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Reaction of Tosylmethyl Isocyanide with *N*-Heteroaryl Formamidines: an Alternative Approach to the Synthesis of *N*-Heteroaryl Tosylimidazoles

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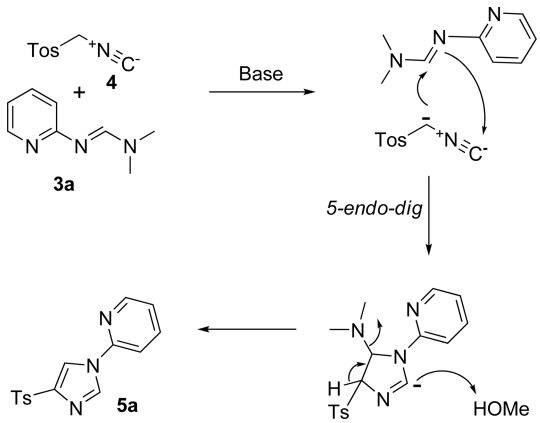
N-Heteroaryl imidazoles are important compounds that have received considerable attention, particularly in pharmaceutical research.[1] Specifically, *N*-arylimidazoles have been studied in relation to the treatment of cytokine mediated diseases[2] and also as tromboxane synthase inhibitors,[3] cardiotonic agents[4] and topical glaucoma agents.[5] Straightforward Ullmann type C-N bond formation is one of the known procedures for the synthesis of these compounds.[6] However, these reactions usually proceed at high temperatures and require the presence of a catalyst. *N*-Arylimidazoles can also be obtained by nucleophilic aromatic substitution, although the process is suitable only for substrates carrying electron withdrawing substituents.[7] Mild, highly efficient methods for building *N*-arylazole have been developed by Thomas, Buchwald, and Taillefer,[8-10] who have carried out the *N*-arylation of nitrogen-containing heterocycles by readily available aryl halides in the presence of nitrogen and oxygen based ligands.

Tosyl methyl isocyanide (TosMIC), a multipurpose commercially available 3-unit synthon introduced by Van Leusen,[11] reacts with a variety of groups to give heterocycles.[12] It is important to emphasize that treatment of TosMIC with various functional groups leads to the formation of the imidazole nucleus, such as is the case with imines, imidoyl chlorides, isothiocyanates, nitrile and ethoxy methylene amino. However, only the latter group yields *N*-heterocycle imidazoles.[13]

To our knowledge there is no report on the use of heteroaryl formamidines for the synthesis of imidazoles using tosylmethyl isocyanide. Hence, we decided to explore the reaction of TosMIC with *N*-heteroaryl formamidines in the construction of 2-(4-tosyl imidazo-1-yl)pyridines and 2-(4-tosyl imidazo-1-yl)pyrimidines based on the following reasoning. Cunningham[14] determined that the initial site of protonation of *N*,*N*′-dimethyl pyridyl formamidines of type **3** was the amidine nitrogen adjacent to the heterocycle nucleus. Analysis of the structure of pyridyl and pyrimidyl formamidines **3a-g** suggests that the amidine carbon may act as an electrophilic center. Then, reaction of compounds **3a** with tosylmethyl isocyanide **4** under basic reaction conditions should form the corresponding carbanion,[15] which in turn would add to the electrophilic amidine carbon. Intramolecular addition of the amidine nitrogen to the isocyanide



Scheme 1. Proposed mechanism of formation of 2-(4-tosylimidazo-1-yl)pyrimidines and pyridines from formamidines and TosMIC.

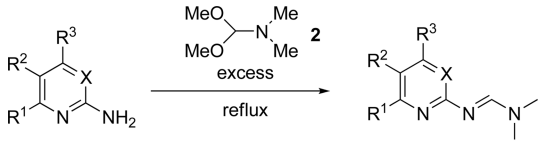
via a *5-endo-dig* process, followed by dimethyl amine elimination should lead to the formation of the imidazole nucleus, as depicted in (Scheme 1).[16]

Accordingly, 2-amino pyridine **1a-c** or 2-amino pyrimidine **1d-g** were treated with an excess of dimethyl formamide dimethyl acetal (DMFDMA) **2** following the protocol described by Cunningham,[14] to give *N*,*N*′-dimethyl amino formamidines **3a-g** with most yields between 71 and 90% (Table 1). Data on the melting points of known pyridyl formamidines reported herein are similar to those reported by Cunningham. Full identification of new and known formamidines was made with the aid of ^{1}H and ^{13}C NMR spectroscopy.

