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DEHYDROGENATION OF 5,6-DIHYDROPYRIDO[2,3-*d*]PYRIMIDIN-7(8*H*)-ONES: A CONVENIENT LAST STEP FOR A SYNTHESIS OF PYRIDO[2,3-*d*]PYRIMIDIN-7(8*H*)-ONES

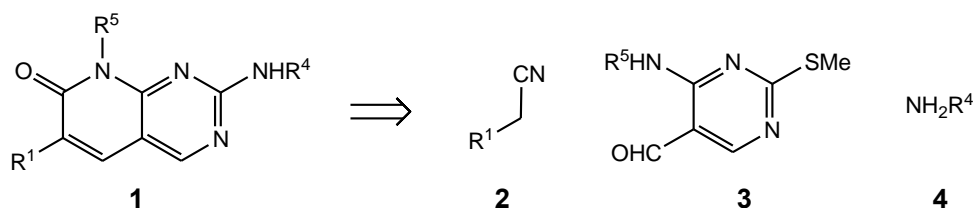
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Abstract – Two new protocols for the dehydrogenation of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones to pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones are described. The first one uses NaH in DMSO and affords the corresponding pyridopyrimidines when an aryl substituent is present at C6. The second one is of a more general use, allowing dehydrogenation of aryl and alkyl substituted 5,6-dihydropyridopyrimidines upon treatment with Na₂SeO₃ in DMSO.

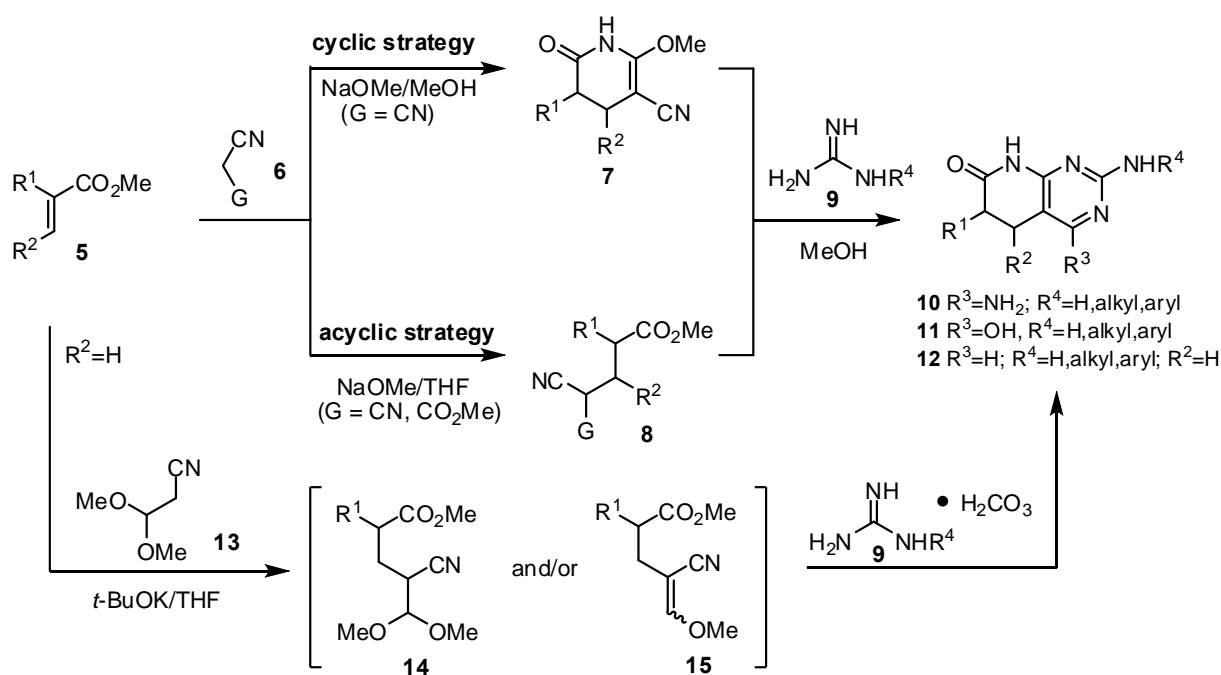
INTRODUCTION

Among the different kinds of structures currently being tested as potential protein kinase inhibitors, pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones have arisen as very promising candidates. Thus, compounds of general structure **1** have shown IC₅₀ in the range μM to nM in front of PDFGR, FGFR, EGFR and c-Src.¹ Usually this kind of compounds are obtained through a multistep strategy in which the pyridine ring is constructed by condensation of a nitrile **2** (bearing the desired substituent R¹) onto preformed pyrimidine aldehyde **3** bearing substituent R⁵ and a methylthio group which can be later substituted by the NHR⁴ substituent using an amine **4** (Scheme 1).



