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

John Limanto,* Richard A. Desmond, Donald R. Gauthier, Jr., Paul N. Devine, Robert A. Reamer, and R. P. Volante

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

john_limanto@merck.com

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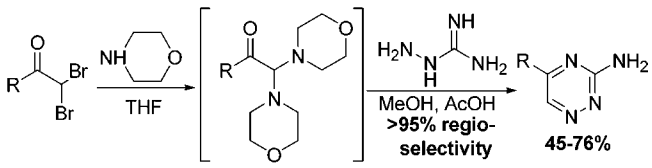
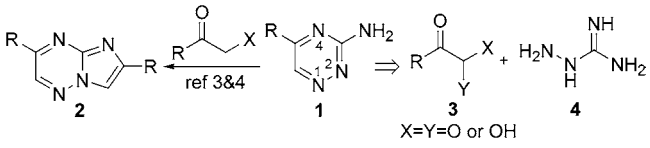
ABSTRACT



Nucleophilic displacement of readily available α,α-dibromoketones with excess morpholine gave the corresponding ketoaminals, which upon condensation with aminoguanidine in MeOH in the presence of AcOH afforded 5-substituted-3-amino-1,2,4-triazines in >95% regioselectivity and 45–76% isolated yield.

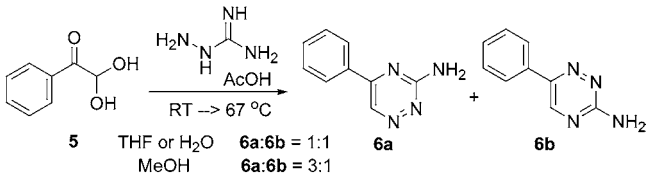
1,2,4-Triazines are a family of heterocycles whose physical, biological, and chemical properties have been previously investigated.[1] While only a few of these heterocycles are found in nature, they have been prepared and tested as potentially active building blocks in agrochemical and medicinal fields.[1b] For example, 3-amino-1,2,4-triazines **1** have been regioselectively condensed with α-halo carbonyl compounds to afford imidazo[2.1-*c*][1,2,4]triazine heterocycles **2**[2] (Scheme 1), which were utilized to probe the mechanisms of antianginal Ca-channel blockers[3] and congestive heart failure.[4] Despite the broad interest in this class of heterocycles, a *short* and *regioselective* route to 5-substituted-3-amino-1,2,4-triazines (**1**, R ≠ H) has been lacking.[5]

Scheme 1



Our initial approach to this class of amino-triazines involved a regioselective condensation between aminoguanidine **4** and the corresponding keto aldehyde **3**.[6] However, subjection of commercially available phenyl glyoxal hydrate **5** to aminoguanidine acetate[7] in either THF or H_2O gave a 1:1 regioisomeric mixture[8] of the corresponding amino-triazines **6** in 50% HPLC assay yield (Scheme 2).[9] When the reaction was carried out in MeOH, a slightly improved ratio of 3:1(**6a**:**6b**) was observed. The low regioselectivity

Scheme 2



(1) (a) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 3, Chapter 2.19, pp 385−456. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 6, Chapter 6.11, pp 507−573.

(2) (a) Montgomery, J. A.; Secrist, J. A., III In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Potts, K. T., Eds.; Pergamon Press: Oxford, UK, 1984; pp 629−631, 652−659. (b) Hajós, G. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1996; pp 445−464.

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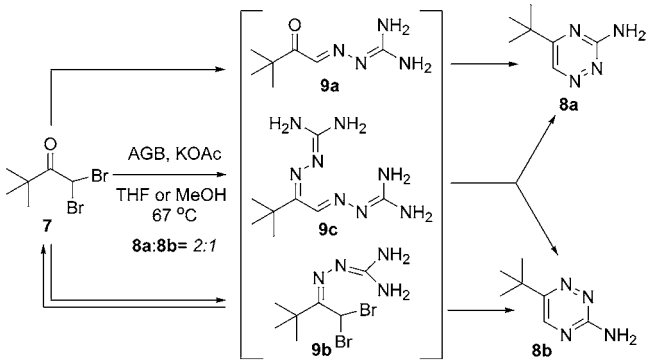
observed in these experiments appears to be consistent with previous reports with pyruvaldehyde.[10]

As various α,α-dibromoketones can be conveniently prepared by bromination of the corresponding methyl ketones,[11] we investigated the reactivity of these compounds as masked keto aldehyde equivalents. In this regard, treatment of dibromopinacolone **7** with aminoguanidine bicarbonate (AGB) in the presence of KOAc in MeOH at 67 °C gave a 2:1 (**8a**:**8b**) mixture of aminotriazines[12] in 35% assay yield (Scheme 3). Addition of a catalytic amount of *n*BuN_4I did

