7.27-7.73 (m, 5 H, Ar H), 4.85 (s, 2 H, -CH_2-), 1.24-1.06 (m, 21 H, *i*-Pr).

[(*tert*-Butyldiphenylsiloxy)methyl]benzene (3): 9.68 g, 91% yield, 98% pure by GC; IR (CCl_4) cm^{-1} 2962 (m), 2931 (m), 2859 (m), 1474 (m), 1428 (m), 1113 (s), 1070 (m), 1028 (m); ^1H NMR ($CDCl_3$) δ 7.69-7.74 (m, 5 H, benzyl Ar H), 7.34-7.42 (m, 10 H, Si Ar H), 4.79 (s, 2 H, $PhCH_2O$), 1.11 (s, 9 H, *t*-Bu).

4-[(*tert*-Butyldimethylsiloxy)methyl][(triisopropylsiloxy)methyl]benzene (5). Methyl 4-(hydroxymethyl)benzoate (9.73 g, 58.6 mmol) was protected using TBDMS-Cl by Corey's procedure[7] to give 17.6 g of methyl 4-[(*tert*-butyldimethylsiloxy)methyl]benzoate (100% yield, 99% pure by GC) after workup and without further purification: oil; IR (CCl_4) cm^{-1} 2955 (s), 2930 (s), 2858 (s), 1728 (s), 1278 (s), 1258 (s), 1103 (s), 1091 (s), 840 (s); ^1H NMR ($CDCl_3$) δ 7.99 (d, 2 H, Ar H, J = 8.3 Hz), 7.37 (d, 2 H, Ar H, J = 8.3 Hz), 4.77 (s, 2 H, $ArCH_2$), 3.89 (s, 3 H, OCH_3), 0.93 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$). The TBDMS-protected material (16.34 g, 57.55 mmol) was dissolved in 70 mL of ether and stirred magnetically under N_2 while a $LiAlH_4$ solution (29 mL, 1.0 M in Et_2O, 29 mmol) was added via syringe over 15 min at a rate which maintained a mild reflux. The reaction mixture was quenched with 200 mL of H_2O after 1 h and then neutralized with 6 M HCl. The aqueous phase was extracted with 3 × 100 mL of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 11.75 g of 4-[(*tert*-butyldimethylsiloxy)methyl](hydroxymethyl)benzene (8) (97% pure by GC, 88% yield): oil; IR (CCl_4) cm^{-1} 3619 (m), 2956 (s), 2931 (s), 2858 (s), 1255 (s), 1091 (s), 840 (s); ^1H NMR ($CDCl_3$) δ 7.30 (s, 4 H, Ar H), 4.72 (s, 2 H, $ArCH_2OSi$), 4.65 (s, 2 H, $ArCH_2OH$), 0.92 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$).

4-[(*tert*-Butyldimethylsiloxy)methyl](hydroxymethyl)benzene (11.2 g, 43.7 mmol) was protected using TIPS-Cl by Corey's procedure.[7] The crude product was purified by flash column chromatography (hexane) to give 16.8 g of 5 (92% pure by GC, 87% yield): oil; IR (CCl_4) cm^{-1} 2947 (s), 2891 (s), 2867 (s), 1089 (s), 839 (s); ^1H NMR ($CDCl_3$) δ 7.28 (d, 4 H, Ar H, J = 1.1 Hz), 4.81 (s, 2 H, $ArCH_2OTIPS$), 4.71 (s, 2 H, $ArCH_2OTBDMS$), 1.13-1.03 (m, 21 H, *i*-Pr), 0.92 (s, 9 H, *t*-Bu), 0.75 (s, 6 H, $SiCH_3$).

