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# A new protocol for masking and unmasking of vicinal hydroxyl and formyl groups in 6- hydroxyarene-1, 3-dicarboxaldehydes

**Koneni V. Sashidhara*, Jammikuntla N. Rosaiah and Abdhesh Kumar**
*Medicinal and Process Chemistry Division,*
*Central Drug Research Institute, Lucknow, 226 001, India*

A simple and efficient protocol is revealed for the masking and unmasking of α hydroxyl benzaldehyde group in aromatic dialdehydes, by foming a keto-enamine Schiff bases and subsequent unmasking by using $NaN_3$/ DMF.

Key words: Schiff bases, Enamine, NMR spectroscopy, regioselectivity, masking, unmasking, 2-hydroxy benzaldehydes.
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*Corresponding author's E-mail: sashidhar123@gmail.com (K V Sashidhara)
Fax: +91-522 2623405, Tel.:+91 522 2612411-18

In continuation of our drug discovery programme to synthesize biologically active compounds, we have recently synthesized a series of novel Schiff bases from two aromatic dialdehydes, in which the reactions were regioselective and products existed in the keto-enamine form, in which the aromaticity of the relevant ring was disrupted.[1] It is worth mentioning that the product **1** formed by the condensation of alkyl amine with the dialdehyde was highly stable and our efforts to react further the free aldehyde failed both with increasing molar ratio of the alkyl amine and also by increasing the reaction temperature to reflux and we rather discovered vicarious nucleophilic substitution in enamine derivatives of 1-hydroxynaphthalene-2,4- dicarbaldehyde[2].

We became curious to see the reactivity of Sodium azide on the system, the results of our investigation form the subject matter of this letter. We thought the $NaN_3$ would act as a nucleophile and may attack the free aldehyde. Recently, Algi F et al have discovered that $NaN_3$ can reduce the carbonyl groups in quinones to the corresponding hydroxyl groups in high yield [3]. Also, very recently a method for the direct conversion of aldehydes to acyl azides using tert- butyl hypochlorite and sodium azide is reported [4]. However, when we treated **1** with $NaN_3$ in DMF resulted in the formation of product in which the carbonyl at position 1 has been converted to alcohol (Scheme 1).

Though, Algi F et al. have shown that 1, 4-Benzoquinones can be reduced to hydroquinones by the action of $NaN_3$, to the best of our knowledge we are the first group to show the unmasking of 1-formyl-2-hydroxy moiety in 6-hydroxyarene-1,3-dicarboxaldehydes. Also it is interesting to note that the free aldehyde did not get reacted under the reaction conditions employed. We also examined the scope and generality of the method in which various enamine derivatives of aromatic dialdehydes were used and the results are summarized in Table 1.

It is interesting observation that all the transformations are isohypsic and no overall redox process is involved (i.e. oxidation level of the starting molecule upon reaction with amine and its next recovery is not changed, as the C-atom of oxo group and OH-substituted $sp^2$-hybridized carbon atom possess the same oxidation state.) Though the role of $NaN_3$ is under investigation in our laboratory, we believe that since we used 5 equivalent of $NaN_3$ per mole of substrate, the most plausible mechanism of this reaction would be nucleophilic attack of the azide-anion at the enamine moiety of the push-pull system, since according to numerous literature data this site is the most electrophilic. Then stable adduct (azido hemiaminal phenolate) is formed, which then on hydrolysis gives rise to unmasked hydroxyl dialdehyde, for which the driving force is to regain aromaticity (Scheme 2). Cho et al.[5] as used Fischer's base to protect the hydroxyl and aldehyde groups of 2-hydroxybenzaldehydes and deprotected it by the Ozonolysis in methanol at -78$^o$c.

In conclusion, a simple and efficient protocol for the masking (by forming enamine Schiff base) and unmasking of α hydroxyl benzaldehyde group in aromatic dialdehydes, is revealed and hopefully be extended to other compounds with different positions of the substituents in question, and we are currently pursuing these ideas.

## Experimental:

Melting points were recorded on Buchi-530 capillary melting point apparatus and are uncorrected. IR spectra of the compounds were recorded on Perkin-Elmer AC-1 spectrometer.$^1$H NMR spectra were run on Bruker Avance DPX 300 MHz spectrometer in ($CDCl_3$: δ 7.28, DMSO-$d_6$: 2.50) and TMS was used as internal standard. Data reported as fallows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hertz, integration assignment]. ESI mass spectra were recorded on JEOL SX 102/DA-6000. Silica gel 60-120 mesh was used as stationary phase to isolate the compounds.

