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General Method for the Preparation of Electron-Deficient Imidazo[1,2-*a*]pyridines and Related Heterocycles

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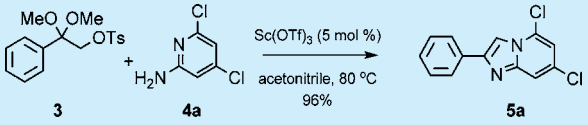
Supporting Information

ABSTRACT: A new annulation method for the preparation of the imidazo[1,2-*a*]pyridine ring system under mild conditions is presented. Treatment of a 2-aminopyridine with a dimethylketal tosylate in acetonitrile at elevated temperature (80−140 °C) in the presence of catalytic $Sc(OTf)_3$ provides the imidazo[1,2-*a*]pyridine product in good yield. The annulation method is broadly applicable to electron-poor 2-aminopyridines and displays a complementary profile to the classic preparation of the imidazo[1,2-*a*]pyridine ring system by reaction of a bromoketone with electron-rich and -neutral substrates. The scope of the process and mechanistic considerations are discussed.



Imidazo[1,2-*a*]pyridines are an important class of pharmacologically active heterocycles widely represented in marketed pharmaceutical drugs (Figure 1).[1,2] The classic preparation of the

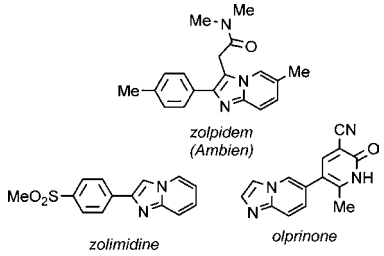
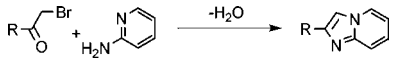


Figure 1. Approved drugs containing imidazo[1,2-*a*]pyridines.

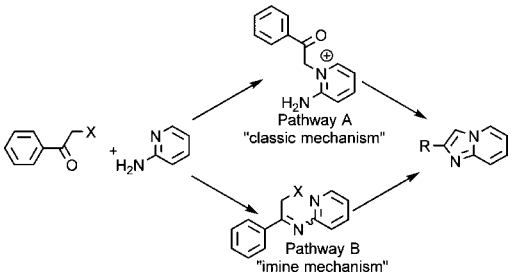
imidazo[1,2-*a*]pyridine ring system involves the reaction of a bromoketone with a 2-aminopyridine (Scheme 1). This reaction

Scheme 1



is generally considered to proceed via alkylation of the pyridine nitrogen by the bromoketone followed by cyclodehydration of the intermediate pyridinium ketone (Scheme 2, pathway A).[3,4] Recently in the course of a medicinal chemistry project, we encountered a group of electron-deficient 2-aminopyridines that provided little or no imidazo[1,2-*a*]pyridine products upon subjection to standard cyclization conditions. We hypothesized that the observed lack of conversion was a result of poor reactivity in the alkylation step. Based on this assumption, we proposed to access an alternative reaction pathway involving first the formation of an intermediate imine followed by cyclization to deliver the imidazo[1,2-*a*]pyridine product (Scheme 2, pathway B). Generally, efforts to improve the classic cyclization reaction have centered upon improving the alkylative capacity of the

Scheme 2



electrophile through the use of a more active leaving group (e.g., sulfonate, iodide, diazo).[2] Only one method has been reported targeting the imine pathway producing imidazo[1,2-*a*]pyridine products in moderate to low yields under forcing conditions ($TiCl_4$, 170 or 110 °C).[4a] However, the suggestion of involvement of the imine pathway has been made in at least one other instance.[5] In the context of the imine pathway, we were intrigued by a report of imine formation under mild conditions via reaction of dimethylketals with aromatic amines upon heating in chlorinated solvents.[6] Our efforts to adapt this reaction to the preparation of imidazo[1,2-*a*]pyridines are detailed herein.

