Straightforward Synthesis of Some 2- or 3-Substituted Naphtho- and Quinolino[1,2,4]triazines via the Cyclocondensation of Nitronaphthalenes and Nitroquinolines with Guanidine Base

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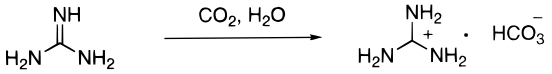
Introduction

Some benzo-annulated 1,2,4-triazine derivatives are important as pharmaceuticals and agrochemicals. The representative examples include 3-amino-1,2,4-benzotriazine 1,4-dioxide, which has received considerable attention as a new class of antitumor agent owing to its high selective toxicity for hypoxic cells both in vitro and in vivo.[1,2] The mechanism of DNA cleavage by this type of compound is therefore of biochemical and pharmaceutical interest.[3−5] The known synthesis for this class of azaaromatic framework involves the thermal reaction of 2-nitroaniline with cyanamide,[6] the base-induced cyclization of 2-nitrophenylurea followed by successive treatment with phosphoryl chloride and gaseous ammonia,[7] and the addition of disodiocyanamide to benzofuroxan followed by acidic workup.[8] However, all these approaches are subject to considerable influence from the electronic effect of substituent groups on the aromatic ring, limiting the generality of these methodologies.

Recently, we have developed a convenient synthesis of 3-amino-1,2,4-benzotriazine derivatives by the reaction of *o*-fluoronitrobenzenes with free guanidine base.[9] However, the versatility of this method is dependent on the availability of aromatic substrates having vicinally located fluorine and nitro functions. In addition, when the aromatic substrates need further functionalization, they are generally quite laborious to prepare. In this Note, we report a new straightforward route to the naphtho- and quinolino-annulated 1,2,4-triazine derivatives which is based on the cyclocondensation of nitronaphthalenes or nitroquinolines with guanidine base and, therefore, free from the above structural requirement.

Although guanidine has long been known as a better nucleophile than ordinary amines,[10] nucleophilic aromatic guanidinylation has not often been exploited for organic synthesis, despite the presence of a highly basic and also nucleophilic structural unit N═C—N. The major reason may be the difficulty in handling free guanidine, which is such a strong base that it rapidly absorbs carbon dioxide and moisture from air to form stable guanidinium hydrogen carbonate. The resulting guanidinium cation is highly resonance-stabilized with low nucleophilicity (Scheme 1). Furthermore, free guanidine is thermally unstable and, when heated at elevated temperatures in the presence of alkali, it readily undergoes decomposition to urea, carbon dioxide, and ammonia.

