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CYCLIZATION OF 5-CYANO-6-CYANOIMINO-3,4-DIHYDRO-PYRIDIN-2(1*H*)-ONES WITH AMINES

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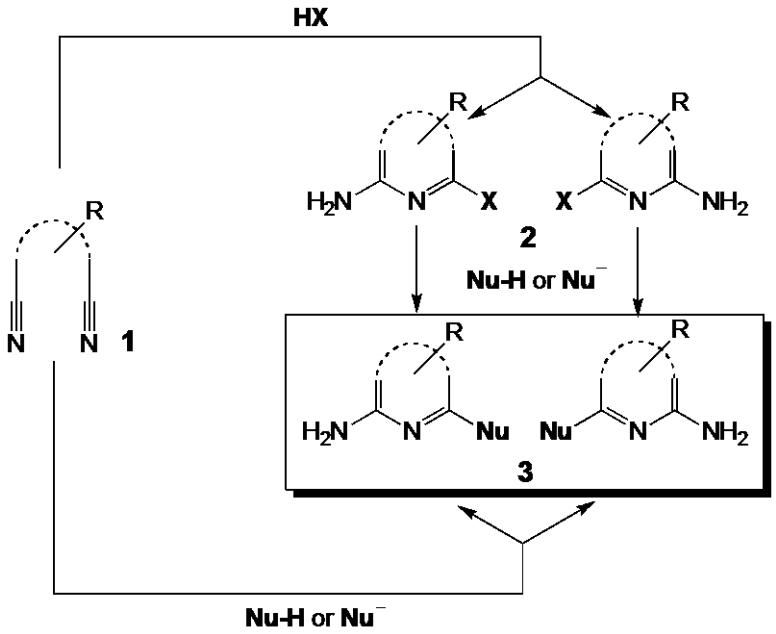
Abstract – The cyclization of 5-cyano-6-cyanoimino-3,4-dihydropyridin-2(1*H*)-ones with amines, leading to pyrido[2,3-*d*]pyrimidines, is studied. Four factors play an important role on the direction of cyclization: (1) the planarity of the reaction area; (2) the cyclization proceeds by the nucleophilic attack of an amidine onto an electrophilic group which can be either a cyano group or an alkylamidine; (3) the basicity of the amine plays an important role, the ionization of the substrate making more difficult the formation of the aforementioned amidine which is needed for the cyclization; and (4) the nucleophilic attack and the tautomerization of the cyclization product are processes which can occur practically simultaneously, so that the electronic movement involved in the tautomerization process coincides with the one which happens in the nucleophilic attack, both processes promoting each other.

INTRODUCTION

Cyclization of α,ω-dinitriles has attracted the interest of organic chemists due to the wide possibilities that offers for the synthesis of nitrogen heterocycles. A good knowledge of the mechanism and factors that influence such cyclizations is crucial because two possible regioisomers can be formed both in the presence of acidic or basic reagents.

Cyclizations of 1,5-dinitriles **1** in acidic media are commonly carried out in the presence of hydrogen halides to afford a mixture of the two halogen-substituted regioisomers **2** (Scheme 1). In most cases, the halogen atom can be substituted by a nucleophile to yield the corresponding compounds **3**.[1-5] Compounds **3** are, generally, also accessible by direct cyclization of the dinitrile system **1** upon treatment with the nucleophilic reagent.

The mechanistic rationalization of such cyclizations in acidic media is very well established as many have been the studies, revisions and updates since the original work of Johnson and Madroñero in 1966,[6] the latest ones being contributions of our group.[7,8] As a result of them, we proposed a mechanistic rationalization based on three factors: (1) the relative basicity of the cyano groups involved in the reaction, (2) the planarity of the reactive site, and (3) the tautomeric equilibrium of the starting dinitrile system.



Scheme 1

In contrast, far less attention has been paid to cyclizations in basic media[6,9] although its synthetic utility is quite obvious as shown above. A better knowledge of the factors implied in such cyclizations would allow a better control of the reaction and, ideally, the synthesis of one or another isomer at will. As a part of our work in the area of α,ω-dinitrile cyclizations, we previously studied the factors affecting the formation of regioisomeric 1,6-naphtyridines by cyclization with different amines of the aromatic 1,5-dinitrile system present in 2-(3-cyano-1*H*-pyridin-2-ylidene)malononitriles.[10] A mechanistic explanation was proposed, which was based on three factors: (1) the cyclization involves an amidine as the nucleophile which attacks either a nitrile or a second amidine, (2) the attack of one amidine onto the other has to fulfill strict geometrical constraints to allow the cyclization to proceed, and (3) the cyclization step should probably involve the aforementioned nucleophilic attack simultaneously with a tautomerism to achieve, in a single step mechanism, the high levels of regioselectivity observed.

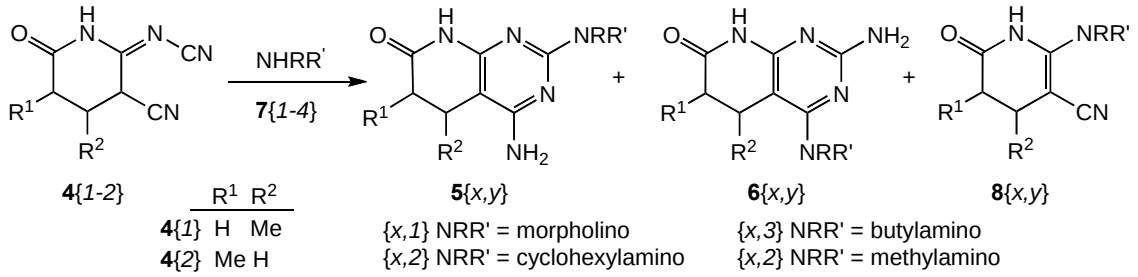
The present paper reports a continuation of such study consisting of studying the cyclization of non-aromatic 5-cyano-6-cyanoimino-3,4-dihydropyridin-2(1*H*)-ones **4** using amines to obtain pyrido[2,3-*d*]pyrimidines **5** and **6** (Scheme 2).

RESULTS AND DISCUSSION

We used the same amines employed in our previous work:[10] morpholine (**7**{*1*}), cyclohexylamine (**7**{*2*}), butylamine (**7**{*3*}) and methylamine (**7**{*4*}) in order to cover a wide range of amine class, basicity and size.

For this study we followed our previously described methodology[8] consisting in analyzing directly the reaction mixture by HPLC in order not to alter the composition of such mixture. We also have used the cyclization with hydrogen halides and the subsequent substitution by the corresponding amine in order to have an unequivocal structural assignment for each cyclization regioisomer.

The study was carried out with two 5-cyano-6-cyanoimino-3,4-dihydropyridin-2(1*H*)-ones **4**: **4**{*1*} (R^1=H, R^2=Me) and **4**{*2*} (R^1=Me, R^2=H) (Scheme 2).



Scheme 2. Cyclization of pyridiones **4** with amines

Cyclizations were carried out by varying three parameters: (a) solvent (1,4-dioxane, methanol, chloroform and net amine), we chose an aprotic solvent (1,4-dioxane), a protic one (methanol) and one apolar ($CHCl_3$); (b) pyridone:amine ratio (1:10, 1:500 and 1:1000) and (c) temperature (room temperature and reflux). The reaction time was fixed in 3 days for all the experiments.

Cyclizations of 4{*1*}

Treatment of **4**{*1*} with morpholine (**7**{*1*}) afforded, whichever reaction conditions employed, the same cyclization regioisomer, the 2-morpholine substituted one **5**{*1,1*}. The best yields were obtained at reflux temperature and with the lowest concentration of amine (10 equivalents of amine per equivalent of **4**{*1*}) in low polarity solvents (chloroform being the best followed by 1,4-dioxane).

In the case of butylamine (**7**{*3*}), it is necessary to point up the low cyclization yields obtained (25% in the best case, using net amine at reflux). These results, probably caused by secondary reactions such as the nucleophilic substitution of the cyanamino group present in **4**{*1*} by the amine to afford compound **8**{*1,3*}, make the interpretation of the results difficult. Yields increase with the thermal level, the formation of the 4-butylamino substituted isomer **6**{*1,3*} being favoured by higher temperatures and polar solvents (MeOH).

Yields of cyclization using cyclohexylamine (**7**{*2*}), although moderated, are better than in the case of butylamine (67% at reflux of net amine) and they slightly increase with temperature. Cyclization produces both isomers, although the 2-cyclohexylamino substituted isomer **5**{*1,2*} predominates. Reflux temperature and polar solvents (MeOH) favour the formation of the 4-cyclohexylamino substituted isomer **6**{*1,2*}. Interestingly, the 2-amino substituted isomer **5**{*1,2*} is more soluble in MeOH than the other isomer.

