

# Synthesis of 3-Acylfurans Using 3-(Phenylthio)propanal Dimethyl Acetal as a New Synthone. Syntheses of Ipomeanine and Isoegomaketone

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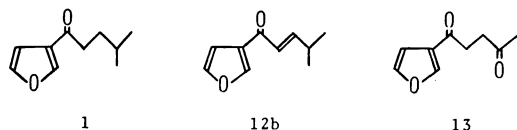
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It was found that 3-(phenylthio)propanal dimethyl acetal is a very useful starting material for the preparation of 3-acylfuranoterpenes. Syntheses of two naturally-occurring furans, isoegomaketone and ipomeanine were described.

In the past, a large number of 3-acylfurans have been found in nature.<sup>1)</sup> A few methods of their syntheses have been reported<sup>2)</sup> except those starting from 3-furyl type synthons,<sup>3)</sup> however, a convenient and effective method of 3-acylfurans have not been reported yet.

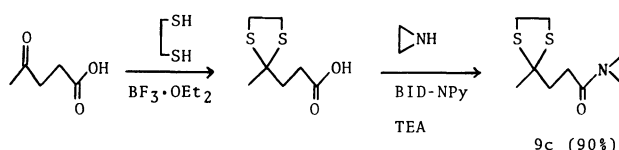
In the previous paper,<sup>4)</sup> it has been reported that the readily available 3-(phenylthio)propanal ethylene acetal (**2**) was proved to be very useful starting material for the preparation of 3-acylfurans. Syntheses of some 3-acylfurans were exemplified and one of naturally-occurring furanoterpenes, perillaketone (**1**) was synthesized in good yield starting from compound **2**.

In order to demonstrate more usefulness of this new method, its application to synthesis of more complex naturally-occurring furanoterpenes was investigated. The target compounds selected are isoegomaketone (**12b**) originally isolated from *Perilla frutescens* Brit.<sup>5)</sup> and ipomeanine (**13**) which was produced by *ceratostomella*.<sup>6)</sup> In this paper, the syntheses of both furanoterpenes **12b** and **13** are described.



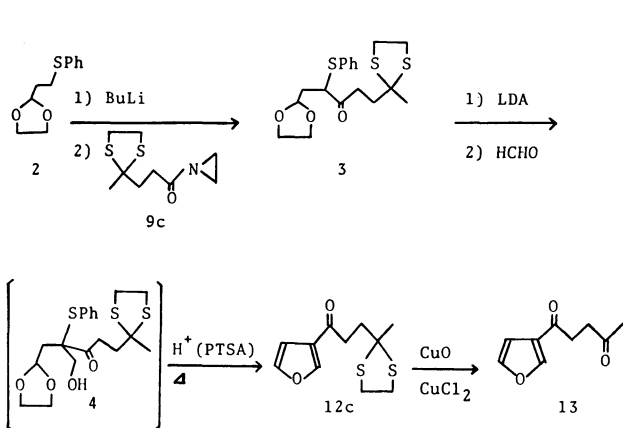
The synthesis of ipomeanine (**13**) was examined according to Scheme 1. Acylation of compound **2** was performed by treatment of a lithiated **2** with acylaziridine **9c** at  $-78^{\circ}\text{C}$  to afford the desired product **3** in 65% yield. Compound **9c** was prepared by the reaction of commercially available levulinic acid with 1.2 equivalent of 1,2-ethanedithiol in the presence of

boron trifluoride etherate followed by condensation reaction of the thiactalized acid obtained with aziridine by 3-(5-nitro-2-oxo-1,2-dihydro-1-pyridyl)-1,2-benzisothiazole 1,1-dioxide (BID-NPy)<sup>7)</sup> in good yield as shown in the following scheme.

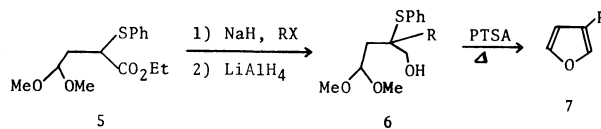


The 3-acyl-3-(phenylthio)propanal ethylene acetal **3** was treated with an equimolar amount of lithium diisopropylamide (LDA) in THF at  $-50^{\circ}\text{C}$  to room temperature followed by the passing of a large excess of gaseous formaldehyde into the reaction solution at room temperature. The resulting crude keto alcohol **4** was refluxed in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) for a couple of hours to give the desired product **12c** in only poor yield (36% based on **3**). All attempts to improve the yield of conversion of compound **4** to the furan derivative **12c** under various conditions were unsuccessful. The thioacetal group of **12c** was deprotected by treatment with  $\text{CuCl}_2$  and  $\text{CuO}$  in refluxing wet acetone<sup>8)</sup> to give the final product, ipomeanine, 1-(3-furyl)-1,4-pentanedione (**13**) in 89% yield.

