An Efficient Preparation of Vinamidinium Hexafluorophosphate Salts

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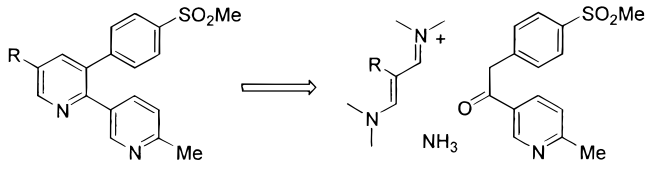
Substituted acetic acids or acetyl chlorides react with phosphorus oxychloride in DMF to yield the vinamidinium salts **3a**−**j** in moderate to excellent recrystallized yields (28−90%). The cations are conveniently isolated as their hexafluorophosphate salts, which are easily handled nonhygroscopic solids. The nitro compound **3l** is prepared in 91% yield by nitration of the parent vinamidinium **3k**. The X-ray crystal structure is reported for the 2-phenyl isomer **3e** and displays minimal overlap of the two π-systems.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) used for the treatment of inflammatory conditions act by inhibition of cyclooxygenase (COX), the first enzyme involved in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid. The major COX isozyme, COX-1, is expressed as a constitutive enzyme and is involved in homeostasis of the gastrointestinal (GI) tract (in addition to other functions).[1] The discovery[2] of an inducible COX isozyme, commonly referred to as COX-2 and expressed principally in inflammatory tissue, has led several groups to search for selective inhibitors of COX-2. The rationale behind these investigations is that such a selective COX-2 inhibitor will greatly reduce the side-effect profile, including gastric ulceration, that is commonly associated with the chronic use of traditional NSAIDs. Recently, a series of novel 2-pyridinyl-3-(4-methylsulfonyl)phenylpyridines **1a**−**l** has been evaluated by Merck for the ability to inhibit the isozymes of cyclooxygenase, COX-1, and COX-2.[3] Optimal COX-2 activity was observed by introduction of a substituent at C-5 of the central pyridine. 5-Chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine **1a** was identified as a very potent and specific COX-2 inhibitor that may provide therapeutically useful alternatives to traditional NSAIDs with a greater GI safety profile.

We envisioned that these compounds may be assembled by construction of the central pyridine ring (Scheme 1) with the introduction of the C-5 substituent

Scheme 1



1a-l **3a-l** **2**

in a single step. This disconnection would lead to a readily accessible ketone **2**, a three-carbon electrophile—the vinamidinium species **3**—and ammonia.[4]

In this paper we describe a safe, efficient procedure useful for the preparation of the chlorovinamidinium species **3a** as the hexafluorophosphate salt. The method is general, and a wide range of vinamidinium salts **3b**−**j** have been prepared in moderate to excellent yield, some of which have previously been unavailable by direct formylation of a carboxylic acid. One additional benefit is that the hexafluorophosphate salts may also prove to be a more judicious choice of salt than the perchlorates that frequently have undesirable thermal and shock-sensitive attributes.[5] In addition we describe the first structural characterization of the 2-phenyl trimethinium species **3e**. The accessibility of these compounds should also allow their application in a wide range of uses, e.g., heterocyclic synthesis of pyrroles, pyrazoles, pyrimidines and materials applications.

Results and Discussion

The reaction of chloroacetic acid to give the vinamidinium species was first described in 1961 as part of Arnold's extensive study of the reaction of Vilsmeier salts that has spanned the past four decades.[6] In the synthesis of the perchlorate salt, chloroacetic acid was added to

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(1) For a review see: Griswold, D. E.; Adams, J. L. *Med. Res. Rev.* **1996**, *16*, 181.

(2) (a) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erickson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692. (b) Kujubu, D. A.; Fletcher, B. S.; Varnum, B. C.; Lim, R. W.; Herschman, H. R. *J. Biol. Chem.* 1991 *226* 2692. (c) Masferrer, J. L.; Seibert, K.; Zweifel, B.; Neddleham, P. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 3917. (d) Hla, T.; Neilson, K. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7384.

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(5) *Prudent Practices in the Laboratory*; National Academy Press: Washington, DC, 1995.

