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Heterocyclizations with Tosylmethyl Isocyanide Derivatives. A New Approach to Substituted Azolopyrimidines

Alejandro Baeza, Javier Mendiola, Carolina Burgos,* Julio Alvarez-Builla, and Juan J. Vaquero*

Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain

juanjose.vaquero@uah.es

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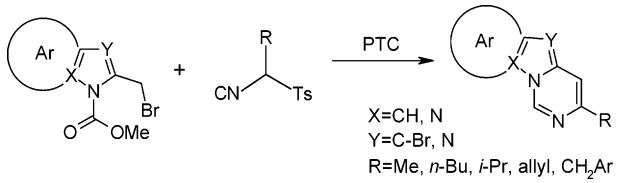

An efficient synthesis of substituted azolopyrimidines such as pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidines, pyrimido[1,6-*a*]indoles, benzo[4,5]imidazo-[1,2-*c*]pyrimidines, an imidazo-[1,2-*c*]pyrimidine, and pyrazolo[1,5-*c*]pyrimidines is described. The method involves the reaction of N-protected bromomethylazoles and tosylmethyl isocyanide (TosMIC) derivatives in nonanhydrous media. The study of the reaction conditions shows that the method is only successful under phase-transfer conditions (CH_2Cl_2/30% aq NaOH) using benzyltriethylammonium chloride as a catalyst.

Since the introduction of tosylmethyl isocyanide (TosMIC) by van Leusen,[1] this class of reagent has been extensively used in azole chemistry,[2] mainly in reactions with activated carbon−carbon double bonds (pyrrole synthesis)[3] and carbon−heteroatom double bonds (oxazole[4] and imidazole[5] synthesis).

In the course of our studies on the total synthesis of variolin B[6] and some analogues, we reported a new synthesis of pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine, which is the heterocyclic core of the variolin family of marine alkaloids. The synthesis is based on an unprecedented reaction between a methyl carbamate-protected 2-(bromomethyl)pyrrolo[2,3-*b*]pyridine and TosMIC under phase-transfer conditions[7] (Scheme 1). The mechanism proposed for this new heterocyclization involves initial nucleophilic substitution of TosMIC followed by intramolecular transfer of the methoxycarbonyl protecting group. Subsequent attack of the pyrrole nitrogen on the isocyanide group would lead to cyclization, and 1,2-elimination of *p*-toluenesulfinic acid would afford the azolopyrimidine derivative.

The ease with which TosMIC reagents react with different bromomethylazoles presents new opportunities for expanding TosMIC chemistry for the synthesis of azines, a use that remains almost unexplored.[8] Described herein are the results of a study that has culminated in the development of a process for the efficient synthesis of substituted azolopyrimidines under phase-transfer catalysis conditions using bromomethyl azoles and different TosMIC derivatives.

The heterocyclization reaction leading to the pyrimidine nucleus shown in Scheme 1 allowed efficient access to different azolopyrimidines, including the tricyclic core of variolins. However, this approach suffers from the drawback associated with the ease of deprotection of the azole under the phase-transfer conditions used, which leads in some cases to low or moderate yields of the azolopyrimidine system.[9] On the other hand, phase-transfer conditions are necessary for successful heterocyclization since we proved that under different homogeneous conditions, TosMIC suffers a competitive double alkylation with the formation of unstable products **12** (Scheme 2).

We envisaged that the use of TosMIC derivatives[10] would avoid the formation of these undesired products resulting from consecutive alkylation, thus facilitating the isolation of the monoalkylated compound **14** (Scheme 3). Compound **14** could then be transformed into the substituted azolopyrimidine by deprotection of the azole and subsequent cyclization. Initial studies using **1a** and

* To whom correspondence should be addressed. Fax: 34-91-8854660.

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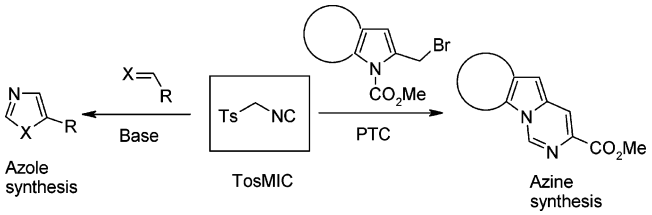
SCHEME 1



