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Construction of pyrazolo[3,4-*b*]pyridines and pyrazolo[4,3-*c*]pyridines by ring closure of 3-acylpyridine *N*-oxide tosylhydrazones

William J. Lominac^a, Megan L. D'Angelo^a, Mark D. Smith^b, Darius A. Ollison^a, and James M. Hanna Jr.^{a,*}

^aDepartment of Chemistry, Physics, and Geology, Winthrop University, Sims Science Building, Rock Hill, SC 29733 USA

^bDepartment of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208 USA

Abstract

3-Acylpyridine *N*-oxide tosylhydrazones give good overall yields of a mixture of pyrazolo[3,4-*b*]pyridines and pyrazolo[4,3-*c*]pyridines when treated with an electrophilic additive and an amine base. (*Z*)-Hydrazones cyclize readily, while (*E*)-hydrazones fail to react under the reported conditions. The reaction takes place at room temperature, and moderate regiocontrol over the cyclization can be achieved by varying the electrophile/solvent combination.

Keywords

Pyrazolo[3,4-*b*]pyridines; Pyrazolo[4,3-*c*]pyridines; Pyridine *N*-oxide hydrazones; Cyclization

Introduction

Nitrogen-containing heterocycles are common structural units found in many natural products and pharmaceuticals.¹ In particular, compounds containing the pyrazolo[3,4-*b*]pyridine ring system (**1**) exhibit a wide variety of biological activities.^{1–11} A common strategy for the synthesis of **1** involves the annulation of a pyrazole ring onto an existing pyridine as shown in Scheme 1.^{11–23}

This approach requires the presence of a leaving group (often a halogen) at the 2-position of the pyridine ring prior to cyclization, and introduction of this functionality often necessitates

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*Corresponding Author: James M. Hanna, Jr., Ph. D., Associate Professor of Chemistry, Department of Chemistry, Physics, and Geology, 313B Sims Science Building, Winthrop University, Rock Hill, SC 29733, Voice: 803-323-4933, Fax: 803-323-2246, hanna.j@winthrop.edu.

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Supplementary data

Supplementary data (experimental procedures, detailed product characterization data, compound spectra, X-ray crystallographic data for **3a**) associated with this Letter can be found in the online version at (**Editor: Please insert DOI here**). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 855254. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or deposit@ccdc.cam.ac.uk).

the use of high temperatures and/or harsh reagents.^{13,24–27} One possible way to eliminate this requirement is to take advantage of the electrophilic 2-position of a suitably activated pyridine *N*-oxide using a strategy (Scheme 2) similar to the Reissert-Henze reaction,²⁸ an approach which has been employed in the preparation of 2-aminopyridines^{29–32} via intermolecular amination of pyridine *N*-oxide, and also has recently been used to functionalize the 2-position of pyridine through the *N*-oxide with oxygen, sulfur and carbon nucleophiles.³³ Since the introduction of a halogen to the 2-position of pyridine typically requires prior formation of the *N*-oxide,¹³ this method would also eliminate a step in the formation of **1** and thus be a more efficient route to these compounds.

When initially considering this approach, we reasoned that reaction of hydrazone **3** with a suitable electrophile would give **4**, which would be activated for nucleophilic attack at C2. We also recognized that attack would be possible at C4, so intramolecular attack of the hydrazone NH onto the pyridine ring could lead to dihydropyridines **5** and/or **5'**. These intermediates could then undergo elimination in the presence of a base to regenerate the pyridine ring and afford the pyrazolopyridines **1** and/or **1'**. We were attracted to the possibility of regiocontrol in the proposed cyclization, which could possibly provide an efficient approach to both pyrazolopyridine ring systems from one common intermediate. Although we could find no literature reports of this strategy being employed to construct pyrazolopyridines through the pyridine *N*-oxide, we found one closely-related account of the intramolecular amination of an alkylpyridinium cation – the cyclization of a pyridinium tosylhydrazone methiodide to give a dihydropyridopyrazole.³⁴

We can now report that tosylhydrazones derived from 3-benzoylpyridine *N*-oxide and 3-pivaloylpyridine *N*-oxide can be cyclized to a mixture of pyrazolopyridines in good overall yield by treatment with an electrophilic additive and an amine base. The reaction takes place under mild conditions (i.e. at room temperature) and the regioselectivity of the cyclization can be controlled to a moderate degree by varying the electrophile/solvent combination. In this Letter we describe the results of our study.

