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α-Azido Acids in Heterocyclic Synthesis

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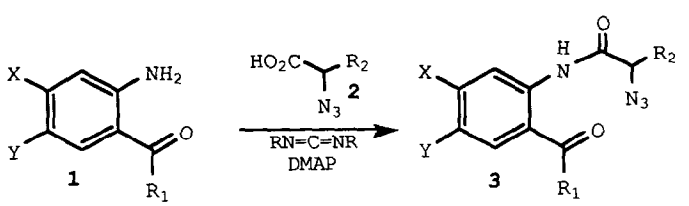
Abstract: 2-Aminobenzophenones and acetophenones were N-acylated with α-azido carboxylic acids to give the corresponding anilides. Reductive cyclization provided 3-substituted-2H-1,4-benzodiazepin-2-ones in good (46-99%) yields.

The 2H-1,4-benzodiazepin-2-one ring system has long been the object of synthetic efforts[1] due to the extraordinary CNS properties of these compounds. Recently, compounds with alkyl substitution at C-3 have been shown[2] to be potent CCK antagonists.

Construction of these C-3 substituted compounds frequently involves[1] condensation of a 2-aminobenzophenone with an appropriately protected α-amino acid. Liberation of the amino group then allows for cyclization to the desired ring system. This sequence is clearly limited by the availability of natural or synthetically accessible unnatural α-amino acids. Alternatively, one could envision a scenario analogous to the C-3 unsubstituted case[1] whereby the amino benzophenone is acylated with a 2-halo-acetyl halide. Displacement with ammonia forms the intermediate α-amino amide which readily cyclizes to form the benzodiazepine ring. One would certainly expect problems with the displacement as the α-halo site becomes more hindered. An ideal solution would be N-acylation of the amino benzophenone with a carboxylic acid functionalized at the α position with a substituent which could liberate the requisite amino group. This array of functionality might be found in a series of α-azido-α-alkyl carboxylic acids.[3] We have found these compounds are easily prepared from readily available α-bromo acids by displacement with NaN_3 in DMF at 60°C for 4 h.[3,4] They readily couple with 2-amino benzophenones under standard carbodiimide conditions to form the amido azides in good yield[4] (see Table 1).



The cyclization via α-azido amides to the C-3 unsubstituted benzodiazepine system has been explored by others. Most commonly, the azides are treated with triphenylphosphine to form an iminophosphorane which frequently requires elevated temperatures for cyclization.[1a,5] When we attempted this reductive cyclization on a variety of α-alkyl-α-azido amides **3** we could find no trace of the corresponding 7-membered ring Indeed, only with use of the sterically less demanding tributylphosphine were we able to recover a rather disappointing 9% yield of benzodiazepine **4f** accompanied by extensive decomposition

While other methods of reduction of the azide to the corresponding amine followed by *in situ* cyclization to the heterocyclic system have been reported (i.e , hydrazine, H_2 or $SnCl_2$)[1a,6], we were reluctant to use these reagents because of the lack of compatibility with some functionalized sidechains. Alternatively, we chose Knowles' method[7] utilizing propanedithiol and triethylamine in methanol, which gives the benzodiazepines in good yields after silica gel chromatography[4] (Table 1)

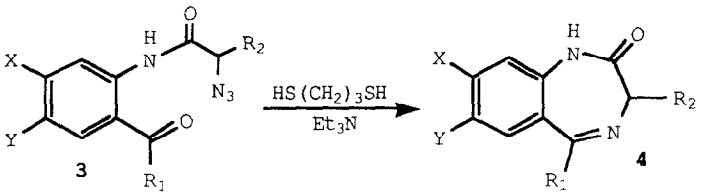


Table 1. Azidoamide and Benzodiazepine Formation

Entry	X	Y	R_1	R_2	Yield **3**	Yield **4**	mp **4** (°C)
a	H	Cl	Ph	$(CH_2)_4CH_3$	70	71	151-152
b	H	Cl	Ph	Ph	60	46[a]	278-279[b]
c	H	Cl	Ph	$(CH_2)_{15}CH_3$	62	96	oil
d	H	Cl	Ph	$(CH_2)_3Ph$	47	76	foam
e	MeO	MeO	Me	$(CH_2)_4CH_3$	60	99	175-176
f	MeO	MeO	Me	Ph	66	79	254-255
g	MeO	MeO	Me	$(CH_2)_{15}CH_3$	68	69	116-117
h	MeO	MeO	Me	$(CH_2)_3Ph$	58	84	164-165
i	MeO	MeO	cC_6H_{11}	$(CH_2)_4CH_3$	88	80	142-143
j	MeO	MeO	Ph	$(CH_2)_3Ph$	82	58	178-179

[a] compound **4b** partially hydrates to the corresponding amino-ketone upon silica gel chromatography. [b] Two melting points have been reported for this compound: 269-270°C, ref 1b; 279°C, ref 9.

In summary, a new method of forming 3-substituted-2H-1,4-benzodiazepin-2-one is described. With this procedure, atoms 2-4 and the C-3 substituent of this ring system come from readily available α-azidoacids. We are investigating the application of this method to other ring systems.[8]

Experimental: 2-Azido-N-(2-benzoyl-4-chlorophenyl)-heptanamide (3a). To a solution of 2-amino-5-chlorobenzophenone (1.02 g, 4.40 mmol), 2-azidoheptanoic acid (685 mg, 4.00 mmol) and CH_2Cl_2 (10 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (841 mg, 4.40 mmol). After stirring at room temperature overnight, the reaction mixture was concentrated and then diluted with 1N HCl (25 mL) and extracted with ethyl acetate (2 X 25 mL). The combined organic layers were washed with 1N HCl (25 mL), water (25 mL), aqueous $NaHCO_3$ (2 X 25 mL), brine (25 mL) and then dried (K_2CO_3) and concentrated. Chromatography on silica gel utilizing 10:1 hexanes-EtOAc gave the amide **3a** (1.06 g, 70%) as a colorless oil.

7-Chloro-3-pentyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (4a). A solution of azido amide **3a** (830 mg, 2.16 mmol), triethylamine (1.12 mL, 8.64 mmol), propanedithiol (0.87 mL, 8.64 mmol) and MeOH (10 mL) was heated to reflux for 16 h. The reaction mixture was concentrated and chromatographed on silica gel utilizing 3:1 hexanes-EtOAc to give benzodiazepine **4a** (523 mg, 71%) as a white solid.

References:

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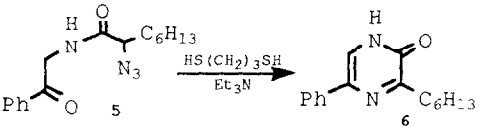
8 To examine the versatility of this method for the construction of other heterocyclic systems, we coupled 2-azido heptanoic acid with 2-aminoacetophenone under the standard conditions to give amide **5**. Reductive cyclization under the standard conditions then gave a disappointing 6% yield of 3-hexyl-5-phenyl-1,2-dihydropyrazin-2-one, **6**.



The *in situ* oxidation of a tetrahydro to a dihydropyrazin-2-one has been observed by others.[5c]

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