JOC*Note*

Reaction of Aldimine Anions with Vinamidinium Chloride: Three-Component Access to 3-Alkylpyridines and 3-Alkylpyridinium Salts and Access to 2-Alkyl Glutaconaldehyde Derivatives

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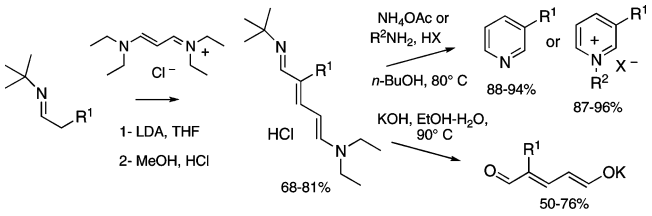
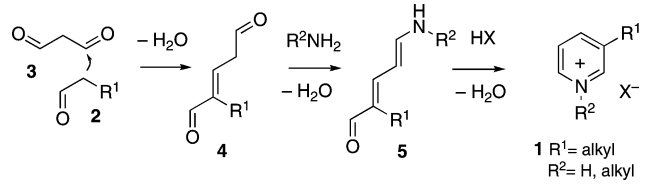


N-tert-Butylimino derivatives of aldehydes were deprotonated with LDA and reacted with vinamidinium chloride to give 2-alkylaminopentadienimine derivatives, which were isolated as their corresponding hydrochloride in 68−81% yield. Reaction of these derivatives with ammonium acetate or salts of primary amines, in *n*-butanol at 80 °C, afforded the corresponding 3-alkylpyridines or 3-alkylpyridinium salts in high yield. Alkaline hydrolysis of 2-alkylaminopentadieneimine derivatives allowed a practical accesss to potassium salts of 2-alkylglutaconaldehyde.

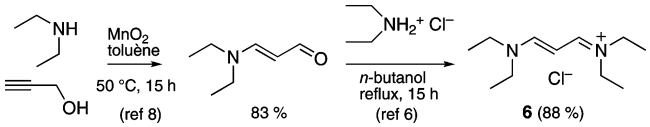
We have suggested[1] that natural 3-alkylpyridine and 3-alkylpyridinium salts **1** (Scheme 1) extracted from sponges in the order *Haplosclerida* can be biosynthesized by condensation of an aldehyde **2** with a three-carbon unit, whose oxidation level corresponds to malonaldehyde **3**, and an amine (ammonia or a primary amine). In this process glutaconaldehyde derivatives **4** and/or aminopentadienal species **5** were likely to be involved as intermediates, while their dimerization could also be at the biosynthetic origin of more complex alkaloids such as manzamines and halicyclamines.

This chemistry is of potential synthetic interest since it constitutes a general three-component access to 3-alkylpyridines (using ammonia as the amine component) or 3-alkylpyridinium salts (using primary amines).[2] In addition, we recently introduced[3] species **4** and **5**, and related derivatives, as useful intermediates in the arena of natural product synthesis.[4]

SCHEME 1. Biogenetic Scenario for the Formation of Natural Pyridine Derivatives Extracted from Sponges in the Order *Haplosclerida* (from ref 1)



SCHEME 2. Preparation of Vinamidinium Salt 6



In search for practical protocols based on the sequence depicted in Scheme 1, we recently reported[5] the successful condensation of aldehyde imino derivatives with malonaldehyde monoacetals or dimethylaminoacrolein, which gives analogues of **4** and **5**. These analogues cyclized in acidic medium to give the corresponding pyridinium salts. This strategy was limited by the low reactivity of imines in these conditions, requiring the use of more reactive silyl derivatives, and the tendency of 2-alkyl-substituted glutaconaldehydes to dimerize in acidic medium. We thus turned our attention to vinamidinium salts (see **6**, Scheme 2) as malonaldehyde equivalents. These reactive intermediates were initially used by Nair[6] for the preparation of dienaminones from ketones and esters. More recently, a series of paper by Davies and Marcoux[7] described the synthesis of 2,3,5-trisubstituted pyridine derivatives from the reaction of ketone enolates with vinamidinium hexafluorophosphates. This last procedure was reported to be limited to vinamidinium species possessing an electron-stabilizing substituent at position 2. In this paper, we now report an efficient procedure for the preparation of 2-alkyl glutaconaldehyde derivatives and the corresponding 3-alkylpyridine and 3-alkylpyridinium salts starting from aldehydes and featuring, as a key step, condensation of aldimine anions with vinamidinium chloride.