Our investigations began with a survey of the reaction of 4,6-dichloro-2-amine-pyridine (**4a**), a prototypical electron-deficient 2-aminopyridine, with several acetophenone dimethyl ketal substrates incorporating potential leaving groups (Cl, Br, OTs) (Table 1). The requisite dimethyl ketals were readily prepared from the corresponding ketones under mild conditions ($CH(OMe)_3$, MeOH, TsOH (cat.), reflux).[7] In the event, both the bromo ketal **2** and the tosylate ketal **3** were able to undergo the desired reaction, while the chloro substrate **1** produced no cyclization product. The reactions of the corresponding ketones,

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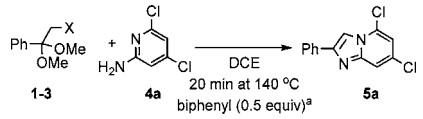
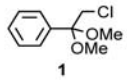
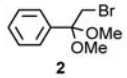
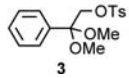
Table 1. Leaving Group Optimization



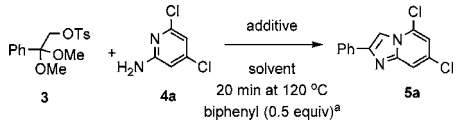
Entry	substrate	Conversion[b] (% **4a**:% **5a**)
1	 **1**	no reaction
2	 **2**	17:62
3	 **3**	0:>95

[a]Biphenyl (0.5 equiv) added as an internal standard. [b]Absolute uncorrected HPLC conversion based on biphenyl standard (starting amine **4a**%/product **5a**%).

in contrast, demonstrated no product formation with the exception of the tosylate ketone which provided trace conversion. This result suggested that the reaction was indeed specific to the ketal. Tosylate ketal **3** provided the highest conversion and the cleanest reaction. Furthermore, tosyl ketal **3** is a stable, isolable crystalline solid. In view of this favorable profile, tosylate ketal **3** was chosen for further development of the annulation reaction.

Consideration of the mechanism suggests imine formation likely proceeds under acid catalysis. With this in mind, we next surveyed a range of acidic and basic additives in several solvent systems in order to evaluate their effect on the imidazo[1,2-*a*]pyridine cyclization reaction (Table 2). Addition of amine bases (pyridine or DIPEA) completely inhibited product formation (entries 2 and 3). Alternatively, addition of a protic acid catalyst (pyridinium tosylate (PPTS) or camphor sulfonic acid (CSA)) significantly improved conversion (entries 4−6). Addition of excess CSA, however, was an exception, presumably due to complete protonation of the 2-aminopyridine (entry 7). Further improvement was observed utilizing the mild Lewis acid catalyst $Sc(OTf)_3$ (entries 8−11). Interestingly, the amount of added $Sc(OTf)_3$ could be reduced to 0.01 equiv without significant reduction in conversion (entry 8). The solvent effect on the reaction was also significant. In the absence of a catalyst, no reaction occurred in dioxane or toluene (entries 15 and 17). In contrast, acetonitrile produced substantially better conversion than DCE in the absence of catalyst (entry 12). However, in the presence of an acid catalyst, condensation to imine and subsequent cyclization occurred readily in all four solvents (entries 13, 14, 16, 18). The efficiency of the subsequent ring closure, however, was superior in acetonitrile. The mass balance in most cases was composed primarily of the two isomers of the intermediate imine typically heavily favoring one confirming the presumed reaction pathway. The results of this survey are consistent with the reaction proceeding via the acid catalyzed formation of an intermediate imine followed by cyclization to the imidazo[1,2-*a*]pyridine product. In the absence of an external acid, it is likely that trace displacement of the leaving group provides a small amount of acid which then can catalyze imine formation thus allowing the cyclization process to proceed. Continued exploration demonstrated that, at 80 °C in the

