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The design of efficient and selective routes to pyridyl analogues of 3-oxo-3,4-dihydro-2*H*-1,4-(benzothiazine or benzoxazine)-6-carbaldehydes

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ABSTRACT

This Letter describes the synthesis of challenging pyridyl analogues of 3-oxo-3,4-dihydro-2*H*-1,4-(benzothiazine or benzoxazine)-6-carbaldehydes. The six different routes described are high yielding, contain no major purification issues and have been used to give gram quantities of each aldehyde.

As part of an antibacterial medicinal chemistry programme we used commercially available 3-oxo-3,4-dihydro-2*H*-(1,4-benzothiazine and benzoxazine)-6-carbaldehydes **1** and **2** (Fig. 1). We also required an access to the non-commercial pyridyl analogues of these aldehydes **3**–**8**.

Although the synthesis of both 3-oxo-3,4-dihydro-2*H*-1,4-(benzothiazine and benzoxazine)-6-carbaldehydes **1** and **2** was known,[1] aldehydes **3**–**8** were unknown in the literature at this time.

For compound **3** we opted to start from commercially available nitrophenol **9** (Scheme 1).[2] Firstly, we protected the phenol as the methoxy derivative, then brominated and removed the methyl group to give the desired bromo nitro alcohol **10** in 96% yield over three steps. Bromo nitro alcohol **10** was then alkylated with bromo ethyl acetate using K_2CO_3 as base to give **11** in 89% yield. The nitro group was reduced by iron which gave the free aniline, that immediately cyclised to give bromide **12**. From here many possible routes are plausible to give the desired aldehyde **3**. In the interest of producing **13** on large scale we opted for a Suzuki reaction followed by oxidative cleavage. Using this route we were able to produce aldehyde **3** on kilogram scale.

For aldehyde **4** (Scheme 2),[4] a literature search revealed a key intermediate 5-bromo-amino ester **15**.[5] This was synthesised from commercially available pyridine **14** using the procedure described by Kelly,[5] via bromination to give **15** in a 1:1 mixture with the undesired 3-bromo isomer **16**. Both isomers were easily separated by column chromatography. The bromine of **15** was then displaced by ethyl 2-mercaptoacetate and the intermediate cyclised immediately to give ester **17**. This ester was converted into the acid, then activated with *iso*-butyl chloroformate and reduced using $NaBH_4$ to give alcohol **19**. Oxidation was carried out using MnO_2 as the oxidant to afford the desired aldehyde **4** in 55% yield.

Aldehyde **5** was synthesised from commercially available 5-hydroxy-2-methylpyridine (**20**) (Scheme 3).[6] The first step involved formation of the *N*-oxide using *m*-CPBA, then alkylation with methyl bromoacetate to give compound **21** in 53% yield over two steps. This material was then nitrated selectively and the resulting free acid was re-protected with MeI to give methyl ester **22**. Rearrangement of **22** gave TFA-protected alcohol **23** in 34% yield. During purification by column chromatography of **23**, some cleavage of the TFA group was observed. Both TFA-protected and unprotected **23** were carried through the next steps to give alcohol **24**. This involved reduction of the nitro group with spontaneous cyclisation and deprotection to give the desired alcohol **24** in 66% yield over

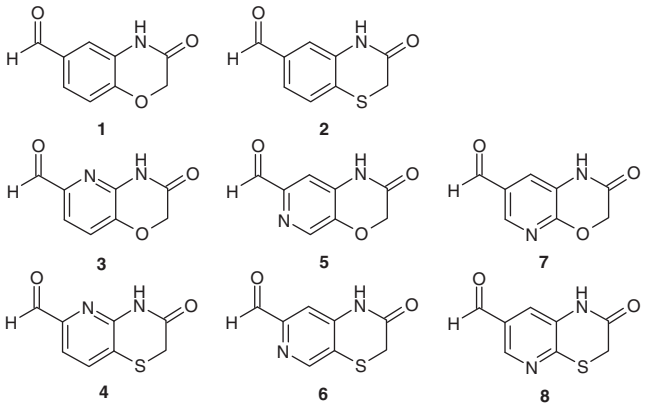

Figure 1. Required pyridyl analogues of 3-oxo-3,4-dihydro-2*H*-1,4-(benzothiazine and benzoxazine)-6-carbaldehydes.