Previously, we had reported that treatment of 2-alkyl-4,4-dimethoxy-2-phenylthio-1-butanol (**6**) easily derived from ethyl 4,4-dimethoxy-2-(phenylthio)butyrate (**5**), with PTSA in refluxing benzene gave 3-alkyl-furan (**7**)<sup>9)</sup> in excellent yield as shown below. These findings



Scheme 1.



suggested that compound **6** was a more favorable starting material for the cyclization to furan ring. From this fact, we have thought that 3-(phenylthio)propanal dimethyl acetal (**8**) was more effective synthon for the preparation of 3-acylfurans than compound **2** (Scheme 2). The starting material **8** was prepared by the reaction of 3-(phenylthio)propanal, which was easily obtained from equimolar quantities of acrylaldehyde and benzenethiol at  $0^{\circ}\text{C}$  and used without further purification, with trimethyl orthoformate (1.1



benzene-hexane-EtOAc (5 : 5 : 1 v/v) gave the desired product in 65% yield (oil, 408 mg): IR (neat) 1702, 1580, 1130, 1012  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.70 (s, 3H), 1.92–2.33 (m, 4H), 2.58–3.07 (m, 2H), 3.23 (s, 4H), 3.63–4.00 (m, 5H), 4.93 (t, 1H,  $J=7.0$  Hz), 7.03–7.50 (m, 5H).

**3-(Phenylthio)propanal Dimethyl Acetal (8).** A mixture of acrylaldehyde (5.482 g, 88.1 mmol) and benzenethiol (8.833 g, 80.3 mmol) was stirred for 2 h at 0 °C. The reaction mixture was diluted with dry methanol (30 ml). A solution of trimethyl orthoformate (9.359 g, 88.3 mmol) in dry methanol (10 ml) and a small amount of PTSA were added to it. The reaction solution was stirred for 2 h, treated with solid  $\text{NaHCO}_3$ , evaporated under reduced pressure to give a residue which was taken up into ether. The ether solution was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Distillation of the residual oil gave pure product as an oily material. Yield, 15.88 g (85%); Bp 89–91 °C/0.3 Torr. IR (neat) 1566, 1112, 869, 734  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.87 (m, 2H), 2.93 (q, 2H,  $J=5.8$ , 8.6 Hz), 3.28 s, (6H), 4.46 (t, 1H,  $J=5.8$  Hz), 7.09–7.33 (m, 5H).

**Preparation of 3-Acyl-3-(phenylthio)propanal Dimethyl Acetal Derivatives (10a–c).** To a solution of **8** (157 mg, 0.74 mmol) in dry THF (5 ml) was added 1.1 equiv. of BuLi at –78 °C under  $\text{N}_2$ . The reaction solution was gradually warmed to room temperature and cooled down at –78 °C again. A solution of **9** (150 mg, 0.89 mmol) in dry THF (4 ml) was slowly added to it. The reaction mixture was kept at –78 °C for 2 h, warmed to room temperature, and quenched with buffer solution of pH 7 and 1 M-HCl. The resulting mixture was extracted with ether. The combined ether extracts were dried over  $\text{Na}_2\text{SO}_4$ . After removal of the solvent a residual oil was purified by TLC using hexane-ether (6 : 1 v/v) as solvent to give pure product **10a** in 68% yield (oil). IR (neat) 1700, 1580, 1120, 1065  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.73 (s, 3H), 1.94–2.33 (m, 4H), 2.73–3.03 (m, 2H), 3.27 (s, 4H), 3.30 (s, 6H), 3.78 (t, 1H,  $J=7.2$  Hz), 4.46 (t, 1H,  $J=5.4$  Hz), 7.16–7.42 (m, 5H).

In the same procedure as the preparation of **10a**, compounds **10b–c** were obtained from compound **8** and the corresponding 1-acylaziridines **9b–c** in 65% and 67% yields, respectively.

**10b:** Oil, IR (neat) 1680, 1655, 1618, 1118, 1070, 1048  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.05 (d, 6H,  $J=7.0$  Hz), 1.67–2.78 (m, 2H), 2.31 (s, 3H), 3.34 (s, 3H), 3.93 (t, 6H,  $J=6.0$  Hz), 4.55 (t, 1H,  $J=6.0$  Hz), 6.36 (d, 1H,  $J=16.0$  Hz), 6.90 (dd, 1H,  $J=6.0$ , 16.0 Hz), 7.26–7.63 (m, 5H).

