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# Strategic studies in the syntheses of novel 6,7-substituted quinolones and 7- or 6-substituted 1,6- and 1,7-naphthyridones

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**Abstract**

This paper describes the different strategies devised and applied to overcome the selectivity issues in the syntheses of 6,7-disubstituted-1*H*-quinolin-4-one, 7-substituted-1*H*-1,6-naphthyridin-4-one and 6-substituted-1*H*-1,7-naphthyridin-4-one derivatives. They allowed us to improve the overall yields and the scaling-up feasibility. Several examples illustrate these strategies with their advantages and drawbacks.

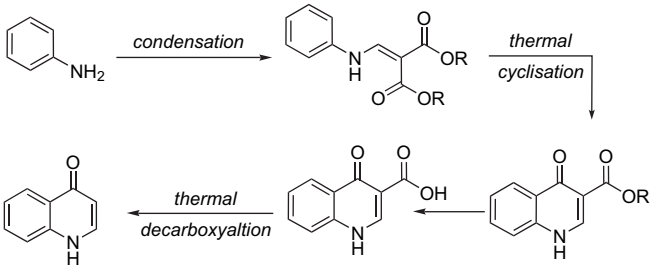

*Keywords:* Quinolone; Naphthyridone; Strategy; Regioselectivity

## 1. Introduction

As part of our continuing interest in 4-phenoxyquinolines and naphthyridines as inhibitors of kinases involved in angiogenesis, we required an efficient access to 7-substituted-1*H*-quinolin-4-ones and 1*H*-1-naphthyridin-4-ones. Different methods are known in the literature to build quinolin-4-one scaffolds.[1]

Probably the most useful preparative method for symmetrical substituted anilines consists of preparing the enamine derivative by reaction with an alkyl methoxymethylidene propanedioate followed by a thermal cyclisation. The 1*H*-quinolin-4-one core is thus obtained after a saponification–decarboxylation sequence (Scheme 1). Since the cyclisation can in theory occur at either of the *ortho* positions of unsymmetrical anilines, it could become tedious to prepare selectively 7-substituted-1*H*-quinolin-4-ones as the regioselectivity of the cyclisation will depend on electronic and steric effects.

To address these issues, we decided to investigate new strategies for the syntheses of 6,7-disubstituted-1*H*-quinolin-4-one (**1**, **2** and **3**), 6-substituted-1*H*-1,7-naphthyridin-4-one (**4** and **5**) and 7-substituted-1*H*-1,6-naphthyridin-4-one (**6** and **7**) derivatives (Fig. 1).




Scheme 1. 4-Step synthesis of 1*H*-quinolin-4-one using an alkyl methoxymethylidene propanedioate.

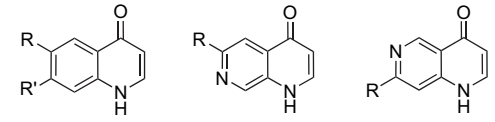



Figure 1.

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## 2. Results and discussion

### 2.1. Synthesis of enamine precursors

The key enamine precursors were obtained by condensation of the anilines with Meldrum's acid derivative **8**.[2] The use of **8** instead of a standard dialkyl 2-(methoxymethylidene)-propanedioate as shown in Scheme 1, allowed us to carry out the thermal cyclisation and the subsequent decarboxylation in one pot.[3] Their syntheses are summarised in Table 1.

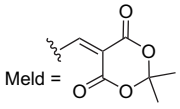
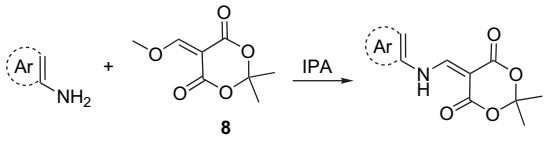



Table 1
Synthesis of enamine precursors




**8**

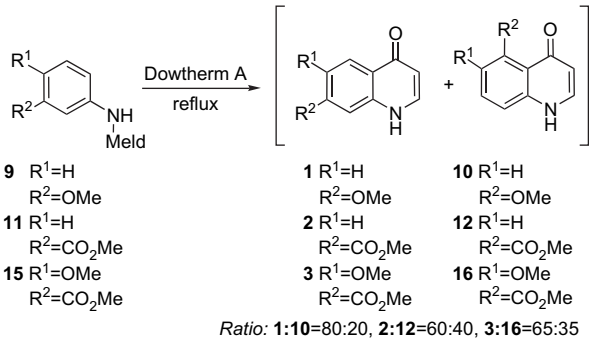
| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 | 3-Methoxyaniline | **9** | 96 |
| 2 | Methyl 3-aminobenzoate | **11** | 92 |
| 3 | Methyl 5-amino-2-methoxybenzoate **14** | **15** | 92 |
| 4 | 3-Amino pyridine *N*-oxide hydrochloride **18** | **19** | 84 |
| 5 | Methyl 3-amino-2-chlorobenzoate **22** | **23** | 92 |
| 6 | 2-Chloropyridin-3-amine | **25** | 88 |
| 7 | 6-Methoxypyridin-3-amine | **27** | 100 |
| 8 | 2-Chloro-6-methoxy-pyridin-3-amine | **29** | 71 |
| 9 | 2-Methoxypyridin-4-amine **31** | **32** | 79 |
| 10 | 3-Bromo-2-methoxypyridin-4-amine **34** | **35** | 93 |
| 11 | 2-Chloropyridin-4-amine | **43** | 71 |
| 12 | 2,6-Dichloropyridin-4-amine | **44** | 92 |

### 2.2. Thermal ring closure strategy and regioisomers separation

#### 2.2.1. Synthesis of 7-methoxy-1H-quinolin-4-one (1)

The synthesis of 7-methoxy-1*H*-quinolin-4-one **1**[4] has previously been described in two steps using Meldrum's acid and 3-methoxyaniline via the corresponding enamine **9**. The electron-donating effects of the *meta* methoxy group favours the cyclisation in its *para* position,[5] giving the desired quinolin-4-one **1** in an 80:20 mixture contaminated with 5-methoxy-1*H*-quinolin-4-one **10** (Scheme 2).[4]

Unfortunately, the two regioisomers could not be easily separated by silica gel chromatography and selective recrystallisation in boiling methanol led to poor recovery.[4] However, in boiling 1 N HCl the desired quinolin-4-one **1** precipitated as a hydrochloride salt in 69% overall yield whereas the salt of 5-methoxy-1*H*-quinolin-4-one **10** remained in solution, allowing an easy separation of the two compounds (Scheme 3).



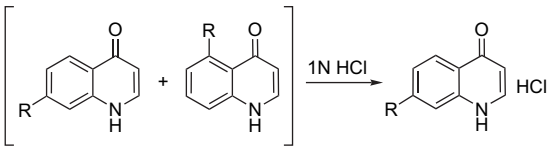

**9** $R^1$=H, $R^2$=OMe
**11** $R^1$=H, $R^2$=$CO_2Me$
**15** $R^1$=OMe, $R^2$=$CO_2Me$

**1** $R^1$=H, $R^2$=OMe
**2** $R^1$=H, $R^2$=$CO_2Me$
**3** $R^1$=OMe, $R^2$=$CO_2Me$

**10** $R^1$=H, $R^2$=OMe
**12** $R^1$=H, $R^2$=$CO_2Me$
**16** $R^1$=OMe, $R^2$=$CO_2Me$

*Ratio:* **1:10**=80:20, **2:12**=60:40, **3:16**=65:35

Scheme 2. Cyclisation reaction.




**1** R=OMe
**2** R=$CO_2Me$

**10** R=OMe
**12** R=$CO_2Me$

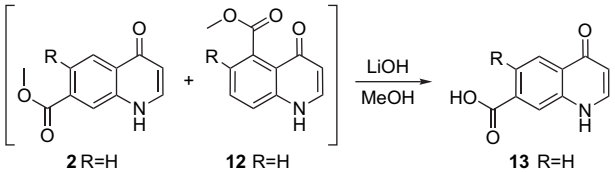
**1** R=OMe
**2** R=$CO_2Me$

*Ratio :* **1:10**=80:20, **2:12**=60:40

Scheme 3. Selective precipitation of hydrochloride salt.

