Prenylation of Aromatic Amines and Nitrogen-containing Aromatic Heterocycles by Prenyl Diisopropyl Phosphate

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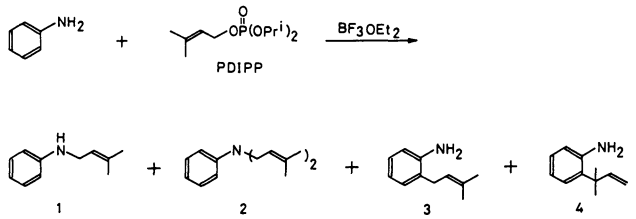
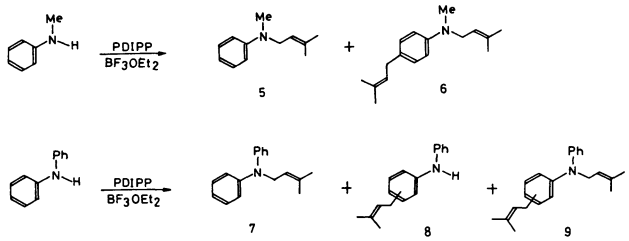
Synopsis. Lewis-acid catalyzed prenylation of aromatic amines with prenyl diisopropyl phosphate gave *N*-prenylated amines, whereas nitrogen-containing aromatic heretocycles gave nucleus prenylated products.

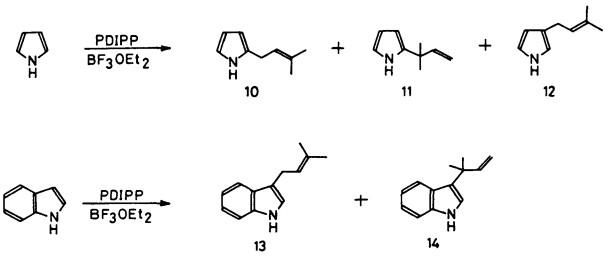
N-Alkylation of amines by trialkyl phosphates is well documented. For example, Billman *et al.* reported that trimethyl and triethyl phosphates readily alkylate various anilines to *N,N*-dialkylanilines in good yields.[1] Recently, Kinoshita and his coworkers described the methylation and ethylation of nucleic acid-bases by means of trimethyl and triethyl phosphates.[2] Moreover, they succeeded the allylation of nucleic acid-bases by triallyl phosphate.[3] *N*-Prenylation of amines by prenyl phosphates is a biogenetically important process, because naturally occurring amines such as cytkinin[4] and acrophylline,[5] which bear a prenyl group on the nitrogen atom, are proposed to be biosynthesized *via* *N*-prenylation with prenyl pyrophosphate. However, there have been no studies describing the prenylation of amines by the use of prenyl phosphate. Here we wish to report the reaction of prenyl diisopropyl phosphate (PDIPP) with aromatic amines and nitrogen-containing aromatic heterocycles in an attempt to have insight into the nature of the prenylation of amines by prenyl phosphate.

When a mixture of aniline and PDIPP was treated with boron trifluoride etherate in dimethyl sulfoxide (DMSO) at room temperature, the reaction proceeded and *N*-prenylaniline (**1**) and *N,N*-diprenylaniline (**2**) were obtained in 12 and 10% yields, respectively, after column chromatography on silica gel. As minor products, trace amounts of 2-prenylaniline (**3**) and 2-(1,1-dimethyl-2-propenyl)aniline (**4**) were also isolated from the reaction mixture. The formation of **3** and **4** may be rationalized in terms of the Lewis acid-catalyzed amino-Claisen rearrangement[6] of the initially formed *N*-prenylaniline (**1**). In the absence of the Lewis acid, the reaction did not occur. The use of polar aprotic solvents such as DMSO and *N,N*-dimethylformamide (DMF) was essential for the present reaction. In other solvent such as ether, dichloromethane, and benzene, no characterized products were obtained. Under the similar conditions, *N*-methylaniline gave 56% yield of *N*-methyl-*N*-prenylaniline (**5**) accompanied by a small amount (1.2% yield) of *N*-methyl-*N*,4-diprenylaniline (**6**). For the latter, the position of the prenyl group on the benzene ring was determined by the ^{13}C NMR spectral analysis. The prenylation of diphenylamine gave *N,N*-diphenylprenylamine (**7**) (24% yield) as the main product. Nucleus-prenylated products, 4-(or 2-)prenyldiphenylamine (**8**) (7%) and *N*-phenyl-*N*,4-(or 2)diprenylaniline (**9**) (3%) were also formed, but the prenylated position remained uncertain. Aliphatic amines such as diisopropylamine and pyrrolidine could not be prenylated by the present method.





