Preparation and Novel Reduction Reactions of Vinamidinium Salts

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Substituted acetic acids and formamides react in the presence of phosphorus oxychloride to yield the vinamidinium hexafluorophosphate salts **5a**−**d**, **6a**−**d**, and **7** in moderate to good unoptimized recrystallized yields (40−67%) as easily handled nonhygroscopic solids. The 1,3-differentially substituted vinamidinium salts **8** was prepared by amine exchange in 81% yield as are the cyclic diazapinium salts **9** and **10** in >76% yield. The symmetrical 2-chlorovinamidinium **11** was prepared by displacement of **3** in 71% yield. The 2-chlorovinamidinium salts are cleanly reduced to the parent vinamidinium salts **12**−**16** using HI or PPh_3/pTSA in up to 99% assay yield.

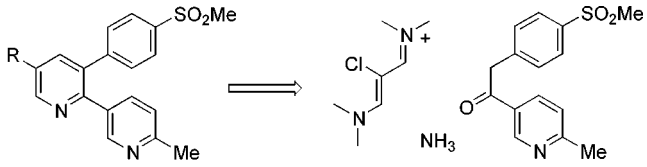
Introduction

Etoricoxib **1** has recently been identified by Merck as a very potent and specific COX-2 inhibitor that may provide therapeutically useful alternatives to traditional NSAIDs with a greater GI safety profile.[1]

We have described how Etoricoxib can be assembled by construction of the central pyridine ring (Scheme 1) with the introduction of the C-5 substituent in a single step from the readily accessible ketone **2**, the vinamidinium species **3** (CDT-phosphate), and ammonia.[2] As a result of these studies CDT-phosphate **3** has become available in commercial quantities. A wide range of other functionalized pyridines have also been prepared by extension of this methodology to substituted vinamidinium salts and aldehyde, ketone,[3] ester, or acid enolates.[4] Vinamidinium salts have also been used very effectively by Gupton for the synthesis of pyrroles,[5] pyrimidines,[6] and pyrazoles.[7] While vinamidinium salts typically react as electrophiles, they also behave as nucleophiles,for example, in nitration reactions.[8]

We have previously described an improved preparation of *N*,*N*-dimethylvinamidinium hexafluorophosphate salts from substituted acetic acids and *N*,*N*-dimethylformamide.[9,10] In this paper we describe the extension of this reaction to more complex formamides and the conversion

Scheme 1



Etoricoxib **1** **3** **2**

of these symmetrical vinamidinium salts into cyclic derivatives and 1,3-differentially substituted salts. We also provide full details of our studies on the reduction of 2-chlorovinamidinium salts.[11]

Results and Discussion

N,N-Disubstituted Vinamidinium Salts. A number of synthetic applications of vinamidinium salts that we are currently pursuing required the use of alkyl and aryl groups at nitrogen. With the extensive precedent for the use of formamides other than DMF (most notably *N*-methylformanilide)[12] in the formylation of aromatic compounds, reaction of the intermediate chloro-iminium species with substituted acetic acids should be feasible. The initial reactions to test the hypothesis were performed with *N*-formylpiperidine and chloroacetic acid **4a** (Scheme 2). The reaction proceeded smoothly using the standard conditions (4−5 equiv of formamide) to cleanly give the vinamidinium chloride as judged by NMR and HPLC analysis.[13] As in the case of DMF, CO_2 was evolved after approximately 50% of the phosphorus oxychloride

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(1) Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, J. L.; Young, R. N. *Bioorg. Med. Lett.* **1998**, *8*, 2777.

(2) Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J. *Org. Chem.* **2000**, *65*, 8415.

(3) Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339.

(4) Davies, I. W.; Marcoux, J.-F.; Reider, P. J. *Org. Lett.*, in press.

(5) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W. Sikorski, J. A. *J. Org. Chem.* **1990**, *55*, 4735.

(6) Gupton, J. T.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Vargas, M.; Hosein, K. N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689

(7) Kase, K.; Katayama, M.; Ishirara, T.; Yamanaka, H.; Gupton, J. T. *J. Fluor. Chem.* **1998**, *90*, 29.

