Notes

Inductive Effect of Positively Charged Nitrogen on the Addition of Iodine Monochloride to Alkynamine Hydrochlorides[†]

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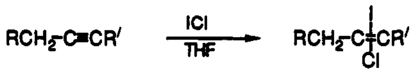
Introduction

The addition of iodine monochloride (ICl) to alkynes is a relatively well-documented process.[1] The addition to terminal alkynes generally occurs stereospecifically and regiospecifically to form the (*E*)-chloroiodoalkene in which the iodine is attached to the terminal alkene carbon atom.[2-6] For identification of these compounds, an extension to the original Markovnikov designation has been proposed which states that "the Markovnikov isomer is that one in which the more electrophilic part of the electrophile is attached to the carbon atom whose sum of Taft's constants (σ^*) is the more positive."[7] Since the Markovnikov orientation is expected for ionic additions, this rule is useful for predicting the regioisomeric outcome of electrophilic additions to alkynes.

The rule has been unsuccessful, however, in predicting the outcome of regioisomers formed when ICl is added to terminal alkynes bearing substituents with varying σ^* values. For example, when ICl is added to terminal (perfluoroalkyl)alkynes,[8] phenylacetylenes,[9] and ethyl 3-butynoate,[5] the iodine would be predicted to be attached to the internal carbon atom since it has the greater σ^* value. This is not in accord with experimental observation since these reactions formed, regiospecifically, the terminal iodides. Because σ^* values are not available for all substituents described in this report, the original Markovnikov (M) and anti-Markovnikov (A) designations are used.

During the course of a study to develop novel radioiodination procedures, we investigated the addition of ICl to several propargylamine hydrochlorides and observed varying degrees of regioselectivity depending on the nature of the nitrogen substituents. In each case the major product was the chloroiodinated (*E*)-alkene in which chlorine was attached to the terminal carbon atom, as predicted by the extended Markovnikov rule. Due to the inconsistencies[5,8,9] of this rule regarding ICl additions to alkynes, we decided to investigate the factors controlling the regiochemistry of these reactions. Based on the experimental results, we found the regioselectivity and rates of these reactions to be dependent upon the inductive effect of the positively charged nitrogen.

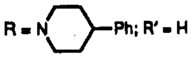
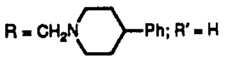
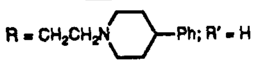
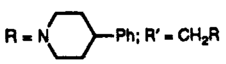
Scheme I



1
R,R' = see Table

2

Table I. Chloroiodination of Alkynamine Hydrochlorides with Iodine Monochloride

hydrochloride of substrate 1	ICl addition product 2	
	isolated yield, %	regioisomeric ratio (A/M)[c]
a, R = NH_2; R′ = H	22[a,b]	4
b, R = $N(CH_3)CH_2Ph$; R′ = H	97[b]	3
c, 	68[b]	5
d, 	71[b]	2
e 	72[b]	0.5
f, 	72	
g, 	70	

[a] The product decomposed readily during workup. [b] Both isomers. [c] Determined by integration of the alkenyl protons.

Results and Discussion

Chemistry. Treatment of the hydrochlorides of alkynamine 1 with ICl in anhydrous THF at reflux temperature provided the corresponding (*E*)-chloroiodoalkenes in good yield (Scheme I). However, reaction of the free base 1 provided a more complex mixture containing unreacted starting material and therefore a substantial decrease in product yield. While the symmetrical alkynes **1f** and **1g** provided only one isomer, the unsymmetrical alkynes **1a–e** consistently provided two regioisomers in varying amounts. Typical reactions with substrates, yields, and regioisomeric ratios are listed in Table I.

The hydrochloride products were converted to the free base for purification by preparative silica gel thin layer chromatography (TLC) and were obtained as oils, which, similar to other chloroiodinated alkenes,[2] were unstable and decomposed slowly. Some chloroiodinated alkenes were converted to the more stable hydrochloride salt in order to obtain analytical-grade samples. The positions of iodine and chlorine in alkenes 2 were determined by ^{13}C

[†] The research described in this report was performed at the Oak Ridge National Laboratory in partial fulfillment of the doctoral thesis requirements of Steven Lambert under administration with the University of Tennessee.

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(1) Schmid, G. H. *The Chemistry of the Carbon Carbon Triple Bond*; Patai, S., Ed.; John Wiley: New York, 1978; Part 1, p 330.