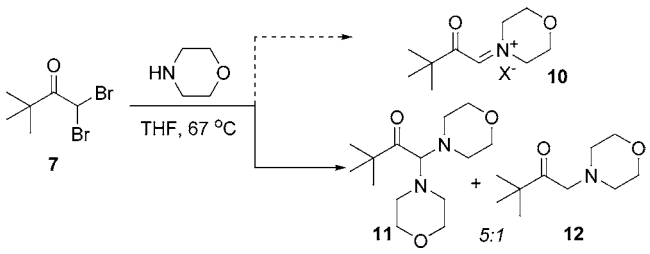
Scheme 3



not appear to change the reaction outcome. A possible explanation for the observed reaction outcome is an initial indiscriminate attack by the hydrazine nitrogen to give a mixture of two hydrazone intermediates (Scheme 3, **9a**,**b**),[13] which after the requisite C═N bond isomerization and cyclization yields the regioisomeric mixture of aminotriazines. On the other hand, a slow cyclization in the final step could lead to the formation of bis-hydrazone species **9c**,[14] which subsequently undergoes a nonselective cyclization.

We reasoned that to drive the formation of hydrazone **9a**, which would lead to the desired aminotriazine, the difference in reactivity between the two electrophilic sites should be more pronounced. In this regard, the possibility of converting the dibromide group to the more reactive iminium species **10** was investigated. However, treatment of **7** with morpholine (4.1 equiv) in THF at 67 °C for 48 h only afforded a 5:1 mixture of keto aminal **11** and mono-morpholinated ketone **12** (Scheme 4).[15] Formation of the reduced product

Scheme 4



12[16] could be minimized (≤10 mol %) if the reaction was carried out at lower temperature (45−50 °C) and longer time (96 h). Similar results were obtained with *N*,*N*-dimethylamine (2 M solution in THF) or *N*-methylpiperazine.

Despite no detected formation of the iminium species **10**, the keto aminal **11** was isolated and subsequently subjected to condensation with AGB in refluxing MeOH or THF. Under these reaction conditions, a 2:1 mixture of aminotriazines (**8a**:**8b**) was obtained after 24 h in 54% assay yield (Table 1). An improved ratio of 7:1 (**8a**:**8b**) was observed when aminoguanidine hydrochloride (AG-HCl) was used instead. On the basis of these latter results, we further investigated the regioselectivity of the reaction under slightly more acidic conditions, where in situ formation of the more

(3) Sanfilippo, P. J.; Urbanski, M.; Press: J. B.; Dubinsky, B.; Moore, J. B., Jr. *J. Med. Chem.* **1988**, *31*, 2221 and references therein.

(4) Spitzer, W. A.; Victor, F.; Don Pollock, G.; Hayes, J. S. *J. Med. Chem.* **1988**, *31*, 1590 and references therein.

(5) The parent 3-amino-1,2,4-triazine and 3-amino-5,6-dimethyl-1,2,4-triazine were prepared by condensation between aminoguanidine and glyoxal and 2,3-butadione, respectively, see: Erickson, J. G. *J. Am. Chem. Soc.* **1952**, *74*, 4706. Other preparations of aminotriazines include but are not limited to the folowing: (a) Ring amination of the corresponding halotriazines with KNH_2 in liquid ammonia (29−54% yield), see: (1) Rykowski, A.; van der Plas, H. C. *J. Org. Chem.* **1980**, *45*, 881. (2) Rykowski, A.; van der Plas, H. C. *J. Heterocycl. Chem.* **1982**, *19*, 653. (b) MnO_2 oxidation of the corresponding 4-substituted-1,2-diaminoimidazoles (6−26% yield), see: Nakajima, M.; Hisada, R.; Anselme, J.-P. *J. Org. Chem.* **1978**, *43*, 2693. For additional methods, see refs 2.

(6) Phenyl glyoxal and pyruvaldehyde are both commercially available as hydrates. Other keto aldehydes can be accessed by oxidation of the corresponding methyl ketones, see for example: (a) Bruce, M. J.; McLean, G. A.; Royles, B. J. L.; Smith, D. M.; Standring, P. N. *J. Chem. Soc., Perkin Trans. I* **1995**, *14*, 1789. (b) Desmond, R.; Mills, S.; Volante, R. P.; Shinkai, I.; Desmond, R. A.; Mills, S.; Volante, R. P.; Shinkai, I. *Synth. Commun.* **1989**, *19*, 379. (c) Floyd, M. B.; Du, M. T.; Fabio, P. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem.* **1985**, *50*, 5022. (d) Uchida, K.; Masuda, G.; Aoi, Y.; Nakayama, K.; Irie, M. *Chem. Lett.* **1999**, *10*, 1071. (e) Pfueller, O. C.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8821. (f) Gleiter, R.; Krennrich, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 449.