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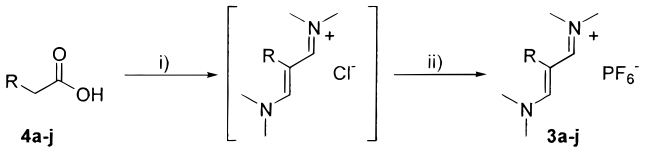
Scheme 2[a]



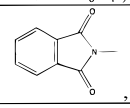
[a] (i) $POCl_3$, DMF, 70−75 °C; (ii) 60% aq. HPF_6, NaOH.

phosphorus oxychloride and DMF, and the mixture was heated to 70 and then 100 °C over a period of 6 h. At the end of reaction excess DMF was removed by distillation, and a 10 M solution of aqueous sodium perchlorate was added at 0 °C. The crude perchlorate was isolated in 70% yield, and a 59% overall yield was realized following recrystallization. Somewhat surprisingly, bromoacetic acid failed to give the vinamidinium salt under these conditions, and the reaction led to formation of a derivative of triformylmethane in moderate yield.[6]

A number of factors made this procedure unsuitable for the preparation of significant quantities of **3a (**CDT-phosphate). First, addition of the chloroacetic acid followed by heating the reaction mixture represented a potential thermal hazard. Second, the need for distillation of DMF prior to isolation of the perchlorate salt made the process impractical at larger scale. Finally, the addition of aqueous perchlorate is very exothermic, which is troublesome since the isolation and stability of perchlorate salts has been the subject of many safety concerns. In one case, during small scale development in our laboratory this exotherm proved to be uncontrollable.

To overcome these concerns we have employed a number of strategies. The controlled addition of the limiting reagent phosphorus oxychloride to a mixture of acetic acid and DMF at 75 °C over 3 h allows for better control of the exothermic reaction (Scheme 2). The reaction proceeded smoothly as determined by ReactIR analysis and reaction calorimetry, leading to the formation of the chloride in >93% HPLC assay yield.[7] Elimination of carbon dioxide commences approximately 50% through the addition of $POCl_3$ with the concomitant formation of the vinamidinium species as judged by the in situ IR analysis. Chloroacetyl chloride was detected as the precursor to CDT in the reaction, and in fact chloroacetyl chloride can be used in place of the acid simply by adjusting the stoichiometry. To avoid the problems associated with the distillation of the excess DMF, a range of salts were examined that would allow for direct isolation from the reaction mixture. The direct isolation of the vinamidinium chloride seems to be the most obvious, but this should be avoided because of the instability of CDT-Cl. In addition to undesirable thermal properties, the chloride is very hygroscopic, which is common for the halide salts of vinamidinium species. The use of other salts including tetrafluoroborate and trifluoromethane sulfonates did not lead to precipitation. The hexafluorophosphate proved to be an ideal salt.[8] Inverse addition of the DMF solution of CDT-Cl to an aqueous solution of $NaPF_6$ at <15 °C led to precipitation of the light yellow salt in >85% yield. For many purposes this material has sufficient purity to be used "as is", although we have found it more appropriate for our intended use (reaction with the ketone enolate) to recrystallize from water/2-propanol in 78−80% overall yield. The inexpensive hexafluorophosphoric acid was routinely used in place of sodium hexafluorophosphate by incorporating a simple pH adjustment using 5 N NaOH.[9]

Table I[a]

Entry	R =	Yield
1	Cl, **3a**	79 %
2	Br, **3b**	78 %
3	I, **3c**	60 %
4	CF_3, **3d**	68 %
5	Ph, **3e**	90 %
6	4-NO_2-C_6H_4-, **3f**	80 %
7	4-OMe-C_6H_4-, **3g**	75 %
8	 , **3h**	68 %
9	Me, **3i**	28 %
10	$PhCH_2$, **3j**	33 %
11	NO_2, **3l** [b]	91 %

[a] **3l** was prepared via nitration of **3k**.

With the revised procedure in hand we sought to examine the generality of the reaction conditions (Table 1). As noted previously, it was reported that bromoacetic acid failed to give the vinamidinium species but led to a derivative of triformyl methane.[6] It was suggested that this change in reactivity was due to the lability of the bromide in the reaction. An alternative approach to bromovinamidinium salt involves a multistep synthesis via bromination of the parent vinamidinium salt.[8] Reaction of bromoacetic acid with phosphorus oxychloride in DMF at 75 °C for 3 h and isolation using HPF_6/NaOH proceeded smoothly to give the hexafluorophosphate in 78% yield after recrystallization from 2-propanol/water.

Reaction of iodoacetic acid has not been reported. However, the standard conditions led to isolation of the crude salt in essentially quantitative yield. The iodide **3c** was recovered in analytically pure form by slurry washing with tetrahydrofuran to afford a 60% overall yield.

