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Reaction of 2-Bromomethylazoles and TosMIC: A Domino Process to Azolopyrimidines. Synthesis of Core Tricycle of the Variolins Alkaloids

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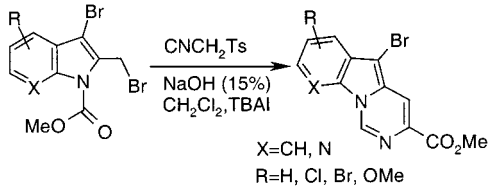
ABSTRACT



A new reaction of N-protected 2-bromomethylazoles and tosylmethyl isocyanide (TosMIC) leading to the preparation of azolopyrimidines is described. This domino sequence was used to synthesize the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core of alkaloids variolins from 4-methoxy-2-methylpyrrolo[2,3-*b*]pyrimidine in two steps.

In 1994, the structure of the variolins, a family of alkaloids isolated from the sponge *Kirtpatrickia varialosa* Kirkpatrick (Scheme 1), was published.[1,2] In addition to being one of the rare examples of natural products containing the pyrrolo-[1,2-*c*]pyrimidine system (the other one example is the alkaloid hinckdentine[3] isolated from the bryozoan *Hinck-sinoflustra denticulata*[4]), it was claimed that variolins have antiviral and antiproliferative activity against P388 leukemia cells.[2]

A total synthesis of these alkaloids has not yet been published;[5] thus we devised a strategy for their synthesis that is in part based on our previous reports concerning to a new synthesis of the pyrrolo[1,2-*c*]pyrimidine nucleus (**9**),[6,7] a system incorporated in these alkaloids. The method rests in an efficient condensation of 2-pyrrole carbaldehydes **7** with tosylmethyl isocyanide (TosMIC) followed by reductive desulfonilation (Scheme 2).

Our synthetic strategy to synthesize variolins is shown in antithetic format in Scheme 1 and is centered on the construction of the key tricyclic precursor **5**. We now report a study in which the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core of variolins and related fused systems are prepared in a domino reaction from 2-bromomethylazoles **4** and TosMIC.

Although the cyclocondensation reactions of aldehydes and TosMIC have been particularly useful in oxazole synthesis,[8] we have found that 2-pyrrolecarboxaldehydes reacted with TosMIC[9] in the presence of 1,8-diazabicyclo[5.4.0]undec-

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(1) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987.

(2) Trimurtuhu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993.

(3) Blackman, A. J.; Hambley, T. W.; Picker, R.; Taylor, W. C.; Thirasana, N.; *Tetrahedron Lett.* **1987**, *28*, 5561.

(4) Billimoria, A. D.; Cava, M. P. *J. Org. Chem.* **1994**, *59*, 6777.

(5) For previous reports on variolins synthesis, see: (a) Alvarez, M.; Fernández, D.; Joule, J. A. *Synthesis* **1999**, *4*, 615. (b) Alvarez, M.; Fernández, D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 215.

(6) Mínguez, J. M.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1996**, *37*, 4263.

(7) Mínguez, J. M.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. L. *J. Org. Chem.* **1999**, *64*, 7888.

(8) For references, see: Grigg, R.; Lansdell, M. I. Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025.

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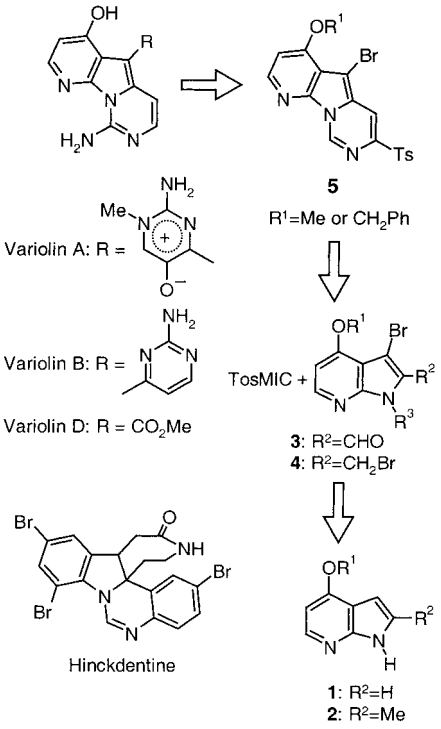
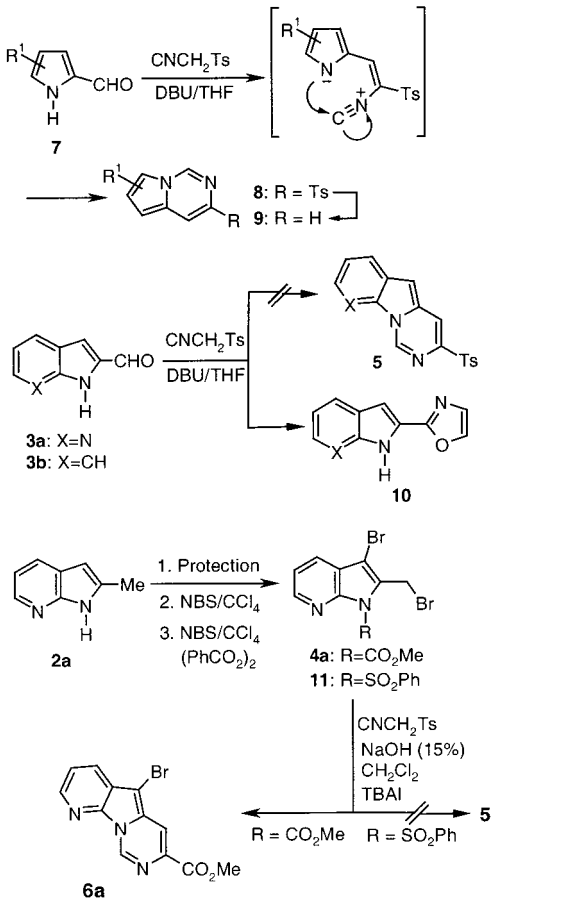
Scheme 1



