

A new and simple approach for the synthesis of 3-acetyl-3,4-dihydro-1(2*H*)-naphthalenones and 3,4-dihydro-3-(2-methyl-1,3-dithiolan-2-yl)-1(2*H*)-naphthalenones

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3-Acetyl-3,4-dihydro-1(2*H*)-naphthalenones and 3,4-dihydro-3-(2-methyl-1,3-dithiolan-2-yl)-1(2*H*)-naphthalenones are prepared using levulinic acid as starting substrate.

3-Acetyl-3,4-dihydro-1(2*H*)-naphthalenone (**1a-f**) have proved to be invaluable intermediates¹⁻⁴ in the synthesis of aglycone moiety daunomycinone (**2**) and its structural analogs belonging to a group of anthracycline antibiotics which are used in the treatment of cancer. Methods reported¹⁻³ for the synthesis of 3-acetyl-3,4-dihydro-1(2*H*)-naphthalenones (**1a-f**) are lengthy and tedious. In the present paper, we report an efficient and simpler approach for the synthesis of the title compounds using easily accessible intermediates and reagents (Scheme 1).

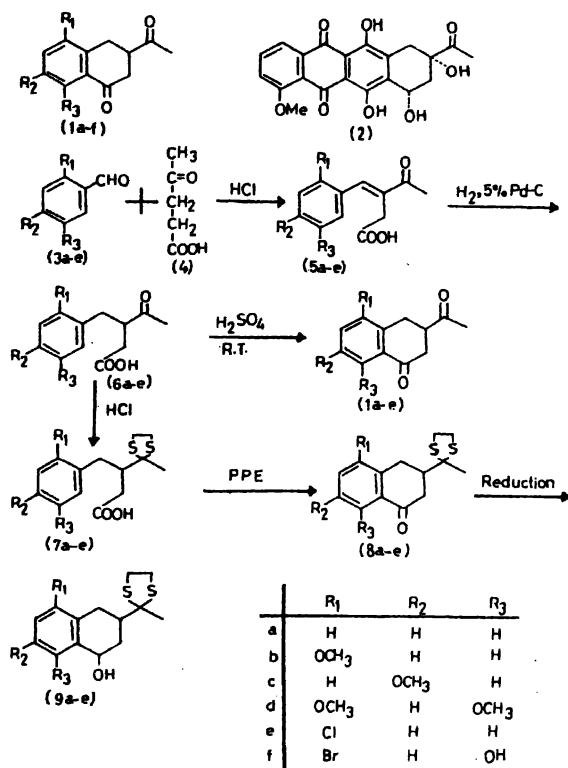
Appropriate aldehyde (**3a-e**) was regioselectively condensed with levulinic acid (**4**) in presence of dry HCl gas⁵ yielding the respective 3-arylidene-4-oxopentanoic acid⁵ (**5a-e**) in good yields. These acids (**5a-e**) were then catalytically hydrogenated⁷ in presence of 5% Pd-C to give the respective dihydro derivatives (**6a-e**). These dihydro acids (**6a-e**) were further cyclized to 3-acetyl-3,4-dihydro-1(2*H*)-naphthalenones (**1a-e**) in concentrated sulfuric acid² (98%) at room temperature in fair yields. It is significant to note that levulinic acid (**4**) has been used as a synthon for the first time in building up 3-acetyl-3,4-dihydro-1(2*H*)-naphthalenone moiety. Further, **4** can be easily prepared from sugar⁸.

The dihydro acids (**6a-e**) were also utilized to prepare compounds having regioselectively protected 3-keto function of the naphthalenones (**1a-e**) by reacting with ethanedithiol. The thioketal acid (**7a-e**) thus prepared were then cyclized in polyphosphate ester (PPE)¹ to 3,4-dihydro-3-(2-methyl-1,3-dithiolan-2-yl)-1(2*H*)-naphthalenones (**8a-e**).

The method utilizes simple substrates and is easy to operate. In addition we believe that **8a-e** could also be utilized for regioselectively generating OH function required at C₇ in daunomycinone and its structural analogs (**9a-e**).

3-Arylidene-4-oxopentanoic acids (5a-e). General procedure : Levulinic acid (**4**; 1.16 g, 0.01 mol) was reacted with various aromatic aldehydes (**4a-e**; 0.01 mol) in presence of dry HCl gas at 0–5°. The reaction mixture was then kept at room temperature (reaction time given in the Table 1). It was then extracted with a saturated solution of sodium bicarbonate (4 × 25 ml). From the bicarbonate extract the acids were precipitated by neutralization with dil. HCl, then dried and crystallized from aqueous ethanol (50%), yields, 59–74 %.