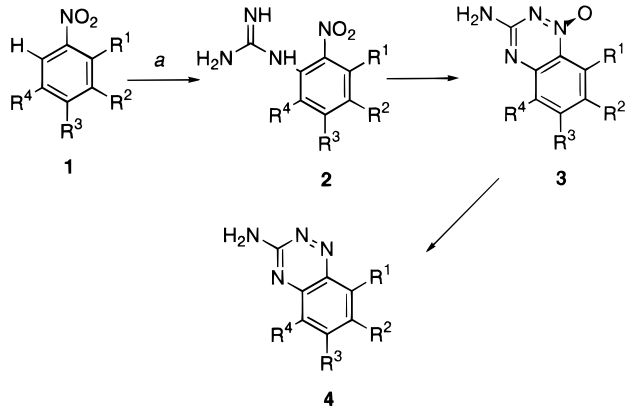
Scheme 1



Results and Discussion

When treated with guanidine in the presence of an excess of a strong base such as sodium hydride or lithium *tert*-butoxide, nitronaphthalenes **1a**−**c** and nitroquinolines **1d**−**g** produced the corresponding 1,2,4-triazine derivatives **4a**−**f** or *N*-oxide **3g** in 31−69% isolated yields (Scheme 2). The results are summarized in Table 1. In the reaction of 2-nitronaphthalene **1c**, N^1-(2-nitro-1-naphthyl)guanidine **2c** was isolated in 6% yield at the stage of 60% conversion, showing that the hydrogen atom next to the nitro group is substituted by guanidine base at the initial stage of the reaction. Subsequent intramolecular cyclization of **2** takes place between the nitro and guanidino groups by the action of a strong base, *tert*-butoxide.[11] The resulting naphtho- and quinolino[1,2,4]-triazine *N*-oxides **3** are readily deoxygenated under strong basic conditions to yield compounds **4**. Such facile removal of the *N*-oxide oxygen atom from naphtho[1,2,4]-triazine *N*-oxides has been reported previously.[12]

Scheme 2[a]



[a] Reaction conditions: $H_2NC(NH_2)$=NH, LiO^tBu, THF, 60 °C,12 h.

Under similar conditions, 1-chloro-4-nitronaphthalene **1b** readily reacted with guanidine to produce the corresponding 3-amino-6-chloronaphtho[2,1-*e*][1,2,4]triazine

(1) (a) Zeman, E. M.; Brown, J. M.; Lemmon, M. J.; Hirst, V. K.; Lee, W. W. *Int. J. Radiat. Onc. Biol. Phys.* **1986**, *12*, 1239. (b) Zeman, E. M.; Baker, M. A.; Lemmon, M. J.; Pearson, C. I.; Adams, J. A.; Brown, J. M.; Lee, W. W.; Tracy, M. *Int. J. Radiat. Onc. Biol. Phys.* **1989**, *16*, 977. (c) Brown, J. M. *Br. J. Cancer* **1993**, *67*, 1163.

(2) Edwards, D. I.; Tocher, J. H.; Dale, L. D.; Widdick, D.; Virk, N. S. *Selective Activation Drugs by Redox Process*; Adams, G. E., Ed.; Plenum: New York, 1990; p 275.

(3) Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 3380.

(4) Laderoute, K.; Wardman, P.; Rauth, M. *Biochem. Pharmacol.* **1988**, *37*, 1487.

(5) Tocher, J. H.; Virk, N. S.; Edwards, D. I. *Biochem. Pharmacol.* **1990**, *39*, 781.

(6) Mason, J. C.; Tennant, G. *J. Chem. Soc. B* **1970**, 911.

(7) Arndt, F. *Chem. Ber.* **1913**, *46*, 3522.

(8) Seng, F.; Ley, K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1009.

(9) Suzuki, H.; Kawakami, T. *Synthesis* **1997**, 855.

(10) Miller, J.; Miyata, Y.; Sakazaki, E.; Santos, T. W. *J. Chem. Res., Synop.* **1986**, 396.

(11) Preston, P. N.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627.

(12) Lalor, F. J.; Scott, F. L.; Ferguson, G.; Marsh, W. C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 789.

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Table 1. Reactions of Nitronaphthalenes 1a−c and Nitroquinolines 1d−f with Guanidine Base[a]

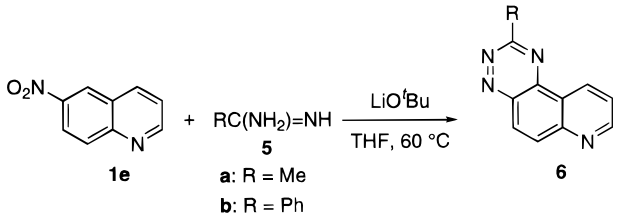
	R^1	R^2	R^3	R^4	Yield (%)[b] 3	4
a	—CH=CH-CH=CH—		H	H	-	39
b	—CH=CH-CH=CH—		Cl	H	-	34
c	H	—CH=CH-CH=CH—		H	-	31
d	—CH=CH-CH=N—		H	H	-	32
e	H	—CH=CH-CH=N—		H	-	45
f	—N=CH-CH=CH—		H	H	-	35
g	H	H	—CH=CH-CH=N—		69	-

[a] All reactions were carried out by stirring a mixture of substrate (2.9 mmol), alkali base (23.9 mmol), and guanidine hydrochloride (5.6 mmol) in THF (30 mL) at 60 °C. [b] Yield refers to isolated compounds.

