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Triflic Anhydride Mediated Synthesis of Imidazo[1,5-*a*]azines

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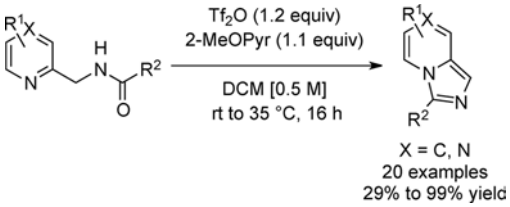
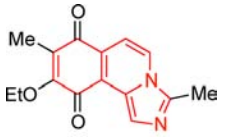
ABSTRACT



Imidazo[1,5-*a*]azines are synthesized in moderate to excellent yields using a mild cyclodehydration/aromatization reaction triggered by the use of triflic anhydride (Tf_2O) and 2-methoxypyridine (2-MeOPyr). Various substitution patterns and functional groups were found to be compatible under the optimized conditions. In addition, a 5-bromo-3-aryl derivative was also shown to be active in a Sonogashira cross-coupling and direct arylation reactions. A tertiary amide was compatible as a substrate leading to the synthesis of an imidazo[1,5-*a*]pyridinium triflate.

The imidazo[1,5-*a*]pyridine motif is a heterocyclic fused bicyclic system[1] applicable in materials chemistry[2] as well as potent pharmacophores.[3] Recently, derivatives of this heterocyclic system were embedded in the structure of many biologically active molecules tested for the treatment of inflammation,[3a,b] cancer,[3a,c] cardiovascular diseases,[3a] fertility disorders,[3d] and HIV.[3e] Moreover, Pettit et al. reported in 2003 a unique example of a naturally occurring imidazo[1,5-*a*]isoquinolinedione in the tricyclic structure of cribrostatin **6**, a highly active antimicrobial and anti-neoplasic agent (Figure 1).[4]



Cribrostatin 6

Figure 1. Imidazo[1,5-*a*]isoquinolinedione highlighted in the structure of cribostatin **6**.

Early synthetic methods targeting various imidazo-[1,5-*a*]azine derivatives were inspired from variants of either Wallach's imidazole synthesis[5] or a Vilsmeier-type cyclization.[6] Indeed, various reagents ($POCl_3$,[3b,c,4c−7a]

(1) For the numbering of these heterocycles, see: Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863.

(2) For selected recent applications, see: (a) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381. (b) Yamaguchi, E.; Shibahara, F.; Murai, T. *J. Org. Chem.* **2011**, *76*, 6146 and references cited therein.

(3) For selected recent applications, see: (a) Alcouffe, C.; Kirsch, R.; Herbert, C.; Lassale, G. 2012004732 A1, 2012. (b) Trotter, B. W..; et al. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2354. (c) Kamalaaa, A.; Ramakrishna, G.; Raju, P.; Subba Rhao, A. V.; Viswanath, A.; Lakshma Nayak, V.; Ramakrishna, S. *Eur. J. Med. Chem.* **2011**, *46*, 2427. (d) Loozen, H. J. J.; Timmer, C. M. WO 2010136438, 2010. (e) Anthony, N. J.; Gomez, R.; Jolly, S. M.; Su, D.-S.; Lim, J. WO 2008076225 A2, 2008.

(4) (a) Pettit, G. R.; Collins, J. C.; Knight, J. C.; Herald, D. L.; Nieman, R. A.; Williams, M. D.; Pettit, R. K. *J. Nat. Prod.* **2003**, *66*, 544. For recent total syntheses of cribrostatin **6**, see: (b) Mubina, M.; Gonçalves, T. P.; Whitby, R. J.; Sneddon, H. F.; Harrowven, D. C. *Chem.—Eur. J.* **2011**, *17*, 13698. (c) Knueppel, D.; Martin, S. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 2569. (d) Markey, M. D.; Kelly, T. R. *J. Org. Chem.* **2008**, *73*, 7441.

(5) (a) Benincori, T.; Brenna, E.; Sannicolo, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 675. (b) Wallach, O. *Justus Liebigs Ann. Chem.* **1877**, *184*, 1.

(6) For a seminal report, see: Bower, J. D.; Ramage, C. R. *J. Chem. Soc.* **1955**, 2834.