Most of the reaction conditions used to generate the carbanion from TosMIC employ a strong base such as sodium hydride or *n*-butyl lithium.[12,17] Thus, several milder experimental conditions were assayed in the present study ($NaHCO_3$/DMF, piperidine, KOH/MeOH, NaOMe/MeCN, among others).

It was found that NaOMe in dry THF was the best combination to deprotonate TosMIC and achieve the transformation of the heteroaryl formamidines **3a-g** into the desired *N*-heteroayl imidazoles **5a-g**. This process (Scheme 2) shows that the currently reported approach has broad applications, as pyrimidine formamidine (containing electron donor groups) was shown to participate in the reaction. The

Table 1. Preparation of *N,N′*-dimethyl pyridyl and pyrimidyl formamidines **3a-g**



1, X=CH, N **3**, X=CH, N

	R^1	R^2	R^3	X	Yield %	mp ºC	Lit.[14] mp ºC
3a	H	H	H	CH	71	31-32	30-32
3b	H	Br	H	CH	72	79-80	78-80
3c	H	Cl	H	CH	88	68-70	68-69
3d	H	H	H	N	80	103-105	-
3e	H	Br	H	N	75	153-154	-
3f	OMe	H	Me	N	82	117-119	-
3g	Me	H	Me	N	90	138-139	-

^{1}H NMR spectra of compounds **5a-g** showed the imidazole ring protons as doublets with a small coupling constant (J = 1 Hz) at low field in the interval δ 8.27-8.59. Complete assignment of signals was achieved by the aid of gHMBC and gHSQC NMR techniques. The yields of compounds **5a-g** were optimized using 1.5 eq. of TosMIC and 1.8 eq. of NaOMe with respect to the starting formamidine (Table 2).

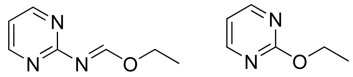
A procedure closely related to the herein described synthesis of heteroaryl *N*-imidazoles was reported in 1982 by Taylor.[13] Four ethoxymethylene derivatives of primary amino heterocycles (4-aminopyrimidine included) were prepared and treated with tosylmethyl isocyanide in the presence of sodium hydride to furnish *N*-heteroaryl tosyl imidazoles, these latter compounds being similar to those synthesized in the current contribution.

It is interesting that neither 2-aminopyridine nor 2-aminopyrimidine were considered in that research. Preparation of 2-ethoxymethylene amino pyridine has been reported in 60% yield,[18,19] but data for the corresponding 2-ethoxymethylene amino derivative **6** were not found. Therefore we decided to prepare **6** following previously described protocol.[13] However, the expected product **6** was not formed and the starting material 2-aminopyrimidine was efficiently recovered from the reaction mixture (cf. preparation of the corresponding *N,N′*-dimethyl pyrimidyl formamidine **3d** in 80% yield). The ethoxymethylene amino heterocycle and the *N,N′*-dimethyl heteroaryl formamidine intermediates have a similar electrophilic carbon and nucleophilic nitrogen, which eventually allowed for the formation of the *N*-imidazoles. However, synthesis of heteroaryl formamidines was more accessible by using a distinct methodology.

Table 2. Synthesis of 2-(4-tosylimidazo-1-yl)pyridines and 2-(4-tosylimidazo-1-yl)pyrimidines, **5a-g**

