Synthesis of 3-Arylpyrroles and 3-Pyrrolylacetylenes by Palladium-Catalyzed Coupling Reactions†

Alejandro Alvarez,‡ Angel Guzmán, Alicia Ruiz,§ and Esperanza Velarde

Syntex, S.A., División de Investigación, Apartado Postal 10-820, México 10, D.F.

Joseph M. Muchowski*

Syntex Research, Institute of Organic Chemistry, 3401 Hillview Avenue, Palo Alto, California 94304

Received November 6, 1991

Efficacious methods for the synthesis of 3-arylpyrroles or 3-pyrrolylacetylenes are described based on the palladium-catalyzed coupling of appropriate 1-(triisopropylsilyl)-3-substituted pyrroles with aryl halides or monosubstituted acetylenes and subsequent tetrabutylammonium fluoride desilylation.

Whereas there are many methods by which polysubstituted 3-arylpyrroles can be prepared,[1] there are relatively few syntheses of simple 3-arylpyrroles.[2-6] Of these, the condensation of tosylmethylisocyanide with activated alkenes,[2] the reductive cyclization of 2-arylsuccinonitriles,[5] and the base-induced ring closure of arylvinamidinium salts[6] have the greatest degree of generality.

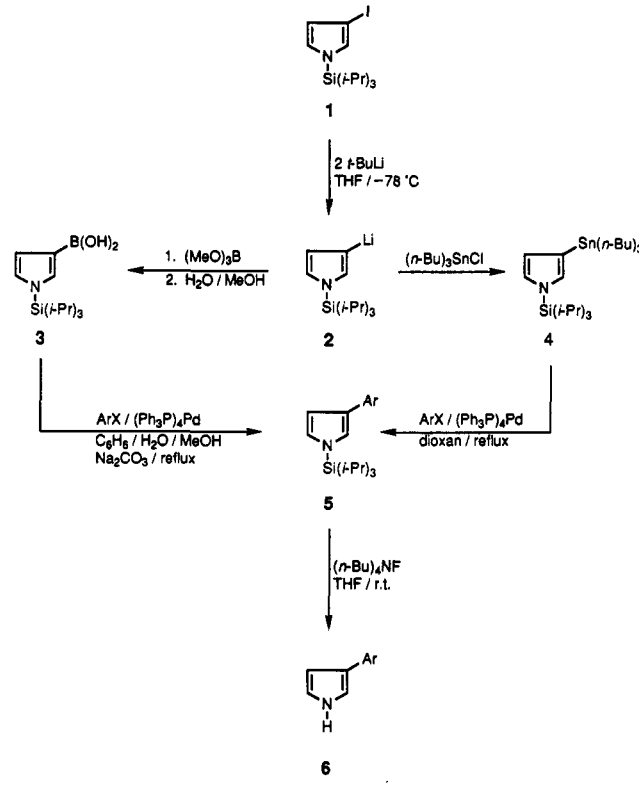
Pyrrolylacetylenes are a relatively rare class of compounds[7-14] of which the 3-pyrrolyl congeners[7,8,10-12] have been studied most frequently. Several syntheses thereof which have considerable breadth have been devised. These include the reaction of primary amines with 2,2-diacetylenic oxiranes,[7] the dehydrohalogenation of the readily available chlorovinylpyrroles,[10] and the palladium-catalyzed coupling of iodopyrroles with monosubstituted acetylenes.[11] Only the first process,[7] however, has been utilized to prepare simple 3-pyrrolylacetylenes.

This manuscript describes efficient and facile means of synthesizing 3-arylpyrroles, 3-pyrrolylacetylenes and 3,4-diacetylenic pyrroles based on the palladium(0)-catalyzed coupling of appropriate 1-(triisopropylsilyl)-3-substituted pyrroles with aryl halides and monosubstituted acetylenes.