3-Acetylarlylbutanoic acids (6a-e). General procedure : 3-Arylidene-4-oxo pentanoic acid (**5a-e**; 0.005 mol) was hydrogenated in ethanol under pressure (15 psi) using 5%



Scheme 1

Pd-C as catalyst. The catalyst was filtered off and the solvent evaporated. The product was extracted with a saturated sodium bicarbonate solution (3 × 25 ml). From the extract the acids was precipitated by neutralization with dil. HCl, then dried and crystallized from petroleum ether (b.p. 60–80°), yields 75–80%.

3-Acetyl-3,4-dihydro-1(2*H*)-naphthalenones (1a-e).

General procedure : 3-Acetylarylbutanoic acid (6a-e; 0.0025 mol) was dissolved in conc. H₂SO₄ (98%, 25 ml) and kept at room temperature (reaction time given in the Table 1). It was then poured into ice and the extract was washed with NaOH solution (10%; 2 × 25 ml) and then with water (25 ml) and (Na₂SO₄). The solvent was evaporated and the products were chromatographed on a silica gel column (25 g) using petroleum ether (b.p. 60–80°)/CHCl₃ (95 : 5) as an eluent, yields 23–60%.

Thioketal acids (8e-e). **General procedure :** 3-Acetylarylbutanoic acid (6a-e; 0.0025 mol) in diethyl ether (25 ml) was reacted with ethanedithiol (0.0025 mol) in presence of dry HCl gas. The reaction was kept at room temperature (reaction time given in the Table 1). The solvent was then evaporated and the product treated with saturated sodium bicarbonate solution (3 × 25 ml). From the bicarbonate extract, the acid was precipitated by neutralization with dil. HCl, then dried and crystallized from petroleum ether (b.p. 60–80°).

3,4-Dihydro-3-(2-methyl-1,3-dithiolan-2-yl)-1(2*H*)-naphthalenones (7a-e). **General procedure :** Thioketal acid (8a-e; 0.003 mol) was heated in PPE (from 15 g P₂O₅, 20 ml diethyl and 140 ml chloroform) on a water-bath. The reaction mixture was poured into ice. The product was extracted with chloroform (2 × 25 ml), washed with water (25 ml) and dried (Na₂SO₄). The solvent was then evaporated and the products were chromatographed on a silica gel column (30 g) using petroleum ether (b.p. 60–80°)/chloroform (80 : 20) as an eluent (reaction time given in the Table 1).

Table 1 (contd.)