Deprotection of Disilyl Ether 5. Compound 5 (10.0 mmol, 4.09 g), Et_3N (1.67 mmol, 232 μL), and 100 mL of CH_3CN were mixed in a 175-mL polyethylene bottle. The bottle was immersed in an ice bath and the solution was stirred magnetically while the temperature equilibrated. H_2SiF_6 (4.17 mmol, 1.54 mL of a ~31% aqueous solution, 2.50 F^- equiv) was added and the progress of the reaction was monitored by GC. At 99% completion (60 min), 10 mL of saturated $NaHCO_3$ was added. After evaporating the CH_3CN at reduced pressure, the concentrate was diluted with 100 mL of EtOAc and extracted with 3 × 50 mL of brine. The combined organic phases were dried ($MgSO_4$) and evaporated at reduced pressure to give a white solid in a colorless oil. Hexane was added to dissolve the soluble oil, which was then separated from the insoluble solid (pure diol 7) by filtration. Upon concentration at reduced pressure, the hexane solution provided 2.88 g of an oil which was 77% compound 6 by GC (75% crude yield). Other constituents of the oil included compound 8, *tert*-butyldimethylsilanol, triisopropylsilanol, *tert*-butyldimethylsilyl fluoride, triisopropylsilyl fluoride, and starting material 5. Purification by flash column chromatography (95:5 hexane:ether) yielded 2.05 g of alcohol 6 as a clear colorless oil (99% pure by GC, 70% yield): IR (CCl_4) cm^{-1} 3617 (w), 2944 (s), 2867 (s), 1117 (m), 1096 (m), 1069 (m), 1014 (m), 883 (m); ^1H NMR ($CDCl_3$) δ 7.32 (s, 4 H, Ar H), 4.82 (s, 2 H, $ArCH_2OSi$), 4.66 (s, 2 H, $ArCH_2OH$), 1.67 (s, 1 H, OH), 1.13-1.03 (m, 21 H, Si-*i*-Pr).

2-(Benzyloxy)tetrahydropyran (9). THP ether 9 was prepared from benzyl alcohol (20.0 mmol, 2.16 g) by Bernady's procedure[8] to give give 3.38 g of product (87% yield, >99% pure by GC) after workup and purification by flash column chromatography (hexane): oil; IR (CCl_4) cm^{-1} 2946 (s) 1455 (m), 1201 (m), 1037 (m), 1028 (m); ^1H NMR ($CDCl_3$) δ 7.28-7.39 (m, 5 H, Ar H), 4.80 (d, 1 H, $ArCH_2$, J = 12.0 Hz), 4.51 (d, 1 H, $ArCH_2$, J = 12.0 Hz), 4.72 (t, 1 H, -OCHO-, J = 3.6 Hz), 3.85-4.01 (m, 1 H, equatorial -CH_2O-), 3.46-3.62 (m, 1 H, axial -CH_2O-), 1.51-1.88 (m, 6 H).

***cis*-4-Methyl-2-phenyl-1,3-dioxane (10).** 2,4-Butanediol (10.9 mmol, 1.06 g), benzaldehyde (13.0 mmol, 1.38 g), TsOH (1.09 mmol, 0.206 g), and $MgSO_4$ (21.7 mmol, 2.61 g, 2.00 equiv) were combined in 10 mL of CH_2Cl_2. After the solution was stirred magnetically at rt for 4.75 h, the reaction mixture was filtered, and 20 mL of CH_2Cl_2 was added. The organic phase was extracted 3 times with 20 mL of saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated at reduced pressure. Purification of the crude product by flash column chromatography (hexane) gave 1.79 g of benzylidene 10 as an oil (91% yield, 99% pure by GC): IR (CCl_4) cm^{-1} 2976 (s), 2854 (s), 1376 (s), 1357 (s), 1247 (s), 1167 (s), 1114 (s), 1062 (s), 1028 (s), 999 (s), 968 (m); ^1H NMR ($CDCl_3$) δ 7.31-7.52 (m, 5 H, Ar H), 5.51 (s, 1 H, PhCH), 4.21-4.30 (m, 1 H, CHMe), 3.89-4.08 (m, 2 H, -OCH_2-), 1.70-1.90 (m, 1 H, equatorial MeCHCH_2), 1.43-1.57 (m, 1 H, axial MeCHCH_2), 1.32 (d, 3 H, Me, J = 6.2 Hz).