Table 2. Survey of Additives



entry	solvent	additive	equivalents of additive	conversion[b] (%**4a**/%**5a**)
1	DCE	–	–	63:10
2	DCE	pyridine	2	no reaction
3	DCE	DIPEA	2	no reaction
4	DCE	PPTS	0.20	9:54
5	DCE	PPTS	2	5:87
6	DCE	CSA	0.20	28:79
7	DCE	CSA	2	no reaction
8	DCE	$Sc(OTf)_3$	0.01	10:49
9	DCE	$Sc(OTf)_3$	0.05	7:64
10	DCE	$Sc(OTf)_3$	0.10	6:61
11	DCE	$Sc(OTf)_3$	0.20	5:86
12	acetonitrile	–	–	24:55
13	acetonitrile	$Sc(OTf)_3$	0.01	10:72
14	acetonitrile	$Sc(OTf)_3$	0.05	13:88
15	dioxane	–	–	no reaction
16	dioxane	$Sc(OTf)_3$	0.05	32:33
17	toluene	–	–	no reaction
18	toluene	$Sc(OTf)_3$	0.05	32:39

[a]Biphenyl (0.5 equiv) added as an internal standard. [b]Absolute uncorrected HPLC conversion based on biphenyl standard (starting amine **4a**%/product **5a**%).

presence of $Sc(OTf)_3$, the reaction still proceeded at a reasonable albeit slower rate. Considering these results together, a general procedure for the annulation reaction was established as heating a solution of the 2-aminopyridine (1 equiv), tosyl ketal **3** (1.2 equiv), and catalytic $Sc(OTf)_3$ (0.05 equiv) in acetonitrile at 80−140 °C based on reactivity (using 120 °C for the initial temperature).

Having identified optimal conditions, we investigated the scope and generality of the annulation reaction using a series of substituted 2-aminopyridine substrates (Scheme 3). All four isomers of both chloro-substituted pyridine substrates **4b−e** and ester-substituted pyridine substrates **4f−i** provided the corresponding imidazo[1,2-*a*]pyridine products in moderate to excellent yields (49−99%, **5b−5i**). In contrast, 3-, 4-, or 5-methoxy substituted pyridine substrates **4k−m** did not produce imidazo[1,2-*a*]pyridine products. 2-Amino-6-methoxypyridine (**4j**), however, did deliver imidazo[1,2-*a*]pyridine **5j** in good yield (82%). Fluoro, bromo, trifluoromethyl, and dichloro substituents were also well tolerated providing imidazo[1,2-*a*]pyridines **5n**, **5o**, **5p**, **5a**, and **5q** in 87%, 76%, 73%, 71%, and 62% yield, respectively. Last, we attempted cyclization of 2-aminopyridine (**5r**) and 2-amino-6-methylpyridine (**5s**), both of which failed to deliver the corrresponding imidazo[1,2-*a*]-pyridine products. Substrates which exhibited high reactivity at 120 °C (see discussion below) can be cyclized at a lower temperature (80 °C or reflux). For example, dichloropyridines **4a** and **4q** both displayed high relative reactivity at 120 °C. Annulation of **5a** and **5q** at 80 °C provided excellent yields of the corresponding imidazo[1,2-*a*]pyridine products **5a** and **5q**, 96% and 97%, respectively.

In addition to imidazo[1,2-*a*]pyridines, the annulation is also applicable to the preparation of the related heterocycles imidazo[1,2-*b*]pyridazine, imidazo[1,2-*c*]pyrimidine, imidazo-