3-Arylpyrroles. Initially, the palladium-catalyzed cross-coupling of 1-(triisopropylsilyl)-3-iodopyrrole (1), which was synthesized as described in the literature[15] or by the iodination of 1-(triisopropylsilyl)pyrrole with *N*-iodosuccinimide (see Experimental Section), with various phenyl boronic acid derivatives[16] was examined. Although 3-arylpyrroles were produced in modest yields (20–35%), the process when effected in this manner was associated with the inconvenience of preparing many different aryl boronic acids. Consequently, the synthesis of 1-(triisopropylsilyl)pyrrole-3-boronic acid (3, Scheme I) was considered to be essential. This was accomplished in high yield by reaction of the lithio species 2 with trimethyl borate and subsequent hydrolysis. Tetrakis(triphenylphosphine)palladium(0)-catalyzed coupling of the crude boronic acid 3 with various aryl halides, under typical Suzuki[16] conditions (method A), gave the expected 3-arylpyrroles 5 in good to excellent yields (Table I). The homo coupling of the iodopyrrole 1 and 3 failed to occur under these conditions.

It was also of interest to study the tin-based palladium-catalyzed coupling process as a route to 3-arylpyrroles.

Scheme I



Therefore, 1-(triisopropylsilyl)-3-(tributylstannyl)pyrrole (4) was prepared (90% yield) by reaction of the 3-lithio-

† Contribution no. 842 from the Syntex Institute of Organic Chemistry.

‡ A portion of this research was completed by A.A. in partial fulfillment for the degree of Maistria en Ciencias at the Departamento de Química, División de Estudios Superiores, Universidad Nacional Autónoma de México, D.F.

§ A part of this research was completed by A.R. in partial fulfillment for the degree of Licenciatura en Química at the Escuela de Química, Escuela Nacional de Estudios Profesionales, Zaragosa, Mexico, D.F.

(1) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977; pp 57, 62–73, 76, 81–85, 91–95, 98–100.

(2) Bean, G. P. In *Pyrroles. Part 1. The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring*; Jones, R. A., Ed.; John Wiley and Sons: New York, 1990; pp 182–183.

(3) Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1978**, *43*, 335.

(4) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.

(5) Babler, J. H.; Spina, K. P. *Tetrahedron Lett.* **1984**, *25*, 1659.

(6) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W.; Sikorski, J. A. *J. Org. Chem.* **1990**, *55*, 4735. Gallagher, P. T.; Palmer, J. L.; Morgan, S. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3212.

(7) Perveev, F. Ya.; Shil'nikova, L. N.; Merinova, G. V. *Zh. Org. Khim.* **1968**, *4*, 47; *Chem. Abstr.* **1968**, *68*, 106054 q. Shil'nikova, L. N.; Perveev, F. Ya. *Zh. Org. Khim.* **1978**, *14*, 251; *Chem. Abstr.* **1978**, *88*, 190516 k.

(8) Howarth, T. T.; Jackson, A. H.; Judge, J.; Kenner, G. W.; Newman, D. J. *J. Chem. Soc., Perkin Trans 1* **1974**, 490.

(9) Brain, E. G.; Eglington, A. J.; James, B. G.; Naylor, J. H. C.; Osborne, N. F.; Pearson, M. J.; Smale, T. C.; Southgate, R.; Tolliday; P.; Basker, M. J.; Mizen, L. W.; Sutherland, R. *J. Med. Chem.* **1977**, *20*, 1086.

(10) Mironov, A. F.; Kozhich, D. T.; Vasilevsky, V. I.; Evstigneeva, R. P. *Synthesis* **1979**, 533. Niszhnik, A. N.; Mironov, A. F. *Zh. Org. Khim.* **1979**, *15*, 1739; *Chem. Abstr.* **1980**, *92*, 41683t. Kozhich, D. T.; Vasilevskii, V. I.; Mironov, A. F.; Evstigneeva, R. P. *Zh. Org. Khim.* **1980**, *16*, 849; *Chem. Abstr.* **1980**, *93*, 46309f. Nizhnik, A. N.; Mironov, A. F. *Zh. Obshch. Khim.* **1984**, *54*, 2316; *Chem. Abstr.* **1985**, *102*, 95487a.