Nitrogen-containing aromatic heterocycles, pyrrole and indole, are also susceptible to prenylation by PDIPP. Pyrrole gave a mixture of 2-prenylpyrrole (**10**) (34% yield), 2-(1,1-dimethyl-2-propenyl)pyrrole (**11**) (10%), and 3-prenylpyrrole (**12**) (6%), and indole gave 3-prenylindole (**13**) (21% yield) and 3-(1,1-dimethyl-2-propenyl)indole (**14**) (5%). Unlike the cases of aromatic amines described above, *N*-prenylated products could not be found in the reaction mixtures. This result contrasts to the fact that the methylation of indole with trimethyl phosphate gives only 1-methylindole.[7]



Experimental

General. Infrared spectra were recorded on a JASCO IRA-1 spectrometer. ^1H NMR spectra were determined with a Hitachi R-24A spectrometer (60 MHz). Chemical shifts (δ) are recorded in ppm downfield from Me_4Si. Mass spectra were measured on a Hitachi M-52 mass spectrometer, operating with an ionization energy of 20 eV. GLPC analyses and preparative GLPC were performed on a Yanaco G1800 gas chromatograph. Elemental analyses were performed at the Elemental Analysis Center of Kyoto University.

Reaction of Aniline with Prenyl Diisopropyl Phosphate. To a solution of aniline (470 mg, 5 mmol) and prenyl diisopropyl phosphate (1.27 g, 5.1 mmol) in DMSO (10 ml) was added boron trifluoride etherate (1.99 g, 14 mmol) at

room temperature and the mixture was stirred for 16 h. Saturated aqueous sodium hydrogencarbonate was added and the products were extracted with light petroleum. The extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was column chromatographed on silica gel with benzene as an eluent to give *N*-prenylaniline (**1**)[6] (92 mg, 12% yield), *N,N*-diprenylaniline (**2**)[6] (118 mg, 10%), and trace amounts of 2-prenylaniline (**3**)[6] (5 mg) and 2-(1,1-dimethyl-2-propenyl)aniline (**4**) (1 mg).

4: ^{1}H NMR (CCl_4) δ=6.40—7.00 (m, 5H, ring), 5.00—5.90 (m, 3H, olefin), 3.20 (br s, 2H, NH_2), 1.35 (s, 6H, CH_3).

Reaction of N-Methylaniline with Prenyl Diisopropyl Phosphate. To a solution of *N*-methylaniline (550 mg, 5.1 mmol) and prenyl diisopropyl phosphate (2.02 g, 8.1 mmol) in DMF (10 ml) was added boron trifluoride etherate (1.26 ml, 10 mmol) under nitrogen at room temperature and the mixture was stirred for 15 h. The reaction mixture was treated as above. Silica-gel column chromatography (benzene as an eluent) gave *N*-methyl-*N*-prenylaniline (**5**) (499 mg, 56%) and *N*-methyl-*N*,4-diprenylaniline (**6**) (15 mg, 1.2%).

5:[8] IR (neat) 2970, 2910, 1670, 1600, 1510, 1450, 1310, 1250, and 695 cm^{-1}; ^{1}H NMR (CCl_4) δ=6.40—7.30 (m, 5H, ring), 5.15 (t, J=6 Hz, 1H, olefin), 3.80 (d, J=6 Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 1.69 (s, 6H, CH_3).

6: IR (neat) 2960, 2920, 1670, 1590, 1510, 1440, 1245, and 693 cm^{-1}; ^{1}H NMR (CCl_4) δ=6.40—7.30 (m, 4H, ring), 5.10 (br t, 2H, olefin), 3.80 (d, J=6 Hz, 2H, CH_2), 3.35 (d, J=6 Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 1.65 (br s, 12H, CH_3); ^{13}C NMR ($CDCl_3$) 151.2 (s), 136.8 (s), 132.5 (s), 121.3 (s), 129.8 (d), 126.3 (d), 123.5 (d), 120.3 (d), 55.2 (t, N-CH_2), 41.5 (t, Ph$\underline{C}H_2$), 29.2 (q, N-CH_3), 25.9 (q), 25.8 (q), 18.0 (q), 17.9 (q); MS *m/z* (rel intensity) 243 (M^+; 13) and 174 (100); Found: C, 84.17; H, 10.60%. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35%.

Reaction of Diphenylamine with Prenyl Diisopropyl Phosphate. To a solution of diphenylamine (852 mg, 5.0 mmol) and prenyl diisopropyl phosphate (2.00 g, 8.0 mmol) in DMF (10 ml) was added boron trifluoride etherate (1.26 ml, 10 mmol) under nitrogen at room temperature and the mixture was stirred for 15 h. Work-up and column chromatography on silica gel with benzene–light petroleum (1:3) gave *N,N*-diphenylprenylamine (**7**)[9] (280 mg, 24%), 4(or 2-)prenyldiphenylamine (**8**) (85 mg, 7%), and *N*-phenyl-*N*,4(or 2)-diprenylaniline (**9**) (40 mg, 3%).

8: IR(neat) 3400, 2980, 2930, 1595, 1500, 1450, 1310, 750, and 695 cm^{-1}; ^{1}H NMR (CCl_4) δ=6.40—7.50 (m, 9H, ring), 5.15 (t, J=6 Hz, 1H, olefin), 5.05 (br s, 1H, NH), 3.24 (d, J=6 Hz, 2H, CH_2), 1.73 (s, 6H, CH_3); MS *m/z* (rel intensity) 237 (M^+; 100); Found: C, 86.09; H, 8.15%. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07%.