#### 2.2.2. Synthesis of methyl 4-oxo-1H-quinoline-7-carboxylate (2)

The same route was applied for the synthesis of methyl 4-oxo-1*H*-quinoline-7-carboxylate **2**. Although methyl 3-aminobenzoate is commercially available, it was synthesised efficiently by treating inexpensive 3-aminobenzoic acid with thionyl chloride and methanol in quantitative yield.[6] Methyl 3-aminobenzoate was subsequently treated with Meldrum's acid derivative **8** to give the corresponding enamine **11** in 92% yield (Table 1—entry 2), which after thermal cyclisation–decarboxylation gave a 60:40 mixture of 7-substituted-quinolin-4-one **2** and 5-substituted-quinolin-4-one **12** in 60% yield (Scheme 2). This lower regioselectivity has already been reported:[5] Effectively, in practice, a strong electron-withdrawing *meta* substituent, such as an ester group, preferentially favours cyclisation in its *ortho* position. As previously seen, the two regioisomers **2** and **12** were difficult to separate by chromatography but treatment with 1 N hydrochloric acid led to a selective precipitation of the desired isomer **2** as its hydrochloride salt in 47% yield (Scheme 3). On the other hand, saponification of the mixture of regioisomers with LiOH in MeOH occurred exclusively with the regioisomer **2**, giving **13** in 53% yield while the regioisomer **12** remained unchanged under these conditions (Scheme 4).




**2** R=H
**3** R=OMe

**12** R=H
**16** R=OMe

**13** R=H
**17** R=OMe

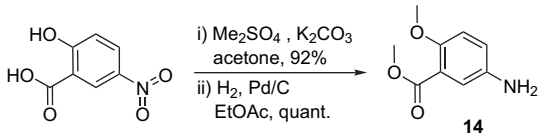
*Ratio:* **2:12**=60:40, **3:16**=65:35

Scheme 4. Selective saponification.

A possible explanation for this difference in reactivity could be that the methyl ester group at the C5 position of the derivative **12** is twisted due to *peri*-interactions with the C4 carbonyl group, thus hampering the access of the hydroxide anion to this ester function. The overall yields for **2** and **13** are 28% and 32%, respectively, starting from methyl 3-aminobenzoate.

### 2.2.3. Synthesis of methyl 6-methoxy-4-oxo-1H-quinoline-7-carboxylate (3)

The above route was applied to the synthesis of methyl 6-methoxy-4-oxo-1*H*-quinoline-7-carboxylate **3**. 2-Hydroxy-5-nitro-benzoic acid was methylated with dimethylsulfate and potassium carbonate in boiling acetone, to give methyl 2-methoxy-5-nitro-benzoate in 92% yield, which was quantitatively transformed into aniline **14** by catalytic reduction over palladium on charcoal (Scheme 5).




Scheme 5. Preparation of aniline **14**.

The methyl 5-amino-2-methoxy-benzoate **14** was then treated with Meldrum's acid derivative **8** to give the corresponding enamine **15** in 92% yield (Table 1—entry 3). Thermal cyclisation–decarboxylation sequence gave a 65:35 mixture of 6,7-disubstituted-quinolin-4-one **3** and 5,6-disubstituted-quinolin-4-one **16** in 53% yield (Scheme 2). Again, the two regioisomers were not easily separated by chromatography. In this case, treatment of the mixture in a 1 N HCl aqueous solution did not allow the separation of the two regioisomers, but a saponification performed with LiOH in MeOH was selective for the isomer **17**. The two products **16** and **17** were thus easily separated and quantitatively recovered (Scheme 4).

### 2.2.4. Synthesis of 1H-1,7-naphthyridin-4-one (4)

The synthesis of 1*H*-1,7-naphthyridin-4-one **4** has previously been described in five steps[7] in 34% yield from 3-amino pyridine *N*-oxide **18**, which seemed to favour cyclisation at the C4 position. The pyridine *N*-oxide **18** can be obtained either from nicotinic amide *N*-oxide via the Hoffmann reaction[8] or from 3-bromo-pyridine *N*-oxide via displacement of the bromine atom with ammonia.[9] We also found that it could be obtained efficiently in 84% yield from pyridine-3-carboxylic acid *N*-oxide via a Curtius rearrangement, followed by a Boc deprotection without any purification (Scheme 6). The intra-molecular cyclisation–decarboxylation reaction of **19**, obtained from **18** by treatment with Meldrum's acid derivative **8** (Table 1—entry 4), was not clean and depended on the concentration. When the ring closure reaction was performed under high dilution (i.e., 0.06 mol/L), as reported by Phuan et al.,[7] cyclisation mainly led to 7-oxido-1*H*-1,7-naphthyridin-4-one **20**, containing 17 mol % of its 5-regioisomer **21** along with other impurities (Table 2—entry 1).

Table 2
Cyclisation results depending on the concentration medium

| Entry | Concentration | Products ratio (**20**/**21**) | Crude yield (%) |
|---|---|---|---|
| 1 | [0.06 M] | 85/15 | 41[a] |
| 2 | [0.4 M] | 33/67 | 93[b] |

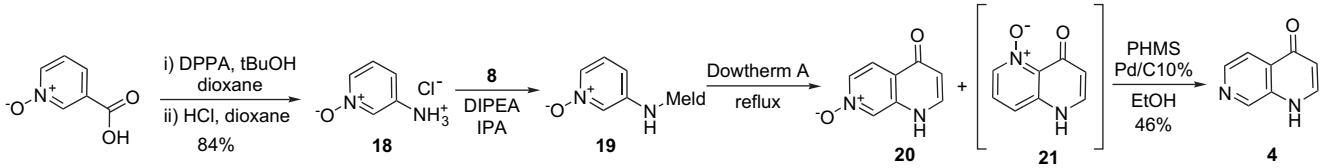
[a] Presence of other impurities by $^1$H NMR.
[b] Unexploitable mixture.

Reduction of the crude naphthyridine *N*-oxide **20** was performed in 46% yield using a method developed by Chandrasekhar et al.[10] with polymethylhydrosiloxane (PMHS) in the presence of palladium on charcoal, giving the desired naphthyridone **4** (Scheme 6). In order to prepare a large amount of this material, the cyclisation was carried out at a higher concentration (i.e., 0.4 mol/L) but under these conditions, an inseparable 33:67 mixture of **20** and **21** was unfortunately obtained (Table 2—entry 2).

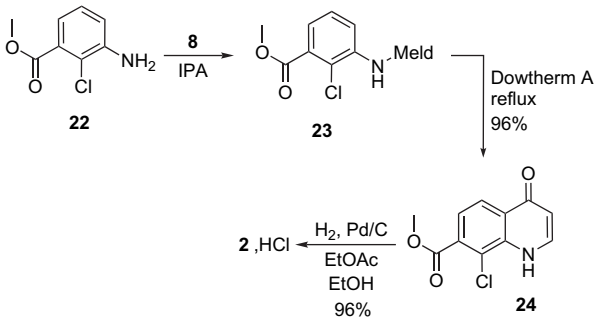
## 2.3. Strategy involving blocking of one of the two α positions

### 2.3.1. Improvement for the synthesis of methyl 4-oxo-1H-quinoline-7-carboxylate (2)

In order to improve the efficiency of the synthesis of **2**, we decided to investigate a route based on blocking one of the two α positions to avoid the regioselectivity issue of the cyclisation step. This strategy was first reported by Breslow et al.[11] in an unambiguous synthesis of 3,5-dimethyl-1*H*-quinolin-4-one. The synthesis of the desired aniline **22**[12] has previously been described in two steps from the commercially available 2-chloro-3-nitro benzoic acid. Aniline **22** was reacted with **8** to give the corresponding enamine **23** in 92% yield (Table 1—entry 5), which led to the 8-chloro-quinoline-4-one **24** in 96% yield after the thermal cyclisation–decarboxylation sequence. The dehalogenation reaction was performed by reduction of **24** under hydrogen in the presence of palladium on charcoal, to give the desired quinoline-4-one **2** in 96% (Scheme 7). The overall yield with this five-step route (80%) compares thus favourably with the yield obtained with the shorter but non-selective approach described in Section 2.2.2 (28%).



