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Practical Synthesis of 7-Prenylindole

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Abstract

7-Prenylindole is a useful building block for natural product and natural product analog synthesis. While there have been several past syntheses of 7-prenylindole, none of them is very practical for its preparation on scale. Using an aza-Claisen rearrangement as the key step, 7-prenylindole has been prepared in four steps from indoline in 62% overall yield.

7-Prenylindole is a component of many natural products, such as the annonidines,¹ astechrome (as its iron complex),² and the asterriquinones³ (Chart 1). It is also a (simple) natural product, mostly from plants, in its own right.⁴ We have used 7-prenylindole in several syntheses of asterriquinone targets, in particular demethylasterriquinone B1⁵ (a lead compound for oral insulin mimics), as have others.⁶ 7-Prenylindole has also served as a starting material for syntheses of the annonidines⁷ and astechrome.⁸ There are several literature preparations of 7-prenylindole,⁹ including one of our own.¹⁰ Because we identified the 7-prenylindole region of demethylasterriquinone B1 as a major part of its pharmacophore,^{5c} we must prepare large numbers of compounds that include 7-prenylindole. This compound is therefore needed in ample supply, but in our experience all of its known preparations have drawbacks. Some do not scale up well, while others require expensive reagents or catalysts. We describe here a synthesis of 7-prenylindole that is readily performed with simple chemistry on a scale to prepare gram quantities.

The synthesis (Scheme 1) begins with indoline, which is *N*-dimethylpropargylated using classical methods¹¹ to give the known compound **1**.¹² The semi-hydrogenation of compound **1** proceeds rapidly, so quickly in fact that prompt monitoring of the reaction, conducted merely with a balloon containing hydrogen, is required. Within 20–30 min, the known dimethylallyl amine **2** is produced. The acid-promoted aza-Claisen rearrangement of *N*-allylanilines¹³ is a known transformation.^{9a,12} Heating **2** with trifluoroacetic acid in a microwave reactor introduces the prenyl group ortho to the nitrogen. Final oxidation of the indoline to the indole is conducted with manganese dioxide.¹⁴ Interestingly, when conducted in chloroform, this reaction gives appreciable quantities of compound **5**. A putative mechanism to explain its formation is provided (Scheme 2), involving protonation (*via* HCl in the chloroform) of 7-prenylindole by analogy to the observations of Van Vranken with tryptophan.¹⁵ Addition of 7-prenylindole to the imminium ion results in compound **4**, which would presumably be more susceptible to MnO₂ oxidation in the indolining that is activated with two nitrogens. Unfortunately, this compound's structure is not related to any of the of dimeric 7-prenylindole natural products. As this reaction is a dimerization, it should be suppressed by conducting it at lower concentration, but given that significant quantities were obtained even at 0.1 M, further dilution was deemed impractical. Conducting the reaction in dichloromethane eliminates dimer formation.

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Each compound in Scheme 1 has been reported, as were each of the conversions shown.¹⁶ Yet, none was described in sufficient detail to use this earlier work to prepare the target (in our hands). Overall, our synthesis proceeds in 62% yield. The fact that it gives the product in crystalline form when 7-prenylindole has such a low melting point attests to the purity of the material delivered by this synthetic route. It can be used to prepare gram batches of 7-prenylindole in one run requiring approx. 3 days of laboratory time to execute. As such, this synthesis should greatly increase access to 7-prenylindole.

EXPERIMENTAL

1-(2-methylbut-3-yn-2-yl)indoline (1)