Results and Discussion

We began this project by examining the cyclization of 3-benzoylpyridine *N*-oxide tosylhydrazone (**3a**). **3a** was produced in moderate yield (65%) by the treatment of 3-benzoylpyridine *N*-oxide (**2a**) with tosyl hydrazide in methanol. Proton NMR analysis indicated that the isolated product consisted of a single stereoisomer which was shown by X-ray analysis to have the (*Z*)-configuration (see supplementary data). **3a** was then treated with tosyl chloride and triethylamine in dichloromethane solution to effect the cyclization. After stirring the mixture overnight at room temperature, we found that the starting tosylhydrazone had disappeared (by TLC) and two products had been formed. Column chromatography of the product mixture afforded the expected products 1*H*-1-(4-methylphenylsulfonyl)-3-phenylpyrazolo[3,4-*b*]pyridine (**1a**, 82%) and the regioisomeric 1*H*-1-(4-methylphenylsulfonyl)-3-phenylpyrazolo[4,3-*c*]pyridine (**1a'**, 12%).

Encouraged by this result, we explored the effect of other electrophilic additives on the product yield and regioselectivity of the reaction. These results are shown in Table 1.

All electrophilic additives gave moderate to very good overall yields of cyclized products. Most electrophiles led to a preponderance of **1a**, derived from attack of the hydrazone NH at the 2-position of the pyridine ring. This is not surprising in light of the observation that “hard” nucleophiles (e. g. nitrogen nucleophiles) tend to attack alkylpyridinium salts primarily at the 2-position via a charge-controlled (polar) mechanism.³⁵ While most of the sulfonic acid-derived activators led to a small amount of **1a'** due to cyclization at the 4-

position (entries 1 – 3), the use of trifluoroacetic anhydride (TFAA, entry 4) and the peptide coupling agent bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, entry 5)³² completely abolished the formation of **1a'**. The use of acetic anhydride (entry 7) proved problematic. As with TFAA and PyBroP, the formation of **1a'** was eliminated, but **1a** could be isolated in ~35% yield (estimated by ¹H-NMR) only as an inseparable mixture with a byproduct which was not further characterized.

A very interesting result stemmed from the use of triflic anhydride (entry 6). In this case, the regioselectivity of the cyclization was reversed, leading to **1a'** as the major product. While a definitive explanation for this reversal of regioselectivity cannot be advanced at this time, it is well-established that alkylpyridinium ions are attacked at the 4-position by “soft” nucleophiles via a single electron-transfer (SET) process,³⁵ and the proportion of **1a'** definitely increases as the electrophile employed in the cyclization becomes more electron-withdrawing. The regioselectivity trend may therefore be the result of a shift in the cyclization mechanism from primarily polar to mainly SET as the pyridine ring becomes more electron deficient.³⁶

It is apparent from the data in Table 1 that the use of tosyl anhydride as the electrophilic additive gave the best overall yield with good regioselectivity toward **1a** (entry 2), while triflic anhydride gave a good overall yield and produced primarily **1a'** (entry 6). Therefore both of these electrophiles were employed in the remainder of the experiments. We next examined the effect of the base on the yield and regioselectivity of the cyclization. The results are shown in Table 2.

The results in Table 2 indicate that upon activation by tosyl anhydride (entries 1 – 5), all of the bases we evaluated favored the formation of **1a** with comparable selectivity, and it appears triethylamine is optimum with respect to overall yield. The use of triflic anhydride (entries 6 – 10) as the electrophile favored **1a'** in all cases, and *N*-methylimidazole (MIm) seemed to give the best selectivity.

We next investigated the effect of solvent on the reaction. The results are shown in Table 3.

It appears that activation using tosyl anhydride (entries 1 – 4) favored the formation of **1a** in all solvents, although the less polar solvents (entries 3 and 4) gave lower yields than the more polar solvents (entries 1 and 2). The use of triflic anhydride gave predominantly **1a'** only in dichloromethane (entry 5). Much lower regioselectivity toward **1a'** was seen in the other solvents evaluated, and in acetonitrile and toluene (entries 6 and 8) the cyclization favored the formation of **1a**. The reason for this pronounced solvent effect is not known at this time.

To further investigate the scope of the reaction and study the effect of hydrazone configuration on the cyclization, we examined the reactions of two tosylhydrazones derived from 3-alkanoilpyridine *N*-oxides: **3b** (from 3-acetylpyridine *N*-oxide) and **3c** (from 3-pivaloylpyridine *N*-oxide). Each was made from the corresponding acylpyridine *N*-oxide in a manner similar to **3a**, and each compound was isolated as a single stereoisomer. The configurations were determined by ¹³C-NMR following the method of Bunnell and Fuchs;³⁷ **3b** was shown to have the (*E*)-configuration and **3c** was the (*Z*)-isomer (Figure 1).