In the case of methylamine (**7**{*4*}), we used the commercially available solutions (2M in THF and 8M in EtOH) but the yields were extremely low (11% at reflux in THF), making it difficult to extract conclusions.

Cyclizations of 4{*2*}

Contrary to the case of **4**{*1*}, the cyclizations of **4**{*2*} with morpholine (**7**{*1*}) afforded both regioisomers, **5**{*2,1*} and **6**{*2,1*}, although the 2-morpholine substituted isomer **5**{*2,1*} usually predominates. The formation of **6**{*2,1*} is favoured by the thermal level (reflux) and excess of amine (the best **5**{*2,1*}:**6**{*2,1*} proportion is 42:58 when the mixture is refluxed in chloroform with 500 equivalents of amine). It is noteworthy that the substitution product **8**{*2,1*} was obtained in higher proportion (40% being the highest yield) than in the case of **4**{*1*}.

As before, cyclizations with butylamine (**7**{*3*}) presented very low yields (best yield 15%) and, even increasing slightly the temperature, they never reach 20%. It seems that the proportion of the 4-butylamino substituted isomer **6**{*2,3*} increases with temperature and with amount of amine. Again, the corresponding substitution product **8**{*2,3*} is formed in a greater amount than when the starting material was **4**{*1*}.

Treatment of **4**{*2*} with cyclohexylamine (**7**{*2*}) afforded, in general, lower yields than those obtained from **4**{*1*} due to the formation of the substitution product **8**{*2,2*} (up to 41%). Such substitution is favoured by increasing the reaction temperature. The 2-cyclohexylamino substituted regioisomer **5**{*2,2*} is predominantly formed, its production being favoured by higher thermal levels and polar solvents.

Once more, cyclizations of **4**{*2*} with methylamine (**7**{*4*}) gave very low yields (best yield 12% when ethanol was used as solvent), although they increase with temperature. However, when the reaction was carried out in EtOH at room temperature, **8**{*2,4*} was formed in a 47% yield. In any case, the 2-methylamino substituted isomer **5**{*2,4*} is predominantly formed at reflux.

Overall comments

From the results obtained in our cyclization study, we can conclude that when **4**{*1*} is used as the starting material, the corresponding 2-alkylamino substituted isomer **5** is predominantly formed. The use of higher temperatures and more polar solvents slightly favours the formation of the 4-alkylamino substituted isomer **6** unless in the case of morpholine (**7**{*1*}). Yields are in general increased with the thermal level.

In the case of **4**{*2*}, the substitution product **8** appears in greater amounts with respect to **4**{*1*} decreasing, consequently, the cyclization yields. This behaviour renders difficult to extract conclusions. Nevertheless,

the 2-alkylamino substituted regioisomer **5** is predominantly formed with all the amines assayed. An increase in the concentration of amine seems to favour the formation of the 4-alkylamino substituted isomer **6**.

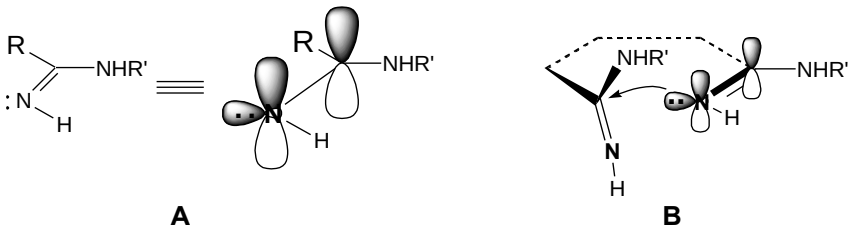
Certainly, the nucleophilic substitution of the cyanoimino group by the corresponding amine is an undesired secondary reaction because, besides of decreasing the cyclization yields, liberates cyanamide which can produce other side reactions.

Finally, the use of chloroform as solvent at reflux temperature afforded, whatever the amine employed, a plentiful precipitate which turns to be the hydrochloride of the corresponding amine.

The formation of such hydrochlorides, in a medium where the only possible source of chlorine is chloroform, can be explained via formation of a carbene. The amine captures the chloroform proton and the resulting stabilized anion releases chlorine to afford dichlorocarbene (similarly to the hydrolysis of chloroform in aqueous basic conditions)[11,12] and the corresponding alkylammonium chloride, which precipitates. Unfortunately, we have not isolated any product coming from the multiple possible evolutions of dichlorocarbene.

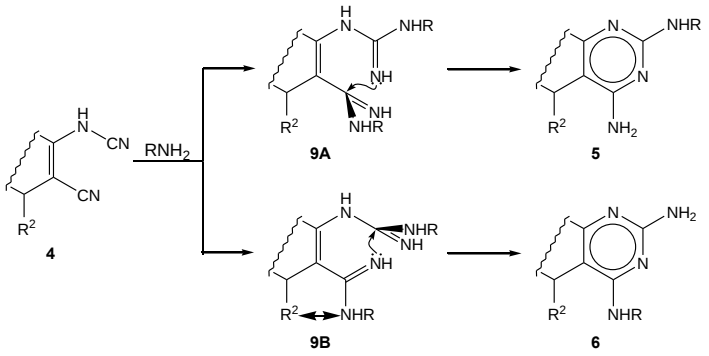
Mechanistic rationalization of the cyclization of 5-cyano-6-cyanoimino-3,4-dihydro-pyridin-2(1*H*)-ones with amines

Similarly to our previous work,[10] the formation of amidines seems to be a key step in the cyclization of 5-cyano-6-cyanoimino-3,4-dihydropyridin-2(1*H*)-ones with amines. Particularly, the geometry of the reaction zone is a decisive factor to predict the direction of the cyclization as it happened in the cyclizations with hydrogen halides. The amidine, which acts as nucleophile, must be coplanar to the area of reaction, whereas the amidine which receives the attack must be perpendicular to such plane (Scheme 3).



Scheme 3. Orbitals in an amidine (A) and geometry of the reaction area (B)

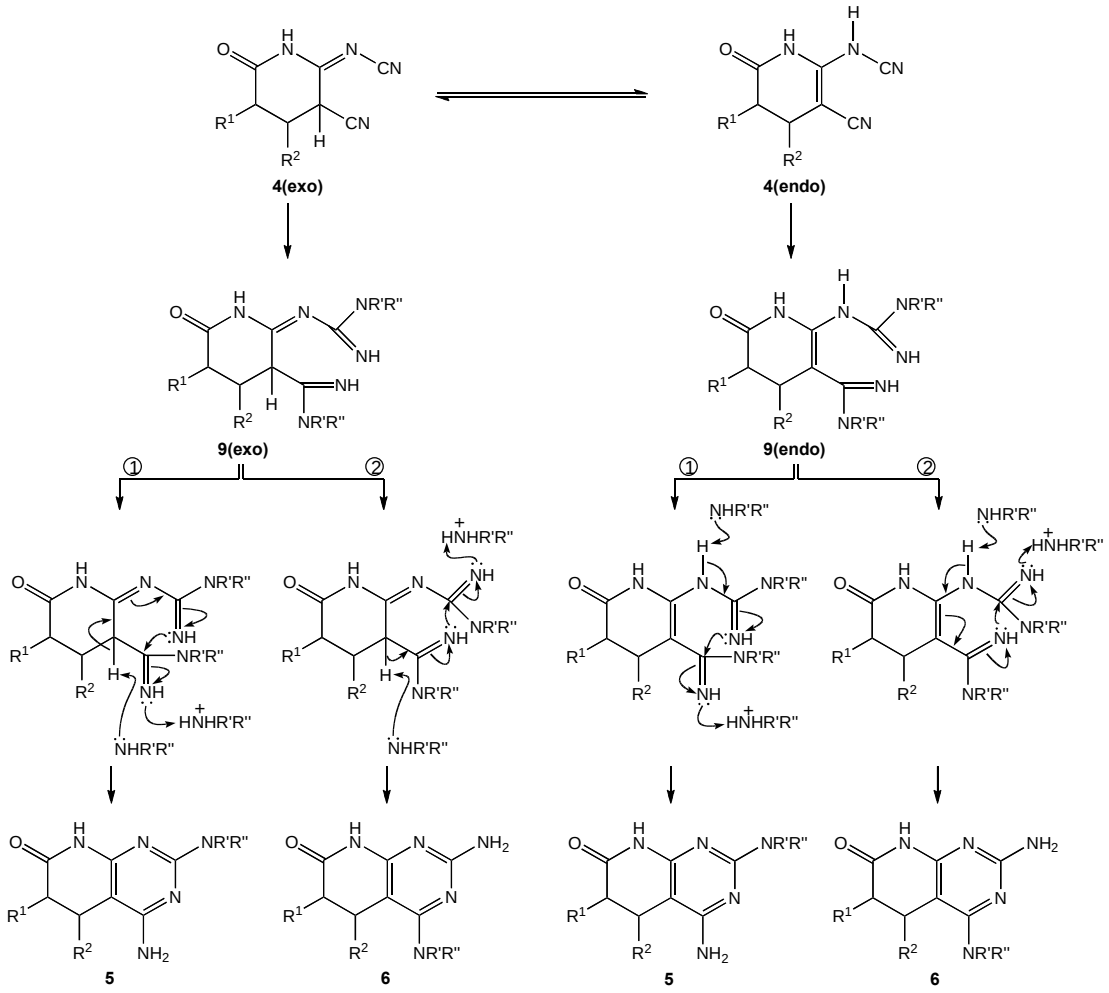
As it can be seen, the presence of a substituent R^2, although it is out of the plane of the reaction because it is linked to a sp^3 carbon, will difficult the intermediate diamidine to adopt the geometry of the intermediate **9B** which leads to the 4-alkylamino substituted isomer **6** (Scheme 4).



