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3-Substituted pentadienals derivatives from condensation of imines anions to malonaldehyde equivalents. A C–C–C + C–C + N type entry to 3-alkyl substituted pyridinium salts

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Abstract—In order to model a biogenetic hypothesis concerning the origin of 3-substituted natural pyridinium type alkaloids extracted from sponges, the reactions of imine anions with malonaldehyde equivalents were investigated. Use of malonaldehyde monoacetals or dimethylaminoacrolein resulted in formation of glutaconaldehyde or aminopentadienal derivatives in moderate yields. Improved yields were observed using β-silyl imines. The so obtained glutaconaldehyde or aminopentadienal derivatives react with primary amines to give 3-alkyl substituted pyridinium salts. Therefore the reported sequence constitutes a C–C–C + C–C + N type entry to 3-alkyl substituted pyridinium salts. 3-Alkylglutaconaldehydes were also shown to dimerize, giving substituted cinnamic dialdehydes.

We recently suggested that the biogenetic origin of sponge alkaloids such as cyclostelletamines and manzamines can be viewed as the result of the condensation of two long chain aminoaldehydes with malonaldehyde or malonaldehyde equivalents (Scheme 1).[1]

This hypothesis raised the question of the feasibility of the related sequence depicted in Scheme 2, that is to say formation of glutaconaldehyde derivatives **1** from aldehydes and malonaldehyde equivalents, followed by reaction with primary amines to give aminopentadienal regioisomers **2** and their final cyclization in acidic medium to give pyridinium salts **3**.[2]

This three step process is of interest since it constitutes a three-component (C–C–C + C–C + N) entry to pyridinium salts.[3] In addition, intermediates glutaconaldehyde **1** or aminopentadienals **2** were shown to be potentially useful synthons.[1,4] In particular, if the preparation of glutaconaldehyde **1** ($R_1 = H$) as a sodium salt was described,[5] the 3-substituted isomers were difficult to obtain owing to their instability. Another problem associated with Scheme 1 sequence is that direct condensation of aldehydes with very unstable malonaldehyde was known not to give glutaconaldehyde intermediates **1**, but instead unstable Knoevenagel adducts.[6,7] For this last reason there is a need for suitable analogs.

To our knowledge few reactions related to Scheme 1 were reported in the literature. Nair[8] described the condensation reaction of ketones with vinamidinium salts which can be considered as malonaldehyde equivalents. Recently a Merck group reported the condensation of ketones with 2-substituted vinamidinium salts to give pyridine derivatives.[9] The closest approach, which was published earlier, consisted in condensation of malonaldehyde diacetals with enol ethers in the presence of $ZnCl_2$.[10]

In this short communication are reported some observations demonstrating that, in appropriate conditions, the condensation of imine anions with malonaldehyde monoacetals or dimethylaminoacrolein constitutes a quite convenient access to glutaconaldehyde monoacetals or aminopentadienal derivatives. Also reported are conditions for their conversion to 3-substituted pyridinium salts in acidic conditions.

First studies started with aldehyde **4** (Scheme 3), a protected analog of malonaldehyde.[11] Condensation

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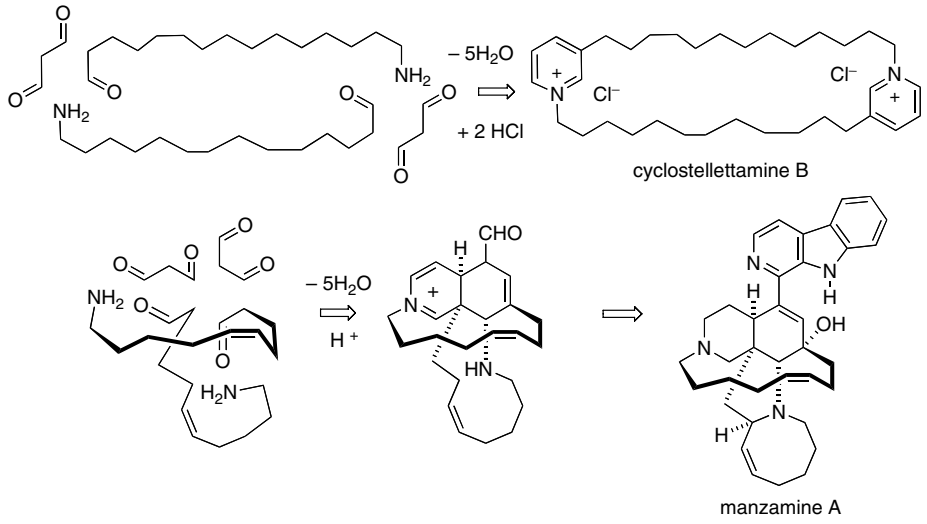
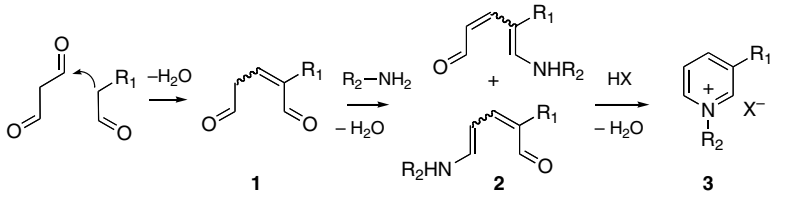


