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

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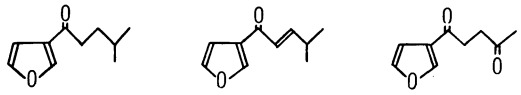
It was found that 3-(phenylthio)propanal dimethyl acetal is a very useful starting material for the preparation of 3-acylfuranoterpenes. Syntheses of two naturally-occurring furans, isoegomaketone and ipomeanine were described.

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

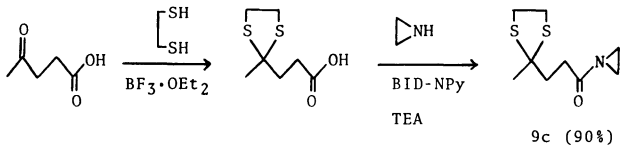
In the previous paper,[4] it has been reported that the readily available 3-(phenylthio)propanal ethylene acetal (**2**) was proved to be very useful starting material for the preparation of 3-acylfurans. Syntheses of some 3-acylfurans were exemplified and one of naturally-occurring furanoterpenes, perillaketone (**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 furutescens* Brit.[5] and ipomeanine (**13**) which was produced by cerato-stomella.[6] In this paper, the syntheses of both furano-terpenes **12b** and **13** are described.



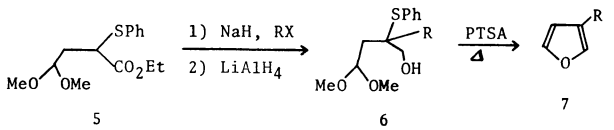
1 12b 13

The synthesis of ipomeanine (**13**) was examined according to Scheme 1. Acylation of compound **2** was performed by treatment of a lithiated **2** with acyl-aziridine **9c** at −78 °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 thiacetalized acid obtained with aziridine by 3-(5-nitro-2-oxo-1,2-dihydro-1-pyridyl)-1,2-benziso-thiazole 1,1-dioxide (BID-NPy)[7] 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 °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 $CuCl_2$ and CuO in refluxing wet acetone[8] to give the final product, ipomeanine, 1-(3-furyl)-1,4-pentane-dione (**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**)[9] in excellent yield as shown below. These findings



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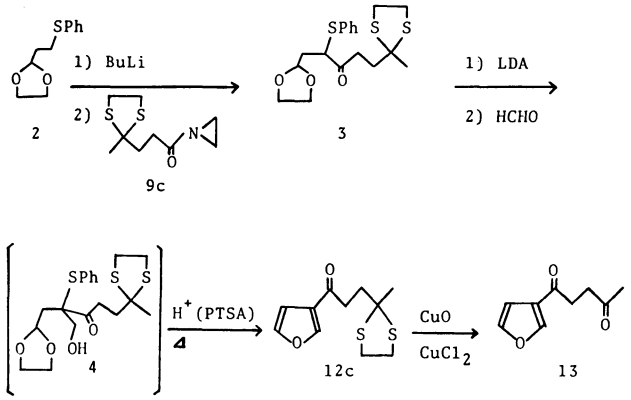
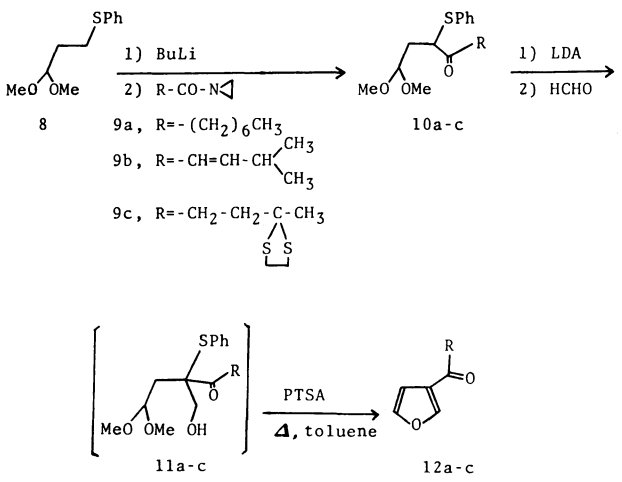
suggested that compound **6** was a more favorable starting material for the cyclization to furan ring. From this fact, we have thought that 3-(phenylthio)-propanal dimethyl acetal (**8**) was more effective synthon for the preparation of 3-acylfurans than compound **2** (Scheme 2). The starting material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



2 9c 3 4 12c 13

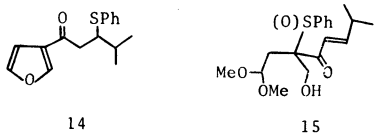
Scheme 1.



