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COMMUNICATION

A cascade reaction of azolopyrimidines. Synthesis of unusual indole and azaindole derivatives†

María Morón,[a] Carolina Burgos,*[a] Julio Alvarez-Builla,[a] Antonio Salgado,[b] Marta E. G. Mosquera[c] and Juan J. Vaquero*[a]

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The reaction of bromo substituted pyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]-pyrimidine and pyrimido[1,6-*a*]indole methyl carboxylates with primary amines is described. The expected amide formation occurs but it is followed by an unexpected cascade process involving attack of the amine to the pyrimidine ring, opening of the pyrimidine ring, loss of the bromine substituent and competitive cyclizations to afford unusual imidazolidene substituted indoles and azaindoles.

The pyrrolo[1,2-*c*]pyrimidine system is a most interesting indolizine analogue having an extra nitrogen heteroatom.[1] This heterocyclic system, although rare in Nature, is found in the marine alkaloid hinckdentine (**1**)[2] and in the variolins, a family of alkaloids isolated from the Antarctic sponge *Kirkpatrickia variolosa*, which have antitumor and antiviral activity (Fig. 1).[3] These alkaloids, in particular variolin B (**2**), have attracted the attention of several groups that have been involved in their total syntheses.[4]

In our works focused on the design and synthesis of new calpain inhibitors, we envisaged the heterocyclic core of variolins, the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system and other related azolopyrimidines as interesting new heterocyclic templates in the development of new calpain inhibitors.[5]

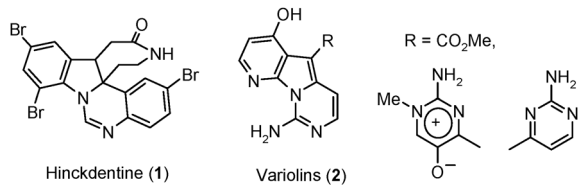
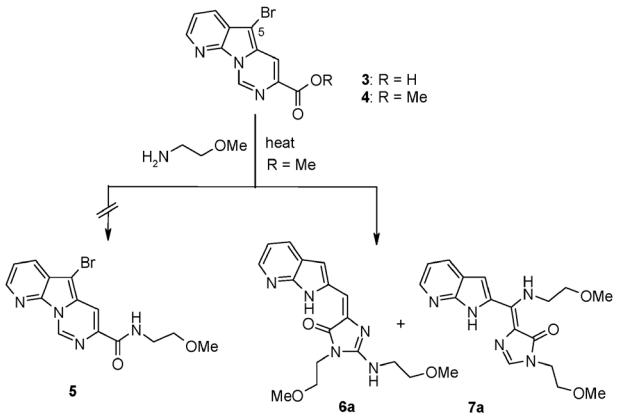


Fig. 1 Structure of alkaloids with a pyrrolo[1,2-*a*]pyrimidine core.



Scheme 1 Synthesis of the azaindole derivatives **6a**/**7a**.

Our strategy for their synthesis involved the reaction of the acid **3** or ester **4**,[6] with different amino acids or amines in order to form the corresponding peptides or amides, respectively.

In the course of these works, we attempted the reaction of **4** with 2-methoxyethylamine. Yet this reaction did not afford the expected amide derivative **5**, but the unexpected azaindole derivatives **6a** and **7a**, as shown in Scheme 1. The two products were separated by chromatography and their structural determination was achieved following their analytical and spectroscopic data and, for **7a**, unequivocally established by X-ray crystal analysis, as shown in Fig. 2 (see ESI†).

Two significant structural features of **6a** and **7a** became evident. First, the presence of two moieties clearly associated with the amine used in the reaction, and second the removal of the bromo substituent from the original C-5 position in **4**.

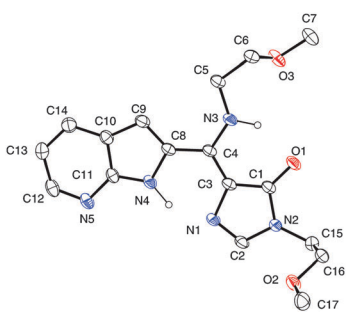


Fig. 2 X-ray crystal structure of **7a**.