(2) Uemura, S.; Okazaki, H.; Onoe, A.; Okano, J. *J. Chem. Soc., Perkin Trans. I* 1977, 676.

(3) Baird, W. C., Jr.; Surridge, J. H.; Buza, M. J. *J. Org. Chem.* 1971, *36*, 3324.

(4) Uemura, S.; Onoe, A.; Okano, M. *J. Chem. Soc., Chem. Commun.* 1975, 925.

(5) Tendil, J.; Verney, M.; Vessiere, R. *Tetrahedron* 1974, *30*(4), 579.

(6) Barluenga, Jose; Rodriguez, Miguel A.; Campos, Pedro J. *J. Org. Chem.* 1990, *55*, 3104.

(7) Reference 1, p 278.

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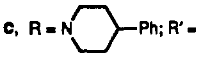
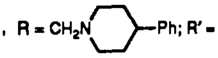
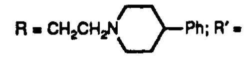
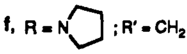
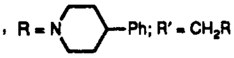
(9) *Synthetic Reagents*; Pizey, Horwood, Ed., 1983; Vol. 5, p 115.

0022-3263/91/1956-3707$02.50/0

Table II. Characterization of the Chloroiodoalkenes

product 2	isomer	^{1}H NMR^a	^{13}C NMR^b I	^{13}C NMR^b T
a, R = NH_2; R′ = H	A	6.50	107 (s)	121 (d)
	M	6.38	138 (s)	73 (d)
b, R = $N(CH_3)CH_2Ph$; R′ = H	A	6.63	103 (s)	121 (d)
	M	6.54	135 (s)	74 (d)
c, 	A	6.65	102 (s)	121 (d)
	M	6.56	135 (s)	76 (d)
d, 	A	6.49	100 (s)	120 (d)
	M	6.33	136 (s)	74 (d)
e 	A	6.46	102 (s)	119 (d)
	M	6.29	139 (s)	73 (d)
f, 			101 (C–I) 131 (C–Cl)	
g, 			103 (C–I) 131 (C–Cl)	

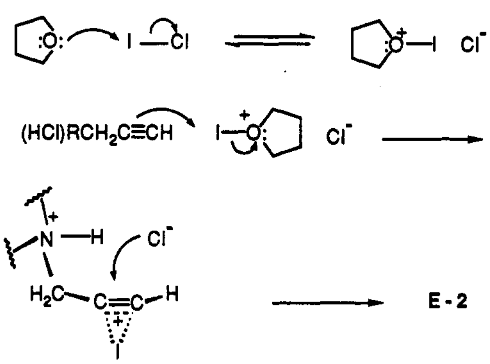
^{a}Chemical shifts of vinyl protons in ppm (TMS: internal standard). ^{b}Chemical shifts of internal (I) and terminal (T) alkene carbons in ppm ($CDCl_3$ or TMS: internal standard).

and ^{1}H NMR data collected for the free amines (Table II).

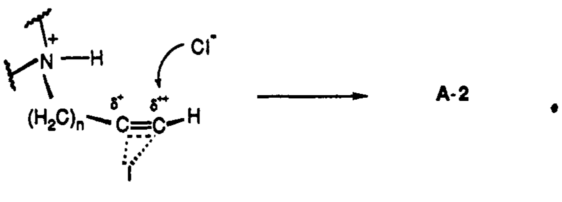
The ^{1}H NMR spectra of (A)-**2a–e** contained vinyl proton resonances downfield from those of the corresponding (M)-**2a–e** isomers, which is expected since a vinyl proton geminal to chlorine should resonate downfield from the vinyl proton geminal to iodine. The ^{13}C NMR data further support assignment of the positions of iodine and chlorine in alkenes **2a–e**. The ^{13}C NMR spectra of products **2f** and **2g**, derived from the symmetrical alkynes, included resonances with chemical shifts typical of internal alkene carbon atoms bearing iodine and chlorine[10] and are consistent with those of the (A)-**2** and (M)-**2** isomers, respectively. Furthermore, the terminal carbons of the (M)-**2** isomers exhibit a large upfield shift from the alkene region due to the heavy atom effect of iodine and appear as doublets in the off-resonance decoupled ^{13}C NMR spectra. The (A)-**2** isomers display doublets at 119–121 ppm, indicating the terminal carbons attachment to chlorine. The presence of *E* and *Z* isomers in the mixture was ruled out on the basis of the large difference in chemical shifts of internal and external alkene carbons between the A and M isomers in the ^{13}C NMR spectra. The *E* assignment was based on the high anti-stereoselective nature of ICl additions to terminal alkynes and the close agreement of the ^{13}C NMR data with that reported for (*E*)-chloroiodoalkenes.[2,10]

