# A Regioselective Approach to 5-substituted-3-amino-1,2,4-triazines

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## *Supporting Information*

**General Methods** All reactions were conducted under $N_2$ atmosphere in oven-dried glassware (100 °C, 6-12 h) using standard air-free manipulation techniques. The following solvents were purchased from Fisher Scientific Company/Acros Organic and used without further purification: Karl Fischer-grade MeOH, anhydrous THF (<500 ppm $H_2O$), HPLC-grade hexanes, HPLC grade MTBE and HPLC grade DME. Commercial reagents were purchased either from Aldrich, Acros Organics, Alfa Aesar, TCI or Pfaltz and Bauer and used without further purification.

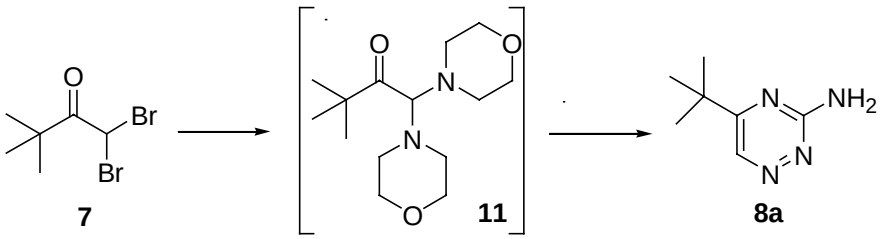
Concentration *in vacuo* refers to removal of the solvent using a Büchi rotary evaporator at reduced pressure (10-20 torr). High Performance Liquid Chromatography (HPLC) analysis was performed using Agilent Technology 1100 series instrument with YMC-Pack Pro 18C (250 x 4.6 mm I.D) column under the following assay conditions: 80% MeCN: 20% 0.1%v $H_3PO_4/H_2O$ mobile phase, 1 mL/min flow rate, 210 nm wavelength, 35 °C column temperature. Proton nuclear magnetic resonance (**$^1$H NMR**) spectra were measured on Bruker Avance-400 instrument (400 MHz). Carbon nuclear magnetic resonance (**$^{13}$C NMR**) spectra were measured on Bruker Avance-400 instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). Infrared (**IR**) spectra were reported in wavenumbers and measured on a Nicolet Magna 560 instrument. Melting points were uncorrected. High Resolution Mass Spectroscopy (**HRMS**) measurements were performed at Merck Research Laboratory, Rahway, NJ, by Mr. Ziqiang Guan.

*General Procedure of Morpholination*:

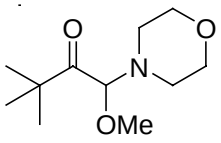
To a solution of the dibromide[1] (1 equiv) in anhydrous THF (5 mL/g) under $N_2$ was added neat morpholine (4.2 equiv) all at once at RT. The resulting solution was slowly heated to 45-67°C over 1h and aged at this temperature for 22-96h, at which a 97% conversion was typically obtained as determined by $^1$H NMR spectroscopy. After cooling to RT, the suspension was filtered through a fritted funnel and the wet cake was washed with THF (3-4 mL/g). The combined filtrate was then concentrated to give the crude aminal intermediate, which was used without further purification.

*General Aminotriazine Formation*:

To a solution of crude aminal in MeOH (5 mL/g) under $N_2$ was added all at once solid aminoguanidine bicarbonate (AGB, 1 equiv with respect to dibromide), followed by slow addition of neat AcOH (3 equiv) over 10-15 min at RT. The resulting suspension was stirred at RT for 2h, at which time $CO_2$ evolution ceased, and then slowly heated to reflux and aged for 14-24h. In general, $^1$H NMR spectra of the crude reaction mixture revealed a 95-99% regioselectivity during the aminotriazine formation. After cooling to RT, the resulting suspension was concentrated to about half its volume, cooled to 0 °C, aged for 1 h, filtered through a fritted funnel and washed with *cold* MeOH:$H_2O$ (4:1). The collected solid was dried *in vacuo* under a stream of $N_2$ affording solely the 5-substituted-3-aminotriazine, whose structure was assigned by 2D NMR-HMBC spectroscopy. In all cases, the corresponding 6-substituted regioisomer of each aminotriazine that were formed during the reaction (1-5%) remained in the mother liquor during the isolation.