**General procedure**

To the aliphatic enamine **1a** (2 mmol) was added Sodium azide (10 mmol) in dimethyl formamide (5ml) and the reaction mixture was stirred at 140-145$^0$c temperatures for three to four hours. After completion of the reaction (TLC monitoring) the reaction mixture was poured in water and then extracted with chloroform. Crude product was purified by column chromatography over silica to provide aromatic dialdehyde **2** in good yield.

***Data***

*4-Methyl-8-methylaminomethylene-2,7-dioxo-7,8-dihydro-2H-benzo[h]chromene-10 carbaldehyde* **1a**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.52 (s, 1H), 11.17 (s, 1H), 8.48 (d, *J* = 6.0 Hz, 1H), 8.12 (s, 1H), 8.03 (d, *J* = 12 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 6.46 (s, 1H), 3.50 (d, 3H), 2.58 (s, 3H); ESI Ms: 296 ($M^{+1}$), 297 ($M^{+2}$); IR (KBr): 3407, 2925, 1729, 1658, 1585, 1459, 1352, 1244, 1083, 1024 cm$^{-1}$; m.p: >290$^0$C;

*8-Ethylaminomethylene-4-methyl-2,7-dioxo-7,8-dihydro-2H-benzo[h]chromene-10-carbaldehyde* **1b**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.54 (s, 1H), 11.16 (s, 1H), 8.47 (d, *J* = 9.0 Hz, 1H), 8.12 (s,1H), 8.04 (d, *J* = 12.0 Hz, 1H), 7.66 (d, , *J* = 9Hz, 1H ), 6.46 (s, 1H), 3.75 (m, 2H), 2.58 (s, 3H), 1.53 (t, 3H); ESI Ms: 310 ($M^{+1}$); IR (KBr): 3437, 1731, 1643, 1587,1352 cm$^{-1}$; m.p: 242$^0$C;

*4-Methyl-2,7-dioxo-8-propylaminomethylene-7,8-dihydro-2H-benzo[h]chromene-10-carbaldehyde* **1c**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.52 (s, 1H), 11.13 (s,1H), 8.44 (d, *J* = 6.0 Hz, 1H), 8.10 (s, 1H) 8.05 (d, *J* =12.0 Hz, 1H), 7.65 (d, *J* = 6.0Hz, 1H), 6.45 (s, 1H), 3.66-3.64 (m, 2H), 2.62 (s, 3H) 1.92 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); ESI Ms: 324 ($M^{+1}$); IR (KBr): 3410, 2932, 1728, 1595, 1449, 1237, 1184, cm$^{-1}$; m.p: 222$^0$C;

*8-Butylaminomethylene-4-methyl-2,7-dioxo-7,8-dihydro-2H-benzo[h]chromene-10-carbaldehyde* **1d**: $^1$H NMR ($CDCl_3$, 300MHz): δ13.50 (s, 1H), 11.16 (s, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.10(s, 1H), 8.02

(d, *J* = 12.0 Hz, 1H), 6.45 (s, 1H), 3.68 (br t, 3H), 2.66 (s, 3H), 1.86 (m, 2H), 1.46 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ESI Ms: 338 ($M^{+1}$), 339 ($M^{+2}$), 360 ($M^{+23}$); IR (KBr): 3415, 2936, 1722, 1598, 1447, 1355, 1239 $cm^{-1}$; m.p: 268$^0$C;

*8-(tert-Butylamino-methylene)-4-methyl-2,7-dioxo-7,8-dihydro-2H-benzo[h]chromene-10-carbaldehy De* **1e**: $^1$H NMR ($CDCl_3$, 300MHz): 13.83 (s, 1H), 11.14 (s, 1H), 8.43 (d, *J* = 9.0Hz, 1H), 8.15 (s, 1H), 8.11 (d, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 6.45 (s, 1H), 2.67 (s, 3H), 1.52 (s, 9H); ESI Ms: 338 ($M^{+1}$); IR(KBr): 3432, 2973, 2816, 1737, 1595 $cm^{-1}$; m.p: >290$^0$C;