Scheme 1

In this context, our group has a broad experience in the synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (**10**; $R^3 = \text{NH}_2$) and (**11**; $R^3 = \text{OH}$) from α,β -unsaturated esters (**5**) (Scheme 2). Thus, in the so called *cyclic strategy* 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridin-3-carbonitriles (**7**) are obtained by reaction of an α,β -unsaturated ester (**5**) and malononitrile (**6**, $G = \text{CN}$) in NaOMe/MeOH.² Treatment of pyridones **7** with guanidine systems (**9**, $R^4 = \text{H}$, alkyl, aryl, heteroaryl) affords 4-amino-pyrido[2,3-*d*]pyrimidines (**10**, $R^3 = \text{NH}_2$).³ On the other hand, we described an *acyclic* variation of the above protocol for the synthesis of pyridopyrimidines (**10**, $R^3 = \text{NH}_2$) based on the isolation of the corresponding Michael adduct (**8**, $G = \text{CN}$) and later cyclization with a guanidine **9**.⁴ This approach also allowed us to obtain 4-oxopyrido[2,3-*d*]pyrimidines (here depicted as the hydroxyl tautomer **11**, $R^3 = \text{OH}$) by treatment of intermediates (**8**, $G = \text{CO}_2\text{Me}$), synthesized by Michael addition of α,β -unsaturated esters (**5**) and methyl cyanoacetate (**6**, $G = \text{CO}_2\text{Me}$), with guanidines **9**.⁵ We have also described a multicomponent microwave-assisted cyclocondensation affording systems **10** and **11** *via* acyclic intermediates **8**.⁶ More recently, we have achieved the synthesis of 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidines (**12**; $R^3 = \text{H}$) through an unusual Michael addition between 2-aryl substituted acrylates (**5**; $R^1 = \text{aryl}$, $R^2 = \text{H}$) and 3,3-dimethoxypropanenitrile (**13**) which leads, depending on the reaction temperature (60 °C or -78 °C, respectively), to a 4-methoxymethylene substituted 4-cyanobutyric ester (**15**) or to a 4-dimethoxymethyl 4-cyanobutyric ester (**14**). These compounds can be subsequently converted to the desired 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidines (**12**; $R^3 = \text{H}$) upon treatment with a guanidine carbonate **9** under microwave irradiation.⁷

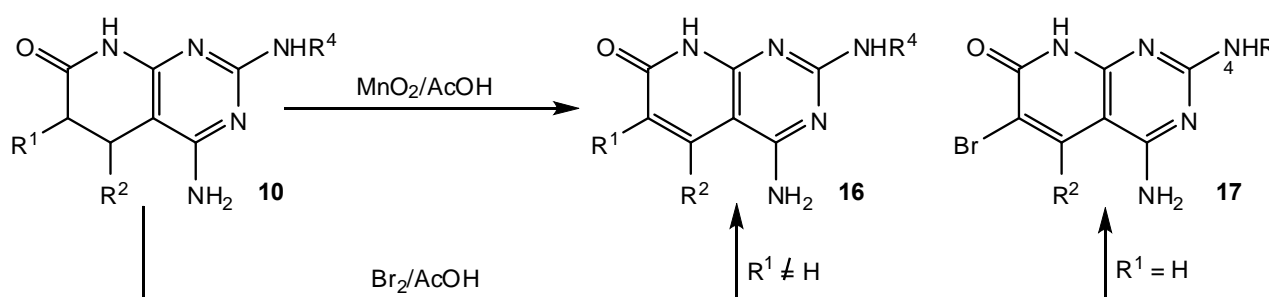


Scheme 2

The main difference between systems **10**, **11** and, particularly, **12** and the biologically active pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (**1**) is the absence of a double bond between C5 and C6. Consequently, a facile dehydrogenation protocol for the conversion of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones to pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones will complete a straightforward synthesis of these later ones. However, in the literature there are only two examples of such dehydrogenation: the use of MnO₂ or Br₂ in AcOH,⁸ and a treatment with Pd in AcOH.⁹ The present paper deals with a re-examination of such dehydrogenation protocols.

