Notes

Synthesis of Substituted 4(6)-Amino-1,3,5-triazin-2-ones and -1,3,5-triazin-2-thiones

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Introduction

1,3,5-Triazin-2-one derivatives include well-known anticancer drugs.[1a−c] 5-Azacytidine (4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one), a synthetic analogue of the natural pyrimidine nucleoside cytidine, has strong antileukemic activity.[2a−c] When used in cancer chemotherapy, 5-azacytidine is phosphorylated in the cell, and after its incorporation into the DNA, it inhibits the methyltransferase, causing a block in the cytosine methylation in newly replicated DNA. Selective modulation of DNA methylation may, therefore, have important clinical implications for the prevention and treatment of cancer.[1c,2b] Other derivatives of the 5-azacytidine, decitabine and gemcitabine, were found active in the treatment of lung, pancreas, bladder, and breast cancer.[3a−c]

Known syntheses of 4(6)-amino-1,3,5-triazin-2-ones[4a−b] include (i) reactions of cyanoguanidines with carboxylic acids,[4c−d] acid anhydrides,[4e] or carboxylic acids in the presence of phosphorus oxychloride;[4f] (ii) cyclizations of *N*-acyl-*N*′-cyanoguanidines;[4f,g] (iii) cyclizations of isobiurets with ethyl orthoformate;[4h,j] (iv) reactions of guanylureas with dimethylformamide dimethylacetal;[4j] (v) sequential displacements of two chlorine atoms followed by hydrolysis of the third chlorine in 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride);[5a−d] and (vi) reactions of biguanides with diethyl azodicarboxylate.[6] 4(6)-Amino-1,3,5-triazin-2-thiones were obtained by the reaction of dicyandiamide with thiocarboxylic acids.[7]

Recently, we published an efficient synthetic procedure for the preparation of 3-amino-1,2,4-triazoles starting from *N*-acyl-1*H*-benzotriazole-1-carboximidamides **1**.[8a] We now report the application of compounds **1** in a new synthetic route to 4(6)-amino-1,6(4)-substituted-1,3,5-triazin-2-ones.

Results and Discussion

N-Acyl-1*H*-benzotriazole-1-carboximidamides **1** can be obtained from reactions of di(benzotriazol-1-yl)methanimine with various primary and secondary amines followed by acylation.[8a−b] We have used known derivatives **1b−d,g** as well as novel compounds **1a,e,f,h**. The construction of the 1,3,5-triazin-2-one ring from **1** involves the displacement of the benzotriazolyl moiety with urea or thiourea in the presence of potassium *tert*-butoxide, followed by cyclocondensation into triazines **2** and **3**.

Independent of the nature of the substituent R^1 in the starting *N*-acyl carboximidamides **1**, reactions of **1** with nonsubstituted urea and thiourea or with their *N*-monoalkyl derivatives in the presence of 3 equiv of potassium *tert*-butoxide proceed smoothly in THF at room temperature to give the desired 4(6)-substituted-6(4)-amino-1,3,5-triazin-2-ones **2a−f** and 4(6)-substituted-6(4)-amino-1,3,5-triazin-2-thiones **3a−c** directly (Scheme 1, Table 1). In contrast, reactions of *N*-acyl carboximidamides **1** with phenylurea lead to noncyclic intermediates **4a−d** (Scheme 1, Table 1), with the exception of the reaction of the derivative **1c** with phenylurea from which the desired 1,3,5-triazin-2-one **6** was isolated exclusively (Scheme 1).