4b, which no doubt arose from the initial guanidinylation at the 3-position, followed by the ring closure between the guanidino and nitro functions and subsequent deoxygenation. In ordinary nucleophilic aromatic substitution, the chlorine atom at the 1-position should be a much better leaving group than the hydrogen atom at the 3-position.[13]

Amindines structurally resemble guanidine. They are strong bases and also good nucleophiles, and we envisioned they would show similar reactivity to guanidine in the present synthesis of fused 1,2,4-triazine derivatives. Thus, this type of annulation reaction has been successfully carried out with two amidines in the presence of an excess of lithium *tert*-butoxide in hot THF. The reactions of 6-nitroquinoline **1e** with acetamidine **5a** and benzamidine **5b** produced the corresponding 2-substituted quinolino[5,6-*e*][1,2,4]triazine derivatives **6a** and **6b** in 30 and 59% isolated yields, respectively. The substituted amidines reacted cleanly with the substrates, but it required longer time to complete as compared with the reaction of guanidine. The *peri*-hydrogen atom adjacent to the nitro group was selectively substituted by free amidine base, leading to angularly condensed quinolinotriazines **6** (Scheme 3).

Scheme 3



In summary, we have established a simple one-pot procedure for the preparation of some 2- or 3-substituted naphtho[1,2,4]triazines and quinolino[1,2,4]triazines via the nucleophilic cyclocondensation of nitronaphthalenes and nitroquinolines with guanidine or amidine bases. Although not applicable to monocyclic nitroarenes, we envisage that a variety of nitroarenes as substrate would allow for further structural elaboration of 1,2,4-triazine-annulated polycyclic aromatic compounds.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra (200 MHz) were recorded in DMSO-d_6 using TMS as an internal reference. EI mass spectra were determined at 70 eV, and IR spectra were obtained as KBr disks; only prominent peaks useful for diagnosis are recorded. Chromatographic separations were performed on a column packed with a Merck silica gel (230−400 mesh), using a mixture of dichloromethane and ethanol as the eluent. THF was distilled from benzophenone ketyl. 1-Chloro-4-nitronaphthalene **1b**[14] and 7-nitroquinoline **1g**[15] were prepared according to the reported procedures. Other nitroarenes were all commercial products.

Reaction of Nitroarenes 1a−g with Guanidine Base. General Procedure. Lithium hydride (0.19 g, 23.9 mmol), *tert*-butyl alcohol (2.20 mL, 23.9 mmol), and guanidine hydrochloride (0.56 g, 5.6 mmol) were stirred in THF (10 mL) at room temperature. To the resulting suspension was added in one portion a solution of nitroarene **1** (0.50 g, 2.9 mmol) in THF (20 mL), and the mixture was stirred at 60 °C, intermittently monitoring progress of the reaction by TLC. After 12 h, the reddish colored reaction mixture was carefully poured into water. Extraction of the organic phase with CH_2Cl_2 followed by evaporation gave a solid residue, which was purified by chromatography on silica gel using CH_2Cl_2/EtOH as the eluent to give the product as yellow crystals.

3-Aminonaphtho[2,1-*e*][1,2,4]triazine (4a): mp 263−265 °C (dec) (lit.[16] mp 292−294 °C); ^{1}H NMR δ 7.45 (d, 1H, J = 9.1), 7.57 (s, br, 2H), 7.65−7.84 (m, 2H), 8.01 (dd, 1H, J = 1.1, 7.8), 8.20 (d, 1H, J = 9.1), 9.07 (dd, 1H, J = 1.4, 8.0); IR (KBr) 3567 (br), 1663, 1534 cm^{-1}; MS (EI) m/z 196 (M^+, 48), 168 (100), 126 (74). Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.01; H, 4.05; N, 28.25.

