Synthesis of 3-Vinylpiperidine

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A novel synthesis of 3-vinylpiperidine from commercially available ethyl 3-pyridylacetate is described.

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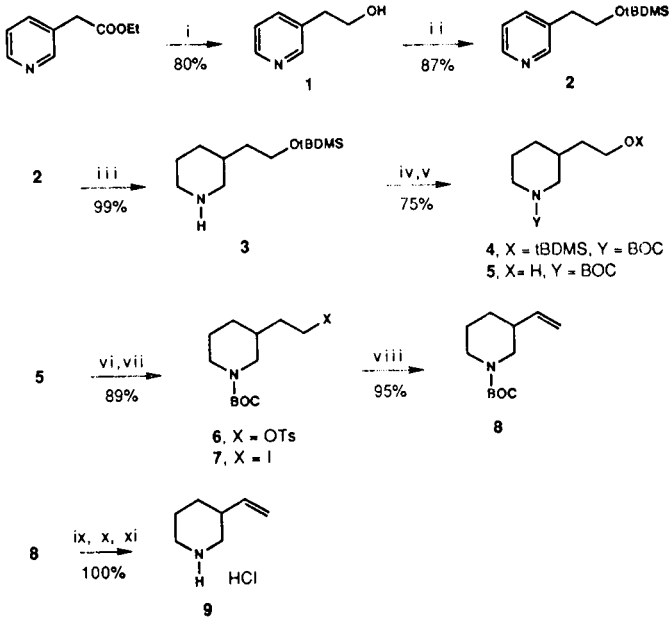
We have developed a synthetic route to 3-vinylpiperidine (**9**) that, because of its structural similarity to natural compounds in the cinchonine and quinine families, is an interesting and useful intermediate in alkaloid construction. Although the compound is listed in the Dictionary of Organic Compounds [1], a literature review did not reveal a facile synthesis for large quantities of material. The compound was first synthesized in 1928 by Marvel and Merchant who reported a six-step synthesis of 3-vinylpiperidine from 3-hydroxymethylpiperidine with less than 5% overall yield [2]. In 1937, Iddles, Lang, and Gregg prepared 3-vinylpiperidine from 3-acetylpyridine in a two-step process where the second step gave less than a 10% yield of the product [3]. More recently, Grob, Kunz, and Marbet have reported identifying 3-vinylpiperidine as a side-product in a solvolytic fragmentation reaction [4]. In 1986, Grieco and Fobare reported the multi-step synthesis of *N*-benzyl-3-vinylpiperidine as part of their investigation into the intramolecular condensation of immonium ions with allysilanes [5]. In 1987, Hiemstra, Speckamp, *et al.* generated *N*-carbomethoxy-3-vinylpiperidine *via* an intramolecular cyclization of *N*-acyliminium ions [6].

Scheme 1



(i) LAH; (ii) tBDMSCl, Et_3N, CH_2Cl_2; (iii) H_2, PtO_2, EtOH, HOAc; (iv) BOC-ON, K_2CO_3; (v) $(n\text{-}Bu)_4NF$; (vi) TsCl, DMAP, Et_3N, CH_2Cl_2; (vii) NaI, acetone; (viii) KOtBu, THF; (ix) TFA, CH_2Cl_2, (x) KOH; (xi) HCl (g)

This note reports a novel and efficient synthesis of 3-vinylpiperidine from a commercial precursor and has the advantage of being both versatile and high-yielding.

Starting with commercially available ethyl 3-pyridylacetate, 3-(2-[*tert*-butyldimethylsilyloxy]ethyl)piperidine (**3**) was synthesized in a three-step process that incorporated protection of the primary hydroxy moiety of a pyridine and subsequent reduction to the piperidine. This sequence allowed generation of **3** selectively protected in the side chain (see Scheme 1). The first step involved reduction of the acetate to alcohol **1** in 80% yield with lithium aluminum hydride in tetrahydrofuran in a modification of the method of Barnden [7].

Protection of the pyridyl alcohol as the *tert*-butyldimethylsilyl ether **2** in 87% yield with triethylamine in dichloromethane was followed by hydrogenation to piperidine **3** according to the method of Najer [8] using platinum oxide, acetic acid, and ethanol in a 99% yield. The next two steps involved protection of the amine with di-*tert*-butyl dicarbonate (BOC anhydride) and potassium carbonate in dioxane to give **4** and deprotection of the alcohol with a 1.0 molar solution of tetrabutylammonium fluoride in tetrahydrofuran to give **5** in an overall yield of 75%. The BOC group was chosen as a nitrogen blocking agent because of its stability in base and its easy removal with acid.