**10c:** Oil, IR (neat) 1700, 1580, 1120, 1065  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.73 (s, 3H), 1.94–2.33 (m, 4H), 2.73–3.03 (m, 2H), 3.27 (s, 4H), 3.30 (s, 6H), 3.78 (t, 1H,  $J=7.2$  Hz), 4.46 (t, 1H,  $J=5.4$  Hz), 7.12–7.42 (m, 5H).

**Preparation of 3-Acyl-3-hydroxymethyl Derivatives (11a–c).** To a solution of 1.2 equiv. of LDA in dry THF (4 ml) was added slowly a solution of **10a** (172 mg, 0.51 mmol) in dry THF (4 ml) at –78 °C under  $\text{N}_2$ . The reaction solution was gradually warmed to room temperature in a period of about 3 h. A solution of formaldehyde in THF (20 ml) where it was generated from 25 equiv. of paraformaldehyde by heating and absorbed in dry THF containing molecular sieves, was added in one portion to the solution at room temperature. The solution was allowed to stand overnight and the insoluble materials were filtered off. The filtrate was treated with buffer solution of pH 7 and 1 M-HCl, and extracted with ether. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give a crude **11a** (197 mg). It was used in the subsequent reaction without further purification.

Crude compounds **11b–c** were obtained in the same way as described for the preparation of **11a**.

**I-(3-Furyl)-I-octanone (12a).** A solution of the crude material **11a** (197 mg) obtained above in dry toluene (30 ml) was added in one portion under  $\text{N}_2$  to a flask containing PTSA (5.2 mg, 6 mol percent), equipped with a Soxhlet's extractor where 6 g of boric acid were placed. The toluene solution was refluxed for 45 min, then cooled down with a cold-bath, treated with 5 ml of 10%- $\text{NaHCO}_3$ , and extracted with ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. A crude residue was subjected to preparative TLC (hexane-ether=4 : 1 v/v) to give the desired furan in 84% yield based on **10a** (65 mg, oil). IR (neat) 3125, 1650, 1150, 869  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  0.90 (t, 3H,  $J=6.0$  Hz), 0.77–1.82 (m, 10H), 2.70 (t, 3H,  $J=7.6$  Hz), 6.75 (m, 1H), 7.40 (m, 1H), 7.96 (m, 1H).

**Isoegomaketone (12b).** Compound **12b** was obtained in 62% yield based on **10b** from a crude material **11b** in the presence of 1.5 equiv. of iodine in a manner similar to the preparation of **12a**. A crude product was purified by preparative TLC using hexane-benzene-AcOEt-ether (7 : 1 : 1 : 1 v/v) as solvent. Its IR and NMR spectra were in accord with the reported values.<sup>3c)</sup> IR (neat) 3140, 1660, 1610, 1147, 865  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.10 (d, 6H,  $J=7.0$  Hz), 2.13–2.70 (m, 1H), 6.40 (d, 1H,  $J=16.0$  Hz), 6.67–7.00 (m, 2H), 7.35 (m, 1H), 7.98 (m, 1H).

**3-[4,4-(Ethyleneedithio)pentanoyl]furan (12c).** **Method A:** The desired product was prepared in 63% yield based on **10c** from a crude material **11c** in the same manner as described for the preparation of **12a** (15 mol percent of PTSA, reflux for 1 h). IR (neat) 3130, 1559, 1306, 865  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.79 (s, 3H), 2.00–2.46 (m, 2H), 2.89–3.27 (m, 2H), 3.30 (s, 4H), 6.70 (m, 1H), 7.19–7.38 (m, 1H), 7.89 (m, 1H).

**Method B:** A crude material **4** which was prepared from **3** in the same way as described for the preparation of **11c** was dissolved in 20 ml of dry toluene and refluxed for 30 min in the presence of PTSA (4 mg) under  $\text{N}_2$ . The reaction mixture was neutralized with  $\text{NaHCO}_3$ , washed with brine, and extracted with ether. The combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give a crude product, which was purified by preparative TLC (36 mg, 25%).

**Ipomeanine (13).** A solution of **12c** (31 mg, 0.128 mmol) in 99%-acetone (15 ml) was refluxed for 1 h in the presence of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (46 mg, 0.27 mmol) and CuO (43 mg, 0.54 mmol). An insoluble material was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residual oil was purified by preparative TLC using ether-hexane (1 : 4 v/v) as solvent to afford compound **13** in 89% yield (23 mg). IR (neat) 1714, 1668, 1561, 1149, 866  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  2.20 (s, 3H), 2.67–3.61 (m, 4H), 6.74 (m, 1H), 7.43 (m, 1H), 8.05 (m, 1H).

The 2,4-dinitrophenylhydrazone was prepared as a red crystalline material, mp 231–233 °C (lit, mp 231–234 °C).<sup>9)</sup>

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respect to previous synthesis of isoegomaketone, see Ref. 3c.

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