The trifluoromethyl vinamidinium **3d** species has been described as the chloride salt.[10] In this case a direct chromatographic isolation was used as a result of a reported facile acid (1 M HCl) or base (0.5 M carbonate) hydrolysis. However, in our hands the reaction proceeded as smoothly, and the hexafluorophosphate was isolated in high purity from the DMF/water. Recrystallization from DMF/THF gave the spectroscopically pure salt in 68% overall yield.

(7) A reverse phase ion-pairing HPLC method was developed for analysis of CDT using a YMC Basic column and acetonitrile/4 mM heptane sulfonic acid sodium salt as mobile phase.

(8) During the course of this work the hexafluorophosphate of the parent trimethinium cation was disclosed. Arnold, Z.; Dvorak, D.; Havranek, M. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1637. Gupton has also recently disclosed the use of sodium hexafluorophosphate for the isolation of vinylogous iminium salts. Gupton, J. T.; Petrich, S.; Hicks, F. A.; Wilkinson, D.; Vargas, M.; Hosein, Kirsten, N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689.

(9) Technical grade HPF_6 was used, which is ~60 wt % in water.

(10) Yamanaka, H.; Takekawa, T.; Morita, K.; Ishihara, T.; Gupton, J. T. *Tetrahedron Lett.* **1996**, *37*, 1829.

Phenyl acetic acid (or chloride) reacted without event to provide the "crude" salt **3e** in essentially quantitative yield. Recrystallization from 2-propanol/water led to 90% isolated yield. The 4-nitrophenyl and 4-methoxyphenyl acetic acids also behaved similarly giving the crude vinamidinium salts in >99% yield. The analytically pure materials were isolated from IPA/water in an unoptimized 75−80% yield.

While disubstituted glycine derivatives have been reported to be unreactive in the formylation reaction,[11] we were gratified that the phthalimidoyl-substituted salt **3h** was obtained in 68% yield following recrystallization.

The nitrile has previously been prepared in a multistep fashion. Formylation of cyanoacetic acid using the Eschenmoser protocol via the neopentyl-DMF acetal gave a β-dimethylaminoacrylonitrile.[12] The second formylation was performed under Vilsmeier conditions to give the perchlorate salt in 40% yield.[13] Our attempt to react the acid directly failed to give any of the desired product (as judged by NMR spectroscopy) and lead to decomposition.

On the basis of literature reports, propionyl chloride was expected to be unreactive.[14] The 2-methyl-substituted isomer was previously prepared as the chloride salt in 20% yield by reaction of propionaldehyde diethyl acetal at 70 °C with the Vilsmeier salt prepared from phosgene and DMF.[15] However, simply treating propionyl chloride with phosphorus oxychloride in DMF at 60 °C led to the 2-methyl species **3i** in an unoptimized 28% yield. The methyl-substituted compound **3i** existed as a mixture of isomers as determined by ^{1}H and ^{13}C NMR, and the signals coalesced at 413 K, indicating a significant barrier to interconversion—this is the only compound prepared to exhibit this behavior since all other compounds existed as a single isomer. Dihydrocinnamoyl chloride behaved similarly to propionyl chloride and led to the benzyl-substituted vinamidinium salt **3j** in an unoptimized 33% yield. Oxygen-containing substrates failed to give the vinamidinium species. Phenoxy and 2-naphthoxy were unreactive, while the 4-nitrophenoxyacetic acid chloride only led to decomposition. This behavior is not easily rationalized by simple electronic arguments.

To examine the utility of the hexafluorophosphate the parent vinamidinium species **3k** was prepared by modification of a literature route and addition of HPF_6.[16] The salt was subjected to nitration conditions using acetic anhydride/nitric acid at 0 °C.[17] The reaction proceeded smoothly, and the analytically pure product **3l** was isolated in 91% yield simply by concentration and addition of 2-propanol.

Structure

An X-ray crystallographic analysis of **3e** revealed a planar, all trans "W" configuration (Figure 1) for the delocalized allyl cation. The C(11),C(1),C(2),C(7) torsion angle is 99.9°, indicating the phenyl group is positioned perpendicular to the allyl chain. The structure is similar to that of a 3,4-dihydronaphthyl derivative reported by Koziol and Katritzky.[18] A preliminary crystallographic analysis of **3a** revealed the same "W" configuration of the allyl chain; however, the crystals were of rather poor quality and further refinement was not attempted.