The alcohol was converted to tosylate **6** in 90% yield with *p*-toluenesulfonyl chloride and 4-dimethylaminopyridine in dichloromethane, but attempts at E2 elimination under a variety of basic conditions failed to generate the olefin. The tosylate was rapidly transformed with sodium iodide in acetone in 99% yield to the iodide **7**, which was treated with potassium *tert*-butoxide in THF to provide the *N*-blocked 3-vinylpiperidine **8** in 95% yield. Quantitative deprotection of **8** with trifluoroacetic acid in dichloromethane gave 3-vinylpiperidine **9** in an overall yield of 43% from ethyl 3-pyridylacetate. The compound was stored as its hydrochloride salt.

We have achieved a novel and high-yielding synthesis of 3-vinylpiperdine from commercial starting materials. Individual steps in the synthesis provide products that re-

quire little or no purification, and reaction times for these steps were generally under one day.

EXPERIMENTAL

All ^{1}H nmr spectra were obtained on a 200 MHz Varian nmr spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc. in Norcross, GA. Unless stated othewise all chemicals were purchased from Aldrich Chemical Co. Purification of compounds was accomplished by a modification of traditional flash chromatography as described by O'Neil [9]. This method is best used for compounds with only minor impurities and represents an efficient, rapid purification process.

2-(3-Pyridyl)ethanol (**1**).

In this modification of the procedure by Barnden *et al.* [7], a 1.0 *M* solution of lithium aluminum hydride in diethyl ether (141 ml, 0.14 mole) was added dropwise over 40 minutes to a stirred solution of ethyl 3-pyridylacetate (25.0 g, 0.15 mole) in anhydrous tetrahydrofuran (400 ml) cooled to 0° (ice bath) in a 1 ℓ three-neck round bottom flask under a nitrogen atmosphere. The ice bath was removed and the reaction was stirred for an additional 2 hours. A saturated solution of potassium sodium tartrate (150 ml) was slowly added (**CAUTION: HYDROGEN GAS**) to the reaction followed by diethyl ether (200 ml), and the layers were separated. The flocculent aqueous layer was filtered over Celite to remove solids and was extracted with ethyl acetate (100 ml). The organic phases were combined and dried over sodium sulfate. Solvent was removed *in vacuo* to give a red oil, which was flash chromatographed over silica gel using chloroform:methanol (95:5) as eluent to provide the alcohol **1** as a yellow oil (14.7 g, 0.12 mole, 80%); ^{1}H nmr (DMSO-d_6): δ 8.42-8.36 (m, 2H, pyr), 7.64-7.59 (m, 1H, pyr), 7.30-7.24 (m, 1H, pyr), 4.73 (t, 1H, OH), 3.65-3.56 (m, 2H, CH_2), 2.71 (t, CH_2).

Anal. Calcd. for $C_7H_9NO \cdot 0.3H_2O$: C, 65.40; H, 7.53; N, 10.90. Found: C, 65.65; H, 7.57; N, 10.75.

3-(2-[*tert*-Butyldimethylsilyloxy]ethyl)pyridine (**2**).

To a solution of 2-(3-pyridyl)ethanol (**1**) (1.0 g, 8.1 mmoles) and triethylamine (2 ml, 14.3 mmoles) in dichloromethane (40 ml) in a 100 ml round bottom flask under a nitrogen atmosphere was added commercial 97% *tert*-butyldimethylsilyl chloride (1.3 g, 8.5 mmoles) in one portion. The reaction was stirred at room temperature for 5 hours before the addition of saturated sodium bicarbonate (15 ml). The layers were separated, and the organic phase was washed with brine (10 ml) and dried over sodium sulfate. Solvent was removed *in vacuo* and the residual brown oil was flash chromatographed over silica gel using chloroform as eluent to provide the protected alcohol **2** (1.68 g, 7.1 mmoles, 87%) as a pale yellow oil; ^{1}H nmr (DMSO-d_6): δ 8.45-8.43 (m, 2H, pyr), 7.70-7.62 (m, 1H, pyr), 7.36-7.19 (m, 1H, pyr), 3.79 (t, 2H, CH_2), 2.76 (t, 2H, CH_2), 0.81 (s, 9H, $SiMe_3$), −0.07 (s, 6H, $SiMe_2$).

3-(2-[*tert*-Butyldimethylsilyloxy]ethyl)piperidine (**3**).

