A Versatile Synthesis of 2-Amino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-ones from 2-Aminopyridines

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The quasi-one pot synthesis of new 2-aminopyrido[1,2-*a*][1,3,5]triazin-4-ones starting from 2-aminopyridine and 2-aminopicolines is herein described in order to obtain a library of cyclic guanidines.

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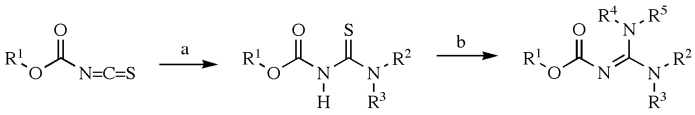
Introduction.

Due to the importance of guanidine groups in molecular biology of receptors capable of binding molecular anions [1-2], and also because of their occurrence in natural products or drugs, several new methods of synthesis have been recently developped to produce various highly substituted guanidino compounds by means of new mild condition protocols [3-8].

In particular, using carbamate protection to reduce the basicity of the guanidines and to simplify their isolation and their purification permitted numerous syntheses and the introduction of guanidine moiety in fragile structures [9-13]. Among all these methods the most common utilize the reactivity of the corresponding thioureas towards amines either in the presence of EDCI [14] or $HgCl_2$ [15-20].

The best illustrations of this emergence are given, for example, by a recent work of Linton *et al* who described a one-pot synthesis of 1,3-substituted guanidines from carbamoyl isothiocyanates [21] according to Scheme 1 or by the search of new agents of guanidylation of aroylthioureas such as bismuth nitrate instead of mercuric chloride recently proposed by Cunha *et al* [22].

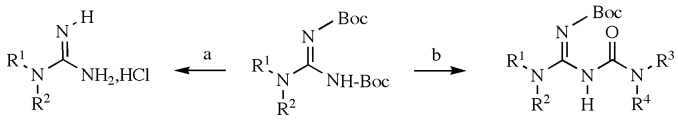
Scheme 1



a,) R^2R^3NH, CH_2Cl_2/THF; b,) R^4R^5NH, EDCI,CH_2Cl_2.

On our part, with the aim of building guanidine libraries of medicinal chemistry interest, we studied the total deprotection of bis Boc-guanidines using $SnCl_4$ [23], and also their conversion to *N*-Boc-amidinoureas by reaction with amines [24] (Scheme 2).

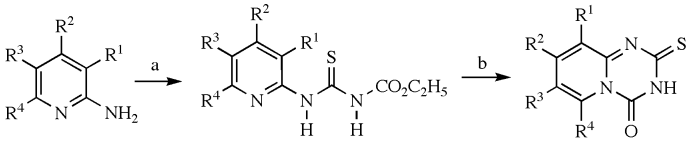
Scheme 2



a,) $SnCl_4$, AcOEt/MeOH; b,) R^3R^4NH,THF

Furthermore, considering that no works have yet taken advantage of these new methods to produce cyclic polysubstituted guanidines by direct ring closure of suitable substrats, we studied the synthesis of compounds of the title, starting from 2-aminopyridines. The methods of synthesis of the pyrido[1,2-*a*][1,3,5]triazine derivatives are abundant and generally involved a 2-aminopyridine with various isocyanates [25-28] or isothiocyanates [29-30] or a reaction between the former and ethoxymethylydene urethane [31], chloroalkylcarbamoyl chloride [32] or dichloromethylene benzamide [33] for example. One of the most efficient synthesis was described by Stanovnik [34] *et al* who prepared 2-thioxo-2,3-dihydro-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one in two steps by condensing 2-aminopyridines with ethoxycarbonyl isothiocyanate to give the corresponding thioureas, which were finally cyclized in the presence of sodium ethoxide according to the Scheme 3.