The anti stereospecificity of these reactions supports the cyclic iodonium ion intermediate previously proposed for electrophilic additions to terminal alkynes.[11-14] In the case of *N*-benzyl-*N*-methylpropargylamine hydochloride (**1b**), the reaction provided the same yield and regioisomeric ratio whether performed in the presence or absence of light or hydroquinone. These observations, therefore, exclude a radical mechanism. The ionic nature of the reaction was expected since a dielectric constant of 7.58 for THF is sufficiently high[15] to promote homolytic cleavage of the ICl bond.[16] The hydrochloride substrate would enhance this process by increasing the ionic strength of the mixture.

Scheme II



Scheme III



1a-d
n = 1 or 2

major product

Since heteroatomic solvents with available lone pairs readily form complexes with ICl,[17-19] it is likely that a hypoiodite iodinating species is involved (Scheme II). The in situ formation of this species would account for the high heat of solvation observed when mixing ICl with THF. Mechanistically, the electrophilic attack by the iodinating species could form a bridged iodonium ion intermediate, which upon subsequent anti attack by chloride would form the (*E*)-chloroiodoalkene (Scheme II).

The regioselectivity observed in products **2a–c** can be explained in terms of an inductive effect. For these reactions the extended Markovnikov rule is obeyed since σ^* for N^+CH_2 is 1.9 and σ^* for H is 0.457.[20] Accordingly, the major product contains internally bound iodine, the A isomer. To determine if the regiochemistry was fixed by

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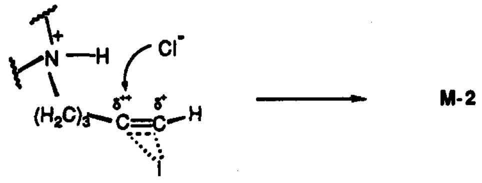
Scheme IV



1e

major product

inductive effects, we synthesized **1d** and **1e** and reacted these substrates with ICl under similar conditions and found the A/M ratio to be 2 and 0.5, respectively.

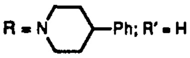
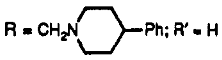
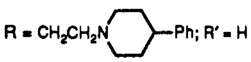
These results support an inductive regiocontrol mechanism. The inductive effect of the positively charged nitrogen results in unsymmetrical bonding of iodine in the intermediate cyclic iodonium ion. The iodine bonding to the internal carbon would be greater and would place the majority of the positive charge on the terminal carbon, which is an energetically favored situation since the positively charged centers are maximally separated as shown in Scheme III. Since the positive charge accumulates on the terminal carbon atom, it becomes more susceptible to nucleophilic attack by chloride, resulting in formation of the A isomer. This preference is maximal for cyclic iodonium ion **1a** as exemplified by an A/M ratio of 4.

In contrast, when the nitrogen is substituted, such as in **1b**, the inductive effect of positive charge on the iodonium ion intermediate is somewhat attenuated, resulting in increased bonding between the external carbon atom and iodine. This leads to increased M isomer formation, decreasing the A/M ratio to 3. The inability of **1c** to fit this regioselective progression is presumably due to steric factors. The anti attack of chloride on the internal carbon atom is hindered by the bulky and rigid nitrogen ring system, thus increasing the probability of attack on the terminal carbon forming an A/M ratio of 5. For verification of the hindering effect of nitrogen substituents, the methyl ammnonium salt of **1b** was synthesized and reacted with ICl under identical conditions. No product was formed, indicating that the addition was prevented by steric factors.

Increasing the distance between the reaction center and the positively charged nitrogen increases M-isomer formation by further increasing iodine bonding to the terminal carbon atom. In progressing from **1d** to **1e**, the majority of charge moves from the external to the internal carbon atom, resulting in an A/M ratio change from 2 to 0.5, respectively (Scheme IV). In accordance with this progression, no inductive effect, as in the addition of ICl to 1-octyne, results in regiospecific formation of the M isomer.[2,4] When these reactions are performed at room temperature, the dependency of the rate of reaction on the inductive effect is reflected in the product yield. All reactions were performed under identical conditions as those described earlier with the exception of temperature. The results are listed in Table III.