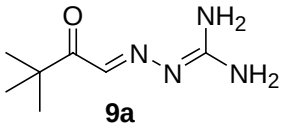


A solution of **7** (30 g, 0.12 mol, 1.0 equiv) and morpholine (42 mL, 0.48 mol, 4.1 equiv) in THF (150 mL) was treated according to the general morpholination procedure (50 °C, 96h). A small sample of the crude product was recrystallized from hexanes:MTBE to give aminal **11** as a pale yellow solid. **mp**: 66-68 °C. **$^{1}$H NMR** (400 MHz, $d_6$-DMSO): δ. 4.00 (s, 1H), 3.49-3.47 (m, 8H), 2.62 (m, 4H), 2.49 (m, 4H), 1.10 (s, 9H). **$^{13}$C NMR** (100MHz, $d_6$-DMSO): δ 207.8, 81.2, 66.5, 49.6, 43.1, 26.2. **IR** (KBr pellet): 2965, 2902, 2856, 2820, 1701, 1479, 1367, 1265, 1158, 1115, 981, 875 cm$^{-1}$. The resulting crude aminal was dissolved in MeOH (150 mL) and treated with AGB (15.8 g, 0.12 mol, 1.0 equiv) and AcOH (20 mL, 0.35 mol, 3.0 equiv) according to the general aminotriazine formation procedure (67 °C, 16h). The aminotriazine **8a** was isolated as a pale yellow solid (11.8 g, 66%).



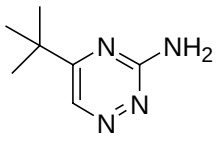

**13**

Partial characterization: **$^{1}$H NMR** (400 MHz, $d_6$-DMSO): δ 4.73 (1H, s), 3.54-3.47 (4H, m), 3.14 (3H, s), 2.67-2.59 (4H, m), 1.14 (9H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 208.8, 92.1, 66.5, 55.2, 46.1, 42.6, 26.3.




**9a**

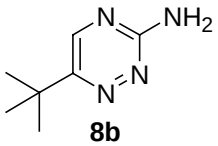
Partial characterization: **$^{1}$H NMR** (400 MHz, $d_6$-DMSO): δ 7.50 (1H, s), 7.40 (br), 1.20 (9H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 202.8, 162.5, 139.0, 42.6, 27.2.




**8a**

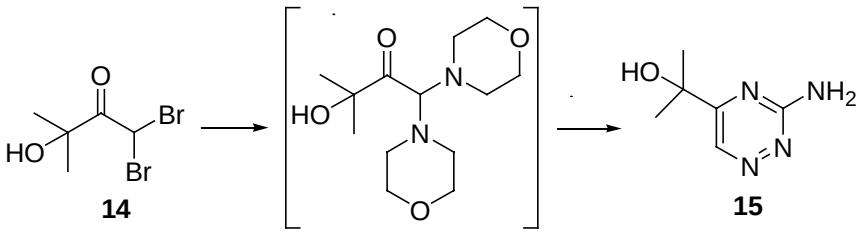
**mp**: 190-191 °C. $^{1}$H **NMR** (400 MHz, $d_6$-DMSO): δ 8.70 (1H, s), 7.00 (2H, br s), 1.24 (9H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 168.9, 162.5, 137.8, 35.9, 28.4. **IR** (KBr

pellet): 3329 (br), 3149 (br), 2962, 1654, 1549, 1474, 1106, 1072, 952, 640 $cm^{-1}$. **HRMS** (ESI) Calc'd for [$C_7H_{12}N_4$+H]: 153.1134. Found: 153.1132.