Scheme 1. Biogenetic hypothesis.

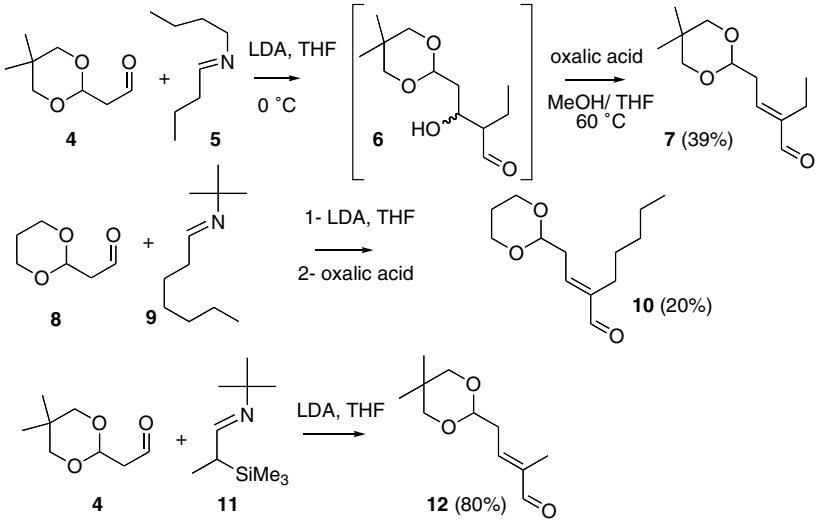


Scheme 2. Targeted synthetic sequence.

of **4** with the lithium salt of imine **5** gave aldol intermediates **6**, as a crude mixture of isomers. These products were quite unstable probably due to a facile retroaldol process. For this reason dehydration to give the protected glutaconaldehyde derivative **7** was conducted on the crude mixture. The dehydration conditions turned out to be critical. Use of Ac_2O-pyridine in the presence of DMAP resulted in product degradation. Treatment with MsCl in pyridine and CH_2Cl_2 resulted in poor yield of **7** while use of TsOH in benzene resulted in only 20% yield. The best conditions made use of oxalic acid, in a MeOH/THF mixture at 60 °C, allowing to obtain **7** in a 39% overall yield.

The reaction also worked with derivative **8** and imine **9** to give aldehyde **10**.[12] However lower yield (20%) was observed using this longer chain imino derivative.

Interestingly, use of a silylimino analog **11**[13] allowed to obtain the protected glutaconaldehyde **12** in a single step and a substantially higher yield (80%).



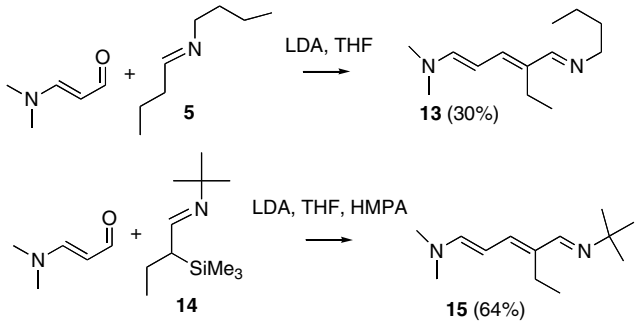
Scheme 3.

Condensation of lithium salts of imines was also successful with dimethylaminoacrolein (Scheme 4) giving, for example, aminopentadienal derivative **13** in a single step and 30% yield. Again, improved yield was obtained starting from silyl derivative **14** which gave diene **15** in 64% yield, but in this case the use of HMPA was necessary.