Vinaminidium chloride **6** was first prepared using a slight modification of reported procedures[6,8] (Scheme 2).

As a model, we first studied the reaction of salt **6** (Scheme 3) with the anion derived from propionaldehyde *tert*-butylimine

(1) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026−8034.

(2) For a recent review on pyridines and pyridinium salts syntheses, see: Spitzner, D. In *Science of Synthesis*; Black, D. StC., Ed.; Georg Thieme Verlag: Stuttgart, New York, 2005; Vol. 15, pp 11−284.

(3) (a) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Almourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381−7387. (b) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890−1897. (c) Sanchez-Salvatori, M. d. R.; Marazano, C. *J. Org. Chem.* **2003**, *68*, 8883−8889.

(4) For a related recent example, see: Kearney, A. M.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7803−7806.

(5) Sanchez-Salvatori, M.; Lopez-Giral, A.; Ben Abdeljelil, K.; Marazano, C. *Tetrahedron Lett.* **2006**, *47*, 5503−5506.

(6) Nair, V.; Cooper, C. S. *J. Org. Chem.* **1981**, *46*, 4759−4765.

(7) (a) Marcoux, J.-F.; Corley, E. J.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339−2341. (b) Davies, I. M.; Taylor, M.; Marcoux, J.-F.; Wu, J.; Dormer, P. G.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 251−255. (c) Marcoux, J. F.; Marcotte, F.-A.; Wu, J.; Dormer, P. G.; Davies, I. W.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 4194−4199. (d) Davies, I. W.; Marcoux, J.-F.; Reider, P. J. *Org. Lett.* **2001**, *3*, 209−211.

(8) Wei, X.-Y.; Zong, Z.-M.; Ji, Y.-F. *Synth. Commun.* **2003**, *33*, 367−371.

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SCHEME 3

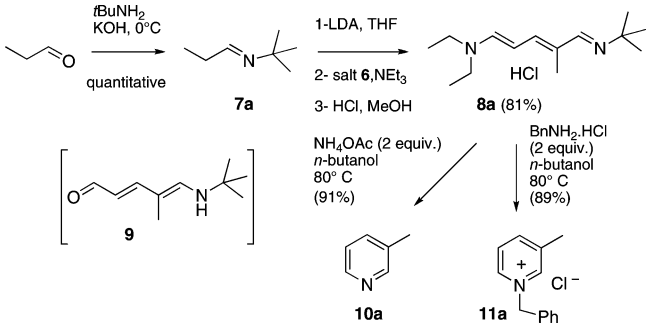


TABLE 1. Preparation of Aminopentadieneimine Salts 8b−f from Reaction of Aliphatic *N-tert*-Butylimines 7b−f with Vinamidinium Salt 6[a]

Entry	starting aldimine	product	Isolated yield (%)
1	**7b**	**8b**	72
2	**7c**	**8c**	69
3	**7d**	**8d**	74
4	**7e**	**8e**	68
4	**7f**	**8f**	56

[a] Conditions: (a) imine **7**, LDA (1 equiv), THF, 0 °C, 1 h; (b) salt **6** (1 equiv), NEt_3, rt, overnight; (c) HCl, MeOH.