(8) Kucera, J.; Arnold, Z. *Collec. Czech. Chem. Commun.* **1967**, *32*, 1704.

(9) 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.

(10) For the first account of a vinamidinium hexafluorophosphate salts see: Gupton, J. T.; Hicks, F. A.; Smith, S. Q.; Main, A. D.; Petrich, S. A.; Wilkinson, D. R.; Sikorski, J. A.; Katritzky, A. *Tetrahedron* **1993**, *49*, 10205.

(11) Davies, I. W.; Taylor, M.; Hughes, D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 3385.

(12) Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225−342.

(13) A reverse phase ion-pairing HPLC method was developed for analysis of vinamidinium salts using a YMC Basic column and acetonitrile/4 mM heptanesulfonic acid sodium salt as mobile phase.

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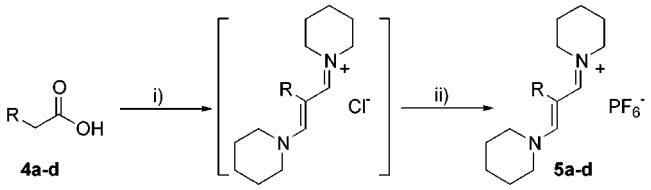
Scheme 2[a]

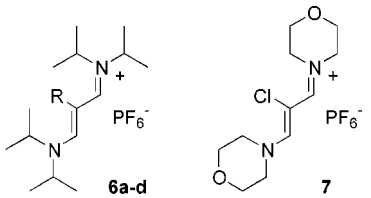


[a] (i) $POCl_3$, *N*-formylpiperidine, 70−75 °C; (ii) $NaPF_6$, aqueous ethanol.

Table 1. Preparation of *N,N*-Disubstituted Vinamidium Salts 5 and 6

entry	R =	yield, %
1	Cl, **5a**	61
2	Ph, **5b**	59
3	4-F−C_6H_4, **5c**	67
4	4-(OMe)-C_6H_4, **5d**	60
5	Cl, **6a**	55
6	Ph, **6b**	40
7	4-F-C_6H_4, **6c**	42
8	4-(OMe)-C_6H_4, **6d**	45

was added. When the reaction mixture was added to aqueous hexafluorophosphate, the salt precipitated, but due to the more lipophilic nature of the *N*-formylpiperidine, the excess reagent formed an oily layer and led to the isolation of a tacky product. To overcome this problem, only a slight excess (2−3 equiv) of the appropriate formamide was used. The hexafluorophosphate salt was prepared using $NaPF_6$ in ethanol or aqueous ethanol. The crude chloride was typically isolated in >75% yield and can be used "as is" in a number of applications. The analytically pure material was obtained in 61% unoptimized yield from ethanol. The reaction proved to be general, and a range of 2-arylvinamidinium salts **5b**−**d** were also prepared (Table 1). *N,N*-Diisopropylformamide also behaved quite effectively, and the derivatives **6a**−**d** were also prepared in 40−55% unoptimized recrystallized yield. Single-crystal X-ray analysis of **6c** revealed an all

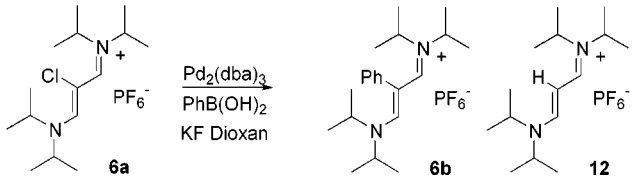


"W" conformation with the aryl group residing orthogonal to the vinamidinium π-system as expected. Bond angles and lengths were in the expected range.[9] *N*-Formylmorpholine led to vinamidinium **7** in low yield (<10%), and a pure sample could not be obtained using this approach.