0022-3263/92/1957-1653$03.00/0

Table I. Synthesis of 1-(Triisopropylsilyl)-3-arylpyrroles (5)

aryl halide	reaction time (h)		mol % catalyst		% yield 5[a]	
	method A	method B	method A	method B	method A	method B
PhI	16		5		96[b]	
4-MePhBr	12	40	5	16	80	69
4-MeOPhBr	12		5		60	
4-MeCONHPhI	36		7		85[c]	
4-ClPhBr	10	40	5	17	77	89
4-NO_2PhBr	16	24	10	10	59[d]	77
4-MeO_2CPhI	14		5		81	
4-HCOPhBr	14	38	5	16	90	85
4-NCPhBr	16	38	5	15	65	81
2-MePhBr	48		10		59	
3-MeOPhBr	16		5		90	
3-BrPy[e]	16		5		88	

[a] The compounds were oils unless indicated otherwise. [b] *m/e* 299.2070 (calcd for $C_{19}H_{29}NSi$ 299.2069). [c] Mp 127 °C (hexane–acetone). [d] Mp 68–70 °C (hexane). [e] 3-Bromopyridine.

Table II. Synthesis of 3-Pyrrolylacetylenes

starting materials		coupling		% yield	
pyrrole	7 (R)	method	product(s)	product(s)[a]	starting material
1	*n*-Pr	A	8	65	
1	*n*-Pr	B	8	60	10
1	*n*-Pr	C	8	70	
1	*n*-C_5H_{11}	B	8	28	20
1	Me_3Si	B	8	76	5
1	Ph	A	8	77	
1	Ph	B	8	77	4
1	Ph	C	8	73	
10	*n*-Pr	D	11	30	
			12	10	
10	Me_3Si	D	11	40	
			12	11	
10	Ph	D	11	52	

[a] All products were oils except 8 (R = Ph) which had mp 79–81 °C (hexane).

pyrrole derivative **2** with tributyltin chloride. The palladium-catalyzed coupling of **4** with various aryl halides in boiling dioxane[17] (method B) gave the corresponding 3-arylpyrrole derivatives **5** in yields quite comparable to those observed with the boronic acid **3** (Table I) but the homo coupling of the iodopyrrole **1** with **3** once again failed to take place.

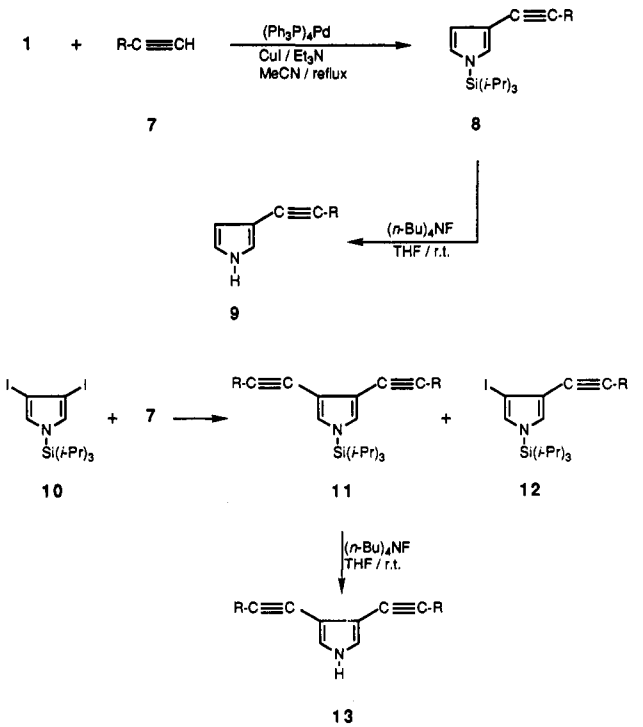
The removal of the silyl moiety from **5** was accomplished with 1 equiv of tetrabutylammonium fluoride in THF at room temperature.[18] The corresponding 3-arylpyrroles **6** were isolated in over 90% yield (Table III). Given the accessibility of the iodo compound **1**, the processes described herein are the most convenient routes to 3-arylpyrroles described to date.