[a] *Departamento de Química Orgánica, Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain. E-mail: juanjose.vaquero@uah.es; Fax: +34-91-8854686; Tel: +34-91-885476*
[b] *Department of Medicinal Chemistry, Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández Almagro 3, E-28029-Madrid, Spain*
[c] *Departamento de Química Inorgánica Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain*

† Electronic supplementary information (ESI) available: Experimental details and characterization of all new compounds. CCDC 884402 (**7a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc34539k

Table 1 Reaction of **4a** with 2-methoxyethylamine

Entry	Amine (equiv.)	Conditions	**6a**[a] (%)	**7a**[a] (%)
1	Solvent	100 °C, 1 h	58	36
2	Solvent	100 °C, 5 h	43	36
3	Solvent	100 °C, 24 h	9	31
4	20	Toluene, 100 °C, 2 h	15	3
5	20	DMF, 100 °C, 2 h	50	16
6	20	*n*-PrOH, 100 °C, 2 h	28	8
7	20	DMF, 100 °C, 7 h	36	15
8	20	DMF, MW, 100 °C, 10 min	24	26
9	20	DMF, MW, 150 °C, 10 min	52	20
10	20	DMF, MW, 50 °C, 10 min	18	24

[a] By HPLC.

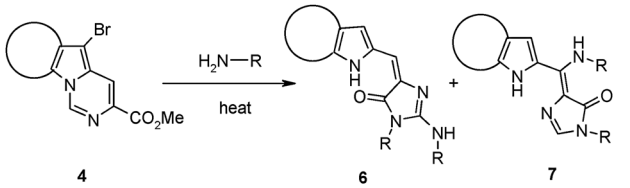
A study of the reaction conditions is shown in Table 1. In all cases **6a** and **7a** were obtained, with **6a** being the major product under most of the conditions tested. The better yields were obtained when the amine was used as solvent (Table 1, entries 1 and 2). Longer reaction times caused extensive decomposition of both reaction products (entry 3). Other experiments using an excess of the amine in different solvents afforded lower yields of **6a** and **7a** (entries 4–7) and further experiments under microwave irradiation in DMF (entries 8–10) also gave lower yields with significant product decomposition (entries 8–10).

To illustrate the versatility and potential synthetic value of this reaction for the preparation of these unusual azole derivatives, we examined the reaction with various representative primary amines and we tested the reaction with different azolopyrimidine substrates using the experimental conditions employed in entry 1 (Table 1). As shown in Table 2, the amine played a significant role in the composition of the mixture **6a–d**/**7a–d** (Table 2, entries 1–4). When the substrate was methyl 5-bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine-7-carboxylate (**4a**), reaction with either 2-methoxyethylamine or isopropylamine produced mixtures of **6a,b**/**7a,b**, being **6a** the major product in the first case (entry 1), while the latter amine gave **7b** as the major component (entry 2). Even more significant was the behavior of benzylamine and cyclohexylamine which, respectively, led to the isolation of **7c** and **7d** without the corresponding **6c** and **6d** derivatives being detected in the reaction mixtures (entries 3 and 4). In the case of methyl 5-bromopyrimido-[1,6-*a*]indole-3-carboxylate (**4b**), all the tested amines afforded mixtures of **6e–i**/**7e–i** (entries 5–9), except for the case of aniline, with which no product could be detected after heating for 24 h (entry 10).

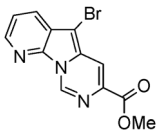
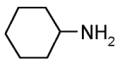
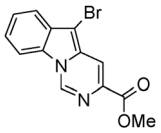
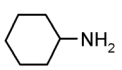
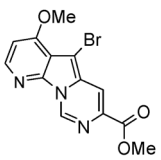
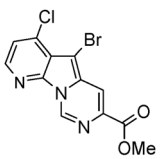
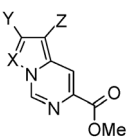
Two 4-substituted azaindoles (**4c** and **4d**) were also reacted with 2-methoxyethylamine with very different results for each substrate. Thus, **4c**, bearing a methoxy group at C-4, produced a 97% yield mixture of both imidazolones **6k**/**7k** (entry 11), whereas **4d**, the substrate having a chloro substituent at C-4, produced the only isolated product **7l** in a moderate yield (entry 12). It is noteworthy that neither a pyrrolopyrimidine (**4e**) nor a pyrazolopyrimidine (**4f**) underwent the pyrimidine ring-opening reaction described for **4a–d**, with the corresponding amides being isolated in 63% and 53% yield, respectively.

