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Hydrogen Iodide-Promoted Reduction of β-Chlorovinamidinium Salts

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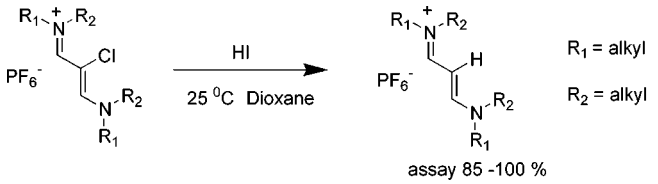
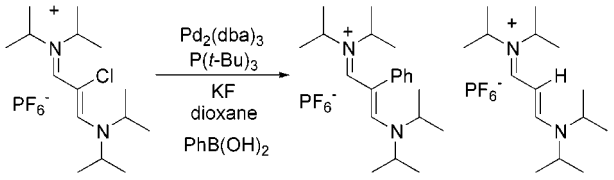
ABSTRACT



HI cleanly reduced chlorovinamidinium salts to the vinamidinium salt in essentially quantitative assay yield and 55–85% isolated yield following recrystallization. The reaction proceeds via protonation of the β-carbon atom of the vinamidinium and dechlorination via the formation of I-Cl.

Vinamidinium salts are synthetically useful intermediates in the synthesis of heterocycles, e.g., pyrroles and pyridines, and may also have materials applications.[1−2] They have also been used for the preparation of other aromatic compounds, e.g., phenols.[3] We have recently started to explore the reactivity of chlorovinamidinium salts which are the most accessible members of this family. The Suzuki cross-coupling reaction of the 2-chloro-*N*,*N*-diisopropylvinamidinium hexafluorophosphate **1a** was selected as a prototypical palladium-catalyzed process. To our knowledge only a single study has examined palladium-catalyzed C−C bond formation of heteroaromatic cations.[4] Probe studies examined the palladium Suzuki cross-coupling reaction using the conditions recently developed by Fu[5] for aryl chlorides (Scheme 1).

Scheme 1



For an initial reaction, the conditions worked remarkably well and the desired phenylvinamidinium **2** was obtained in 65% assay yield. One other compound was observed by HPLC at 20% assay yield and was confirmed to be the reduced vinamidinium **3a** by LC-MS. Buchwald has previously reported the reduction of the aryl chloride in Suzuki reactions[6] which have implicated a "Pd-H" species.[7] However, control experiments revealed that palladium was not involved in the competitive reduction to **3a**. After excluding palladium, further experiments revealed that phosphine and the boronic acid or the boronic acid/halide led to significant reduction at a bath temperature of 100 °C. Further studies revealed that a boric acid/nucleophile combination, e.g.,

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$B(OH)_3$/KI, also led to reduction. In this Letter we describe our studies which have uncovered a remarkable reduction mechanism and have led to a simple, convenient two-step preparation of the parent vinamidinium salts from chloroacetic acid.[8]

In our first panel of experiments, the effect of the acid was examined using iodide as a nucleophile in toluene at 25 °C (Table 1).

Table 1. Reduction of Chlorovinamidinium **1a** to **3a** in Toluene at 0.3 M Using 1.1 equiv of KI and 1.1 equiv of Acid at 25 °C for 14 h

entry	acid	pK_a	**3a** assay yield (%)
1	CH_3CO_2H	4.76	4
2	CF_3CO_2H	−0.25	39
3	CH_3SO_3H	−2.6	30
4	$PhSO_3H$	−3	53
5	HCl	−8.0	86
6	HBr	−9.0	87
7	HI	−10	93

A clear trend was observed, and the stronger the acid the higher the rate and assay yield of reduced product. The mass balance closed and is accounted for by unreacted starting material. The use of HI alone in the absence of KI led to the formation of **3a** in 94% assay yield. The reactions were accompanied by the generation of an orange/brown coloration which we speculated to be I-Cl. The identity was confirmed qualitatively by thiosulfate /starch−iodide titration and capillary zone electrophoresis.

With HI selected as the optimal acid−nucleophile partner, we examined the effect of solvent in our next panel of experiments (Table 2). Dioxane proved to be an optimal

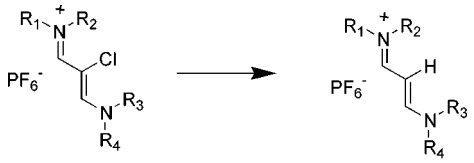
Table 2. Reduction of Chlorovinamidinium **1a** to **3a** at 0.2−0.3 M Using 1.1 equiv of 57% Aqueous HI at 25 °C

entry	solvent	time (h)	**3a** assay yield (%)
1	toluene	14	81
2	dioxane	2.5	95
3	CH_2Cl_2	14	84
4	THF	14	85
5	methanol	14	0

solvent in terms of rate and yield although all of the reactions were complete after 14 h with the exception of methanol which failed to lead to reaction under these conditions.[9]

The reduced compound **3a** was isolated in analytically pure form after a simple aqueous workup and recrystallization in an unoptimized 83% yield.[10] With optimal conditions for the reduction determined, the scope of the reaction was examined using a range of nitrogen-substituted vinamidinium salts (Table 3). The chlorovinamidinium salts **1a**−**d** were prepared

Table 3. Reduction of Chlorovinamidinium Salts **1a**−**g** to **3a**−**g** in Dioxane at 0.2−0.3 M Using 1.1 equiv of 57% Aqueous HI at 25 °C for 14 h