(7) For selected examples, see: (a) Satyanarayana, V. A.; Guangwu, C.; Kosarev, S.; Meifen, E. T.; Deijan, X.; Yet, L. *Tetrahedron Lett.* **2010**, *51*, 284. (b) Tachikawa, R.; Tanaka, S.; Terada, A. *Heterocycles* **1981**, *15*, 369. (c) Crawforth, J. M.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916. (d) Wamhoff, H.; Zahran, M. *Synthesis* **1987**, 876. (e) Li, J. J.; Li, J. J.; Li, J.; Trehan, A. K.; Wong, H. S.; Krishnananthan, S.; Kennedy, L. J.; Gao, Q.; Ng, A.; Robl, J. A.; Balasubramanian, B.; Chen, B.-C. *Org. Lett.* **2008**, *10*, 2897. (f) Kim, D..; et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.

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PCl_5,[7b] 1-propanephosphoric anhydride (T3P),[7c] Ph_3PCl_2,[7d] Burgess' reagent,[7e] and polyphosphoric acid (PPA)[7f]) were reported to trigger the latter intramolecular cyclodehydration/aromatization sequence from a secondary *N*-(2-pyridinylmethyl)amide. The respective secondary thioamides could also be cyclized by treatment with an oxidant.[8] However, the most commonly disclosed procedures imply the use of a large excess of activating reagent, have a narrow scope, and/or are performed at elevated temperatures. Alternatively, these heterocycles can be accessed through a Rh-catalyzed transannulation of pyridotriazoles,[9] via nucleophilic addition of 2-aminomethylpyridine onto 1,1-*gem*-dibromoalkenes,[10] or from oxidative cyclization between a 2-pyridocarboxaldehyde and an amino acid equivalent.[11] While these methods are milder than the previous electrophilic activations, there is still a need for general procedures suited for the synthesis of imidazo[1,5-*a*]azines at ambient temperatures. To address this issue, we decided to elaborate a triflic anhydride (Tf_2O) mediated cyclodehydration/aromatization strategy under operationally simple and mild conditions applicable to a wide variety of substitution patterns.

Recently, various electrophilic activations using amides and Tf_2O have found broad application in the synthesis of various building blocks.[12] We reported in 2009 an intramolecular activation/dearomatization strategy toward the synthesis of polysubstituted indolizidine and quinolizidine alkaloids (Scheme 1).[13] In these studies we determined that the use of 2-chloropyridine (2-ClPyr) as a slightly basic additive was required to obtain smooth conversion to the target product. Inspired by these results, we thought to optimize a generally applicable cyclization/aromatization route for the synthesis of aromatic imidazo[1,5-*a*]azines (**2**) from *N*-(2-pyridinylmethyl)benzamide (**1**) while adding minimal amounts of Tf_2O at ambient temperatures.[14,15] We first probed conditions that were operative in secondary amide reductions using 2-fluoropyridine (2-FPyr) as a base additive which gave a reasonable 66% yield (Table 1, entry 1).[12e,16]

Scheme 1. Synthesis of Indolizidine and Quinolizidines and Its Transposition Towards the Synthesis of Imidazo[1,5-*a*]azines (**2**)

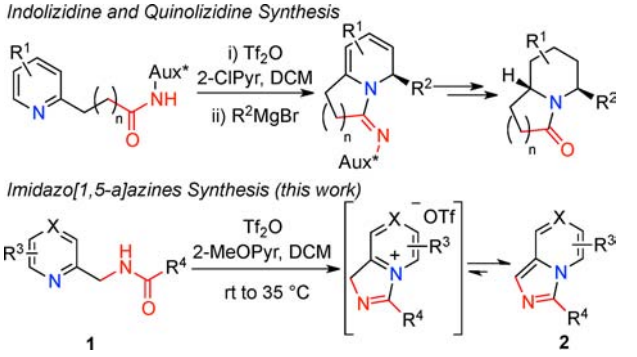
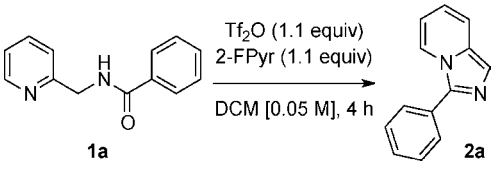


Table 1. Optimization for the Cyclodehydration/Aromatization



entry	base additive	temp (°C)	time (h)	Tf_2O (equiv)	yield **2a** (%)[a]
1	2-FPyr	−78 °C to rt	4	1.1	66[b]
2	2-FPyr	−78 °C to rt	4	1.1	69
3	2-FPyr	rt	4	1.1	70
4	2-FPyr	rt	4	1.0	63
4	2-FPyr	rt	4	1.2	75
5	2-MeOPyr	rt	4	1.2	80
6	none	rt	4	1.2	48
7	2-MeOPyr	rt	6	1.2	89
8	2-MeOPyr	rt to 35 °C	16	1.2	94

[a] Yields determined on the crude reaction mixture by ^{1}H NMR analysis using Ph_3CH as an internal standard. [b] Concentration of amide in DCM of 0.05 M instead of 0.5 M.