Table III. Synthesis of 3-Arylpyrroles 6, 3-Pyrrolylacetylenes 9, and 3,4-Diacetylenic Pyrroles 13

compd	Ar or R	% yield	crystallization solvent	mp (°C) obsd	mp (°C) reptd
6	Ph	92	hexane	40–41	42–44[a]
6	4-MePH	90	hexane	92–93	93–95
6	4-MeOPh	91	MeOH–H_2O	100	99–100
6	4-ClPh	93	hexane	116	116–118
6	3-Py[b]	96	benzene	133	133
9	H	62		oil[c]	
9	*n*-C_5H_{11}	74		oil[d]	
9	Ph	85	hexane–ether	74–75	
13	H	82	hexane–ether	80–81	
13	Ph	85	hexane–ether	105	

[a] All of these 3-arylpyrroles 6 are reported in ref 24. [b] 3-Pyridyl. [c] *m/e* 91.0422 (calcd for C_6H_5N 91.0422). [d] *m/e* 161.1204 (calcd for $C_{11}H_{15}N$ 161.1204).

Scheme II



3-Pyrrolylacetylenes and 3,4-Diacetylenic Pyrroles. The cross-coupling of the monoiodopyrrole **1** and various acetylenes **7** to **8** was easily effected in the presence of catalytic tetrakis(triphenylphosphine)paladium(0)[19] (ex

(11) Vasilevskii, S. F.; Sundukova, T. A.; Shvartsberg, M. S.; Kotlyarevskii, I. L. *Izv. Akad. Nauk SSSR, Ser Khim.* **1979**, 1661; *Chem. Abstr.* **1979**, *91*, 157544g. Sundukova, T. A.; Vasilevskii, S. F.; Shvartsberg, M. S.; Kotlyarevskii, I. L. *Izv. Akad Nauk SSSR, Ser Khim.* **1980**, 726; *Chem. Abstr.* **1980**, *93*, 71446f. Vasilevskii, S. F.; Sundokova T. A.; Shvartsberg, M. S.; Kotlyarevskii, I. L. *Izv. Akad Nauk SSSR, Ser Khim.* **1980**, 1871; *Chem. Abstr.* **1981**, *94*, 30464n.

(12) Vo-Quang, L.; Vo-Quang, Y. J. *Heterocycl. Chem.* **1982**, *19*, 145.

(13) Jux, N.; Koch, P.; Schmickler, H.; Lex, J.; Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1385.

(14) Kesseler, K.; Bartmann, W.; Wess, G.; Granzer, E. *Ger. Offen.* DE 3832570, 1990; *Chem. Abstr.* **1990**, *113*, 172038m.

(15) Bray, B. L.; Mathies P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.

(16) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. For other leading references, see also: Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(17) The method used was slightly modified (no LiCl) from that described for aryl triflates. Echavarran, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(18) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(19) Akita, Y.; Otita, A. *Heterocycles* **1982**, *19*, 329.