Scheme 2.

equiv.) in dry methanol in 85% yield. First of all, as a model experiment synthesis of 3-octanoylfuran (**12a**) was undertaken. Compound **8** was allowed to react with 1.1 equivalent of BuLi in THF at −78 °C followed by treatment with 1-octanoylaziridine (**9a**) to give the expected acyl compound **10a** in 64% yield. Compound **10a** was lithiated with 1.2 equivalent of LDA at −78 °C in THF followed by reaction with a large excess of formaldehyde to give the corresponding hydroxymethyl derivative **11a**, which was refluxed in toluene for 50 min in the presence of 6 mol percent of PTSA. The desired 3-octanoylfuran (**12a**) was obtained in 67% yield from **10a**. Many attempts to improve the yield of **12a** from **11a** were examined under various conditions. Subsequently, successive removal of the methanol formed *in situ* using Soxhlet's extractor where a large amount of boric acid was placed gave an outstanding result. Namely, the yield of **12a** was raised up to 84% yield under the same reaction conditions as used before. This good result prompted us to employ compound **8** as the starting material for the preparation of more complex furanoterpenes such as **12b** and **13**.

In a manner similar to the preparation of **12a**, treatment of **9b**—**c** gave the corresponding 3-acylfurans **10b**—**c** in 65% and 67% yields, respectively. Next, they were allowed to react with LDA at −78 °C and treated with formaldehyde as mentioned above to give the desired products **11b**—**c**. The resulting crude **11c** was transformed into the protected 3-acylfuran **12c** in 63% yield based on **10c**. This yield was greatly raised compared with the result starting from compound **3**. Compound **12c** was converted to ipomeanine **13** according to the procedure as shown before.



14 15

Similarly, when the crude material **11b** was refluxed in toluene including a small amount of PTSA, the reaction was accompanied by formation of 3-[4-methyl-3-(phenylthio)pentanoyl]furan (**14**) as by-product besides **12b**. In order to solve this problem, compound **11b** was converted into sulfoxide **15** with *m*-chloroperbenzoic acid, which was treated with PTSA in refluxing toluene. Unfortunately, the desired product was only produced in an unsatisfactory yield from **10b**. Next, the crude **11b** was refluxed for 17 min in toluene in the presence of 1.5 equivalent of iodine to oxidize the benzenethiol liberated in the reaction to the disulfide, 6 mol percent of PTSA, and boric acid. Eventually, isoegomaketone, 1-(3-furyl)-4-methyl-2-penten-1-one (**12b**) was obtained in 62% yield based on **10b**.

As mentioned above, it is evident that 3-(phenylthio)-propanal dimethyl acetal (**8**) is synthetically versatile starting material for more complex 3-acylfurans.

Experimental

The NMR spectra were recorded on a JEOL/MH-60, and a JEOL/PMX-60. The chemical shifts are reported on the δ scale relative to TMS as an internal standard. The IR spectra were measured with a JASCO IRA-1 diffraction grating infrared spectrometer.

Materials. All the solvents were distilled according to the usual methods and stored over a drying agent. Thin-layer chromatography (TLC) was performed on Merck's Silica gel 60 PF_{254} (Type 7749).

