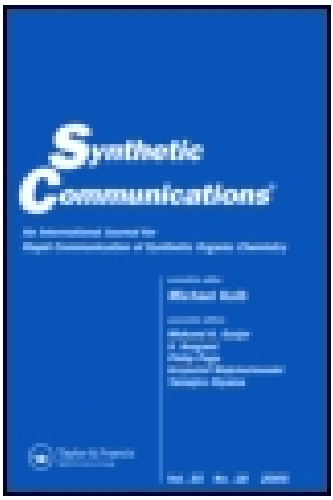

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A Convenient Preparation of Farnesylamine

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A CONVENIENT PREPARATION OF FARNESYLAMINE

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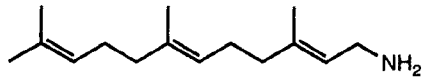
ABSTRACT: The efficient synthesis of farnesylamine (**1**) was accomplished by two separate routes. The first, by the alkylation of triflouroacetamide with farnesyl bromide followed by base hydrolysis. The second, by displacement of the halogen of farnesyl bromide with lithium bis(trimethylsilyl)amide followed by methanolysis.

Farnesylamine (**1**) serves as an important intermediate in our program on the synthesis of squalene synthetase inhibitors. Its use for this purpose was reported[1] but not its synthesis. Patent literature describes the preparation of farnesylamine from farnesyl bromide and sodium amide in liquid ammonia[2]. Substitution of ether for ammonia as the solvent resulted in the formation of trifarnesyl-amine. In a recent patent[3], Squibb scientists prepared **1** using classical methodology by converting farnesyl bromide to 2-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-1H-isoindole-1,3(2H)-dione followed by treatment with methyl hydrazine which is a highly toxic, cancer suspect agent.



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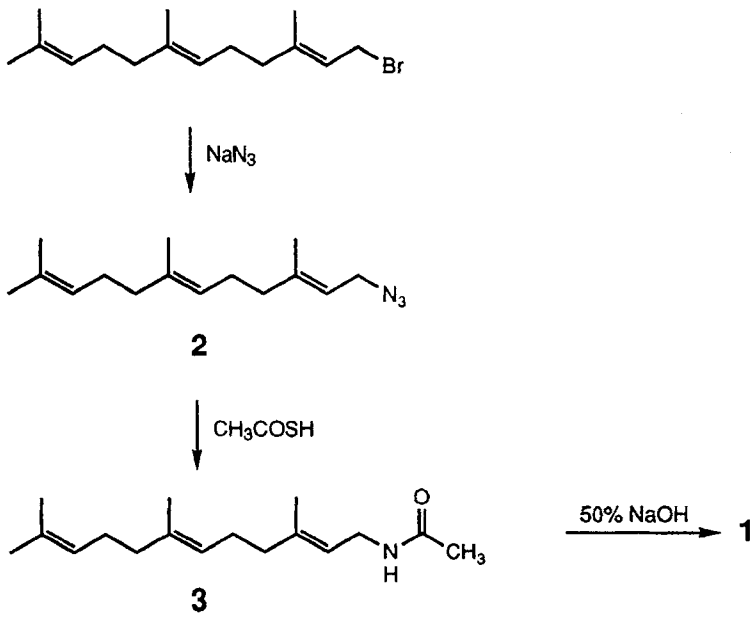
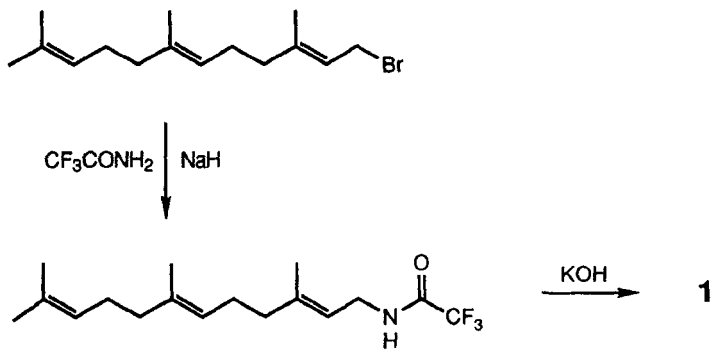
Since we required large quantities of **1** we felt that there was a need for a convenient, reliable method for the synthesis of farnesylamine. We investigated several methods to achieve this goal and we wish to report our successful results.

