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Synthesis of Nitrogen Heterocycles from Vinyl Glycine Derivatives via Palladium Catalysis

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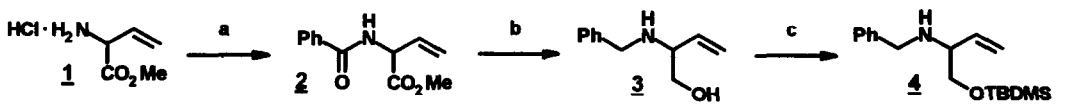
Abstract: Useful transformations of vinyl glycine derivatives to nitrogen heterocycles bearing pyrrolidine or isoquinoline moieties are described, using palladium catalysed reactions as key steps.

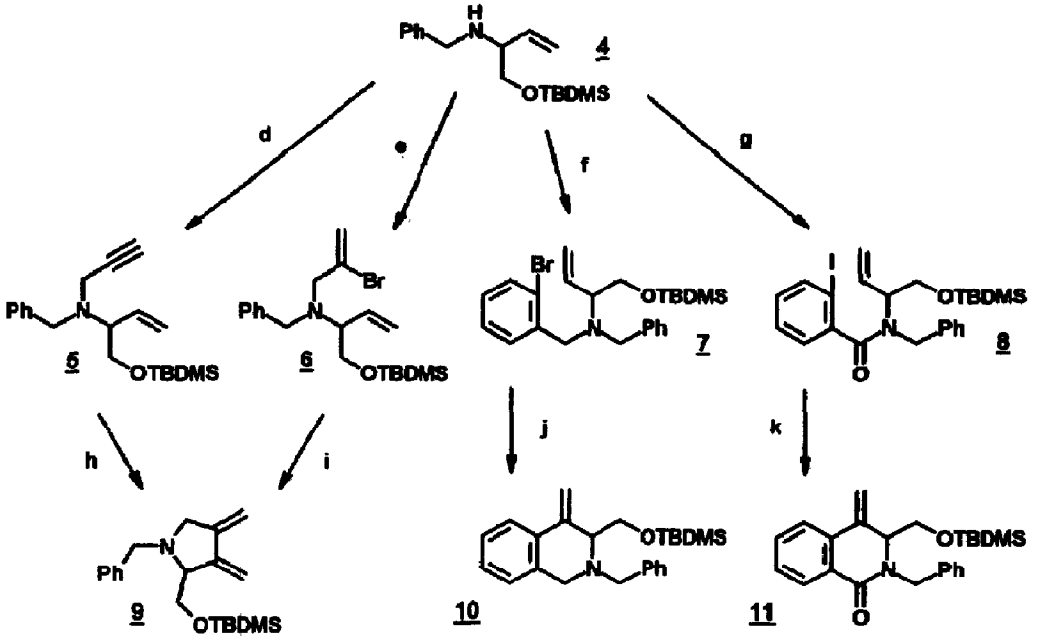
Introduction. The isoquinoline and pyrrolidine skeleton can be found in a large number of natural products, e.g. in the isoquinoline alkaloid corydalic acid.[1] In the context of our efforts to use vinyl glycine derivatives as chiral building blocks in the synthesis of heterocycles,[2] we prepared the protected vinyl glycinol **4**[3] from vinyl glycine methyl ester **1**. *N*-derivatization of **4** gave the intermediates **5-8** in good yields. Cyclisation of **5-8** with palladium catalyst systems yielded the pyrrolidine and isoquinoline heterocycles **9-11** (moderate to good yields), which bear one or two double bonds. These double bonds should be useful for further stereocontrolled functionalization using the neighbouring oxygenated sidechain.[4]

Synthesis.[7] Vinyl glycine methyl ester hydrochloride **1** was treated with benzoyl chloride in a two phase system consisting of saturated aqueous sodium bicarbonate and methylene chloride yielding *N*-benzoyl vinyl glycine methyl ester **2**. Reduction of **2** with $LiAlH_4$ in diethyl ether gave *N*-benzyl vinyl glycinol **3**, which was then converted to the TBDMS-ether **4** by reaction with tert.-butyldimethylsilyl chloride and imidazole in DMF.



Reagents and conditions: (a) PhCOCl, $NaHCO_3$, H_2O, CH_2Cl_2, RT, 30min. (50%) (b) $LiAlH_4$, Et_2O, reflux, 14h (93%) (c) TBDMSCl, imidazole, DMF, 0°C, 30min., then RT, 3h (99%).