5,5-Diethyl-2,2-dimethyl-1,3-dioxane (11). Acetonide 11 was prepared from 2,2-diethyl-1,3-propanediol (50.0 mmol, 6.61 g) by Schmidt's procedure[11] (7.75 g, 90% yield, >99% pure by GC) after workup without further purification: oil; IR (CCl_4) cm^{-1} 2967 (s), 2863 (m), 1386 (m), 1370 (m), 1199 (s), 1099 (s), 836 (m); ^1H NMR ($CDCl_3$) δ 3.56 (s, 4 H, -OCH_2C-), 1.41 (q, 4 H, CCH_2Me, J = 7.6 Hz), 1.40 (s, 6 H, MeCMe), 0.80 (t, 6 H, $MeCH_2C$, J = 7.5 Hz).

[(Methoxymethoxy)methyl]benzene (12). MOM ether 12 was prepared from benzyl alcohol (50.0 mmol, 5.41 g) by Fuji's procedure[9] (7.23 g, 91% yield, 95% pure by GC) after workup without further purification: oil; IR (CCl_4) cm^{-1} 2950 (m), 2881 (m), 1455 (m), 1211 (m), 1150 (s), 1102 (s), 1050 (s), 1026 (s), 915 (m); ^1H NMR ($CDCl_3$) δ 7.35 (m, 5 H, Ar H), 4.71 (s, 2 H, -OCH_2O-), 4.60 (s, 2 H, $ArCH_2$), 3.42 (s, 3 H, Me).

[[(Methoxyethoxy)methoxy]methyl]benzene (13). MEM ether 13 was prepared from benzyl alcohol (26.8 mmol, 2.89 g) using MEM-Cl by Corey's procedure[10] (5.57 g, 100% yield, 94% pure by GC) after workup without further purification: oil; IR (CCl_4) cm^{-1} 2929 (s), 2896 (s), 1450 (m), 1110 (s), 1048 (s); ^1H NMR ($CDCl_3$) δ 7.05 (m, 5 H, Ar H), 4.82 (s, 2 H, -OCH_2O-), 4.63 (s, 2 H, $ArCH_2$), 3.75 (m, 2 H, $MeOCH_2CH_2O$), 3.57 (m, 2 H, $MeOCH_2CH_2O$), 3.41 (s, 3 H, Me).

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Efficient Synthesis of 2-Chloro-, 2-Bromo-, and 2-Iodoindole

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Halogenation of simple indoles takes place preferentially at the 3-position,[1] and high-yielding syntheses of 3-chloro-,[2] 3-bromo-,[2-4] and 3-iodoindole[4-6] are today available. In

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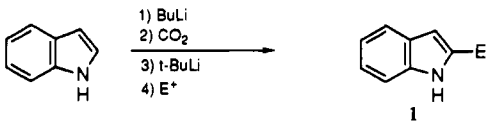
0022-3263/92/1957-2495$03.00/0

Scheme I



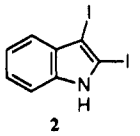
1

Compound	Electrophile	2-Substituent	Yield %
1a	ICH_2CH_2I	I	90
1b	$BrCl_2CCCl_2Br$	Br	87
1c	C_2Cl_6	Cl	90

contrast, only low-yield syntheses of 2-chloro-[2,7] and 2-bromoindole[2] (via Vilsmeier salts from oxindole) and 2-iodoindole[8] (via iodination of various N-protected 2-lithioindoles) have been reported.

We here report the synthesis of 2-chloro-, 2-bromo-, and 2-iodoindole in excellent yields, using the Katritzky method[9] (see Scheme I) which is an efficient method for functionalization of an indole at the 2-position. Carbon dioxide is introduced as an activating and an N-protecting group.[9] Several electrophiles have been employed previously in the reaction;[9,10] however, no report on the use of halogenating reagents has so far appeared in the literature. Halogenation of organolithium compounds can usually be accomplished with a number of halogenating agents,[11] but for the present purpose, hexachloroethane, 1,2-dibromotetrachloroethane, and 1,2-diiodoethane were found to be optimal. The use of elemental bromine and iodine, for instance, gave considerably lower yields.