The mode of the addition of the base is important: 1 equiv does not lead to complete reaction. Adding 2 equiv of potassium *tert*-butoxide in one portion gives the desired

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(1) (a) Steuber, C. P.; Krischer, J.; Holbrook, T.; Camitta, B.; Land, V.; Sexauer, C.; Mahoney, D.; Weinstein, H. *J. Clin. Oncol.* **1996**, *14*, 1521. (b) Kantarjian, H. M.; Talpaz, M.; O'Brien, S.; Kurzrock, R.; Gutterman, J.; Keating, M. J.; McCredie, K. B.; Freireich, E. J. *Clin. Cancer Res.* **1997**, *3*, 2723. (c) Momparler, R. L.; Bovenzi, V. *J. Cell Physiol.* **2000**, *183*, 145.

(2) (a) Marin, D.; Teijeiro, C.; Pina, J. J. *J. Electroanal. Chem.* **1996**, *407*, 189. (b) Singal, R.; Ginder, G. D. *Blood* **1999**, *93*, 4059. (c) Smith, R. D.; Li, J.; Noguchi, C. T.; Schechter, A. N. *Blood* **2000**, *95*, 863.

(3) (a) Gregoire, V.; Hittelman, W. N.; Rosier, J. F.; Milas, L. *Oncol. Rep.* **1999**, *6*, 949. (b) Sacchi, S.; Kantarjian, H. M.; O'Brien, S.; Cortes, J.; Rios, M. B.; Giles, F. J.; Beran, M.; Koller, C. A.; Keating, M. J.; Talpaz, M. *Cancer* **1999**, *86*, 2632. (c) Poplin, E.; Roberts, J.; Tombs, M.; Grant, S.; Rubin, E. *Invest. New Drugs* **1999**, *17*, 57.

(4) (a) Quirke, J. M. E. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 457 and references herein. (b) Bartholomew, D. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon Press: Oxford, 1996; Vol. 6, p 575 and references herein. (c) Grundmann, C.; Schwennicke, L.; Beyer, E. *Chem. Ber.* **1954**, *87*, 19. (d) Davydov, A. V.; Finkel'shtein, A. I.; Shcherbakov, E. K.; Fokin, A. V.; Roginskaya, Ts. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1968**, *38*, 2415. (e) Andreasch, R. *Monatsh. Chem.* **1927**, *48*, 149. (f) Klosa, J. *Arch. Pharm.(Weinheim, Ger.)* **1955**, *228*, 139. (g) Adams, P.; Kaiser, D. W.; Nagy, D. E.; Peters, G. A.; Sperry, R. L.; Thurston, J. T. *J. Org. Chem.* **1952**, *17*, 1162. (h) Piskala, A.; Sorm, F. *Collect. Czech. Chem. Commun.* **1964**, *29*, 2060. (j) Piskala, A. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3966.

(5) (a) Thurston, J. T.; Dudley, J. R.; Kaiser, D. W.; Hechenbleikner, I.; Schaefer, F. C.; Holm-Hansen, D. *J. Am. Chem. Soc.* **1951**, *73*, 2981. (b) Dudley, J. R.; Thurston, J. T.; Schaefer, F. C.; Holm-Hansen, D.; Hull, C. J.; Adams, P. *J. Am. Chem. Soc.* **1951**, *73*, 2986. (c) Schaefer, F. C.; Dudley, J. R.; Thurston, J. T. *J. Am. Chem. Soc.* **1951**, *73*, 2996. (d) Schaefer, F. C.; Dudley, J. R.; Thurston, J. T. *J. Am. Chem. Soc.* **1951**, *73*, 3004.

(6) Kihara, Y.; Kabashima, S.; Yamasaki, T.; Ohkawara, T.; Furukawa, M. *J. Heterocycl. Chem.* **1990**, *27*, 1213.

(7) Russel, P. B.; Hitchings, G. H.; Chase, B. H.; Walker, J. *J. Am. Chem. Soc.* **1952**, *74*, 5403.

(8) (a) Katritzky, A. R.; Rogovoy, B. V.; Vvedensky, V.; Kovalenko, K.; Steel, P. J. Markov, V. I. *Synthesis* **2001**, 897. (b) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080.