Deprotonation of **4** with sodium hydride in THF and treatment with the appropriate electrophile gave the intermediates **5-8**, which were cyclisized using palladium catalyst systems. The compounds **10**[13] and **11**[14] were produced using *Heck*[8,10] reactions, compound **9**[15] could be synthesized either via *Heck*[8,11] or *Trost*[9,12] cyclisation.



Reagents and conditions: (d,e,f,g) 1. NaH, THF, RT, 30min. (d) 2. propargyl bromide, RT, then reflux, 20h (77%) (e) 2. 2,3-dibromopropene, RT, then reflux, 17h (72%) (f) 2. 2-bromo-benzyl bromide, RT, then reflux, 9h (72%) (g) 2. 2-iodo-benzoyl chloride, RT, then reflux, 1h (90%) (h) 5mol% $Pd(OAc)_2$, 10mol% PPh_3, PhH, 65°C, 4.5h (50%) (i) 10mol% $Pd(OAc)_2$, 20mol% PPh_3, K_2CO_3, CH_3CN, reflux, 5.5h (68%) (j,k) 10mol% $Pd(OAc)_2$, 20mol% PPh_3, K_2CO_3, NEt_4Cl, CH_3CN, reflux, 30h (42%, 87%).

Since vinyl glycine derivatives can be produced in both enantiomeric forms (by enzymatic resolution of racemic derivatives[5] or by enantioselective synthesis[6]) and no racemization is expected for the steps performed, a potentially enantiopure approach to the heterocycles **9-11** was developed. The application of the stated strategy for the synthesis of nitrogen heterocycles from vinyl glycine derivatives to enantioselective syntheses of natural products is under current investigation in our laboratories.

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7. All synthesized compounds gave satisfactory spectroscopic data (^{1}H-NMR, MS, IR). Stated yields are unoptimized.
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10. Typical experimental procedure: A mixture of 253mg (0.5mmol) *N*-benzyl-2-iodo-*N*-[1-(tert.-butyldimethylsilyloxymethyl)-allyl]-benzamide **8**, 27mg (0.1mmol) triphenylphosphine, 138mg (1mmol) potassium carbonate, 83mg (0.5mmol) tetraethylammonium chloride, 12mg (0.05mmol) palladium acetate and 70ml of dry acetonitrile was stirred for 30h at 90°C bath temperature under argon. The mixture was filtered, the solvent removed, and the residue purified by chromatography on silica (methyl tert.-butyl ether/hexanes 1:4) yielding 171mg (87%) of 2-benzyl-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylene-3,4-dihydro-2H-isoquinolin-1-one **11**[14] as a yellowish oil.
11. The same procedure[10] as for **10** and **11** was used, except no tetraethylammonium chloride was added.
12. Experimental procedure: A mixture of 800mg (2.43mmol) benzyl-[1-(tert.-butyldimethylsilyloxy-methyl)-allyl]-(2-propinyl)-amine **5**, 63mg (0.24mmol) triphenylphosphine, 27mg (0.12mmol) palladium acetate and 8.9ml of dry benzene was stirred for 4.5h at 65°C bath temperature under argon. The solvent was removed and the residue purified by chromatography on silica (methyl tert.-butyl ether/hexanes 1:200) yielding 403mg (50%) of 1-benzyl-2-(tert.-butyldimethylsilyloxymethyl)-3,4-dimethylene-pyrrolidine **9**[15] as a yellow oil.