7a, generated with LDA in THF. The reaction was conducted in the presence of triethylamine.[9] After extraction, a crude material was obtained whose ^1H NMR analysis revealed that it was essentially composed of aminopentadieneimino derivative **8a** (base). The only other product observed (about 10%) was identified as aminopentadienal **9**, resulting from hydrolysis of **8a**. Structural assignments were secured by comparison with similar compounds obtained previously[5] and with those prepared from aminolysis of Zincke salts.[10] Chromatographic purification of the product as a base resulted in some decomposition. For this reason, it was converted to the corresponding more stable hydrochloride which could be chromatographed on silica gel and isolated in 81% yield from **7a**.

Cyclization of **8a** proceeded easily in the presence of ammonium acetate, at 80 °C in *n*-butanol overnight, to give 3-picoline **10a** in 91% yield. Under the same conditions, benzylamine hydrochloride gave pyridinium salt **11a** in 89% yield.

After these encouraging results, working on a simple model, the methodology was extended to long-chain aliphatic aldehydes, in connection with our work concerning manzamine alkaloids.[1,3] Condensation of aldimines **7b−f** in the conditions used for imine **7a** afforded a series of aminopentadieneimines isolated as the hydrochloride **8b−f** (Table 1) showing the generality of the reaction.

Conditions used for preparation of pyridine **10a** or pyridinium salt **11a** afforded in good yield the corresponding compounds **10b−f** and salts **11b−f** from **8b−f** (Table 2).

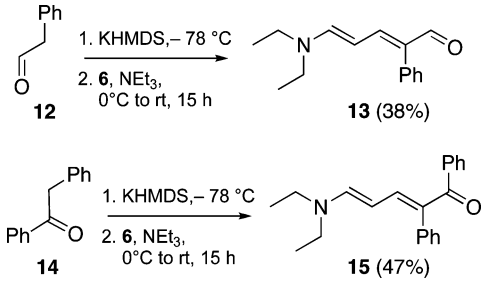
Phenylacetaldehyde **12** (Scheme 4) displayed a different behavior since its corresponding imino anion did not react with

TABLE 2. Cyclization to Pyridines or Pyridinium Salts

starting material	pyridine[a] (yield)	pyridinium salt[b] yield
8b	**10b** (90%)	**11b** (89%)
8c	**10c** (88%)	**11c** (87%)
8d	**10d** (92%)	**11d** (90%)
8e	**10e** (92%)	**11e** (91%)
8f	**10f** (80%)	**11f** (80%)
13	**16** (94%)	**17** (96%)
15	**18** (92%)	**19** (91%)

[a] Conditions: NH_4OAc (2 equiv), *n*-butanol, 80 °C overnight. [b] Conditions: $BnNH_2$·HCl, (2 equiv), *n*-butanol, 80 °C overnight.

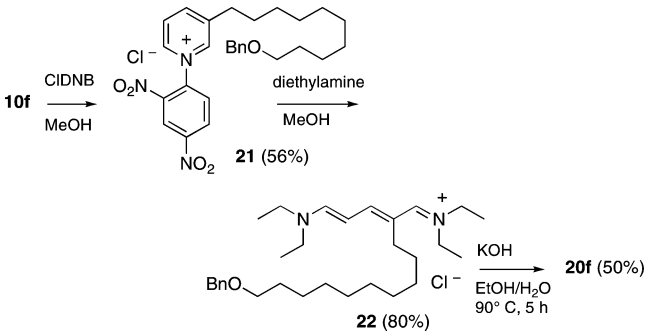
SCHEME 4. Preparation of Phenyl-Substituted Aminopentadienal and Aminopentadienone



(9) The use of a tertiary amine in these reactions is recommended (see refs 6 and 7). Its role can be to facilitate elimination of diethylamine from the primary adduct of the reaction, but this was not proven yet.

(10) (a) Nguyen, T. M.; Sanchez-Salvatori, M. d. R.; Wypych, J.-C.; Marazano, C. *J. Org. Chem.* **2007**, *72*, 5916−5919. (b) For a review on the synthesis and reactions of glutaconaldehyde and the corresponding amino derivatives (aminopentadienals), see: Becher, J. *Synthesis* **1980**, 589−612.