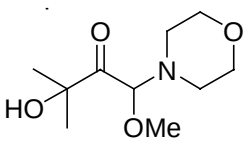
**8b**

Partial characterization: **$^1$H NMR** (600 MHz, $d_6$-DMSO): δ 8.35 (1H, s), 6.88 (2H, br s), 1.30 (9H, s). **$^{13}$C NMR** (150 MHz, $d_6$-DMSO): δ 162.0, 157.8, 147.6, 34.7, 29.5.

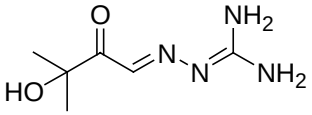


**14** **15**

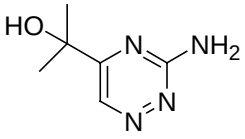
A solution of **14** (113.6 g, 0.437 mol, 1.0 equiv) and morpholine (156 mL, 1.79 mol, 4.1 equiv) in THF (575 mL) was treated according to the general morpholination procedure (67 °C, 22h). A small sample was recrystallized from hexanes:MTBE to give the aminal as a pale yellow solid. **mp**: 78-81 °C. **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ. 5.28 (br s, 1H), 4.30 (s, 1H), 3.55-3.45 (m, 8H), 2.59 (m, 4H), 2.47 (m, 4H), 1.20 (s, 6H). **$^{13}$C NMR** (100MHz, $d_6$-DMSO): δ 210.2, 80.4, 75.6, 66.5, 49.4, 26.6. **IR** (KBr pellet): 3374 (br), 2969, 2853, 2820, 1705, 1456, 1267, 1116, 1102, 1011, 880 $cm^{-1}$. The remaining crude aminal was dissolved in MeOH (575 mL) and treated with AGB (59.4 g, 0.437 mol, 1.0 equiv) and AcOH (75 mL, 1.31 mol, 3.0 equiv) at 67 °C for 14h. At the end of reaction, the dark brown solution was cooled to RT, concentrated to about half its volume, diluted with equal volume of $H_2O$ and extracted with heptane (2 mL/g wrt dibromide **14**). The aqueous layer was concentrated to half its volume, at which the desired aminotriazine crystallized from the solution. After aging at 0 °C for 12h, the suspension was filtered and the wet cake obtained was washed with cold $H_2O$ (200 mL), yielding solely the 5-substituted aminotriazine **15** as a pale yellow solid (32.6 g, 65%).



**$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 5.20 (1H, br s), 4.97 (1H, s), 3.57-3.49 (4H, m), 3.17 (3H, s), 2.64-2.56 (4H, m), 1.28 (3H, s), 1.21 (3H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 208.6, 91.3, 75.4, 66.4, 55.6, 47.8, 27.2.

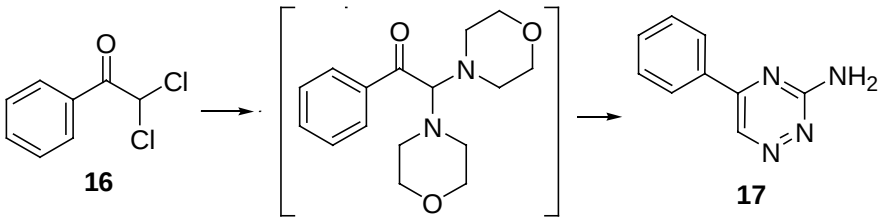


**$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 7.85 (br), 7.77 (1H, s), 1.31 (6H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 201.3, 161.8, 137.9, 75.5, 27.3.