RESULTS AND DISCUSSION

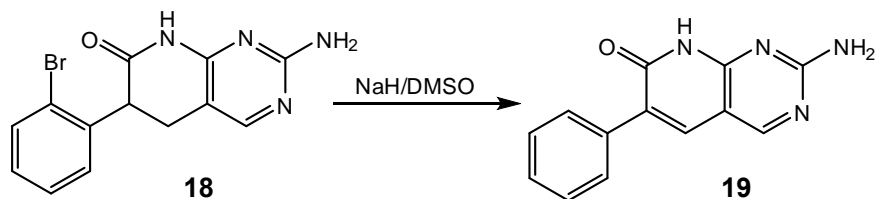
In 1989, our group described⁸ the use of both MnO₂ (freshly prepared by the Attenburrow method¹⁰) in AcOH and the treatment with Br₂ in AcOH to transform 5,6-dihydropyridopyrimidines **10** (R³ = NH₂) into the aromatic ones **16** (Scheme 3). The results obtained mainly depended on the nature of substituents R¹ and R². Thus, in the case of MnO₂, the dehydrogenation to **16** (R¹ = Me, R² = R⁴ = H) took place in 95% yield while **16** (R¹ = H, R² = Me, R⁴ = H) gave a 75% yield. On the other hand, the treatment of **10** (R¹ = Me, R² = R⁴ = H) with Br₂ in AcOH afforded **16** (R¹ = Me, R² = R⁴ = H) in 90% yield. However, when **10** (R¹ = H, R² = Me, R⁴ = H) was treated in the same reaction conditions, the dehydrogenation product **17** (R¹ = H, R² = Me, R⁴ = H) included a bromine atom at C6 (30% yield).



Scheme 3

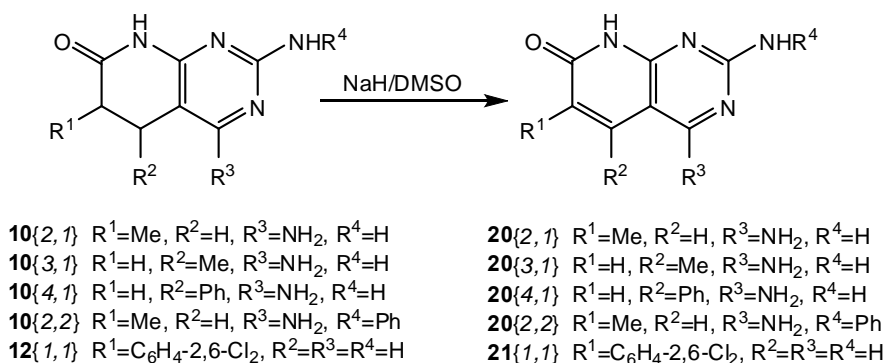
Although the results were good for 2,4-diamino substituted 5,6-dihydropyridopyrimidines **10**, the fact that the MnO₂ should be freshly prepared (nowadays activated MnO₂ is commercially available from Aldrich ref. n° 217646, but yields were lower) and our idea of extending the dehydrogenation protocol to a wide range of substituents, prompted us to test new dehydrogenating agents.

The first one arose in front of us as an example of serendipity. As a part of the development of the synthetic protocol to obtain 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidines (**12**; R³ = H),⁷ we were interested in the debromination of compound **18**. When we tested NaH/DMSO for such purpose, the debromination took place but also the dehydrogenation at C5-C6 affording compound **19** in 80% yield.



Scheme 4

Such result led us to use NaH/DMSO as dehydrogenating agent, so we tested it on 5 model compounds: **10**{2,1}, **10**{3,1}, **10**{4,1}, **10**{2,2}, and **12**{1,1}; selected to cover a wide range of substituent type, substitution position and nature of R³ (NH₂ and H) and R⁴ (H and Ph). These compounds were synthesized according to Scheme 2 from the corresponding α,β -unsaturated esters **5**{1-4}, malononitrile (**6**, G = CN) (for compounds **10**) or 3,3-dimethoxypropanenitrile (**13**) (for compound **12**{1,1}), and guanidine **9**{1} or phenylguanidine **9**{2}. The results of the dehydrogenation with NaH/DMSO are summarized in Scheme 5.