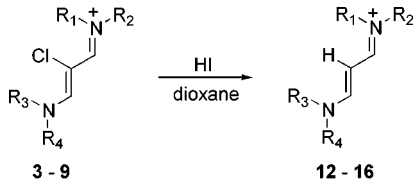
All of the yields are rather modest but the formylation reaction did provide a rapid entry to these 2-substituted vinamidinium hexafluorophosphate salts.

1,3-Differentially Substituted Vinamidinium Salts. Mechanistic studies in a number of our programs required vinamidinium salts that have differential steric or electronic properties at the termini, and these molecules have become important targets. To our knowledge, only one method has been reported for the preparation of differentially substituted vinamidinium salts, and in this case 2-fluorovinamidinium iodides were prepared in a rather unique reaction of a geminyl difluoride.[14] Reaction of the *N,N*-diisopropylvinamidinium salt **6a** with 1

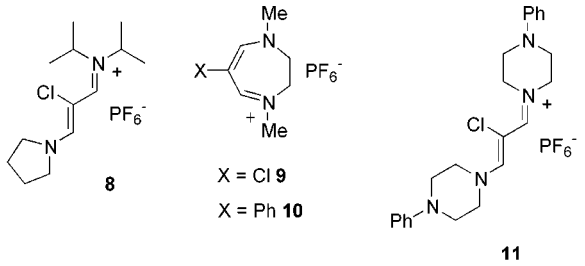
Scheme 3[a]



Scheme 4



equiv of pyrrolidine in toluene at 90 °C gave the differentially substituted vinamidinium **8** in 99% crude yield and an unoptimized 81% following recrystallization from ethanol. CDT-phosphate **3** also underwent substitution reactions (toluene, 40 °C). For example, reaction with *N,N*-dimethylethylenediamine gave the 1,4-diazepinium hexafluorophosphate **9** in 80% yield following recrystallization, and the phenyl derivative **10** was also prepared in an analogous manner (76%).[15] The symmetrical *N*-phenylpiperazine derivative **11** was prepared in 75% yield significantly extending the availability of symmetrical analogues when the corresponding formamide is unavailable.



Reduction of 2-Chlorovinamidinium Salts. During the course of the development of a Suzuki cross-coupling reaction of the 2-chlorovinamidinium of **6a** in addition to the desired compound **6b**, the reduced compound **12** was obtained in up to 20% assay yield (Scheme 3). Although the focus of the research remained the Suzuki reaction, the reduction was pursued at some length. There are no general preparations of the parent vinamidinium salts[16] which are important precursors to other substrates which are inaccessible via the formylation reaction, e.g., 2-nitro.

Previous studies have implicated "Pd−H" in the reduction of aryl chlorides in the Suzuki reaction.[17] Control

(14) 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. Fluor. Chem.* **1998**, *90*, 29.

(15) For other cyclic vinamidinium salts prepared from the malonaldehyde derivatives see: Reichardt, C.; Budnik, U. *Chem. Ber.* **1990**, *123*, 2023. Reichardt, C.; Halbritter, K. *Liebigs Ann. Chem.* **1975**, 470.

(16) For a preparation of the parent *N,N*-dimethylvinamidinium hexafluorophophate salt, see: Arnold, Z.; Dvorak, D.; Havranek, M. *Collec. Czech. Chem. Commun.* **1996** *61* 1637. See also: Malhorta, S. S.; Whiting, M. C. *J. Chem. Soc.* **1960** 3812.

(17) Wolfe, J. P.; Singer, R. A.; Young, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.

Table 2. Reduction of Chlorovinamidium Salt 6a to 12 with *p*-Toluenesulfonic Acid

entry	nucleophile	assay yield of **12**, %
1	KF	–
2	KCl	7
3	KBr	17
4	KI	81
5	PPh_3	93
6	P-(*t*-Bu)$_3$	–

Table 3. Reduction of Chlorovinamidinium 6a to 12 in Presence of Various Acids[a]

entry	acid	pK_a	assay yield of **12** (%)
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] Reduction of chlorovinamidinium **6a** to **12** in toluene at 0.3 M using 1.1 equiv of KI and 1.1 equiv of acid at 25 °C for 14 h.

experiments excluding palladium implicated the phosphine or KF in the presence of boronic acid in the competitive reduction to **12**. Either combination led to significant reduction in dioxane at 100 °C, and significantly the use of wet reagents further promoted the reduction pathway to **12**. Substituting the phenylboronic acid by $B(OH)_3$ and KI for KF further enhanced the reduction. These preliminary results led to the hypothesis that an electrophile (H^+)/nucleophile partnership was involved in the reduction.