(7) Aminoguanidine is commercially available as a hydrochloride or bicarbonate salt. The relatively inexpensive bicarbonate was extensively used in our studies and it was converted to the more soluble acetate salt by treatment with 1 equiv of AcOH.

(8) In all cases, the regioisomeric ratio during the aminotriazine formation was calculated by using ^{1}H NMR integration values of the sp^2 C−H of the triazine ring (see Supporting Information).

(9) The assay was run with an Agilent 1100 HPLC instrument and YMC-Pack Pro 18C column (250 × 4.6 mm i.d.) under the following conditions: 80% MeCN:20% 0.1% v H_3PO_4/H_2O mobile phase, 1 mL/min flow rate, UV detector (210 nm wavelength), and 35 °C column temperature.

(10) (a) Merck & Co., Inc.: British Patent 755,036, 1956; *Chem. Abstr.* **1957**, *51*, 8151. (b) Saikawa, I.; Maeda, T. *Yakugaku Zasshi* **1967**, *87*, 1501. (c) Suzuki, T.; Okazaki, M.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1986**, *23*, 935.

(11) (a) Bromine: Nan'ya, S.; Ishida, H.; Moiji, E. J.; Butsugan, Y.; Bajji, A. C. *J. Heterocycl. Chem.* **1994**, *31*, 401. (b) Boeykens, M.; De Kimpe, N. *Tetrahedron* **1994**, *50*, 12349. (c) $PhMe_3NBr_3$: Jacques, J.; Marquet, A. *Org. Synth.* **1988**, 175.

(12) For a previous preparation of **8a**, see: Rykowski, A.; van der Plas, H. C. *J. Heterocycl. Chem.* **1982**, *19*, 653.

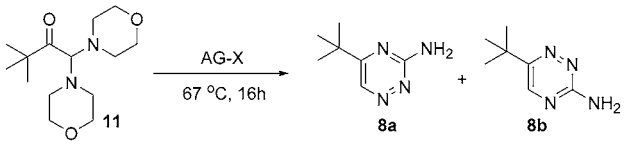
(13) Only hydrazone **9a** was identifiable by ^{1}H NMR during the reaction.

(14) Condensation of **14** with AG-HCl in THF:H_2O (1:1) at 67 °C for 24 h afforded a similar bis-hydrazone species, which upon addition of K_2CO_3 or KOAc cyclized to give a 1.5:1 mixture of the aminotriazines (**8a**:**8b**).

(15) For conversion of various dibromides to the corresponding aminals, see: (a) Kerfanto, M.; Brault, A.; Venien, F.; Morvan, J. M.; Le Rouzic, A. *Bull. Chem. Soc. Fr.* **1975**, 196. (b) Morvan, J. M.; Kerfanto, M.; Brault, A. *Bull. Chem. Soc. Fr.* **1975**, 1679.

(16) For a previously observed reduction capability of a secondary amine during a halide displacement reaction, see: Howk, B. W.; McElvain, S. M. *J. Am. Chem. Soc.* **1932**, *54*, 282.

Table 1. Optimization of Reaction Yields and Regioselectivity

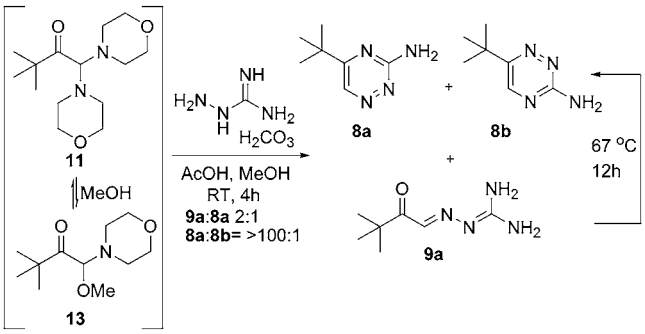


solvents	AGX/X	additives	regioisomeric ratio/(**8a**:**8b**)	HPLC yield, %
MeOH	H_2CO_3	none	2:1	54
MeOH	HCl	none	7:1	68
MeOH	H_2CO_2	1 equiv AcOH	9:1	78
MeOH	H_2CO_3	2 equiv AcOH	39:1	80
MeOH	**H_2CO_3**	**3 equiv AcOH**	**>100:1**	**80**
MeOH	H_2CO_3	4 equiv AcOH	>100:1	77
MeOH	H_2CO_3	50% v AcOH	>100:1	70
AcOH	H_2CO_3	none	>100:1	45
THF	H_2CO_3	3 equiv AcOH	22:1	70
THF	HCl	2 equiv AcOH	24:1	68
THF:H_2O	H_2CO_3	3 equiv AcOH	3:1	55