**15**

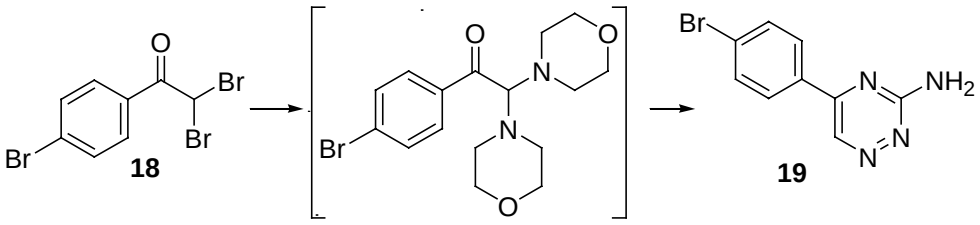
**mp**: 129-131 °C (dec.). **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 8.81 (1H, s), 7.06 (2H, br s), 5.43 (1H, s), 1.38 (6H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 168.2, 162.3, 137.1, 71.1, 29.3. **IR** (KBr pellet): 3324 (br), 3144 (br), 3005, 2975, 1654, 1554, 1487, 1471, 1371, 1154, 1105, 1066, 960, 936, 845, 648 cm$^{-1}$. **HRMS** (ESI) Calc'd for [$C_6H_{10}N_4O$+H]: 155.0927. Found: 155.0927.



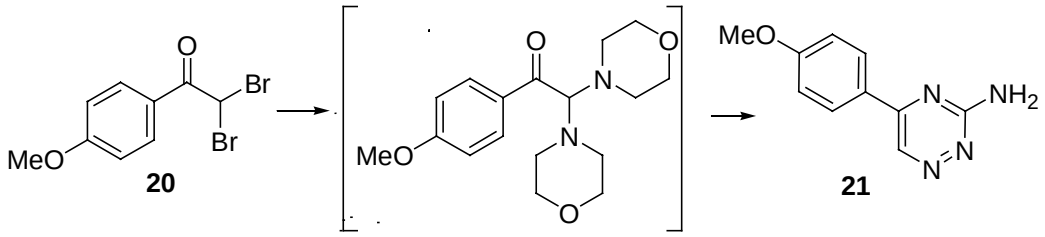
**16** **17**

A solution of **16** (24g, 0.127 mol, 1.0 equiv) and morpholine (45.4 mL, .0521 mol, 4.1 equiv) in THF (150 mL) was subjected to the general morpholination procedure (67 °C, 48h). The crude aminal was dissolved in MeOH (150 mL) and treated with AGB (17g, 0.127 mol, 1.0 equiv) and AcOH (21.8 mL, 0.381 mol, 3.0 equiv) according to the aminotriazine formation procedure. The aminotriazine **17** was isolated as an orange solid as a single regioisomer (14.21 g, 65%). **mp**: 232-235 °C dec (lit.[2] 233-235 °C). **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 9.22 (1H, s), 8.17 (2H, dd, $J$= 7.9, 1.52 Hz), 7.57-7.54 (3H, m), 7.25 (2H, br s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 163.1, 154.9, 137.1, 134.0,

131.8, 129.0, 127.2. **IR** (KBr pellet): 3311 (br), 3143 (br), 1644, 1530, 1473, 1313, 1288, 1110, 1052, 769, 686, 512, 495 $cm^{-1}$. **HRMS** (ESI) Calc'd for [$C_9H_8N_4$+H]: 173.0822. Found: 173.0818.