Scheme 4. Intermediates in the dinitrile cyclization of **4** with amines

Nevertheless, the regioselectivity is not so high as in the cyclizations of aromatic dinitriles described in our previous work[10] because in that case the sterical hindrance of the R^2 substituent was much more important due to its coplanarity with the reaction zone.

Therefore, the sterical hindrance is not the decisive factor as before and the results obtained do not show clear tendencies from which one can extract solid conclusions. Consequently, the following mechanistic proposal (Scheme 5) should be considered as a rationalization which helps to understand how each regioisomer is formed although its predictive capability is limited.



Scheme 5

The first factor to be considered in such mechanistic proposal is the possible tautomerism of the starting materials **4**. It is evident that the cyclization through the endocyclic tautomer **4(endo)** should be favoured due to the greater planarity of the reaction zone. However, such kind of tautomer has never detected by direct means although some indirect tests seem to indicate that it plays a key role in the cyclizations with hydrogen halides. In this study it is difficult to establish how the reaction medium can affect the equilibrium between the **4(endo)** and the **4(exo)** tautomers. Perhaps this fact could explain the lack of tendencies observed. What is clear is that both tautomers can lead to both regioisomers **5** and **6** as it is depicted in Scheme 5.

A second factor to be considered is the reactivity of the amine used for the cyclization. The best results, both in regioselectivity and conversion, have been obtained with morpholine (**7**{*1*}) while cyclohexylamine (**7**{*2*}) and butylamine (**7**{*3*}) afforded lower conversions and more secondary products. Taking into account that compounds **4** present an acidic proton that can be abstracted by the amine, it is interesting to note that morpholine is the less basic amine used. Obviously, the ionized form of compounds **4** will difficult the nucleophilic attack of the amine thus reducing the cyclization yield. This assumption seems to justify why morpholine gave the best results for both substrates **4**{*1*} and **4**{*2*}.

The solvent, the third factor to be considered, seems to point out in the same direction and MeOH, the more polar solvent used, which can favour the formation of ionized species, gave also the worst yields of cyclization.

A final factor that, in this case, makes more difficult the interpretation of the obtained data is the side-reaction by which the cyanamine moiety of compounds **4** is substituted by the corresponding amine to afford compounds **8**.

Consequently, the cyclization of systems **4** with amines seems to be influenced by the following factors: 1) the planarity of the reaction area seems to play a major role on the direction of the cyclization although in this case the presence of an R^2 substituent is not so dramatic. 2) The cyclization proceeds by the nucleophilic attack of an amidine onto an electrophilic group which can be either a cyano group or an alkylamidine. 3) The basicity of the amine plays an important role because the ionization of the substrate **4** makes more difficult the formation of the aforementioned amidine that is needed for the cyclization. 4) The nucleophilic attack and the tautomerization of the cyclization product are processes which can occur practically simultaneously, so that the electronic movement involved in the tautomerization process coincides with the one which happens in the nucleophilic attack, both processes promoting each other.

CONCLUSION

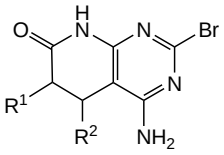
In conclusion, although the cyclization of the dinitrile system present in pyridones **4** is an attractive one-step process for the synthesis of 2-alkylamino and 4-alkylamino substituted pyrido[2,3-*d*]pyrimidines

5 and **6**, it has a more erratic behaviour than other α,ϖ-dinitriles studied by our group. Consequently, it is better to carry out the cyclization of systems **4** with hydrogen halides and then substitute the halogen atom by the corresponding amine.

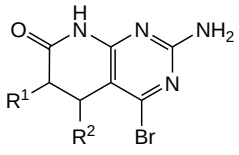
EXPERIMENTAL

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. ^{1}H and ^{13}C NMR spectra were determined in a Varian Gemini-300 operating in field strength of 300 and 75.5 MHz, respectively. Chemical shifts were reported in parts per million (δ) and Coupling constants (J) in Hz, using in the case of ^{1}H NMR, sodium 2,2,3,3-tetradeuteriotrimethylsilylpropionate as an internal standard and setting, in the case of ^{13}C NMR, the references at the signal of the solvent (163.8 ppm, CF_3CO_2D, 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. Elemental microanalyses were obtained in a Carlo-Erba CHNS-OR/EA 1108 analyzer and gave results for the elements stated with ±0.4% of the theoretical values.

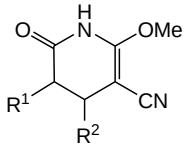
The UV-VIS absorption spectra were recorded in a spectrophotometer Varian Cary 5E of double beam. The high performance liquid chromatography (HPLC) was carried out in a Nebula™ Gilson with a Gilson 322 HPLC Pump, manual injector Rheodyne and a Gilson 151 UV/VIS Detector. The column employed was an amino column Kromasil 100 NH2 10 μm 15x0.46 Ref TR-011993 Teknokroma. The thin layer chromatography (TLC) was carried out with Polygram® SIL G/UV254 (Macherey-Nagel) plates. The reagents and solvents were purchased from Sigma-Aldrich and were used directly. Compounds **10**{*1*}, **10**{*2*}, **11**{*1*}, **11**{*2*}, **12**{*1*}, and **12**{*2*} were prepared according to reported procedures.[13]



10{*1*} R^1=H, R^2=Me
10{*2*} R^1=Me, R^2=He



11{*1*} R^1=H, R^2=Me
11{*2*} R^1=Me, R^2=He



12{*1*} R^1=H, R^2=Me
12{*2*} R^1=Me, R^2=He

Preparation of standards

Substitution by amines in 4-amino-2-bromo-5-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (**10**{*1*})[8,14-17]

a) Substitution by morpholine (**5**{*1,1*}): 4-amino-2-bromo-5-methyl-5,6-dihydropirido[2,3-*d*]pirimidin-

7(8*H*)-one (**10**{*1*}) (0.5 g, 1.9 mmol), morpholine (8.5 mL, 0.10 mol) and dry MeOH (15 mL) were heated under reflux for 24 h. After cooling, the solvent was removed under reduced pressure and the residue obtained was suspended in water, filtered, washed with water and dried under vacuum, to afford 4-amino-5,6-dihydro-5-methyl-2-morpholinopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*1,1*}) (490 mg, 1.86 mmol, 98%); mp 248-249 ºC. IR (KBr): ν(cm^{-1}): 3472 and 3347 (NH_2), 3226 (NHCO), 1675 (C=O), 1631, 1615 and 1558 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.56 (m, 8H, N-C**H**$_2$-C**H**$_2$-O), 2.97 (m, 1H, C(5)-**H**), 2.65 (dd, $^3J_{HH}$ = 6.3 Hz, $^2J_{HH}$ = 15.6 Hz, 1H, C(6)-**H**) and 2.20 (d, $^2J_{HH}$ = 15.6 Hz, 1H, C(6)-**H**), 0.94 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 9.89 (br, 1H, -N**H**CO-), 6.31 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 170.6 (C-7), 160.9 (C-4), 159.9 (C-2), 155.4 (C-8a), 89.6 (C-4a), 66.1 (-**C**H$_2$-OR), 43.9 (-**C**H$_2$-NH), 38.4 (C-6), 23.2 (C-5), 18.8 (-**C**H$_3$). MS, m/z (%): 263 (72) $[M]^+$, 248 (100), 177 (3), 86 (3). *Anal*. Calcd for $C_{12}H_{17}N_5O_2$; C, 54.74; H, 6.51; N, 26.60. Found: C, 54.62; H, 6.23; N, 26.98.