The rate of product formation of **1e** > **1d** > **1c**, **1b** > **1a** is in the expected order of the relative stabilities of the iodonium ion transition states. This is expected since the nitrogen of **1a** has no substituents to attenuate the positive charge as in **1b** and **1c**. The destabilization of the transition state results in decreased product formation as indicated by a yield of only 9%, for **1a**, whereas the nitrogen-substituted compounds **1b** and **1c** have slightly higher yields. Greater stability is added to the transition state of **1d** and **1e** by increasing the distance between the positive nitrogen and the iodonium ion, which results in significantly higher yields. This order of reactivity also suggests that formation of the iodonium ion is the rate-determining step since factors that decrease the inductive effect result in an increased rate via increased iodonium ion stability.

Table III. Chloroiodination of Alkynamine Hydrochlorides with Iodine Monochloride at Room Temperature

	ICl addition product 2		
hydrochloride of substrate 1	yield,[a] %	regioisomeric ratio (A/M)[a]	rel rate[a]
a, R = NH_2; R′ = H	9	4.5	1
b, R = $N(CH_3)CH_2Ph$; R′ = H	14	3.2	1.6
c, 	15	all A	1.7
d, 	38	1.8	4.2
e, 	50	0.5	5.6

[a] Determined from the integration of the alkenyl protons of the crude reaction product at 2 h of reaction time. The product and starting material were the only components.

The regiochemistry observed at room temperature is not significantly different than that at elevated temperatures with the exception of **1c**. The reaction of **1c** at room temperature is regiospecific, forming the A isomer. Evidently the system lacks the energy required for chloride to overcome the steric hindrance inherent in attachment to the internal carbon atom. A tenfold dilution of the reaction mixture containing **1b** was made in order to rule out intermolecular ionic contributions to the regiochemistry. This had no effect on the yield or regioisomeric ratio.

Conclusion. The mechanistic interpretation described is in agreement with the experimental findings and provides a plausible explanation for the regiochemistry and rates of ICl addition to the alkynamine hydrochlorides. The regiochemistry is controlled mainly by inductive effects of substituents via destabilization of the iodonium ion intermediate. Three carbons in a straight chain that separate the positively charged nitrogen and the reaction center are necessary to decrease the A/M ratio to less than unity. This provides an idea of the magnitude of the inductive effect on the reaction center caused by the ammonium group and the dampening effect exerted by the carbon–carbon bonds.

We have exploited the utility of this reaction as a direct method for labeling compounds of biological interest by adding [^{125}I]ICl to the alkyne functions of **1b**,**c**,**f**,**g**. The method is especially useful since it incorporates radioactive iodine into molecules containing reactive amines, which are destructive to reagents used in many iododemetalations.[21,22] Furthermore, preliminary studies indicate relative superiority of the A-2 isomer, for certain biological applications, making this synthetic method particularly useful since it produces the A orientation.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrophotometer and are reported in ppm from the internal tetramethylsilane (TMS = 0) standard and deuterated chloroform ($CDCl_3$ = 77.1), respectively. Mass spectral data were obtained by electron impact (EI) and recorded by a ZAB-EQ hybrid mass spectrometer. Chromatography was performed on Analtech 1000-μm preparatory silica gel plates, using

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[21] Srivastava, P. C.; Knapp, F. F., Jr.; Kabalka, G. W.; Kunda, S. A. *Synth. Commun.* **1985**, *15*(4), 355.

[22] Brown, H. C.; Larock, R. C.; Gupta, S. K.; Rajagopalan, S.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6079.

0–15% MeOH in $CHCl_3$ as eluant. Elemental analyses were obtained from Galbraith Laboratories, Knoxville, TN. Propargylamine hydrochloride (**1a**), propargylbromide, *N*-methyl-*N*-benzylpropargylamine (**1b**), 4-phenylpiperidine, 1-butyn-4-yl tosylate, 1-pentyn-5-yl chloride, 1,4-dichlorobutyne, tremorine (**1f**), and anhydrous tetrahydrofuran (THF) were purchased from commercial suppliers. All compounds were analyzed by ^{1}H and ^{13}C NMR. In addition, some representative compounds were also characterized by mass spectral and elemental analyses. Several of these compounds were isolated as oil, which were found to be difficult to analyze, and for these cases the elemental analyses are not reported. All reactions using hazardous chemicals and reagents were performed in a well-ventilated hood to minimize occupational health hazard.

