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A NOVEL APPROACH TO [1,2,3]TRIAZOLO[1,5-*a*]PYRAZINES[#]

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Abstract –A simple method for the preparation of [1,2,3]triazolo[1,5-*a*]pyrazines involving the cyclization of alkyl 2-benzoylamino-(4,5-dicyano-1*H*-1,2,3-triazol-1-yl)propenoates (**5**) is reported.

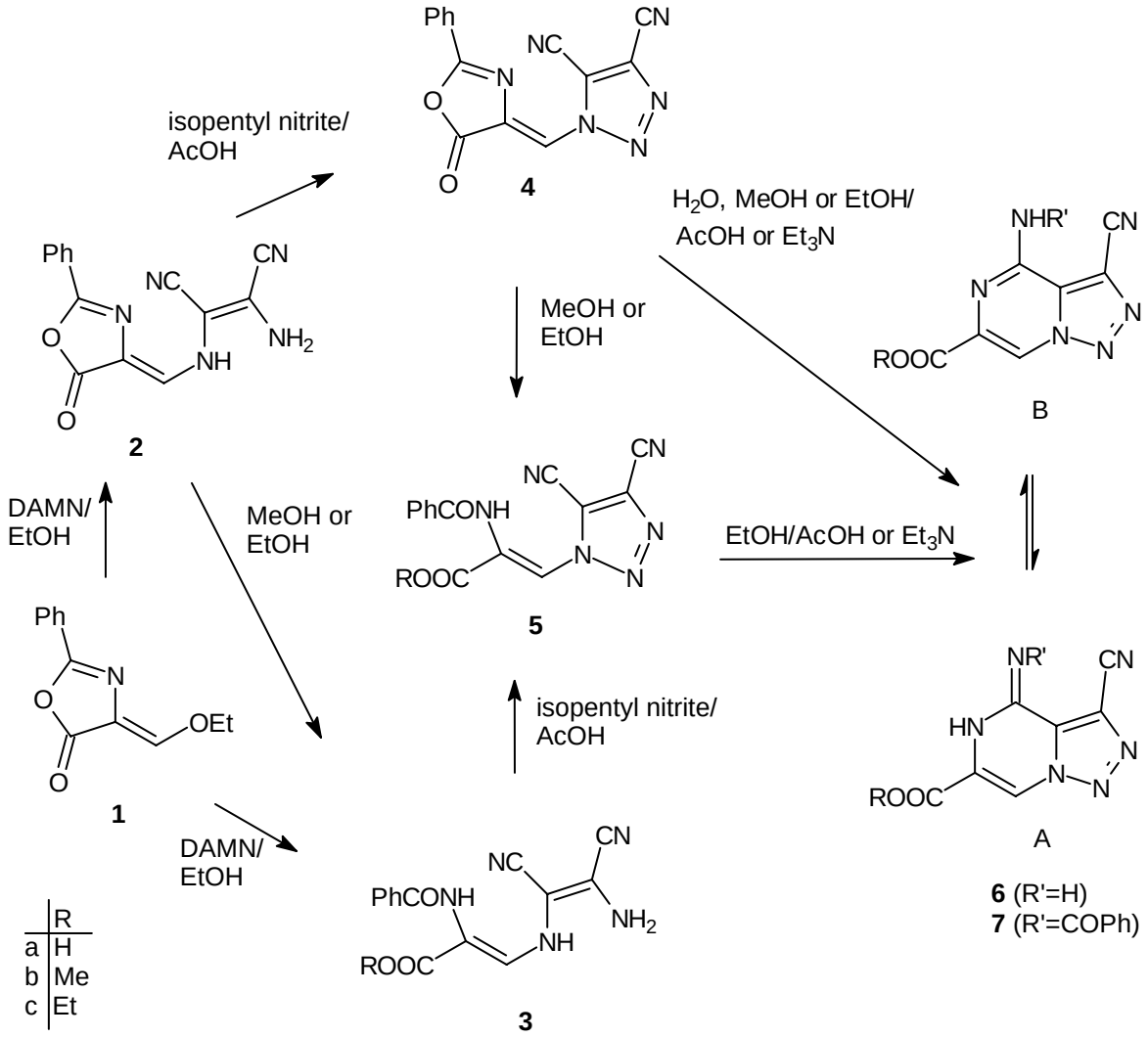
[1,2,3]Triazolo[1,5-*a*]pyrazine[1] is one of the less known systems of the azaindolizine group. Two approaches to this 10 π heteroaromatic system were reported in the case of the parent compound involving the pyrolysis of 2-(tetrazol-4-yl)pyrazine[2] and the oxidative cyclization of pyrazine-2-carbaldehyde hydrazone with lead tetraacetate.[3] Interestingly, the parent compound was also found as one of the products of the Maillard reaction of phenylalanine with fructose in a mixture of cocoa butter and water.[4] Hydrogenated derivatives of this system can be produced by two-fold heterocyclization of some acyclic azides.[5,6] Recently, we designed methods for the formation of some *N*-1,2,3-triazolyl substituted amino acid derivatives[7] and imidazo[1,5-*a*]pyrazines[8] starting from diaminomaleonitrile (DAMN). As a continuation of this research we describe herein a novel approach to the [1,2,3]triazolo[1,5-*a*]pyrazine system.

