REACTIONS OF ACYLGLYCINES WITH HETEROARYLHYDRAZINES

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Abstract: Reactions of *N*-acylglycines with heteroarylhydrazines leading to acylamino substituted fused 1,2,4-triazoles and *N*-{2-[2-(heteroaryl)hydrazino]-2-oxoethyl}benzamides have been investigated.

Introduction

Aminomethyl substituted heterocyclic compounds are useful compounds in heterocyclic synthesis. Their use in the synthesis of imidazo[1,5-*a*]pyrazine,[1-3] pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine,[4] pyrrolo[1,2-*a*][1,4]benzodiazepine,[5] and 3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline,[6] pyrrole,[7] and other systems is well documented.

Recently, we reported on a new procedure for the preparation of the benzoylaminomethyl substituted fused 1,2,4-triazoles, possible precursors of the aminomethyl derivatives, based on the oxidative cyclization of *N*-(heteroarylhydrazonoethyl)benzamides.[8,9] Since these compounds might also be prepared from hippuric acid **1** and the corresponding hydrazines, as it had been done in the case of *N*-[([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)methyl]benzamide **2**,[10] we decided to reinvestigate this possibility for their preparation.

Results and Discussion

Reactions of hippuric acid **1** with heteroarylhydrazines (2-hydrazinopyridine, 3-hydrazinopyridazine hydrochloride, 3-chloro-6-hydrazinopyridazine, 2-chloro-6-hydrazinopyrazine, 6-hydrazinoimidazo[1,2-*b*]pyridazine, 6-hydrazino[1,2,4]triazolo[4,3-*b*]pyridazine, and 6-hydrazinotetrazolo[1,5-*b*]pyridazine) were carried out by two procedures.

In the procedure A, a mixture of equimolar amounts of **1** and heteroarylhydrazine was heated on an oil bath at 140-190°C under solvent-free conditions for 2-4 h. Upon cooling to room temperature the crude residue was suspended in 5% HCl and filtered. After addition of 1M NaOH to filtrate (pH=10) the separated solid was filtered off, and washed with water.

In the procedure B, a mixture of **1** (0.5 mmol) and heteroarylhydrazine (0.5 mmol) in toluene or xylene (2 ml) was heated under reflux for 8-12 h. Upon cooling to room temperature the separated solid was filtered off, washed with the same solvent and ethanol.

We found that besides 2-hydrazinopyridine, only two other hydrazines, 3-hydrazinopyridazine and 3-chloro-6-hydrazinopyridazine, gave the benzoylaminomethyl substituted fused triazoles. Isolated products **2**, **3**, and **4** were identified by comparison with authentic samples[8,9] (Scheme 1, Table 1).

Scheme 1

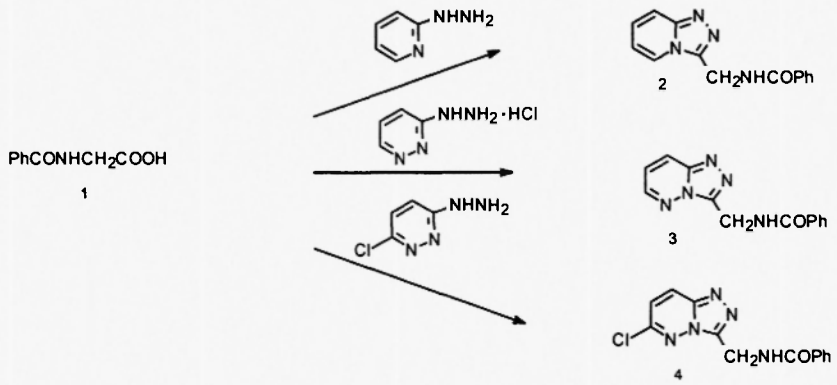


Table 1. Formation of *N*-(heteroarylmethyl)benzamides **2**-**4**.

	Procedure A			Procedure B		
Product	Temp.[°C]	Time [h]	Yield [%]	Solvent	Time [h]	Yield [%]
2	(140-150)[a]	(4)[a]	(80)[a]	toluene	12	80
3	160-170	4	37	xylene	8	62
4	140-160	2	25[b]	toluene	9	43[c]

[a] lit. 10; [b] isolated by radial chromatography (chloroform/methyl alcohol, 5:1); [c] isolated by column chromatography (chloroform/methyl alcohol, 5:1).