Entry	Substrate	NaH	atm	Temperature	time	Product	Yield (%)
1	10 {2,1}	3 eq	air	120 °C	15 h	20 {2,1}	30
2	10 {3,1}	3 eq	air	120 °C	9h	20 {3,1}	- ^a
3	10 {4,1}	3 eq	air	120 °C	15 h	20 {4,1}	- ^a
4	10 {2,2}	3 eq	air	120 °C	48 h	20 {2,2}	30
5	12 {1,1}	3 eq	air	100 °C	2 h	21 {1,1}	81

^a The starting 5,6-dihydropyrido[2,3-*d*]pyrimidine is recovered

Scheme 5

As it can be seen the reaction only proceeded when the substituent is present in the pyridone ring at position C6 although the yield obtained strongly depends on the nature of R¹, being higher when it is a phenyl ring. This result is in agreement with our interpretation of the possible mechanism by which this oxidation can take place. The calculated pK_a values (SPARC v. 4.5, <http://ibmcl2.chem.uga.edu/sparc/>)¹¹

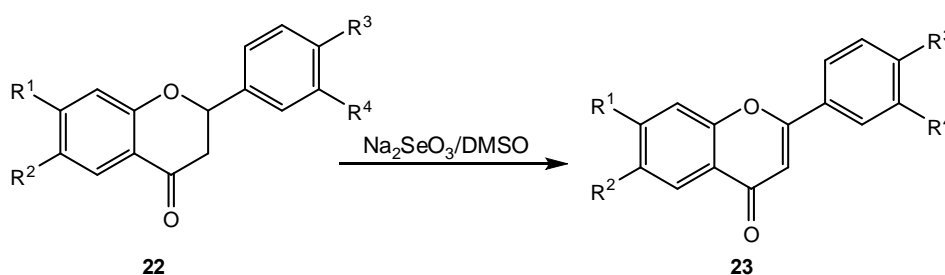
of the α - and β -carbonyl hydrogens, the lactam NH, and the NHR^4 and R^3 substituents are summarized on Table 1.

Table 1. Calculated pKa values

Compound	R^1	R^2	R^1CHCO	R^2CH	CONH	NHR^4	R^3
10 {2,1}	Me	H	10.93	36.11	10.83	19.45 (H)	18.96 (NH_2)
10 {3,1}	H	Me	17.12	34.76	10.83	19.44 (H)	19.05 (NH_2)
10 {4,1}	H	Ph	16.81	30.52	10.58	19.14 (H)	18.92 (NH_2)
10 {2,2}	Me	H	10.51	35.50	10.26	16.56 (Ph)	18.44 (NH_2)
12 {1,1}	C_6H_4 -2,6- Cl_2	H	6.16	34.64	9.66	19.33 (Ph)	- (H)
18	$\text{C}_6\text{H}_5\text{Br}$	H	7.64	34.54	9.89	19.35 (H)	- (H)

It is easy to see that those compounds giving the best results in this dehydrogenation (**12**{1,1} and **18**) present an α -carbonyl hydrogen more acidic than the lactam NH, while the situation is the contrary in those compounds which have not reacted (**10**{3,1} and **10**{4,1}). When the pKa values are similar (**10**{2,1} and **10**{2,2}) the reaction proceed but the yield is very low. Although there are some examples of direct dehydrogenation of an heterocyclic ring by heating in DMSO,¹² we postulate for this case a mechanism in which an initial loss of proton from α -carbonyl (C6) is followed by a hydride transfer from C5 to the DMSO. The possible role of air oxygen as coadjuvant in this oxidation can not be denied because when the reaction was carried out in an inert atmosphere (Ar) the conversions obtained were much lower. Such dehydrogenation is favoured by the presence of aryl substituents at C6, precisely the kind of substituents present in biologically active compounds **1**.¹

