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(3-Pyridazinamin-3-yl) α-Aminoacids : A Facilitated Method of Preparation of Phenylalanine and Proline Representatives

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Abstract: The presence of an easy removable cyano group in position 4 of 3-chloropyridazines increased significantly their reactivity towards nucleophiles including α-aminoacids.
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There is an increasing interest in the chemistry of peptidomimetics[1]. In this view substituted N-heteroaryl α-amino acid esters **1** are valuable intermediates for the preparation of short peptidic fragment derivatives **2**. When linked to the C-terminal part of peptides, heterocyclic amidines served as efficient prodrugs.[2] In addition, we hypothesized that they may mimic efficiently a peptidic bond in a typical environment (R_1, R_2, R_3) of the N-terminal part of a given small peptide (Figure 1). We selected here 3-aminopyridazines for that purpose (compounds **9**).

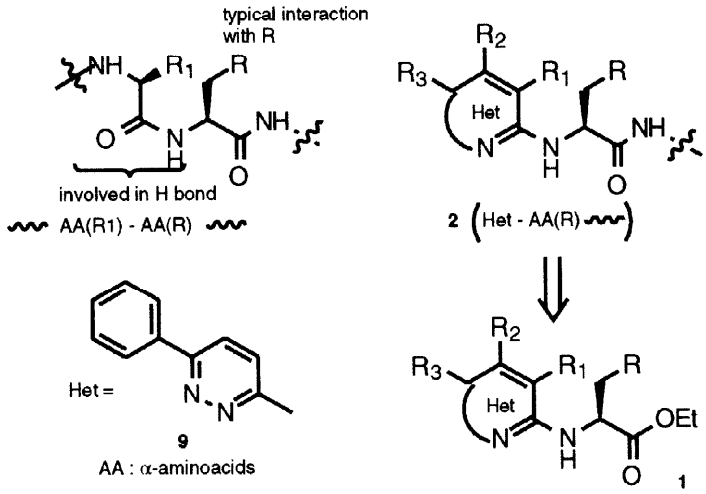

Figure 1. Mimetism of a peptidic bond by an heterocyclic amidine in a given peptide

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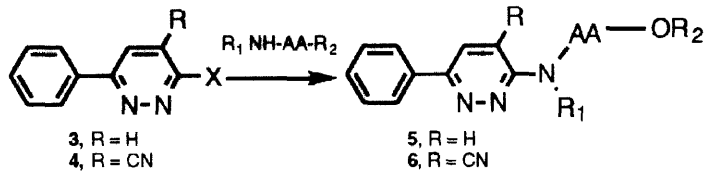
They are classically obtained from the corresponding 3-chloropyridazines (**3**, X = Cl), which are known to be poorly reactive, particularly towards amines.[3] The rate-limiting step involves addition of the amine onto the carbon C-3 of the pyridazine leading to a transient increase in charge density of N(2) nitrogen. This is highly disfavored by the presence in the pyridazine ring of a second vicinal sp2 nitrogen (N1). Thus drastic experimental conditions including high temperature reactions, excess of amine and acid catalysis are generally needed.[4] When reacted with phenylalanine ethyl ester, whatever the experimental conditions tested, the awaited reaction did not occur, probably as a result of the complete transformation of the α-aminoacid into the corresponding piperazinedione. During earlier experiments dealing with the preparation of 3-alkylaminopyridazines as antidepressants[5], we observed that the presence of a cyano group in position 4 dramatically increased the reactivity of 3-chloropyridazines **4** towards amines.

We present here a novel method of preparation of substituted N-(3-pyridazinyl)-α-amino esters **9** via a 4-cyanopyridazine intermediate. We selected for this study two aminoacids (AA), proline and phenylalanine as representatives of secondary and primary α-aminoacids, respectively. Experiments were conducted with 3-chloropyridazines **3** or their 4-cyano derivatives **4** in solvent or without solvent, at different temperatures and reaction times, in absence or in presence of acid catalysis. When stoechiometric amounts of reactants were used, tetramethylethylenediamine (TMEDA) was added in the reaction mixture as proton scavenger. Results are reported in Table 1.

Concerning the reactivity of the non-activated 3-chloropyridazines **3** (entries 1-4), it is interesting to note that i) in contrast with the absence of reaction observed with phenylalanine (entries 3,4), a reaction occurred with proline (entries 1,2). It results from a greater nucleophilicity towards 3-chloropyridazines of secondary amines such as pyrrolidine derivatives (Pro), when compared to primary amines (Phe). In addition cyclocondensation of proline leading to the corresponding constrained piperazine dione is less favourable, ii) the same reaction with pyridazine-3-O-triflate[6] afforded the desired compound in low yield (entry 2).

When using the corresponding 4-cyano 3-chloropyridazine **4**, we observed a significant increase in reactivity with proline (compare yields and reaction times entries 1 and 5). This is particularly the case with phenylalanine. The t-butyl ester was chosen in order to restrict cyclodimerization. In this case without solvent but with acid catalysis the corresponding derivative **6c** was obtained in good yield (entries 8 and 9, Table 1).