3-Amino-6-chloronaphtho[2,1-*e*][1,2,4]triazine (4b): mp >300 °C; ^{1}H NMR δ 7.72 (s, 1H), 7.75 (s, br, 2H), 7.80−8.00 (m, 2H), 8.28 (dd, 1H, J = 1.6, 7.7), 9.12 (dd, 1H, J = 1.5, 7.9); IR (KBr) 3301 (br), 1634, 1522, 1391 cm^{-1}; MS (EI) m/z 232 (M^+ + 2, 15), 230 (M^+, 44), 204 (34), 202 (100). Anal. Calcd for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.28; H, 3.08; N, 24.09.

2-Aminonaphtho[1,2-*e*][1,2,4]triazine (4c): mp 230−232 °C (dec) (lit. mp 200−201,[16] 240[17] °C); ^{1}H NMR δ 7.68 (s, br, 2H), 7.70−7.90 (m, 3H), 7.98 (d, 1H, J = 9.0), 8.01 (dd, 1H, J = 1.4, 8.0), 8.93 (dd, 1H, J = 1.2, 7.7); IR (KBr) 3440 (br), 1636, 1528 cm^{-1}; MS (EI) m/z 196 (M^+, 33), 168 (100), 126 (76). Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.52; H, 4.04; N, 28.54.

3-Aminoquinolino[6,5-*e*][1,2,4]triazine (4d): mp 275−277 °C (dec); ^{1}H NMR δ 7.73 (d, 1H, J = 9.4), 7.74 (s, br, 2H), 7.80 (dd, 1H, J = 4.5, 8.3), 8.25 (d, 1H, J = 9.4), 8.99 (dd, 1H, J = 1.6, 4.5), 9.38 (dd, 1H, J = 1.6, 8.3); IR (KBr) 3450 (br), 1684, 1557, 839 cm^{-1}; MS (EI) m/z 197 (M^+, 23), 169 (100), 142 (47), 127 (44). Anal. Calcd for $C_{10}H_7N_5$: C, 60.91; H, 3.58; N, 35.51. Found: C, 61.30; H, 3.41; N, 35.32.

2-Aminoquinolino[5,6-*e*][1,2,4]triazine (4e): mp 280−282 °C (dec); ^{1}H NMR δ 7.77 (dd, 1H, J = 4.8, 8.3), 7.83 (d, 1H, J = 9.3), 7.88 (s, br, 2H), 8.26 (d, 1H, J = 9.3), 9.11 (dd, 1H, J = 1.3, 4.8), 9.19 (dd, 1H, J = 1.3, 8.3); IR (KBr) 3400 (br), 1653, 1531 cm^{-1}; MS (EI) m/z 197 (M^+, 42), 169 (100), 142 (74). Anal. Calcd for $C_{10}H_7N_5$: C, 60.91; H, 3.58; N, 35.51. Found: C, 60.58; H, 3.35; N, 35.47.

(13) Terrier, F. *Nucleophilic Aromatic Displacement*; VCH: New York, 1991.

(14) Bassilios, H. F.; Shawki, M.; Salem, A. Y. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 358.

(15) Filippi, J. *Bull. Soc. Chim. Fr.* **1968**, 259.

(16) Fusco, R.; Bianchettic, G. *Gazz. Chim. Ital.* **1957**, *87*, 446; through Neunhoeffer, H.; Wiley, P. F. In *The Chemistry of Heterocyclic Compounds*, Vol. 33; Wiley: New York, 1978; p 737.

(17) De, S. C. *J. Indian Chem. Soc.* **1927**, *4*, 183.