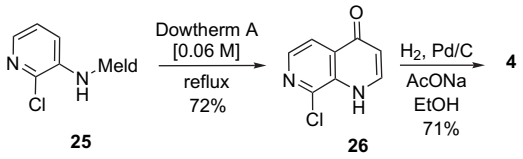

Scheme 6. Note: *N*-oxide reduction step from the crude **20** of Table 2—entry 1.




Scheme 7.

### 2.3.2. Improvement for the synthesis of 1H-1,7-naphthyridin-4-one (4)

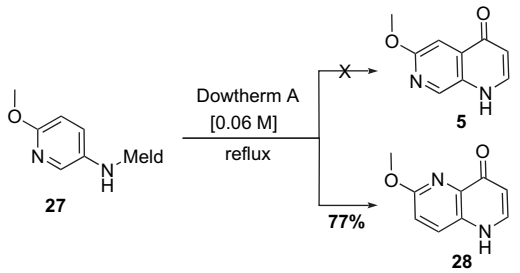
Although the classical route was usable enough to access to **4** in 13% yield, we decided to apply the above strategy to this closely related target. When a high concentration of **25** (Table 1—entry 6) was heated in Dowtherm A at 220 °C, the thermal cyclisation failed. High dilution was required and furnished **26** in 72% yield. The following dehalogenation step was also carried out by palladium-catalysed hydrogenolysis in 71% yield. However, owing to the high dilution required, another route was devised and will be discussed in Section 2.4.1 (Scheme 8).



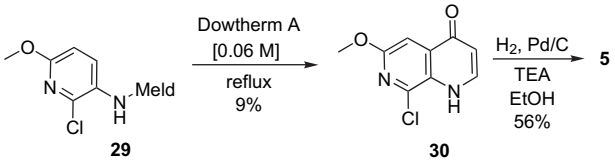

Scheme 8.

### 2.3.3. Synthesis of 6-methoxy-1H-1,7-naphthyridin-4-one (5)

It is known that the most nucleophilic position in compounds such as **27** is the α position of the pyridine ring.[13] Therefore, we attempted the synthesis of 6-methoxy-1*H*-1,7-naphthyridin-4-one **5** under high dilution conditions (i.e., 0.06 mol/L), which should favour the obtention of the desired regioisomer **5** and minimise side reactions. However, when **27** (Table 1—entry 7) was heated in Dowtherm A at 220 °C the sole product formed was the regioisomer **28** in 77% yield (Scheme 9).




Scheme 9.




Scheme 10.

When the α-blocked position strategy was applied to **29**, which was prepared by reduction of the nitro group of the commercially available 2-chloro-6-methoxy-3-nitro-pyridine, followed by reaction with **8** (Table 1—entry 8), ring closure occurred only in very low yield, even under high dilution conditions. Dehalogenation of the intermediate **30** gave the desired product **5** in 56% (Scheme 10). A more efficient synthesis was therefore necessary and will be discussed in Section 2.4.2.

### 2.3.4. Synthesis of 7-methoxy-1H-1,6-naphthyridin-4-one (6)

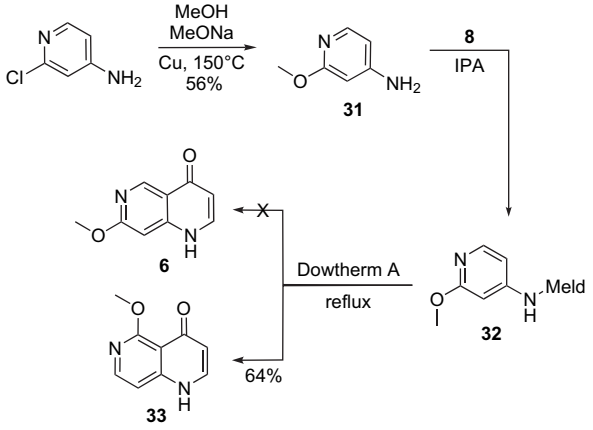
The standard approach for the synthesis of 7-methoxy-1*H*-1,6-naphthyridin-4-one **6** was first attempted starting from **31**[14] (readily obtained as shown in Scheme 11) but the sole product formed when **32** (Table 1—entry 9) was heated in Dowtherm A at 220 °C was the regioisomer **33** in 64% yield. This result showed that the C-3 position is the most nucleophilic of **32** (Scheme 11).

Therefore, we decided to take advantage of the nucleophilic reactivity of this position and block it by introduction of a halogen atom. Indeed, the bromination was completely selective for the C-3 position when **31** was treated with NBS in acetonitrile, giving the intermediate **34**. The enamine pyridine **35** (Table 1—entry 10) was cleanly converted into the 8-bromo-7-methoxy-1,6-naphthyridin-4(1*H*)-one **36**, which was subsequently debrominated with palladium on charcoal to give the desired product **6** (Scheme 12).

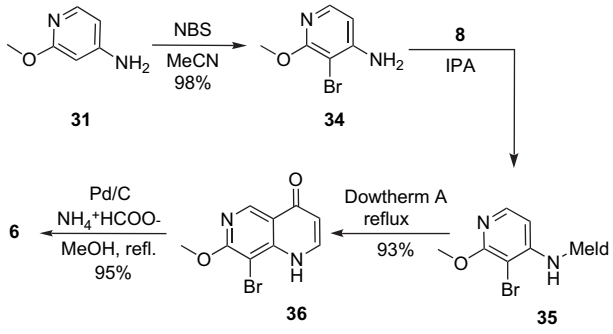
## 2.4. The modified Leimgruber–Batcho approach

### 2.4.1. Revisited synthesis of 1H-1,7-naphthyridin-4-one (4)

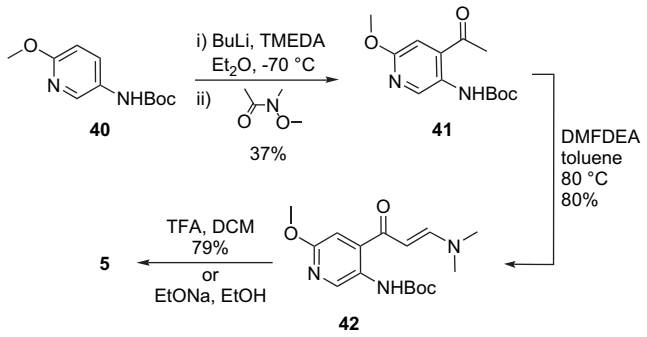
Koskinen et al.[15] reported a modified Leimgruber–Batcho[16] procedure to form the 1*H*-quinolin-4-one core. We




Scheme 11.

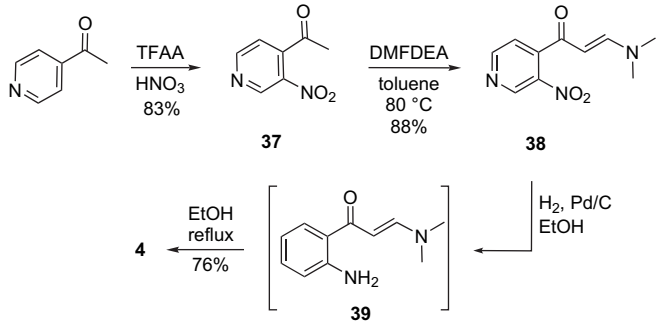



Scheme 12.




Scheme 14.

decided to apply this methodology to the 1*H*-1,7-naphthyridin-4-one series. Katritzky et al.[17] have described a straightforward route to 1-(3-nitropyridin-4-yl)ethanone **37** in 83% yield by nitration of the 1-pyridin-4-ylethanone with the unstable dinitrogen pentoxide,[18] generated in situ from TFAA and nitric acid.[19] Treatment of **37** with *N*-(diethoxymethyl)-*N*-methylmethanamine (DMFDEA) gave the enaminone **38** in 88% yield. Reduction of the nitro function in **38** gave the intermediate **39**, which underwent ring closure on reflux to give **4** in 76% yield (Scheme 13). We believe this strategy could be seen as an efficient alternative route to the one described in Section 2.2.4.