Our previous work has established a facile route to **4** and **5** by the condensation of the oxazolone (**1**) with DAMN followed by the heterocyclization of the intermediates (**2**) or (**3**) with isopentyl nitrite.[6] Based on these results and our novel approach to the imidazo[1,5-*a*]pyrazine system,[8] it was anticipated that treatment of **4** and **5**, under similar reaction conditions, should lead to the formation of the [1,2,3]triazolo-[1,5-*a*]pyrazine derivative (**7**) (Scheme 1).

Surprisingly, refluxing of **4** in water for 5.5 h in the presence of acetic acid gave the 8-amino substituted [1,2,3]triazolo[1,5-*a*]pyrazine derivative (**6a**) (form B) in 66% yield. Under similar conditions compound

[#] *Dedicated to Professor James P. Kutney on the occasion of his 70th birthday.*

(**4**) was transformed with methanol in 34 h into the methyl ester (**6b**) (form B) in 55% yield**,** whereas heating in ethanol for 17 h afforded the ester (**6c**) (form B) in 65% yield.



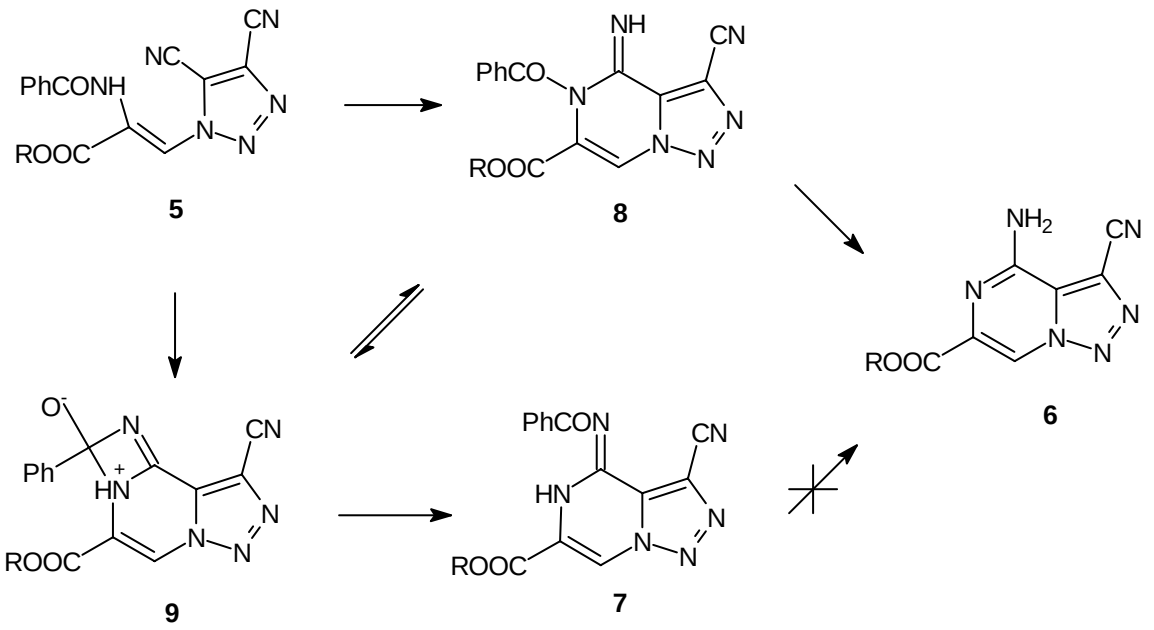
Scheme 1

Refluxing of **4** in methanol or ethanol with triethylamine as a catalyst for 1.5 h gave the benzoylimino substituted triazolopyrazines (**7b**) and (**7c**) in 53 and 48% yields, respectively. Crystallization of the benzoylimino tautomer (form A) of **7c** sometimes gave the benzoylamino