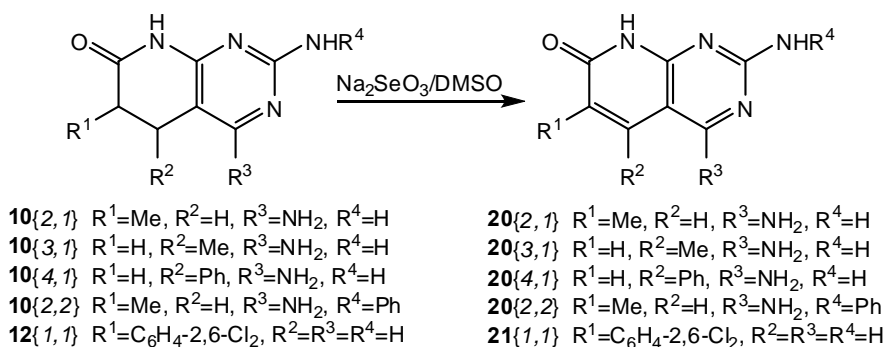
The second methodology tested for the dehydrogenation of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones was based on a recent paper by Lamba and Makrandi¹³ in which they describe the use of sodium selenite (Na_2SeO_3) in DMSO as a highly efficient reagent for dehydrogenation. Thus, the treatment of flavonones (**22**) with Na_2SeO_3 in DMSO affords flavones (**23**), both with conventional heating or under microwave irradiation, in high yields (60-85%) (Scheme 6).



Scheme 6

Consequently, we tested such oxidizing agent on the same model compounds previously used in the dehydrogenation with NaH/DMSO. The results are summarized in Scheme 7.

The dehydrogenation was tested by varying the following parameters: (i) ratio between the corresponding 5,6-dihydropyrido[2,3-*d*]pyrimidine and Na₂SeO₃ (1:1, 1:1.2, and 1:1.5), (ii) volume of DMSO (2, 3, and 4 mL), (iii) reaction temperature (110 °C, 140 °C, and 160 °C), (iv) conventional heating or microwave irradiation, and (v) air or Ar atmosphere. The best reaction conditions were 1.2 equivalents of Na₂SeO₃, 2 mL of DMSO (in order to favour precipitation of the final product by addition of water), conventional heating at 160 °C for 6 h, and air atmosphere protected from moisture or Ar atmosphere depending on the nature of the substituents (alkyl substituents proceeded better with air atmosphere). Using this protocol, all the 5,6-dihydropyrido[2,3-*d*]pyrimidines tested (unless **10**{3,1}, R¹ = H, R² = Me, R³ = NH₂, R⁴ = H) afforded the corresponding pyrido[2,3-*d*]pyrimidin-7(8*H*)-one in high yield (90-100%). In the case of **10**{2,2} (R¹ = Me, R² = H, R³ = NH₂, R⁴ = Ph), it was necessary to increase the ratio **10**{2,2}: Na₂SeO₃ to 1:6 in order to drive the reaction to completeness.



Entry	Substrate	Na ₂ SeO ₃	DMSO	Temperature	atm	Product	Yield (%)
1	10 {2,1}	1.2 eq	2 mL	160 °C	air	20 {2,1}	88
2	10 {3,1}	1.2 eq	2 mL	160 °C	air	20 {3,1}	- ^a
3	10 {4,1}	1.2 eq	2 mL	160 °C	Ar	20 {4,1}	98
4	10 {2,2}	6 eq	2 mL	160 °C	air	20 {2,2}	90
5	12 {1,1}	1.2 eq	2 mL	160 °C	Ar	21 {1,1}	98

^a The starting 5,6-dihydropyrido[2,3-*d*]pyrimidine is recovered

Scheme 7

Although in the paper by Lamba and Makrandi¹³ there is not a mechanistic proposal for the dehydrogenation with Na₂SeO₃, it is possible to assume a mechanism similar to that proposed by Corey and Schaefer¹⁴ for the dehydrogenation of 1,4-diketones with SeO₂. Thus, the formation of the

pyrido[2,3-*d*]pyrimidin-7(8*H*)-one could proceed *via* an intermediate enol selenite ester followed by a concerted 1,4-elimination from the enol ester. However, other reaction paths can not be excluded.

In summary, we have developed two new protocols for the conversion of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones into pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones by dehydrogenation. The use of NaH/DMSO is particularly interesting for those cases in which an aryl group is present at C6 (the kind of substituents present in biologically active compounds **1**). On the other hand, sodium selenite is of a more general use, providing good yields unless for alkyl substituents at C5.