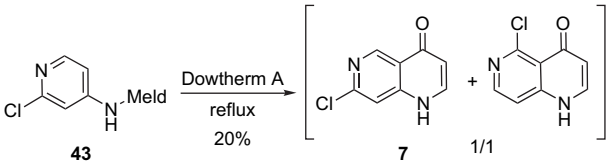

Scheme 13.

### 2.4.2. Synthesis of 6-methoxy-1H-1,7-naphthyridin-4-one (5)

It is known that lithiation of *tert*-butyl *N*-(6-methoxypyridin-3-yl)carbamate **40**[20] with *n*-butyllithium–TMEDA in diethyl ether generates a carbanion at the 4 position of the pyridine ring and minimises any nucleophilic addition of *n*-butyllithium at C-4. Using this knowledge, we managed to quench the dianion with Weinreb's amide, *N*-methoxy-*N*-methyl-acetamide, to obtain the acetyl pyridine **41** in 37% yield. Treatment of **41** by DMFDEA gave the enaminone **42** in 90% yield and surprisingly, ring closure and Boc deprotection readily occurred in one pot using either TFA in dichloromethane or sodium ethoxide in EtOH, to yield the desired 6-methoxy-1*H*-1,7-naphthyridin-4-one **5** (Scheme 14).

### 2.5. Synthesis of 7-chloro-1H-1,6-naphthyridin-4-one (7)

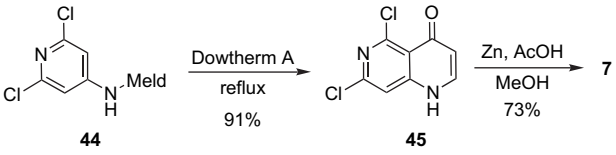
The thermal cyclisation–decarboxylation approach for the synthesis of 7-chloro-1*H*-1,6-naphthyridin-4-one **7** was first attempted with **43** (Table 1—entry 11), but a 1/1 mixture of inseparable isomers was obtained in poor yield (Scheme 15).




Scheme 15.

Dehalogenation selectivity issues of 8-halo-7-chloro-1*H*-1,6-naphthyridin-4-one derivatives could be anticipated in the α-blocked position strategy. We therefore focused on devising a new route starting from the symmetrical enamine pyridine **44**. In precedent investigations, we found that the C-5 position was more reactive than the C-7 in the quinazoline series[21] and this observation proved useful in the selective dehalogenation of **45**. The key intermediate **44** (Table 1—entry 12) was cyclised to give the naphthyridone **45** in good yield when heated in Dowtherm A at reflux.

When treated with zinc and acetic acid, **45** underwent a selective dehalogenation of the C-5 chlorine to furnish the desired compound **7** in 73% yield (Scheme 16).

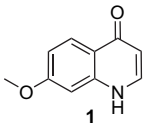
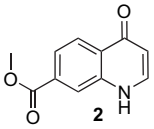
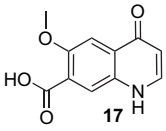
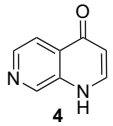
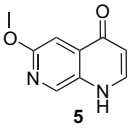
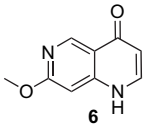
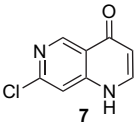



Scheme 16.

## 3. Conclusion

In this work,[22] we have developed various strategies for the syntheses of 6,7-disubstituted-1*H*-quinolin-4-one, substituted 1,6- and 1,7-naphthyridin-4-one derivatives to overcome

Table 3
Table summarising global yields from available starting materials according to the different strategies

| Entry | Starting material | Strategy | Number of steps | Desired product | Overall yield (%) |
|---|---|---|---|---|---|
| 1 | 3-Methoxyaniline | Classical[e] | 3 |  **1** | 66 |
| 2 | 3-Aminobenzoic acid | Classical[e] | 4 |  **2** | 28[a] |
| 3 | 2-Chloro-3-nitro benzoic acid | α-Blocked position | 5 | | 80 |
| 4 | 2-Hydroxy-5-nitro-benzoic acid | Classical[e] | 5 |  **17** | 53[b] |
| 5 | 1-Oxidopyridine-3-carboxylic acid | Classical[e] | 5 | | 13[c] |
| 6 | 2-Chloropyridin-3-amine | α-Blocked position | 3 |  **4** | 45[c] |
| 7 | 1-Pyridin-4-ylethanone | Enaminone[f] | 4 | | 55 |
| 8 | 6-Methoxypyridin-3-amine | Classical[e] | 2 | | 0[d] |
| 9 | 2-Chloro-6-methoxy-3-nitro-pyridine | α-Blocked position | 4 |  **5** | 3[c] |
| 10 | 6-Methoxypyridin-3-amine | Enaminone[f] | 4 | | 30 |
| 11 | 2-Chloropyridin-4-amine | Classical[e] | 3 | | 0[d] |
| 12 | | α-Blocked position | 5 |  **6** | 43 |
| 13 | 2,6-Dichloropyridin-4-amine | Starting from symetrical aniline | 3 |  **7** | 61 |

[a] The corresponding acid **13** was isolated in 32% overall yield with selective saponification.
[b] **17** is the corresponding acid of the target **3**.
[c] High dilution conditions were required for cyclisation.
[d] The undesired regioisomer was obtained.
[e] Strategy using thermal ring closure and separation of the two regioisomers if necessary.
[f] Strategy using the modified Leimgruber–Batcho approach.

selectivity issues when unsymmetrical substituted anilines are used in high temperature cyclisation reactions. Results and yields showing the efficacy of the various approaches are summarised in Table 3.

## 4. Experimental section

### 4.1. General

All experiments were carried out under an inert atmosphere and at room temperature unless otherwise stated. Flash chromatography was carried out on Merck Kieselgel 50 (Art. 9385). NMR spectra were obtained on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are expressed in $\delta$ (ppm) units, and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; br s, broad singlet; m, multiplet. Mass spectrometry was carried out on an analytical Waters LC/MS system with positive and negative ion data collected automatically. NMR and mass spectra were run on isolated products and were consistent with the proposed structures and compounds described in the literature. The following abbreviations have been used: Boc, *tert*-butoxycarbonyl; DCM, dichloromethane; DIPEA, *N*,*N*-diisopropylethylamine; DMFDEA, *N*-(diethoxymethyl)-*N*-methyl-methanamine (*N*,*N*-dimethylformamide diethyl acetal); DMSO, dimethyl sulfoxide; DPPA, diphenylphosphoryl

azide; IPA, propan-2-ol; NBS, 1-bromopyrrolidine-2,5-dione (*N*-bromosuccinimide); PHMS, polymethylhydrosiloxane; TEA, *N*,*N*,*N*-triethylamine; TFA, trifluoroacetic acid; TFAA, (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (trifluoroacetic anhydride); TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine. Dowtherm® A is a eutectic mixture of two very stable compounds: 26.5% of diphenyl ($C_{12}H_{10}$) and 73.5% of diphenyl oxide ($C_{12}H_{10}O$). Dowtherm® A is commonly used as a heat transfer agent.

### 4.2. General procedures

#### 4.2.1. Synthesis of enamine derivatives *9*, *11*, *15*, *19*, *23*, *25*, *27*, *29*, *32*, *35*, *43* and *44*

To a suspension of Meldrum's acid derivative **8** (1 equiv) in propan-2-ol (2 mL per mmol of substrate) was portionwise added the appropriate aniline (1 equiv) at room temperature (1 equiv of DIPEA was added when aniline hydrochloride was used). A precipitate slowly formed. The mixture was heated to reflux for 5 min and then cooled down to room temperature. The precipitate was collected by filtration, washed with propan-2-ol and diethyl ether, giving the expected product.