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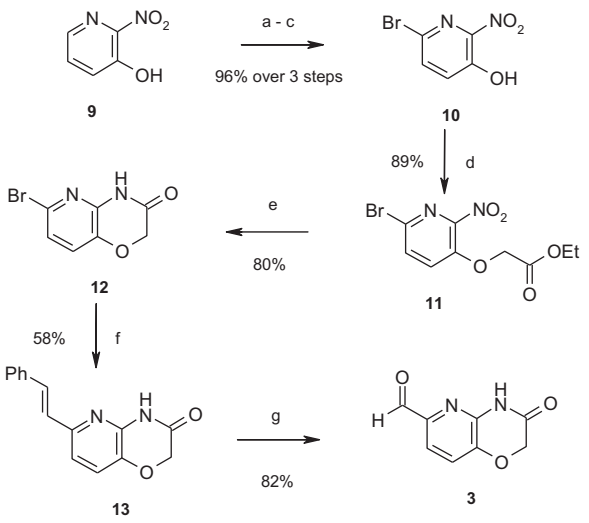
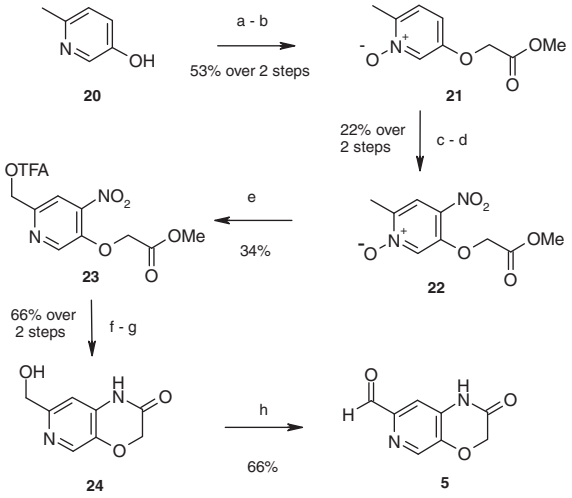
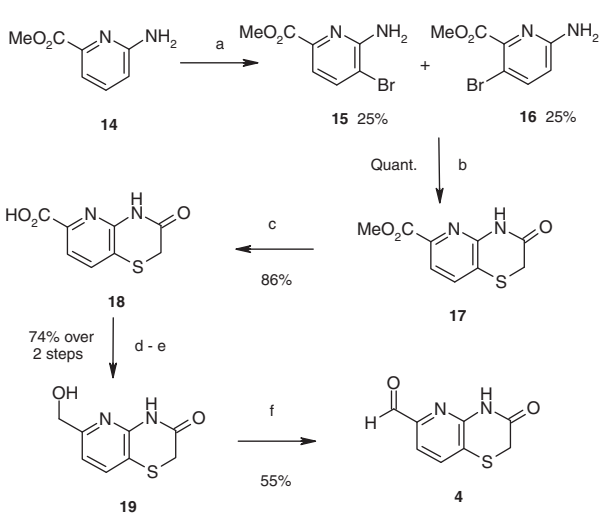


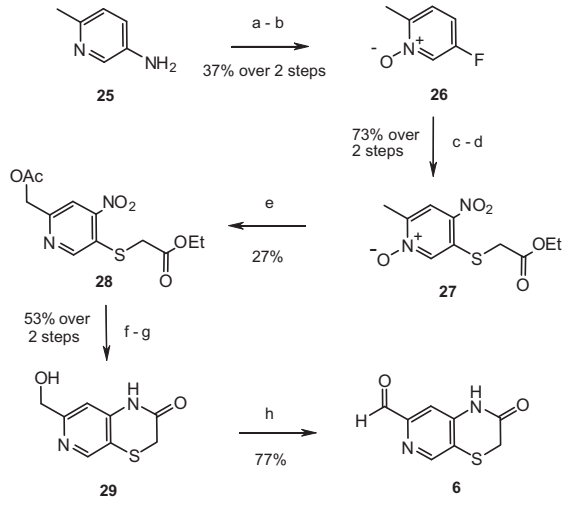
Scheme 1. Synthetic approach to 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carbaldehyde (**3**).[3] Reagents and conditions: (a) NaOMe, MeOH, rt; (b) Br_2, 0 °C, 30 min; (c) AcOH; (d) $BrCH_2CO_2Et$, K_2CO_3, Me_2CO, reflux, 10 h; (e) NH_4Cl, Fe, H_2O, MeOH, reflux, o/n; (f) $(HO)_2BCH$ = CHPh, K_2CO_3, $Pd(PPh_3)_4$, H_2O, 1,4-dioxane, reflux, o/n; (g) O_3, CH_2Cl_2, −78 °C, 15 min, then Me_2S, −78 °C, 3 h then rt, o/n. o/n, overnight.



Scheme 3. Synthetic approach to 2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-7-carbaldehyde (**5**).[3] Reagents and conditions: (a) *m*-CPBA, $CHCl_3$, rt, 1 h; (b) $BrCH_2CO_2Me$, K_2CO_3, rt, o/n; (c) fuming HNO_3, concd H_2SO_4, 65 °C, o/n; (d) MeI, K_2CO_3, rt, 3 days; (e) $(CF_3CO)_2O$, reflux, o/n; (f) AcOH, Fe, 60 °C, 1 h; (g) NaOH, 1,4-dioxane, H_2O, rt, o/n; (h) MnO_2, THF, $ClCH_2CH_2Cl$, 60 °C, 20 h.