tautomer B. Differentiation between these two forms could be done on the basis of IR spectrometry. The pattern of IR spectrum of the form A corresponds to the pattern of the spectrum of the equally substituted imidazo[1,5-*a*]pyrazine whose structure was determined by X-Ray analysis.[8] Similar example is quinazolylthiocarbamic acid ester.[9] ^{1}H and ^{13}C NMR spectra show that the esters (**7**) exist in solutions in two tautomeric forms. For example, **7c** exists as the benzoylamino tautomer B in DMSO-d_6 solution, and as a mixture of tautomers A and B in a ratio of about 3:4 in $CDCl_3$ solution. It is of interest to note, that we observed in the triazolopyrazine series greater

amount of the form B in comparison with the corresponding imidazopyrazines.[8] On the other hand, treatment of **4** with hot water in the presence of triethylamine for 30 min gave the amine (**6a**) (form B) in 42% yield.

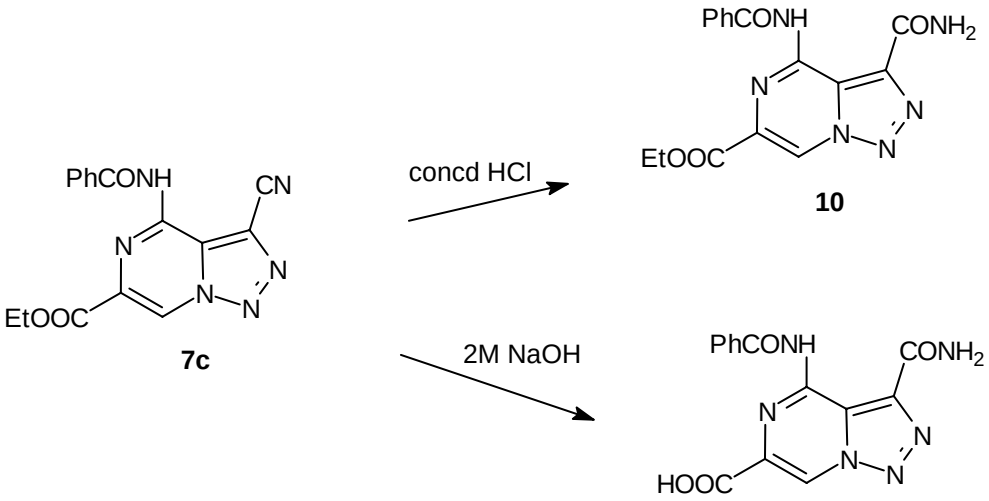
The key compounds in the syntheses of these fused pyrazines are the triazoles (**5a-c**) formed by a solvolysis of the oxazolone ring. In order to confirm this statement, we refluxed the ester (**5c**) with a mixture of ethanol and acetic acid (1:1) for 5.5 h to obtain the amine (**6c**) in 58% yield. Treatment of **5c** with ethanol and triethylamine gave **7c** in 41% yield.