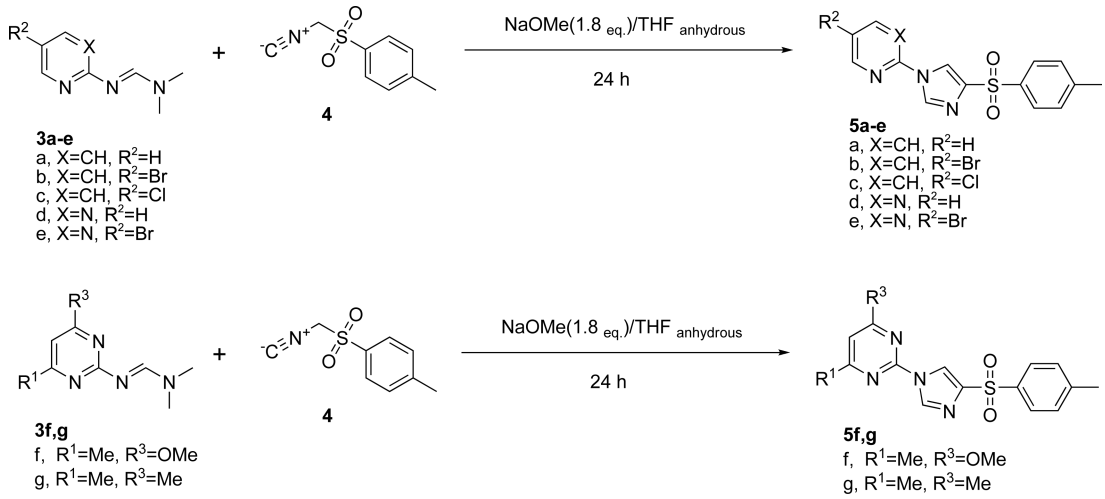
	mp °C	Isolated yield %
5a	153-155	90
5b	191-193	80
5c	171-172	74
5d	185-187	73
5e	197-198	71
5f	154-156	86
5g	163-164	81

Finally, we carried out a reaction with *N*-tosylimidazole **5d**, using a methodology previously reported,[13] to demonstrate the feasibility of nucleophilic tosyl imidazole displacement by sodium ethoxide. Indeed, 2-ethoxy pyrimidine **7** was isolated as an oil[20] although in rather low (non-optimized) yield (20%). Thus, these procedures should complement each other for the construction of *N*-heteroayl imidazoles.



6 **7**

In conclusion, an alternative procedure was developed under mild conditions for the synthesis of 2-(4-tosylimidazo-1-yl)pyridines and pyrimidines by the reaction of TosMIC



Scheme 2. The synthesis of 2-(4-tosylimidazo-1-yl)pyrimidines and pyridines.

with the corresponding heteroaryl *N,N′*-dimethyl formamidines. This approach does not involve a nucleophilic displacement of a leaving group and constitutes a further application of amidines, in which TosMIC acts as both a nucleophile and an electrophile on the heteroaryl formamidine. This process offers advantages over previously reported procedures.

Experimental

General. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectral data were recorded at 300 and 75 MHz, respectively, using a Varian Mercury 300 MHz NMR spectrometer or at 500 and 125 MHz, respectively, using a Varian NMR System 500 MHz spectrometer. Chemical shifts (δ) are given in parts per million downfield from TMS (δ = 0). Elemental analyses were performed on an EAI External Analytical, Inc. CE-440 elemental analyzer.

2-(4-Tosylimidazo-1-yl)pyridine (5a). In a 50 mL two neck round bottom flask, adapted with a reflux condenser, was placed a solution of dry (sodium) THF (6 mL) containing 0.65 g (12 mmol) of sodium methoxide (NaOMe) under a nitrogen atmosphere. Then, *p*-toluensulphonylmethyl isocyanide (TosMIC; 1.96 g, 10 mmol) in dried (sodium) THF (10 mL) was added. The mixture was vigorously stirred at room temperature for 10 min and then heated at 50 °C until the yellow color of the mixture turned brown. The reaction mixture was slightly cooled and *N,N′*-dimethyl-*N*-pyridylformamidine (1 g, 6.71 mmol) dissolved in dry THF (10 mL) was added in one portion. The reaction mixture was stirred constantly under gentle reflux until the starting materials disappeared (TLC Hexane/EtOAc 1:1). The reaction mixture, after being allowed to cool to room temperature, was added to a flask containing 50 mL of cold water. Extraction was carried out with $CHCl_3$ (3 × 20 mL). Organic extracts were combined and dried (anhydrous Na_2SO_4), solvent was removed under reduced pressure to release a brown solid, which was further purified by re-crystallization from a isopropyl alcohol/water (60/40) mixture. The title compound was isolated as a dark yellow amorphous solid, in 90% yield, mp 153-155 °C. ^{1}H NMR δ 2.39 (s, 3H), 7.31 (d, 2H, *J* = 8 Hz), 7.32 (m, 1H, 7.32-7.35), 7.41 (d, 1H, *J* = 8 Hz), 7.87 (td, 1H, *J* = 8.5 Hz, *J* = 2 Hz), 7.95 (d, 2H, *J* = 8 Hz), 8.33 (d, 1H, *J* = 1 Hz), 8.35 (d, 1H, *J* = 1 Hz), 8.49 (d, 1H, *J* = 8.5 Hz). ^{13}C NMR δ 21.5, 112.6, 120.2, 123.3, 128, 129.7, 136.4, 137.5, 139.5, 143.7, 144.3, 147.8, 149.3. Found, %: C, 60.18; H, 4.51; N, 13.77. Calculated %: $C_{15}H_{13}N_3O_2S$: C, 60.25; H, 4.36; N, 14.01; S, 10.6.