Results of the cyclizations of **3b** and **3c** in dichloromethane are shown in Table 4. As evident from the data, cyclization proceeded smoothly for the (*Z*)-hydrazone **3c**, giving primarily **1a** using tosyl anhydride and slightly favoring **1a'** using triflic anhydride, but failed for the (*E*)-hydrazone **3b**. This result is not entirely unexpected, given the similar observations in attempted cyclizations of (*E*)-hydrazones derived from 2-chloro-3-formylquinolines.³⁸

Summary

We have developed a synthesis of regioisomeric pyrazolo[3,4-*b*]pyridines and pyrazolo[4,3-*c*]pyridines via the cyclization of pyridine *N*-oxide tosylhydrazones. Although the method is currently limited to the use of (*Z*)-hydrazones, we believe it is a valuable complement to existing methods of pyrazolopyridine synthesis since it proceeds under mild conditions (i. e. room temperature) and eliminates the need for the introduction of a leaving group onto the pyridine ring. Furthermore, the regioselectivity of the cyclization can be controlled to a moderate degree by varying the electrophile/solvent combination. Additional studies of the scope and limitations of this cyclization protocol and its application to the synthesis of other nitrogen-containing heterocycles are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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3b (*E*) **3c** (*Z*)

Figure 1.
Compounds **3b** and **3c** (configurations determined by ^{13}C -NMR³⁷).

Scheme 1. Synthesis of the pyrazolo[3,4-*b*]pyridine ring system (**1**)

Scheme 2.
Proposed approach to pyrazolopyridines **1** and **1'**.

Table 1Effect of electrophilic additive on the cyclization of **3a**^a

Entry	Additive	% Yields ^b	
		1a	1a'
1	TsCl	82	12
2	Ts ₂ O	85	11
3	Ms ₂ O	66	4
4	TFAA	75	0
5	PyBroP	56	0
6	Tf ₂ O	25	56
7	Ac ₂ O	~35 ^c	0

^a **3a** (0.5 mmol), additive (0.55 mmol), Et₃N (1.1 mmol), CH₂Cl₂ (5 mL).^b Isolated yields; average of at least 2 experiments.^c See text.

Table 2Effect of additive/base combinations on the cyclization of **3a**^a

Entry	Additive	Base	% Yields ^b	
			1a	1a'
1	Ts ₂ O	Et ₃ N	85	11
2	Ts ₂ O	DIPEA	70	9
3	Ts ₂ O	DABCO	68	15
4	Ts ₂ O	MIm ^c	63	9
5	Tf ₂ O	Et ₃ N	25	56
6	Tf ₂ O	DIPEA	28	52
7	Tf ₂ O	DABCO	26	51
8	Tf ₂ O	MIm ^c	14	60

^a **3a** (0.5 mmol), additive (0.55 mmol), base (1.1 mmol), CH_2Cl_2 (5 mL).^b Isolated yields; average of at least 2 experiments.^c N-Methylimidazole

Table 3Effect of additive/solvent combinations on the cyclization of **3a**^a

<p>The reaction scheme shows the cyclization of compound 3a (a pyridine ring with a phenyl group and an NHTs group) to products 1a and 1a' (indole derivatives). The reaction conditions are Additive, Et₃N, Solvent, RT.</p>				
Entry	Additive	Solvent	% Yields ^b	
			1a	1a'
1	Ts ₂ O	CH ₂ Cl ₂	85	11
2	Ts ₂ O	CH ₃ CN	79	9
3	Ts ₂ O	PhCl	57	10
4	Ts ₂ O	PhCH ₃	57	9
5	Tf ₂ O	CH ₂ Cl ₂	25	56
6	Tf ₂ O	CH ₃ CN	63	8
7	Tf ₂ O	PhCl	39	39
8	Tf ₂ O	PhCH ₃	59	31

^a **3a** (0.5 mmol), additive (0.55 mmol), Et₃N (1.1 mmol), solvent (5 mL).^b Isolated yields; average of at least 2 experiments.

Table 4

Cyclization of **3b** and **3c**^a

Entry	Additive	Products	% Yields ^b	
			1	1'
1	R = CH ₃ Ts ₂ O	1b, 1b'	0	0
2	(3b) Tf ₂ O		0	0
3	R = <i>t</i> -Bu Ts ₂ O	1c, 1c'	64	8
4	(3c) Tf ₂ O		36	42

^a **3** (0.5 mmol), additive (0.55 mmol), Et₃N (1.1 mmol), CH₂Cl₂ (5 mL).^b Isolated yields; average of at least 2 experiments.