To a 50 mL round-bottomed flask containing indoline (1.12 mL, 10.0 mmol), 2-chloro-2-methylbut-3-yne (1.37 mL, 12.0 mmol), and CuCl (99 mg, 1.0 mmol) in anhydrous THF (20 mL) under an argon atmosphere was added Et₃N (1.67 mL, 12.0 mmol) dropwise at 0°C. After the addition, the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a plug of silica gel and concentrated under reduced pressure. The crude material was purified by column chromatography (CH₂Cl₂:hexane 1:4) to give the title compound (1.68 g, 91%) as a pale yellow oil. *R*_f = 0.34 (ethyl acetate:hexane 1:10); IR (neat) 3286, 2985, 2844, 1605, 1483, 1254, 744 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30 (1H, d, *J* = 7.9 Hz), 7.18–7.13 (1H, m), 6.80 (1H, m), 3.45 (2H, t, *J* = 8.1 Hz), 2.98 (2H, t, *J* = 8.1 Hz), 2.46 (1H, s), 1.69 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 150.2, 131.8, 127.0, 124.6, 118.6, 111.9, 87.7, 71.1, 51.2, 49.7, 28.4, 27.4; HRMS Calcd. for C₁₃H₁₅NH⁺ (M + H)⁺ 186.1278, found 186.1278; Anal. Calcd. for C₁₃H₁₅N: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.21; H, 8.20; N, 7.32.

1-(2-methylbut-3-en-2-yl)indoline (2)

To a solution of alkyne **1** (3.18 g, 17.0 mmol) in MeOH (50 mL) was added Lindlar catalyst (308 mg). The reaction mixture was then degassed and stirred under an atmosphere of H₂ (balloon with needle) until starting material disappears, within 30 min, as indicated by TLC (longer exposure of the reactant to the reaction conditions leads to significant over-reduction, even complete conversion to the corresponding alkane). The reaction mixture was filtered through a short plug of silica gel and concentrated under reduced pressure. The crude material was purified by column chromatography (ethyl acetate:hexane 1:30) to yield the title compound (2.73 g, 86%) as a colorless oil. *R*_f = 0.51 (ethyl acetate:hexane 1:10); IR (neat) 2977, 2843, 1606, 1483, 1471, 1458, 1254, 1195, 913, 743 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.07 (1H, d, *J* = 7.1 Hz), 6.96 (1H, dt, *J* = 8.0, 0.6 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.64 (1H, m), 6.15 (1H, dd, *J* = 17.6, 10.7 Hz), 5.24 (1H, dd, *J* = 17.6, 0.9 Hz), 5.15 (1H, dd, *J* = 10.7, 1.0 Hz), 3.44 (2H, t, *J* = 8.3 Hz), 2.92 (2H, t, *J* = 8.3 Hz), 1.36 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 151.0, 147.3, 131.6, 126.8, 124.5, 117.5, 112.4, 111.4, 57.6, 49.3, 28.4, 24.4; HRMS Calcd. for C₁₃H₁₇NH⁺ (M + H)⁺ 188.1435, found 188.1434; Anal. Calcd. for C₁₃H₁₇N: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.36; H, 9.20; N, 7.44.

7-(3-methylbut-2-enyl)indoline (3)

To a solution of **2** (1.87 g, 10.0 mmol) in toluene (3 mL) was added TFA (0.1 mL, 1.3 mmol). The reaction mixture and a magnetic stir bar were sealed in the reaction vessel of a Discover[®] monomode microwave apparatus (CEM) and irradiated for 10 min at 150 °C. The reaction mixture was concentrated *in vacuo* and purified by chromatography on silica gel (ethyl acetate:hexane 1:8) to give the title compound (1.69 g, 90%) as a pale yellow oil. *R*_f = 0.20 (ethyl acetate:hexane 1:10); IR (neat) 3375, 2969, 2913, 2850, 1601, 1455, 1306, 1254, 1059, 748 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.02 (1H, dd, *J* = 7.2, 0.6 Hz), 6.88 (1H, d, *J* = 7.5 Hz), 6.70 (1H, t, *J* = 7.4 Hz), 5.27 (1H, m), 3.70 (NH, br s), 3.58 (2H, t, *J* = 8.4 Hz), 3.20 (2H, d, *J* = 7.1 Hz), 3.06 (2H, t, *J* = 8.4 Hz), 1.78–1.75 (6H, m); ¹³C NMR (75 MHz,

CDCl₃) δ 150.2, 133.4, 129.3, 127.3, 122.9, 122.6, 122.1, 119.1, 47.5, 30.8, 30.3, 26.0, 18.1; HRMS Calcd. for C₁₃H₁₇NH⁺(M + H)⁺ 188.1435, found 188.1436; Anal. Calcd. for C₁₃H₁₇N: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.34; H, 9.27; N, 7.42.