To a solution of 3-(2-[*tert*-butyldimethylsilyloxy]ethyl)pyridine (**2**) (1.5 g, 6.3 mmoles) and glacial acetic acid (0.72 ml, 12.6 mmoles) in 95% ethanol (100 ml) in a Parr bottle was added platinum oxide hydrate (0.10 g, 0.44 mmole). The vessel was then put on a Parr shaker where it was agitated for 20 hours under 40 psi of hydrogen gas. The reaction was filtered through Celite and washed with several portions of 95% ethanol. After the combined ethanol was removed *in vacuo*, ethyl acetate (150 ml) and saturated sodium bicarbonate (50 ml) were added and the layers were separated. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product which was flash chromatographed over silica gel using chloroform:methanol (90:10 to 80:20) in increasingly polar increments to give the piperidine **3** as a pale yellow oil (1.5 g, 6.1 mmoles, 99%); ^{1}H nmr (DMSO-d_6): δ 4.09 (bs, 1H, NH), 3.61 (t, 2H), 2.95-2.84 (m, 2H), 2.55-2.13 (m, 2H), 1.81-0.94 (m, 7H), 0.87 (s, 9H, $SiMe_3$), 0.04 (s, 6H, $SiMe_2$).

tert-Butyl 3-(2-[*tert*-Butyldimethylsilyloxy]ethyl)-1-piperidinecarboxylate (**4**).

To a rapidly stirring solution of 3-(2-[*tert*-butyldimethylsiloxy]-ethyl)piperidine (**3**) (1.0 g, 4.1 mmoles) in 1,4-dioxane (20 ml) and 5% potassium carbonate (20 ml) in a 100 ml round bottom flask was added di-*tert*-butyl dicarbonate (1.3 g, 6.2 mmoles) in one portion. A drying tube was placed on top of the flask, and the reaction was vigorously stirred for 24 hours. Ethyl acetate (100 ml) and brine (15 ml) were added and the layers were separated. The aqueous layer was extracted with additional ethyl acetate (50 ml), and the combined organic layers were dried over sodium sulfate, filtered and removed *in vacuo*. The resulting yellow oil was flash chromatographed over silica gel using hexane:ethyl acetate (6:1) to provide the protected piperidine **4** as a pale yellow oil (1.4 g), which was used in the next step without further purification; ^{1}H nmr (DMSO-d_6): δ 3.76-3.69 (m, 2H), 3.64 (bt, 2H), 2.90-2.75 (m, 2H), 1.83-1.15 (m, 7H), 1.40 (s, 9H, CMe_3), 0.88 (s, 9H, $SiMe_3$), 0.05 (s, 6H, $SiMe_2$).

tert-Butyl 3-(2-hydroxyethyl)-1-piperidinecarboxylate (**5**).

To a stirring solution of *tert*-butyl 3-(2-[*tert*-butyldimethylsilyl-oxy]ethyl)-1-piperidinecarboxylate (**4**) (1.4 g, 4.1 mmoles) in tetrahydrofuran (10 ml) in a 50 ml round bottom flask under nitrogen atmosphere was added 1.0 *M* tetrabutylammonium fluoride (4.9 ml, 4.9 mmoles) in one portion. The reaction was stirred for 20 hours after which the volatiles were removed *in vacuo*. The crude semisolid was flash chromatographed over silica gel using hexane:ethyl acetate (3:1 to 1:1) in increasingly polar increments to provide the alcohol **5** as a yellow oil (0.70 g, 3.1 mmoles, 75% over two steps); ^{1}H nmr (DMSO-d_6): δ 4.41 (t, 1H, OH), 3.94-3.61 (m, 2H), 3.45 (dd, 2H), 2.79 (dt, 2H), 1.80-1.72 (m, 2H), 1.65-1.00 (m, 5H), 1.40 (s, 9H, CMe_3).

tert-Butyl 3-(2-[4-tolylsulfonyloxy]ethyl)-1-piperidinecarboxylate (**6**).

To a solution of *tert*-butyl 3-(2-hydroxyethyl)-1-piperidinecarboxylate (**5**) (1.1 g, 4.8 mmoles), 4-dimethylaminopyridine (30 mg, 0.25 mmole), and triethylamine (0.9 ml, 6.2 mmoles) in dichloromethane (50 ml) in a 100 ml round bottom flask under a nitrogen atmosphere was added *p*-toluenesulfonyl chloride (0.96 g, 5.0 mmoles) in one portion. The reaction was stirred overnight before the addition of saturated sodium bicarbonate (10 ml). The layers were separated and the organic phase was washed with water (10 ml), brine (10 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude yellow oil was flash chromatographed over silica gel using hexane:ethyl acetate (5:1 to 3:1) in increasingly polar increments to provide the tosylate **6** as a colorless oil (1.7 g, 4.3 mmoles, 90%); ^{1}H nmr (DMSO-d_6): δ 7.81 (d, 2H, Ph), 7.50 (d, 2H, Ph), 4.07 (t, 2H), 3.69-3.63 (m, 2H), 2.80 (bt, 2H), 2.43 (s, 3H, CH_3), 1.60-1.00 (m, 7H), 1.39 (s, 9H, CMe_3).