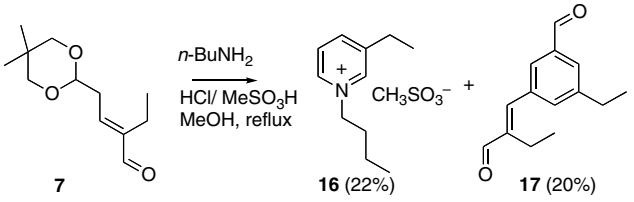
We then turned our attention to the last step of the sequence depicted in Scheme 2, that is to say access to pyridinium salts from our condensation products. The reaction of glutaconaldehyde derivatives was first studied.[14] As a result, treatment of aldehyde **7** with *n*-butylamine, using a mixture of methanesulfonic and hydrochloric acid in methanol at reflux, afforded the desired pyridinium salt **16** but in practically equal proportions with the aromatic cinnamic dialdehyde **17** (see Scheme 5).

Adduct **17** resulted from an easy dimerization of the intermediate 2-ethyl glutaconaldehyde in acidic conditions. This was clearly demonstrated by an independent study. Thus, it was observed, by ^{1}H NMR in $CDCl_3$, that salt **18**[1c] (Scheme 6) gave cleanly 2-methyl glutaconaldehyde **19** when treated with 1 equiv of acid for short time at low temperature. Longer exposure and acid excess resulted in complete formation of cinnamic dialdehyde **20**. The process can be controlled in order to isolate either glutaconaldehyde **19** or dimer **20**.[15]

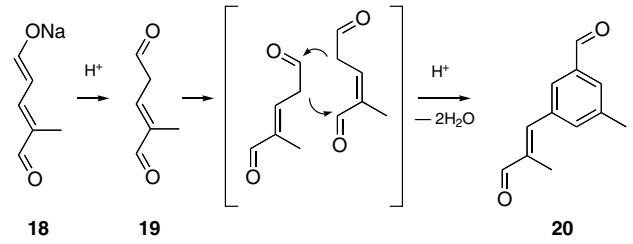
Formation of cinnamic type dimers is clearly a limitation for the formation of pyridinium salts from protected glutaconaldehydes such as **7**. The need for deprotection prior to primary amine attack seems to favor dimer formation since derivative **10**, in which the dioxane group is more sensitive to hydrolysis, was found to give a higher yield (60%) of pyridinium salt **21**[16]



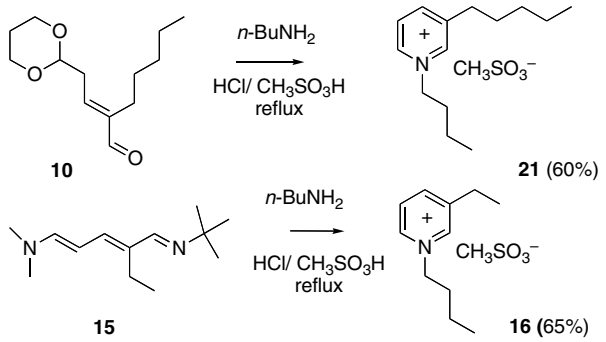
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

(Scheme 7). Diamino derivative **15**, when treated with *n*-butylamine in acidic medium also gave pyridinium salt **22** in similar yields.