These protocols complete a very convenient synthesis of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones in which the pyridopyrimidine skeleton is formed in one or two steps from an α,β -unsaturated ester (**5**), an active methylene compound (malononitrile (**6**, G = CN), methyl cyanoacetate (**6**, G = CO₂Me) or 3,3-dimethoxypropanenitrile (**13**)) and a guanidine (**9**) (Scheme 2), and subsequently converted to a pyrido[2,3-*d*]pyrimidin-7(8*H*)-one by dehydrogenation with one of the aforementioned protocols.

EXPERIMENTAL

All melting points were determined with a Büchi 530 capillary apparatus and were uncorrected. Infrared spectra were recorded in a Nicolet Magna 560 FTIR spectrophotometer. ¹H and ¹³C NMR spectra were determined in a Varian-400MR operating in field strength of 400 and 100.5 MHz, respectively. Chemical shifts were reported in parts per million (δ) and Coupling constants (*J*) in Hz, using in the case of ¹H NMR, tetramethylsilane (TMS) or sodium 2,2,3,3-tetradeuteriotrimethyl-silylpropionate (TSPNa) as internal standards and setting, in the case of ¹³C NMR, the reference at the signal of the solvent (39.5 ppm, DMSO-*d*₆ and 163.8 ppm, CF₃CO₂D, TFA-*d*). Standard and peak multiplicities were designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; br, broad signal; m, multiplet. MS (EI, 70 EV) were registered on a Agilent Technologies 5975. HRMS were registered at the Unidade de Espectrometria de Masas (Universidade de Santiago de Compostela) using a Micromass Autospec spectrometer. All microwave irradiation experiments were carried out in a dedicated Biotage-Initiator microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 400 W with utilization of the standard absorbance level of 400 W maximum power. Reactions were carried out in 10-mL glass tubes, sealed with aluminium/Teflon crimp tops, which can be exposed up to 250 °C and 20 bar internal pressure. Temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60–120 s) to ambient temperature by air jet cooling.

The reagents and solvents were purchased from Sigma-Aldrich and were used directly. Compounds **10**{2,*I*}, **10**{3,*I*}, **10**{4,*I*}, and **12**{*I*,*I*} were prepared according to reported procedures.^{2b,6,7}

2,4-Diamino-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (20{2,1}):

Method a) Using NaH in DMSO: A mixture of 0.193 g (1 mmol) of 2,4-diamino-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**10{2,1}**)^{2b,6} and 0.120 g (3 mmol) of NaH (60% dispersion in mineral oil) in 10 mL of DMSO was heated for 15 h at 120 °C in an air atm. The resulting solution was cooled down, water (200 mL) was added and it was neutralized with AcOH. The resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 57.4 mg (0.30 mmol, 30%) of **20{2,1}**, mp >250 °C (lit.,⁸ >350 °C). IR (KBr): ν (cm⁻¹) 3334-3163 (NH₂), 2919, 2784, 1626 (C=O), 1546 (C=N), 1465, 793. ¹H NMR (400 MHz, TFA-*d*): 8.15 (s, 1H, H-C5), 2.25 (s, 3H, Me). ¹³C NMR (100.5 MHz, DMSO-*d*₆): δ (ppm) 165.2 (C8a), 162.8 (C2), 161.4 (C7), 155.7 (C4), 133.0 (C5), 120.4 (C6), 90.8 (C4a), 16.3 (Me). MS (EI): m/z : 190.09 [M]⁺. HRMS (EI): Calc. for C₈H₉N₅O: 191.0807. Found: 191.0808.

Method b) Using Na₂SeO₃ in DMSO: A mixture of 0.193 g (1 mmol) of **10{2,1}** and 0.207 g of Na₂SeO₃ (1.2 mmol) in 2 mL of DMSO was heated at 160 °C for 6h protected from moisture. Upon cooling, 200 mL of water were added and the resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 168.2 mg (0.88 mmol, 88%) of **20{2,1}**.

2,4-Diamino-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (20{4,1}):