The mechanism of the formation of the trizolopyrazine system is depicted in Scheme 2. We believe that the attack of the benzamido group to the cyano group should take place giving the pyrazine ring accompanied with a migration of the benzoyl group *via* the intermediate (**9**). Such migration of the acyl group is well-known in the amidine system.[10] Elimination of the benzoyl group in the formation of the amine (**6**) might be caused by an interaction of the applied alcohol on the intermediate (**8**) having the benzoyl group on the ring nitrogen. It is of interest to note that under reaction conditions used for the formation of the triazolopyrazine system no elimination of the benzoyl group from **7c** was observed.



Scheme 2

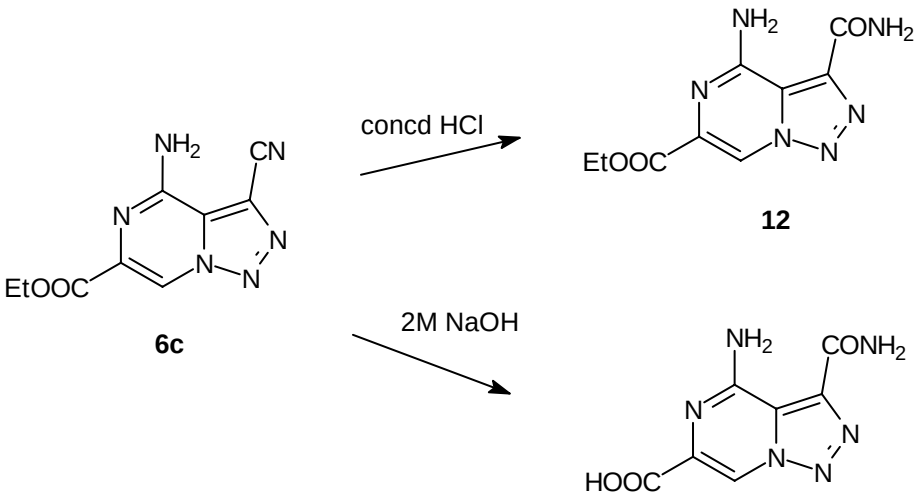
Further functionalization of **7c** proceeded similarly as with the corresponding imidazopyrazine derivative.[8] Reaction of **7c** with concentrated HCl at room temperature for 6 days afforded the ester (**10**) in 92% yield whereas treatment with 2M NaOH at room temperature for 10 days gave the acid (**11**) in 57% yield (Scheme 3).



7c

Scheme 3

Similar selective transformations were carried out with the ester (**6c**). Hydrolysis of **6c** with HCl yielded the ester (**12**) in 91% yield while hydrolysis with NaOH provided the acid (**13**) in 72% yield (Scheme 4).



6c

Scheme 4

In conclusion, we designed a novel approach to the [1,2,3]triazolo[1,5-*a*]pyrazine system using readily available starting compounds prepared from DAMN and 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-one.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer with TMS as an internal standard. The coupling constants (*J*) are given in Hz. Elemental analysis for C, H, N were obtained on a Perkin-Elmer CHN

Analyzer 2400. IR spectra were recorded on a Perkin-Elmer 1310 or 727 B spectrophotometer. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Compounds (**4**), (**5b**), and (**5c**) were prepared as described in the literature.[7] All other compounds were used without purification as obtained from commercial sources.

