SYNTHESIS OF 2-AMINO-4-(4-PYRIDINYL)-1,3,5-TRIAZINE AND ITS NOVEL REACTION WITH ISOCYANATES

Baldev Singh

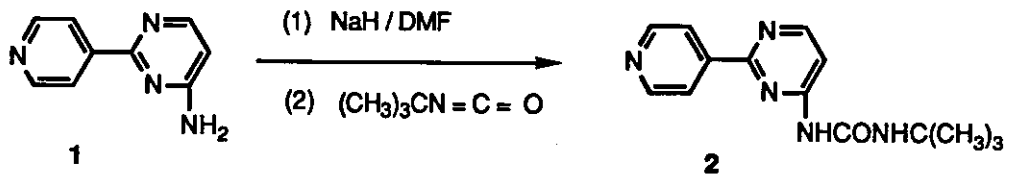
Department of Medicinal Chemistry, Sterling Winthrop Pharmaceuticals Research Division, Rensselaer, NY 12144, U.S.A.

Abstract - The reaction of the sodium salt of 2-amino-4-(4-pyridinyl)-1,3,5-triazine (4) with t-butyl, isopropyl, phenyl, and p-chlorophenyl isocyanates formed the corresponding N-(alkyl or aryl)-2-amino-4-(4-pyridinyl)-1,3,5-triazines (6) whereas the reaction with methyl isocyanate and propyl isocyanate formed the expected N-alkyl-N'-[4-(4-pyridinyl)-1,3,5-triazin-2-yl]ureas (7).

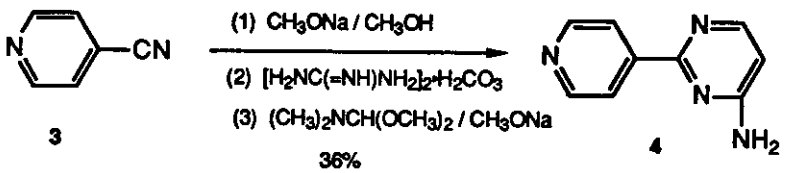
Several years ago, we reported[1] the synthesis and antiallergic activity of N-alkyl-N'-[2-(4-pyridinyl)-4-pyrimidinyl]ureas. The most active compound, N-t-butyl-N'-[2-(4-pyridinyl)-4-pyrimidinyl]urea (2) was prepared by reacting the sodium salt of 4-amino-2-(4-pyridinyl)pyrimidine (1) with t-butyl isocyanate. However, the attempted preparation of its triazine analog (5a) from 4 under similar conditions resulted only in the formation of 2-amino-N-(t-butyl)-4-(4-pyridinyl)-1,3,5-triazine (**6a**) in 69% yield. This finding prompted further investigation of this reaction using other isocyanates. Isopropyl, phenyl, and p-chlorophenyl isocyanates gave similar results (71-84%). However, the reaction with methyl isocyanate and propyl isocyanate gave only the expected ureas (7) in 65% and 68% yield, respectively. The ^{1}H nmr spectra of **6a** and **6b** displayed two sets of signals indicating mixtures of two tautomeric forms (imine and amine).

To my knowledge N-(alkyl or aryl)-2-amino-4-aryl-1,3,5-triazines are not known in literature. The reaction described herein constitutes the first synthesis of this class of compounds.

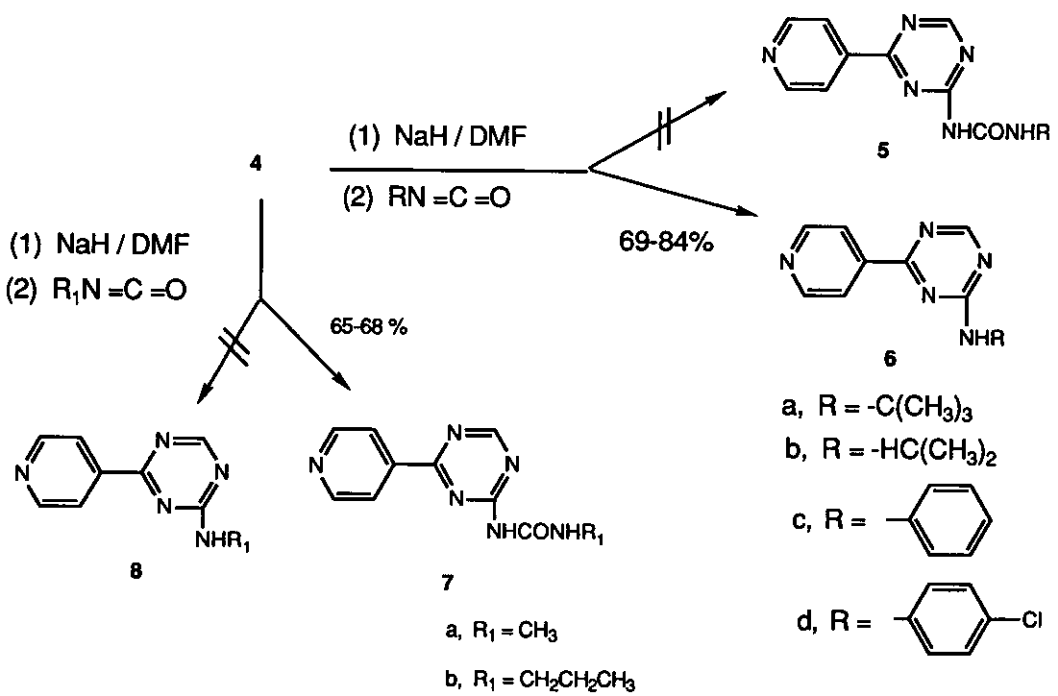
The starting amine (4) was prepared in a three-step, one-pot synthesis in 36% yield. The base-catalysed addition of methanol to 4-cyanopyridine gave the corresponding amidate[2] which in turn was reacted with guanidine carbonate. The resulting guanidino intermediate underwent ring closure upon treatment with N,N-dimethylformamide dimethyl acetal to produce 4.