*7-Hydroxy-4-methyl-2-oxo-2H-benzo[h]chromene-8,10-dicarbaldehyde* **2**: $^1$H NMR (DMSO-$d_6$, 300 MHz); δ10.96 (s, 1H), 10.32 (s, 2H), 8.33- 8.29 (m, 2H), 7.95 (d, *J* = 9Hz, 1H), 6.65 (s, 1H), 2.52 (s, 3H); ESI Ms: 283 ($M^{+1}$); IR (KBr): 3398, 2925, 2854, 1727, 1631, 1488, 1365, 1228, 1165, 1067, 1031$cm^{-1}$; m.p: 204$^0$C;

*3-Methylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde* **3a**: $^1$H NMR (DMSO-$d_6$, 300 MHz): δ12.43, (s, 1H), 9.77, (s, 1H), 9.11, (d, *J* = 8.28 Hz, 1H), 8.45, (d, *J* = 13.8 Hz, 1H), 8.32, (d, *J* = 8.82 Hz, 1H), 7.85, (s, 1H), 7.7-7.65, (m, 1H), 7.5-7.45, (m, 1H), 3.39, (s, 1H); ESI Ms: 214($M^{+1}$); IR (KBr): 3444, 2938, 1633, 1596, 1351 $Cm^{-1}$; m.p: 213$^0$C;

*3-Ethylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde* **3b**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.22, (s, 1H), 9.88, (s, 1H), 9.2, (d, *J* = 12.4 Hz, 1H), 8.49, (d, *J* = 9.1 Hz, 1H), 7.9, (d, *J* = 12.5 Hz, 1H), 7.74-7.68, (m, 1H), 7.54-7.50, (m, 2H), 3.73-3.64, (m, 2H), 1.50-1.45, (t, *J* = 7.26 Hz, 3H); ESI Ms: 228 (M+1); IR (K Br): 3442, 2941, 1632, 1595, 1350$Cm^{-1}$; m.p: 225$^0$C;

*3-Butylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde* **3c**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.14, (s, 1H), 9.85, (s, 1H), 9.17, (d, *J* = 8.2 Hz, 1H), 8.46, (d, *J* = 8.3 Hz, 1H), 7.82, (d, *J* = 9.93 Hz, 1H), 7.7-7.65, (t, *J* = 9.2 Hz, 1H), 7.52-7.46, (m, 2H), 3.57, (m, 2H), 1,78-1.70, (m, 2H), 1.52-1.43, (m, 2H), 1.01-0.96, (t, *J* = 7.9 Hz, 3H); ESI Ms: 256 ($M^{+1}$); IR (KBr): 3426, 2925, 2845, 1628, 1594, 1352$Cm^{-1}$; m.p: 95$^0$C;

*3-(tert-Butylamino-methylene)-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde***3d**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.57, (s, 1H), 9.86, (s, 1H), 9.19, (d, *J* = 8.46 Hz, 1H), 8.46, (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 13.8 Hz, 1H), 7.69, (t, *J* = 7.17 Hz, 1H), 7.53-7.48, (m, 2H), 1.52, (s, 9H); IR (KBr): 3424, 2925, 1638, 1595, 1355$Cm^{-1}$; m.p: 184$^0$C;

*3-Heptylaminomethylene-4-oxo-3,4-dihydro-naphthalene-1-carbaldehyde* **3e**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.17, (s, 1H), 9.87, (s, 1H), 9.19, (d, *J* = 8.22 Hz, 1H), 8.48-8.45, (m, 1H), 7.9, (d, *J* = 12.81, 1H), 7.69, (m, 1H), 7.54-7.48, (m, 2H), 3.67-3.58, (m, 2H), 1.46-1.22, (m, 10H), 0.91-0.86, (t, *J* = 6.24 Hz, 3H); ESI Ms: 298 ($M^{+1}$); IR (KBr): 3429, 2923, 2860, 1632, 1595, 1352$Cm^{-1}$; Liquid.