Scheme 2



7-ene (DBU), furnishing 3-tosylpyrrolo[1,2-*c*]pyrimidines **8** in yields up to 60%. On the basis of these results, at the outset it was envisaged that the intermediate[10] **5** could be formed by means of a simple condensation of the appropriate 7-azaindolecarboxaldehyde **3a** and TosMIC. This condensation, however, failed to afford the expected tosyl derivative **5** either under the conditions previously employed for **8** or under other tested conditions, with the oxazole derivatives **10** being formed not only with **3a** but also with the 2-indolecarboxaldehyde **3b**, a much more π-excessive system than its 7-aza analogue (Scheme 2).

Consequently, the cyclocondensation process was tested with the corresponding N-protected 2-bromomethylazaindole **4** and TosMIC under basic conditions in the hope that the product of the nucleophilic substitution was stable enough for further transformation into the corresponding tricyclic system after deprotection. Initially, N-Boc carbamate was chosen as the protecting group, but results showed there was difficulty in the subsequent bromination step. Using the phenylsulfonyl as the protecting group, the N-protected 7-azaindole was easily brominated with NBS under ionic and radical conditions, affording the dibromo derivative **11** in a 60% yield. This result was very convenient because with our strategy the introduction of the 5-substituents present in variolins requires a 5-halo derivative as a precursor. Reaction of **11** with TosMIC, however, resulted in mixtures of the mono- and dialkylated derivatives, the latter being the main reaction product. When the methyl carbamate was used as the protecting group, the 3-bromo-2-bromomethylpyrrolo-[2,3-*b*]pyridine derivative **4a** was obtained in a 82% yield. Unexpectedly, when **4a** was treated with TosMIC, a clean reaction afforded the 5-bromopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine 3-carboxylic acid methyl ester **6a** in a 42% yield, which was improved to 65% by conducting the reaction in a two-phase medium [CH_2Cl_2/NaOH (15%)] in the presence of a phase transfer catalyst (TBAI). Thus, the same procedure also allowed us to prepare the key tricycle intermediate **6b** in just two steps from the known 4-methoxy-7-methylpyrrolo[2,3-*b*]-pyridine.[11]

Other 2-bromomethylazoles[12] were studied in an attempt to demonstrate the generality of the process,[13] with bicyclic and tricyclic systems **6c**−**i** being obtained in yields shown in Table 1. In general, yields of the cyclocondensation

(9) (a) Saikachi, H.; Kitigawa, T.; Sasaki, H.; Van Leusen, A. M. *Chem. Pharm. Bull.* **1979**, *27*, 793. (b) Saikachi, H.; Kitigawa, T.; Sasaki, H.; Van Leusen, A. M. *Chem. Pharm. Bull.* **1982**, *30*, 4199.

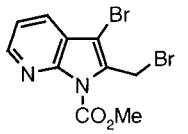
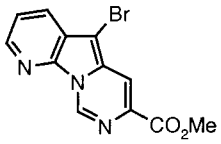
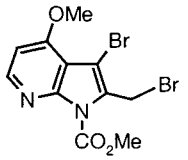
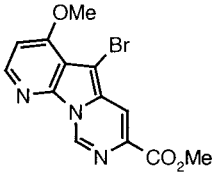
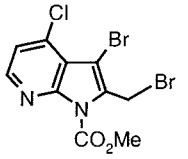
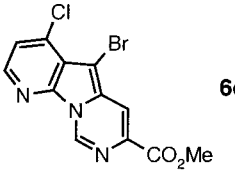
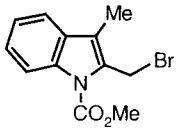
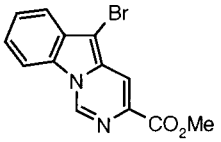
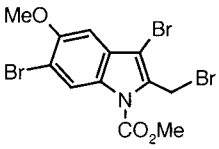
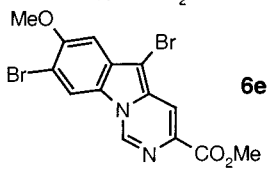
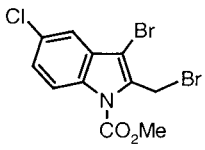
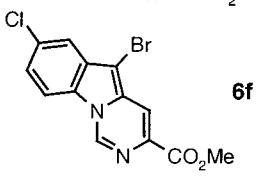
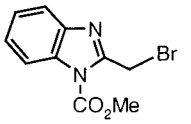
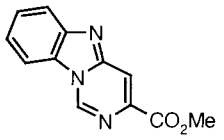
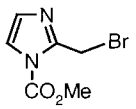
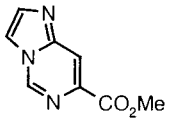
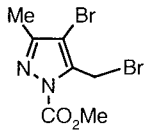
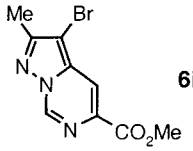
(10) For the only previous synthesis of this system, see: Capuano, L.; Schrepfer, H. J.; Müller, K.; Roos, H. *Chem. Ber.* **1974**, *107*, 929.