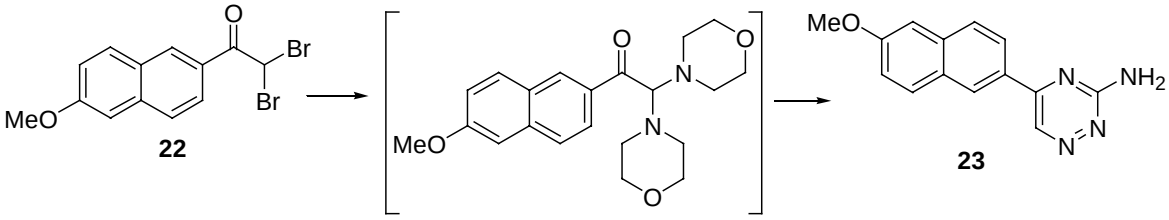



A solution of **18** (14.55 g, 40.77 mmol, 1.0 equiv) and morpholine (14.6 mL, 167. 2 mol, 4.1 equiv) in THF (75 mL) was treated according to the general morpholination procedure (50 °C, 22h). The crude aminal was dissolved in MeOH (75 mL) and subjected to AGB (5g, 36.7 mol, 0.9 equiv) and AcOH (7 mL, 122.3 mol, 3.0 equiv) according to the general aminotriazine formation procedure (67 °C, 14h). The product was isolated as a green solid as a single regioisomer (6g, 60%). **mp**: 257-260 °C dec (lit.[2] 249-253 °C dec). **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 9.22 (1H, s), 8.10 (2H, d, *J*= 8.7 Hz), 7.75 (2H, d, *J*= 8.7 Hz), 7.25 (2H, br s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 163.0, 153.8, 136.8, 133.2, 132.1, 129.2, 125.6. **IR** (KBr pellet): 3293 (br), 3106 (br), 1653, 1531, 1074, 1010, 831 $cm^{-1}$. **HRMS** (ESI) Calc'd for [$C_9H_7N_4Br$+H]: 250.9927. Found: 250.9937.



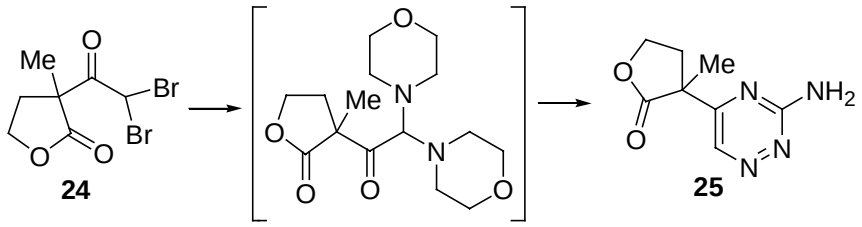

A solution of **20** (10.0 g, 32.5 mmol, 1.0 equiv) and morpholine (11.3 mL, 129.9 mmol, 4.1 equiv) in THF (50 mL) was treated according to the general morpholination procedure (45 °C, 24h) to give the crude aminal as yellow solid: **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 7.95 (2H, d, *J*= 8.8 Hz), 6.91 (2H, d, *J*= 8.8 Hz), 4.26 (1H, s), 3.39-3.37 (8H, m), 2.42-2.26 (8H, m). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 194.1, 163.6, 131.4, 131.0, 114.2, 84.2, 66.4, 55.6, 49.2. The aminal was dissolved in MeOH (50 mL) and treated

with AGB (4.42 g, 32.47 mmol, 1.0 equiv) and AcOH (5.6 mL, 97.4 mmol, 3.0 equiv) according to the general procedure (67 °C, 24h). The product was isolated as a light tan solid as a single regioisomer (4.9 g, 75%). **mp**: 252-254 °C dec (lit.[2] 214-216 °C). **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 9.17 (1H, s), 8.15 (2H, d, *J*= 8.8 Hz), 7.10 (2H, br s), 7.08 (2H, d, *J*= 8.8 Hz), 3.84 (3H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 162.9, 162.3, 154.4, 136.7, 129.0, 126.0, 114.5, 55.4. **IR** (KBr pellet): 3313 (br), 3124 (br), 2932, 2840, 1644, 1607, 1512, 1455, 1320, 1257, 1175, 1110, 1025, 827, 645 584, 514 cm$^{-1}$. **HRMS** (ESI) Calc'd for [$C_{10}H_{10}N_4O$+H]: 203.0928. Found: 203.0930.