*4.2.1.1. 5-[[(3-Methoxyphenyl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**9**).* Yield: 96%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 11.21 (d, $J$=14.0 Hz, 1H), 8.63 (d, $J$=14.0 Hz, 1H), 7.33 (t, $J$=8.1 Hz, 1H), 6.82 (m, 2H), 6.76 (t, $J$=2.2 Hz, 1H), 3.85 (s, 3H), 1.76 (s, 6H). MS (ESI) *m*/*z* 220 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.2. Methyl 3-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino]benzoate (**11**).* Yield: 92%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 11.32 (d, $J$=13.9 Hz, 1H), 8.70 (d, $J$=13.9 Hz, 1H), 7.95 (m, 2H), 7.53 (t, $J$=8.3 Hz, 1H), 7.43 (dd, $J$=7.3 Hz, 1.6 Hz, 1H), 3.97 (s, 3H), 1.77 (s, 6H). MS (ESI) *m*/*z* 248 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.3. Methyl 5-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino]-2-methoxy-benzoate (**15**).* Yield: 92%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 11.24 (d, $J$=14.4 Hz, 1H), 8.56 (d, $J$=14.4 Hz, 1H), 7.74 (d, $J$=3.0 Hz, 1H), 7.36 (dd, $J$=8.9 Hz, 3.0 Hz, 1H), 7.05 (d, $J$=8.9 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 1.76 (s, 6H). MS (ESI) *m*/*z* 278 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.4. 2,2-Dimethyl-5-[[(1-oxidopyridin-3-yl)amino]methylidene]-1,3-dioxane-4,6-dione (**19**).* Yield: 84%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.16 (d, $J$=13.4 Hz, 1H), 8.66 (t, $J$=1.2 Hz, 1H), 8.53 (d, $J$=13.4 Hz, 1H), 8.06 (dd, $J$=6.5 Hz, 1.2 Hz, 1H), 7.61 (dd, $J$=8.5 Hz, 1.2 Hz, 1H), 7.44 (dd, $J$=8.5 Hz, 6.5 Hz, 1H), 1.69 (s, 6H). MS (ESI) *m*/*z* 263 $(M-H)^-$.

*4.2.1.5. Methyl 2-chloro-3-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino] benzoate (**23**).* Yield: 92%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.71 (d, $J$=13.5 Hz, 1H), 8.79 (d, $J$=13.5 Hz, 1H), 8.12 (d, $J$=7.5 Hz, 1H), 7.67 (d, $J$=7.5 Hz, 1H), 7.56 (t, $J$=7.5 Hz, 1H), 3.88 (s, 3H), 1.69 (s, 6H). MS (ESI) *m*/*z* 338 and 340 $(M-H)^-$.

*4.2.1.6. 5-[[(2-Chloropyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**25**).* Yield: 88%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 11.63 (d, $J$=13.6 Hz, 1H), 8.62 (d, $J$=13.6 Hz, 1H), 8.31 (dd, $J$=4.8 Hz, 1.5 Hz, 1H), 7.75 (dd, $J$=8.1 Hz, 1.5 Hz, 1H), 7.39 (dd, $J$=8.1 Hz, 4.8 Hz, 1H), 1.78 (s, 6H). MS (ESI) *m*/*z* 225 and 227 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.7. 5-[[(6-Methoxypyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**27**).* Yield: 100%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 11.18 (d, $J$=13.9 Hz, 1H), 8.49 (d, $J$=13.9 Hz, 1H), 8.12 (d, $J$=2.8 Hz, 1H), 7.52 (dd, $J$=9.0 Hz, 2.8 Hz, 1H), 6.83 (d, $J$=9.0 Hz, 1H), 3.96 (s, 3H), 1.76 (s, 6H). MS (ESI) *m*/*z* 221 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.8. 5-[[(2-Chloro-6-methoxy-pyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**29**).* Yield: 71%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 11.52 (d, $J$=13.8 Hz, 1H), 8.50 (d, $J$=13.8 Hz, 1H), 7.65 (d, $J$=8.7 Hz, 1H), 6.81 (d, $J$=8.7 Hz, 1H), 3.97 (s, 3H), 1.76 (s, 6H). MS (ESI) *m*/*z* 255 and 257 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.9. 5-[[(2-Methoxypyridin-4-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**32**).* Yield: 79%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.13 (s, 1H), 8.67 (s, 1H), 8.14 (d, $J$=5.7 Hz, 1H), 7.25 (dd, $J$=5.7 Hz, 2.0 Hz, 1H), 7.06 (d, $J$=2.0 Hz, 1H), 3.86 (s, 3H), 1.69 (s, 6H). MS (ESI) *m*/*z* 279 $(MH)^+$.

*4.2.1.10. 5-[[(3-Bromo-2-methoxy-pyridin-4-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**35**).* Yield: 93%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.58 (d, $J$=13.6 Hz, 1H), 8.87 (d, $J$=13.6 Hz, 1H), 8.15 (d, $J$=5.8 Hz, 1H), 7.57 (d, $J$=5.8 Hz, 1H), 3.96 (s, 3H), 1.71 (s, 6H). MS (ESI) *m*/*z* 299 and 301 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.11. 5-[[(2-Chloropyridin-4-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**43**).* Yield: 71%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.21 (br s, 1H), 8.73 (s, 1H), 8.37 (d, $J$=5.5 Hz, 1H), 7.86 (d, $J$=1.8 Hz, 1H), 7.66 (dd, $J$=5.5 Hz, 1.8 Hz, 1H), 1.69 (s, 6H). MS (ESI) *m*/*z* 225 and 227 $(MH-(CH_3)_2C{=}O)^+$.

*4.2.1.12. 5-[[(2,6-Dichloropyridin-4-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**44**).* Yield: 92%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.21 (br s, 1H), 8.73 (s, 1H), 7.92 (s, 2H), 1.69 (s, 6H). MS (ESI) *m*/*z* 315, 317 and 319 $(M-H)^-$.

#### 4.2.2. Ring closure reaction. Synthesis of compounds *1–3*, *10*, *12*, *16*, *20*, *21*, *24*, *26*, *28*, *30*, *33*, *36* and *45*

To Dowtherm A (appropriate dilution—see Sections 4.2.2.1 and 4.2.2.2) at 220 °C was added portionwise the enamine derivative. After bubbling stopped, the mixture was heated for an additional 10 min, and then allowed to cool to

room temperature. The mixture was diluted with petroleum ether, the solid was collected by filtration and washed with petroleum ether. Depending on the synthesised compound, one of the work-ups described in the main text was carried out.

*4.2.2.1. High dilution conditions*. A dilution of 60 mL of Dowtherm A per gram of substrate was used for the syntheses of **20**, **21**, **26**, **28** and **30**. Substrates **25**, **27**, **29**, respectively, gave **26**, **28**, **30** whereas substrate **19** led to a mixture of **20** and **21**.

*4.2.2.1.1. 7-Oxido-1H-1,7-naphthyridin-4-one (**20**)*. Crude yield: 41%. Extrapolated $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.48 (s, 1H), 8.02 (dd, $J$=6.8 Hz, 1.3 Hz, 1H), 7.97 (d, $J$=7.5 Hz, 1H), 7.89 (d, $J$=6.8 Hz, 1H), 6.07 (d, $J$=7.5 Hz, 1H). MS (ESI) *m/z* 163 $(MH)^+$.

*4.2.2.1.2. 8-Chloro-1H-1,7-naphthyridin-4-one (**26**)*. Yield: 72%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.98 (br s, 1H), 8.25 (d, $J$=5.3 Hz, 1H), 7.94 (m, 2H), 7.25 (br s, 1H). MS (ESI) *m/z* 181 and 183 $(MH)^+$.