*4-Hydroxy-naphthalene-1,3-dicarbaldehyde* **4**: $^1$H NMR ($CDCl_3$, 300 MHz): δ13.11, (s, 1H), 10.10, (s, 1H), 9.93, (s, 1H), 9.18, (d, *J* = 8.9 Hz, 1H), 8.40, (d, *J* = 8.9 Hz, 1H), 7.92, (s, 1H), 7.78-7.72 (m, 1H), 7.58-7.53, (m, 1H); IR (KBr):3408, 2849, 1628, 1592,1508$cm^{-1}$; m.p: 137$^0$C;

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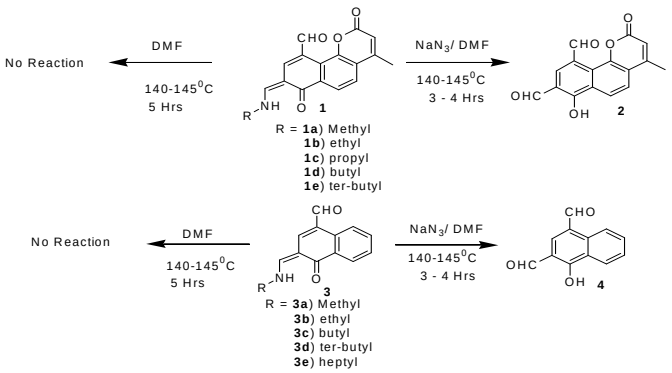
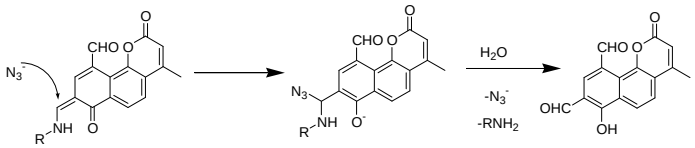
**Scheme 1**




**Scheme 2**

Pausible Mechanism:



| Entry | Substrate | Product [a] | Yield (%) | Time (Minutes) |
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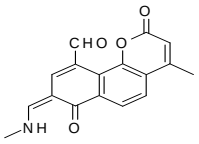
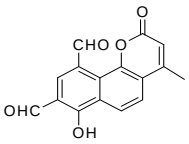
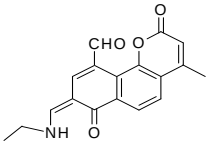
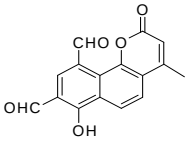
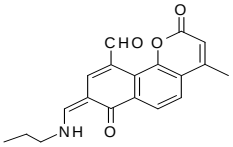
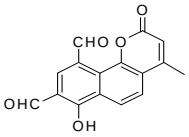
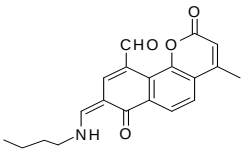
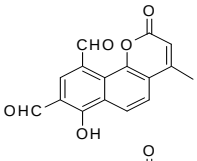
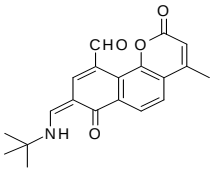
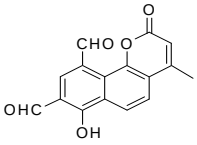
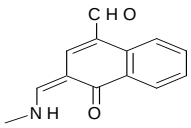
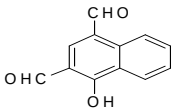
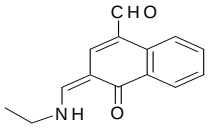
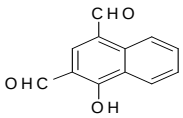
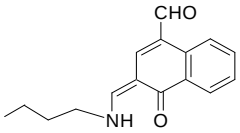
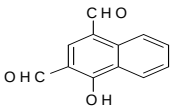
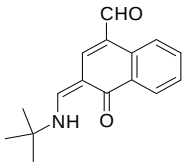
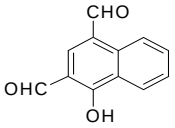
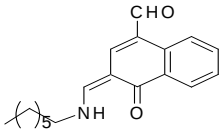
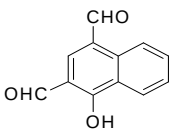
| 1 |  |  | 75 | 160 |
| 2 |  |  | 66 | 191 |
| 3 |  |  | 72 | 180 |
| 4 |  |  | 60 | 146 |
| 5 |  |  | 55 | 188 |
| 6 |  |  | 60 | 177 |
| 7 |  |  | 52 | 157 |
| 8 |  |  | 40 | 174 |
| 9 |  |  | 55 | 158 |
| 10 |  |  | 45 | 188 |

Table:1 Masking and unmasking in different enamine derivatives of aromatic dialdehydes.
[a] Structures confirmed by IR, $^{1}$H NMR and Mass spectroscopy..

**References and notes**

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