13. Spectroscopic data of 2-benzyl-3-(tert.-butyldimethylsilyloxymethyl)-4-methylene-1,2,3,4-tetrahydro-4H-isoquinoline **10**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = -0.05 (s, 3H, $SiCH_3$), -0.02 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 3.58 (brt, 1H, J=6.5 Hz, NCH), 3.66 (dd, 1H, J=6/10.5 Hz, OCH_2), 3.69 (d, 1H, J=17 Hz, NCH_2Ph), 3.80 (d, 1H, J=14 Hz, NCH_2), 3.85 (d, 1H, J=14 Hz, NCH_2), 3.91 (dd, 1H, J=6/10.5 Hz, OCH_2), 4.12 (d, 1H, J=17 Hz, NCH_2Ph), 5.02 (brs, 1H, $C=CH_2$), 5.70 (brs, 1H, $C=CH_2$), 6.99 (m, 1H, ArH), 7.17-7.38 (m, 7H, ArH), 7.66 (m, 1H, ArH). MS (EI): m/z = 380 (2%, M+1), 379 (7%, M^+), 364 (2%, M-CH_3), 322 (3%), 279 (10%), 246 (4%), 234 (100%), 167 (12%), 149 (27%), 91 (20%), 59 (2%), 57 (11%), 55 (6%). HR-MS ($C_{24}H_{33}NOSi$): calcd 379.2331, found 379.2331. IR (CCl_4): 1/υ [cm^{-1}] = 837 (m), 840 (m), 1072 (m), 1121 (s), 1258 (s), 1271 (s), 1288 (s), 1463 (w), 1730 (vs), 2859 (s), 2875 (m), 2930 (s), 2960 (s), 3030 (w), 3066 (w).
14. Spectroscopic data of 2-benzyl-3-(tert.-butyl-dimethylsilyloxymethyl)-4-methylene-3,4-dihydro-2H-isoquinolin-1-one **11**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = -0.13 (s, 3H, $SiCH_3$), -0.11 (s, 3H, $SiCH_3$), 0.77 (s, 9H, $SiC(CH_3)_3$), 3.58 (dd, 1H, J=6/10 Hz, OCH_2), 3.66 (dd, 1H, J=5.5/10 Hz, OCH_2), 4.11 (dd, 1H, J=5.5/6 Hz, NCH), 4.28 (d, 1H, J=15.5 Hz, NCH_2), 5.12 (brs, 1H, $C=CH_2$), 5.58 (d, 1H, J=15.5 Hz, NCH_2), 5.61 (brs, 1H, $C=CH_2$), 7.11-7.33 (m, 5H, ArH), 7.40-7.55 (m, 3H, ArH), 8.17 (dd, 1H, J=1/7.5 Hz, ArH). MS (EI): m/z = 394 (5%, M+1), 393 (10%, M^+), 378 (2%), 336 (39%), 302 (4%), 262 (14%), 248 (96%), 215 (2%), 105 (6%), 91 (100%), 73 (28%), 65 (6%), 57 (19%). HR-MS ($C_{24}H_{31}NO_2Si$): calcd 393.2124, found 393.2124. IR (CCl_4): 1/υ [cm^{-1}] = 837 (s), 1112 (m), 1258 (m), 1271 (w), 1443 (w), 1455 (w), 1464 (w), 1471 (m), 1604 (w), 1655 (vs), 2858 (m), 2886 (w), 2897 (w), 2930 (m), 2956 (m), 3031 (w), 3067 (w).
15. Spectroscopic data of 1-benzyl-2-(tert.-butyldimethylsilyloxymethyl)-3,4-dimethylene-pyrrolidine **9**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.06 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 3.04 (dt, 1H, J=3/13.5 Hz, $NCH_2C=C$), 3.40 (m, 1H, NCH), 3.47 (d, 1H, J=13 Hz, NCH_2Ph), 3.52 (brd, 1H, J=13.5 Hz, $NCH_2C=C$), 3.77 (dd, 1H, J=5.5/10.5 Hz, OCH_2), 3.81 (dd, 1H, J=5.5/10.5 Hz, OCH_2), 4.26 (d, 1H, J=13 Hz, NCH_2Ph), 4.82 (brt, 1H, J=2 Hz, $C=CH_2$), 5.09 (brd, 1H, J=2.5 Hz, $C=CH_2$), 5.34 (brt, 1H, J=2 Hz, $C=CH_2$), 5.46 (brd, 1H, J=2.5 Hz, $C=CH_2$), 7.24 (tt, 1H, J=1.5/7.5 Hz, ArH), 7.31 (brt, 2H, J=7.5 Hz, ArH), 7.36 (brd, 2H, J=7.5 Hz, ArH) MS (EI): m/z = 329 (9%, M^+), 314 (3%, M-CH_3), 272 (4%), 198 (4%), 184 (100%), 91 (23%), 73 (3%), 65 (2%), 57 (2%). HR-MS ($C_{20}H_{31}NOSi$): calcd 329.2175, found 329.2175. IR (CCl_4): 1/υ [cm^{-1}] = 838 (vs), 889 (m), 1072 (m), 1104 (s), 1257 (s), 1362 (w), 1462 (w), 1472 (m), 1496 (w), 2793 (w), 2858 (s), 2928 (s), 2959 (s).

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