*4.2.2.1.3. 6-Methoxy-1H-1,5-naphthyridin-4-one (**28**)*. Yield: 77%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.57 (d, $J$=5.3 Hz, 1H), 8.23 (d, $J$=9.0 Hz, 1H), 7.16 (d, $J$=9.0 Hz, 1H), 7.05 (d, $J$=5.3 Hz, 1H), 4.09 (s, 3H). MS (ESI) *m/z* 177 $(MH)^+$.

*4.2.2.1.4. 8-Chloro-6-methoxy-1H-1,7-naphthyridin-4-one (**30**)*. Yield: 9%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.92 (br s, 1H), 7.27 (s, 1H), 6.12 (br s, 1H), 3.91 (s, 3H). MS (ESI) *m/z* 211 and 213 $(MH)^+$.

*4.2.2.2. Low dilution conditions*. A dilution of 10 mL per gram of substrate was used for the syntheses of **1**, **2**, **3**, **10**, **12**, **16**, **21**, **24**, **33**, **36** and **45**. Substrates **19**, **23**, **32**, **35**, **44**, respectively, gave **21**, **24**, **33**, **36**, **45** whereas substrates **9**, **11**, **15**, respectively, led to mixtures of **1** and **10**, **2** and **12**, **3** and **16**.

*4.2.2.2.1. 5-Oxido-1H-1,5-naphthyridin-4-one (**21**)*. Crude yield: 93%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.80 (d, $J$=6.1 Hz, 1H), 8.78 (d, $J$=5.9 Hz, 1H), 8.28 (d, $J$=9.0 Hz, 1H), 7.91 (dd, $J$=9.0 Hz, 6.1 Hz, 1H), 7.10 (d, $J$=5.9 Hz, 1H). MS (ESI) *m/z* 163 $(MH)^+$.

*4.2.2.2.2. Methyl 8-chloro-4-oxo-1H-quinoline-7-carboxylate (**24**)*. Yield: 96%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.06 (d, $J$=8.4 Hz, 1H), 7.86 (d, $J$=6.6 Hz, 1H), 7.56 (d, $J$=8.4 Hz, 1H), 6.12 (d, $J$=6.6 Hz, 1H), 3.85 (s, 3H). MS (ESI) *m/z* 238 and 240 $(MH)^+$.

*4.2.2.2.3. 5-Methoxy-1H-1,6-naphthyridin-4-one (**33**)*. Yield: 64%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.05 (d, $J$=5.9 Hz, 1H), 7.75 (d, $J$=7.6 Hz, 1H), 6.94 (d, $J$=5.9 Hz, 1H), 6.02 (d, $J$=7.6 Hz, 1H), 3.89 (s, 3H). MS (ESI) *m/z* 177 $(MH)^+$.

*4.2.2.2.4. 8-Bromo-7-methoxy-1H-1,6-naphthyridin-4-one (**36**)*. Yield: 93%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.18 (br s, 1H), 8.85 (s, 1H), 7.80 (d, $J$=7.8 Hz, 1H), 6.09 (d, $J$=7.8 Hz, 1H), 4.03 (s, 3H). MS (ESI) *m/z* 255 and 257 $(MH)^+$.

*4.2.2.2.5. 5,7-Dichloro-1H-1,6-naphthyridin-4-one (**45**)*. Yield: 91%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.0 (br s, 1H), 7.92 (dd, $J$=7.8 Hz, 5.0 Hz, 1H), 7.47 (s, 1H), 6.17 (d, $J$=7.8 Hz, 1H). $^1$H NMR (500 MHz, DMSO-$d_6$/TFA-$d$) $\delta$: 7.93 (d, $J$=7.5 Hz, 5.0 Hz, 1H), 7.51 (s, 1H), 6.19 (d, $J$=7.5 Hz, 1H). MS (ESI) *m/z* 215, 217 and 219 $(MH)^+$.

*4.2.3. Selective precipitation. Synthesis of compounds **1** and **2***

A mixture of regioisomers was stirred at the appropriate temperature in a 1 N HCl solution for the appropriate time. The solid was collected by filtration, washed with water and dried overnight under vacuum at 50 °C over phosphorous pentoxide. The dry solid was washed with ethyl acetate and diethyl ether, to give the pure desired regioisomer as the hydrochloride salt.

This procedure was applied to an 80/20 mixture of **1** and **10** and a 60/40 mixture of **2** and **12** to prepare, respectively, **1** and **2**. **10** and **12** were not isolated.

*4.2.3.1. 7-Methoxy-1H-quinolin-4-one hydrochloride (**1**)*. Precipitation reaction conditions. 100 °C, 5 min. Yield: 69%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.46 (br s, 1H), 8.16 (d, $J$=9.7 Hz, 1H), 7.26 (m, 2H), 6.74 (br s, 1H), 3.94 (s, 3H). MS (ESI) *m/z* 176 $(MH)^+$.

*4.2.3.2. Methyl 4-oxo-1H-quinoline-7-carboxylate hydrochloride (**2**)*

*4.2.3.2.1. Classical strategy*. Precipitation reaction conditions: 25 °C, 15 h. Yield: 47%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.9 (br s, 1H), 8.28 (s, 1H), 8.23 (d, $J$=8.4 Hz, 1H), 8.17 (d, $J$=7.3 Hz, 1H), 7.87 (dd, $J$=8.4 Hz, 1.2 Hz, 1H), 6.30 (d, $J$=7.3 Hz, 1H), 3.93 (s, 3H). MS (ESI) *m/z* 204 $(MH)^+$.

*4.2.3.2.2. α-Blocked position strategy*. A mixture of **24** (3.3 g, 13.9 mmol), palladium on charcoal 5% (50% $H_2O$, 2.5 g) in a mixture of ethanol (125 mL) and ethyl acetate (10 mL) was stirred at room temperature under a hydrogen atmosphere (3 bar) for 8 h. The catalyst was removed by filtration over a pad of Celite®, washed with methanol and the filtrate was concentrated to dryness, giving 2.7 g (99%) of methyl 4-oxo-1*H*-quinoline-7-carboxylate hydrochloride **2** as a solid.

*4.2.4. Selective saponification. Synthesis of compounds **13**, **16** and **17***

A mixture of regioisomers (1 equiv) and $LiOH\cdot H_2O$ (4 equiv) in MeOH (10 mL per gram of mixture) was stirred overnight at room temperature. The solution was concentrated and water (10 mL per gram of mixture) was added. The pH was adjusted to 7 by addition of a 6 N HCl solution, the aqueous phase was extracted with DCM, the organic phase was dried over magnesium sulfate, filtered and concentrated to give the unreacted regioisomer. The aqueous phase's pH was adjusted to 2 by addition of a 2 N HCl solution. The precipitate was collected by filtration, washed with water, ethyl acetate and ether, to afford the desired acid.

This procedure was applied to a 60/40 mixture of **2** and **12** and a 65/35 mixture of **3** and **16** to prepare, respectively, **13**, **16** and **17**. **12** was not isolated.

*4.2.4.1. 4-Oxo-1H-quinoline-7-carboxylic acid (**13**).* Yield: 53%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 13.4 (br s, COOH), 12.0 (br s, 1H), 8.15 (m, 2H), 7.99 (dd, $J$=7.3 Hz, 4.8 Hz, 1H), 7.79 (dd, $J$=8.5 Hz, 1.4 Hz, 1H), 6.09 (d, $J$=7.3 Hz, 1H). MS (ESI) $m/z$ 190 $(MH)^+$.

*4.2.4.2. Methyl 6-methoxy-4-oxo-1H-quinoline-5-carboxylate (**16**).* Yield: 31%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.8 (br s, 1H), 7.87 (d, $J$=7.3 Hz, 1H), 7.63 (d, $J$=9.1 Hz, 1H), 7.55 (d, $J$=9.1 Hz, 1H), 5.91 (d, $J$=7.3 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H). MS (ESI) $m/z$ 234 $(MH)^+$.

*4.2.4.3. 6-Methoxy-4-oxo-1H-quinoline-7-carboxylic acid (**17**).* Yield: 69%. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 13.15 (br s, 1H), 11.8 (br s, 1H), 7.94 (m, 1H), 7.83 (s, 1H), 7.59 (s, 1H), 6.05 (d, $J$=7.4 Hz, 1H), 3.88 (s, 3H). MS (ESI) $m/z$ 220 $(MH)^+$.