Rate Study. The alkynylamine hydrochloride **1** (0.22 mmol) was dissolved in THF (1 mL) containing ICl (0.26 mmol) and allowed to stand at room temperature protected from light for 2 h. The mixture was partitioned between water (5 mL) and $CHCl_3$ (10 mL) while $Na_2S_2O_3$ was added until the color faded. The mixture was made basic by the addition of 1 N NaOH (2 mL) followed by saturation with sodium chloride. The organic layer was collected and the aqueous phase extracted with additional $CHCl_3$ (10 mL) until the aqueous layer was free of product and starting material, as determined by TLC analysis. The extractions were combined, dried (Na_2SO_4), filtered, and evaporated at room temperature to constant mass providing an oil. The mass of the oil was determined and analyzed by ^{1}H NMR. The spectrum of each oil produced from **1a–e** was consistent with a mixture of starting material and product. Proton integration was used to determine the molar ratio of product to starting material from which the yields were calculated. Over 95% of the mass was accounted for except in the case where propargylamine volatilized with the solvent and the ICl addition product did not.

General Procedure for the Synthesis of the Alkynamines. Preparation of 1c–e,g. A mixture of the amine (8 mmol, 16 mmol for **1g**), alkynylating agent (4 mmol), and THF (15 mL) was refluxed overnight and partitioned between 1 N NaOH (10 mL) and $CHCl_3$ (20 mL). The organic layer was isolated and the aqueous phase extracted once more with $CHCl_3$ (20 mL). The extracts were combined, dried ($MgSO_4$), filtered, and evaporated to provide a residue, which was purified by silica gel (30 g) column chromatography using 0–5% MeOH/$CHCl_3$ as eluant. This provided the alkynylated amine in a 70–80% yield. Physical, spectral, and analytical data are recorded below.

***N*-Propargyl-4-phenylpiperidine (1c)**: white crytals mp 60–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 4 H), 2.25 (m, 4 H), 2.98 (d, br, 2 H), 3.32 (d, 2 H, $J = 2$ H), 7.23 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 33.4 (t), 42.1 (d), 47.2 (t), 53.0 (t), 73.0 (d), 79.1 (s), 126.1 (d), 126.8 (d), 128.4 (d), 146.1 (s).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.55; H, 8.96; N, 6.89.

***N*-(3-Butyn-1-yl)-4-phenylpiperidine (1d)**: oil; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4 H), 1.96 (t, 1, $J = 2$ Hz), 2.20–2.75 (m, 6 H), 2.98 (d, br, 2 H), 7.23 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.9, 33.3, 42.5, 53.9, 57.3, 69.0, 82.8, 126.1, 126.7, 128.4, 146.2.

Anal. Calcd for $C_{15}H_{19}N\cdot 0.2H_2O$: C, 83.05; H, 9.01. Found: C, 82.99; H, 8.77.

***N*-(4-Pentyn-1-yl)-4-phenylpiperidine (1e)**: oil, ^{1}H NMR ($CDCl_3$) δ 1.62–2.55 (m, br, 16 H), 2.98 (d, br, 2 H), 7.20 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.5, 26.0, 33.5, 42.7, 54.3, 57.7, 68.4, 84.1, 126.0, 128.3, 146.3.

Anal. Calcd for $C_{16}H_{21}N\cdot 0.1H_2O$: C, 83.86; H, 9.33. Found: C, 83.76; H, 9.26.

1,4-Bis(4-phenylpiperidinyl)-2-butyne (1g): oil; ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 8 H), 2.10–2.62 (m, br, 6 H), 2.99 (d, br, 4 H), 3.35 (s, 4 H), 7.20 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 33.3, 42.2, 47.6, 53.2, 80.1, 126.1, 126.7, 128.3, 146.1.

Anal. Calcd for $C_{26}H_{32}N_2\cdot 0.2H_2O$: C, 83.02; H, 8.68. Found: C, 82.78; H, 8.52.

General Procedure for the Synthesis of the Alkynamine Hydrochlorides. Preparation of 1b–g. The amine (2 mmol) was dissolved in dry ether (100 mL) followed by the dropwise addition of an ethereal solution of HCl until precipitation ceased. The precipitate was filtered, washed with ether, and dried under vacuum to provide the amine hydrochloride as a white powder in quantitative yield.