We could confirm the reports that 2-chloro- and 2-bromoindole are quite unstable and decompose at room temperature.[2,7] Additionally we found the order of stability to be: 2-iodoindole ≫ 2-chloroindole > 2-bromoindole. These compounds could, however, be stored unchanged at −20 °C indefinitely. This procedure makes 2-chloro-, 2-bromo-, and 2-iodoindole readily available, and since haloindoles have been utilized in a number of transition-metal-catalyzed coupling reactions,[12] we anticipate these compounds will come to use in e.g. vinylation and arylation reactions. The 2-haloindoles can also be useful in the synthesis of di- and polyhalogenated indoles.[13] By way of example, 2,3-diiodoindole (2) was made by iodination of 2-iodoindole (1a) in 82% yield. Mingoia[14] claimed to have synthesized 2 by iodination of 2,3-dichloromercuriindole, and he reported 2 to have a mp of 220 °C. This seemed to be a rather high melting point for that kind of compound, and we recorded a mp of 130–131 °C on our sample. Attempts to repeat Mingoia's synthesis gave, in our hands, only an intractable residue. It should be noted that the authenticity of most of the iodoindoles reported by Mingoia[14] has already been questioned by Powers.[15] Finally, 1a was correlated with the known compound 1-methyl-2-iodoindole[12b] by methylation, and 2 was correlated with 1-(phenylsulfonyl)-2,3-diiodoindole[6] using benzenesulfonyl chloride.



2

Experimental Section

All reactions were performed under a positive nitrogen pressure. Glassware were dried in an oven (160 °C) for 2 h. THF was distilled from sodium benzophenone ketyl. Indole and the halogenation reagents were purchased from Aldrich and used without further purification. Butyllithium solutions were purchased from Aldrich. Carbon dioxide gas was generated from dry ice. Flash chromatography[16] was performed with the solvents indicated using Merck silica gel 60 (particle size 0.040–0.063 mm). Melting points were determined on a calibrated Reichert WME Kofler hot stage. NMR spectra were recorded on a Bruker ACF 250 spectrometer, ^1H at 250 and ^{13}C at 62.86 MHz, respectively. Chemical shifts are reported relative to tetramethylsilane. IR spectra were obtained using a Perkin-Elmer 1600 FTIR instrument. Mass spectra were obtained with a Finnigan MAT INCOS instrument (EI, 70 eV). The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden.

All lithiation reactions were run on the same scale (10 mmol) using the following general procedure:

2-Iodoindole (1a). Butyllithium (4.2 mL, 2.5 M hexane solution) was added dropwise to a solution of indole (1.17 g, 10.0 mmol) in dry THF (20 mL) at −70 °C. The resulting suspension was kept at −70 °C for 30 min, CO_2 (g) was then bubbled through the mixture for 10 min, and the clear solution was allowed to stand for 10 min. The solvent was evaporated (0 °C, 1 mmHg), the crystalline residue was dissolved in 20 mL dry THF and cooled to −70 °C, and *tert*-butyllithium (6.2 mL, 1.7 M pentane solution) was added dropwise. After having held the resulting yellow solution at −70 °C for 1 h, 1,2-diiodoethane (2.82 g, 10.0 mmol) was added. The reaction mixture was kept at −70 °C for 1 h, water (1 mL) was added, and the solution was allowed to reach room temperature. It was then poured into NH_4Cl (saturated aqueous, 50 mL) under stirring, ether (50 mL) was added, and the organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The solid residue was purified by flash chromatography (hexane/ether, 4:1), yielding 2.19 g (90%) of 2-iodoindole: mp 98–99 °C dec (lit.[8] mp 95 °C); IR (KBr) 3380, 1436, 1400, 1336, 1313, 1272, 908, 783, 749, 612 cm^{-1}; mass spectrum, m/z 243 (M^+, base peak); ^1H NMR ($CDCl_3$) δ 6.72 (dd, J = 1.0, 1.9 Hz, 1 H), 7.0–7.2 (m, 2 H), 7.3 (m, 1 H), 7.5 (m, 1 H), 8.1 (br s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 74.8, 110.1, 112.7, 119.2, 120.2, 122.2, 129.6, 138.6 ppm.