reactive iminium species (**11** → **10**) might occur. After screening several reaction conditions, we found that subjection of **11** to AGB in the presence of 3 equiv of AcOH in MeOH at 67 °C for 16 h afforded the desired aminotriazine **8a** in >99% regioselectivity and 80% assay yield (Table 1). Interestingly, when the reaction was carried out in THF or if fewer than 2 equiv of AcOH were employed in MeOH, a lower regioselectivity was observed. In addition, the use of excess AcOH (≥4 equiv or 50% v/v in MeOH) resulted in much lower reaction yields, although the high regioselectivity was retained.

To probe the reaction mechanism, several preliminary experiments were performed and analyzed by in situ NMR spectroscopy. In MeOH, ketoaminal **11** appeared to exist in equilibrium with the corresponding *N,O*-acetal **13** (Scheme 5). No significant changes in the ^{1}H NMR spectra were

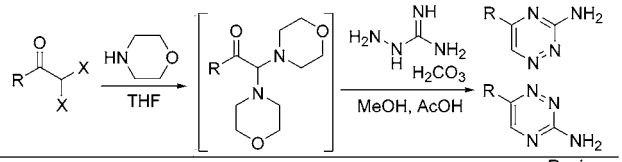
Scheme 5

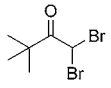
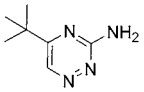
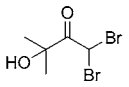
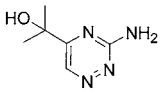
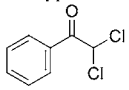
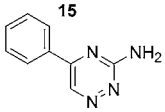
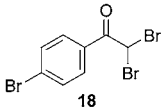
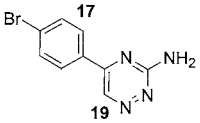
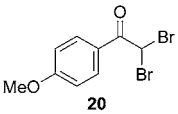
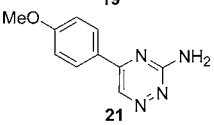
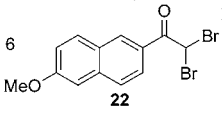
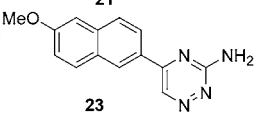
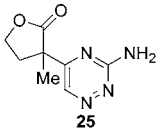
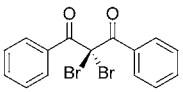
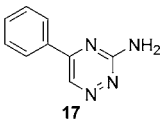


observed upon treatment of this equilibrium mixture with AcOH. When AGB was added at rt and the suspension was stirred for 4 h, the keto hydrazone intermediate **9a** was observed along with the desired aminotriazine **8a** (**9a**:**8a** = 2:1). Upon heating at 67 °C for 12 h, the mixture converged to the desired aminotriazine. If excess AcOH was used, the final cyclization (**9a** → **8a**) occurred slowly even after stirring at reflux for 3 days, resulting in the observed lower yield (Table 1). Hence, the reaction appeared to work best under slightly acidic conditions with 3 equiv of AcOH, in which two neutralized the morpholine byproducts and the other converted the bicarbonate to the more soluble aminoguanidine acetate salt.

We later discovered that similar results could be obtained when the reaction was performed without incorporating an

Table 2. Regioselective Formation of Aminotriazines[a]



Entry	Dihalide[b]	Aminotriazines[c]	Yields[d]	Regio-selectivity[e]
1	 **7**	 **8a**	66	99
2	 **14**	 **15**	65	95
3	 **16**	 **17**	65	98
4	 **18**	 **19**	60	98
5	 **20**	 **21**	75	99
6	 **22**	 **23**	76	99
7	 **24**	 **25**	47[f]	99
8	 **26**	 **17**	45[f]	99

[a] Morpholination was carried out in THF at 45−67 °C for 24−48 h and the aminals were used without further purification. Unless otherwise noted, the cyclization was carried out in MeOH with 3 equiv of AcOH and 1 equiv of AGB at rt→67 °C for 14−20 h. [b] Commercially unavailable materials were prepared by bromination of the corresponding ketones with $PhNMe_3Br_3$ in THF at rt or with Br_2/MeOH. [c] Isolated as a single regioisomer. [d] Isolated yields. [e] Calculated by using the ^{1}H NMR integration values of the aminotriazine ring hydrogen. The structure of the major regioisomer was assigned by 2D NMR-HMBC experiment. [f] The aminal was isolated and the value represents a 2-step process; the aminotriazine formation for **24** was carried out at 0 °C (24 h)→rt (24 h), using AG-HCl and 2 equiv of AcOH.