A range of nucleophiles was examined for the reduction of **6a** to **12** in dichloromethane at 25 °C using *p*-toluenesulfonic acid as a representative acid (Table 2). All of the reactions were performed for 14 h, and the mass balance is accounted for by unreacted starting material. Potassium iodide (entry 4) clearly outperforms the other halides. Triphenylphosphine performs very well, which might be due to the effective concentration of the nucleophile in dichloromethane. Under similar conditions, the 2-chlorovinamidinium salts **3** and **5a** were reduced to **14** and **13** in >87% assay yield. However, the net introduction of a hydrogen atom using pTSA/PPh_3 seemed egregious[18] even though it confirmed the electrophile(H^+)/nucleophile hypothesis. Further optimization uncovered a more practical solution.

The effect of acid strength was examined in our next panel of experiments using toluene as solvent at 25 °C (Table 3).

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 **12** 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.

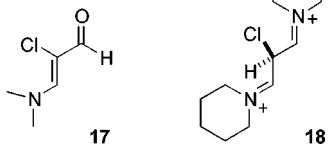
With HI selected as the optimal acid−nucleophile partner, we examined the effect of solvent in our next panel of experiments (Table 4). Dioxane proved to be an optimal solvent in terms of rate and yield although all of the reactions were complete after 14 h with the exception of methanol, which failed to lead to reaction under these conditions. The reduced compound was isolated in analytically pure form after a simple aqueous workup and recrystallization in an unoptimized 83% yield. With optimal conditions for the reduction determined, the scope of the reaction was examined using a range of nitrogen-substituted vinamidinium salts.

Table 4. [b]Effect of Solvent in the Reduction of Chlorovinamidinium Salt 6a to 12

entry	solvent	time (h)	assay yield (%) of **12**
1	toluene	14	81
2	dioxane	2.5	95
3	CH_2Cl_2	14	84
4	THF	14	85
5	methanol	14	0

[b] Reduction of chlorovinamidinium **6a** to **12** at 0.2−0.3 M using 1.1 equiv of 57% aq HI at 25 °C.

The 1,3-bis(piperidinyl) derivative **5a** (entry 1) behaved in essentially the same manner as the *N*,*N*-diisopropyl analogue, and the reduced product **12** was isolated in 99% crude yield (>99 A% by HPLC) and an unoptimized 85% yield following recystallization from ethanol. In the case of the (*N*,*N*-dimethylamino)vinamidinium **3** (entry 3) the yield was somewhat depressed by the competing hydrolysis reaction to the vinylogous amide **17**.[19] However, increasing the concentration of the nucleophile by the addition of 1 equiv of KI restored the yield of **14** to 85% assay. While this is acceptable, the use of the anhydrous conditions (triphenylphosphine/pTSA) provides superior results leading to **14** with 93% assay and 75% isolated yield. The bis-*N*,*N*-dimethylvinamidinium has previously been prepared from propargyl alcohol or ethyl vinyl ether.[16]



17 **18**

The use of other 2-substituted bis-*N*,*N*-dimethylvinamidinium salts, e.g., Br, I, CF_3,[9] using either the HI or PPh_3 conditions only led to decomposition.

The mechanistic hypothesis consistent with all our observations is as follows. Protonation at the β-carbon of the vinamidinium to give the dication **18** initiates the reaction, and nucleophilic attack at Cl generates the reduced vinamidinium and I−Cl. This mechanism is reminiscent of the Meyer method[20] for determination of enolic content in haloketones using acidified potassium iodide and joins the small class of reactions involving nucleophilic attack at chloride.