2-Bromoindole (1b). The same procedure was used except that 1,2-dibromotetrachloroethane (3.26 g, 10.0 mmol) was used as the halogenating reagent. Flash chromatography (hexane/ether, 4:1) of the crude product gave a solid which was triturated with hexane, whereupon the crystals were collected: yield 1.70 g (87%) of 2-bromoindole; mp 78–82 °C dec (lit.[2] mp 82–84 °C); ^1H NMR ($CDCl_3$) δ 6.53 (d, J = 2.2 Hz, 1 H), 7.0–7.3 (m, 3 H), 7.52 (d, J = 8.0 Hz), 8.1 (br s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 104.8, 108.6, 110.3, 119.6, 120.5, 122.2, 128.7, 136.4 ppm.

2-Chloroindole (1c). Using the same procedure, but with hexachloroethane (2.37 g, 10.0 mmol) as halogenating agent, 1.37 g (90%) of 2-chloroindole was obtained after flash chromatography

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(hexane/ether, 4:1): mp 88–89 °C dec (lit.[2,7] mp 71–73 °C dec, 72–76 °C); ^{1}H NMR ($CDCl_3$) δ 6.41 (d, J = 1.7 Hz, 1 H), 7.1–7.3 (m, 3 H), 7.51 (dd, J = 7.4, 1.1 Hz, 1 H), 8.0 (br s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 100.7, 110.3, 119.8, 120.5, 122.2, 123.3, 128.1, 134.9 ppm.

2,3-Diiodoindole (2). The general method of Bocchi and Palla[4] was used. KOH (0.56 g, 10 mmol) was added to a solution of 2-iodoindole (0.972 g, 4.0 mmol) in DMF (20 mL). A solution of iodine (1.03 g, 4.05 mmol) in DMF (10 mL) was added dropwise during 8 min. After 30 min the reaction mixture was poured onto ice water (containing 4 mL of NH_3 and 200 mg of $K_2S_2O_5$), and the resulting fine suspension was extracted with ether (2 × 50 mL). The combined ether extracts were washed with water (5 × 20 mL) followed by brine, dried ($MgSO_4$), and evaporated. The crude product was recrystallized from hexane: yield 1.21 g (82%) of white needles; mp 130–131 °C (lit.[14] mp 220 °C); IR (KBr) 3361, 1434, 1396, 1334, 1302, 1221, 966, 747 cm^{-1}; mass spectrum, m/z 369 (M^+, base peak); ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 2 H), 7.3 (m, 1 H), 7.4 (m, 1 H), 8.4 (br s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 73.23, 87.13, 110.41, 121.1, 121.2, 123.4, 131.3, 138.8 ppm. Anal. Calcd for $C_8H_5NI_2$: C, 26.03; H, 1.37; N, 3.80; I, 68.81. Found: C, 25.65; H, 1.35; N, 3.70; I, 68.55.

1-(Phenylsulfonyl)-2,3-diiodoindole. To a solution of 2 (369 mg, 1 mmol) in dry DMF (5 mL) was added NaH (26 mg, 1.1 mmol) under nitrogen. The mixture was stirred for 30 min, whereafter benzenesulfonyl chloride (194 mg, 1.1 mmol) was added. The reaction mixture was stirred for 2 h, and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), and the organic phase was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (hexane/ether, 1:1): yield 380 mg (76%) of a whitish powder; mp 166–167 °C (lit.[6] mp 166–167 °C); IR (KBr) 1440, 1430, 1369, 1188, 1128, 1087, 1013, 742, 725, 682, 590, 565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.0–7.6 (m, 6 H), 7.7–8.3 (m, 3 H) ppm.