SCHEME 5



vinamidinium chloride **6**. However, it was found that aldehyde **12** reacted with **6**, after deprotonation with KHMDS, to give aminopentadienal **13** in 38% yield. Starting from ketone **14**, aminopentadienone **15** was obtained in 47% yield under the same conditions.[11]

These derivatives **13** and **15** cyclized to pyridines **16** and **18** or pyridinium salts **17** and **19**, respectively, in very good yield (see Table 2).

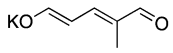
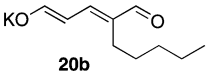
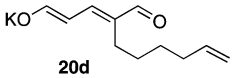
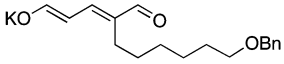
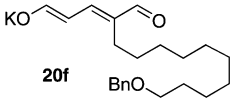
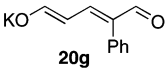
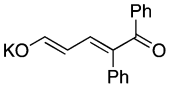
Finally it was shown that alkaline hydrolysis of aminopentadieneimine salts **8a**−**f** afforded the corresponding 2-substituted glutacondialdehyde potassium salts **20a**−**f**[12] (Table 3) in fair to good yields. Previous syntheses of these derivatives were limited to glutaconaldehyde sodium salt[13] and the corresponding 2-methyl derivative.[3a,14] Aryl derivatives **20g**,**h** were also obtained using the same conditions.

As an alternate approach, it should be worth mentionning that glutaconaldehyde salts of general structure **20** could also be obtained via aminolysis of Zincke salts such as **21**, as illustrated in Scheme 5.

Thus treatment of Zincke salt **21** with 2 equiv of diethylamine afforded salt **22**, which was hydrolyzed in alkaline medium under the conditions used for hydrolysis of derivatives **8** (see Table 3) to yield glutaconaldehyde salt **20f** in 50% yield.

In conclusion, we believe that this new three-component synthesis of pyridines and pyridinium salts significantly extends the scope of related approaches reported previously.[7] It also complements our work[1,3,10a] concerning the preparation and use of glutaconaldehyde derivatives, in particular their amino derivatives, as useful intermediates in synthesis, in particular in the natural product field. Further work is in progress in our laboratory to extend the scope of the chemistry of these species whose potential in synthesis has been probably largely underestimated in the past.

TABLE 3. Alkaline Hydrolysis of Aminopentadienimine Derivatives 8a−f, Aminopentadienal 13, and Aminopentadienone 15 to Glutaconaldehyde Salt 20a−h[a]

starting product	glutaconaldehyde salt	Isolated yield (%)
8a	 **20a**	70
8b	 **20b**	50
8d	 **20d**	53
8e	 **20e**	63
8f	 **20f**	42
13	 **20g**	60
15	 **20h**	76

[a] Conditions: KOH (2 equiv), EtOH/H_2O (1:1), 90 °C, 5 h.