Scheme 3

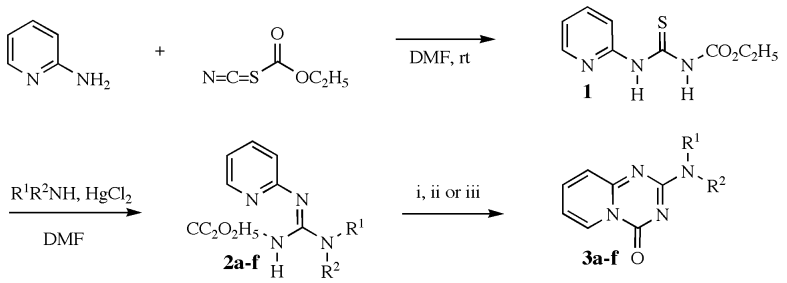


a,) $SCN\text{-}CO_2C_2H_5$, $CHCl_3$; b,) EtONa, EtOH

In light of all these works we firstly verified that the reaction of 2-aminopyridine with ethoxycarbonyl isothiocyanate in dimethylformamide at room temperature after 2 hours gave the *N*-ethoxycarbonyl-*N'*-(2-pyridyl)thiourea intermediate which was next able to produce by reaction with amines in the presence of mercuric chloride the $N^{(1)}$-ethoxycarbonyl-$N'^{(2)}$-(2-pyridyl)-$N''^{(3)}$ substituted (or not) corresponding guanidines at room temperature. After isolation of these stable guanidines, we searched for good conditions of ring closure. With numerous attempts in various conditions we found that this intramolecular ring closure occured when heating either in neutral, alkaline or acidic media. So, in boiling *ortho*-dichlorobenzene **3b** was obtained from **2b** in 15% yield with a lot of tars. In refluxing methanolic sodium hydroxide solution the results were not better. Surprisingly when the guanidine intermediate was heated in a saturated hydrochloric dioxane solution for 4 hours the results were very acceptable. Thus, the ring

closure of **2b** into **3b** occurred with 51% yield after displacement of the hydrochloride salt with sodium or potassium hydrogenocarbonate (Scheme 4).

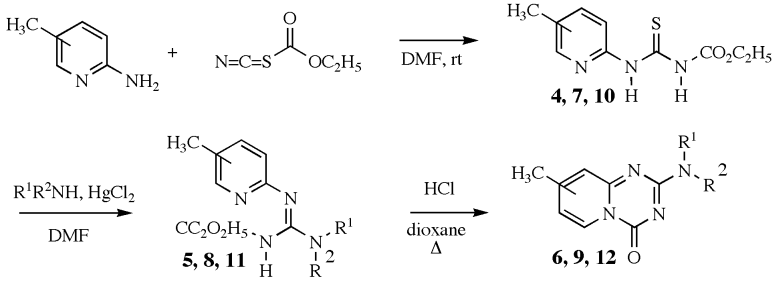
Scheme 4



i,) ODB Δ; ii,) NaOH, MeOH Δ; iii,) HCl, dioxane Δ/$NaHCO_3$
a,) R^1=R^2=H; b,) R^1=R^2=CH_3; c,) R^1=R^2=C_2H_5;
d,) R^1=R^2=C_3H_7; e,) R^1=H R^2=iC_3H_7; f,) R^1=H, R^2=cyclohexyl;

Finally the simplicity of the sequence prompted us to prepare the 2-amino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one derivatives **3a-f** in a quasi-one pot procedure from 2-aminopyridine as described in the experimental section. Since the isolation of the two intermediates is not necessary, this sequence has become applicable in parallel chemistry. Enlargement of this methodology to 2-amino-3, -4 or 6-picoline gave, in a similar manner, the corresponding methylpyridotriazinones **6, 9, 12** (Scheme 5).

Scheme 5



a,) R^1=R^2=H; c,) R^1=R^2=C_2H_5; d,) R^1=R^2=C_3H_7; f,) R^1=H, R^2=cyclohexyl;

In conclusion, the methodology we propose herein is able to produce numerous *N*,*N*-substituted aminopyridotriazinones with great potential in the medicinal chemistry of guanidino compounds.

EXPERIMENTAL

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at an ionizing potential of 70 eV. Elemental analysis for new compounds were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen). Organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography was carried out using silica gel 60 (0.063-0.2 mm) (Merck). Filtration was carried out using celite 545 (Prolabo).

General Procedure for the Preparation of 2-(Alkyl)amino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one.

Ethoxycarbonyl isothiocyanate (0.02 mole) and 2-aminopyridine or 2-aminopicoline (0.02 mole) were mixed in dimethylformamide (100 mL) at room temperature for 2 hours to form the *N*-ethoxycarbonyl-N'-(pyridin-2-yl)thiourea intermediate. The solution was then cooled to 0 °C before saturation with the amine (0.05 mole if the amine is not a gas) and addition of mercuric chloride (0.02 mole). After 15 minutes, the ice bath was removed and the solution was allowed to warm to room temperature, the black color that appeared was due to the formation of mercuric sulfide. After stirring for 4 hours ethyl acetate (150 mL) was added and the reaction mixture was filtered through celite. The *N*-ethoxycarbonylguanidine residue that remained after removal of solvent under reduced pressure was then poured in dioxane (500 mL) saturated with hydrochloric acid before, the solution was then heated under reflux for 4 hours. The crude product was

obtained as a precipitate salt that was collected by filtration and treated with potassium hydrogenocarbonate to give the bases.