General Procedure for the Addition of ICl to the Alkynamine Hydrochlorides. Preparation of 2a–g. To a solution of ICl (0.29 g, 1.6 mmol) in THF (6 mL) was added the alkynamine hydrochloride (0.25 g, 1 mmol), and the solution was refluxed for 2 h under Ar in the absence of light. The mixture was partitioned between 1 N NaOH (10 mL) and $CHCl_3$ (20 mL) while $Na_2S_2O_3$ was added until the color faded. The organic phase was collected, dried ($MgSO_4$), filtered, and evaporated. The residue was loaded onto a silica gel preparatory plate and eluted with 0–15% MeOH/$CHCl_3$. This provided the chloroiodinated alkene in a 22–97% yield. The A and M isomers of **2b** and **2c** were separated by this method. Physical, spectral, and analytical data are listed below.

***N*-((*E*)-2(3)-Chloro-3(2)-iodo-2-propen-1-yl)amine (2a)**: oil; ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 2 H, NH_2), 3.53 (s, 1.6 H, CH_2 of A isomer), 3.62 (s, 0.4 H, CH_2 of M isomer), 6.38 (s, 0.2 H, vinyl H *of M isomer*), 6.50 (s, 0.8 H, vinyl H of A isomer); ^{13}C NMR ($CDCl_3$) δ 48.2 (t, CH_2 of A isomer), 50.1 (t, CH_2 of M isomer), 73.3 (d, CHI of M isomer), 107.4 (s, CI of A isomer), 121.1 (d, CHCl of A isomer), 138.1 (s, CCI of M isomer); MS *m/e* (M^+, rel int) 217 (^{35}Cl) (100).

***N*-Methyl-*N*-benzyl-*N*-((*E*)-2(3)-chloro-3(2)-iodo-2-propen-1-yl)amine (2b)**: M isomer, oil; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3 H, CH_3), 3.45 (s, 2 H, $PhCH_2$), 3.59 (s, 2 H, CH_2CCl), 6.54 (s, 1 H, CHI), 7.31 (s, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 41.5 (q), 61.0 (t), 61.9 (t), 74.4 (d), 126.5 (d), 127.5 (d), 128.5 (d), 135.0 (s), 138.5 (s); MS *m/e* (M^+, rel int) 321 (^{35}Cl) (6.3); A isomer, oil; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3 H, CH_3), 3.21 (s, 2 H, CH_2CI), 3.53 (s, 2 H, $PhCH_2$), 6.63 (s, 1 H, CHCl), 7.31 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 41.6 (q), 60.0 (t), 61.2 (t), 102.7 (s), 120.9 (d), 127.1 (d), 128.2 (d), 129.0 (d), 127.1 (d), 128.2 (d), 129.0 (d), 138.6 (s); MS *m/e* (M^+, rel int) 321 (^{35}Cl) (6.2).

Anal. Calcd for $C_{11}H_{13}NICl\cdot HCl$: C, 36.90; H, 3.94; N, 3.91. Found (A and M mixture): C, 36.73; H, 4.15; N, 3.90.

***N*-((*E*)-2(3)-Chloro-3(2)-iodo-2-propen-1-yl)-4-phenylpiperidine (2c)**: M isomer, oil; ^{1}H NMR ($CDCl_3$) δ 1.71–2.25 (m, 9 H, piperidine H), 3.48 (s, 2 H, CH_2CCl), 6.56 (s, 1 H, CHI), 7.25 (s, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 33.5 (t), 42.4 (d), 53.8 (t), 64.8 (t), 75.7 (d), 125.6 (d), 126.5 (d), 127.1 (d), 134.8 (s), 146.5 (s); MS *m/e* (M^+, rel int) 361 (^{35}Cl) (47); A isomer, oil that crystallizes on standing, mp 51–52 °C; ^{1}H NMR ($CDCl_3$) δ 1.65–2.12 (m, 9 H, piperidine H), 3.26 (s, 2 H, CH_2CI), 6.65 (s, 1 H, CHCl), 7.25 (s, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 33.4 (t), 42.5 (d), 53.7 (t), 61.3 (t), 102.0 (s), 121.1 (d), 126.1 (d), 126.9 (d), 128.4 (d), 146.4 (s); MS *m/e* (M^+, rel int) 361 (^{35}Cl) (48).