(11) Girgis, N. S.; Larson, S. B.; Robins, R. K.; Cottam, H. B. *J. Heterocycl. Chem.* **1989**, *26*, 317.

(12) Bromomethylazoles were prepared from commercially available methylazoles according to a literature procedure: Nagarathnam, D. *Synthesis* **1992**, 743.

(13) **Typical procedure:** A mixture of the bromomethyl derivative **4** (1.0 mmol), TosMIC (0.22 g, 1.1 mmol), and TBAI (0.08 g, 0.2 mmol) in CH_2Cl_2 (7 mL) and aqueous sodium hydroxide (7 mL) was stirred at the temperature indicated in Table 1. After the appropriate time (20 min−2 h), the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure, providing a crude product that was purified by flash chromatography (silica gel, hexane/EtOAc) to yield compounds **6a**−**i**.

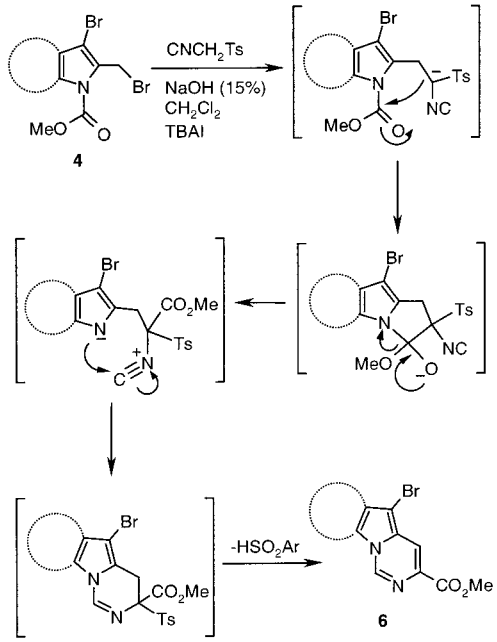
Table 1. Azolopyrimidines **6** from 2-Bromomethylazoles and TosMIC

entry	2-bromomethylazole	conditions[a]	azolopyrimidine derivatives (**6**)	yield (%)
1	 **4a**	-10ºC, 20 min	 **6a**	65
2	 **4b**	-10ºC, 1 h	 **6b**	61
3	 **4c**	0ºC, 2 h	 **6c**	27
4	 **4d**	r.t., 2 h	 **6d**	89
5	 **4e**	r.t., 2 h	 **6e**	56
6	 **4f**	r.t., 2 h	 **6f**	58
7	 **4g**	-20ºC, 2 h	 **6g**	41
8	 **4h**	-10ºC, 2 h	 **6h**	traces
9	 **4i**	-10ºC, 20 min	 **6i**	44

[a] Reactions were conducted in the two-phase system CH_2Cl_2/NaOH/TBAI except for **6h**, which was carried out in THF/triethylamine.

products were moderate to good except for **6c**, obtained in a 27% yield (entry 3), and **6h** (entry 8), which was formed along with a multicomponent mixture. The highly fluorescent nature of all these derivatives allowed us to identify traces of **6h** in the reaction mixture using thin-layer chromatography. The lower yield obtained for **6c** when compared with **6a** and **6b** is probably related to the lower nucleophilicity of the pyrrole nitrogen in **6c**.

Scheme 3



The mechanism hypothesized to account for this unusual cyclocondensation reaction involves initial nucleophilic substitution of TosMIC to the bromomethylazole followed by intramolecular transfer of the methoxycarbonyl protecting group. Subsequent cyclization and 1,2-elimination of toluenesulfonate would afford the desired azolopyrimidine derivative (Scheme 3).

In summary, an unusual and efficient domino reaction of 2-bromomethyl-7-azaindoles and TosMIC is reported, thus providing a straightforward preparation of the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine ring system and opening a simple route for the synthesis of the natural alkaloids, variolins. This process is also useful for other 2-bromomethylazoles with azolopyrimidines being obtained in moderate to good yields.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4** and **6**. This material is available free of charge via the Internet at http:\\pubs.acs.org.

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