Scheme 2. Synthetic approach to 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (**4**).[3] Reagents and conditions: (a) Br_2, $CHCl_3$, rt; (b) $HSCH_2CO_2Et$, NaH, DMF, 0 °C, 1 h, then **15**, rt, o/n; (c) NaOH, H_2O, 1,4-dioxane, reflux, o/n; (d) $ClCO_2Bu^i$, Et_3N, THF, −10 °C, 20 min; (e) $NaBH_4$, H_2O, −10 °C, 30 min, then HCl, H_2O, rt, pH 7; (f) MnO_2, THF, CH_2Cl_2, rt, o/n.



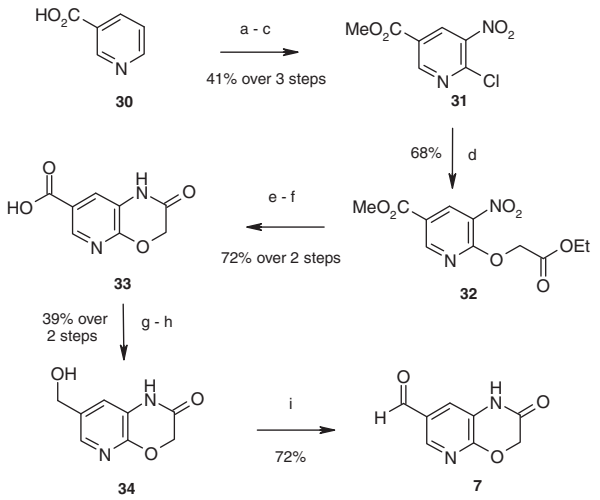
Scheme 4. Synthetic approach to 2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazine-7-carbaldehyde (**6**).[3] Reagents and conditions: (a) HBF_4, Bu^nONO, EtOH, −5 °C, 3 h; (b) *m*-CPBA, CH_2Cl_2, rt, o/n; (c) fuming HNO_3, concd H_2SO_4, 70 °C, 5.5 h; (d) $HSCH_2CO_2Et$, 1,4-dioxane, NaH, rt, 3 days; (e) Ac_2O, 80 °C, 6 h; (f) AcOH, Fe, 60 °C, 3 h; (g) NaOH, 1,4-dioxane, H_2O, rt, o/n; (h) MnO_2, THF, $ClCH_2CH_2Cl$, 65 °C, o/n.

two steps. Finally, we obtained aldehyde **5** in 66% yield via oxidation of alcohol **24** using MnO_2.

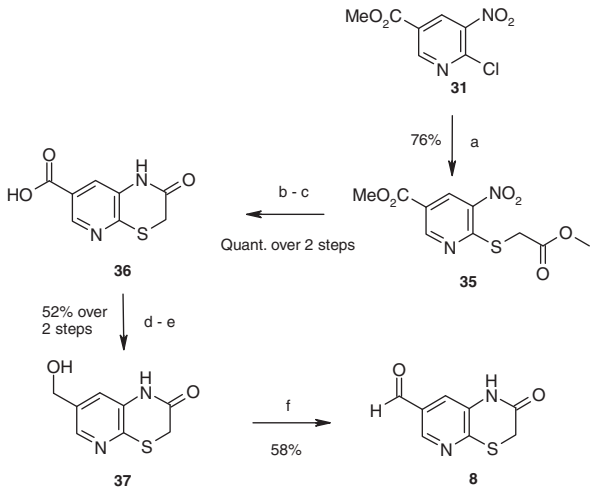
Scheme 4 shows our route which utilises intermediate **26** to give aldehyde **6**.[4] Blanz et al. had synthesised compound **26** using commercially available 5-amino-2-picoline (**25**),[7] via a Sandmeyer reaction, then N-oxidation to give *N*-oxide **26** in 37% yield over two steps. The first step of our synthesis involved nitration of **26** followed by a fluoride displacement using ethyl 2-mercaptoacetate to give methyl ester **27** in 73% yield over two steps. The *N*-oxide rearrangement was performed using Ac_2O instead of trifluoroacetic anhydride (TFAA), otherwise the synthesis followed a very similar path as that for aldehyde **5** in Scheme 3.

For aldehyde **7** (Scheme 5),[6] Berrie et al. had synthesised 6-chloro-5-nitro-nicotinic acid methyl ester (**31**) via nitration followed by chlorination of 6-hydroxynicotinic acid (**30**) in 41% yield over three steps.[8] We displaced the chloride of **31** using ethyl hydroxyacetate to give ethyl ester **32**. This ester was then reduced with iron and cyclised to afford acid **33** in 72% over two steps. The acid **33** was then activated with *iso*-butyl chloroformate and reduced using $NaBH_4$ to give alcohol **34**. Oxidation of alcohol **34** using MnO_2 gave the desired aldehyde **7** in 72% yield.