1-Cyano-8-amino[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylic Acid (6a):

a) A mixture of **4** (290 mg, 1 mmol), acetic acid (40 mg, 0.666 mmol), and water (20 mL) was refluxed for 6 h. Upon cooling, the separated solid was filtered off and washed with water (3 x 1 mL) to give 135 mg (66%) of **6a**; mp 290°C (decomp) (DMF/H_2O); IR (KBr) 3457, 3304, 3146, 3080, 2246, 1707, 1649, 1618, 1537. ^{1}H NMR (DMSO-d_6) δ 7.59 (br s, 2H, NH_2), 9.05 (s, 1H, H-5), 13.46 (br, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 111.6 (C-1), 111.7 (CN), 113.5 (C-5), 124.1 (C-8a), 135.2 (C-6), 149.9 (C-8), 164.5 (CO). MS (EI, *m/z*, %) 204 (M^+, 13), 78 (100). *Anal*. Calcd for $C_7H_4N_6O_2$: C, 41.17; H 1.97; N 41.17. Found: C, 41.21; H 2.09; N, 39.97.

b) A mixture of **4** (290 mg, 1 mmol), triethylamine (35 mg, 0.346 mmol), and water (15 mL) was refluxed for 30 min. Upon cooling, the separated solid was collected by filtration to give 86 mg (42%) of **6a**.

Methyl 1-Cyano-8-amino[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylate (6b):

a) A mixture of **4** (871 mg, 3 mmol), acetic acid (90 mg, 1.5 mmol), and methanol (24 mL) was refluxed for 34 h. Upon cooling, the separated solid was filtered off and washed with methanol (1 mL) to give 360 mg (55%) of **6b**; mp 262-264°C (decomp) (MeOH); IR (KBr) 3475, 3417, 3258, 3121, 3088, 2246, 1740, 1625, 1541. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H, CH_3), 7.69 (br s, 2H, NH_2), 9.14 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6) δ 52.5 (CH_3), 111.5 (C-1), 111.8 (CN), 113.7 (C-5), 124.2 (C-8a), 134.1 (C-6), 150.0 (C-8), 163.6 (CO). MS (EI, *m/z*, %) 218 (M^+, 19), 78 (100). HRMS Calcd for $C_8H_6N_6O_2$: 218.056050. Found: 218.055224. *Anal*. Calcd for $C_8H_6N_6O_2$: C, 44.04; H 2.77; N 38.52. Found: C, 43.82; H 2.55; N 38.24.

b) A suspension of **4** (581 mg, 2 mmol) in methanol (10 mL) was refluxed for 34 h. Upon cooling, the separated solid was filtered, and washed with methanol (1 mL) to give 234 mg (54%) of product (**6b**).

Ethyl 1-Cyano-8-amino[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylate (6c):

a) A mixture of **4** (1.16 g, 4 mmol), acetic acid (75 mg, 1.25 mmol), and ethanol (30 mL) was refluxed for 17 h. Upon cooling, the separated solid was filtered off and washed with ethanol (2 mL) to give 0.61 g (65%) of **6c**; mp 241-244°C (decomp) (EtOH); IR (KBr) 3476, 3415, 3259, 3125, 3097, 2246, 1732, 1624, 1539. ^{1}H NMR (DMSO-d_6) δ 1.35 (t, 3H, *J* 7.0, CH_3), 4.37 (q, 2H, *J* 7.0, CH_2), 7.68 (br s, 2H, NH_2), 9.10 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6) δ 14.0 (CH_3), 61.5 (CH_2), 111.5 (C-1), 111.8 (CN), 113.6 (C-5), 124.2 (C-8a), 134.4 (C-6), 150.0 (C-8), 163.2 (CO). MS (EI, *m/z*, %) 232 (M^+, 3), 105 (100). *Anal*. Calcd for $C_9H_8N_6O_2$: C, 46.55; H 3.47; N 36.19. Found: C, 46.47; H 3.13; N, 35.84.

b) A mixture of **5c** (340 mg, 1.01 mmol), acetic acid (1 mL), and ethanol (1 mL) was refluxed for 5.5 h.