We subsequently determined that the reaction can be performed in concentrated DCM media (0.5 M, 69%, entry 2) while adding Tf_2O at room temperature (70%, entry 3). These conditions are in contrast to those obtained in the indolizidine/quinolizidine synthesis where Tf_2O was added to a diluted DCM solution of **1a** (0.05 M) at −78 °C.[13] A screening of basic additives proved the importance of having a non-nucleophilic base present, as a much lower yield was obtained without it (48%, entry 6). Performing the reaction in the presence of 2-methoxypyridine (2-MeOPyr) for 16 h from 25 to 35 °C gave optimal conversions and yields for the desired product **2a** (94%, entry 8).[17]

(8) (a) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621. (b) Moulin, A.; Garcia, S.; Martinez, J.; Fehrentz, J.-A. *Synthesis* **2007**, 2667. (c) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566 and references cited therein.

(9) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757.

(10) Zhang, A.; Xiaoling, Z.; Junfa, F.; Wang, S. *Tetrahedron Lett.* **2010**, *51*, 828.

(11) Wang, Q.; Shuai, Z.; Fengfeng, G.; Baiqun, Z.; Ping, H.; Zhiyong, W. *J. Org. Chem.* **2012**, *77*, 11161.

(12) For recent examples, see: (a) Valerio, V.; Petkova, D.; Madelaine, C.; Maulide, N. *Chem.—Eur. J.* **2013**, *19*, 2606. (b) Xiao, K.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2012**, *124*, 8439. (c) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228. (d) Medley, J. M.; Movassaghi, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4572. (e) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817.

(13) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398.

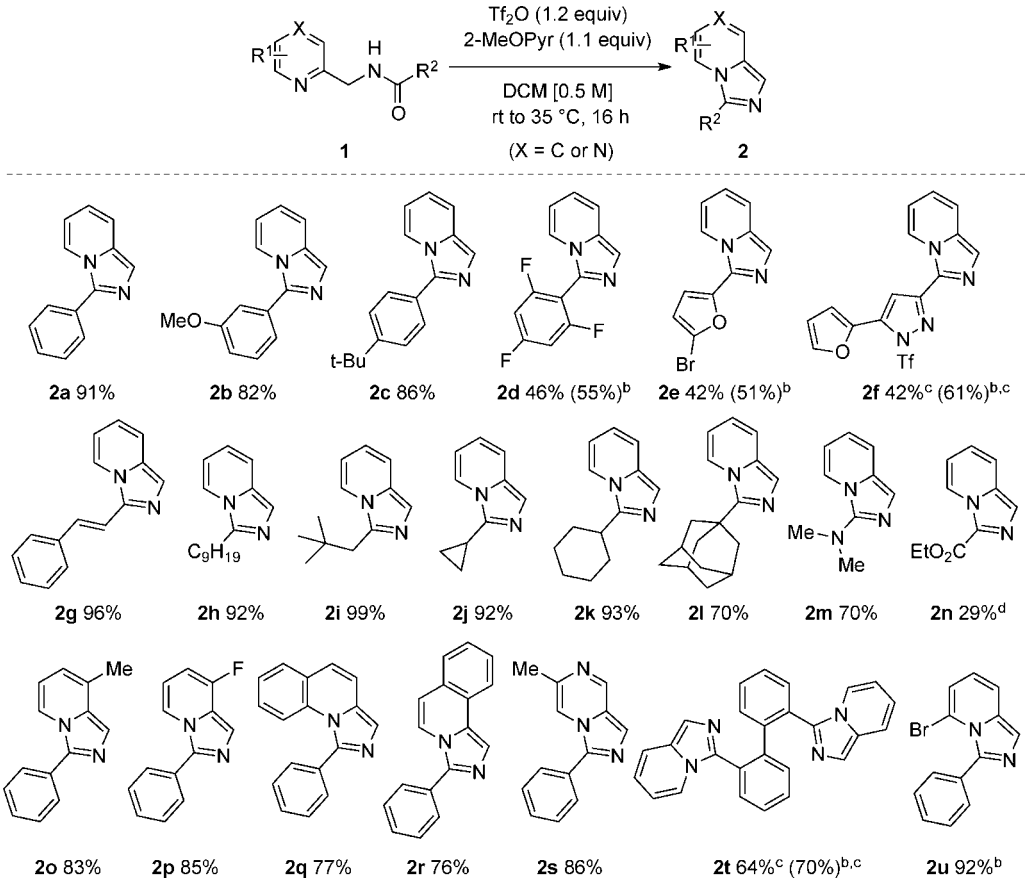
(14) We recently reported the synthesis of pyrazolo[1,5-*a*]pyridines via a divergent approach: Mousseau, J. J.; Bull, J. A.; Ladd, C. L.; Fortier, A.; Sustac Roman, D.; Charette, A. B. *J. Org. Chem.* **2011**, *76*, 8243.

