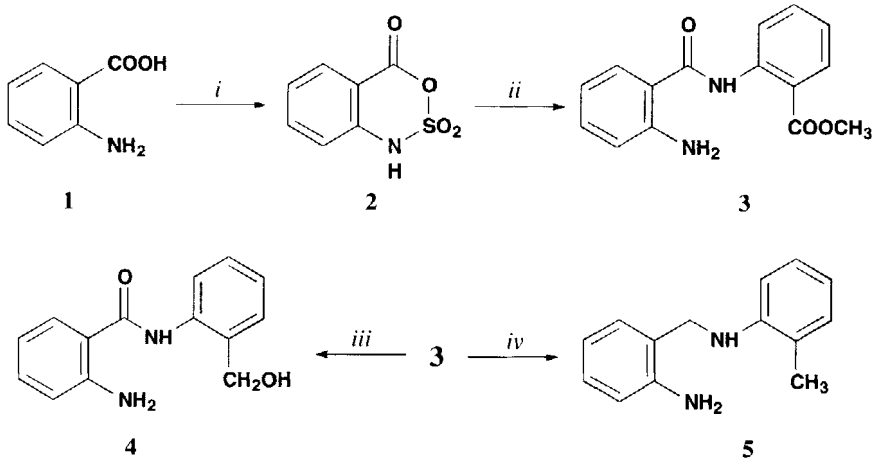
The isolation and characterization of some simple aromatic amines from the leaves of *Justicia gendarussa* Burm known for their medicinal value has been described by Chakravarty *et al.*[1] Structure **9** which was assigned to one of the amines based on spectral data was confirmed by a multi-step synthesis starting from *o*-toluidine. We sought to prepare the amine **9** by a simpler and shorter route and our results are presented herein.

Our initial approach (Scheme 1) consisted of reaction of methyl anthranilate with sulfinamide anhydride (**2**, obtained by heating anthranilic acid (**5**) with thionyl chloride in dry benzene under reflux)[2] to give **3**, which was expected to furnish the amine **9** on reduction with LAH. When reduction of **3** was carried out with LAH in THF at room temperature for 24 hrs, only carbomethoxy group was converted to primary alcohol to yield **4**; the amide carbonyl remained unaffected. Under a




*i*) $SOCl_2$, PhH, Δ *ii*) Methyl anthranilate *iii*) LAH, THF, RT *iv*) LAH, $Et_2O$, RT

**Scheme 1**