9: IR (neat) 2980, 2930, 1595, 1500, 1450, 1355, 1260, 750, and 695 cm^{-1}; ^{1}H NMR (CCl_4) δ=6.20—7.20 (m, 9H, ring), 5.20 (m, 2H, olefin), 4.03 (d, J=6 Hz, 2H, N-CH_2), 3.10 (d, J=6 Hz, 2H, CH_2), 1.62 (s, 6H, CH_3), 1.50 (s, 6H, CH_3); MS *m/z* (rel intensity) 305 (M^+; 35) and 236 (100); Found; C, 86.53; H, 9.21%. Calcd for $C_{22}H_{27}N$: C, 86.51; H, 8.91%.

Reaction of Pyrrole with Prenyl Diisopropyl Phosphate. To a solution of pyrrole (680 mg, 10.1 mmol) and prenyl diisopropyl phosphate (4.01 g, 16 mmol) in DMF (20 ml) was added boron trifluoride etherate (2.52 ml, 20 mmol) under nitrogen at room temperature and the mixture was stirred for 15 h. Work-up and column chromatography on silica gel (benzene–light petroleum=1:1) gave a mixture (679 mg, 50% yield) of 2-prenylpyrrole (**10**), 2-(1,1-dimethyl-2-propenyl)pyrrole (**11**), and 3-prenylpyrrole (**12**). GLPC analysis (Apiezon Grease L on Uniport B (15%), 1 m×3 mm, temp 130 °C, He 90 ml/min) revealed that the ratio of **10**:**11**:**12** was 68:20:12. They were separated by preparative GLPC.

10: IR (neat) 3400, 2970, 1678, 1568, 1440, 1378, 1022, 768, and 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.60 (m, 1H, pyrrole H^5), 5.75—6.20 (m, 2H, pyrrole H^3 and H^4), 5.30 (t, J=7 Hz, 1H, olefin), 3.30 (d, J=7 Hz, 2H, CH_2), 1.70 (s, 6H, CH_3); MS *m/z* (rel intensity) 135 (M^+; 100). Found: C, 80.16; H, 9.79%. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69%.

11: IR (neat) 3400, 2980, 1700, 1455, 1378, 1020, and 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.65 (m, 1H, pyrrole H^5), 5.75—6.25 (m, 3H, olefin and pyrrole H^3 and H^4), 4.85—5.20 (m, 2H, olefin), 1.35 (s, 6H, CH_3); MS *m/z* (rel intensity) 135 (M^+; 100); Found: C, 80.24; H, 9.89%. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69%.

12: IR (neat) 3400, 2910, 1680, 1550, 1436, 1372, 1052, 760 and 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.45—6.80 (m, 2H, pyrrole H^2 and H^5), 6.10 (m, 1H, pyrrole H^4), 5.35 (t, J=7 Hz, 1H, olefin), 3.20 (d, J=7 Hz, 2H, CH_2), 1.69 (s, 6H, CH_3); MS *m/z* (rel intensity) 135 (M^+; 100); Found: C, 79.97; H, 9.98%. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69%.

Reaction of Indole with Prenyl Diisopropyl Phosphate. To a solution of indole (586 mg, 5.0 mmol) and prenyl diisopropyl phosphate (2.00 g, 8.0 mmol) in DMF (10 ml) was added boron trifluoride etherate (1.26 ml, 10 mmol) under nitrogen at room temperature. The reaction mixture was stirred for 13 h and treated as above. Column chromatography on silica gel (benzene–light petroleum=1:1) gave a mixture (242 mg, 26% yield) of 3-prenylindole (**13**) and 3-(1,1-dimethyl-2-propenyl)indole (**14**) as a yellow oil. GLPC (Apiezon Grease L on Uniport B (15%), 1 m×3 mm, temp 200 °C, He 90 ml/min) of the oil showed two peaks of **13** and **14** in the ratio of 82:18. They were separated by preparative GLPC.

13:[10] IR (neat) 3420, 2960, 1640, 1450, 1360, and 740 cm^{-1}; ^{1}H NMR (CCl_4) δ=6.90—7.70 (m, 5H, benzene ring and NH), 6.70 (br s, 1H, H^2), 5.40 (t, J=7 Hz, 1H, olefin), 3.40 (d, J=7 Hz, 2H, CH_2), 1.73 (s, 6H, CH_3); MS *m/z* (rel intensity) 185 (M^+; 100).

14: IR (neat) 3420, 2960, 1640, 1450, 1360, and 740 cm^{-1}, ^{1}H NMR (CCl_4) δ=6.70—8.00 (m, 6H, benzene ring and NH), 4.75—6.50 (m, 3H, olefin), 1.49 (s, 6H, CH_3); MS *m/z* (rel intensity) 185 (M^+; 51) and 170 (100).

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