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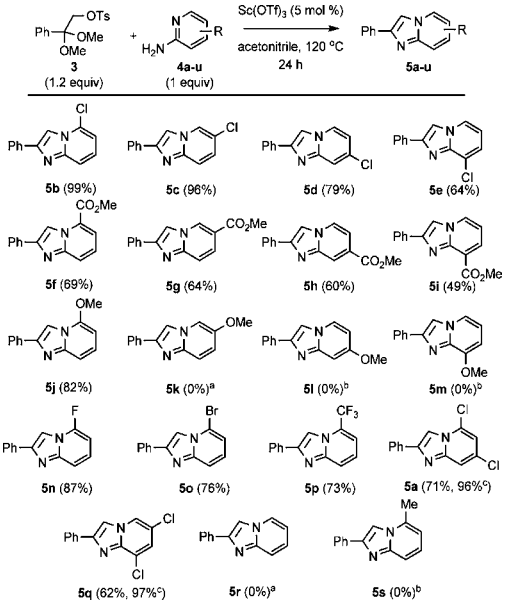
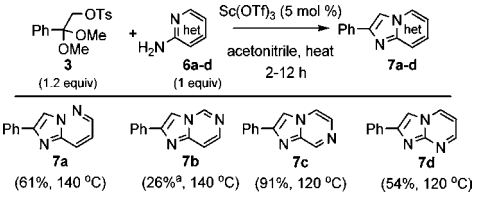
Scheme 3



[a]Trace conversion observed. [b]No conversion observed. [c]Cyclization conducted at 80 °C.

[1,2-*a*]pyrazine, and imidazo[1,2-*a*]pyrimidine (Scheme 4). Treatment of pyridazin-3-amine (**6a**), pyrimidin-4-amine (**6b**),

Scheme 4

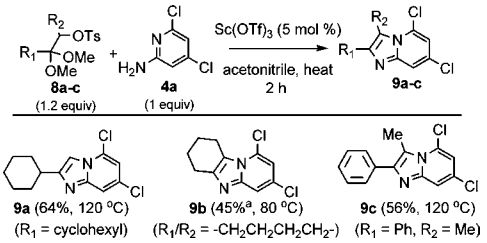


[a]Amine not completely soluble.

pyrazin-2-amine (**6c**), or pyrimidin-2-amine (**6d**) with tosyl ketal **3** under the standard conditions provided heterocycles **7a**, **7c**, and **7d** in good yields (54%−91%) with the exception of imidazo[1,2-*c*]pyrimidine **7b** (26%). Pyrimidin-4-amine (**6b**), however, exhibited poor solubility under these conditions which may have contributed to the low observed yield. Even with the single lower yield, the cyclization is remarkable for delivering product in all cases thus demonstrating significant generality. Syntheses of the imidazo[1,2-*b*]pyridazine, imidazo[1,2-*c*]-pyrimidine, imidazo[1,2-*a*]pyrazine, and imidazo[1,2-*a*]-pyrimidine ring systems often exhibit highly variable yields depending on substitution patterns and can be quite challenging. These challenges highlight the utility of alternative methods of preparation of these heterocycles.

Next, we evaluated the annulation reaction for the preparation of 2- and 3-alkyl substituted imidazo[1,2-*a*]pyridines (Scheme 5). Reaction of dimethyl ketal **8a** (R_1 = cyclohexyl) with dichloropyridine **4a** under the standard conditions provided 2-cyclohexyl imidazo[1,2-*a*]pyridine **9a** in 64% yield. 2,3-Disubstituted imidazo[1,2-*a*]pyridines also proved accessible utilizing the cyclization reaction. Annulation of ketal **8b** (R_1/R_2 = $-CH_2CH_2CH_2CH_2-$) with dichloropyridine **4a** delivered tricyclic imidazo[1,2-*a*]pyridine **9b** in 45% yield. Finally, cyclization of propiophenone derived ketal **8c** (R_1 = Ph, R_2 =

Scheme 5

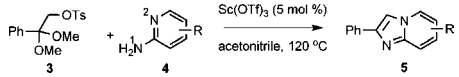


[a]Yield reduced by a competing aromatization reaction of cyclohexyl intermediate.

Me) with dichloropyridine **4a** produced imidazo[1,2-*a*]pyridine **9c** in 56% yield.