With this mechanism in mind we have briefly attempted to use other electrophiles to initiate the reaction with **3**. Me-I, TMS-I, 1-chloro-1-methylsilacyclobutane,

(18) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(19) Arnold, Z. *Collect. Commun. Czech. Chem. Commun.* **1961**, *26*, 3051. Spectroscopic data is provided in the Experimental Section.

(20) Meyer, K. H. *Ann.* **1911**, *320*, 212.

Table 5. Reduction of Chlorovinamidinium Salts with HI in Dioxane[c]

entry	chlorovinamidinium	reduced vinamidinium	assay yield (%)	isolated yield (%)
1	**5a**, R_1, R_2, R_3, $R_4 = (CH_2)_5$	**13**, R_1, R_2, R_3, $R_4 = (CH_2)_5$	100	85
2	**6a**, $R_{1-4} = i$-Pr	**12**, $R_{1-4} = i$-Pr	95	83
3	**3**, R_{1-4} = Me	**14**, R_{1-4} = Me	69 (85)	55
4	**9**, R_1, R_3 = Me, R_2, $R_4 = (CH_2)_2$	**15**, R_1, R_3 = Me, R_2, $R_4 = (CH_2)_2$	55	49
5	**8**, R_1, $R_2 = i$-Pr, R_3, $R_4 = (CH_2)_4$	**16**, R_1, $R_2 = i$-Pr, R_3, $R_4 = (CH_2)_4$	97	82

[c] Reduction of chlorovinamidinium salts in dioxane at 0.2−0.3 M using 1.1 equiv of 57% aq HI at 25 °C for 14 h.

CH_3COCl/KI, or "NO_2^+"/KI failed to give any of the substituted vinamidinium species.

Summary

We have described a straightforward method for the synthesis of substituted trimethinium salts. The novel acid-promoted reduction of the 2-chlorovinamidinium salts provides a straightforward preparation of synthetically useful parent vinamidinium salts. The procedures provide access to compounds that are useful in heterocyclic synthesis and materials applications.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Water content was determined by Karl Fischer titration.

5a: 2-Chloro-1,3-bis(piperidinyl)trimethinium Hexafluorophosphate. General Procedure. Chloroacetic acid (4.75 g, 0.05 mol) was added to *N*-formylpiperidine (13.5 mL, 15.5 mol), and the mixture was heated to 70 °C to give a clear yellow solution. Phosphorus oxychloride (9.5 mL, 0.10 mol) was added at 5 mL/h maintaining the temperature at 70 °C, and the mixture was heated for 3 h. The mixture was cooled to ambient temperature. The reaction mixture was added over 0.5 h to a solution of sodium hexafluorophosphate (9 g, 0.05 mol) in water/ethanol (9:1, 100 mL) at a temperature <10 °C. The mixture was aged for 0.5 h and then filtered washing the crude solids with water. The crude solid was recrystallized from ethanol/water (5:1) by heating to ∼70 °C. The mixture was cooled to 0 °C and filtered. The light yellow solid was washed with cold ethanol and dried in vacuo to give **5a** as a colorless to light yellow solid (12.0 g, 61%). mp 201.2 °C (DSC); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76−1.82 (m, 12 H), 3.63 (t, 4H, J = 5.18 Hz), 4.14−4.16 (m, 4H), 7.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 26.3, 26.9, 48.7, 59.8, 91.3, 158.6. Anal. Calcd for $C_{13}H_{22}ClF_6N_2P$: C, 40.37; H, 5.73; N, 7.24. Found: C, 40.33; H, 5.75; N, 7.37.

Representative Procedure for HI Reduction. To a solution of **6a** (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 sat. 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 **12** as an off-white solid (83%). mp 262−263 °C (decomp); ^{1}H NMR (400 MHz $CDCl_3$) δ 1.33 (d, 12 H, J = 6.8 Hz), 1.39 (d, 12H, J = 6.8 Hz), 3.78−3.83 (m, 2H,), 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 (100 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.