Method b) Using Na₂SeO₃ in DMSO: A mixture of 0.255 g (1 mmol) of 2,4-diamino-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**10{4,1}**)^{2b,6} and 0.207 g of Na₂SeO₃ (1.2 mmol) in 2 mL of DMSO was heated at 160 °C for 6 h in an Ar atm. Upon cooling, 200 mL of water were added and the resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 248.2 mg (0.98 mmol, 98%) of **20{4,1}**, mp >250 °C. IR (KBr): ν (cm⁻¹) 3477 (NH), 3309-3178 (NH₂), 1636 (C=O), 1611 (C=N), 1611,1570,1525 (C=N), 1472, 1385, 701. ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 11.94 (s, 1H, H-N8), 7.47 (m, 5H, H-Ph), 6.78 (br, 2H, NH₂), 5.70 (s, 1H, H-C6). ¹³C-NMR (100.5 MHz, DMSO-*d*₆): δ (ppm) 163.0 (C8a), 162.6 (C7), 161.3 (C2), 157.8 (C4), 151.1 (C5), 139.0 (Ph), 129.5 (Ph), 129.5 (Ph), 128.0 (Ph), 114.9 (C6), 90.0 (C4a). MS (EI): m/z : 253.1 [M]⁺(100), 252.10 [M-1]⁺ (88). HRMS (EI): Calc. for C₁₃H₁₁N₅O: 253.0964. Found: 253.0964.

4-Amino-6-methyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (20{2,2}):

A mixture of 536 mg (3 mmol) of phenyl guanidine carbonate and 324 mg (6 mmol) of NaOMe in 5 mL of MeOH are heated in a sealed microwave vial with stirring under microwave irradiation for 15 min at 65 °C. The resulting mixture is transferred by filtration to a second microwave vial and 0.1 mL (1 mmol) of methyl methacrylate and 79 mg (1.2 mmol) of malononitrile were added. The mixture was heated under microwave irradiation for 10 min at 140 °C. The resulting precipitate was filtered off, washed with water, cold EtOH and Et₂O to give 27.5 mg (0.11 mmol, 11%) of 4-amino-5,6-dihydro-6-methyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one **10{2,2}**, mp >250 °C (lit.,¹⁵ 367 °C). ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 10.03 (s, 1H, H-N8), 8.69 (s, 1H, NHPh), 7.82 (d, J = 7.6 Hz, 2H, *o*-PhH),

7.18 (m, 2H, *m*-PhH), 6.83 (t, $J = 7.3$ Hz, 1H, *p*-PhH), 6.34 (s, 2H, NH₂), 2.79 (dd, $J = 15.6$ Hz, $J = 6.8$ Hz, 1H, H-C6), 2.56 (m, 1H, H-C5), 2.24 (dd, $J = 15.6$ Hz, $J = 11.3$ Hz, 1H, H-C5). ¹³C NMR (100.5 MHz, TFA-*d*): δ (ppm) 179.2 (C8), 156.6 (C2), 155.3 (C4), 152.8 (C8a), 133.4 (Ph), 132.5 (Ph), 131.9 (Ph), 127.4 (Ph), 88.0 (C4a), 36.2 (C5), 25.4 (C6), 15.7 (Me).

Method a) Using NaH in DMSO: A mixture of 0.269 g (1 mmol) of **10**{2,2} and 0.120 g (3 mmol) of NaH (60% dispersion in mineral oil) in 10 mL of DMSO was heated for 15 h at 120 °C in an air atm. The resulting solution was cooled down, water (200 mL) was added and it was neutralized with AcOH. The resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 80.1 mg (0.30 mmol, 30%) of **20**{2,2}.

Method b) Using Na₂SeO₃ in DMSO: A mixture of 0.269 g (1 mmol) of **10**{2,2} and 1.038 g of Na₂SeO₃ (6 mmol) in 4 mL of DMSO was heated at 160 °C for 6 h protected from moisture. Upon cooling, 200 mL of water were added and the resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 247.3 mg (0.90 mmol, 90%) of **20**{2,2}, mp >250 °C. IR (KBr): ν (cm⁻¹) 3461 (NH), 3314 (NH₂), 3171, 3074, 2961, 1643 (C=O), 1592, 1570, 1532 (C=N), 1500, 1439, 1292, 905, 794. ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 11.75 (s, 1H, H-N8), 9.23 (s, 1H, NHPh), 7.90 (s, 1H, C5), 7.89 (d, $J = 4$ Hz, 2H, H-Ph), 7.25 (br, 2H, NH₂), 7.22 (d, $J = 4$ Hz, 2H, H-Ph), 6.91 (t, $J = 7.2$ Hz, 1H, H-Ph), 2.00 (s, 3H, Me). ¹³C NMR (100.5 MHz, DMSO-*d*₆): δ (ppm) 164.6 (C8a), 160.9 (C2), 159.1 (C7), 155.3 (C4), 141.3 (C5), 132.1 (C6), 128.7 (Ph), 122.4 (Ph), 121.5 (Ph), 119.6 (Ph), 91.65 (C4a), 16.64 (Me). MS (EI): m/z : 267.1 [M]⁺ (75), 266.1 [M-H]⁺ (100). HRMS (EI): Calc. for C₁₄H₁₃N₅O: 267.1120. Found: 267.1120.