(15) For application in the synthesis of the kedarcidin chromophore, see: Yoshimura, F.; Lear, M. J.; Ohashi, I.; Koyama, Y.; Hirama, M. *Chem. Commun.* **2007**, 3057.

(16) See Supporting Information for more details.

(17) We think that 2-methoxypyridine provides an ideal basicity and nucleophilicity needed for this transformation versus other pyridine derivatives. For a discussion on the basicity of 2-MeOPyr and derivatives, see: Murphy, R. A.; Sarpong, R. *Org. Lett.* **2012**, *14*, 632–635 and references cited therein.

Scheme 2. Synthesis of Imidazo[1,5-*a*]azines Using Optimized Cyclodehydration/Aromatization Conditions[a]



[a] Reaction performed on 1.0 mmol scale. Isolated yield. [b] Reaction was performed at 50 °C instead of 35 °C. [c] Reaction was performed in presence of 2.4 equiv of Tf_2O and 2.2 equiv of 2-MeOPyr instead of 1.2 equiv and 1.1 equiv. [d] Reaction was performed in DCE [0.5 M] at 65 °C for 16 h instead of DCM [0.5 M] at 35 °C for 16 h.

Under these optimized conditions, we tested variously substituted secondary amides toward their cyclization to the corresponding bicyclic heterocycles (Scheme 2). We rapidly identified that electron-rich benzamides underwent clean and high-yielding conversions while electron-poor substrates furnished moderate yields and conversions to the desired imidazo[1,5-*a*]pyridines (compare **2a**−**2c** and **2d**). With the latter 2,4,6-trifluorophenyl substrate **2d**, the reaction was found to be more productive when heated to 50 °C. With alkyl substituted substrates, the cyclodehydration/aromatization sequence gave very high yields and complete conversions at 35 °C (>92%; see **2h**−**2k**). The reaction is sluggish only with a very bulky *N*-(1-adamantyl) amide substituent (70%, **2l**). Moreover, a sharp contrast in reactivity was observed where a *N*′,*N*′-dialkyl urea **1m** could be readily activated by Tf_2O while the electron-poor ethyl oxalate derivative **1n** was heated to 65 °C to achieve a reasonable conversion. Variation of the substituents on the pyridine moiety was well tolerated (**2o**−**2r**), and imidazo[1,5-*a*]pyrazine could also be synthesized without seeing overtriflation on the pyrazine moiety (**2s**). A *N*,*N*′-bis(2-pyridinylmethyl)benzamide (**1t**) was also found to be efficiently doubly activated/cyclized using 2.4 equiv of Tf_2O.

To further explore the applicability of the developed method, we envisioned that the synthesis of 5-bromo-3-aryl imidazo[1,5-*a*]pyridine derivative **2u** could be possible (Scheme 3). Recently, some 5-substituted imidazo[1,5-*a*]pyridines (pyridinium) have found interesting applications in the treatment of cancer,[18a,b] as CCR1 receptor antagonists,[18c] and as efficient *N*-heterocyclic carbene precursors.[18d]

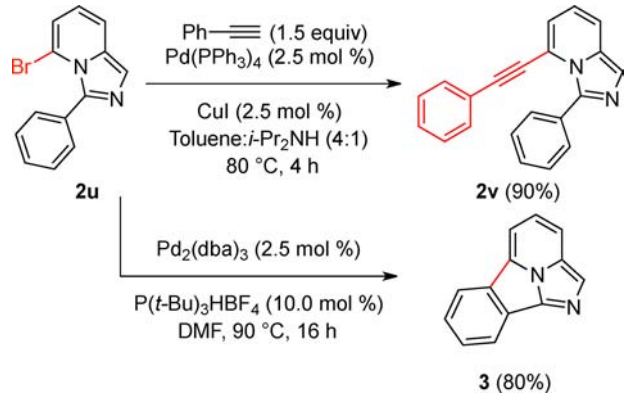
First, benzamide **1u** underwent clean conversion to the corresponding heterocycle **2u** under the optimized conditions at 50 °C (92%; see Scheme 2). The product was then treated under unoptimized Sonogashira cross-coupling conditions, and the 5-alkynyl derivative **2v** was isolated in high yield (90%).[19] However, when **2u** underwent Suzuki−Miyaura cross-coupling with 4-methoxyphenylboronic acid,[20] an inseparable mixture of the desired