To help elucidate the factors which contribute to the observed reactivity pattern, partial charge and pK_a[8] were calculated for each nitrogen atom of the various 2-aminopyridine substrates. The observed relative rate of the annulation reaction correlated remarkably well with the calculated pK_a of the endocyclic pyridine nitrogen (Table 3), while little or no correlation was

Table 3. Calculated pK_a and Relative Reaction Rate



entry	pyridine substrate	R	relative cyclization rate[a]	calculated pK_a of ^2N of pyridine **4**[b]
1	**4b**	6-Cl	+++	1.7
2	**4c**	5-Cl	+	4.5
3	**4d**	4-Cl	+	5.3
4	**4e**	3-Cl	+	4.3
5	**4f**	6-CO_2Me	+	4.8
6	**4g**	5-CO_2Me	+	4.4
7	**4h**	4-CO_2Me	+	4.8
8	**4i**	3-CO_2Me	+	4.4
9	**4j**	6-OMe	+	3.2
10	**4k**	5-OMe	−	6.3
11	**4l**	4-OMe	−	7.2
12	**4m**	3-OMe	−	6.4
13	**4n**	6-F	+++	0.8
14	**4o**	6-Br	++	2.0
15	**4p**	6-CF_3	++	1.0
16	**4a**	4,6-diCl	+++	0.5
17	**4q**	3,5-diCl	++	2.1
18	**4r**	-H	−	6.7
19	**4s**	6-Me	−	7.1

[a]Relative rate based on LCMS approximate qualitative conversion after 2 h (+++: >50% conversion, ++: 50−20% conversion, +20−0% conversion, −: no reaction). [b]*Ab initio* pK_a of pyridine nitrogen calculated using Jaguar module within Maestro Elements 1.4.

observed with the pK_a of the exocyclic primary amine or with the calculated partial charge on either nitrogen atom. Substrates with a calculated pyridine nitrogen pK_a of greater than 6 failed to undergo the reaction. This trend is effectively highlighted by the series of methoxypyridines **4j−m**. The calculated pK_a values of 6-, 5-, 4-, and 3-methoxy pyridines **4j−m** are 3.2, 6.3, 7.2, and 6.4, respectively, (Table 3, entries 9−12). Of the methoxy pyridines **4j−m**, only 6-methoxy pyridine **4j** with a pK_a of 3.2 is observed to undergo the annulation reaction. This reactivity pattern stands in contrast with what is generally observed where the more basic/nucleophilic 2-aminopyridine substrates undergo reaction with

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bromoacetophenone presumably via the alkylative pathway, while the less basic/nucleophilic aminopyridine substrates provide little or no conversion. In fact, of the imidazo[1,2-*a*]pyridines **5a**–**s** prepared, none represent previously known compounds when the precursor 2-aminopyridine **4** has a calculated pK_a of less than 4. In the course of the reaction condition optimization studies, we observed that basic additives inhibited the annulation reaction (Table 2, entries 2 and 3). A question therefore arises: do the more basic substrates that do not undergo the annulation reaction fail because of inadequate reactivity or because they actively inhibit condensation to the imine. To address this question, the cyclization of 4,6-dichloropyridine **4a** was conducted in the presence of 2-aminopyridine (**5r**). In this experiment, no cyclization of 4,6-dichloropyridine **4a** to imidazo[1,2-*a*]pyridine **5a** was observed. This result suggests that the more basic substrates do indeed inhibit the condensation step, presumably through sequestration of the scandium catalyst and explains why pK_a correlates with relative reactivity. As a practical matter, 2-aminopyridine substrates which demonstrate high relative reaction rates (+++ and ++) should proceed well under reflux conditions (82 °C).

The two distinct reaction pathways, the alkylative pathway and the imine pathway (Scheme 2), represent a continuum of reactivity rather than a strict dichotomy. The operable pK_a range of <6 for the imine pathway overlaps significantly with the pK_a range observed for the alkylative pathway of >4 (Figure 2). Both

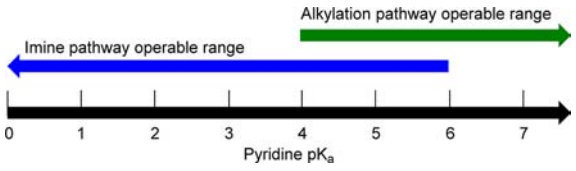
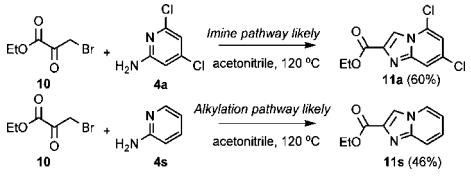