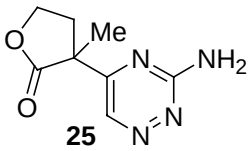

A solution of **22** (10.0 g, 27.9 mmol, 1.0 equiv) and morpholine (9.80 mL, 112 mmol, 4.0 equiv) in THF (50 mL) was treated according to the general morpholination procedure (45 °C, 23h) to give the crude aminal as a yellow solid: **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 8.75 (1H, s), 8.06 (1H, d, *J*= 9.0 Hz), 7.99 (1H, dd, *J*= 8.7, 1.6 Hz), 7.89 (1H, d, *J*= 8.7 Hz), 7.40 (1H, d, *J*= 2.5 Hz), 7.26 (1H, dd, *J*= 9.0, 2.5 Hz), 4.63 (1H, s), 3.91 (3H, s), 3.55-3.52 (8H, m), 2.63-2.60 (4H, m), 2.49-2.45 (4H, m). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 195.0, 159.6, 137.0, 133.6, 131.4, 130.3, 127.4, 127.3, 124.3, 119.5, 106.0, 83.7, 66.4, 55.4, 49.2. The crude solid was dissolved in MeOH (50 mL) and subjected to AGB (3.8 g, 27.9 mmol, 1.0 equiv) and AcOH (4.80 mL, 83.8 mmol, 3.0 equiv) according to the general aminotriazine formation procedure (67 °C, 24h). The product was isolated as a tan solid as a single regioisomer (5.4 g, 76%). **mp**: 287-292 °C (dec). **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 9.33 (1H, s), 8.74 (1H, s), 8.21 (1H, dd, *J*= 8.7, 1.8 Hz), 7.97 (1H, d, *J*= 8.9 Hz), 7.96 (1H, d, *J*= 8.7 Hz), 7.40 (1H, d, *J*= 2.5 Hz), 7.25 (1H, dd, *J*= 8.9, 2.5 Hz), 7.21 (2H, br s), 3.91 (3H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 163.0, 158.9, 154.9, 137.2, 136.2, 130.6, 128.9, 128.0, 127.8, 127.5, 124.1, 119.5, 106.1, 55.4. **IR** (KBr pellet): 3302 (br), 3143 (br), 2935, 1625, 1529, 1472, 1263, 1208,

1098, 1026, 895, 854, 473 $cm^{-1}$. **HRMS** (ESI) Calc'd for [$C_{14}H_{12}N_4O$+H]: 253.1084. Found: 253.1079.



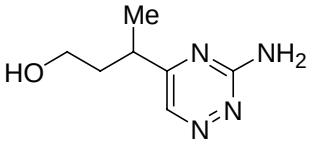

A solution of **24** (5.0g, 16.7 mmol, 1.0 equiv) and morpholine (6.0 mL, 68.3 mmol, 4.1 equiv) in THF (25 mL) was treated according to the general morpholination procedure (RT, 3h). After filtration and concentration, the resulting crude solid was washed with hexanes:MTBE (9:1) and the resulting slurry was aged at RT for 1.5h. The suspension was filtered to give the aminal intermediate as a white solid (4.5g, 87%). **mp**: 114-116 °C. **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ 4.30 (1H, dt, *J*= 8.7, 1.9 Hz), 3.98 (1H, ddd, *J*= 10.3, 9.0, 6.2 Hz), 3.92 (1H,s ), 3.59-3.53 (4H, m), 3.45-3.41 (4H, m), 2.83-2.73 (3H, m), 2.59-2.57 (2H, m), 2.45-2.44 (2H, m), 2.37-2.34 (2H, m), 2.14 (1H, ddd, *J*= 10.4, 4.4, 1.9 Hz), 1.34 (3H, s). **$^{13}$C NMR** (100 MHz, $d_6$-DMSO): δ 195.1, 176.1, 82.2, 66.6, 65.8, 65.1, 53.9, 50.2, 48.5, 32.2, 20.1. **IR** (KBr pellet): 2964, 2855, 2833, 1769, 1712, 1164, 1118, 1109, 1014, 987, 871 $cm^{-1}$.