References and notes

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2. Intermediates **2** are analogs of those involved in the Zincke synthesis of pyridinium: for our work concerning Zincke reaction see Ref. 1d and references therein, for a recent review of the Zincke synthesis of pyridinium salts see: Rojas, C. M. In *Named Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; John Wiley and Sons, 2005; pp 355–374.
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12. *Preparation of protected glutaconaldehyde derivative* **10** *as a typical procedure*: A solution of *n*-BuLi in hexanes (2.45 mL, 3.9 mmol) was added at 0 °C to a solution of diisopropylamine (0.56 mL, 3.9 mmol) in THF (0.85 mL). The resulting mixture was stirred for 0.5 h. Imine **9** (0.65 g, 3.8 mmol) in THF (0.85 mL) was then added dropwise at 0 °C under stirring. After 1 h at 0 °C aldehyde **8** (0.2 g, 1.5 mmol) was added dropwise during 0.5 h. The mixture was maintained under stirring during 12 h after which the solution was hydrolyzed with H_2O (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×5 mL). After removal of the solvent under reduced pressure, the residue was dissolved in a MeOH/THF mixture (1/1.3, 5.6 mL), oxalic acid (0.39 g, 3.07 mmol) was added and the mixture was refluxed during 1 h. H_2O (0.4 mL) was added and the reflux maintained for an additional 1 h. After addition of H_2O (10 mL) extraction with CH_2Cl_2 and removal of solvent under reduced pressure afforded derivative **10** (0.69 g, 20% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, $J = 5.4$ Hz, 3H), 1.29 (m, 7H), 2.08 (m, 1H), 2.18 (t, $J = 6.9$ Hz, 2H), 2.62 (dd, $J = 5.4$, 6 Hz, 2H), 3.76 (t, $J = 10.8$ Hz, 2H), 4.09 (dd, $J = 4.2$, 10.8 Hz, 2H), 4.66 (t, $J = 5.4$ Hz, 1H), 6.51 (t, $J = 6.9$ Hz, 1H), 9.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 24.1, 25.6, 28.2, 31.8, 34.9, 67.0 (2C), 100.3, 145.5, 147.9, 194.9; MS (IE) *m*/*z* 226 ($M^{+\cdot}$), 87.
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15. *Preparation of glutaconaldehyde* **19**: To a solution of salt **18** (186 mg, 1.38 mmol) in a biphasic mixture of EtOAc and H_2O was added dropwise, under vigorous stirring, a solution of 5 N HCl until the pH was below 3. After additional stirring for 10 min, the organic phase was collected, dried over $MgSO_4$ and concentrated in vacuo. Free glutaconaldehyde **19** was isolated as a pale yellow oil (112 mg, 72% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.76 (s, 3H), 3.58 (m, 2H), 6.77 (m, 1H), 9.49 (s, 1H), 9.81 (d, $J = 0.9$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (CH_3), 43.2 (CH_2), 141.6 (CH), 142.2 (C_{quat}), 194.4 (CH), 196.6 (CH) ppm; IR (neat) $\nu = 3356$ cm^{-1}, 2969, 2921, 1680, 1618; MS (CI): *m*/*z* (%) 113 (100) $[M+H]^+$. *Cinnamic aldehyde* **20**: To a solution of salt **18** (70 mg, 0.52 mmol), in CH_2Cl_2 (10 mL), was added *p*-toluenesulfonic acid (99 mg, 0.52 mmol) under stirring. After one night at room temperature, the organic phase was washed with an NH_4Cl solution. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give cinnamic aldehyde **20** as a colorless oil (40 mg, 0.2 mmol, 80% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.50 (s, 3H), 7.30 (s, 1H), 7.58 (s, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 9.62 (s, 1H), 10.04 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1 (CH_3), 21.3 (CH_3), 128.2 (CH), 131.1 (CH), 136.1 (C_{quat}), 136.3 (CH), 136.9 (C_{quat}), 139.7 (C_{quat}), 148.0 (CH), 191.9 (CH), 195.2 (CH) ppm; IR (neat) ν 3428, 2943, 2924, 1685, 1626, 1600 cm^{-1}; MS (CI) *m*/*z* (%) 189 (100) $[MH]^+$; HRMS (CI) calculated for $C_{12}H_{13}O_2^+$ 189.0914, found 189.0912.
16. *Pyridinium salt* **21**: Aldehyde **10** (0.35 g, 1.5 mmol) and *n*-butylamine (0.15 mL, 1.5 mmol) were dissolved in MeOH and the resulting solution refluxed during 2 h. A mixture of hydrochloric acid (2 N in H_2O) and methanesulfonic acid (1/1, 0.5 mL) was then added and the mixture refluxed overnight. After removal of solvents, the residue was chromatographed over silica gel, using a mixture of CH_2Cl_2/MeOH (80/20) as eluent, to give pure salt **21** (0.28 g, 60% yield) as an orange sirup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3H), 0.90 (t, $J = 7.5$ Hz, 3H), 1.33 (m, 6H), 1.67, (q, $J = 7.5$ Hz, 2H), 1.96 (m, $J = 7$ Hz, 2H), 2.71 (s, 3H), 2.86 (m, $J = 7.5$ Hz, 2H), 4.83 (t, $J = 7$ Hz, 2H), 8.06 (dd, $J = 6$, 8.4 Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 8.93 (s, 1H), 9.16 (d, $J = 6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.9, 19.4, 22.3, 30.1, 31.1, 32.6, 33.8, 39.5, 61.8, 128.2, 143.1, 144.1, 143.9, 144.6; MS (ESI) *m*/*z* 206 (M^+), 150 ($C_{10}H_{16}N^+$).