3-Aminoquinolino[7,8-*e*][1,2,4]triazine (4f): mp >300 °C; ^{1}H NMR δ 7.54 (d, 1H, J = 9.2), 7.71 (dd, 1H, J = 4.5, 8.1), 7.78 (s, br, 2H), 8.22 (d, 1H, J = 9.2), 8.43 (dd, 1H, J = 1.7, 8.1), 9.06 (dd, 1H, J = 1.7, 4.5); IR (KBr) 3375 (br), 1647, 1535 cm^{-1}; MS (EI) m/z 197 (M$^+$, 43), 169 (100), 142 (100). Anal. Calcd for $C_{10}H_7N_5$: C, 60.91; H, 3.58; N, 35.51. Found: C, 60.61; H, 3.47; N, 35.30.

2-Aminoquinolino[8,7-*e*][1,2,4]triazine-4-oxide (3g): mp 261−263 °C (dec); ^{1}H NMR δ 7.54 (d, 1H, J = 9.0), 7.78 (m, 3H), 8.21 (d, 1H, J = 9.0), 8.42 (d, 1H, J = 8.1), 9.05 (dd, 1H, J = 1.7, 4.3); IR (KBr) 3499 (br), 1620, 1526, 1381 cm^{-1}; MS (EI) m/z 213 (M$^+$, 40), 197 (14), 169 (100), 142 (75). Anal. Calcd for $C_{10}H_7N_5O$: C, 56.34; H, 3.31; N, 32.85. Found: C, 56.60; H, 3.28; N, 33.05.

Reaction of 6-Nitroquinoline 1e with Amidines 5a,b. Typical Procedure. Lithium hydride (0.19 g, 23.9 mmol), *tert*-butyl alcohol (2.20 mL, 23.9 mmol), and benzamidine hydrochloride **5b** (0.96 g, 5.6 mmol) were stirred in THF (10 mL) at room temperature. To the resulting suspension was added in one portion a solution of 6-nitroquinoline **1e** (0.50 g, 2.9 mmol) in THF (20 mL), and the mixture was stirred at 60 °C, intermittently monitoring progress of the reaction by TLC. After disappearance of the nitroarene, the reddish colored reaction mixture was diluted with water. The organic phase was extracted with CH_2Cl_2, and the combined extracts were evaporated to give a solid residue, which was purified by chromatography on silica gel using CH_2Cl_2/EtOH as the eluent to give the expected product **6b** as yellow crystals (0.44 g, 59%).

2-Methylquinolino[5,6-*e*][1,2,4]triazine (6a): mp 178−179 °C; ^{1}H NMR δ 3.22 (s, 3H), 7.73 (dd, 1H, J = 4.5, 8.3), 8.28 (d, 1H, J = 9.5), 8.51 (d, 1H, J = 9.5), 9.19 (dd, 1H, J = 1.8, 4.5), 9.54 (dd, 1H, J = 1.8, 8.3); IR (KBr) 3400 (br), 1483, 1331, 1300 cm^{-1}; MS (EI) m/z 196 (M$^+$, 2.5), 168 (69), 127 (100). Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 66.99; H, 4.46; N, 28.33.

2-Phenylquinolino[5,6-*e*][1,2,4]triazine (6b): mp 202−203 °C; ^{1}H NMR δ 7.60−7.66 (m, 3H), 7.77 (dd, 1H, J = 4.4, 8.2), 8.31 (d, 1H, J = 9.2), 8.56 (d, 1H, J = 9.2), 8.84−8.89 (m, 2H), 9.21 (dd, 1H, J = 1.6, 4.4), 9.68 (dd, 1H, J = 1.6, 8.2); IR (KBr) 3432 (br), 1482, 1342, 1294 cm^{-1}; MS (EI) m/z 258 (M$^+$, 1.7), 230 (100), 229 (66), 127 (79). Anal. Calcd for $C_{16}H_{10}N_4$: C, 74.40; H, 3.90; N, 21.69. Found: C, 74.34; H, 3.76; N, 21.62.

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