b) Substitution by butylamine (**5**{*1,2*}): As above for **5**{*1,1*} but using 0.5 g (1.9 mmol) of **10**{*1*}, butylamine (10 mL, 0.10 mol) and dry MeOH (15 mL) at reflux for 48 h to afford 4-amino-2-(butylamino)-5,6-dihydro-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*1,2*}) (430 mg, 1.73 mmol, 91%); mp 213-214 ºC. IR (KBr): ν(cm^{-1}): 3503, 3325 and 3267 (NH_2), 3198 (NHCO), 1687 (C=O), 1637, 1588 and 1545 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.97 (m, 1H, C(5)-**H**), 2.65 (dd, $^3J_{HH}$ = 6.9 Hz, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H$_2$**) and 2.19 (d, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H$_2$**), 1.45 (m, 2H, NH-CH$_2$-C**H**$_2$-), 1.29 (m, 2H, -C**H**$_2$-CH$_3$), 0.94 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 0.88 (t, $^3J_{HH}$= 7.2 Hz, 3H, -CH$_2$-C**H$_3$**), 9.97 (br, 1H, -N**H**CO-), 6.16 (br, 1H, -N**H**-), 6.16 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.4 (C-7), 161.1 (C-4), 160.7 (C-2), 155.4 (C-8a), 88.9 (C-4a), 40.3, 31.5, 19.7, 13.9 (-But), 38.4 (C-6), 23.2 (C-5), 18.8 (-**C**H$_3$). MS, m/z (%): 249 (58) $[M]^+$, 234 (100), 220 (20), 206 (73), 192 (21), 178 (32). *Anal*. Calcd for $C_{12}H_{19}N_5O_1$; C, 57.81; H, 7.68; N, 28.09. Found: C, 57.69; H, 7.83; N, 27.79.

c) Substitution by cyclohexylamine (**5**{*1,3*}): As above for **5**{*1,1*} but using 0.5 g (1.9 mmol) of **10**{*1*}, cyclohexylamine (12 mL, 0.10 mol) and dioxane (25 mL) heated at reflux for 75 h to give 4-amino-2-(cyclohexylamino)-5,6-dihydro-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*1,3*}) (439 mg, 1.56 mmol, 84%); mp >290 ºC. IR (KBr): ν(cm^{-1}): 3499 and 3276 (N-H), 3206 (NHCO), 1687 (C=O), 1639, 1594 and 1549 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.65 (m, 1H, -NH-C**H$_2$**(-CH$_2$-)$_2$), 2.97 (m, 1H, C(5)-**H**), 2.66 (dd, $^3J_{HH}$ = 6.9 Hz, $^2J_{HH}$ = 16.2 Hz, 1H, C(6)-**H$_2$**) and 2.20 (d, $^2J_{HH}$ = 16.2 Hz, 1H, C(6)-**H$_2$**), 1.80-1.10 (m, 10H, -C**H**$_2$- cyclohexyl), 0.94 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 10.09 (br, 1H, -N**H**CO-), 6.17 (br, 1H, -N**H-**), 6.17 (br, 2H, -N**H$_2$**). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.5 (C-7), 161.1 (C-4), 160.0 (C-2), 155.3 (C-8a), 88.8 (C-4a), 48.5, 32.9, 25.4, 25.0

(cyclohexyl), 38.4 (C-6), 23.2 (C-5), 18.9 (-**C**H_3). MS, m/z (%): 275 (68) [M^+], 260 (51), 232 (39), 193 (72), 178 (100). *Anal*. Calcd for $C_{14}H_{21}N_5O_1$; C, 61.07; H, 7.69; N, 25.43. Found: C, 61.45; H, 7.98; N, 25.15.

d) Substitution by methylamine (**5**{*1,4*}): As above for **5**{*1,1*} but using 0.5 g (1.9 mmol) of **10**{*1*}, 8 M methylamine in EtOH (12.5 mL, 0.10 mol) heated at reflux for 70 h. After cooling, the precipitated was filtered, washed with MeOH and dried. The filtered solution was concentrated *in vacuo*, the residue obtained suspended in water, filtered and washed with water/MeOH. The combined solids were dried under vacuum to give 4-amino-5,6-dihydro-5-methyl-2-(methylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*1,4*}) (295 mg, 1.43 mmol, 75%); mp>290 ºC. IR (KBr): ν(cm^{-1}): 3470, 3322 and 3268 (N-H), 3196 (NHCO), 1679 (C=O), 1628, 1576 and 1549 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.98 (m, 1H, C(5)-**H**), 2.70 (d, $^3J_{HH}$ = 4.8 Hz, 3H, -NH-C**H**$_3$), 2.65 (dd, $^3J_{HH}$ = 6.9 Hz, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H**$_2$) and 2.20 (d, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H**$_2$), 0.94 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 10.07 (br, 1H, -N**H**CO-), 6.22 (br, 1H, -N**H**-), 6.22 (brp, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.1 (C-7), 161.3 (C-4), 161.1 (C-2), 155.4 (C-8a), 89.0 (C-4a), 38.5 (C-6), 27.9 (-NH-**C**H_3), 23.2 (C-5), 18.9 (-**C**H_3). MS, m/z (%): 207 (37) [$M]^+$, 192 (100).

Substitution by amines in 4-amino-2-bromo-6-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (**10**{*2*})[8,14-17]

a) Substitution by morpholine (**5**{2,1}): A mixture of 4-amino-2-bromo-6-methyl-5,6-dihydro-pirido[2,3-*d*]pirimidin-7(8*H*)-one (**10**{*2*}) (0.5 g, 1.9 mmol), morpholine (8.5 mL, 0.10 mol) and dry MeOH (15 mL) was heated at reflux for 48 h. After cooling, the precipitate was filtered, washed with MeOH and dried under vacuum. The filtrate was concentrated *in vacuo*, the residue obtained was suspended in water, filtered, washed with water/MeOH. The combined solids were dried under vacuum to give 4-amino-5,6-dihydro-6-methyl-2-morpholinopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*2,1*}) (440 mg, 1.69 mmol, 89%); mp>290 ºC. IR (KBr): ν(cm^{-1}): 3449 and 3347 (N-H), 3231 (NHCO), 1679 (C=O), 1628, 1561 and 1527 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.56 (m, 8H, -C**H**$_2$-morpholine), 2.76-2.13 (m, 2H, C(5)-**H** and C(6)-**H**), 1.11 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 9.84 (br, 1H, -N**H**CO-), 6.25 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 173.9 (C-7), 161.4 (C-4), 159.9 (C-2), 156.4 (C-8a), 84.1 (C-4a), 66.1 (-**C**H_2-OR), 43.9 (-**C**H_2-NH), 34.7 (C-6), 25.2 (C-5), 15.6 (-**C**H_3). MS, m/z (%): 263 (100) [$M]^+$, 248 (6), 178 (46).

b) Substitution by butylamine (**5**{*2,2*}): As above for **5**{*2,1*} but using 0.5 g (1.9 mmol) of **10**{*2*}, butylamine (10 mL, 0.10 mol) and dry MeOH (15 mL) heated at reflux for 48 h to afford 4-amino-2-(butylamino)-5,6-dihydro-6-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*2,2*}) (416 mg, 1.73 mmol, 88%); mp 229-230 ºC. IR (KBr): ν(cm^{-1}): 3493, 3325 and 3267 (N-H), 3198 (NHCO), 1688

(C=O), 1636, 1586 and 1546 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3,16 (m, 2H, -NH-C**H**$_2$-) 2,74-2,10 (m, 3H, C(5)-**H** and C(6)-**H**), 1,45 (m, 2H, NH-CH$_2$-C**H**$_2$-), 1.30 (m, 2H, -C**H**$_2$-CH$_3$), 1.11 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 0.88 (t, $^3J_{HH}$ = 7.2 Hz, 3H, -CH$_2$-C**H**$_3$), 9.92 (br, 1H, -N**H**CO-), 6.19 (br, 1H, -N**H**-), 6.10 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.4 (C-7), 161.6 (C-4), 160.8 (C-2), 156.3 (C-8a), 83.3 (C-4a), 40.3, 31.5, 19.7, 13.8 (-But), 34.8 (C-6), 25.3 (C-5), 15.6 (-**C**H$_3$). MS, m/z (%): 249 (49) [M]$^+$, 234 (3), 220 (27), 206 (100), 192 (9), 178 (12).