1 2



3 4

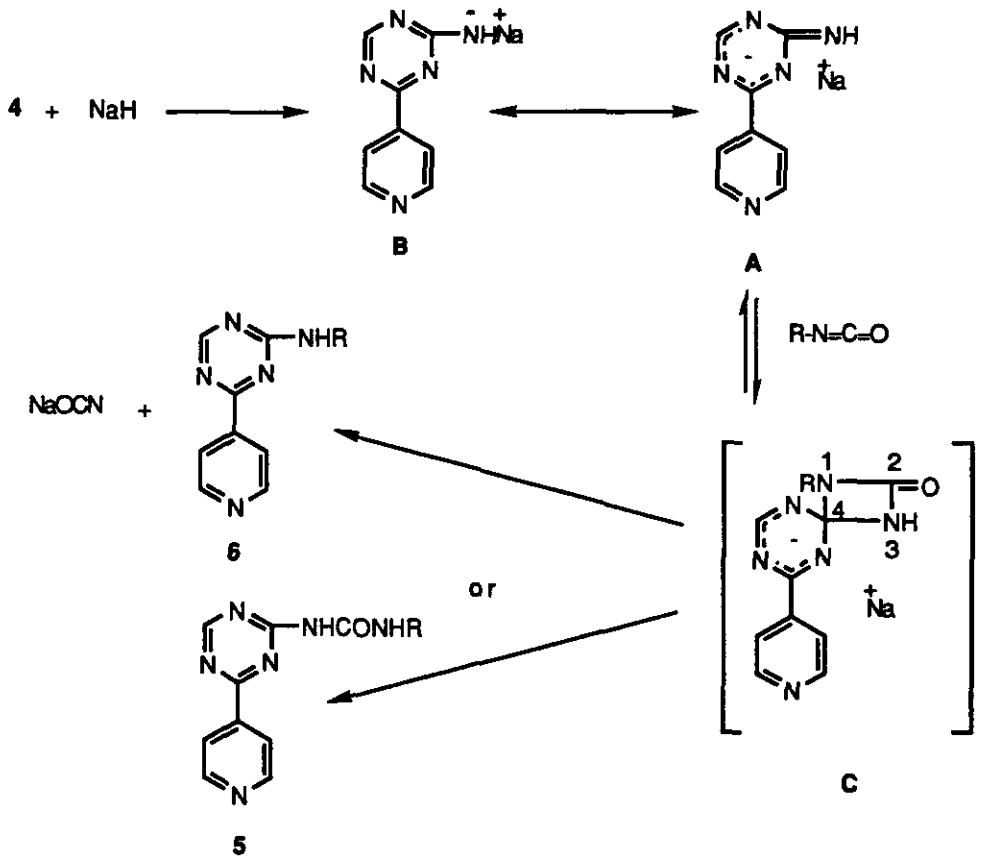


5 6 8 7

a, $R_1 = CH_3$

b, $R_1 = CH_2CH_2CH_3$

According to the proposed mechanism, the resonance form A (imine) of the anion generated by the reaction of NaH with 4 is overwhelmingly dominant over form B (amine). It is further assumed that only A participates in the next step due to the following reason. The reaction of B with isocyanates should result in the formation of ureas. However, no urea formation was detected even when NaH was reacted with 4 in the presence of isocyanates. On the other hand, the imine anion (A) could form [2+2] adducts with isocyanates giving spiro-1,3-diazetidinones (C). These intermediates can undergo further transformation in the rate determining step to yield either amines (6) or ureas (5) depending upon the nature of the R group (bulky versus non-bulky). The cleavage of the 3,4-bond accompanied by the expulsion of sodium cyanate would result in the formation of 6 whereas the cleavage of 1,4-bond would give 5. The confirmation of this mechanism needs further studies.



EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The nmr spectra were obtained with a General Electric QE-300 spectrometer using tetramethylsilane as the internal standard, and chemical shifts are reported in parts per million and are given in δ units. The yields have not been optimized.

2-Amino-4-(4-pyridinyl)-1,3,5-triazine (4). A solution of 4-cyanopyridine (41.6 g, 0.4 mol) and sodium methoxide (4 g, 18.5 mmol) in methanol (400 ml) was stirred at ambient temperature for 4 h. To the resulting solution was added guanidine carbonate (36 g, 0.2 mol) and the mixture was stirred at room temperature overnight. This was followed by the addition of N,N-dimethylformamide dimethyl acetal (47.8 g, 0.4 mol) and sodium methoxide (22 g, 0.4 mol). The resulting mixture was heated under reflux for 10 h and then concentrated to dryness under reduced pressure. The white solid residue was washed with water (200 ml) and collected. Recrystallization of the fluffy white solid from DMF gave 24.8 g (36%) of **2**; mp 264-266°C; ms: MH^+ m/z 174; ^1H nmr (DMSO-d_6): δ 8.80, 8.17 (A_2B_2, J=5.9 Hz, 4H, C_5H_4N), 8.68 (s, 1H, H-6), 7.82 (br s, 2H, NH_2). Anal. Calcd for $C_8H_7N_5$: C, 55.48; H, 4.07; N, 40.44. Found: C, 55.26; H, 4.19; N, 40.25.

2-Amino-N-(1,1-dimethylethyl)-4-(4-pyridinyl)-1,3,5-triazine (**6a**). A mixture of 4 (12 g, 69.3 mmol), 60% NaH/oil dispersion (2.8 g, 70 mmol), and DMF (100 ml) was stirred at ambient temperature until all the NaH had reacted (20 min). To the resulting light yellow solution was added t-butyl isocyanate (7 g, 70 mmol) dropwise over a period of 10 min. The resulting mixture was stirred at room temperature for 5 h and then DMF was removed under reduced pressure. The residue was slurried in water (100 ml), the white solid was collected, and washed successively with water and hexane. Recrystallization from ethanol gave 10.9 g (69%) of **6a**; mp 200-201°C; ms: MH^+ m/z 230; ^1H nmr (DMSO-d_6): δ 8.78-8.00 (m, 6H, C_5H_4N, H-6, NH), 1.44 [s, ≈5.2H, $-NC(CH_3)_3$], 1.39 [s, ≈3.7H, $-HNC(CH_3)_3$]; imine:amine/7:5. Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.68; H, 6.48; N, 30.93.

2-Amino-N-(1-methylethyl)-4-(4-pyridinyl)-1,3,5-triazine (**6b**). A mixture of **4** (4.35 g, 25.1 mmol), 60% NaH/oil dispersion (1.2 g, 30 mmol), and DMF (75 ml) was stirred at ambient temperature until the reaction of NaH was complete and then isopropyl isocyanate (3 ml, 30.9 mmol) dissolved in DMF (10 ml) was added over a 20 min period. The resulting mixture was further stirred for 5 h at room temperature and then concentrated under reduced pressure. The residue was treated with water (50 ml), the gummy solid was collected, and washed with hexane. Recrystallization from isopropanol-hexane gave 3.8 g (71%) of white needles of **6b**; mp 130-134°C; ms: MH^+ m/z 216; ^1H nmr (DMSO-d_6): δ 8.75-8.09 (m, 6H, C_5H_4N, H-6, NH), 4.23 [m, ≈0.5H, -NC<u>H</u>$(CH_3)_2$], 4.12 [m, ≈0.5H, -HNC<u>H</u>$(CH_3)_2$], 1.17 (d, J=7.0 Hz, ≈3H, -NCH(C<u>H</u>$_3)_2$], 1.15 [d, J=7.5 Hz, ≈3H, -HNCH(C<u>H</u>$_3)_2$]; imine:amine/≈1. Anal. Calcd for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.29; H, 6.00; N, 32.72.

2-Amino-N-phenyl-4-(4-pyridinyl)-1,3,5-triazine (**6c**). A mixture of 4 (8.65 g, 50 mmol), phenyl isocyanate (6 g, 50.4 mmol), 60% NaH/oil dispersion (2.4 g, 60 mmol), and DMF (100 ml) was stirred at ambient temperature for 5 h and then concentrated under reduced pressure. The white solid residue was treated with water (100 ml), the product was collected, and washed with hexane. Recrystallization from DMF gave 9.8 g (79%) of **6c**; mp 201-203°C; ms: MH^+ m/z 250; ^1H nmr (DMSO-d_6): δ 10.47 (br s, 1H, NH), 9.04 (s, 1H, H-6), 8.83, 8.23 (A_2B_2, J=5.9 Hz, 4H, -C_5H_4N), 7.79-7.15 (m, 5H, C_6H_5). Anal. Calcd for $C_{14}H_{11}N_5$: C, 67.46; H, 4.45; N, 28.09. Found: C, 67.35; H, 4.29; N, 28.09.