situ (method A) or generated in situ[20] (method B)) or bis(triphenylphosphine)palladium(II) chloride[21] (method C) (Scheme II, Table II). 3,4-Diacetylenic pyrroles 11 could be prepared in an analogous manner from 1-(triisopropylsilyl)-3,4-diiodopyrrole (10, method D).[15] In these cases a small amount of the monocoupled product 12 was usually isolated as well. The removal of the triisopropylsilyl moiety from 8 and 11 was effected in the same manner as described for the desilylation of 5. Under these conditions both the mono(trimethylsilyl) and the bis(trimethylsilyl) compounds 8 (R = Me_3Si) and 11 (R = Me_3Si) were converted into the completely desilylated ethynylpyrroles 9 (R = H) and 13 (R = H) even though only 1 equiv of tetrabutylammonium fluoride was used. Whereas 3-ethynylpyrrole (9, R = H) is a very unstable oil, the other acetylenic pyrroles including 3,4-bisethynylpyrrole (13, R = H) can be kept at 0 °C for long periods of time without significant decomposition. The acetylenic pyrroles 9 and 13 are potential precursors of other 3-substituted pyrrole derivatives and in addition may be of interest for the synthesis of conducting polypyrroles.[22]

Experimental Section

The physical constants of the compounds described herein were obtained as described previously.[23] The ^1H NMR spectra were measured at 200 MHz and are expressed as parts per million (δ) from internal tetramethylsilane.

Unless indicated otherwise, all new compounds had elemental analyses within ±0.3% for C, H, and N.

1-(Triisopropylsilyl)-3-iodopyrrole (1). *N*-Iodosuccinimide (27.0 g, 0.12 mol) was added to a stirred suspension of 1-(triisopropylsilyl)pyrrole[15] (22.3 g, 0.10 mol) in acetone (1.0 L) at −78 °C maintained in an atmosphere of argon. The mixture was stirred at this temperature for 6 h and then left to reach ambient temperature after which stirring was continued for a further 3 h. The solvent was then removed in vacuo, hexane (200 mL) was added to the residue, and the mixture was filtered through a column of neutral alumina (50 g, Act I). The filtrate was concentrated in vacuo, and the residual oil was distilled at reduced pressure to give the iodo compound 1 (21.6 g, 62% yield), bp 118 °C (0.05 mm). The ^1H NMR and infrared spectra were identical to those of an authentic specimen of this compound.[15]

1-(Triisopropylsilyl)pyrrole-3-boronic Acid (3). A solution of *tert*-butyllithium in pentane (12.4 mL of a 1.7 M solution; 21 mmol) was added to a stirred solution of 1-(triisopropylsilyl)-3-iodopyrrole (3.49 g, 10 mmol) in anhydrous THF (50 mL) at −78 °C in an argon atmosphere. The solution was stirred at this temperature for 25 min, and then trimethyl borate (11.4 mL, 10.43 g, 100 mmol), dissolved in THF (200 mL) and precooled to −78 °C was added via a cannula. The reaction mixture was stirred at −78 °C for 45 min, and then 50% aqueous methanol (4 mL) was added and the reaction was left to reach room temperature. The mixture was poured into water, the phases were separated and the aqueous phase was extracted with ether. The organic phases were combined, dried over magnesium sulfate, and the solvent was removed in vacuo. The crude oily boronic acid 3 (2.3 g) was used as such in the coupling reactions. This material, on solution in hexane–acetone gave a crystalline solid (1.15 g, 43%) with mp 122–124 °C. A satisfactory elemental analysis (CHN) could not be obtained on this substance: IR (KBr) 3284, 1380, 1333, 1246 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 1.10 (d, 18 H, J = 7.2 Hz, Me), 1.52 (sept. 3 H, J = 7.2 Hz, CH), 6.63 (dd, 1 H, $J_{2,4}$ = 1.3 Hz, $J_{4,5}$ = 2.5 Hz, H-4), 6.84 (dd, 1 H, $J_{2,5}$ = 1.9 Hz, $J_{4,5}$ = 2.5 Hz, H-5), 7.38 (dd, $J_{2,4}$ = 1.3 Hz, $J_{2,5}$ = 1.9 Hz, H-2); mass spectrum m/z 267 (100), 224 (80), 182 (48).