isolation and recrystallization step at the aminal stage. Hence, treatment of **7** with morpholine (4.1 equiv) in THF at 50 °C for 96 h gave the crude aminal, which upon subjection to AGB and AcOH (3 equiv) in MeOH at 67 °C afforded the desired aminotriazine **8a** in >99% regioselectivity (Table 2, entry 1). Upon cooling the reaction mixture to rt, the desired product crystallized from the solution. After concentration and aging at 0 °C for 1 h, the product was conveniently isolated, yielding analytically pure material in 66% yield from dibromide **7**.

To explore the scope and limitation of this methodology, transformations involving other α,α-dihalocarbonyl compounds were investigated. Unless otherwise noted, the sequential two-step process was executed without isolation and purification of the aminal intermediates. Treatment of the readily available dibromohydroxy ketone **14** (entry 2, Table 2) with morpholine in refluxing THF for 22 h gave the corresponding keto aminal intermediate, which upon subjection to the optimized condensation conditions afforded aminotriazine **15** in a 19:1 regioisomeric ratio (95% regioselectivity) and 65% isolated yield. Aromatic-containing dihalocarbonyl compounds could also be converted to their corresponding aminals in shorter time (24 h at 45 °C) and underwent subsequent regioselective aminotriazine formation. For example, the known aminotriazines of phenyl **17**,[17] 4-bromophenyl **19**,[17a] 4-methoxyphenyl **21**,[17a] and naphthalene substrate **23** (entry 3−6, Table 2) were all obtained in good yields (60−76%) and ≥98% regioselectivity. Despite a slight difference in isolated yields, variation of the *para* substituent on the aromatic ring had virtually no effect on the observed regioselectivities in these transformations.

The scope of substrate was further extended to include 1,3-dicarbonyl compounds such as **24** and **26**. Morpholination of these substrates occurred at milder reaction conditions (rt, 3−12 h), affording the corresponding aminals in 88% isolated yield. Subjection of the isolable ketoaminal of **24**[18] to the typical condensation conditions afforded a mixture of products.[19] However, if AG-HCl was used and the reaction was carried out in MeOH at 0 °C for 24 h followed by warming to rt and additional aging for 24 h, the desired aminotriazine **25** was isolated in 53% yield and >99% regioselectivity.[20] On the other hand, while no desired aminotriazine was obtained in ethereal solvents (THF, DME), condensations of the isolable aminal of **26**[18] with AGB in alcohol solvents (MeOH, EtOH, *i*PrOH) gave only **17** and benzoate esters. The formation of aminotriazine **17** might result from a facile retro-Claisen condensation of the aminal with the protic solvent**,** affording the corresponding benzoate ester and the aminal of acetophenone (i.e., aminal of **16**, entry 3, Table 2), which would then condense with AGB and cyclize to give **17**.

In conclusion, a new regioselective approach to 5-substituted-3-amino-1,2,4-triazines, which involves a nucleophilic displacement of readily available α,α-dihalocarbonyl compounds, followed by a condensation of the resulting crude ketoaminals with aminoguanidine in the presence of AcOH in MeOH, has been successfully demonstrated. The titled aminotriazines were conveniently isolated as a single regioisomer in good yield (45−76%) by simple filtration of the reaction solution, affording analytically pure materials.

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Supporting Information Available: Experimental details for the preparation of aminotriazines, as well as their characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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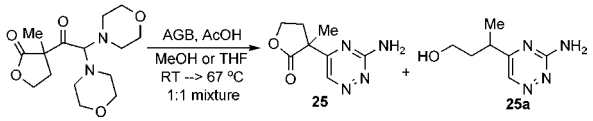
(17) (a) Nakajima, M.; Hisada, R.; Anselme, J.-P. *J. Org. Chem.* **1978**, *43*, 2693. (b) Rykowski, A.; van der Plas, H. C. *J. Org. Chem.* **1980**, *45*, 881.

(18) See Supporting Information for its isolation and partial characterization

(19) Under typical conditions, a 1:1 mixture of the desired aminotriazine **25** and **25a** was obtained in either MeOH or THF, with or without 4 Å molecular sieves.



(20) Under these reaction conditions, a 4:1 mixture of aminotriazine **25** and ketoaminal intermediate **25b** was obtained at the end of the reaction.