For the final aldehyde **8** we used the same general route as for aldehyde **7** (Scheme 6),[4] but used methyl 2-mercaptoacetate instead of ethyl hydroxyacetate for the chlorine displacement. As



Scheme 5. Synthetic approach to 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carbaldehyde (**7**).[3] Reagents and conditions: (a) fuming HNO_3, concd H_2SO_4, 50 °C, 3 h; (b) $SOCl_2$, DMF, 80 °C, o/n; (c) MeOH, 30 min; (d) $HOCH_2CO_2Et$, 1,4-dioxane, NaH, rt, o/n; (e) AcOH, Fe, 60 °C, 2.5 h; (f) NaOH, THF, H_2O, rt, 2.5 h; (g) $ClCO_2Bu^i$, CH_3Cl, DMF, THF, 0 °C, 2 h; (h) $NaBH_4$, H_2O, 0 °C, 1 h, then HCl, H_2O, rt, pH 7; (i) MnO_2, THF, CH_3Cl, rt, o/n.



Scheme 6. Synthetic approach to 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]thiazine-7-carbaldehyde (**8**).[3] Reagents and conditions: (a) $HSCH_2CO_2Me$, CH_2Cl_2, Et_3N, rt, 1 h; (b) AcOH, Fe, 60 °C, 1 h; (c) NaOH, THF, H_2O, rt; (d) $ClCO_2Bu^i$, Et_3N, THF, −10 °C, 20 min; (e) $NaBH_4$, H_2O, 0 °C, 30 min, then HCl, H_2O, rt, pH 7; (f) MnO_2, THF, CH_3Cl, rt, 18 h.

for aldehyde **7** this route was able to deliver gram quantities of aldehyde **8**.

In conclusion, we have demonstrated that all six aldehydes can be accessed and that all the routes were able to deliver multi-gram quantities of material.

Acknowledgements

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3. Selected analytical data: *Compound* **3**: White solid; mp 208–211 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.81 (s, 2H), 7.51 (d, J = 12 Hz, 1H), 7.62 (d, J = 12 Hz, 1H), 9.77 (s, 1H), 11.63 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 66.9, 119.8, 123.1, 142.0, 143.4, 144.4, 165.4, 191.0 ESI-HRMS: m/z calcd for $C_8H_7N_2O_3$: 179.0457; found 179.0456 $[M+H]^+$.
Compound **4**: White solid; mp 187–189 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.67 (s, 2H), 7.55 (d, J = 12 Hz, 1H), 8.07 (d, J = 12 Hz, 1H), 9.78 (s, 1H), 11.33 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 28.3, 117.2, 122.8, 136.4, 148.5, 149.7, 165.8, 192.0. ESI-HRMS: m/z calcd for $C_8H_7N_2O_2S$: 195.0228; found 195.0229 $[M+H]^+$.
Compound **5**: White solid; mp 211–213 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.83 (s, 2H), 7.39 (s, 1H), 8.36 (s, 1H), 9.82 (s, 1H), 11.31 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 66.9, 108.2, 134.4, 137.8, 143.4, 147.5, 164.2, 192.3. ESI-HRMS: m/z calcd for $C_8H_7N_2O_3$: 179.0457; found 179.0458 $[M+H]^+$.
Compound **6**: White solid; mp 216–218 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.66 (s, 2H), 7.40 (s, 1H), 8.65 (s, 1H), 9.86 (s, 1H), 11.18 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 27.7, 108.3, 121.9, 144.5, 147.6, 150.8, 164.7, 192.8. ESI-HRMS: m/z calcd for $C_8H_7N_2O_2S$: 195.0228; found 195.0219 $[M+H]^+$.
Compound **7**: White solid; mp 261–263 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.82 (s, 2H), 7.39 (s, 1H), 8.36 (s, 1H), 9.82 (s, 1H), 11.31 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 66.9, 108.2, 134.4, 137.8, 143.4, 147.5, 164.2, 192.3. ESI-HRMS: m/z calcd for $C_8H_7N_2O_3$: 179.0457; found 179.0458 $[M+H]^+$.
Compound **8**: White solid; mp 204–207 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.72 (s, 2H), 7.58 (s, 1H), 8.60 (s, 1H), 10.01 (s, 1H), 10.90 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 28.6, 120.5, 129.4, 134.0, 145.7, 149.8, 164.0, 191.3. ESI-HRMS: m/z calcd for $C_8H_7N_2O_2S$: 195.0228; found 195.0227 $[M+H]^+$.
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