### *4.3. Specific procedures*

#### *4.3.1. Synthesis of compounds **4–8**, **14**, **18**, **31**, **34**, **38**, **41**, **42***

*4.3.1.1. 1H-1,7-Naphthyridin-4-one (**4**)*

*4.3.1.1.1. Classical strategy.* To a mixture of crude **20** (15.6 g, 86.6 mmol) and PHMS (13 g, 216 mmol) in ethanol (500 mL) was added palladium on charcoal 10% (2.5 g) under argon. The reaction mixture was heated to reflux for 2 h. Further palladium on charcoal 10% (2.5 g) was added and the reaction mixture was heated for an additional 2 h. The hot mixture was filtered and then allowed to cool down to room temperature. The filtrate was concentrated and then taken up into diethyl ether. The upper phase was removed and the lower phase was stirred at room temperature over weekend. The resulting precipitate was collected by filtration and purified by flash chromatography on silica gel eluting with 10% of methanol in DCM, giving the 1*H*-1,7-naphthyridin-4-one **4** as a solid (5.8 g, 46%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.15 (br s, 1H), 9.00 (s, 1H), 8.45 (d, $J$=5.3 Hz, 1H), 8.06 (d, $J$=7.3 Hz, 1H), 7.09 (d, $J$=5.3 Hz, 1H), 6.17 (d, $J$=7.3 Hz, 1H). MS (ESI) $m/z$ 147 $(MH)^+$.

*4.3.1.1.2. α-Blocked position strategy.* A mixture of **26** (52 mg, 0.29 mmol), AcONa (94 mg, 1.15 mmol) and palladium on charcoal 5% (50% $H_2O$, 20 mg) in ethanol (5 mL) was stirred at room temperature under hydrogen atmosphere (1.1 bar) for 30 min. The catalyst was removed by filtration through a pad of Celite® and the filtrate was concentrated down. Purification by flash chromatography on silica gel eluting with 10% of methanol in DCM gave 30 mg (71%) of 1*H*-1,7-naphthyridin-4-one **4** as a solid.

*4.3.1.1.3. Enaminone strategy.* A mixture of **38** (2.8 g, 12.7 mmol) and palladium on charcoal 5% (590 mg) in ethanol (140 mL) was stirred under hydrogen atmosphere (1.3 bar) for 2 h. The catalyst was removed by filtration through a pad of Celite®. An aliquot was concentrated to dryness, to afford 1-(3-aminopyridin-4-yl)-3-dimethylamino-prop-2-en-1-one **39**. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.11 (s, 1H), 7.91 (d, $J$=5.2 Hz, 1H), 7.78 (d, $J$=12.2 Hz, 1H), 7.37 (d, $J$=5.2 Hz, 1H), 5.78 (br s, 2H), 5.65 (d, $J$=12.2 Hz, 1H), 3.18 (br s, 3H), 2.94 (br s, 3H). MS (ESI) $m/z$ 192 $(MH)^+$. The filtrate containing the intermediate **39** was heated to reflux for 10 h. The solution was concentrated down and the crude was purified by flash chromatography on silica gel eluting with 0–15% of methanol in DCM, giving 1.4 g (76%) of 1*H*-1,7-naphthyridin-4-one **4** as a solid.

*4.3.1.2. 6-Methoxy-1H-1,7-naphthyridin-4-one (**5**)*

*4.3.1.2.1. α-Blocked position strategy.* A mixture of **30** (270 mg, 1.28 mmol), TEA (178 μL, 1.28 mmol) and palladium on charcoal 5% (50% $H_2O$, 60 mg) in ethanol (27 mL) was stirred at room temperature under hydrogen atmosphere (3 bar) overnight. The catalyst was removed by filtration over a pad of Celite® and the filtrate was concentrated down. The crude was purified by flash chromatography on silica gel eluting with 0–10% methanol in a 1/1 mixture of ethyl acetate and DCM, giving 126 mg (56%) of 6-methoxy-1*H*-1,7-naphthyridin-4-one **5** as a solid. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.0 (br s, 1H), 8.71 (s, 1H), 7.97 (d, $J$=7.2 Hz, 1H), 7.24 (s, 1H), 6.02 (d, $J$=7.2 Hz, 1H), 3.91 (s, 3H). MS (ESI) $m/z$ 177 $(MH)^+$.

*4.3.1.2.2. Enaminone strategy (only acidic conditions are described here).* A solution of **42** (1.5 g, 4.66 mmol) and TFA (4 mL) in DCM (15 mL) was stirred at room temperature overnight. The solution was concentrated down and taken up into ethyl acetate and stirred for 10 min. The solid was collected by filtration, washed with ethyl acetate, diethyl ether and dried, giving 1 g (79%) of the trifluoroacetate salt of 6-methoxy-1*H*-1,7-naphthyridin-4-one **5** as a solid. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.25 (br s, 1H), 8.74 (s, 1H), 8.03 (d, $J$=7.4 Hz, 1H), 7.25 (s, 1H), 6.10 (d, $J$=7.4 Hz, 1H), 3.92 (s, 3H). MS (ESI) $m/z$ 177 $(MH)^+$.

*4.3.1.3. 7-Methoxy-1H-1,6-naphthyridin-4-one (**6**).* To a solution of **36** (9.18 g, 36 mmol) in methanol (180 mL) were added ammonium formate (9 g, 144 mmol) and palladium on charcoal 5% (900 mg). The mixture was heated to reflux for 3.5 h. The hot mixture was filtered, the solid was washed with methanol and the filtrate was concentrated down. The crude was dissolved in a 2/3 mixture of methanol and DCM and stirred overnight in the presence of $CaCO_3$ (9 g). The insoluble was removed by filtration and the filtrate was concentrated down, giving 6 g (95%) of 7-methoxy-1*H*-1,6-naphthyridin-4-one **6** as a solid. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.16 (br s, 1H), 8.89 (s, 1H), 7.86 (d, $J$=7.6 Hz, 1H), 6.67 (s, 1H), 5.97 (d, $J$=7.6 Hz, 1H), 3.92 (s, 3H). MS (ESI) $m/z$ 177 $(MH)^+$.

*4.3.1.4. 7-Chloro-1H-1,6-naphthyridin-4-one (**7**).* To a suspension of **45** (215 mg, 1 mmol) in methanol (5 mL) were added zinc powder (325 mg, 5 mmol) and acetic acid (572 μL, 10 mmol). The reaction mixture was heated to 60 °C for 1.5 h and then the insoluble was removed by filtration. The filtrate was concentrated down; the crude was taken up into water and stirred for 15 min. The precipitate was collected by filtration, washed with a 1/1 mixture of ethanol and diethyl

ether and dried, giving 132 mg (73%) of 7-chloro-1*H*-1,6-naphthyridin-4-one **7**. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.99 (s, 1H), 8.0 (d, $J$=6.7 Hz, 1H), 7.50 (s, 1H), 6.17 (d, $J$=6.7 Hz, 1H). MS (ESI) *m/z* 181 and 183 $(MH)^+$.

*4.3.1.5. 5-(Methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**8**).*[2] A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (100 g, 0.7 mol) in trimethyl orthoformate (360 mL) was heated to reflux overnight. The solution was allowed to cool to room temperature and concentrated down. The resulting brown solid was taken up into diethyl ether, collected by filtration and washed with diethyl ether, giving 69.5 g (54%) of **8** as a white solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.15 (s, 1H), 4.28 (s, 3H), 1.73 (s, 6H).