In order to know the role of the bromo substituent at C-5 in the ring opening reaction of the pyridopyrrolopyrimidine and pyrimidoindole systems, methyl pyrimido[1,6-*a*]indole-3-carboxylate (**4g**) was prepared and subjected to the same reaction

Table 2 Synthesis of azaindole and indole derivatives **6** and **7**



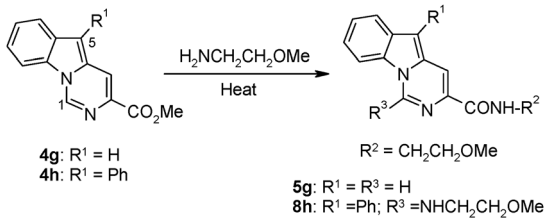
4 **6** **7**

Entry	Substrate (**4**)	Amine	Yield **6**/**7**[a] (%)
1		$MeOCH_2CH_2NH_2$	57/34 (**6a**/**7a**)
2		$(CH_3)_2CHNH_2$	19/49 (**6b**/**7b**)
3		$PhCH_2NH_2$	—/42 (**6c**/**7c**)
4			—/67 (**6d**/**7d**)
	4a		
5		$MeOCH_2CH_2NH_2$	45/41 (**6e**/**7e**)
6		$CH_3(CH_2)_3NH_2$	22/52 (**6f**/**7f**)
7		$(CH_3)_2CHNH_2$	24/17 (**6g**/**7g**)
8		$PhCH_2NH_2$	34/42 (**6h**/**7h**)
9			33/39 (**6i**/**7i**)
	4b		
10		$PhNH_2$	—/—[b]
11		$MeOCH_2CH_2NH_2$	27/70 (**6k**/**7k**)
	4c		
12		$MeOCH_2CH_2NH_2$	—/41 (**6l**/**7l**)
	4d		
13		$MeOCH_2CH_2NH_2$	—/—[b]
	4e:X = CH, Y=Z=H **4f**: X = N, Y= Me, Z= Br		

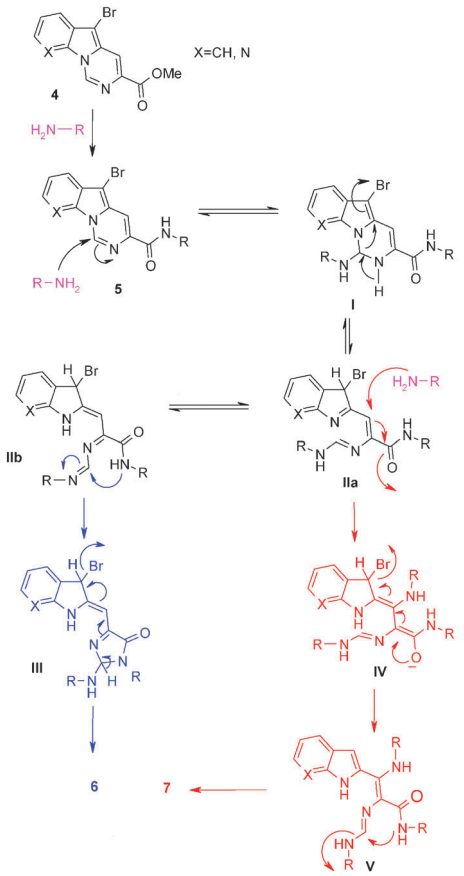
[a] Isolated yields. [b] The corresponding amide was obtained.

with 2-methoxyethylamine as with **4a–f**. Our results showed that the amide **5g** was the only formed product along with some starting material which was not consumed after refluxing for 24 h (Scheme 2).

In the light of these results, a plausible mechanistic hypothesis would involve a cascade process starting with the initial formation of the amide **5**, which would further react with a second equivalent of the amine to cause the ring-opening of the pyrimidine ring *via* intermediate **I**. Formation of **6** and **7** can be rationalized from the formamidine-type intermediates **IIa** and **IIb** throughout a 5-*exo*-trig cyclization for **6**[7] and an intermolecular Michael



Scheme 2 Reaction of pyrimidoindoles **4g** and **4h** with 2-metoxyethylamine.