2-Amino-N-(4-chlorophenyl)-4-(4-pyridinyl)-1,3,5-triazine (**6d**). A mixture of **4** (8.65 g, 50 mmol), 60% NaH/oil dispersion (2.4 g, 60 mmol), and DMF (100 ml) was stirred at ambient temperature until the reaction of NaH was complete and then 4-chlorophenyl isocyanate (7.8 g, 50 mmol) dissolved in DMF (25 ml) was added over a 20 min period. The resulting mixture was stirred for 5 h and then concentrated under reduced pressure. The yellow solid residue was slurried in water (100 ml). The product was collected, washed with hexane, and recrystallized from DMF to yield 11.84 g (84%) of **6d** as a pale yellow granular solid; mp 288-290°C; ms: MH^+ m/z 284; ^1H nmr (DMSO-d_6): δ 10.56 (br s, 1H, NH), 8.93 (s, 1H, H-6), 8.83, 8.21 (A_2B_2, J=6.0 Hz, 4H, C_5H_4N), 7.82, 7.43 [A_2B_2, J=8.5 Hz, 4H, -C_6H_4-).

Anal. Calcd for $C_{14}H_{10}N_5Cl$: C, 59.27; H, 3.55; N, 24.68. Found: C, 58.95; H, 3.48; N, 24.29.

N-Methyl-N'-[4-(4-pyridinyl)-1,3,5-triazin-2-yl]urea (7a). A mixture of 4 (5.53 g, 32 mmol), 60% NaH/oil dispersion (1.4 g, 35 mmol), and DMF (50 ml) was stirred at ambient temperature until the reaction with NaH was complete (15 min). To the resulting solution was added methyl isocyanate (2.5 ml, 43 mmol) over a 10 min period. After the reaction mixture had been stirred for 2.5 h at room temperature, it was concentrated under reduced pressure. The residual solid was slurried in water (50 ml), collected and washed successively with water and hexane. Recrystallization from DMF yielded 4.8 g (65%) of 7a as white flakes; mp 238-240°C dec.; ms: MH^+ m/z 231; ^1H nmr (CF_3COOD): δ 9.43 (s, 1H, H-6), 9.23, 9.21 (A_2B_2, J=6.1 Hz, 4H, C_5H_4N), 3.19 (s, 3H, CH_3). Anal. Calcd for $C_{10}H_{10}N_4O$: C, 52.17; H, 4.38; N, 36.50. Found: C, 52.24; H, 4.33; N, 36.44.

N-Propyl-N'-[4-(4-pyridinyl)-1,3,5-triazin-2-yl]urea (7b). A mixture containing 4 (8.65 g, 50 mmol), 60% NaH/oil dispersion (2.4 g, 60 mmol), and DMF (100 ml) was stirred at ambient temperature until the reaction of NaH was complete. To the resulting solution was added propyl isocyanate (5.1 ml, 60 mmol) dropwise over a 15 min period. After the reaction mixture had been stirred for 5 h, it was concentrated under reduced pressure. The residue was treated with water (100 ml). The light yellow solid was collected, washed successively with water and hexane, and recrystallized from DMF to yield 8.7 g (68%) of 7b as a white solid; mp 236-238°C; ms: MH^+ m/z 259; ^1H nmr (CF_3COOD): δ 9.45 (s, 1H, H-6), 9.20 (s, 4H, C_5H_4N), 3.53 (t, J=7.6 Hz, 2H, $-CH_2CH_2CH_3$), 1.79 (m, 2H, $CH_2CH_2CH_3$), 1.13 (t, J=7.3 Hz, 3H, $CH_2CH_2CH_3$). Anal. Calcd for $C_{12}H_{14}N_6O$: C, 55.80; H, 5.46; N, 32.54. Found: C, 55.85; H, 5.29; N, 32.76.

ACKNOWLEDGEMENT

I am grateful to the Department of Molecular Characterization for the ^1H nmr spectra and Dr. T. J. Nitz for helpful discussions regarding the mechanism of this reaction.

REFERENCES

1 G. Y. Lesher, B. Singh, and Z. E. Mielens, J. Med. Chem., 1982, *25*, 837.

2 F. C. Schaefer and G. A. Peters, J. Org. Chem., 1961, *26*, 412.

Received, 2nd December, 1991