1 a - g **3 a - g**

entry	vinamidinium	assay yield (%)	isolated yield (%)
1	**1a**, R_{1-4} = *i*-Pr	95	83
2	**1b**, $R_1, R_2, R_3, R_4 = (CH_2)_5$	100	85
3	**1c**, R_{1-4} = Me	69 (85)	55
4	**1d**, R_1, R_3 = Ph, R_2, R_4 = Me	0	
5	**1e**, R_2 = Me, R_3 = Me, $R_1, R_4 = (CH_2)_2$	55	49
6	**1f**, R_1, R_2 = *i*-Pr, $R_3, R_4 = (CH_2)_4$	97	82
7	**1g**, R_1 = Ph, R_2 = Me, $R_3, R_4 = (CH_2)_5$	0	

from the corresponding commercially available formamides, which significantly extends the scope of the formylation reaction. **1e** was prepared by a substitution reaction of **1c** with the dimethylethylene diamine. **1f**,**g** were prepared by straightforward monosubstitution reactions of **1a** and **1d** in toluene with pyrrolidine and piperidine, respectively, followed by recrystallization from ethanol.[11] These differentially masked 1,3-dicarbonyl compounds may prove to be synthetically useful.

The piperidinyl derivative **1b** (entry 2) behaved in essentially the same manner as the *N*,*N*-diisopropyl analogue, and the reduced product was isolated in 99% crude yield (>99 A% by HPLC) and an unoptimized 85% yield following recystallization from ethanol. In the case of dimethylamino vinamidinium **1c** (entry 3), the yield was

(8) The chlorovinamidinium hexafluorophosphate salt **1a** was prepared from the commercially available diisopropyl formamide by a slight modification of the procedure published for dimethylformamide. Davies, I. W.; Marcoux, J.-F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. *J. Org. Chem.* **2000**, *65*, 4571.

(9) Addition of KI restored the reactivity, and **3a** was formed in 78% assay yield.

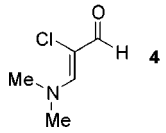
(10) **Representative procedure:** To a solution of **1a** (1.00 g, 0.24 mmol) in dioxane (10 mL) at 25 °C was added hydrogen iodide (57 wt % aq., 0.35 mL, 1.1 equiv). The mixture rapidly developed an orange/brown color and was monitored by HPLC for the complete consumption of starting material (2.5 h). The mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen sulfite followed by water. The extract was concentrated to a yellow solid which was recrystallized from ethanol to give 0.765 g of an off-white solid (83%): mp 262−263 °C (decomp); ^{1}H NMR (400 MHz $CDCl_3$) δ 1.33 (d, 18 H, J = 6.8 Hz), 1.39 (d, 18H, J = 6.8 Hz), 3.81 (septet, 2H, J = 6.8 Hz), 4.13−4.19 (m, 2H), 5.48 (t, 1H, J = 11.8 Hz), 7.79 (d, 2H, J = 11.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.7, 22.9, 50.7, 50.9, 90.1, 159.3. Anal. Calcd for $C_{15}H_{31}F_6N_2P$: C, 46.87; H, 8.13; N, 7.29. Found: C, 46.94; H, 8.25; N, 7.22.

(11) We are aware of one other method for the preparation differentially substituted vinamidinium salts. The β-F vinamidinium iodides were prepared in a rather unique reaction of a geminyl difluoride. Yamanaka, H.; Yamashita, S.; Isihara, T. *Tetrahedron Lett.* **1992**, *33*, 357. Yamanaka, H.; Yamashita, S.; Isihara, T. *Synlett* **1993**, 353. Kase, K.; Katayama, M.; Ishirara, T.; Yamanaka, H.; Gupton, J. T. *Chem. Lett.* **1997**, *9*, 893. Kase, K.; Katayama, M.; Ishirara, T.; Yamanaka, H.; Gupton, J. T. *J. Fluorine Chem.* **1998**, *90*, 29.

somewhat depressed by competing hydrolysis reaction to the vinylogous amide **4**.[12] However, increasing the concentration of the nucleophile by the addition of 1 equiv of KI restored the yield to acceptable levels. The *N*,*N*-dimethyl analogue **3c** has previously been prepared from propargyl alcohol or ethyl vinyl ether.[13] The 1,4-diazepinium hexafluorophosphate salt **1e** (entry 5) was also reduced under these conditions.

The *N*-methylaniline derivative **1d** (entry 4) failed to give **3d**,[14] and monosubstitution with piperidine (entry 7) failed to restore the reactivity. In both cases, additional iodide did not lead to reactivity and presumably the aniline substantially reduces the basicity of vinamidinium salts.

The use of bromo- and iodovinamidinium salts **5** and **6** [8] was briefly examined, but in these cases only decomposition was observed.



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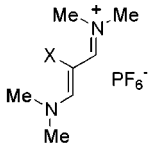
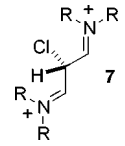


5 X = Br
6 X = I

The mechanistic hypothesis consistent with all our observations is as follows. Protonation at the β-carbon of the vinamidinium to give the dication **7** initiates the reaction and nucleophilic attack at Cl generates the reduced vinamidinium and I-Cl. This mechanism is reminiscent of the Meyer



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method[15] for determination of enolic content in haloketones using acidified potassium iodide and joins the small class of reactions involving nucleophilic attack at chloride.

In summary, we have described a novel reduction of chlorovinamidinium salts **1a**−**f** promoted by HI. This reaction coupled with the general formylation of chloroacetic acid represents an efficient, straighforward way to prepare a series of vinamidinium salts **3a**−**f**. The data obtained from this study should enable us to optimize the Suzuki reaction to minimize the competing reduction pathway, and this is the focus of our current research.

Supporting Information Available: Combustion analysis and NMR spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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