c) Substitution by cyclohexylamine (**5**{*2,3*}): As above for **5**{*2,1*} but using 0.5 g (1.9 mmol) of **10**{*2*}, cyclohexylamine (12 mL, 0.10 mol) and dioxane (25 mL) heated at reflux for 70 h to give 4-amino-2-(cyclohexylamino)-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*2,3*}) (397 mg, 1.44 mmol, 76%); mp 288-289 ºC. IR (KBr): ν (cm^{-1}): 3470, 3342 and 3310 (N-H), 3180 and 3077 (NHCO), 1672 (C=O), 1628, 1581 and 1543 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.65 (m, 1H, -NH-C**H**(-CH$_2$-)$_2$), 2.73-2.10 (m, 3H, C(5)-**H** and C(6)-**H$_2$**), 2.00-1.20 (m, 10H, -C**H**$_2$-cyclohexyl), 1.10 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 9.84 (br, 1H, -N**H**CO-), 6.08 (br, 2H, -N**H$_2$**), 5.96 (d, $^3J_{HH}$ = 8.4 Hz, 1H, -N**H**-). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.5 (C-7), 161.6 (C-4), 160.0 (C-2), 156.3 (C-8a), 83.3 (C-4a), 48.5, 32.9, 25.4, 25.0 (cyclohexyl), 34.7 (C-6), 24.0 (C-5), 15.6 (-**C**H$_3$). MS, m/z (%): 275 (54) [M$^+$], 260 (3), 232 (37), 193 (100), 178 (18).

d) Substitution by methylamine (**5**{*2,4*}): As above for **5**{*2,1*} but using 0.5 g (1.9 mmol) of **10**{*2*}, 8 M methylamine in ethanol (12.5 mL, 0.10 mol) heated at reflux for 70 h to give 4-amino-5,6-dihydro-6-methyl-2-(methylamino)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**{*2,4*}) (267 mg, 1.29 mmol, 68%); mp > 290 ºC. IR (KBr): ν(cm^{-1}): 3485 and 3309 (N-H), 3042 (NHCO), 1685 (C=O), 1630, 1553 and 1525 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.69 (d, $^3J_{HH}$ = 4.8 Hz, 3H, -NH-C**H**$_3$) 2.76-2.14 (m, 3H, C(5)-**H** and C(6)-**H**), 1.11 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 9.78 (br, 1H, -N**H**CO-), 6.15 (br, 1H, -N**H**-), 6.15 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.3 (C-7), 161.5 (C-4), 161.3 (C-2), 156.4 (C-8a), 83.4 (C-4a), 34.8 (C-6), 28.0 (-NH-**C**H$_3$), 25.3 (C-5), 15.6 (-**C**H$_3$). MS, m/z (%): 207 (34) [M$^+$], 192 (100).

Substitution by amines in 2-amino-4-bromo-5-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (**11**{*1*})[8,14-17]

a) Substitution by morpholine (**6**{1,1}): A mixture of 2-amino-4-bromo-5-methyl-5,6-dihydro-pirido[2,3-*d*]pirimidin-7(8*H*)-one (**11**{*1*}) (0.5 g, 1.9 mmol), morpholine (8.5 mL, 0.10 mol) and dry MeOH (15 mL) was heated at reflux for 24 h. After cooling, the precipitate was filtered, washed with MeOH and dried under vacuum. The filtrate was concentrated *in vacuo* and the residue obtained was suspended in water, filtered, washed with water and dried under vacuum. Both solids were combined to

afford 2-amino-5,6-dihydro-5-methyl-4-morpholinopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{1,1}) (395 mg, 1.52 mmol, 80%); mp >290 ºC. IR (KBr): ν(cm^{-1}): 3420 and 3326 (N-H), 3221 (NHCO), 1683 (C=O), 1643, 1609 and 1547 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.69 (m, 4H,-C**H**$_2$-OR-), 3.26 (m, 4H, -C**H**$_2$-N), 3.10 (m, 1H, C(5)-**H**), 2.71 (dd, $^3J_{HH}$ = 6.0 Hz, $^2J_{HH}$ = 15.3 Hz, 1H, C(6)-**H**) and 2.24 (d, $^2J_{HH}$ = 15.3 Hz, 1H, C(6)-**H**), 1.02 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 10.31 (br, 1H, -N**H**CO-), 6.21 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 173.1 (C-7), 165.6 (C-4), 161.5 (C-2), 157.9 (C-8a), 97.2 (C-4a), 66.7 (-**C**H$_2$-OR), 49.8 (-**C**H$_2$-NH), 38.4 (C-6), 25.6 (C-5), 19.6 (-**C**H$_3$). MS, (70 eV): m/z (%): 263(100)[M]$^+$, 248(89), 177(15), 86(37). *Anal*. Calcd for $C_{12}H_{17}N_5O_2$; C, 54.74; H, 6.51; N, 26.60. Found: C, 54.42; H, 6.91; N, 26.21.

b) Substitution by butylamine (**6**{*1,2*}): As above for **6**{*1,1*} but using 0.5 g (1.9 mmol) of **11**{*1*}, butylamine (10 mL, 0.10 mol) and dry MeOH (15 mL) heated at reflux for 70 h to give 2-amino-4-(butylamino)-5,6-dihydro-5-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{*1,2*}) (359 mg, 1.44 mmol, 76%); mp 271-272 ºC. IR (KBr): ν(cm^{-1}): 3380 and 3342 (N-H), 3210 (NHCO), 1687 (C=O), 1651, 1623 and 1577 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.04 (m, 1H, C(5)-**H**), 2.68 (dd, $^3J_{HH}$ = 6.9 Hz, $^2J_{HH}$ = 16.2 Hz, 1H, C(6)-**H$_2$**) and 2.21 (d, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H$_2$**), 1.50 (m, 2H, NH-CH$_2$-C**H**$_2$-), 1.30 (m, 2H, -C**H**$_2$-CH$_3$), 0.93 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 0.90 (t, $^3J_{HH}$ = 7.2 Hz, 3H, -CH$_2$-C**H$_3$**), 10.41 (BR, 1H, -N**H**CO-), 6.44 (t, $^3J_{HH}$ = 5.4 Hz, -N**H**-), 6.00 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.5 (C-7), 161.5 (C-4), 159.9 (C-2), 154.4 (C-8a), 89.5 (C-4a), 39.7, 31.4, 19.6, 13.8 (-But), 38.2 (C-6), 22.7 (C-5), 18.9 (-**C**H$_3$). MS, m/z (%): 249 (49) [M]$^+$, 234 (100), 220 (19), 206 (21), 192 (18), 178 (16). *Anal*. Calcd for $C_{12}H_{19}N_5O_1$; C, 57.81; H, 7.68; N, 28.09. Found: C, 57.44; H, 7.59; N, 28.17.

c) Substitution by cyclohexylamine (**6**{*1,3*}): As above for **6**{*1,1*} but using 0.5 g (1.9 mmol) of **11**{*1*}, cyclohexylamine (12 mL, 0.10 mol) and dioxane (25 mL) heated at reflux for 70 h to give 2-amino-4-(cyclohexylamino)-5,6-dihydro-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{*1,3*}) (266 mg, 1.01 mmol, 51%); mp 286-287 ºC. IR (KBr): ν(cm^{-1}): 3449 and 3329 (N-H), 3225 (NHCO), 1673 (C=O), 1628, 1577 and 1474 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.95 (m, 1H, -NH-C**H**(-CH$_2$-)$_2$), 3.04 (m, 1H, C(5)-**H**), 2.65 (dd, $^3J_{HH}$ = 6.6 Hz, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H$_2$**) and 2.17 (d, $^2J_{HH}$ = 15.9 Hz, 1H, C(6)-**H$_2$**), 1.80-1.10 (m, 10H, -C**H**$_2$- cyclohexyl), 0.94 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 10.01 (br, 1H, -N**H**CO-), 5.99 (d, $^3J_{HH}$ = 8.4 Hz, 1H, -N**H**-), 5.82 (br, 2H, -N**H$_2$**). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.2 (C-7), 161.6 (C-4), 159.1 (C-2), 154.7 (C-8a), 89.4 (C-4a), 48.2, 33.1, 32.8, 25.3, 25.1, 24.1 (cyclohexyl), 38.2 (C-6), 22.6 (C-5), 18.9 (-**C**H$_3$). MS, m/z (%): 275 (82) [M$^+$], 260 (77), 232 (19), 193 (100), 178 (79). *Anal*. Calcd for $C_{14}H_{21}N_5O_1$; C, 61.07; H, 7.69; N, 25.43. Found: C, 61.38; H, 7.85; N, 25.22.