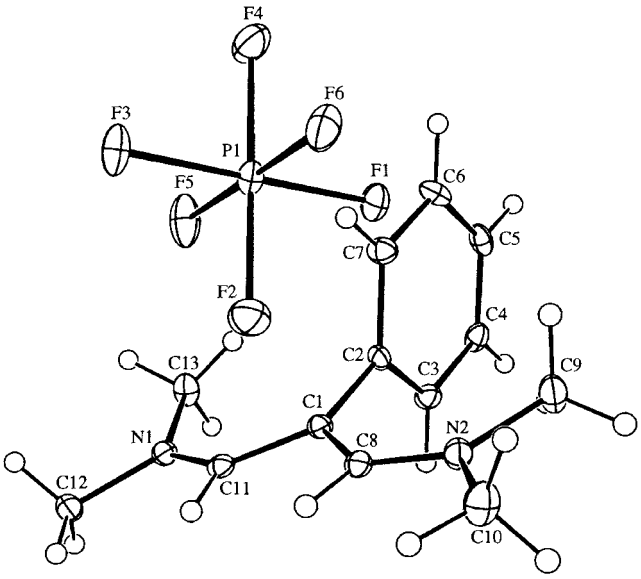


Figure 1. ORTEP representation of **3e**. Non-hydrogen atoms are represented by ellipsoids corresponding to 30% probability. Hydrogen atoms have been drawn at an arbitrary size.

Summary

We have described a straightforward method for the synthesis of trimethinium salts. A wide range of substrates can be prepared by this method, many of which were previously inaccessible from the substituted acetic acids. We have also documented the limitations of this method in that oxygen substitution shuts down the reactivity. The hexafluorophosphates are easily handled and may provide a general substitution to the more commonly used perchlorate and chloride salts of organic cations.

Experimental Section

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

2-Chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3a). General Procedure. Chloroacetyl chloride (14.13 g, 0.125 mol) was added to DMF (60 mL) at 50 °C, and the mixture was heated to 70 °C to give a clear yellow solution. Phosphorus oxychloride (19.20 g, 0.125 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 and 5,N NaOH (70 mL) were added concurrently over 1 h to a mixture of 60% hexafluorophosphoric acid (33.15 g, ~0.135 mol) and 5 N NaOH (37 mL) in water (150 mL) at a temperature <10 °C. The reaction flask was rinsed with DMF, which was added to the quench mixture. The mixture was aged for 1 h and then filtered, washing the crude solids with water. The crude solid was recrystallized from water (225 mL) and 2-propanol (60 mL) by heating to 70 °C. The mixture was cooled to 0 °C and filtered. The light yellow solid was washed with water/2-

(11) Arnold, Z. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1168.
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(17) Kucera, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1704.
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propanol (20:1) and dried in vacuo at < 40 °C to give CDT-phosphate **3a** as a colorless to light yellow solid (29.88 g, 78%): mp 125−126 °C; ^{1}H NMR (300 MHz DMF-d_7) δ 3.40 (s, 6H), 3.57 (s, 6H), 7.87 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7) δ 39.9, 49.7, 92.6, 161.0. Anal. Calcd for $C_7H_{14}ClN_2PF_6$: C, 27.42; H, 4.60; N, 9.14. Found: C, 27.60; H, 4.29; N, 9.07.

2-Bromo-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3B): obtained as a bright yellow solid; mp 180−181 °C; ^{1}H NMR (300 MHz DMF-d_7) δ 3.66 (s, 6H), 3.74 (s, 6H), 8.84 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7) δ 43.13, 48.74, 91.86, 165.39. Anal. Calcd for $C_7H_{14}BrN_2PF_6$: Br, 22.75. Found: Br, 22.76.

2-Iodo-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3c): obtained as an off-white solid; mp 195−196 °C; ^{1}H NMR (300 MHz DMF-d_7) δ 3.71 (s, 6H), 3.65 (s, 6H), 8.76 (s, 2H). Anal. Calcd for $C_7H_{14}IN_2PF_6$: C, 21.12; H, 3.54; N, 7.04. Found: C, 20.62; H, 3.77; N, 7.02.

2-Trifluoromethyl-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3d): obtained as an off-white solid; mp 177−179 °C; ^{1}H NMR (400 MHz DMF-d_7) δ 3.66 (s, 6H), 3.74 (s, 6H), 8.81 (s, 2H); ^{13}C NMR (100.55 MHz DMF-d_7) δ 43.3, 49.0, 92.0, 165.5; ^{19}F NMR (376.61 MHz DMF-d_7) −68.8 (s, 6), −70.7 (s, 3). Satisfactory combustion analysis could not be obtained for this compound, and the identity of **3d** was confirmed by conversion to pyridine **1d**, which was characterized by spectroscopy and combustion analysis.