Anal. Calcd for $C_{14}H_{17}NICl$: C, 46.50; H, 4.74; N, 3.87. Found (A and M mixture): C, 46.86; H, 4.79; N, 3.81.

***N*-((*E*)-3(4)-Chloro-4(3)-iodo-3-buten-1-yl)-4-phenylpiperidine (2d)**: oil; ^{1}H NMR ($CDCl_3$) δ 1.65–3.15 (m, 13 H, piperidine and alkyl H), 6.32 (s, 0.3 H, CHI), 6.49 (s, 0.7 H, CHCl); ^{13}C NMR, alkyl resonances overlap, δ 73.8 (d, CHI), 99.9 (s, CI), 120.0 (d, CHCl), 125.5 (d), 127.8 (d), 128.9 (d), 136.1 (s, CCl), 146.5 (s); MS *m/e* (M^+, rel int) 375 (^{35}Cl) (43).

***N*-((*E*)-4(5)-Chloro-5(4)-iodo-4-penten-1-yl)-4-phenylpiperidine (2e)**: oil; ^{1}H NMR ($CDCl_3$) δ 1.65–3.19 (m, 15 H, piperidine and alkyl H), 6.29 (s, 0.7 H, CHI), 6.46 (s, 0.3 H, CHCl), 7.25 (s, 5 H, Ar); ^{13}C NMR ($CDCl_3$) alkyl resonances overlap, δ 72.6 (d, CHI), 102.0 (s, CI), 118.9 (d, CHCl), 125.9 (d), 126.8 (d), 128.2 (d), 137.7 (s, CCl), 146.0 (s); MS *m/e* (M^+, rel int) 389 (^{35}Cl) (30).

1,1′-((*E*)-2-Chloro-3-iodo-2-butene-1,4-diyl)dipyrrolidine (2f): oil; ^{1}H NMR ($CDCl_3$) δ 1.80 and 2.61 (m, br, 16 H, pyrrolidine H), 3.57 (s, 2 H, CH_2CI), 3.73 (s, 2 H, CH_2Cl); ^{13}C NMR ($CDCl_3$) δ 23.85, 23.93, 53.59, 53.75 (t, nonequivalent pyrrolidine rings), 63.4 (t), 65.6 (t), 100.6 (s, CI), 130.6 (s, CCl).

Anal. Calcd for $C_{12}H_{20}H_2ICl$: C, 40.64; H, 5.68; N, 7.90. Found: C, 40.86; H, 5.77; N, 7.67.

1,1′-((*E*)-2-Chloro-3-iodo-2-butene-1,4-diyl)bis(4-phenylpiperidine) (2g): oil; 1.65–3.16 (m, 18 H, piperidine), 3.44 (s, 2 H, CH_2CI), 3.67 (s, 2 H, CH_2CCl), 7.23 (s, 10 H, Ar); ^{13}C NMR ($CDCl_3$) δ 33.5 (t, equivalent C-3, C-5, and C′-3, C′-5 of piperidine rings), 42.7 (d, equivalent C-4 of piperidine rings), 53.8 and 54.0 (t, nonequivalent C-2, C-6, and C′-2, C′-6 of piperidine rings), 65.6 (t, CH_2CI), 68.5 (t, CH_2CCl), 103.0 (s, CI), 126.2 (d), 127.0 (d), 128.5 (d), 130.7 (s, CCl), 146.5 and 146.6 (s, nonequivalent C-1 and C′-1 of aromatic rings).

Anal. Calcd for $C_{26}H_{32}N_2ICl$: C, 58.38; H, 6.03; N, 5.24. Found: C, 58.15; H, 6.15; N, 5.04.

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Palladium-Mediated Coupling of a 3-Deoxy Pyranoid Glycal: Stereochemistry of *C*-Glycosyl Bond Formation