*Preparation of Acylaziridine Derivatives (**9a**—**c**).* *1-[4,4-(Ethylenedithio)pentanoyl]aziridine (**9c**)*: To a solution of BID–NPy (610 mg, 2 mmol) and 4,4-(ethylenedithio)-pentanoic acid (384 mg, 2 mmol)[10] in dry CH_2Cl_2 (5 ml) was added a solution of triethylamine (TEA) (222 mg, 2.2 mmol) in dry CH_2Cl_2 (5 ml) at 0 °C under N_2. The reaction mixture was stirred for 1.5 h at 0 °C and a solution of aziridine (220 mg, 2 mmol) in dry CH_2Cl_2 (5 ml) was added to the above solution at 0 °C. The reaction mixture was warmed to room temperature, stirred for 30 min, and treated with 10%-$NaHCO_3$ (10 ml). The mixture was extracted with ether several times and the combined extracts were washed with brine, dried over Na_2SO_4, concentrated *in vacuo* to give a residue which was subjected to preparative TLC (solvent; AcOEt: hexane=1 : 5 v/v). Compound **9c** was obtained in 90% yield as an oily product (365 mg); IR (neat) 1689, 1143, 1117, 1088 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3H), 2.11—2.38 (m, 2H), 2.60—2.85 (m, 2H), 2.24 (s, 4H), 3.33 (s, 4H).

Other 1-acylaziridine compounds **9a**—**b** were obtained from aziridine and the corresponding acyl chlorides in 69% and 58% yields, respectively.

9a: Oil IR (neat) 1693, 1373, 1145, 996 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (t, 3H, J=6.6 Hz), 1.03—2.00 (m, 10H), 2.17 (s, 4H), 2.41 (t, 2H, J=7.0 Hz).

9b: Oil bp 55—65 °C/0.4 Torr); IR (neat) 1670, 1630, 1107, 973 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (d, 6H, J=6.0 Hz), 2.25 (s, 4H), 2.08—2.81 (m, 1H), 5.96 (dd, 1H, J=2.0, 16.0 Hz), 7.00 (dd, 1H, J=6.0, 16.0 Hz).

*7,7-Ethylenedithio-4-oxo-3-(phenylthio)octanal Dimethyl Acetal (**3**).* To a solution of **2** (344 mg, 1.64 mmol) in dry tetrahydrofuran (THF) (5 ml) was added 1.1 equiv. of BuLi at −78 °C under N_2. The solution was warmed from −78 °C to −20 °C in a period of 2 h and cooled down at −78 °C again. A solution of **9c** (364 mg, 1.80 mmol) in dry THF (5 ml) was added to it at −78 °C and the reaction mixture was gradually warmed to room temperature and allowed to stand overnight. After quenching with buffer solution of pH 7 and 1 M-HCl, the resulting solution was extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give a residual oil. Purification with preparative TLC in which development was repeated twice with solvent system of

benzene–hexane–EtOAc (5 : 5 : 1 v/v) gave the desired product in 65% yield (oil, 408 mg): IR (neat) 1702, 1580, 1130, 1012 cm^{-1}; NMR ($CDCl_3$) δ 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 acryladehyde (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 $NaHCO_3$, evaporated under reduced pressure to give a residue which was taken up into ether. The ether solution was washed with brine, dried over Na_2SO_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 cm^{-1}; NMR ($CDCl_3$) δ 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 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 Na_2SO_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 cm^{-1}; NMR ($CDCl_3$) δ 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 cm^{-1}; NMR ($CDCl_3$) δ 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 cm^{-1}; NMR ($CDCl_3$) δ 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 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 Na_2SO_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**.

*1-(3-Furyl)-1-octanone (**12a**).* A solution of the crude material **11a** (197 mg) obtained above in dry toluene (30 ml) was added in one portion under 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%-$NaHCO_3$, and extracted with ether. The organic layer was dried over Na_2SO_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 cm^{-1}; NMR ($CDCl_3$) δ 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 silmiar 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.[3c] IR (neat) 3140, 1660, 1610, 1147, 865 cm^{-1}; NMR ($CDCl_3$) δ 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-(Ethylenedithio) 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 cm^{-1}; NMR ($CDCl_3$) δ 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 N_2. The reaction mixture was neutralized with $NaHCO_3$, washed with brine, and extracted with ether. The combined extracts were dried over Na_2SO_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 $CuCl_2 \cdot 2H_2O$ (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 cm^{-1}; NMR ($CDCl_3$) δ 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).[6]

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