Representative Procedure for pTSA/PPh_3 Reduction. To a solution of **6a** (1.00 g, 0.24 mmol) in dichloromethane (15 mL) at 25 °C were added triphenylphosphine (0.69 g, 1.1 equiv) and *p*-toluensulfonic acid (0.55 g, 1.1 equiv), and the mixture was stirred at 25 °C for 5 h. The mixture was worked up in an analogous manner to the HI reaction.

2-Chloro-1,3-bis(diisopropylamino)trimethinium hexafluorophosphate (6a): obtained as a light yellow solid. mp 122−123 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 1.34 (d, 12H, J = 6.6 Hz), 1.41 (d, 12H, J = 6.8 Hz), 3.77−3.92 (m, 2H), 5.31−5.44 (m, 2H), 7.57 (s, 2H). ^{13}C NMR (100 MHz $CDCl_3$) δ 20.4, 22.8, 50.9, 51.6, 93.1, 156.9. Anal. Calcd for $C_{15}H_{29}ClF_6N_2P$: C, 43.02; H, 7.22; N, 6.69; Found: C, 43.26; H, 7.25; N, 6.69.

2-Phenyl-1,3-bis(diisopropylamino)trimethinium hexafluorophosphate (6b): obtained as a pale yellow solid; mp 217−219 °C (decomp); ^{1}H NMR (400 MHz, MeOD-d_4): δ 0.91 (d, 12 H, J = 6.7 Hz), 1.46 (d, 12 H, J = 6.8 Hz), 3.60−3.67 (m, 2H), 3.81−3.91 (m, 2H), 7.36−7.42 (m, 2H), 7.48−7.55 (m, 3H), 7.78 (s, 2H); ^{13}C NMR (75 MHz, MeOD-d_4): δ 19.5, 23.0, 50.2, 50.3, 106.1, 129.3, 129.7, 129.9, 135.8, 159.6. Anal. Calcd for $C_{21}H_{35}F_6N_2P$: C, 54.77; H, 7.66; N, 6.08. Found: C, 54.93; H, 7.75; N, 5.99

2-(4-Fluorophenyl)-1,3-bis(diisopropylamino)trimethinium hexafluorophosphate (6c): obtained as a pale yellow solid; mp 196−197 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, 12H, J = 6.7 Hz), 1.49 (d, 12H, 6.8 Hz), 3.49−3.71 (m, 4H), 7.13−7.19 (m, 2H), 7.28−7.30 (m, 2H), 7.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 22.9, 50.0, 50.3, 104.6, 116.8 (d, J = 21.4 Hz) 131.3 (d, J = 3.8 Hz), 131.6 (d, J = 8.0 Hz), 159.5, 162.9 (d, J = 250.7 Hz). Anal. Calcd for $C_{21}H_{34}F_7N_2P$: C, 52.71; H, 7.16; N, 5.85. Found: C, 51.40; H, 6.69; N, 5.63.

2-(4-Methoxyphenyl)-1,3-bis(diisopropylamino)trimethinium hexafluorophosphate (6d): obtained as a pale yellow solid; mp 212−213 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, 12H, J = 6.8 Hz), 1.45 (d, 12H, J = 6.8 Hz), 3.62−3.75 (m, 4H), 3.87 (s, 3H), 6.96 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 8.8 Hz), 7.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 23.0, 50.0, 50.2, 55.4, 105.7, 115.1, 127.1, 130.9, 160.0, 160.1. Anal. Calcd for $C_{22}H_{37}F_6N_2OP$: C, 53.87; H, 7.60; N, 5.71. Found: C, 53.82; H, 7.65; N, 5.65.

2-(Phenyl)-1,3-bis(piperidyl)trimethinium hexafluorophosphate (5b): obtained as a white solid; mp 226−228 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27−1.31 (m, 4H), 1.57−1.60 (m, 4H), 1.75−1.78 (m, 4H), 2.81 (t, 4H, J = 5.5 Hz), 3.58 (t, 4H, J = 5.5 Hz), 7.25−7.28 (m, 2H), 7.42−7.44 (m, 3H), 7.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 25.4, 26.7, 48.2, 59.2, 104.1, 129.2, 129.6, 130.6, 133.6, 162.0. Anal. Calcd for $C_{19}H_{27}F_6N_2P$: C, 53.27; H, 6.35; N, 6.54. Found: C, 53.03; H, 6.32, N, 6.48.