1-(Triisopropylsilyl)-3-(tributylstannyl)pyrrole (4). A solution of *tert*-butyllithium in pentane (24.0 mL of a 1.7 M solution; 40.8 mmol) was added to a stirred solution of 1-(triisopropylsilyl)-3-iodopyrrole (6.98 g, 20 mmol) in dry THF (100 mL) at −78 °C in an argon atmosphere. After 25 min at this temperature, freshly distilled tributylstannyl chloride (5.43 mL, 6.51 g, 20 mmol) was added, and stirring at −78 °C was continued for 0.5 h. The reaction mixture was left to reach ambient temperature, and after 12 h the solvent was removed in vacuo. Hexane (100 mL) was added to the residue, the mixture was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was distilled at reduced pressure. A pale yellow oil (9.26 g, 90% yield) bp 155 °C (6 mm) was obtained: ^1H NMR ($CDCl_3$) δ 0.89 (t, 9 H, J = 7.3 Hz, $MeCH_2$), 0.98 (t, 6 H, J = 7.8 Hz, $CH_2(CH_2)_2Me$), 1.11 (d, 18 H, J = 7.3 Hz, Me_2CH), 1.23–1.60 (m, 15 H), 6.36 (m, 1 H, H-4), 6.73 (m, 1 H, H-5), 6.97 (m, 1 H, H-2); HRMS calcd for $C_{25}H_{51}NSiSn$ 513.2813, found 513.2815.

Coupling of Aryl Halides and 1-(Triisopropylsilyl)-pyrrole-3-boronic Acid. Method A. Tetrakis(triphenylphosphine)palladium (0.058–0.120 g, 0.05–0.10 mmol) was added to a stirred mixture consisting of the aryl halide (2 mmol), the crude boronic acid 3 (0.267 g, 1 mmol) in benzene (20 mL), 2 M aqueous sodium carbonate solution (1.0 mL, 2 mmol), and methanol (4 mL) under an argon atmosphere. The mixture was heated at reflux temperature for the time period indicated in Table I, and then the solvent was removed in vacuo. Ethyl acetate (20 mL) was added to the residue, and the mixture was filtered through a pad of anhydrous sodium sulfate. The filtrate was evaporated in vacuo, and the residue was subjected to column chromatographic purification on silica gel (10 g) using hexane–ether (9:1) to elute the 3-arylpyrrole derivative 5. The yields, mps, etc., for these compounds are found in Table I. The ^1H NMR and infrared spectra are found in Table IV (supplementary material).

Coupling of Aryl Halides and 1-(Triisopropylsilyl)-3-(tributylstannyl)pyrrole. Method B. Tetrakis(triphenylphosphine)palladium (0.115–0.195 g, 0.10–0.17 mmol) was added to a stirred solution of the stannyl compound 4 (0.513 g, 1 mmol) and the aryl halide (1 mmol) in dry dioxane (20 mL) and the mixture was heated at reflux temperature (argon atmosphere) for the time period indicated in Table I. The reaction mixture was filtered through Celite, the filtrate was evaporated in vacuo, and the residue was purified as described in Method A.

Desilylation of 1-(Triisopropylsilyl)-3-arylpyrroles. A 1.0 M solution of tetrabutylammonium fluoride in THF (0.33 mL) was added to a stirred solution of the silylated 3-arylpyrrole 5 (0.33 mmol) in THF (5 mL). After 5 min, the solvent was removed in vacuo and the residue was purified by preparative thin-layer chromatography on silica gel using hexane–ethyl acetate (4:1) as the developing solvent. The chromatographically pure material was then crystallized from the appropriate solvent system. The yields and physical constants of the 3-arylpyrroles 6 are found in Table III.