2-Amino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**3a**).

Recrystallization of the crude product from acetonitrile gave **3a** as a white powder (1.55 g, 48%), mp > 260 °C; IR (KBr): ν 3287, 3119, 1713, 1630 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.60 (d, *J* = 6.84 Hz, 1H), 7.86 (dd, J = 8.92 Hz, *J* = 6.68 Hz, 1H), 7.24 (s, 2H), 7.12 (d, *J* = 8.92 Hz, 1H), 7.00 (dd, *J* = 6.84 Hz, *J* = 6.68 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 164.1, 155.3, 149.6, 140.5, 128.8, 121.7, 113.1.

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.56; H, 3.55; N, 34.62.

2-Dimethylamino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**3b**).

Recrystallization of the crude product from ether gave **3b** as a yellow powder (1.94 g, 51%), mp 135 °C; IR (KBr): ν 3085, 1715, 1637 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.53 (d, *J* = 6.80 Hz, 1H), 7.80 (dd, *J* = 8.88 Hz, *J* = 6.84 Hz, 1H), 7.10 (d, *J* = 8.88 Hz, 1H), 6.94 (m, 1H), 3.09 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 161.6, 154.8, 149.9, 141.5, 129.3, 122.8, 113.9, 36.5, 36.3.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.78; H, 5.34; N, 29.61.

2-Diethylamino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**3c**).

Recrystallization of the crude product from acetonitrile gave **3c** as a white powder (1.66 g, 38%), mp 176 °C; IR (KBr): ν 2974, 1683, 1633 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.59 (d, *J* = 6.84 Hz, 1H), 7.85 (dd, *J* = 8.92 Hz, *J* = 6.84 Hz, 1H), 7.17 (d, *J* = 8.92 Hz, 1H), 6.99 (m, 1H), 3.60 (q, *J* = 6.96 Hz, 2H), 3.53 (q, *J* = 6.84 Hz, 2H), 1.12 (t, *J* = 6.96 Hz, 3H), 1.11 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 160.6, 155.0, 149.9, 141.3, 129.3, 122.8, 113.7, 41.2, 41.0, 13.4, 12.9.

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.68; H, 6.32; N, 25.56.

2-Dipropylamino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**3d**).

Recrystallization of the crude product from petroleum ether gave **3d** as a yellow powder (1.92 g, 39%), mp 90 °C; IR (KBr): ν 2962, 1710, 1631 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.58 (d, *J* = 6.96 Hz, 1H), 7.83 (dd, *J* = 8.88 Hz, *J* = 6.76 Hz, 1H), 7.14 (d, *J* = 8.88 Hz, 1H), 6.98 (m, 1H), 3.50 (m, 2H), 3.44 (m, 2H), 1,56 (m, 4H), 0.84 (t, *J* = 7.00 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 161.2, 154.8, 149.8, 141.3, 129.2, 122.8, 113.7, 48.5, 48.3, 20.9, 20.4, 11.2, 10.9.

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.16; H, 7.41; N, 22.65.

2-Isopropylamino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**3e**).

Recrystallization of the crude product from ether gave **3e** as a white powder (0.60, 15%), mp 139 °C; IR (KBr): ν 3212, 1720, 1595 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.55 (d, *J* = 6.72 Hz, 1H), 7.80 (dd, *J* = 8.80 Hz, *J* = 6.76 Hz, 1H), 7.66 (d, *J* = 7.20 Hz, 1H), 7.20 (d, *J* = 8.80 Hz, 1H), 6.93 (m, 1H), 4.12 (m, 1H), 1.13 (d, *J* = 5.72 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 160.8, 155.0, 149.8, 141.4, 129.2, 122.7, 113.8, 44.3, 22.5.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.92; H, 5.86; N, 27.34.

2-Cyclohexylamino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**3f**).

Recrystallization of the crude product from acetonitrile gave **3f** as a grey powder (1.05 g, 21%), mp 180 °C; IR (KBr): ν 3211, 2925, 1717 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.55 (d, *J* = 6.84 Hz, 1H), 7.80 (dd, *J* = 8.28 Hz, *J* = 6.84 Hz, 1H), 7.03 (d, *J* = 8.28 Hz, 1H), 6.93 (m, 1H), 3.73 (m, 1H), 3.35 (br, 1H), 1.80 (m, 2H), 1.68 (m, 2H), 1.56 (m, 1H), 1.24 (m, 4H), 1.08 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 161.8, 155.6, 150.3, 141.6, 129.5, 122.8, 113.8, 49,0, 32,4, 24,7.