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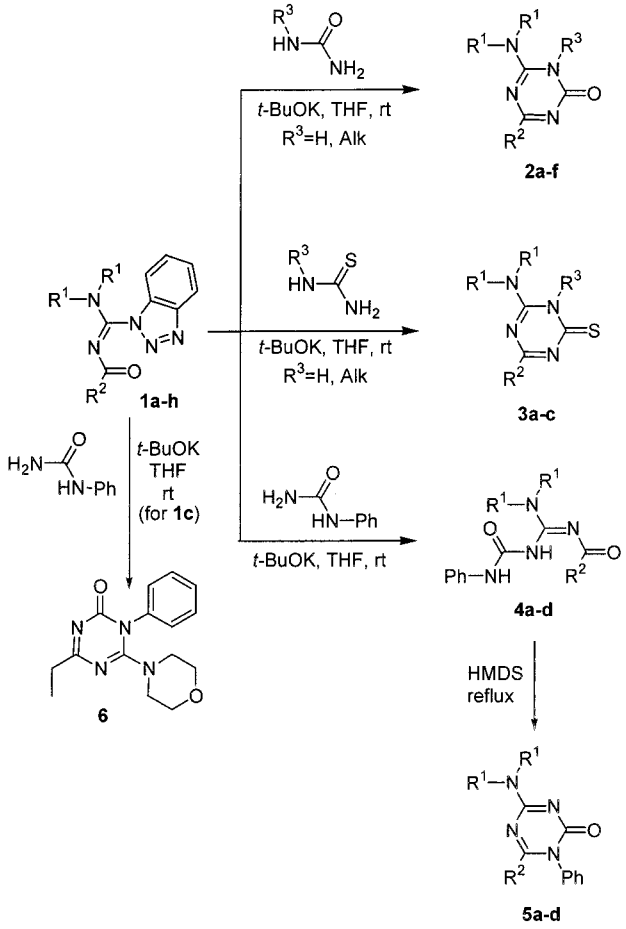
Table 1. Preparation of Starting Materials 1, Intermediates 4, and Final Products 2, 3, and 5

			yield, % (R^3)					
entry	R^1	R^2	**1**	**2**	**3**	**4**	**5**	**6**
1	$(CH_2)_2O(CH_2)_2$	4-CH_3-C_6H_4	**a**: 86	**a:** 89 (H)				
2	$(CH_2)_2O(CH_2)_2$	Ph	**b**: 93	**b:** 85 (H) **c:** 79 (CH_3)		**a**: 68	**a**: 95	
3	$(CH_2)_2O(CH_2)_2$	ethyl	**c**: 91		**a**: 88 (H) **b**: 44 (Et)			94
4	$(CH_2)_2O(CH_2)_2$	thiophen-2-yl	**d**: 64	**d:** 76 (CH_3)				
5	$(CH_2)_2O(CH_2)_2$	4-F-C_6H_4	**e**: 98	**e:** 91 (CH_3)				
6	ethyl, ethyl	4-CH_3-C_6H_4	**f**: 86	**f:** 87 (H)	**c**: 63 (H)	**b**: 82	**b**: 96	
7	ethyl, ethyl	*tert*-butyl	**g**: 88			**c**: 89	**c**: 51	
8	allyl, allyl	4-CH_3-C_6H_4	**h**: 72			**d**: 61	**d**: 88	

Scheme 1



products **2a**−**f**, **3a**−**c**, or intermediates **4a**−**d** along with unidentified side products. The optimal conditions were found to be the portionwise addition of 3 equiv of potassium *tert*-butoxide for 1 h, which gave the intermediates **4a**−**d** or final products **2a**−**f** and **3a**−**c** in high yields. Replacement of potassium *tert*-butoxide by sodium methoxide in the reaction of **1b** with phenylurea decreases the yield of the desired compound **4a**. Attempts to synthesize the compound **4a** in the presence of DBU failed.