Figure 2. Operable pK_a ranges for the alkylative pathway and the imine pathway.

mechanistic pathways, however, reflect the innate propensity of the acetophenone substrate to undergo either imine formation via a ketal precursor or undergo alkylation via a halo ketone precursor. Ethyl bromopyruvate (**10**) presents an interesting substrate wherein the halo ketone component is capable of both modes of reactivity since it presents both a reactive alkyl halide and an electrophilic carbonyl and thus should have a broad substrate scope. In our hands, the unoptimized reaction of ethyl bromopyruvate (**10**) with either dichloropyridine **4a** or unsubstituted pyridine **4s** under conditions very similar to the general protocol delivers the imidazo[1,2-*a*]pyridine **11a** (60%) and **11s** (46%), respectively (Scheme 6). This result confirms the reactivity of ethyl bromopyruvate (**10**) with both classes of substrates, electron-deficient and -rich pyridines, consistent with accessing both reaction pathways. The key feature of this new annulation reaction is the enablement of the imine pathway through the use of the ketal as the substrate.

Scheme 6



A new procedure for the preparation of the imidazo[1,2-*a*]pyridine ring system from 2-aminopyridine substrates has been presented. The new cyclization reaction relies upon the reaction proceeding via an imine intermediate rather than a pyridinium through the use of a dimethyl ketal precursor. Importantly, the scope of electron-deficient, non-nucleophilic 2-aminopyridine substrates is complementary to the well-known classic reaction of nucleophilic 2-aminopyridines with α-halo ketones. This new annulation procedure expands the range of potential substrates that can undergo conversion to imidazo[1,2-*a*]pyridine and the related imidazo[1,2-*b*]pyridazine, imidazo[1,2-*c*]pyrimidine, imidazo[1,2-*a*]pyrazine, and imidazo[1,2-*a*]pyrimidine and thus provides a valuable addition to the heterocycle preparation literature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02966.

Procedures, characterization data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.

(2) (a) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun.* **2015**, *51*, 1555. (b) Pericherla, K.; Kaswan, P.; Pandey, K.; Kumar, A. *Synthesis* **2015**, *47*, 887. (c) Koubachi, J.; El Kazzouli, S.; Bousmina, M.; Guillaumet, G. *Eur. J. Org. Chem.* **2014**, *2014*, 5119.

(3) Elliott, A. J.; Guzik, H.; Soler, J. R. *J. Heterocycl. Chem.* **1982**, *19*, 1437.

(4) (a) Cai, L.; Brouwer, C.; Sinclair, K.; Cuevas, J.; Pike, V. W. *Synthesis* **2006**, *2006*, 133. (b) Cai, L.; Chin, F. T.; Pike, V. W.; Toyama, H.; Liow, J. S.; Zoghbi, S. S.; Modell, K.; Briard, E.; Shetty, H. U.; Sinclair, K.; Donohue, S.; Tipre, D.; Kung, M. P.; Dagostin, C.; Widdowson, D. A.; Green, M.; Gao, W.; Herman, M. M.; Ichise, M.; Innis, R. B. *J. Med. Chem.* **2004**, *47*, 2208.

(5) Yadav, J. S.; Subba Reddy, B. V.; Gopal Rao, Y.; Srinivas, M.; Narsaiah, A. V. *Tetrahedron Lett.* **2007**, *48*, 7717.

(6) Carreño, M. C.; Cuerva, J. M.; Ribagorda, M.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1449.

(7) Giordano, C.; Castaldi, G.; Casagrande, F.; Belli, A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2575.

(8) The use of the term pK_a in this context refers to the pK_a of deprotonation of the conjugate acid pyridinium species.

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