(18) (a) Adams, N. D.; Aquino, C. J.; Chaudhari, A. M.; Ghergurovitch, J. M.; Kiesow, T. J.; Parrish, C. A.; Reif, A. J.; Wiggall, K. WO 2011103546 A1, 2011. (b) Price, S.; Heald, R.; Lee, W.; Zak, M. E.; Hewitt, J. F. M. WO 2009085983 A1, 2009. (c) Cook, B. N.; Kuzmich, D. WO 2011056440 A1, 2011. (d) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *26*, 6207.

(19) Severin, R.; Reimer, J.; Doye, S. *J. Org. Chem.* **2010**, *75*, 3518.

(20) Shibahara, F.; Yamaguchi, E.; Kitagawa, A.; Imai, A.; Murai, T. *Tetrahedron* **2009**, *65*, 5062.

Scheme 3. Synthesis of 5-Bromo-3-phenylimidazo[1,5-*a*]-pyridine (**2u**) and Subsequent Catalytic Functionalization[a]



[a] Reaction performed on a 0.5 mmol scale. Isolated yields.

5-(4-methoxy)phenyl heterocycle along with benzo[*a*]-imidazo[2,1,5-*c*,*d*]indolizine **3** was observed. When the boronic acid was omitted in the reaction conditions, only **3** was isolated in high yield (80%). Interestingly, this represents an unprecedented example of this type of heterocycle synthesized via an intramolecular direct arylation.[21]

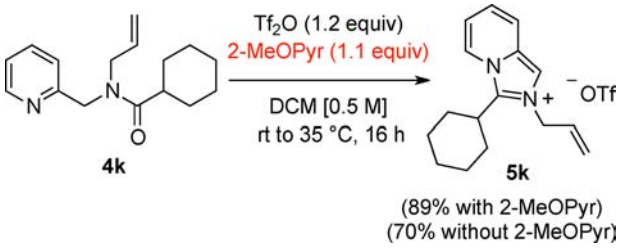
We decided to explore furthermore the electrophilic activations of tertiary amides toward the formation of imidazo[1,5-*a*]pyridinium salts (Scheme 4). In 2005, Glorius[18d] and Lassaletta[22] reported the use of such salts as *C*,*N*-substituted NHC and their further uses as ligands for Pd, Ag, Rh, Ir, and Se catalysts. As shown in Scheme 4, treatment of **4k** under the optimized conditions lead to the corresponding imidazo[1,5-*a*]pyridinium triflate **5k** in high yield (89%). Since a tertiary amide was used, the synthesis of **5k** could also be effective without the inclusion of 2-MeOPyr as a basic additive (70%).

In conclusion, we successfully developed a mild cyclodehydration/aromatization process that is effective at

(21) Recently, benzo[*a*]imidazo[5,1,2-*c*,*d*]indolizines which are isomers to **3** were synthesized via a tandem [8 + 2] cycloaddition/[2 + 6 + 2] dehydrogenative sequence: Aginagalde, M.; Vara, Y.; Arrieta, A.; Zanagi, R.; Cebolla, V. L.; Delgado-Camón, A.; Cossío, F. P. *J. Org. Chem.* **2010**, *75*, 2776.

(22) Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernandez, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290.

Scheme 4. Synthesis of Imidazo[1,5-*a*]pyridinium Triflate **5k**[a]



[a] Reaction performed on a 1.0 mmol scale. Isolated yields.

relatively low temperatures while using minimal amounts of an activating reagent. These conditions were applied to a large panel of secondary *N*-(2-pyridinylmethyl)amides with various substitution patterns. A 5-bromo-3-aryl imidazo-[1,5-*a*]pyridine was shown to be reactive in a Sonogashira reaction and was used as a handle toward the synthesis of more complex benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizines. Tertiary amides are also suitable partners in such reactions as illustrated by an example of an NHC precursor that was synthesized using the optimized Tf_2O activation conditions.

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Supporting Information Available. Experimental procedures, NMR spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.