7-(3-methylbut-2-enyl)-1*H*-indole

A mixture of **3** (0.42 g, 2.2 mmol) and activated manganese(IV) oxide (0.57 g, 6.6 mmol) in dichloromethane (20 mL) was heated at reflux. After 1.5 h, additional activated manganese(IV) oxide (0.57 g, 6.6 mmol) was added to the reaction mixture. The mixture was kept refluxing for another 1.5 h, allowed to cool, and filtered through a short plug of silica gel. Concentration of the filtrate under reduced pressure was followed by column chromatography (ethyl acetate:hexane 1:30) to yield the title compound (0.36 g, 88%) as an off-white solid, mp 43–44 °C (lit., 1 mp 43–44 °C). *R*_f = 0.21 (ethyl acetate:hexane 1:10); ¹H NMR (300 MHz, CDCl₃) δ 8.15 (NH, br s), 7.54 (1H, d, *J* = 7.56 Hz), 7.21 (1H, t, *J* = 2.8 Hz), 7.11–7.02 (2H, m), 6.58 (1H, dd, *J* = 3.2, 2.1 Hz), 5.45 (1H, m), 3.61 (2H, d, *J* = 7.0 Hz), 1.85 (3H, s), 1.82 (3H, d, *J* = 1.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 135.4, 133.6, 128.1, 124.2, 124.1, 122.5, 121.8, 120.3, 119.0, 103.2, 31.1, 26.0, 18.2; HRMS Calcd. for C₁₃H₁₅NH⁺(M + H)⁺ 186.1278, found 186.1282. Anal. Calcd. for C₁₃H₁₅N: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.28; H, 8.28; N, 7.43.

7,7'-bis(3-methylbut-2-enyl)-2,3-dihydro-1'*H*-1,2'-biindole (5)

A mixture of **3** (0.56 g, 3.0 mmol) and activated manganese(IV) oxide (0.78 g, 9.0 mmol) in chloroform (30 mL) was heated at reflux. After 1.5 h, additional activated manganese(IV) oxide (0.78 g, 9.0 mmol) was added to the reaction mixture. The mixture was kept refluxing for another 1.5 h, allowed to cool, and filtered through a short plug of silica gel. Concentration of the filtrate under reduced pressure was followed by column chromatography (ethyl acetate:hexane 1:30) to yield the title compound (0.19 g, 35%) as a greenish-yellow oil. *R*_f = 0.19 (ethyl acetate:hexane 1:10). IR (neat) 3419, 2967, 2912, 2853, 1589, 1471, 1448, 1434, 1316, 1100, 1067, 848, 758, 723 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.07 (NH, br s), 7.20–7.16 (2H, m), 7.08 (1H, d, *J* = 7.1 Hz), 6.94 (1H, d, *J* = 7.6 Hz), 6.87–6.80 (2H, m), 6.43 (1H, m), 5.41 (1H, m), 5.14 (1H, m), 3.93 (2H, t, *J* = 8.4 Hz), 3.54 (2H, d, *J* = 6.9 Hz), 3.11 (2H, t, *J* = 8.4 Hz), 2.83 (2H, d, *J* = 7.1 Hz), 1.82 (3H, s), 1.78 (3H, s), 1.64 (3H, s), 1.38 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 148.5, 143.1, 133.6, 133.0, 132.6, 132.4, 128.5, 128.3, 126.8, 124.7, 124.5, 123.0, 122.6, 122.4, 120.6, 119.1, 113.0, 103.1, 59.5, 31.2, 30.7, 29.8, 26.02, 26.00, 18.3, 17.9; HRMS Calcd. for C₂₆H₃₀N₂H⁺(M + H)⁺ 371.2483, found 371.2499.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

1. Achenbach H, Renner C. Heterocycles 1985;23:2075–81. Achenbach H. Pure Appl Chem 1986;58:653–662.
2. Arai K, Sato S, Shimizu S, Nitta K, Yamamoto Y. Chem Pharm Bull 1981;29:1510–17.
3. Shimizu S, Yamamoto Y, Koshimura S. Chem Pharm Bull 1982;30:1896–9. [PubMed: 7116522]
4. a Benesova V, Samek Z, Herout V, Sorm F. Coll Czech Chem Commun 1969;34:1807–9. b Benesova V, Herout V, Sorm F. Coll Czech Chem Commun 1969;34:1810–14. c Delle Monache F, Delle Monache G, De Moraes e Souza MA, Cavalcanti MS, Chiappeta A. Gazz Chim Ital 1989;119:435–9.