In search of a general method for the cyclization of compounds **4** into triazinones **5**, we refluxed compound **4a** (a) in toluene in the presence of *p*-toluenesulfonic acid and (b) in TFA. Derivative **4b** was treated with an EtOH/KOH mixture under reflux. Although all these attempts were unsuccessful, it was found that compounds **4** can be easily cyclized into triazinones **5** using HMDS as a dehydrating agent under reflux (Scheme 1, Table 1).

Conclusion

In summary, we have developed a new, efficient procedure for the preparation of 4(6)-amino-1,6(4)-disubstituted-1,3,5-triazin-2-ones **2a**−**f**, **5a**−**d**, and **6**, and 4(6)-amino-1,6(4)-disubstituted-1,3,5-triazin-2-thiones **3a**−**c**. Our method allows the introduction of a variety of amino group substituents which is not possible by direct reactions with cyanoguanidines[4a,b,d,e] or is limited by the availability of *N*,*N*-disubstituted formamide diacetals.[4g] Use of acyl cyanoguanidines could give a diversity in the 4(6)-position, but once again, it does not allow the introduction of a substituent in the amino group at the same time. The proposed protocol does not need rigorous control of the reaction conditions in comparison to the protocol for the condensation of cyanuric chloride with amines.[5a] The option of introducing the thione group increases the usefulness of the reported protocol. Each step of the reaction sequence gave the desired final products **2a**−**f**, **3a**−**c**, and **6** or intermediates **4a**−**d** in high yields with good purity.

Experimental Section

General Methods. Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer (300 and 75 MHz, respectively) using $CDCl_3$ or DMSO-d_6 as solvent, with tetramethylsilane as an internal standard. Tetrahydrofuran (THF) was distilled under nitrogen from sodium/benzophenone immediately before use. Column chromatography was conducted with silica gel grade 230−400 mesh. All other reagents were of reagent grade and were used without purification.

General Procedure for the Preparation of Acyl Derivatives of 1*H*-Benzotriazol-1-carboximidamides 1a−h. An appropriate 1*H*-benzotriazol-1-carboximidamide (1 equiv) was dissolved in chloroform, and an acyl chloride (1 equiv) was added, followed by the addition of triethylamine (1 equiv). The mixture was allowed to react for 2−4 h at ambient temperature. The completion of the reaction was monitored by TLC. Then the chloroform solution was washed with water to remove triethylamine hydrochloride. The chloroform layer was separated, dried, and concentrated under reduced pressure. The preparation and characterization of compounds **1b**−**d,g** were described previously in our earlier work.[8a−b]

***N*-(1*H*-Benzotriazol-1-yl(morpholino)methylidene)-4-methylbenzamide (1a).** White needles (ethyl acetate), mp 294−295 °C. ^{1}H NMR: δ 2.36 (s, 3H), 3.56−3.60 (m, 4H), 3.80−3.84 (m, 4H), 7.26 (d, J = 7.9 Hz, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.58−7.69 (m, 2H), 7.84 (d, J = 7.9 Hz, 2H), 8.17 (t, J = 8.2 Hz, 1H). ^{13}C NMR: δ 21.1, 47.2, 65.6, 110.9, 119.9, 125.3, 128.9, 129.3, 129.6, 132.3, 132.6, 142.7, 144.6, 146.1, 174.0. Anal. Calcd for $C_{19}H_{19}N_5O_2$: C, 65.31; H, 5.48; N, 20.04. Found: C, 65.08; H, 5.53; N, 20.16.

Procedure for the Preparation of Compounds 2, 3, 4 and 6. *N*-Acyl benzotriazole-1-carboximidamide **1** (1 mmol) and urea (thiourea) (1 mmol) were mixed in THF (10 mL). Potassium *tert*-

butoxide (3 mmol) was added portionwise by 1 equiv in 15 min. The reaction mixture was allowed to react for 6−8 h. Then water (15 mL) was added to give a clear solution. Water solution was extracted with ethyl acetate (3 × 30 mL). Sodium bicarbonate was added to a water layer, and the water layer was additionally extracted with chloroform (2 × 30 mL). Extracts were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The residue obtained was recrystallized from an appropriate solvent to give **2**, **3**, **4**, and **6**.