d) Substitution by methylamine (**6**{*1,4*}): As above for **6**{*1,1*} but using 0.5 g (1.9 mmol) of **11**{*1*}, 8 M methylamine in EtOH (12.5 mL, 0.10 mol) heated at reflux for 70 h to yield 2-amino-5,6-dihydro-5-methyl-4-(methylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{*1,4*}) (287 mg, 1.38 mmol, 73%); mp > 290 ºC. IR (KBr): ν(cm^{-1}): 3385 and 3341 (N-H), 3216 (NHCO), 1692 (C=O), 1622, 1580 and 1545 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.94 (m, 1H, C(5)-**H**), 2.79 (d, $^3J_{HH}$ = 4.2 Hz, 3H, -NH-C**H**$_3$), 2.66 (dd, $^3J_{HH}$ = 6.9 Hz, $^2J_{HH}$ = 16.2 Hz, 1H, C(6)-**H**$_2$) and 2.20 (d, $^2J_{HH}$ = 16.2 Hz, 1H, C(6)-**H**$_2$), 0.93 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 10.08 (br, 1H, -N**H**CO-), 6.47 (d, $^3J_{HH}$ = 4.2 Hz, 1H, -N**H**-), 5.94 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 170.9 (C-7), 161.6 (C-4), 160.4 (C-2), 154.5 (C-8a), 89.7 (C-4a), 38.4 (C-6), 27.6 (-NH-**C**H$_3$), 22.9 (C-5), 18.9 (-**C**H$_3$). MS m/z (%): 207 (36) [M]$^+$, 192 (100).

Substitution by amines in 2-amino-4-bromo-6-methyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (**11**{*2*})[8,14-17]

a) Substitution by morpholine (**6**{*2,1*}): A mixture of 2-amino-4-bromo-6-methyl-5,6-dihydropirido-[2,3-*d*]pirimidin-7(8*H*)-one (**11**{*2*}) (0.5 g, 1.9 mmol), morpholine (8.5 mL, 0.10 mol) and dry MeOH (15 mL) was heated at reflux for 24 h. After cooling, the precipitate was filtered, washed with MeOH and dried under vacuum. The filtrate was concentrated *in vacuo* and the residue obtained was suspended in water, filtered, washed with water and dried under vacuum to afford 2-amino-5,6-dihydro-6-methyl-4-morpholinopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{*2,1*}) (424 mg, 1.63 mmol, 86%); mp>290 ºC. IR (KBr): ν(cm^{-1}): 3440 and 3326 (N-H), 3222 (NHCO), 1675 (C=O), 1617 and 1551 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.67 (m, 8H, -C**H**$_2$- morpholine), 3.73-3.31 (m, 2H, C(5)-**H** and C(6)-**H**), 1.11 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -C**H**$_3$), 10.12 (br, 1H, -N**H**CO-), 6.10 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d$_6$): δ = 173.9 (C-7), 165.0 (C-4), 161.1 (C-2), 158.4 (C-8a), 90.6 (C-4a), 66.0 (-**C**H$_2$-OR), 48.5 (-**C**H$_2$-NH), 34.7 (C-6), 27.8 (C-5), 15.0 (-**C**H$_3$). MS, m/z (%): 263 (100) [M]$^+$, 248 (72), 178 (33), 86 (30).

b) Substitution by butylamine (**6**{*2,2*}): As above for **6**{*2,1*} but using 0.5 g (1.9 mmol) of **11**{*2*}, butylamine (10 mL, 0.10 mol) and dry MeOH (15 mL) heated at reflux for 48 h to give 2-amino-4-(butylamino)-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{*2,2*}) (349 mg, 1.40 mmol, 74%); mp 275-276 ºC. IR (KBr): ν(cm^{-1}): 3444 and 3332 (N-H), 3228 (NHCO), 1678 (C=O), 1629 and 1572 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.10 (m, 2H, -NH-C**H**$_2$-) 2.73-2.07 (m, 3H, C(5)-**H** and C(6)-**H**), 1.50 (m, 2H, NH-CH$_2$-C**H**$_2$-), 1.30 (m, 2H, -C**H**$_2$-CH$_3$), 1.12 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -C**H**$_3$), 0.89 (t, $^3J_{HH}$ = 7.5 Hz, 3H, -CH$_2$-C**H**$_3$), 10.04 (br, 1H, -N**H**CO-), 6.30 (t, $^3J_{HH}$ = 5.4 Hz, 1H, -N**H**-), 5.85 (br, 2H, -N**H**$_2$). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.2 (C-7), 161.6 (C-4), 160.5 (C-2),

155.6 (C-8a), 84.0 (C-4a), 39.9, 31.4, 19.7, 13.9 (-But), 34.8 (C-6), 25.3 (C-5), 15.6 (-CH_3). MS, m/z (%): 249 (100) $[M]^+$, 234 (66), 220 (79), 206 (82), 192 (55), 178 (82).

c) Substitution by cyclohexylamine (**6**{*2,3*}): As above for **6**{*1,1*} but using 0.5 g (1.9 mmol) of **11**{*1*}, cyclohexylamine (12 mL, 0.10 mol) and dioxane (25 mL) heated at reflux for 70 h to give 2-amino-4-(cyclohexylamino)-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6**{*2,3*}) (344 mg, 1.31 mmol, 66%); mp 282-283 ºC. IR (KBr): ν(cm^{-1}): 3508, 3382 and 3316 (N-H), 3207 and 3141 (NHCO), 1683 (C=O), 1627 and 1571 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.92 (m, 1H, -NH-CH(-CH_2-)$_2$), 2.77-2.11 (m, 3H, C(5)-H and C(6)-H_2), 2.0-1.2 (m, 10H, -CH_2- cyclohexyl), 1.12 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -CH_3), 9.77 (br, 1H, -NHCO-), 5.93 (d, $^3J_{HH}$ = 7.5 Hz, 1H, -NH-), 5.72 (br, 2H, -NH_2). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.2 (C-7), 161.5 (C-4), 159.6 (C-2), 155.7 (C-8a), 84.0 (C-4a), 48.3, 32.8, 32.7, 25.3, 25.1, 25.0 (cyclohexyl), 34.5 (C-6), 25.0 (C-5), 15.6 (-CH_3). MS, m/z (%): 275 (62) $[M^+]$, 260 (44), 232 (12), 193 (100), 178 (90).

d) Substitution by methylamine (**6**{*2,4*}): As above for **6**{*2,1*} but using 0.5 g (1.9 mmol) of **11**{*2*}, 8 M methylamine in EtOH (12.5 mL, 0.10 mol) heated at reflux for 70 h to afford 2-amino-6-methyl-4-methylamino-5,6-dihydropirido[2,3-*d*]pirimidin-7(8*H*)-one (**6**{*2,4*}) (234 mg, 1.11 mmol, 59%); mp >290 ºC. IR (KBr): ν(cm^{-1}): 3421 and 3317 (N-H), 3217 (NHCO), 1674 (C=O), 1629, 1580 and 1528 (C=C and C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.78 (d, $^3J_{HH}$ = 4.8 Hz, 3H, -NH-CH_3) 2.73-2.08 (m, 3H, C(5)-H and C(6)-H), 1.12 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -CH_3), 10.26 (br, 1H, -NHCO-), 6.43 (br, 1H, -NH-), 6.01 (br, 2H, -NH_2). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.3 (C-7), 161.6 (C-4), 161.0 (C-2), 155.3 (C-8a), 84.0 (C-4a), 34.5 (C-6), 27.6 (-NH-CH_3), 25.0 (C-5), 15.6 (-CH_3). MS, m/z (%): 207 (92) $[M^+]$, 192 (100).