Cross Coupling of 1-(Triisopropylsilyl)-3-iodopyrrole (1) with Monosubstituted Acetylenes. Method A: Ex Situ Tetrakis(triphenylphosphine)palladium. A mixture consisting of the silylated iodopyrrole 1 (0.500 g, 1.43 mmol), tetrakis(triphenylphosphine)palladium (0.100 g, 0.086 mmol), cuprous iodide (0.022 g, 0.116 mmol), the acetylene (2.14 mmol), anhydrous acetonitrile (2 mL), and anhydrous triethylamine (5 mL) was stirred at reflux temperature (argon atmosphere) for 3 h. The solvent was removed in vacuo, and the residue was subjected to flash column chromatography on silica gel (27 g) using hexane to elute the product. The product yields are found in Table II. The ^1H NMR spectra and the infrared spectra for these compounds are found in Table IV (supplementary material).

Method B. In Situ Generated Tetrakis(triphenylphosphine)palladium. A mixture consisting of 10% Pd–C (0.850 g, 0.8 mmol), triphenylphosphine (0.839 g, 3.2 mmol), cuprous iodide (0.304 g, 1.6 mmol), the iodo compound 1 (3.50 g, 10 mmol), the acetylene (15 mmol), anhydrous acetonitrile (12.5 mL), and anhydrous triethylamine (25 mL) was heated at reflux temperature (argon atmosphere) with stirring for 3 h. The cooled mixture was filitered through Celite, and the filtrate was evaporated in vacuo. The residue was purified as in method A.

(20) De la Rosa, M. A.; Velarde, E.; Guzmán, A. *Synth. Commun.* **1990**, *20*, 2059.
(21) Tanji, K.; Sakamoto, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1982**, *30*, 1865 and references cited therein.
(22) Inagaki, T.; Hunter, M.; Yang, X. Q.; Skotheim, T. A.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 126.
(23) Guzman, A.; Romero, M.; Maddox, M. L.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 5793.
(24) Sakai, K.; Suzuki, M.; Nunami, K.; Yoneda, N.; Onodu, Y.; Iwasawa, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2384.

Method C. Bis(diphenylphosphine)palladium Chloride. The reaction was carried out as described in method A except that 1.43 mmol of the iodopyrrole 1, bis(diphenylphosphine)-palladium chloride (0.075 g, 0.288 mmol), and cuprous iodide (0.027 g, 0.143 mmol) were used.

Cross Coupling of 1-(Triisopropylsilyl)-3,4-diiodopyrrole (10) with Monosubstituted Acetylenes. Method D. The reaction (10 mmol scale) was carried out exactly as in method B except that the amount of all the other reagents was doubled. The amounts of acetonitrile and triethylamine were the same as these of method B. The reaction time was 2 h.

Desilylation of 1-(Triisopropylsilyl)-3-pyrrolylacetylenes 8 and 11. The desilylation was effected as described above for a 10-min period (45 min for 8, R = Me_3Si). The solution was diluted with ether, washed with water, dried over magnesium sulfate, and evaporated in vacuo. Compound **9** (R = H) was obtained as a very unstable oil which was not manipulated further. The other crude acetylenic pyrroles were purified by column chromatography on Act II neutral alumina using hexane–ethyl acetate (85:15) as the eluting solvent. The yields, mps, etc. for those compounds are found in Table III. The ^1H NMR and infrared spectra are found in Table IV (supplementary material).

Supplementary Material Available: ^1H NMR, IR, and analytical data for 3-substituted pyrroles (6 pages). Ordering information is given on any current masthead page.

A Simple Asymmetric Synthesis of 2-Substituted Pyrrolidines and 5-Substituted Pyrrolidinones