Upon cooling, the separated solid was filtered off and washed with ethanol (5 x 1 mL) to give 137 mg (58%) of **6c**.

Methyl 1-Cyano-8-benzoylamino[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylate (7b):

A mixture of **4** (871 mg, 3 mmol), methanol (24 mL), and triethylamine (115 mg, 1.14 mmol) was heated under reflux for 1.5 h. Upon cooling, the separated solid was filtered off and washed with methanol (1 mL) to give 510 mg (53%) of **7b**; (form A) mp 216-218°C (methanol); IR (KBr) 3096, 2249, 1724, 1589, 1556. MS (EI, *m/z*, %) 322 (M^+, 3), 105 (100). HRMS Calcd for $C_{15}H_{10}N_6O_3$: 322.082250. Found: 322.081438. *Anal*. Calcd for $C_{15}H_{10}N_6O_3$: C, 55.90; H, 3.13; N, 26.08. Found: C, 56.22; H, 3.01; N, 26.37.

Compound (**7b**) exists in DMSO-d_6 solution as the tautomer B: ^{1}H NMR δ: 3.97 (s, 3H, Me), 7.64 (m, 3H, Ph), 8.12 (m, 2H, Ph), 9.91 (s, 1H, H-5), 12.26 (br s, 1H, NHCO). ^{13}C NMR δ 53.0 (CH_3), 111.6 (C-1), 114.2 (CN), 121.8 (C-5), 128.6 (C-2', C-3', C-5' C-6'), 128.8 (C-8a), 131.9 (C-1'), 132.4 (C-6), 133.0 (C-4'), 145.5 (C-8), 162.7 (COO), 167.6 (NHCO).

In $CDCl_3$ solution, **7b** exists as a mixture of A and B in a ratio of about 2/3: ^{1}H NMR δ 4.09 (s, 3H, Me, B), 4.11 (s, 3H, A), 7.62 (m, 3H, Ph, A and B), 8.02 (m, 2H, Ph, B), 8.47 (m, 2H, Ph, A), 8.66 (s, 1H, H-5, A), 8.90 (br s, 1H, NHCO, B), 9.37 (s, 1H, H-5, B), 14.47 (br s, 1H, H-6, A).

Ethyl 1-Cyano-8-benzoylamino[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylate (7c):

a) A mixture of **4** (1.16 g, 4 mmol), ethanol (30 mL), and triethylamine (150 mg, 1.49 mmol) was heated under reflux for 1.5 h. Upon cooling, the separated solid was filtered off and washed with ethanol (2 mL) to give 650 mg (48%) of **7c** (form A). Crystallization of **7c** gives tautomer A or tautomer B.

b) A mixture of **5c** (170 mg, 0.51 mmol), ethanol (7.5 mL), and triethylamine (48 mg, 0.474 mmol) was refluxed for 45 min. Upon cooling, the separated solid was filtered off and washed with ethanol to give 70 mg (41%) of **7c** (form A).

Tautomer A: mp 197-199°C (decomp) (EtOH); IR (KBr) 3115, 2246, 1734, 1612, 1590, 1558. MS (FAB, *m/z*, %): 337 (MH^+, 47). *Anal*. Calcd for $C_{16}H_{12}N_6O_3$: C, 57.14; H, 3.60. Found: C, 57.04; H, 3.64.

Tautomer B: mp 193-195 °C (decomp) (EtOH); IR (KBr) 3441, 3277, 3084, 2248, 1728, 1675, 1594, 1527. MS (EI, *m/z*, %): 336 (M^+, 4), 105 (100). HRMS Calcd for $C_{16}H_{12}N_6O_3$: 336.098200. Found: 336.097088. *Anal*. Calcd for $C_{16}H_{12}N_6O_3$: C, 57.14; H, 3.60; N, 24.99. Found: C, 56.98; H, 3.52; N, 25.28.