Substitution by amines in 2-methoxy-4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitrile (**12**{*1*})[18,19]

a) Substitution by morpholine (**8**{*1,1*}): A mixture of 2-methoxy-4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitrile (**12**{*1*}) (0.83 g, 5 mmol) and morpholine (0.9 mL, 10 mmol) in 10 mL of dry MeOH was stirred at rt for 24 h. The resulting precipitate was filtered, washed with EtOH, dried under vacuum and recrystallized from acetone/hexane to give 4-methyl-2-morpholino-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**8**{*1,1*}) (0.78 g, 3.6 mmol, 71%); mp 209-210 ºC. IR (KBr): ν(cm^{-1}): 3186, 3110 (NHCO), 2186 (CN), 1678 (C=O), 1613 (C=C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.99 ppm (br,1H, NHCO), 3.61 (m, 4H, -CH_2-OR), 3.26 ppm (m, 4H, -CH_2-N); 2.85-2.45 (m, 2H, C(3)-H and C(4)-H), 2.17 (dd, $^3J_{HH}$ = 7.5 Hz, $^2J_{HH}$ = 15.3 Hz, 1H, C(3)-H), 1.05 (d, $^3J_{HH}$ = 6.6 Hz, 3H, -CH_3). ^{13}C-NMR (300 MHz, DMSO-d_6): δ = 170.7 ppm (C-2), 154.2 (C-6), 120.5 (CN), 67.7 (C5), 66.1 (-CH_2-OR), 48.6 (-CH_2-N); 39.2 (C-3), 27.0 (C-4), 18.9 (-CH_3).

b) Substitution by butylamine (**8**{*1,2*}): As above for **8**{*1,1*} but using 0.83 g of **12**{*1*} (5 mmol) and butylamine (1.0 mL, 10 mmol) in 10 mL of dry MeOH to give 2-butylamino-4-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**8**{*1,2*}) (0.64 g, 3.1 mmol, 62%); mp 138-139 ºC. IR (KBr): ν(cm^{-1}): 3313 (N-H), 3232 (NHCO), 2174 (CN), 1688 (C=O), 1625 (C=C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.51 ppm (br, 1H, NHCO), 5.89 (t, $^3J_{HH}$ = 5.7 Hz, 1H, -NH-), 3.37 (m, 2H, NH-CH$_2$-), 2.60-2.46 (m, 2H, C(3)-H and C(4)-H), 2.13 (dd, $^3J_{HH}$ = 7.5 Hz, $^2J_{HH}$ = 15.3 Hz, 1H, C(3)-H), 1.45 (m, 2H, -NH-CH$_2$-CH$_2$-), 1.32 (m, 2H, -CH$_2$-CH$_3$), 1.03 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C(4)-CH$_3$), 0.88 (t, $^3J_{HH}$ = 7.2 Hz, 3H, -CH$_2$-CH$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6): δ = 170.1 ppm (C-2), 151.9 (C-6), 121.5 (CN), 58.7 (C-5), 42.1 (NH-CH$_2$-), 38.9 (C-3), 31.5 (-NH-CH$_2$-CH$_2$-), 26.8 (C-4), 19.7 (C(4)-CH$_3$), 19.2 (-CH$_2$-CH$_3$), 13.6 (-CH$_2$-CH$_3$).

c) Substitution by cyclohexylamine (**8**{*1,3*}): As above for **8**{*1,1*} but using 0.83 g of **12**{*1*} (5 mmol) and cyclohexylamine (1.2 mL, 10 mmol) in dry MeOH (10 mL) to give 2-cyclohexylamino-4-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**8**{*1,3*}) (0.76 g, 3.25 mmol, 65%); mp 286-287 ºC. IR (KBr): ν(cm^{-1}): 3335 (N-H), 3225 (NHCO), 2170 (CN), 1695 (C=O), 1619 (C=C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.38 ppm (br, 1H, NHCO), 5.77 (d, $^3J_{HH}$ = 8.7 Hz, 1H, D, -NH-), 3.65 (m, 1H, NH-CH-), 2.60-2.47 (m, 2H, C(3)-H and C(4)-H), 2.13 (dd, $^3J_{HH}$ = 7,5 Hz, $^2J_{HH}$ = 15.6 Hz, 1H, C(3)-H), 1.90-1.86, 1.69-1.65, 1.55 and 1.32-1.11 (m, 10H, -(CH$_2$)$_5$- cyclohexylamine), 1.03 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C(4)-CH$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6): δ = 170.0 ppm (C-2), 150.5 (C-6), 121.5 (CN), 58.7 (C-5), 50.5 (NH-CH-), 38.8 (C-3), 32.9, 25.0, 24.0 (-(CH$_2$)$_5$- cyclohexylamine), 27.0 (C-4), 19.7 (C(4)-CH$_3$).

d) Substitution by methylamine (**8**{*1,4*}):[20] As above for **8**{*1,1*} but using 0.83 g of **12**{*1*} (5 mmol) and 8M methylamine in ethanol (1.3 mL, 10 mmol) to give 4-methyl-2-methylamino-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**8**{*1,4*}) (0.59 g, 0.36 mmol, 71%); mp 199-200 ºC.

Substitution by amines in 2-methoxy-5-methyl-6-oxo-1,4,5,6-tetrahydro-pyridine-3-carbonitrile (**12**{*2*})[18,19]

a) Substitution by morpholine (**8**{*2,1*}): A mixture of 2-methoxy-5-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**12**{*2*}) and morpholine (0.9 mL, 10 mmol) in dry MeOH (10 mL) was stirred at rt for 24 h. The precipitate obtained was filtered, washed with EtOH dried under vacuum and recrystallized from acetone/hexane to afford 5-methyl-2-morpholino-6-oxo-1,4,5,6- tetrahydropyridine-3-carbonitrile (**8**{*2,1*}) (0.75 g, 3.5 mmol, 68%); mp 195-196 ºC. IR (KBr): ν(cm^{-1}): 3244 and 3120 (NHCO), 2185 (CN), 1680 (C=O), 1610 (C=C). ^{1}H- NMR (300 MHz, DMSO-d_6): δ = 9.96 ppm (br, 1H, NHCO), 3.60 (m, 4H, -CH$_2$-OR), 3.25 ppm (m, 4H, -CH$_2$-N), 2.52-2.09 (m, 3H, C(3)-H and C(4)-H)), 1.05 (d, $^3J_{HH}$ = 6.9 Hz, 3H, -CH$_3$). ^{13}C-NMR (300 MHz, DMSO-d_6): δ = 174.1 ppm (C-2), 154.5 (C-6), 121.5 (CN), 66.1 (-CH$_2$-OR), 60.3 (C5), 48.6 (-CH$_2$-N), 35.4 (C-3), 29.5 (C-4), 14.0 (-CH$_3$).

b) Substitution by butylamine (**8**{*2,2*}): As above for **8**{*2,1*} but using 0.83 g of **12**{*2*} (5 mmol) and butylamine (1 mL, 10 mmol) in dry MeOH (10 mL) to afford 2-butylamino-5-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**8**{*2,2*}) (0.59 g, 2.9 mmol, yield 57%). IR (KBr): ν(cm^{-1}): 3345 (N-H), 3223 (NHCO), 2219 (CN), 1692 (C=O), 1642, 1477. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.63 ppp(br, 1H, NHCO), 5.89 (t, $^3J_{HH}$= 5.7 Hz, 1H, N-H), 3.34 (m, 2H, -N-CH_2), 2,60-2.46 (m, 2H, C(3)-H, C(4)-H), 2.13 (dd, $^3J_{HH}$= 7.5 Hz, $^2J_{HH}$= 15.3 Hz, 1H, C(3)-H), 1.45 (m, 2H. –C**H**$_2$-CH_2-Me), 1.32 (m, 2H, -CH_2-CH_3), 1.03 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C(4)-CH_3), 0.88 (t, $^3J_{HH}$ = 7.2 Hz, 3H, -CH_2-CH_3).

c) Substitution by cyclohexylamine (**8**{*2,3*}): As above for **8**{*2,1*} but using 0.83 g of **12**{*2*} (5 mmol) and cyclohexylamine (1.2 mL, 10 mmol) in dry MeOH (10 mL) to give 2-cyclohexylamino-5-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile **(8**{*2,3*}) (0.97 g, 4.15 mmol, 83%); mp 229-230 ºC. IR (KBr): ν(cm^{-1}): 3302 (N-H), 3254 (NHCO), 2177 (CN), 1687 (C=O), 1633 (C=C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.50 ppm (br, 1H, NHCO), 6.06 (d, $^3J_{HH}$ = 8.7 Hz, 1H, -NH-), 3.65 (m, 1H, NH-CH-), 2.48-2.10 (m, 3H, C(3)-H and C(4)-H_2), 1.90-1.13 (m, 10H, -$(CH_2)_5$- cyclohexylamine), 1.05 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C(4)-CH_3). ^{13}C-NMR (300 MHz, DMSO-d_6): δ = 173.2 ppm (C-2), 150.9 (C-6), 122.3 (CN), 51.0 (C-5), 50.5 (NH-CH-), 34.5 (C-3), 33.0, 32.8, 25.0, 24.1 and 24.0 (-$(CH_2)_5$- cyclohexylamine), 29.5 (C-4), 14.4 (C(4)-CH_3).

d) Substitution by methylamine (**8**{*2,4*}): As above for **8**{*2,1*} but using 0.83 g of **12**{*2*} (5 mmol) and 8 M methylamine in EtOH (1.3 mL, 10 mmol) to give 5-methyl-2-methylamino-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile **(8**{*2,4*}) (0.52 g, 0.32 mmol, 63%). mp 255-256 ºC. IR (KBr): ν(cm^{-1}): 3346 (N-H), 3222 (NHCO), 2218 (CN), 1692 (C=O), 1619 (C=C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.82 (br, 1H, -NH-), 3.83 (s, 3H, NH-CH_3), 2.90-2.10 (m, 3H, C(3)-H and C(4)-H_2), 1.12 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C(4)-CH_3).