Reactions with other heteroarylhydrazines under the same reaction conditions gave *N*-acylated derivatives **5**-**8** (Scheme 2, Table 2).

Scheme 2

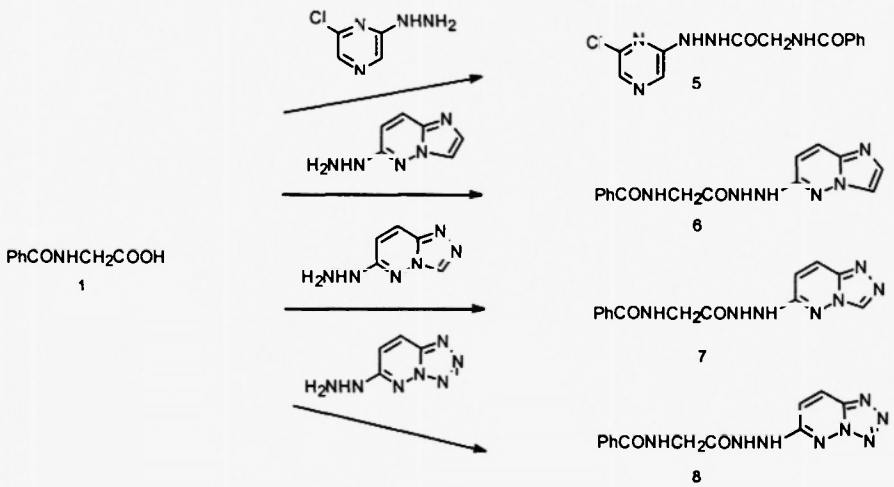


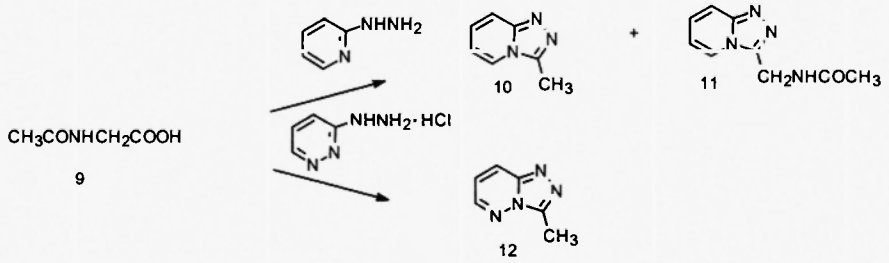
Table 2. Formation of *N*-{2-[2-(heteroaryl)hydrazino]-2-oxoethyl}benzamides **5-8.**

	Procedure A			Procedure B		
Product	Temp.[°C]	Time [h]	Yield [%]	Solvent	Time [h]	Yield [%]
5[a]	140	4	69	xylene	10.5	82
6[b]	150-160	4	39	-	-	-
7[c]	190	4	76	xylene	9	86
8[d]	190	4	24	xylene	10.5	62

[a] crystallization from ethyl alcohol; [b] radial chromatography (chloroform/methyl alcohol, 5:1); [c] crystallization from isopropyl alcohol/methyl alcohol; d) crystallization from methyl alcohol

In two cases *N*-acetylglycine **9** was used instead of hippuric acid. Heating of **9** with 2-hydrazinopyridine at 140-150°C under solvent-free conditions for 5 h afforded methyl and acetylaminomethyl substituted [1,2,4]triazolo[4,3-*a*]pyridines, compounds **10** and **11**, isolated by extraction with chloroform and radial chromatography (chloroform) in 36 and 15% yield, respectively. Reaction of 9 with 3-hydrazinopyridazine hydrochloride under the same reaction conditions gave 3-methyl[1,2,4]triazolo[4,3-*b*]pyridazine **12**, isolated by extraction with chloroform and radial chromatography (chloroform/methyl alcohol, 10:1) in 11% yield (Scheme 3). Products **10**[11] and **12**[12] were identified by comparison with authentic samples prepared by known methods.