The aminal (3.5 g, 11.2 mol, 1.0 equiv) was dissolved in MeOH (20 mL) and cooled to 0 °C. Acetic acid (1.3 mL, 22.4 mol, 2.0 equiv) was then added, followed by solid AG-HCl (1.24 g, 11.2 mol, 1.0 equiv). The resulting suspension was stirred at 0 °C for 24h, warmed to RT, and aged for additional 24h. At this point, a 4.6:1.7:1 mixture of aminotriazine **25**, keto imine of **25** and decarboxylated keto imine **25b** was obtained, respectively. The yellow suspension was concentrated to about half its volume, aged at 0 °C for 2h, and filtered. The wet cake was washed with cold MeOH:$H_2O$ (4:1) and dried *in vacuo* under a stream of $N_2$. The aminotriazine **25** was obtained as a white solid as a single regioisomer (1.15g, 53%). The yellow filtrate was heated to 67 °C and aged for 24h to give predominantly the decarboxylated aminotriazine **25a**.



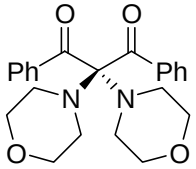

**25**

**mp**: 203-205 °C (dec.). **$^1$H NMR** (400 MHz, $d_6$-DMSO): δ. 8.78 (1H, s), 7.31 (2H, br s), 4.40 (1H, m), 4.30 (1H, m), 2.74 (1H, ddd, *J*= 12.9, 7.5, 5.5Hz), 2.33 (1H, dt, *J*= 12.9, 7.5 Hz), 1.56 (3H, s). **$^{13}$CNMR** (100 MHz, $d_6$-DMSO): δ 178.2, 162.7, 162.0, 138.0, 66.0, 48.4, 35.7, 21.0. **IR** (KBr pellets): 3324 (br), 3147 (br), 2988, 2912, 1785, 1646, 1548, 1485, 1453, 1190, 1070, 1014, 971, 922, 644, 506 cm$^{-1}$. **HRMS** (ESI) Calc'd for [$C_8H_{10}N_4O_2$+H]: 194.0877. Found: 195.0873.




**25a**

**$^1$H NMR** (600 MHz, $d_6$-DMSO): δ 8.50 (1H, s), 7.01 (2H, br s), 3.34 (2H, m), 2.80 (1H, m), 1.82 (1H, m), 1.63 (1H, m), 1.67 (3H, d, *J*= 6.8 Hz). **$^{13}$C NMR** (150 MHz, $d_6$-DMSO): δ 166.6, 163.0, 140.0, 58.46, 38.0, 35.1, 19.0.




The ketoaminal above was isolated as a yellow solid in 90% yield using the general morpholination protocol (19h, RT). Partial characterization: **$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.24 (4H, d, *J*= 7.5 Hz), 7.49 (2H, t, *J*= 7.4 Hz), 7.37 (4H, dd, *J*= 7.5, 7.4 Hz), 3.73 (8H, br m), 2.94 (8H, br m). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 193.2, 137.4, 133.0, 130.1, 128.2, 94.2, 67.4, 50.0 (br). **IR** (KBr pellet): 3079, 3066, 2961, 2946, 2848, 1680, 1593, 1447, 1274, 1142, 1111, 967, 930, 690, 663 cm$^{-1}$.

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[1] For general bromination procedure, see: (a) $PhNMe_3Br_3$: Jacques, J.; Marquet, A. *Org. Synth.* **1988**, 175. (b) $Br_2$: Nan'ya, S.; Ishida, H.; Moiji, E. J.; Butsugan, Y.; Bajji, A. C. *J. Heterocycl. Chem.* **1994**, *31*, 401.
[2] Nakajima, M.; Hisada, R.; Anselme, J-P. *J. Org. Chem.* **1978**, *43*, 2693.