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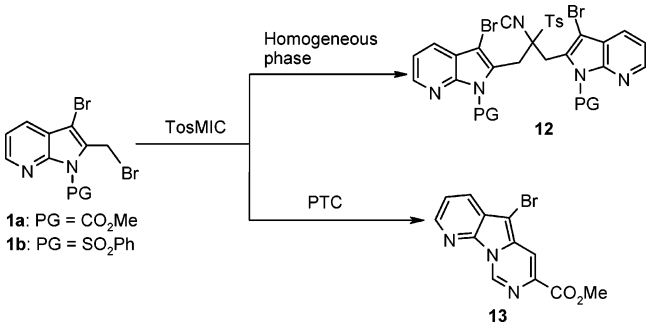

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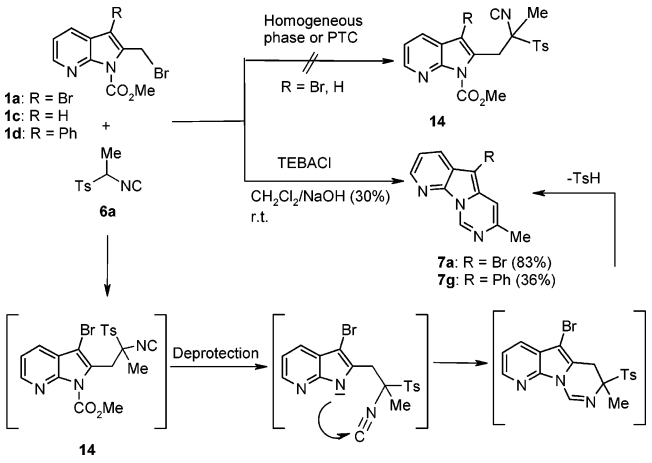

1b showed that in homogeneous conditions (Et_3N/THF, NaOMe/MeOH), these bromomethyl derivatives did not react with α-methyl-α′-tosylmethyl isocyanide (**6a**), and extensive decomposition of both reactants was observed at room temperature and at 0 °C. It was therefore decided to re-examine the phase-transfer conditions used in the reaction of TosMIC with these substrates,[9] despite the fact that several previously described procedures employing substituted TosMIC reagents required anhydrous conditions.[10b,c] The attempted reaction of **1c** under phase-transfer conditions failed using different catalysts [tetrabutylammonium iodide (TBAI), benzyltriethylammonium chloride (TEBACl), tricaprylylmethylammonium chloride (Aliquat), tributylmethylammonium chloride] and biphasic media (NaOH/CH_2Cl_2, MeCN/K_2CO_3), with deprotection and concomitant decomposition of the azaindole derivative observed. In contrast, 3-bromo-2-bromomethyl-1-methoxycarbonylpyrrolo[2,3-*b*]pyridine (**1a**) did react with **6a** in the presence of TEBACl or tributylmethylammonium chloride in a liquid−liquid biphasic medium.

The structure of reaction product was unambiguously established by two-dimensional NMR (gHMQC) to be 5-bromo-7-methylpyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine (**7a**). This product is presumably formed by nucleophilic displacement of the bromo substituent, in situ deprotection of the azole under the basic conditions, cyclization, and, finally, 1,2-elimination of *p*-toluenesulfinic acid (Scheme 3).

TABLE 1. Synthesis of 7a in Homogeneous and Phase-Transfer Catalysis Conditions

entry	catalyst[a]	conditions[b]	yield %
1		MeOH/NaOMe	
2		NEt_3/THF	
3	TEBACl (10%)	40 °C, 4 h	62
4	TEBACl (20%)	rt, 4 h	83
5	TEBACl (20%)	40 °C, 4 h	82
6	TEBACl (20%)	$CHCl_3$, 60 °C	40
7	Aliquat (20%)	rt, 4 h	
8	$MeBu_3NCl$ (20%)	rt, 4 h	70
9	TBAI (20%)	rt, 4 h	
10	TBAI (20%)	40 °C, 4 h	
11	TBACl (20%)	40 °C, 4 h	traces

[a] TBAI(Cl), tetrabutylammonium iodide (chloride); TEBACl, benzyltriethylammonium chloride. [b] General conditions, unless otherwise indicated: CH_2Cl_2/NaOH (30% aq).