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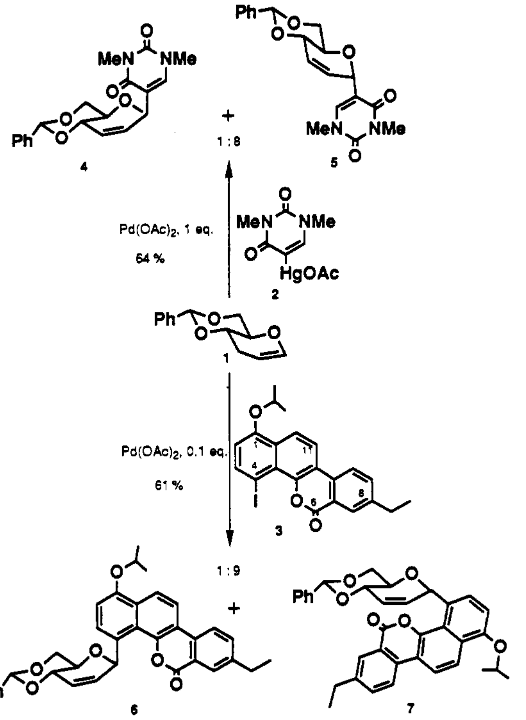
A direct and efficient synthetic route to *C*-glycosides involves palladium-mediated coupling of furanoid or pyranoid glycals (1,2-unsaturated carbohydrates) with appropriate aryl or heterocyclic aglycon derivatives.[1,2] Typical glycals, which bear hydroxy or substituted hydroxy groups (acetoxy, alkoxy, silyloxy) at the allylic (C-3) carbon, undergo palladium-mediated coupling with formation of a *C*-glycosyl bond in a regio-[3] and stereospecific[4] sense. We have now extended this study to include a 3-deoxy pyranoid glycal, 1,5-anhydro-2,3-dideoxy-4,6-*O*-(phenylmethylene)-D-*erythro*-hex-1-enitol[5] (1), in which the allylic (C-3) carbon bears only hydrogen. Pyranoid glycal 1 was subjected to palladium-mediated coupling reactions with (1,3-dimethyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)mercuric acetate[6] (2) in the presence of stoichiometric palladium(II) acetate and with 8-ethyl-4-iodo-1-[(1-methylethyl)oxy]benzo[*d*]naphtho[1,2-*b*]pyran-6-one (3) in the presence of a catalytic portion of palladium acetate.[7] In each of these coupling reactions, a mixture of anomeric α- and β-*C*-glycosides was produced.

Reaction of 3-deoxy glycal 1[5] with organomercurial 2[6] in the presence of stoichiometric palladium acetate in acetonitrile at room temperature yielded a 1:8 mixture of two stereoisomeric *C*-glycosides (4 and 5), which are β- and α-anomers, respectively. Products 4 and 5 were separated from the reaction mixture by sequential silica gel column and thin layer chromatographic steps in 7% and 57% yields, respectively. The β-anomer (4), produced in this reaction, was indistinguishable from an authentic sample synthesized previously by a different route.[8] In a similar reaction, involving palladium-mediated coupling under catalytic conditions,[9] 3-deoxy glycal 1[5] and iodo aglycon derivative 3 produced an anomeric pair of anthracyclic *C*-glycosides (6 and 7) in a ratio of 1:9 (61% combined yield).

In previous studies involving pyranoid glycals[1,7,10-12] attack of the intermediate organopalladium reagent derived from the aglycon derivative (e.g. 2 or 3) has occurred invariably from the face of the glycal opposite the C-3 oxy substituent.[1] In 3-deoxy glycal 1, the remaining chiral centers at C-4 and C-5 are sufficiently remote that approach of the organopalladium reagent to either face of the glycal double bond for π-complex formation[1] appears unimpeded. Nonetheless, as the present results make clear, the absence of stereodirecting groups at C-3 does not preclude significant stereocontrol of π-complex and *C*-glycosyl bond formation. Asymmetry at the more remote sites of the glycal, C-4 and C-5, effects high (8 or 9 to 1) reaction stereoselectivity. This result indicates that a stereo-directing group at carbon C-3 is not essential for synthetically efficient construction of a stereocontrolled *C*-glycosyl linkage.[1]



It is noteworthy that the present result is important in a second respect. Palladium-mediated coupling of a 3-deoxy glycal with an appropriate aglycon derivative leads to intermediate σ-organopalladium adducts (8 and 9, respectively) which must, invariably, decompose to form products by syn β-hydride elimination.[13] This represents

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[13] We have deliniated several different decomposition modes for the intermediate σ-organopalladium adducts formed in these reactions (see 8 and 9). The absence of a leaving group at C-3 other than hydrogen and the lack of reaction mixture acidity[1,8,10] required for palladium elimination with pyran ring opening, leaves β-hydrogen elimination as the only accessible σ-adduct decomposition mode.[1]

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