Compound (**7c**) exists in DMSO-d_6 solution as the tautomer B: ^{1}H NMR δ 1.38 (t, 3H, *J* 7.1, CH_3), 4.44 (q, 2H, *J* 7.1, CH_2), 7.64 (m, 3H, Ph), 8.12 (m, 2H, Ph), 9.91 (s, 1H, H-5), 12.24 (s, 1H, NHCO). ^{13}C NMR δ 14.0 (CH_3), 62.1 (CH_2), 111.6 (C-1), 114.1 (CN), 121.9 (C-5), 128.5 (C-2', C-3', C-5' C-6'), 128.8 (C-8a), 131.2 (C-1'), 132.6 (C-6), 133.0 (C-4'), 145.4 (C-8), 162.2 (COO), 167.6 (NHCO).

In $CDCl_3$ solution, **7c** exists as a mixture of A and B in a ratio of about 3/4: ^{1}H NMR δ 1.49 (m, 3H, CH_3, A and B), 4.56 (m, 2H, CH_2, A and B), 7.60 (m, 3H, Ph, A and B), 8.02 (m, 2H, Ph, B), 8.47 (m, 2H, Ph,

A), 8.65 (s, 1H, H-5, A), 8.89 (br s, 1H, NHCO, B), 9.37 (s, 1H, H-5, B), 14.43 (br s, 1H, H-6, A).

Ethyl 8-Benzoylamino-3-carbamoyl[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylate (10):

A mixture of **7c** (336 mg, 1 mmol) and concd HCl (4 mL) was allowed to stand at rt for 6 d. The reaction mixture was diluted with water (4 mL) and the separated solid was filtered off to give 327 mg (92%) of **10**; mp 241-243°C (EtOH); IR (KBr) 3549, 3474, 3416, 1732, 1704, 1675, 1618, 1595, 1561, 1509. ^{1}H NMR (DMSO-d_6) δ 1.38 (t, 3H, *J* 7.0, CH_3), 4.42 (q, 2H, *J* 7.0, CH_2), 7.64 (m, 3H, Ph), 8.11 (m, 2H, Ph), 8.56 (s, 1H, $CONH_2$), 8.97 (s, 1H, $CONH_2$), 9.49 (s, 1H, H-5), 13.67 (s, 1H, NHCO). ^{13}C NMR (DMSO-d_6) δ 14.1 (CH_3), 61.6 (CH_2), 118.3 (C-5), 123.3 (C-8a), 127.8 (C-2', C-6'), 128.8 (C-3', C-5'), 132.6 (C-4'), 132.8 (C-6), 133.0 (C-1), 133.9 (C-1'), 145.3 (C-8), 162.9 (COO), 163.2 ($CONH_2$), 163.8 (NHCO). MS (EI, *m/z*, %) 355 (MH^+, 2), 105 (100). HRMS Calcd for $C_{16}H_{14}N_6O_4$: 354.108800. Found: 354.107653. *Anal*. Calcd for $C_{16}H_{14}N_6O_4$: C, 54.24; H, 3.98; N, 23.72. Found: C, 53.99; H, 3.85; N, 23.90.

8-Benzoylamino-3-carbamoyl[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylic Acid (11):