To optimize the synthesis of **7a**, different catalysts and reaction conditions were examined (Table 1). Results also showed decomposition of both reactants under homogeneous conditions (entries 1 and 2). A lack of reactivity was also observed in the presence of catalysts such as TBAI (entries 9 and 10) and tricaprylmethylammonium chloride (Aliquat) (entry 7), with deprotection of the azole being observed after prolonged heating (24 h, 40 °C). Employing TEBACl (20%) at room temperature in CH_2Cl_2/NaOH resulted in the formation of **7a** with 83% isolated yield (entry 4). Reducing the catalyst loading (entry 3) or changing the solvent (entry 6) resulted in a significant decrease in the yield. Increasing the temperature (40 °C) had little effect on the yield (83 vs 82%, entry 5). Under the same conditions, TEBACl proved to be a better catalyst than tributylmethylammonium chloride (entry 8). Finally, the use of TBACl resulted in the formation of traces of the heterocyclization product (entry 11).

These results indicate that the structure of the quaternary ammonium cation (*quat*) seems to be crucial for the success of the reaction. Thus, the most lipophilic *quats*, the Aliquat, and the tetrabutylammonium cation (TBA) are ineffective as phase-transfer catalysts. Changing the counterion in the TBA *quat* [iodide (TBAI) or chloride (TBACl)] was also unsuccessful, thus discarding the possibility that the lack of reactivity in the presence of the catalyst could be due to the effect of the iodide counterion (e.g., decomposition of the TosMIC reagent or "catalyst poisoning" by association with the *quat* in the organic phase[11]). On the other hand, smaller and more hydrophilic cations such as tributylmethylammonium and benzyltriethylammonium (TEBA) clearly facilitate the reaction of **1a** and **6a**. This behavior could be explained assuming an interfacial mechanism[12] for the nucleophilic substitution reaction under the PTC/OH conditions used for the formation of **7a**.

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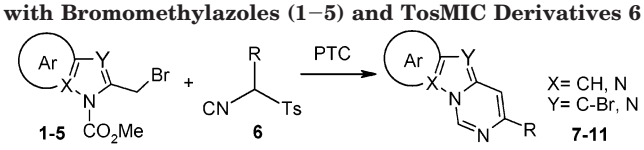
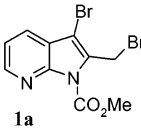
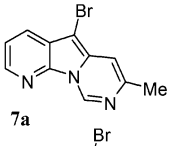
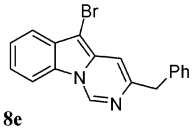
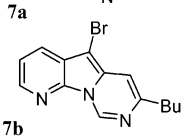
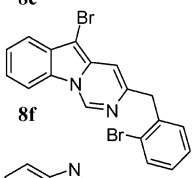
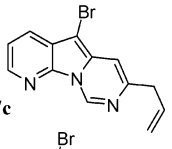
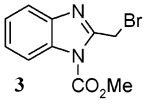
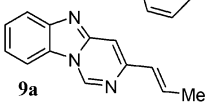
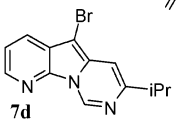
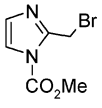
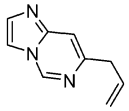
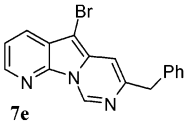
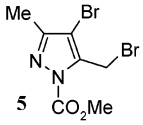
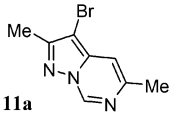
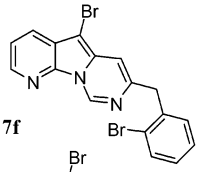
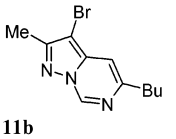
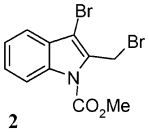
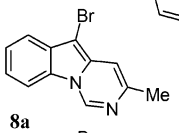
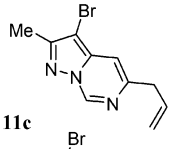
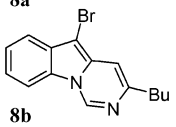
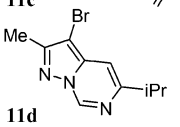
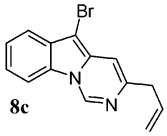
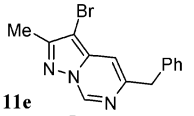
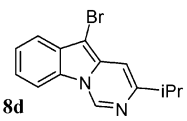
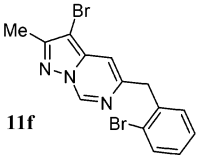
TABLE 2. Heterocyclizations with Bromomethylazoles (1−5) and TosMIC Derivatives 6