Our first attempt at preparing **1** involved the treatment of farnesyl bromide with sodium azide. The resulting farnesyl azide (**2**) was produced in 68% yield, however, as an inseparable mixture of E and Z isomers of the 2,3-double bond. Treatment of **2** with thiolacetic acid gave an isomeric mixture of N-farnesyl-acetamide in 68% yield. The desired E-isomer (**3**) was isolated by column chromatography in 34% yield. Base hydrolysis of **3** required 44 hours to produce **1** which was formed in 95% yield.



N-Farnesylacetamide (**3**) could also be prepared in one step by direct alkylation of acetamide with farnesyl bromide in the presence of sodium hydride, however the yield was rather low (36%).

A prime concern of ours was to improve the sluggish hydrolysis step **3** → **1**. We reasoned that replacing the acetamide with trifluoroacetamide would increase the ease in which the acyl group would be hydrolyzed. Thus, alkylation of trifluoroacetamide with farnesyl bromide in the presence of sodium hydride gave N-farnesyltrifluoroacetamide (**4**) in 48% yield. Hydrolysis with potassium hydroxide only required 4 hours and farnesylamine was isolated in 97% yield.



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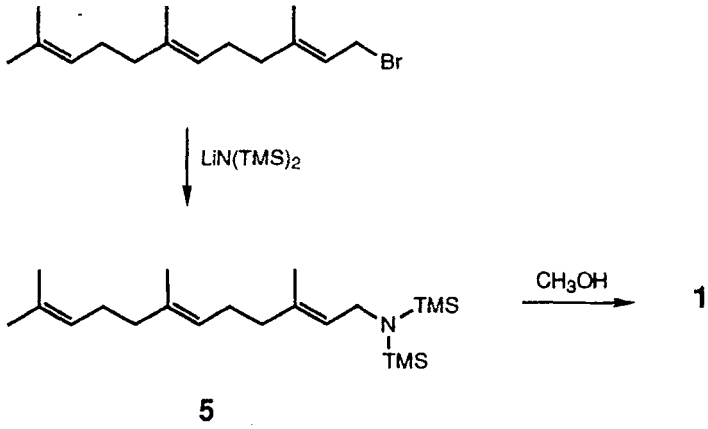
A further simplification of the synthesis of farnesylamine was achieved in essentially one step by treating farnesyl bromide with lithium bis(trimethylsilyl)amide. The intermediary bis(trimethylsilyl)farnesylamine (**5**), without purification, was treated with methanol to afford the desired product **1** in quantitative yield. The farnesylamine prepared by this method is of sufficient purity (90% by gas chromatography) for use in subsequent reactions. Further

purification can be accomplished either by distillation or flash chromatography using ethyl acetate/isopropylamine as the eluent.



5

EXPERIMENTAL

N-Farnesylacetamide (3)

To a stirred slurry of 0.432 g (10.8 mmol) of sodium hydride (60% dispersion in mineral oil) in 30 ml of dry tetrahydrofuran was added dropwise a solution of 0.584 g (9.9 mmol) of acetamide in 5 ml of tetrahydrofuran under an argon atmosphere. The mixture was cooled to 0°C and 2.56 g (9 mmol) of farnesyl bromide and 0.29 g (9 mmol) of tetrabutylammonium bromide were added sequentially. The mixture was stirred at room temperature for 20 hr. then was quenched with saturated sodium chloride solution. The aqueous phase was extracted with ether and the combined organic phases were dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting crude oil was chromatographed on a column of silica gel using petroleum ether/ethyl acetate (95 : 5) to elute the product, 0.96 g (37% yield) of 3 as an oil; IR (film): 1659 cm^{-1}; NMR ($CDCl_3$): δ

5.35 (s, broad, 1H), 5.19 (t, 1H), 5.08 (m, 2H), 3.85 (t, 2H), 2.00 (s, 3H), 1.90-2.20 (m, 8H), 1.68 (s, 6H), 1.60 (s, 6H); MS: m/z 264 (MH^+).