- d Nagashima F, Sari Y, Tori M, Asakawa Y, Huneck S. *Phytochemistry* 1993;34:1341–3. e Agnani H, Menut C, Bessiere J-MJ. *Essential Oil-Bearing Plants* 2004;7:201–209. f Boti JB, Koukoua G, N'Guessan T, Yao Muselli A, Bernardini A-F, Casanova. *J Phytochem Anal* 2005;16:357–363.
5. a Pirrung MC, Li Z, Park K, Zhu J. *J Org Chem* 2002;67:7919–7926. [PubMed: 12423119] b Pirrung MC, Deng L, Li Z, Park K. *J Org Chem* 2002;67:8374–8388. [PubMed: 12444614] c Pirrung MC, Liu Y, Deng L, Halstead DK, Li Z, May JF, Wedel M, Austin DA, Webster NJG. *J Am Chem Soc* 2005;127:4609–4624. [PubMed: 15796526]
6. a Liu K, Wood HB, Jones AB. *Tetrahedron Lett* 1999;40:5119–5122. b Tatsuta K, Mukai H, Mitsumoto K. *J Antibiot* 2001;54:105–108. [PubMed: 11269708]
7. a Achenbach H, Franke D. *Arch Pharm* 1987;320:91–2. b Achenbach H, Franke D. *Arch Pharm* 1987;320:574–6.
8. Jing H, Shimada A, Maeda A, Arai Y, Goto M, Aoyagi Y, Ohta A. *Chem Pharm Bull* 1994;42:277–9.
9. a Somei M, Funamoto T, Ota T. *Heterocycles* 1987;26:1783–4. b Muratake H, Natsume M. *Heterocycles* 1989;29:771–82. c Kondo Y, Kojima S, Sakamoto T. *Heterocycles* 1996;43:2741–2746. d Hartung CG, Fecher A, Chapell B, Snieckus V. *Org Lett* 2003;5:1899–1902. [PubMed: 12762681]
10. Pirrung MC, Wedel M, Zhao Y. *Synlett* 2002:143–145.
11. a Hennion GF, Hanzel RS. *J Am Chem Soc* 1960;82:4908–12. b Easton NR, Dillard RD, Doran WJ, Livezey M, Morrison DE. *J Org Chem* 1961;26:3772–6. c Barmettler P, Hansen H. *J Helv Chim Acta* 1990;73:1515–73. d Wipf P, Venkatraman S. *J Org Chem* 1996;61:6517–6522. [PubMed: 11667514]
12. a Roe JM, Webster RAB, Ganesan A. *Org Lett* 2003;5:2825–2827. [PubMed: 12889884] b Izumi T, Kasahara A. *J Heterocyclic Chem* 1990;27:1173–5.
13. Cooper MA, Lucas MA, Taylor JM, Ward AD, Williamson NM. *Synthesis* 2001:621–625.
14. Walsh DA, Moran HW, Shamblee DA, Uwaydah IM, Welstead WJ, Sancilio LF, Dannenburg WN. *J Med Chem* 1984;27:1379–1388. [PubMed: 6436487]
15. Stachel SJ, Habeeb RL, Van Vranken DL. *J Am Chem Soc* 1996;118:1225–1226.
16. a Sugiyama H, Yokokawa F, Aoyama T, Shioiri T. *Tetrahedron Lett* 2001;42:7277–7280. b Hansen DB, Lewis AS, Gavalas SJ, Joullie MM. *Tetrahedron: Asymmetry* 2006;17:15–21. c Yokokawa F, Sugiyama H, Aoyama T, Shioiri T. *Synthesis* 2004:1476–1480.

Scheme 1.
The preparation of 7-prenylindole

Scheme 2.
The formation of a 7-prenylindole/7-prenylindoline dimer

Chart 1.
7-Prenylindole-containing natural products