Scheme 3



Experimental

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded on a Varian EM 360L (60 MHz for ^{1}H) or a Bruker AVANCE DPX-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) in DMSO-d_6 with TMS as an internal standard. Elemental analyses for C, H, N were obtained on a Perkin-Elmer CHN Analyzer 2400. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. 3-Hydrazinopyridazine hydrochloride,[13] 3-chloro-6-hydrazinopyridazine,[14] 2-chloro-6-hydrazinopyrazine,[15] 6-hydrazinoimidazo[1,2-*b*]-pyridazine,[16] 6-hydrazino[1,2,4]triazolo[4,3-*b*]pyridazine,[17] and 6-hydrazinotetrazolo[1,5-*b*]pyridazine[17] were prepared as described in the literature. All other compounds were used without purification as obtained from commercial sources. ***N*-{2-[2-(6-Chloropyrazin-2-yl)hydrazino]-2-oxoethyl}benzamide 5.** m.p. 200-202°C; MS (EI, *m/z*): 305 (M^+); ^{1}H NMR δ 4.00 (d, 2H, *J*=5.8Hz, CH_2), 7.51 (m, 3H, Ph), 7.91 (m, 2H, Ph), 7.96 (s, 1H, H-3 or H-5), 8.03 (s, 1H, H-5 or H-3), 8.90 (t, 1H, *J*=5.8Hz, CH_2NH), 9.29 (s, 1H, NH), 10.13 (s, 1H, NH); ^{13}C NMR δ 127.3, 128.2, 128.6, 131.3, 131.5, 133.8, 145.5, 155.2, 166.7, 169.0; *Anal.* Calcd. for $C_{13}H_{12}ClN_5O_2$: C, 51.07; H, 3.96; N, 22.91. Found: C, 50.98; H, 3.66; N, 22.62.

***N*-{2-[2-(Imidazo[1,2-*b*]pyridazin-6-yl)hydrazino]-2-oxoethyl}benzamide 6**. m.p. 232-234°C decomp.; MS (EI, *m/z*): 310 (M^+); ^{1}H NMR δ 4.06 (d, 2H, *J*=5.5Hz, CH_2), 6.83 (d, 1H, *J*=9.5Hz, H-7), 7.55 (m, 4H, three H of Ph, H-2 or H-3), 7.95 (m, 4H, two H of Ph, H-3 or H-2, H-8), 8.93 (broad, 2H, two NH), 10.13 (broad, 1H, NH); *Anal.* Calcd. for $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08. Found: C, 57.71; H, 4.28; N, 26.98.

***N*-{2-Oxo-2-[2-([1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)hydrazino]ethyl}benzamide 7**. m.p. 281-284°C; MS (EI, *m/z*): 311 (M^+); ^{1}H NMR δ 4.03 (d, 2H, *J*=5.5Hz, CH_2), 6.92 (d, 1H, *J*=9.5Hz, H-7), 7.52 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.10 (d, 1H, *J*=9.5Hz, H-8), 8.86 (t, 1H, *J*=5.5Hz, CH_2NH), 9.18 (s, 1H, H-3), 9.37 (broad, 1H, NH), 10.13 (broad, 1H, NH); *Anal.* Calcd. for $C_{14}H_{13}N_7O_2$: C, 54.02; H, 4.21; N, 31.50. Found: C, 53.73; H, 3.99; N, 31.67.

***N*-{2-Oxo-2-[2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hydrazino]ethyl}benzamide 8**. m.p. 231-234°C; MS (EI, *m/z*): 312 (M^+); ^{1}H NMR δ 4.10 (d, 2H, *J*=5.5Hz, CH_2), 7.35 (d, 1H, *J*=9.5Hz, H-7), 7.57 (m, 3H, Ph), 7.99 (m, 2H, Ph), 8.51 (d, 1H, *J*=9.5Hz, H-8), 8.98 (t, 1H, *J*=5.5Hz, CH_2NH), 10.18 (broad, 2H, two NH); *Anal.* Calcd. for $C_{13}H_{12}N_8O_2$: C, 50.00; H, 3.87; N, 35.88. Found: C, 49.60; H, 3.70; N, 35.75.

***N*-([1,2,4]Triazolo[4,3-*a*]pyridin-3-ylmethyl)acetamide 11.** m.p. 175-178°C; MS (EI, *m/z*): 190 (M^+); ^{1}H NMR δ 1.87 (s, 3H, CH_3), 4.28 (d, 2H, *J*=5.5Hz, CH_2), 7.02 (m, 1H, H-6), 7.39 (m, 1H, H-7), 7.80 (m, 1H, H-8), 8.48 (m, 1H, H-5), 8.65 (bt, 1H, *J*=5.5Hz, CH_2NH); *Anal.* Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.57; H, 5.10; N, 29.50.

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