entry	azole	TosMIC/ conditions[a]	product	yield (%)	entry	azole	TosMIC/ conditions[a]	product	yield (%)
1	 **1a**	**6a** (R=Me) 4 h, r.t	 **7a**	83	11	**2**	**6e** 4 h, 40 °C	 **8e**	60
2	**1a**	**6b** (R=nBu) 5 h, r.t.	 **7b**	73	12	**2**	**6f** 4 h, 40 °C	 **8f**	60
3	**1a**	**6c** (R=Allyl) 6 h, r.t.	 **7c**	65	13	 **3**	**6c** 24 h, 0 °C	 **9a**	63
4	**1a**	**6d** (R=iPr) 4 h, r.t	 **7d**	34	14	 **4**	**6c** 4 h, 0 °C	 **10a**	25
5	**1a**	**6e** (R=Bn) 4 h, r.t	 **7e**	60	15	 **5**	**6a** 24 h, 0 °C	 **11a**	58
6	**1a**	**6f** (R=2-BrBn 5 h, r.t	 **7f**	60	16	**5**	**6b** 24 h, 0 °C	 **11b**	55
7	 **2**	**6a** 4 h, 40 °C	 **8a**	75	17	**5**	**6c** 24 h, 0 °C	 **11c**	59
8	**2**	**6b** 5 h, 40 °C	 **8b**	75	18	**5**	**6d** 24 h, 0 °C	 **11d**	-
9	**2**	**6c** 4 h, 40 °C	 **8c**	70	19	**5**	**6e** 24 h, 0 °C	 **11e**	47
10	**2**	**6d** 24 h, -10 °C	 **8d**	30	20	**5**	**6f** 24 h, 0 °C	 **11f**	43

[a] CH_2Cl_2/NaOH (30% aq)/TEBACl (20%).

The presence of an electron-withdrawing substituent in the C3 position of **1** also seems to be crucial to the success of this heterocyclization reaction. Thus, while **1a** (R = Br) afforded the tricyclic derivatives **7a** in high yield (83%), **1d** (R = Ph) gave the corresponding heterocyclization compound **7g** in only 36% yield under the optimal conditions used for the synthesis of **7a** (Scheme 3). Apparently, the bromo substituent has a double effect, facilitating nucleophilic substitution and enhancing the stability of the deprotected bromomethylazole intermediate toward the reaction conditions (C-3-unsubstituted

(12) For a discussion of the extraction and interfacial mechanisms in PTC, see: Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 960−970.

pyrrolo[2,3-*b*]pyridines are prone to decomposition under basic conditions[9,13]).

The optimal conditions found for the heterocyclization to give **7a** were successfully applied to the reaction of **1a** and different TosMIC derivatives **6b**−**f** (Table 2, entries 2−6). The 7-substituted 5-bromopyrido[3′,2′:4,5]pyrrolo-[1,2-*c*]pyrimidines **7b**−**f** were obtained with yields ranging from 30 to 73%. The resistance of the substrate to deprotection under the phase-transfer conditions is crucial for the success of the reaction. Thus, the low yields obtained in the reaction of **1a** and α-isopropyl-α′-tosylmethyl isocyanide (**6d**) are associated with the lower reactivity of this TosMIC derivative toward the azole, with extensive deprotection and decomposition of **1a** observed.

The success of this heterocyclization led us to study the general scope of this reaction. Therefore, in addition to 2-bromomethyl-7-azaindole (**1a**), a range of different azoles were tested in an attempt to explore the behavior of different heterocycles in this cyclization reaction. Indole **2**, benzimidazole **3**, imidazole **4**, and 3-methylpyrazole derivatives **5** were reacted with the same TosMIC derivatives used with 7-azaindole **1a**. The results are summarized in Table 2 and indicate that the reactions of 3-bromo-2-bromomethyl-1-methoxycarbonylindole (**2**) also proceeded in moderate yields. It is worth noting that initial attempts to carry out the reactions with **2** at room temperature failed and that a temperature of 40 °C was found to be optimal for the success of these reactions. The only exception to this trend was the tosylmethyl isocyanide derivative **6d**, which afforded **8d** in only 30% yield after 24 h at −10 °C. The 3-substituted 5-bromopyrimido[1,6-*a*]indoles (**8a**−**f**), obtained from the reaction of **2** and **6a**−**f**, are shown in Table 2 (entries 7−12).