A mixture of **7c** (336 mg, 1 mmol) and 2M NaOH (4 mL) was allowed to stand at rt for 10 d. The reaction mixture was diluted with water (4 mL), the separated solid was filtered off, suspended in diluted HCl (1:1)(1 mL), and allowed to stand at rt for 12 h. The separated solid was filtered off to give 185 mg (57%) of **11**; mp 290-292°C (EtOH); IR (KBr) 3412, 3313, 3252, 3105, 1706, 1673, 1619, 1512. ^{1}H NMR (DMSO-d_6) δ 7.64 (m, 3H, Ph), 8.11 (m, 2H, Ph), 8.53 (s, 1H, $CONH_2$), 8.97 (s, 1H, $CONH_2$), 9.43 (s, 1H, H-5), 13.62 (br s, 1H, COOH), 13.66 (s, 1H, NHCO). ^{13}C NMR (DMSO-d_6) δ 118.1 (C-5), 123.3 (C-8a), 127.8 (C-2', C-6'), 128.8 (C-3', C-5'), 132.6 (C-4'), 133.0 (C-1), 133.5 (C-6), 134.0 (C-1'), 145.2 (C-8), 163.2 ($CONH_2$), 163.9 (NHCO), 164.3 (COOH). MS (EI, *m/z*, %) 326 (M^+, 1), 105 (100). HRMS Calcd for $C_{14}H_{10}N_6O_4$: 326.077100. Found: 326.076353. *Anal*. Calcd for $C_{14}H_{10}N_6O_4 \cdot 0.8\ H_2O$: C, 49.36; H 3.43; N 24.67. Found: C, 49.14; H, 3.43; N, 24.82.

Ethyl 8-Amino-3-carbamoyl[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylate (12):

A mixture of **6c** (232 mg, 1 mmol) and concd HCl (4 mL) was allowed to stand at rt for 6 d. The reaction mixture was diluted with water (4 mL) and the separated solid was filtered off to give 227 mg (91%) of **12**; mp 303-305°C (EtOH/H_2O); IR (KBr) 3430, 3366, 3276, 3183, 3094, 1737, 1652, 1624, 1528. ^{1}H NMR (DMSO-d_6) δ 1.33 (t, 3H, *J* 7.1, CH_3), 4.34 (q, 2H, *J* 7.1, CH_2), 8.17 (s, 1H, $CONH_2$), 8.37 (br s, 1H, NH_2), 8.61 (s, 1H, $CONH_2$), 8.89 (s, 1H, H-5), 9.35 (br s, 1H, NH_2). ^{13}C NMR (DMSO-d_6) δ 14.1 (CH_3), 61.2 (CH_2), 112.2 (C-5), 121.6 (C-8a), 133.9 (C-1), 134.1 (C-6), 151.1 (C-8), 162.6 ($CONH_2$), 163.6 (COO). MS (EI, *m/z*, %) 250 (M^+, 33), 167 (100). HRMS Calcd for $C_9H_{10}N_6O_3$: 250.082100. Found: 250.081438. *Anal*. Calcd for $C_9H_{10}N_6O_3$: C, 43.20; H 4.03; N 33.59. Found: C, 42.91; H, 4.03; N, 33.89.

8-Amino-3-carbamoyl[1,2,3]triazolo[1,5-*a*]pyrazine-6-carboxylic Acid (13):

A mixture of **6c** (232 mg, 1 mmol) and 2M NaOH (4 mL) was allowed to stand at rt for 24 h. The reaction

mixture was diluted with water (4 mL), the separated solid was filtered off, suspended in diluted HCl (1:1)(1 mL), and allowed to stand at rt for 12 h. The separated solid was filtered off to give 160 mg (72%) of **13**; mp over 350°C (DMF/H_2O); IR (KBr) 3357, 3269, 3137, 3007, 1698, 1678, 1666, 1642. ^{1}H NMR (DMSO-d_6) δ 8.15 (s, 1H, $CONH_2$), 8.23 (br s, 1H, NH_2), 8.60 (s, 1H, $CONH_2$), 9.06 (s, 1H, H-5), 9.31 (br s, 1H, NH_2), 13.26 (br, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 112.0 (C-5), 121.5 (C-8a), 133.8 (C-1), 134.8 (C-6), 151.0 (C-8), 162.7 ($CONH_2$), 164.9 (COOH). MS (EI, *m/z*, %) 222 (M, 24), 139 (100). HRMS Calcd for $C_7H_6N_6O_3$: 222.050850. Found: 222.050138.

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