N-Farnesyltrifluoroacetamide (4)

To a stirred slurry of 0.432 g (10.8 mmol) of sodium hydride (60% dispersion in mineral oil) in 30 ml of dry tetrahydrofuran was added dropwise a solution of 1.12 g (9.9 mmol) of trifluoroacetamide in 5 ml of tetrahydrofuran under an argon atmosphere. The mixture was cooled to 0°C and 2.56 g (9 mmol) of farnesyl bromide and 0.29 g (9 mmol) of tetrabutylammonium bromide were added sequentially. The mixture was stirred at room temperature for 20 hr. then was quenched with saturated sodium chloride solution. The aqueous phase was extracted with ether and the combined organic phases were dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting crude oil was chromatographed on a column of silica gel using petroleum ether/ethyl acetate (95 : 5) to elute the product, 1.51 g (48% yield) of **4** as an oil; IR (film): 3304, 1702 cm^{-1}; NMR ($CDCl_3$): δ 6.19 (b, 1H), 5.24 (t, 1H), 5.12 (m, 2H), 3.98 (t, 2H), 1.90-2.22 (m, 8H), 1.72 (s, 3H), 1.69 (s, 3H), 1.60 (s, 6H); MS (ammonia): m/z 318 (MH^+), 335 (MNH_4^+).

Anal. Calcd for $C_{11}H_{26}NOF_3$: C, 64.33; H, 8.26; N, 4.41. Found: C, 64.23; H,8.39; N, 4.36.

Farnesylamine (1)

Method 1

To a solution of 1.3 g (4.13 mmol) of **4** in 12 ml of methanol was added a solution of 2.31 g (41.3 mmol) of potassium hydroxide in 3 ml

of water and the resulting mixture was refluxed for 4 hr. The solvent was evaporated under reduced pressure and water was added to the residue. The mixture was extracted with methylene chloride and the organic phase was dried over magnesium sulfate. The solvent was removed under reduced pressure to give 0.91 g (97% yield) of pure 1 as an oil; IR (film): 3371, 3287 cm^{-1}; NMR ($CDCl_3$): δ 5.29 (t, 1H), 5.12 (m, 2H), 3.29 (d, 2H), 1.90-2.20 (m, 8H), 1.69 (s, 3H), 1.64 (s, 3H), 1.60 (s, 6H), 1.11 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 136.21, 135.04, 131.13, 125.96, 124.33, 123.95, 39.65, 39.50, 26.71, 26.42, 25.60, 17.61, 16.00, 15.94; MS: m/z 222 (MH^+).

Anal. Calcd for $C_{15}H_{27}N+0.3\ H_2O$: C, 79.44; H, 12.27; N, 6.18. Found: C, 79.71; H, 12.22; N, 5.75.

Method 2

To 50 ml (0.05 mol) of lithium bis(trimethylsilyl)amide (1.0M in tetrahydrofuran, Aldrich Chemical Co.) under a blanket of argon was added 12.4 g (0.044 mol) of *trans,trans*--farnesyl bromide. After stirring at room temperature for 18 hr., the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted twice with methyl *t*-butyl ether and the organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 14.2 g of **5** as a pale brown oil; NMR ($CDCl_3$) δ 5.13 (m, 2H), 5.00 (t, 1H), 3.43 (d, J = 5 Hz, 2H), 2.18 - 1.89 (m, 8H), 1.68 (s, 3H), 1.61 (s, 6H), 1.56 (s, 3H), 0.10 (s, 18H).

To this oil was added 200 ml of methanol and 25 ml of methylene chloride and the resulting solution was stirred at room

temperature for 18 hr. The solvent was removed under reduced pressure to give 9.9 g (100% yield) of **1** as a straw-colored oil.

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