2-(4-Fluorophenyl)-1,3-bis(piperidyl)trimethinium hexafluorophosphate (5c): obtained as a pale yellow solid; mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31−1.33 (m, 4H), 1.58−1.62 (m, 4H), 1.76−1.78 (m, 4H), 2.83 (t, 4H, J = 5.6 Hz), 3.59 (t, 4H, J = 5.6 Hz), 7.15 (dd, 2H, J = 8.6 Hz, 8.6 Hz), 7.27−7.29 (m, 2H), 7.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 25.4, 26.7, 48.2, 59.2, 102.8, 116.8 (d, J = 21.4 Hz), 129.4 (d, J = 3.8 Hz), 132.4 (d, J = 8.0 Hz), 162.3, 163.0 (d, J = 250.7 Hz). Anal. Calcd for $C_{19}H_{26}F_7N_2P$: C, 51.12; H, 5.87; N, 6.28. Found: C, 51.02; H, 5.84, N, 6.20.

2-(4-Methoxyphenyl)-1,3-bis(piperidyl)trimethinium hexafluorophosphate (5d): obtained as a pale yellow solid; mp 145−146 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29−1.35 (m, 4H), 1.57−1.62 (m, 4H), 1.73−1.76 (m, 4H), 2.86 (t, 4H, J = 5.5 Hz), 3.58 (t, 4H, J = 5.5 Hz), 3.85 (s, 3H), 6.96 (d, 2H, J = 2.0 Hz), 7.14 (d, 2H, J = 2.0 Hz), 7.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 25.5, 26.7, 48.1, 55.3, 59.1, 103.7, 114.9, 124.9, 131.6, 160.1, 162.4. Anal. Calcd for $C_{20}H_{29}F_6N_2OP$: C, 52.40; H, 6.38; N, 6.11. Found: C, 52.42; H, 6.42, N, 6.09.

2-Chloro-1-diisopropylamino-3-pyrrolidinotrimethinium hexafluorophosphate (8): obtained as a colorless solid;

mp 163−164 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, 6H, J = 6.7 Hz), 1.41 (d, 6H, J = 6.8 Hz), 1.90−1.98 (m, 2H), 2.04−2.11 (m, 2H), 3.77−3.84 (m, 1H), 3.94 (t, 2H, J = 6.9 Hz), 4.10 (t, 2H, J = 6.7 Hz), 5.39−5.46 (m, 1H), 7.59 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 23.1, 23.6, 26.0, 50.1, 50.8, 50.9, 57.3, 93.4, 155.9, 158.9. Anal. Calcd for $C_{13}H_{24}ClF_6N_2P$: C, 40.16; H, 6.22; N, 7.21. Found: C, 40.34; H, 6.43; N, 7.14.

6-Chloro-1,4-dimethyl-2,3-dihydro-1,4-diazepinium Hexafluorophosphate (9). Representative procedure for amine exchange: To a slurry of CDT-phosphate **3** (12.2 g, 0.04 mol) in toluene (50 mL) was added *N*,*N*-dimethylethylenediamine (4 mL, 0.04 mol), and the mixture was heated at 40 °C for 1 h. The solvent was removed in vacuo at 40−50 °C, and the residue was recrystallized from ethanol/water (95:5) to give the diazepinium **11a** as an off-white solid (9.6 g, 80%); mp 150.4 °C (DSC); ^{1}H NMR (400 MHz, DMF-d_7): δ 3.57 (s, 6H), 3.90−3.96 (br.s., 4H), 8.21 (s, 2H); ^{13}C NMR (100 MHz, DMF-d_7): δ 47.3, 56.3, 92.7, 157.6. Anal. Calcd for $C_7H_{12}ClF_6N_2P$: C, 27.60; H, 3.97; N, 9.20. Found: C, 27.60; H, 3.90; N, 8.88.