Cyclizations of 2-cyanamide-6-oxopiperidine-3-carbonitriles 4{*1*} *and* 4{*2*} *with amines Cyclizations with morpholine* **7**{*1*}: 50 mg (0.30 mmol) of the corresponding 2-cyanamide-6-oxopiperidine-3-carbonitriles **4**{*1*} and **4**{*2*} were treated at rt and at reflux for 70 h with: (a) 25 mL of net morpholine (**7**{*1*}) (1:1000 molar ratio), (b) 12.5 mL of morpholine (**7**{*1*}) in 12.5 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:500 molar ratio), and (c) 0.25 mL of morpholine (**7**{*1*}) in 10 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:10 molar ratio). The solvent was removed *in vacuo* and the residue obtained was analyzed by HPLC using an amino column and a mobile phase consisting of MeCN with 1% of ammonia. The peak assignment was carried out by comparison with the retention time of the corresponding standards **5**{*1,1*}, **6**{*1,1*} and **8**{*1,1*}, in the case of **4**{*1*}, and **5**{*2,1*}, **6**{*2,1*} and **8**{*2,1*}, The relative proportions between the cyclization products were established by using the absorbances at λ=254 nm of the standards obtained by nucleophilic substitution by the corresponding

amine onto the bromo substituted pyrido[2,3-*d*]pyrimidines **10**{*1*} and **11**{*1*}, in one side, and **10**{*2*} and **11**{*2*}, on the other side (see Table 1). The results are summarized in Table 2.

Cyclizations with butylamine **7**{*2*}: As above for cyclizations with morpholine but using 50 mg (0.30 mmol) of the corresponding 2-cyanamide-6-oxopiperidine-3-carbonitriles **4**{*1*} and **4**{*2*} treated at rt and at reflux for 70 h with: (a) 29 mL of net butylamine **7**{*2*} (1:1000 molar ratio), (b) 14.5 mL of butylamine **7**{*2*} in 14.5 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:500 molar ratio), and (c) 0.29 mL of butylamine **7**{*2*} in 10 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:10 molar ratio). The results are summarized in Table 2.

Cyclizations with cyclohexylamine **7**{*3*}: As above for cyclizations with morpholine but using 50 mg (0.30 mmol) of the corresponding 2-cyanamide-6-oxopiperidine-3-carbonitriles **4**{*1*} and **4**{*2*} treated at rt and at reflux for 70 h with: (a) 33 mL of net cyclohexylamine **7**{*3*} (1:1000 molar ratio), (b) 16.5 mL of cyclohexylamine **7**{*3*} in 16.5 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:500 molar ratio), and (c) 0.33 mL of cyclohexylamine **7**{*2*} in 10 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:10 molar ratio). The results are summarized in Table 2.

Cyclizations with methylamine **7**{*4*}: As above for cyclizations with morpholine but using 50 mg (0.30 mmol) of the corresponding 2-cyanamide-6-oxopiperidine-3-carbonitriles **4**{*1*} and **4**{*2*} treated at rt and at reflux for 70 h with: (a) 25 mL of 8 M methylamine **7**{*4*} in EtOH and (b) 25 mL of cyclohexylamine **7**{*2*} in 10 mL of solvent (MeOH, $CHCl_3$, and 1,4-dioxane respectively) (1:10 molar ratio). The results are summarized in Table 2.

Table 1. Absorbances (λ=254 nm) for compounds **5**{*x,y*} and **6**{*x,y*} prepared by nucleophilic substitution with the corresponding amine **7**{*y*} onto pyrido[2,3-*d*]pyrimidines **10**{*x*} and **11**{*x*}, respectively

Entry	mg/10 mL MeCN	Absorbance (λ=254 nm)
5{*1,1*}	0.474	1.342
5{*1,2*}	0.480	0.736
5{*1,3*}	0.470	1.182
5{*1,4*}	0.506	0.937
5{*2,1*}	0.475	1.489
5{*2,2*}	0.530	0.863
5{*2,3*}	0.511	0.772
5{*2,4*}	0.505	0.344
6{*1,1*}	0.455	1.182
6{*1,2*}	0.531	1.016
6{*1,3*}	0.522	0.656
6{*1,4*}	0.518	1.019
6{*2,1*}	0.490	0.842
6{*2,2*}	0.482	0.315
6{*2,3*}	0.494	0.790
6{*2,4*}	0.489	0.416

Table 2. Cyclizations of 2-cyanamide-6-oxopiperidine-3-carbonitriles **4**{*1*} and **4**{*2*} with amines **7**{y}

				4{*1*}				**4**{*2*}		
Amine **7**{*y*}	Solvent	**4**{x}:amine	Temperature	**5**{*1,y*}:**6**{*1,y*}	**5** + **6***	**4**{*1*}*	**8**{*1,y*}	**5**{*2,y*}:**6**{*2,y*}	**5** + **6***	**8**{*2,y*}
Morpholine **7**{*1*}	Amine	1:1000	R.t.	100:0	19	5	3	83:17	49	40
			Reflux	100:0	53	2	2	51:49	88	8
	$CHCl_3$	1:500	R.t.	100:0	39	3	0	96:4	57	40
			Reflux	100:0	68	0	2	42:58	60	23
		1:10	R.t.	100:0	70	4	0	97:3	89	6
			Reflux	100:0	97	0	0	98:2	90	3
	Dioxane	1:500	R.t.	100:0	20	6	8	96:4	76	14
			Reflux	100:0	67	2	4	70:30	52	21
		1:10	R.t.	100:0	90	3	2	97:3	84	15
			Reflux	100:0	92	0	5	75:25	75	8
	MeOH	1:500	R.t.	100:0	63	13	5	74:26	75	17
			Reflux	100:0	67	2	4	95:5	70	23
		1:10	R.t.	100:0	68	7	2	99:1	82	9
			Reflux	100:0	82	4	2	96:4	75	20
Butylamine **7**{*2*}	Amine	1:1000	R.t.	100:0	10	X	13	100:0	5	26
			Reflux	61:39	25	2	33	0:100	1	25
	$CHCl_3$	1:500	R.t.	0:0	0	X	35	100:0	10	10
			Reflux	100:0	0	X	37	13:87	2	11
		1:10	R.t.	100:0	1	X	29	0:0	0	36
			Reflux	0:0	0	X	29	54:46	15	37
	Dioxane	1:500	R.t.	0:0	0	X	28	0:0	0	23
			Reflux	77:23	7	X	31	33:67	15	27
		1:10	R.t.	0:0	0	X	30	0:0	0	13
			Reflux	100:0	22	X	38	50:50	8	50
	MeOH	1:500	R.t.	52:48	7	10	28	100:0	9	15
			Reflux	0:100	2	X	37	26:74	15	17
		1:10	R.t.	0:0	0	3	14	0:0	0	20
			Reflux	32:68	23	X	35	0:0	0	20
Cyclohexylamine **7**{*3*}	Amine	1:1000	R.t.	82:18	32	0	11	32:68	24	1
			Reflux	90:10	67	0	X	33:67	73	13
	$CHCl_3$	1:500	R.t.	100:0	14	X	7	0:100	22	7
			Reflux	76:24	33	X	11	56:44	19	9
		1:10	R.t.	67:33	24	0	12	33:67	23	29
			Reflux	65:35	38	0	20	74:26	9	41
	Dioxane	1:500	R.t.	85:15	15	13	16	63:37	9	16
			Reflux	68:32	25	X	9	76:24	21	X
		1:10	R.t.	82:18	24	10	10	45:55	23	14
			Reflux	67:3	33	1	2	58:42	47	23
	MeOH	1:500	R.t.	99:1	30	0	X	42:58	13	11
			Reflux	34:66	52	8	X	100:0	20	27
		1:10	R.t.	69:31	44	X	9	44:56	37	6
			Reflux	49:51	19	X	2	81:19	49	21
Methylamine **7**{*4*}	THF	1:176	R.t.	0:100	1	42	18	0:0	0	26
			Reflux	100:0	11	30	8	100:0	8	43
	EtOH	1:705	R.t.	0:0	0	39	10	64:36	12	47
			Reflux	15:85	3	26	8	100:0	12	33

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