*4.3.1.6. Methyl 5-amino-2-methoxy-benzoate (**14**).* A mixture of 2-hydroxy-5-nitro-benzoic acid (2 g, 11 mmol) and potassium carbonate (3.2 g, 23 mmol) in acetone (20 mL) was stirred at 40 °C for 10 min. Dimethylsulfate (2.2 mL, 23 mmol) was slowly added and the yellow reaction mixture was heated to reflux for 6 h. The mixture was allowed to cool to room temperature and diluted with water (200 mL). The aqueous phase was extracted twice with diethyl ether and the combined organic phases were dried over magnesium sulfate, giving 2 g (88%) of methyl 2-methoxy-5-nitro-benzoate. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.71 (d, $J$=2.7 Hz, 1H), 8.37 (dd, $J$=9.4 Hz, 2.7 Hz, 1H), 7.08 (d, $J$=9.4 Hz, 1H), 4.03 (s, 3H), 3.94 (s, 3H).

A solution of methyl 2-methoxy-5-nitro-benzoate (2 g, 94 mmol) in ethyl acetate (30 mL) was stirred under hydrogen atmosphere (1.4 atm) in the presence of palladium on charcoal 5% (150 mg) for 5 h. The catalyst was removed by filtration through pad of Celite® and the filtrate was concentrated, giving 1.7 g (99%) of methyl 5-amino-2-methoxy-benzoate **14**. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 6.89 (d, $J$=2.9 Hz, 1H), 6.85 (d, $J$=8.7 Hz, 1H), 6.73 (dd, $J$=8.7 Hz, 2.9 Hz, 1H), 4.87 (br s, 2H), 3.74 (s, 3H), 3.67 (s, 3H). MS (ESI) *m/z* 182 $(MH)^+$.

*4.3.1.7. 1-Oxidopyridin-3-amine hydrochloride (**18**).* A suspension of 1-oxidopyridine-3-carboxylic acid (60 g, 0.43 mol), DIPEA (150 mL, 0.86 mol) and DPPA (98 mL, 0.45 mol) in a mixture of dioxane (900 mL) and *tert*-butanol (300 mL) was stirred at room temperature for 30 min under argon. The resulting solution was heated at reflux for 2 h. The solution was allowed to cool to room temperature and concentrated down. The crude was diluted with DCM, washed with a saturated aqueous solution of $NaHCO_3$, twice with a saturated aqueous solution of ammonium chloride and then water. The organic phase was dried over magnesium sulfate, giving 263 g of crude Boc-intermediate, which was used in the next step without any further purification.

A solution of the crude obtained above was stirred in a 4 N solution of HCl in dioxane (1 L) at room temperature overnight. The resulting precipitate was collected by filtration, washed with dioxane, diethyl ether and dried, giving 53 g (84%) of 1-oxidopyridin-3-amine hydrochloride **18** as a white solid. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.15 (t, $J$=2.1 Hz, 1H), 8.10 (dd, $J$=6.2 Hz, 1.4 Hz, 1H), 7.60 (dd, $J$=8.7 Hz, 6.2 Hz, 1H), 7.41 (dd, $J$=8.7 Hz, 1.4 Hz, 1H).

*4.3.1.8. 2-Methoxypyridin-4-amine (**31**).*[14] A mixture of 2-chloropyridin-4-amine (15.4 g, 120 mmol), copper powder (1.1 g, 18 mmol) and sodium methylate (16.2 g, 300 mmol) in methanol (35 mL) was heated to 160 °C in an autoclave overnight. The insoluble was removed by filtration and the filtrate was concentrated down. The residue was taken up into water and extracted several times with diethyl ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated down, giving 8.3 g (56%) of 2-methoxypyridin-4-amine **31** as an oil, which crystallised on standing. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.61 (d, $J$=5.7 Hz, 1H), 6.16 (dd, $J$=5.7 Hz, 1.6 Hz, 1H), 5.9 (br s, 2H), 5.80 (d, $J$=1.6 Hz, 1H), 3.70 (s, 3H). MS (ESI) *m/z* 125 $(MH)^+$.

*4.3.1.9. 3-Bromo-2-methoxy-pyridin-4-amine (**34**).* To a solution of **31** (6.82 g, 55 mmol) in acetonitrile (40 mL) was added at 10 °C under argon a solution of NBS (9.8 g, 55 mmol) in acetonitrile (80 mL) over a period of 15 min. The yellow solution was allowed to warm to room temperature, stirred 30 min and concentrated down. The residue was taken up into diethyl ether, washed with water, dried over magnesium sulfate and concentrated down, giving 11 g (98%) of 3-bromo-2-methoxy-pyridin-4-amine **34**, which crystallised on standing. It was used in the next step without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.60 (d, $J$=5.5 Hz, 1H), 6.16 (d, $J$=5.5 Hz, 1H), 6.21 (br s, 2H), 3.80 (s, 3H). MS (ESI) *m/z* 203 and 205 $(MH)^+$.

*4.3.1.10. 3-Dimethylamino-1-(3-nitropyridin-4-yl)prop-2-en-1-one (**38**).* A solution of acetyl pyridine **37**[17] (2.4 g, 14.5 mmol) and DMFDEA (3.46 mL, 20.2 mmol) in toluene (30 mL) was heated to 80 °C for 4 h and then the solution was concentrated down. The resulting dark oil was stirred in diethyl ether (10 mL) for 10 min and the formed precipitate was collected by filtration, giving 2.8 g (88%) of (*E*)-3-dimethylamino-1-(3-nitropyridin-4-yl)prop-2-en-1-one **38** as an yellow solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 9.21 (br s, 1H), 8.83 (d, $J$=4.7 Hz, 1H), 8.2–7.5 (br s, 1H), 7.41 (d, $J$=4.7 Hz, 1H), 5.22 (br s, 1H), 3.16 (br s, 3H), 2.90 (s, 3H). MS (ESI) *m/z* 222 $(MH)^+$.

*4.3.1.11. tert-Butyl N-(4-acetyl-6-methoxy-pyridin-3-yl)carbamate (**41**).* A solution of *tert*-butyl *N*-(6-methoxypyridin-3-yl)-carbamate **40**[20] (3.6 g, 16.1 mmol) and TMEDA (7.45 mL, 49.8 mmol) in ether (84 mL) was cooled down to −70 °C under Argon and treated slowly with a 1.6 M solution of *n*-BuLi in hexanes (30 mL, 48.2 mmol). The resulting solution was allowed to warm to −10 °C and kept under −10 °C for 2 h. The milky slurry was cooled down to −70 °C and *N*-methoxy-*N*-methyl-acetamide (Weinreb's acetamide) (3.4 mL, 32.1 mmol) was added dropwise and then the reaction mixture was allowed to warm to 10 °C. The solution was poured into a mixture of ice

and solid ammonium chloride and then diluted with ethyl acetate. The two phases were separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated down. The crude was purified by flash chromatography on silica gel eluting with 2% of ethyl acetate in DCM, giving 1.6 g (37%) of *tert*-butyl *N*-(4-acetyl-6-methoxy-pyridin-3-yl)carbamate **41** as a solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 9.59 (br s, 1H), 9.18 (s, 1H), 7.08 (s, 1H), 3.95 (s, 3H), 2.62 (s, 3H), 1.52 (s, 9H). MS (ESI) *m*/*z* 267 $(MH)^+$.

*4.3.1.12. tert-Butyl N-[4-[(E)-3-dimethylaminoprop-2-enoyl]-6-methoxy-pyridin-3-yl]carbamate (**42**).* A solution of **41** (1.45 g, 5.45 mmol) and DMFDEA (1.31 mL, 7.63 mmol) in toluene (10 mL) was heated to 85 °C for 1.5 h. The solution was concentrated down. The crude was purified by flash chromatography on silica gel eluting with 0–2% methanol in DCM, giving 1.4 g (80%) of *tert*-butyl *N*-[4-[(*E*)-3-dimethylaminoprop-2-enoyl]-6-methoxy-pyridin-3-yl]carbamate **42**. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.49 (br s, 1H), 8.99 (br s, 1H), 7.77 (d, $J$=12.3 Hz, 1H), 6.92 (s, 1H), 5.54 (d, $J$=12.3 Hz, 1H), 3.94 (s, 3H), 3.19 (s, 3H), 2.94 (s, 3H), 1.50 (s, 9H). MS (ESI) *m*/*z* 322 $(MH)^+$.

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