Laurence E. Burgess and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

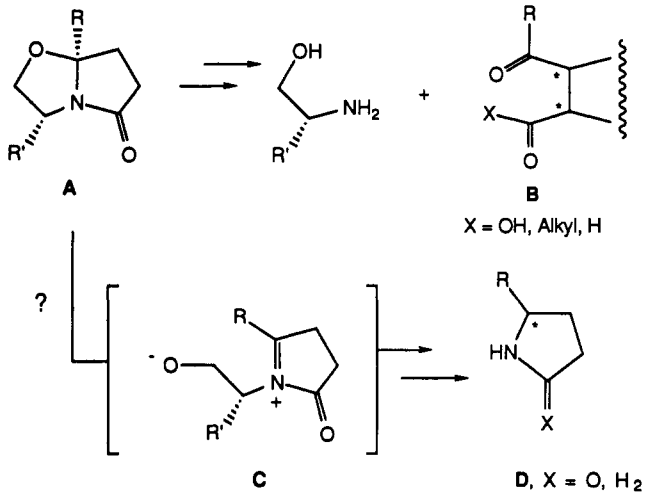
Received October 16, 1991

An efficient procedure for the preparation of the title compounds in high enantiomeric purity has been realized starting from 3-acylpropionic acids. Stereoselective reduction of chiral bicyclic lactams **2a–h**, prepared from the corresponding γ-keto acid and (*R*)-phenylglycinol, using alane or triethylsilane with titanium tetrachloride provided the N-substituted pyrrolidines and pyrrolidinones, respectively. Subsequent cleavage of the phenylglycinol returned the desired amines and lactams. The enantiomeric purity of these compounds was determined to be >98% by chiral stationary-phase HPLC.

Introduction

The pyrrolidine ring system is common to many naturally occurring[1] and medicinally important compounds.[2] Furthermore chiral auxiliaries,[3] chiral bases,[4] and chiral ligands[5] for asymmetric synthesis often employ this heterocyclic moiety. Although there are several procedures for the preparation of chiral pyrrolidines and pyrrolidinones, the majority of these exhibit poor enantiomeric excesses, lack versatility, suffer low yields or some com-

Scheme I



(1) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. (b) Hart, D. J. *Ibid.* 1988; Vol. 6; Chapter 3. (c) Elbein, A. D.; Molyneux, R. J. *Ibid.* 1987; Vol. 5, Chapter 1. (d) Gellert, E. *Ibid.* 1987; Vol. 5, Chapter 2. (e) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, Chapter 4. (f) Massiot, G.; Delaude, C. *Ibid.* 1986; Vol. 27, Chapter 3. (g) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949. (h) Jones, T. H.; Blum, M. S.; Howard, R. W.; McDaniel, C. A.; Fales, H. M.; Dubois, M. B.; Torres, J. *J. Chem. Ecol.* **1982**, *8*, 285. (i) Rüger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331. (j) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (k) Stevens, R. V. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, p 439.

(2) (a) Psychotropic agents: Rigo, B.; Fasseur, D.; Cherepy, N.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 7057. (b) Muscarinic acid agonists: Nilsson, B. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 580. (c) Lundkvist, J. R.; Wistrand, L.-G.; Hacksell, U. *Tetrahedron Lett.* **1990**, *31*, 719. (d) Peptide mimics: Garvey, D. S.; May, P. D.; Nadzan, A. M. *J. Org. Chem.* **1990**, *55*, 936. (e) Heffner, R. J.; Joullié, M. M. *Tetrahedron Lett.* **1989**, *30*, 7021. (f) Novel amino acids: Silverman, R. B.; Nanavati, S. M. *J. Med. Chem.* **1990**, *33*, 931. (g) Anti cancer: Bick, I. R. C.; Hai, M. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 24, Chapter 3. (h) Neuromuscular transmission blocker: Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albequerque, E. X. *Neurochemical Res.* **1986**, *11*, 1227. (i) Immunoregulator: Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohasaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926. (j) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res.* **1988**, *48*, 1410. (k) Anti fungal: Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; Part 2, Vol. 5, pp 1–19 and references cited therein.

(3) (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590. (b) See: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2.

(4) (a) Tomioka, K. *Synthesis* **1990**, 541 and references therein. (b) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *42*, 523. (c) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

(5) (a) Kagan, H. B. In *Asymmetric Synthesis*; J. D. Morrison, Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 1. (b) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423 and references cited therein.

0022-3263/92/1957-1656$03.00/0