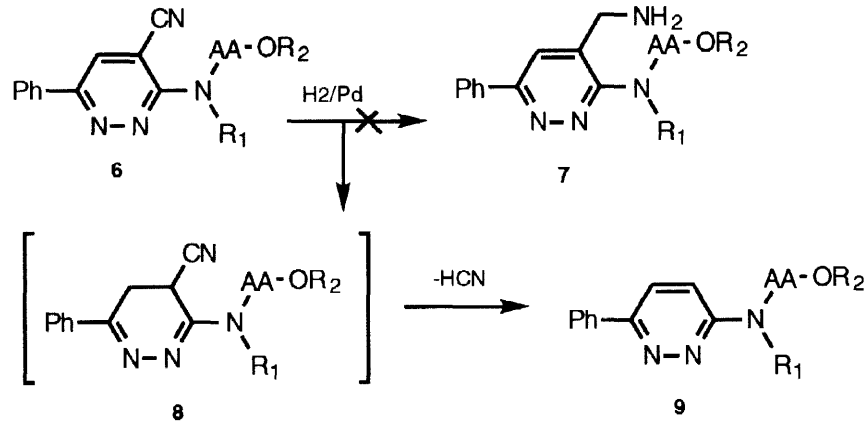
3, R = H
4, R = CN

5, R = H
6, R = CN

Entry	Starting pyridazine R	X	N(R_1)AA	R_2	Experimental Conditions	5 or 6	Yield %
	N(R_1)AA : Phe (R_1 = H), or Pro ($R_1 \neq$ H)						
1	H	Cl	Pro	Me	MeOH, TMEDA, ↑↓ 40 h	5a	60
2	H	OTf	Pro	Me	MeOH, TMEDA, ↑↓ 40 h	5a	20
3	H	Cl	Phe	Et		5b	no reaction
4	H	Cl	Phe	t-Bu	NH_4Cl 100°C, 24 h	5c	no reaction
5	CN	Cl	Pro	Me	MeOH/TMEDA ↑↓ 4 h	6a	77
6	CN	Cl	Phe	Et	EtOH/TMEDA ↑↓ 24 h	6b	no reaction
7	CN	Cl	Phe	t-Bu	EtOH/TMEDA ↑↓ 24 h	6c	no reaction
8	CN	Cl	Phe	t-Bu	NH_4Cl, 100°C, 10 h	6c	68
9	CN	Cl	Phe	t-Bu	SiO_2, 130°C, 4 h	6c	75

Table 1

The different 4-cyanopyridazines **6** were submitted to catalytic hydrogenation using palladium on charcoal at 50 psi. However, instead of the awaited aminomethyl derivatives **7**[7], the 4-unsubstituted pyridazines **9** were recovered nearly quantitatively[8]. This compound may result from a first step hydrogenation of the electron-poor pyridazine double bond of **6**. The resulting instable 4-cyano dihydropyridazines **8** might easily aromatize after HCN elimination (scheme 1).



Scheme 1

As shown by ^{1}H NMR analysis using the Mosher salt, the typical compound **9a** (AA = Phe, R_1 = H, R_2 = t-Bu) was found optically pure (ee > 97 %).

A preliminary work described recently the preparation of phenylalanine deriving from 2-aminopyridines and 2-aminothiazoles by means of a Mitsunobu reaction[9]. However, this reaction cannot be

systematically extended to other heterocycles, as the pK_{HA} of the NH acid reactant (N-acyl heterocyclic amidine) has to be appropriate.

As no general method of preparation of optically-pure α-aminoacid deriving pyridazines is available[10], the method we have presented here is valuable. Particularly the activation step involving the presence of a cyano group in position 4 is efficient, as this group can be easily removed by classical catalytic hydrogenation.

References and Notes

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8. 6a: Yield, 70%, mp 94°C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.02-2.30 (4H, m, $-CH_2CH_2-$); 3.69-3.64 (5H, NCH_2 + OCH_3); 4.78 (1H, dd, J = 2.6 Hz, >N-CH<); 6.69 (1H, B from AB, JAB = 9.3 Hz, H_4); 7.32-7.45 (3H, m, ArH); 7.58 (1H, A from AB, J_{AB} = 9.3 Hz, H5); 7.90-7.96 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.66; 30.13; 46.96; 52.04; 59.20; 112.45; 125.02; 125.69; 128.26; 128.52; 136.79; 150.39; 155.94; 173.54; Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83; Found: C, 67.92; H, 6.15; N, 14.62; MS (FAB): 284.2 $(MH)^+$; $[\alpha]_D^{23°C}$ = -10,2 (c= 0,59; $CHCl_3$).

6c: Yield, 72%; m.p. 183°C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (9H, s, $C(CH_3)_3$); 3.22 (1H, A from ABX, J_{AB} = 13.8 Hz, J_{AX} = 5.6 Hz, CH_AH_B); 3.36 (1H, B from ABX, J_{AB} = 13.8 Hz, J_{BX} = 5.9 Hz, CH_AH_B); 5.15 (1H, X from ABX, J_{AX} + J_{BX} = 11.5 Hz, -CH-); 5.29 (1H, s broad, NH); 6.68 (1H, B from AB, J_{AB} = 9.3 Hz, H_4); 7.18-7.29 (5H, m, ArH); 7.30-7.49 (3H, m, ArH); 7.54 (1H, A from AB, J_{AB} = 9.3 Hz, H_5); 7.97-7.98 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.79; 29.51; 37.49; 54.98; 115.22; 125.33; 125.81; 126.62; 128.12; 128.59; 129.45; 136.39; 151.79; 156.32; 170.58; Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19; Found: C, 73.62; H, 6.50; N, 11.25; MS (FAB): 376.2 $(MH)^+$; $[\alpha]_D^{23°C}$ = +118.6 (c = 0,61; $CHCl_3$).
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