5-Bromo-2-(4-tosylimidazo-1-yl)pyridine (5b). Similarly, sodium methoxide (0.21 g, 3.9 mmol), TosMIC (0.64 g, 3.28 mmol) and 5-bromo-*N,N′*-dimethyl-*N*-pyridylformamidine (0.5 g, 2.19 mmol) gave the title compound as a dark yellow amorphous solid in 80% yield, mp 191-193 °C. ^{1}H NMR δ 2.41 (3H, s), 7.31 (d, 2H, *J* = 8 Hz), 7.34 (d, 1H, *J* = 8.5 Hz), 7.95 (d, 2H, *J* = 8 Hz), 7.99 (dd, 1H, *J* = 8.5 Hz *J* = 2.0 Hz), 8.29 (d, 1H, *J* = 1 Hz), 8.31 (d, 1H, *J* = 1 Hz), 8.53 (d, 1H, *J* = 2.0 Hz). ^{13}C NMR δ 21.6, 113.9, 119.4, 120.1, 28.1, 129.8, 136.5, 137.4, 142, 144.1, 144.5, 146.5, 150.4. Found, %: C, 47.85; H, 3.30; N, 10.92. Calculated, %: $C_{15}H_{12}N_3O_2BrS$: C, 47.7; H, 3.19; N, 11.09; Br, 21.09; S, 8.46.

5-Chloro-2(4-Tosylimidazo-1-yl)pyridine (5c). Similarly, sodium methoxide (0.26 g, 4.8 mmol), TosMIC (0.79 g, 4.09 mmol) and 5-chloro-*N,N′*-dimethyl-*N*-pyridylformamidine (0.5 g, 2.72 mmol) gave the title compound as a brownish amorphous solid, in 74% yield, mp 171-172 °C. ^{1}H NMR δ 2.4 (s, 3H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.36 (d, 2H, *J* = 8.5 Hz), 7.85 (dd, 2H, *J* = 8.5Hz, *J* = 2.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 8.27 (d, 1H, *J* = 1.0 Hz), 8.29 (d, 1H, *J* = 1.0 Hz), 8.45 (d, 1H, *J* = 2.0 Hz). ^{13}C NMR δ 21.6, 113.3, 120, 128.1, 129.8, 131.3, 136.4, 137.4, 139.1, 144.2, 144.5, 146.1, 148.3. Found, %: C, 53.71; H, 3.59; N, 12.43. Calculated, %: $C_{15}H_{12}N_3O_2ClS$: C, 54.04; H, 3.6; N, 12.57; Cl, 10.6; S, 9.59.