1-Methyl-2-iodoindole. To a solution of 1a (673 mg, 2.77 mmol) in dry DMF (7.5 mL) was added NaH (73 mg, 3.05 mmol), and the mixture was stirred for 30 min. Methyl iodide (590 mg, 4.16 mmol) was then added, and the reaction mixture was stirred at 50 °C for 4 h. The solvent was evaporated, the oily residue was dissolved in ether (30 mL), and the organic phase was washed with water, dried ($MgSO_4$), and evaporated. Flash chromatography (hexane/ether, 4:1) of the crude product gave 640 mg (90%) of white crystals: mp 76 °C (lit.[12b] mp 76–77 °C); ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 6.78 (s, 1 H), 7.0–7.2 (m, 2 H), 7.3 (m, 1 H), 7.5 (m, 1 H) ppm.

Registry No. 1a, 26340-49-8; 1b, 139409-34-0; 1c, 7135-31-1; 2, 139409-35-1; indole, 120-72-9; 1-(phenylsulfonyl)-2,3-diiodoindole, 80360-26-5; 1-methyl-2-iodoindole, 75833-63-5.

1*H*-Pyrazole-1-carboxamidine Hydrochloride: An Attractive Reagent for Guanylation of Amines and Its Application to Peptide Synthesis

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Introduction

The possibility of preparing arginine-containing peptides by guanylation of the δ-amino groups of the appropriate ornithine-containing precursors has long been recognized.[1] Such a strategy is attractive for its potential to eliminate the many problems associated with the use of conventionally protected arginine starting materials in peptide synthesis.[2] It is also attractive because it allows for the preparation of various ornithine-derived analogues from a single common precursor peptide. Despite the potential advantages of this strategy, only a few examples of its successful use have appeared in the literature.[3] Presumably the commonplace use of this approach has been impeded by the lack of general availability of guanylating reagents with the appropriate reactivity and solubility characteristics. Preliminary studies in this laboratory have shown that the widely used commercially available guanylating reagents cyanamide,[4] *O*-methylisourea hydrogen sulfate,[3d,e] 2-ethyl-2-thiopseudourea hydrobromide,[5] and 3,5-dimethylpyrazole-1-carboxamidine nitrate[6] did not possess sufficient reactivity for practical and generalized use in the context of solid-phase peptide synthesis. Tian and Roeske have arrived at similar conclusions in a recent report noting the shortcomings of such reagents.[7] As a consequence of these observations, an interest in generalizing the "ornithine → arginine" strategy, and the potential medicinal chemistry applications of guanidines, some of the work in this laboratory was focused on the development and characterization of more suitable reagents for the conversion of amines to guanidines. In the course of this investigation it was found that 1*H*-pyrazole-1-carboxamidine hydrochloride[8] (1) (1-guanylpyrazole hydrochloride) was reactive enough to merit further study. Although 1 has been previously used to convert some amines and hydrazines to the corresponding guanidines (Figure 1) in good yields (using 2 mol of amine for each mole of 1 in refluxing tetrahydrofuran or dibenzyl ether, 160 °C in the case of aniline)[8] and has also been applied to the synthesis of Edeine B and F,[9] systematic studies designed to provide a better understanding of its relative reactivity and compatibility with other potentially nucleophilic functional groups, and detailed optimized synthetic procedures for its more generalized and widespread use as a guanylating reagent were lacking. Reported here are experiments designed to provide a better understanding of 1 with regard to its reactivity as well as to

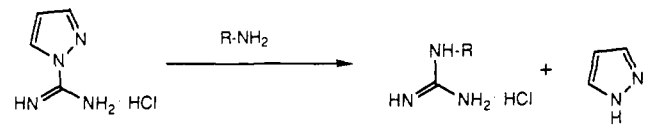

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Figure 1. Reaction of 1*H*-pyrazole-1-carboxamidine hydrochloride (1) with a primary amine.

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