2-Phenyl-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3e): obtained as a pale yellow solid; mp 191−192 °C; ^{1}H NMR (300 MHz $CDCl_3$) δ 2.41 (s, 6H), 3.22 (s, 6H), 7.30−7.35 (m, 3H), 7.18−7.23 (m, 2H), 7.42 (s, 2H); ^{13}C NMR (75 MHz $CDCl_3$) δ 39.3, 48.8, 105.7, 128.5, 128.9, 131.8, 132.1, 163.3. Anal. Calcd for $C_{13}H_{19}N_2PF_6$: C, 44.83; H, 5.50; N, 8.04. Found: C, 44.65; H, 5.51; N, 8.24.

2-(4-Nitrophenyl)-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3f): obtained as a pale yellow solid; mp 180−181 °C; ^{1}H NMR (300 MHz DMF-d_7) δ 2.62 (s, 6H), 3.4 (s, 6H), 7.83 (d, 2H, J = 8.8 Hz), 7.93 (s, 2H), 8.33 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz DMF-d_7) δ 40.80, 49.19, 103.93, 123.93, 134.31, 141.43, 148.43, 163.86. Anal. Calcd for $C_{13}H_{18}N_3O_2PF_6$: C, 39.70; H, 4.61; N, 10.68. Found: C, 39.87; H, 4.43; N, 10.45.

2-(4-Methoxyphenyl)-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3g): obtained as a light brown solid; mp 131−133 °C; ^{1}H NMR (300 MHz DMF-d_7) δ 2.58 (s, 6H), 3.34 (s, 6H), 3.85 (s, 3H), 7.04 (d, 2H, J = 8.7), 7.27 (d, 2H, J = 8.7), 7.80 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7) δ 39.69, 49.00, 55.70, 106.26, 114.54, 124.92, 134.26, 160.71, 164.26. Anal. Calcd for $C_{14}H_{21}N_2OPF_6$: C, 44.45; H, 5.60; N, 7.41. Found: C, 44.37; H, 5.22; N, 7.02.

2-(*N*-Phthalomidoyl)-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3h): obtained as a tan solid; mp 272−275 °C (dec); ^{1}H NMR (300 MHz DMF-d_7) δ 3.04 (s, 6H), 3.46 (s, 6H), 4.10 (s, 2H), 7.97−8.10 (m, 4H), 8.15 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7) δ168.6, 163.1, 136.2, 132.0, 125.3, 94.4, 49.6, 38.4. Anal. Calcd for $C_{18}H_{18}N_3O_2PF_6$: C, 43.17; H, 4.35; N, 10.07. Found: C, 43.14; H, 4.28; N, 9.92.

2-Methyl-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3i): obtained as a pale brown solid; mp 93−95.5 °C; ^{1}H NMR (300 MHz DMF-d_7 413 K) δ 2.22(s, 3H), 3.25−3.38 (m, 12H), 7.55 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7 413 K) δ13.1, 39.8, 47.2, 99.5, 166.7; exact mass (FAB) on cation gave m/z 141.1381. $C_8H_{17}N_2$ requires 141.1392.

2-(Phenylmethano)-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (3j): obtained as a pale yellow solid; mp 165−166 °C; ^{1}H NMR (300 MHz DMF-d_7) δ 3.01−3.28 (br. s, 6H), 3.28−3.57 (br. s, 6H), 4.10 (s, 2H), 7.19−7.34 (m, 3H), 7.34−7.49 (m, 2H), 7.80 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7) δ 39.00−40.60, 48.80−49.90, 100.53, 127.31, 128.57, 129.69, 141.41, 167.58. Anal. Calcd for $C_{14}H_{21}N_2PF_6$: C, 46.41; H, 5.84; N, 7.73. Found: C, 46.43; H, 5.63; N, 7.56.

2-Nitro-1,3-bis(dimethylamino) trimethinium hexafluorophosphate (3l): obtained as a white solid; mp 156−158 °C (dec); ^{1}H NMR (300 MHz DMF-d_7) δ 3.41 (s, 6H), 3.81 (s, 6H), 8.96 (s, 2H); ^{13}C NMR (75 MHz DMF-d_7) δ 44.1, 49.1, 116.7, 160.4. Anal. Calcd for $C_7H_{14}N_3O_2PF_6$: C, 26.51; H, 4.45; N, 13.25. Found: C, 26.45; H, 4.14; N, 12.86.

Supporting Information Available: X-ray crystallographic data of **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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