Compd. no.	Reaction time, h	M.p.	ν_{\max} °C	δ	6b	8	94	1700	2.1 (3H, s, COCH ₃), 2.2–3.2 (5H, m, CH ₂ CHCH ₂), 3.8 (3H, s, OCH ₃), 6.6–7.3 (4H, m, ArH)
5a	168	125 ^a			6c	8	168 (dec)	1700	2.1 (3H, s, COCH ₃), 2.2–3.3 (5H, m, CH ₂ CHCH ₂), 3.7 (3H, s, OCH ₃), 6.7–7.4 (4H, m, ArH)
5b	15	106–108	1720, 1700, 1640	2.3 (3H, s, COCH ₃), 5.2 (2H, s, CH ₂), 3.8 (3H, s, OCH ₃), 6.7–7.9 (5H, m, ArCH=)	6d	8	105–107 ^d	1700	2.1 (3H, s, COCH ₃), 2.4–3.3 (5H, m, CH ₂ CHCH ₂), 3.75 (6H, s, 2 × OCH ₃), 6.6–6.8 (3H, m, ArH), 8.6 (1H, br, COOH)
5c	15	139 ^b		2.3 (3H, s, COCH ₃)	6e	12	132	1700	2.1 (3H, s, COCH ₃), 2.4–3.3 (5H, m, CH ₂ CHCH ₂), 7.0–8.0 (4H, m, ArH)
5d	15	152	1720, 1710, 1640	3.2 (2H, s, CH ₂), 3.6 (3H, s, OCH ₃), 3.7 (3H, s, OCH ₃), 6.6–7.7 (4H, m, ArCH=)	1a	8	Oil	1710, 1680	2.2 (3H, s, COCH ₃), 2.7–3.2 (5H, m, CH ₂ CHCH ₂), 7.1–8.1 (4H, m, ArH)
5e	15	99 ^b			1b ^c	48	Oil	1710, 1680	2.2 (3H, s, COCH ₃), 2.4–3.4 (5H, m, CH ₂ CHCH ₂), 3.7 (3H, s, OCH ₃), 7.0–7.5 (3H, m, ArH)
6a	8	99–100 ^c	1700	2.1 (3H, s, COCH ₃), 2.2–3.2 (5H, m, CH ₂ CHCH ₂), 6.6–7.2 (5H, m, ArH)	1c ^e	24	Oil	1720, 1680	2.2 (3H, s, COCH ₃), 2.4–3.2 (5H, m, CH ₂ CHCH ₂), 3.7 (3H, s, OCH ₃), 7.2–7.4 (3H, m, ArH)
					1d	8	120–122	1720, 1680	2.2 (3H, s, COCH ₃), 2.7–3.6 (5H, m, CH ₂ CHCH ₂), 4.0 (6H, s, 2 × OCH ₃), 7.0–7.5 (2H, q, ArH)
					1e	8	Oil	1720, 1680	2.2 (3H, s, COCH ₃), 2.4–3.3 (5H, m, CH ₂ CHCH ₂), 7.0–7.8 (3H, m, ArH)
					7a	16	108	1710	1.85 (3H, s, CH ₃), 2.3–3.0 (5H, m, CH ₂ CHCH ₂), 3.2 (4H, s, SCH ₂ SCH ₂ S), 7.2 (5H, s, ArH), 9.7 (1H, br, COOH)
					7b	16	95–97	1700	1.8 (3H, s, CH ₃), 2.6–3.2 (5H, m, CH ₂ CHCH ₂), 3.4 (4H, s, SCH ₂ CH ₂ S), 3.7 (3H, s, OCH ₃), 6.6–7.3 (4H, m, ArH)
					7c	16	171	1700	1.9 (3H, s, CH ₃), 2.2–3.3 (5H, m, CH ₂ CHCH ₂), 3.45 (4H, s, SCH ₂ CH ₂ S), 3.75 (3H, s, OCH ₃), 6.6–7.3 (4H, m, ArH), 9.2 (1H, br, COOH)
					7d	16	109–112	1700	1.8 (3H, s, CH ₃), 2.3–3.3 (5H, m, CH ₂ CHCH ₂), 3.4 (4H, s, SCH ₂ CH ₂ S), 3.8 (6H, s, 2 × OCH ₃)
					7e	16	114	1700	6.9 (2H, s, ArH)
					8a	12	102	1680	1.9 (3H, s, CH ₃), 2.2–3.3 (5H, m, CH ₂ CHCH ₂), 3.2 (4H, s, SCH ₂ CH ₂ S), 6.9 (4H, s, ArH), 8.45 (1H, br, COOH)
									1.85 (3H, s, CH ₃), 2.4–3.2 (5H, m, CH ₂ CHCH ₂), 3.3 (4H, s, SCH ₂ CH ₂ S), 7.0–8.0 (4H, m, ArH)

Table 1 (contd.)

8b	12	Oil	1680	1.85 (3H, s, CH ₃), 2.5–3.2 (5H, m, CH ₂ CHCH ₂), 3.4 (4H, s, SCH ₂ CH ₂ S), 3.9 (3H, s, OCH ₃), 6.8–7.4 (3H, m, ArH)
8c	12	158	1680	1.9 (3H, s, CH ₃), 2.3–3.4 (5H, m, CH ₂ CHCH ₂), 3.4 (4H, s, SCH ₂ CH ₂ S), 3.7 (3H, s, OCH ₃), 6.4–7.0 (3H, m, ArH)
8d	12	143–145 ^d	1670	1.9 (3H, s, CH ₃), 2.4–3.0 (5H, m, CH ₂ CHCH ₂), 3.3 (4H, s, SCH ₂ CH ₂ S), 3.8 (6H, s, 2 × OCH ₃), 6.8 (2H, s, ArH)
8e	12	Oil	1675	1.8 (3H, s, CH ₃), 2.4–3.0 (5H, m, CH ₂ CHCH ₂), 3.6 (4H, s, SCH ₂ CH ₂ S), 7.3 (3H, s, ArH)

*All compounds gave satisfactory elemental analyses.

^aRef. 5, 6. ^bRef. 6. ^cRef. 7. ^dRefs. 1, 3.

^eCyclization using acid chloride instead of acid.

M.ps. (uncorrected) were determined on a Gallenkamp apparatus. IR spectra were recorded on Shimadzu FTIR-

4200 spectrometer and ¹H NMR spectra (CDCl₃) on a Varian EM 360L (60 MHz) spectrometer with TMS as internal standard.

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