Anal. Calcd. for $C_{19}H_{29}NO_5S$: C, 59.51; H, 7.62; N, 3.65; S, 8.36. Found: C, 59.34; H, 7.63; N, 3.72; S, 8.44.

tert-Butyl 3-(2-Iodoethyl)-1-piperidinecarboxylate (**7**).

tert-Butyl 3-(2-[4-tolylsulfonyloxy]ethyl)-1-piperidinecarboxylate (**6**) (1.00 g, 2.61 mmoles) and sodium iodide (1.17 g, 7.82 mmoles) were dissolved in acetone (40 ml) in a 100 ml round bottom flask under a nitrogen atmosphere and equipped with a condenser. The reaction was heated at reflux for 2 hours and cooled before the addition of diethyl ether (200 ml) and water (50 ml). The layers were separated, and the organic phase was washed with brine (25 ml), dried over magnesium sulfate, filtered and concentrated *in vauco* to give the iodide **7** as a yellow oil (0.88 g, 2.58 mmoles, 99%) which was used immediately without further purification; ^{1}H nmr (DMSO-d_6): δ 3.81-3.45 (m, 2H), 3.31 (t, 2H), 2.86 (dt, 2H), 1.78-1.00 (m, 7H), 1.41 (s, 9H, CMe_3).

tert-Butyl 3-vinyl-1-piperidinecarboxylate (**8**).

To a solution of *tert*-butyl 3-(2-iodoethyl)-1-piperidinecarboxylate (**7**) (0.75 g, 2.2 mmoles) in anhydrous tetrahydrofuran (30 ml) in a 100 ml round bottom flask under a nitrogen atmosphere was added commercial 97% potassium *tert*-butoxide (0.31 g, 2.6 mmoles) in one portion. The reaction, which became milky white in approximately ten seconds, was monitored by thin-layer chromatography. When loss of starting material was indicated, water (30 ml) and ethyl acetate (100 ml) were added and the layers were separated. The organic phase was washed with brine (20 ml), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude liquid was flash chromatographed over silica gel using 5:1 hexane:ethyl acetate as eluent to provide the vinylpiperidine **8** as a pale yellow oil (0.44 g, 2.1 mmoles, 95%). ^{1}H nmr (DMSO-d_6): δ 5.83-5.66 (m, 1H, $CH=CH_2$), 5.14-5.00 (m, 2H, $CH=CH_2$), 3.89-3.68 (m, 2H), 2.85-2.54 (m, 2H), 2.10-1.97 (m, 1H, $CH-CH=CH_2$), 1.81.-1.00 (m, 4H), 1.40 (s, 9H CMe_3).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.00; H, 10.03; N,6.56.

3-Vinylpiperidine (**9**).

To a solution of *tert*-butyl 3-vinyl-1-piperidinecarboxylate (**8**) (0.50 g, 2.4 mmoles) in dichloromethane (20 ml) in a 50 ml round bottom flask under a nitrogen atmosphere was added trifluoroacetic acid (5 ml). After the reaction was stirred for 1 hour at room temperature, all volatiles were removed *in vacuo* and ethyl acetate (10 ml) and water (20 ml) were added. The layers were separated and the aqueous layer was adjusted to *p*H 10 with 30% potassium hydroxide solution and extracted with ethyl acetate (50 ml). The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo* to a yellow oil that was immediately dissolved in absolute ethanol (5 ml). A commercial 1.0 *M* ethereal solution of hydrogen chloride (2.8 ml) was added followed by diethyl ether (20 ml). The resulting precipitate was filtered and dried under house vacuum overnight to provide the hydrochloride salt of 3-vinylpiperidine **9** (0.35 g, 2.3 mmoles, 99%) as a white powder; ^{1}H nmr (DMSO-d_6): δ 9.56-9.25 (bs, 2H, NH_2), 5.83-5.66 (m, 1H, $CH=CH_2$), 5.14-5.05 (m, 2H, $CH=CH_2$), 3.55-3.23 (bs, 1H, $CH-CH=CH_2$), 3.19-3.07 (m, 2H), 2.82-2.40 (m, 2H), 1.80-1.13 (m, 4H).

Anal. Calcd. for $C_7H_{14}NCl\cdot 0.20H_2O\cdot 0.15HCl$: C, 53.65; H, 9.36; N, 8.94; Cl, 26.02. Found: C, 53.83; H, 9.29; N, 9.00; Cl, 25.76.

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