Anal. Calcd. for $C_{13}H_{16}N_4O$: C, 63.90; H, 6.60; N, 22.94. Found: C, 64.03; H, 6.42; N, 22.66.

2-Amino-9-methyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**6a**).

Recrystallization of the crude product from acetonitrile gave **6a** as a pink powder (1.38 g, 39%), mp >260 °C; IR (KBr): ν 3377, 1694, 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.50 (d, *J* = 6.76 Hz, 1H), 7.74 (d, *J* = 6.60 Hz, 1H), 7.27 (s, 2H), 6.91 (m, 1H), 2.27 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 164.2, 155.4, 150.0, 139.0, 130.7, 126.9, 112.5, 16.4.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.37; H, 4.42; N, 31.67.

2-Dipropylamino-8-methyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**9d**).

Recrystallization of the crude product from petroleum ether gave **9d** as a white powder (2.24 g, 43%), mp 72 °C; IR (KBr): ν 2961, 1713, 1648 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.48 (d, *J* = 7,08 Hz, 1H), 7,00 (s, 1H), 6.85 (d, *J* = 7.08 Hz, 1H), 3.50 (t, *J* = 7.08 Hz, 2H), 3.44 (t, *J* = 7.08 Hz, 2H), 2.34 (s, 3H), 1.56 (m, 4H), 0.85 (t, *J* = 7.08 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 161.4, 154.5, 153.3, 149.9, 128.5, 120.7, 116.0, 48.5, 48.3, 20.9, 20.5, 11.2.

Anal. Calcd. for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.36; H, 7.95; N, 21.64.

2-Diethylamino-6-methyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**12c**).

Purification of the residue obtained from the organic extract by column chromatography (SiO_2, ether) gave **12c** as a yellow powder (1.68 g, 36%), mp 52 °C; IR (KBr): ν 2974, 1714, 1634 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.31 (m, 1H), 6.84 (d, *J* = 8.60 Hz, 1H), 6.38 (d, *J* = 6.16 Hz, 1H), 3.57 (q, *J* = 6.32 Hz, 4H), 2.82 (s, 3H), 1.12 (t, *J* = 6.32 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 160.5, 157.8, 153.2, 145.0, 138.7, 121.9, 115.9, 41.5, 41.3, 24.3, 13.6, 13.3.

Anal. Calcd. for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 61.78; H, 6.87; N, 24.25.

2-Dipropylamino-6-methyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**12d**).

Recrystallization of the crude product from ether gave **12d** as a white powder (2.90 g, 56%), mp 120 °C; IR (KBr): ν 2961, 1699, 1614 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.29 (m, 1H), 6.44 (d, *J* = 7.24 Hz, 1H), 6.40 (d, *J* = 8.12 Hz, 1H), 3.27 (t, *J* = 7.40 Hz, 4H), 2.27 (s, 3H), 1.52 (st, *J* = 7.40 Hz, 4H), 0.83 (t, *J* = 7.40 Hz, 6H); ^{13}C NMR (DMSO-d_6): δ 162.8, 155.2, 153.2, 136.9, 116.7, 112.2, 48.3, 24.1, 21.1, 11.2.

Anal. Calcd. for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.66; H, 7.55; N, 21.38.

2-Cyclohexylamino-6-methyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-one (**12f**).

Recrystallization of the crude product from ether gave **12f** as a green powder (0.68 g, 14%), mp 116 °C; IR (KBr): ν 2941, 1683, 1643 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.31 (dd, *J* = 7.88 Hz, *J* = 6.68 Hz, 1H), 6.49 (d, *J* = 6.68 Hz, 1H), 6.47 (d, *J* = 7.88 Hz, 1H),

4.19 (br, 1H), 3.67 (m, 1H), 2.30 (s, 3H), 1.87 (m, 2H), 1.67 (m, 2H), 1.54 (m, 1H), 1.36 (m, 2H), 1.26 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 161.8, 154.7, 153.1, 136.4, 115.1, 112.2, 106.3, 48.0, 32.4, 24.8, 23.5.

Anal. Calcd. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.92; H, 7.16; N, 21.44.

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