2(4-Tosylimidazo-1-yl)pyrimidine (5d). Similarly, sodium methoxide (0.32 g. 5.9 mmol), TosMIC (0.97 g, 5.0 mmol) and *N,N′*-dimethyl-*N*-pyrimidylformamidine (0.5 g, 3.33 mmol) gave the title compound as a brown amorphous solid, in 73% yield, mp 185-187 °C. ^{1}H NMR δ 2.40 (s, 3H), 7.31 (m, 3H, 7.31-7.33), 7.97 (d, 2H, *J* = 8.0 Hz), 8.57 (d, 1H, *J* = 1.0 Hz), 8.59 (d, 1H, *J* = 1.0 Hz), 8.72 (s, 1H), 8.73 (s, 1H). ^{13}C NMR δ 21.8, 120.2, 120.5, 128.1, 129.7, 137.3, 137.5, 143.8, 144.4, 153.8, 159. Found, %: C, 56.68; H, 3.83; N, 18.46. Calculated, %: $C_{14}H_{12}N_4O_2S$, C, 56.06; H, 4.01; N, 18.62; S, 10.65.

5-Bromo-2(4-Tosylimidazo-1-yl)pyrimidine (5e). Similarly, sodium methoxide (0.21 g. 3.9 mmol), TosMIC (0.64 g, 3.27 mmol) and 5-bromo-*N,N′*-dimethyl-*N*-pyrimidylformamidine (0.5 g, 2.18 mmol) gave the title compound as a dark yellow amorphous solid, in 71% yield, mp 197-198 °C. ^{1}H NMR δ 2.39 (s, 3H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.95 (d, 2H, *J* = 8.0 Hz), 8.50 (d, 1H, *J* = 1.0 Hz), 8.52 (d, 1H, *J* = 1.0 Hz), 8.75 (s, 2H). ^{13}C NMR δ 21.5, 118, 120.4, 128.1, 129.8, 137.2, 137.3, 144.2, 144.5, 152.12, 159, 159.6. Anal Calcd for $C_{14}H_{11}BrN_4O_2S$: C, 44.41; H, 2.9; N, 14.75; Br, 21.04; S, 8.44. Found: C, 44.34; H, 2.65; N, 14.92.

4-Methoxy-6-methyl-2-(4-Tosylimidazo-1-yl)pyrimidine (5f). Similarly, sodium methoxide (0.25 g, 4.6 mmol), TosMIC (0.75 g, 3.86 mmol) and 4-methoxy-6-methyl-*N,N′*-dimethyl-*N*-pyrimidylformamidine (0.5 g, 2.57 mmol) gave the title compound as a dark yellow amorphous solid, in 86% yield, mp 154-156 °C. ^{1}H NMR δ 2.36 (s, 3H), 2.41 (s, 3H), 4.08 (s, 3H), 6.51 (s, 1H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.94 (d, 2H, *J* = 8.0 Hz), 8.52 (d, 1H, *J* = 1.0 Hz), 8.54 (d, 1H, *J* = 1.0 Hz). ^{13}C NMR δ 21.6, 23.7, 54.4, 105.49, 120.79, 128.8, 129.8, 136.5, 137.4, 137.6, 144.4, 152.8, 169.4, 171.3. Found, %: C, 55.81, H, 4.62; N, 16.28. Calculated, %: $C_{16}H_{16}N_4O_3S$: C, 55.8; H, 4.61; N, 16.27; S, 9.31.

4,6-Dimethyl-2-(4-Tosylimidazo-1-yl)pyrimidine (5g). Similarly, sodium methoxide (0.27 g, 5.0 mmol), TosMIC (0.82 g, 4.19 mmol) and 4,6-dimethyl-*N,N′*-dimethyl-*N*-pyrimidylformamidine (0.5 g, 2.8 mmol) gave the title compound as a dark yellow amorphous solid, in 81% yield,

mp 163-164 °C. ^{1}H NMR δ 2.39 (s, 3H), 2.50 (s, 6H), 6.98 (s, 1H), 7.30 (d, 2H, J = 8.0 Hz), 7.93 (d, 2H, J = 8.0 Hz), 8.56 (s, 1H) 8.6 (s, 1H). ^{13}C NMR δ 21.6, 23.8, 119.05, 120.8, 128, 129.7, 137.4, 137.6, 142.7, 144.2, 148.5, 169.3. Found, %: C, 58.32; H, 4.68; N, 17.27. Calculated, %: $C_{16}H_{16}N_4O_2S$, C, 58.52; H, 4.9; N, 17.06; S, 9.76.

Supporting Information. Instruments data, full details of synthetic preparations of heteroaryl formamidines, original NMR spectra and representative gHMBC and gHSQC experiments are provided.

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