Procedure for the Preparation of Compounds 5a−d Starting from 4a−d. Noncyclic products **4a−d** (1 mmol) were refluxed in HMDS (30 mL) for 1−3 d (TLC control). Then HMDS was evaporated under reduced pressure, and the residues obtained were recrystallized from an appropriate solvent to give the desired compounds **5a−d**.

4-(4-Methylphenyl)-6-morpholino-1,3,5-triazin-2(3*H*)-one (2a). White needles (ethanol/water), mp 301−302 °C. ^{1}H NMR: δ 2.44 (s, 3H), 3.77 (br s, 4H), 3.98 (br s, 2H), 4.07 (br s, 2H), 7.35 (d, J = 7.9 Hz, 2H), 8.21 (d, J = 8.1 Hz, 2H), 12.93 (s, 1H). ^{13}C NMR: δ 21.7, 44.1, 44.7, 66.7, 66.8, 127.8, 128.2, 129.8, 144.1, 159.4, 163.5, 164.4. Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.85; H, 5.62; N, 20.63.

4-Ethyl-6-morpholino-1,3,5-triazine-2(1*H*)-thione (3a). White needles (benzene/hexanes), mp 252−253 °C. ^{1}H NMR (DMSO-d_6): δ 1.22 (t, J = 7.4 Hz, 3H), 2.54 (q, J = 7.4 Hz, 2H), 3.65−3.69 (m, 4H), 3.89−3.95 (m, 4H), 12.91 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 10.0, 26.7, 43.5, 43.8, 56.8, 65.9, 158.9, 168.3, 182.7. Anal. Calcd for $C_9H_{14}N_4OS$: C, 47.77; H, 6.24; N, 24.76. Found: C, 48.02; H, 6.44; N, 24.90.

***N*-(Anilinocarbonyl)amino(morpholino)methylidenebenzamide (4a).** White prisms (ethanol/water), mp 136−137 °C. ^{1}H NMR: δ 3.66 (br s, 4H), 3.69−3.81 (m, 4H), 7.03 (t, J = 7.2 Hz, 1H), 7.19 (br s, 1H), 7.25−7.30 (m, 2H), 7.43−7.58 (m, 5H), 8.01 (d, J = 7.7 Hz, 2H), 12.60 (s, 1H). ^{13}C NMR: δ 40.7 (br s), 66.5, 119.1, 123.2, 128.1, 128.9, 128.9, 132.7 133.0, 138.6, 154.3, 162.1, 164.9. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.74; H, 5.77; N, 15.99.

4-(Diallylamino)-6-(4-methylphenyl)-1-phenyl-1,3,5-triazin-2(1*H*)-one (5d). White prisms (benzene/hexanes), mp 123−124 °C. ^{1}H NMR: δ 2.28 (s, 3H), 4.31−4.35 (m, 4H), 5.20−5.24 (m, 4H), 5.83−5.93 (m, 2H), 6.99 (d, J = 7.9 Hz, 2H), 7.14−7.20 (m, 4H), 7.24−7.32 (m, 3H). ^{13}C NMR: δ 21.4, 48.7, 48.9, 117.3, 117.6, 128.2, 128.6, 128.8, 128.9, 129.3, 130.6, 132.6, 133.1, 137.7, 141.1, 155.7, 162.8, 165.4. Anal. Calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.46; H, 6.47; N, 15.61.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and CHN analysis data for compounds **1e,f,h**, **2b−f**, **3b,c**, **4b−d**, **5a−c**, and **6** and ^{1}H NMR and ^{13}C NMR spectra for compounds **2d, 4c,d**, **5a−c**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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