6-Phenyl-1,4-dimethyl-2,3-dihydro-1,4-diazepinium hexafluorophosphate (10): obtained as a colorless solid. mp 176−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 6H), 4.07 (br s., 4H), 7.29−7.45 (5H, m), 8.13 (s, 2H). Anal. Calcd for $C_{13}H_{15}F_6N_2P$: C, 45.09; H, 4.95; N, 8.09. Found: C, 44.65; H, 4.80; N, 7.97.

2-Chloro-1,3-bis(*N*′-phenyl-*N*-piperazinyl)trimethinium hexafluorophosphate (11): obtained as a yellow solid: mp 217−221 °C (decomp); ^{1}H NMR (400 MHz, DMF-d_7): 3.40−3.55 (m, 8H), 3.95−4.05 (m, 4H), 4.45−5.55 (m, 4H), 6.84 (t, 2H, J = 7.5 Hz), 7.04 (t, 4H, J = 7.5 Hz), 7.31 (t, 4H, J = 7.5), 8.17 (s, 2H), ^{13}C NMR (100 MHz, DMF-d_7): δ 47.9, 48.8, 49.6, 57.6, 92.1, 116.3, 120.2, 129.4, 150.6, 159.5. Anal. Calcd for $C_{15}H_{31}F_6N_2P$: C, 51.1; H, 5.2; N, 10.4. Found: C, 51.1; H, 5.2; N, 10.3.

1,3-Bis(piperidyl)trimethinium hexafluorophosphate (13): obtained as a colorless solid; mp 109−112 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72−1.77 (br, 12 H), 3.43−3.53 (br s., 4H), 3.53−3.59 (br s., 4H), 5.31 (t, 1H, J = 11.7 Hz), 7.61 (d, 2H, J = 11.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 25.1, 26.4, 47.4, 56.5, 88.2, 161.5. Anal. Calcd for $C_{13}H_{23}F_6N_2P$: C, 44.32; H, 6.58; N, 7.95. Found: C, 44.16; H, 6.70; N, 7.75.

1,4-Dimethyl-2,3-dihydro-1,4-diazepinium hexafluorophosphate (15): obtained as a light yellow solid; mp 113.3 °C (DSC); ^{1}H NMR (400 MHz $CDCl_3$) δ 3.51 (s, 6H), 3.81−3.93 (br s., 4H), 5.03 (t, 1H, J = 7.8 Hz), 7.75 (d, 2H, J = 7.8 Hz), ^{13}C NMR (100 MHz $CDCl_3$) δ 46.5, 55.5, 87.2, 157.4. Anal. Calcd for $C_7H_{11}F_6N_2P$ C, 31.13; H, 4.85; N, 10.37. Found: C, 31.14; H, 4.85; N, 10.33.

1-Diisopropylamino-3-pyrrolidyltrimiethinium hexafluorophosphate (16): obtained as a colorless solid; mp 155−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, 6H, J = 6.7 Hz), 1.36 (d, 6H, J = 6.7 Hz), 1.93−2.00 (m, 2H), 2.02−2.13 (m, 2H), 3.43 (t, 2H, J = 6.7 Hz), 3.74−3.83 (m, 3H), 4.09−4.18 (m, 1H), 5.21 (dd, 1H, J = 12.0, 11.4 Hz), 7.89 (d, 1H, J = 12.0 Hz), 8.34 (d, 1H, J = 11.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 23.0, 24.8, 48.0, 49.9, 50.9, 53.8, 90.6, 158.3, 160.0. Anal. Calcd for $C_{13}H_{25}F_6N_2P$: C, 44.07; H, 7.11; N, 7.91. Found: C, 44.2; H, 7.2; N, 7.7.

(Z)-2-Chloro-3-dimethylaminopropenal (17): isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (s, 6H), 6.93 (s, 1H), 8.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.2, 104.5, 152.8, 182.9.

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