2-Amino-6-(2,6-dichlorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (21**{*I*,*I*}):**

Method a) Using NaH in DMSO: A mixture of 0.150 g (0.48 mmol) of 2-amino-6-(2,6-dichlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12**{*I*,*I*}⁷) and 0.058 g (1.44 mmol) of NaH (60% dispersion in mineral oil) in 10 mL of DMSO was heated for 2 h at 100 °C in an air atm. The resulting solution was cooled down, water (200 mL) was added and it was neutralized with AcOH. The resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 0.12 g (0.39 mmol, 81%) of **21**{*I*,*I*} as a yellowish solid, mp >250 °C (lit., ^{1b} 410 °C). IR (KBr): ν (cm⁻¹) 3595 (NH), 3314-3174 (NH₂), 1624 (C=O), 1548 (N=C), 1512 (N=C), 1429, 1400, 784. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 11.94 (s, 1H, H-N8), 8.61 (s, 1H, H-C4), 7.71 (s, 1H, H-C5), 7.53 (d, $J = 7.81$ Hz, 2H, H-Ph), 7.41 (m, $J = 7.44$ Hz, $J = 8.73$ Hz, 1H, H-Ph), 7.24 (s, 2H, NH₂). ¹³C NMR (100.5 MHz, DMSO-*d*₆): δ (ppm) 163.6 (C8a), 161.8 (C2), 159.7 (C7), 156.4 (C4), 138.6 (C6), 135.5 (Ph), 134.7 (C5), 130.9 (Ph), 128.5 (Ph), 124.3 (Ph), 104.5 (C4a). MS (EI): m/z : 306.0 (2) [M]⁺, 271.0 (100) [M-Cl]⁺. HRMS (EI): Calc. for C₁₃H₈Cl₂N₄O: 306.0075. Found: 306.0071.

Method b) Using Na₂SeO₃ in DMSO: A mixture of 0.309 g (1 mmol) of **12**{*I*,*I*} and 0.207 g of Na₂SeO₃ (1.2 mmol) in 2 mL of DMSO was heated for 6 h at 160 °C in Ar atm. The resulting solution was cooled

down and water (200 mL) was added. The resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 0.30 g (0.98 mmol, 98%) of **21** {*1,1*}.

2-Amino-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**19**):

Using NaH in DMSO: A mixture of 0.100 g (0.31 mmol) of 2-amino-6-(2-bromophenyl)-5,6-dihydro-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**18**)⁷ and 40 mg (1.00 mmol) of NaH (60% dispersion in mineral oil) in 10 mL of DMSO was heated for 15 h at 80 °C in an Ar atm. The resulting solution was cooled down, water (200 mL) was added and it was neutralized with AcOH. The resulting precipitate was filtered, washed with EtOH and Et₂O, and dried to afford 60 mg (0.25 mmol, 80%) of **19**, mp >250 °C (lit.,¹⁶ 390 °C). IR (KBr): ν (cm⁻¹) 3595 (NH), 3306-3177 (NH₂), 1641 (C=O), 1548 (N=C), 1513 (N=C), 1402, 1270, 1225. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.07 (s, 1H, H-N8), 8.58 (s, 1H, H-C4), 7.91 (s, 1H, H-C5), 7.67 (d, 2H, H-Ph), 7.42 (m, 1H, H-Ph), 7.35 (m, 1H, H-Ph), 7.15 (s, 2H, NH₂). ¹³C NMR (100.5 MHz, DMSO-*d*₆): δ (ppm) 162.9 (C8a), 162.7 (C2), 159.0 (C7), 155.3 (C4), 136.1 (C6), 135.4 (C5), 128.4 (Ph), 127.9 (Ph), 127.3 (Ph), 126.6 (Ph), 104.8 (C4a). MS (EI): *m/z*: 306.0 (2) [M]⁺, 271.0 (100) [M-Cl]⁺. HRMS (EI): Calc. for C₁₃H₁₁N₄O: 239.0933 [M⁺+1]. Found: 239.0929.

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