The reactivities of 2-bromomethyl-1-methoxycarbonylbenzimidazole (**3**) and 2-bromomethyl-1-methoxycarbonylimidazole (**4**) toward TosMIC derivatives **6a**−**f** are similar to each other but clearly different from those observed for bromomethylindole and bromomethyl-azaindole. Both azoles **3** and **4** are prone to deprotection either at 40 °C or room temperature and only reacted with α-allyl-α′-tosylmethyl isocyanide (**6c**) at 0 °C, affording the 3-(1-propenyl)benzo[4,5]imidazo[1,2-*c*]pyrimidine (**9a**) and 7-(2-propenyl)imidazo[1,2-c]pyrimidine (**10a**) in 63 and 25% yields, respectively. The difference in yield between **9a** and **10a** is associated with the faster deprotection of **4** when compared with **3** under the phase-transfer conditions. Structural data for **9a** and **10a** showed that the heterocyclization process with **3** is accompanied by isomerization of the allylic moiety to give the vinylic heterocycle **9a**, while in the case of **10a** this isomerization was not observed under reaction conditions. The higher acidity of the allylic protons in **9a** when compared with those in **10a** likely accounts for the different behavior of both compounds toward isomerization. In fact, **10a** slowly isomerizes to the corresponding vinylic derivative in a basic solution at room temperature.

Finally, 4-bromo-5-bromomethyl-1-methoxycarbonyl-3-methylpyrazole (**5**) showed behavior similar to that found for **1a** and **2**. In this case, the yield of the 3-bromo-2,5-dimethylpyrazolo[1,5-*c*]pyrimidine (**11a**) was lower than those obtained for **7a** and **8a**, and the reaction with **6f** failed. The yields for the series of pyrazolo[1,5-*c*]pyrimidines **11b**−**e** are similar to those obtained with bicyclic substrates **1a** and **2**. In summary, the reaction of 2-bromomethylazoles and TosMIC derivatives under phase-transfer conditions (CH_2Cl_2/30% aq NaOH), using TEBACl as a catalyst, allowed the preparation of substituted azolopyrimidines. The products obtained included pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidines, which contain the ring system present in the variolin alkaloids. Further studies on the application of this heterocyclization method in the synthesis of variolin B analogues are currently in progress.

Experimental Section

General. TosMIC derivates **6a**−**e** were prepared following the general procedure described by van Leusen.[10a] Compound **6f** was also prepared following this general procedure. The bromomethyl azoles **1**−**5** were prepared following the method described in ref 9.

α-(2-Bromobenzyl)-α′-tosylmethyl Isocyanide (6f). A mixture of TosMIC (976 mg, 5 mmol), 1-bromo-2-bromomethylbenzene (2.5 g, 10 mmol), and Bu_4NI (1 mmol) in CH_2Cl_2 (10 mL) and 30% NaOH (10 mL) was vigorously stirred for 5 h at room temperature. Water (50 mL) was added, and the reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. Extraction of the residue with cold ether and removal the solvent in vacuo yielded **6f** (1.13 g, 62%) as a white solid: mp 113−115 °C; IR (KBr) 3061, 2937, 2137, 1593, 1329, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 2H, J = 8.2 Hz), 7.54 (m, 1H), 7.43 (d, 2H, J = 8.2 Hz), 7.2−7.3 (m, 3H), 4.85 (dd, 1H, J = 11,4 and 3.1 Hz), 3.83 (dd, 1H, J = 13,7 and 3.1 Hz), 3.05 (dd, 1H, J = 13.7 and 11.4 Hz), 2.48 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$) δ 146.7, 133.1, 132.4, 131.3, 130.2, 129.9, 129.6, 127.9, 127.2, 126.5, 124.2, 38.1, 35.4, 21.9; MS (EI) *m/z* (relative intensity) 363, 365 [34, 34 (M^+)], 284 (29), 210 (21), 208 (21), 155 (27), 129 (57), 91 (100), 63 (18). Anal. Calcd for $C_{16}H_{14}BrNO_2S$: C, 52.76; H, 3.87; N, 3.85. Found: C, 52.83; H, 3.72; N, 3.98.

Synthesis of Azolopyrimidines 7−11. General Procedure. A mixture of the bromomethylazole (**1**−**5**) (0.29 mmol), the TosMIC derivative **6a**−**f** (0.32 mmol), and TEBACl (13 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) and 30% NaOH (3 mL) was stirred at the indicated temperature for 4−24 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give a crude product, which was chromatographed on silica gel to yield pure compounds **7**−**11**.

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Supporting Information Available: Complete experimental procedures for the synthesis and characterization data for compounds **7**−**12** and copies of ^1H NMR (500 MHz) and two-dimensional NMR (gHMQC) spectra for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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