Experimental Section

Preparation of Aminopentadieniminium Salt 8a as a Typical Procedure. To a cooled (0 °C) solution of diisopropylamine (968 μL, 6.84 mmol) in THF (10 mL) was added *n*-BuLi (1.5 M, 4 mL, 6 mmol). The reaction mixture was stirred at 0 °C during 20 min, and imine **7a** (620 mg, 5.48 mmol) in THF (4 mL) was added dropwise. The solution was stirred during 1 h at 0 °C, and vinamidinium chloride **6** (1.2 g, 5.48 mmol) and triethylamine (4 mL) were added. The reaction mixture was slowly warmed to rt and stirred overnight. H_2O (100 mL) and CH_2Cl_2 (100 mL) were added, and the two layers were separated. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with H_2O and brine. The organic phase was dried over $MgSO_4$ and concentrated. The orange oil, diluted in MeOH (4 mL), was added to a solution of MeOH and HCl obtained from careful addition of acetyl chloride (782 μL, 11 mmol) in MeOH (4 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 15 min. The solution was concentrated to give an orange oil. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH= 95:5) gave salt **8a** (1.15 g, 81%) as an orange oil: FTIR (film) /cm^{-1} 3377, 2971, 1594, 1536, 1463, 1434, 1178; ^{1}H NMR (CD_3-OD, 300 MHz) δ 1.27 (3H, t, J = 6.9 Hz, $H_{7'}$), 1.30 (3H, t, J = 6.9 Hz, H_7), 1.40 (9H, s, H_{10}), 1.86 (3H, s, H_8), 3.54 (4H, q, J = 6.9 Hz, $H_{6\ and\ 6'}$), 5.77 (1H, dd, J = 12.8, 11.8 Hz, H_4), 7.45 (1H, d, J = 12.8 Hz, H_3), 7.62 (1H, d, J = 11.8 Hz, H_5), 7.68 (1H, s, H_1); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 9.8 (C_8), 12.3 ($C_{7'}$), 14.7 (C_7), 29.6 (C_{10}), 44.7 ($C_{6'}$ or 6), 52.5 ($C_{6\ or\ 6'}$), 56.3 (C_9), 100.6 (C_4), 112.8 (C_2), 159.5 (C_1), 160.8 (C_5), 164.4 (C_3); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{27}N_2$ (M − Cl)$^+$ 223.2174, found 223.2169.

General Procedure for Preparation of Pyridines 10a−f and Pyridinium Salts 11a−f from Aminopentadieneiminium Salts 8a−f. To a solution of aminopentadieneiminium salt in *n*-butanol was added 2 equiv of NH_4OAc or $BnNH_2$·HCl (see the Supporting Information for details). The reaction mixture was heated at 80 °C

(11) A similar reaction was reported starting from a diaryl ketone and using a chlorovinamidinium salt. The chloropyridine obtained in 35% yield was further reduced to give a 2,3-diarylpyridine: Simoni, D.; Grisolia, G.; Giannini, G.; Roberti, M.; Rondanin, R.; Piccagli, L.; Baruchello, R.; Rossi, M.; Romagnoli, R.; Invidiata, F. P.; Grimaudo, S.; Jung, M. K.; Hamel, E.; Gebbia, N.; Crosta, L.; Abbadessa, V.; Di Cristina, A.; Dusonchet, L.; Meli, M.; Tolomeo, M. *J. Med. Chem.* **2005**, *48*, 723−736.

(12) Free glutacondialdehyde derivatives are very unstable intermediates (glutaconaldehyde is stable for only ∼30 mn at ∼−70 °C (see ref 10b) or prone to dimerization (see ref 5)).

(13) Becher, J. *Org. Synth.* **1979**, *59*, 79.

(14) Becher, J.; Haunso, N.; Pedersen, T. *Acta. Chim. Scand. B* **1975**, *29*, 124−132.

overnight and then concentrated, and the residue was purified by column chromatography on silica gel. See the Supporting Information for details.

General Procedure for Preparation of Glutaconaldehyde Potassium Salts 20a−h. To a solution of the aminopentadieneiminium salt in a mixture of EtOH/H_2O (1:1) was added KOH (1.8 equiv). The reaction mixture was heated at 90 °C during 5 h and concentrated on a rotary evaporator. H_2O and CH_2Cl_2 were added, and the H_2O phase was washed 4 times with CH_2Cl_2. The aqueous phase was concentrated, and a cooled (−10 °C) mixture of EtOH/MeOH (1/1) was added to precipitate KOH and KCl. The organic phase was concentrated, and the operations (precipitation and concentration) were repeated until the pH of ethanol phase was around 8−9. See the Supporting Information for details.

Supporting Information Available: Full experimental procedures, copies of ^1H and ^{13}C NMR spectra of vinamidinium salt **6**, aldimines **7a**−**f**, aminopentadieneimine salts **8a**−**f**, pyridines **10b**−**f**, pyridinium salts **11a**−**f**, aryl derivatives **13** and **15**−**19**, glutaconaldehyde salts **20a**−**h**, and salts **21** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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