Scheme 3 Tentative mechanism for the formation of **6–7**.

reaction involving a third amine equivalent followed by an intramolecular cyclization for **7** (Scheme 3).

Additional support for this mechanism was provided by attempted reaction of methyl-5-phenylpyrimido[1,6-*a*]indole-3-carboxylate (**4h**) with 2-methoxyethylamine that allowed the isolation of the corresponding amide derivative **8h**, (Scheme 2), this latter being produced by nucleophilic attack of the amine at the C-1 position of the pyrimidoindole ring and loss of hydrogen.[8]

In summary, we have shown that bromo substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine and pyrimido[1,6-*a*]-indole methyl carboxylates react with a variety of primary amines leading to novel and unusual substituted indoles or azaindoles. This was rationalized with a cascade process consisting of pyrimidine ring-opening and imidazolone ring-forming reactions, and involving either two or three amine equivalents. Ongoing studies have shown that some derivatives **7** possess a very high calpain inhibitory activity, but derivatives **6** are inactive. Moreover, compounds **6** are structurally related to green fluorescent protein chromophores,[9] and are highly fluorescent but the presence of the amine moiety makes compounds of type **7** less fluorescent.

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Notes and references

1 J. J. Vaquero and J. Alvarez-Builla, Heterocycles Containing a Ring-Junction Nitrogen, in *Modern Heterocyclic Chemistry*, ed. J. Alvarez-Builla, J. J. Vaquero and J. Barluenga, Wiley-VCH, Weinheim, 2011, vol. 4, ch. 22, pp 1989–2070.

2 (*a*) K. Higuchi, Y. Sato, M. Tsuchimochi, K. Sugiura, M. Hatori and T. Kawasaki, *Org. Lett.*, 2009, **11**, 197; (*b*) A. J. Blackman, T. W. Hambley, K. Picker, W. C. Taylor and N. Thirasasana, *Tetrahedron Lett.*, 1987, **28**, 5561.

3 (*a*) N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin and H. Hope, *Tetrahedron*, 1994, **50**, 3987; (*b*) G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro and G. B. Jameson, *Tetrahedron*, 1994, **50**, 3993.

4 (*a*) A. Baeza, J. Mendiola, C. Burgos, J. Alvarez-Builla and J. J. Vaquero, *Eur. J. Org. Chem.*, 2010, 5607; (*b*) S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.*, 2009, **109**, 3080.

5 (*a*) I. O. Donkor, *Expert Opin. Ther. Pat.*, 2011, **21**, 601; (*b*) M. Pietsch, K. C. H. Chua and A. D. Abell, *Curr. Top. Med. Chem.*, 2010, **10**, 270; (*c*) M. E. Saez, R. Ramirez-Lorca, F. J. Moron and A. Ruiz, *Drug Discovery Today*, 2006, **11**, 917; (*d*) A. T. Neffe and A. D. Abell, *Curr. Opin. Drug Discovery Dev.*, 2005, **8**, 684.

6 (*a*) J. Mendiola, A. Baeza, J. Alvarez-Builla and J. J. Vaquero, *J. Org. Chem.*, 2004, **69**, 4974; (*b*) J. Mendiola, J. M. Minguez, J. Alvarez-Builla and J. J. Vaquero, *Org. Lett.*, 2000, **2**, 3253.

7 Although cyclization of intermediates **IIb** could give compounds **6** as *Z*–*E* mixtures, NMR studies (see ESI†) showed that the *E* isomer was exclusively formed in every case. For instance, with compound **6e**, irradiation at the C*H*$_2$CH$_2$OMe residue attached to imidazolone's N-3 (3.78 ppm) resulted in nOe interaction with indole's H-3 (7.75 ppm), which was only compatible with the *E* configuration of its exocyclic double bond.

8 This reaction gave complex reaction mixtures from which the amide, **8h** and a small amount of an unidentified product were isolated.

9 (*a*) S. J. Remington, *Protein Sci.*, 2011, **20**, 1509; (*b*) T. D. Craggs, *Chem. Soc. Rev.*, 2009, **38**, 2865.