

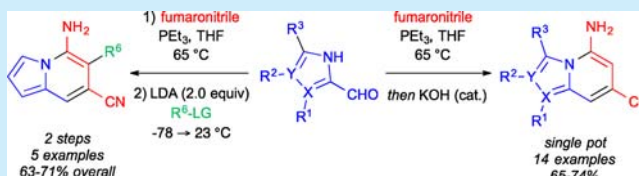
# One-Pot Synthesis of Highly Substituted *N*-Fused Heteroaromatic Bicycles from Azole Aldehydes

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**S** Supporting Information

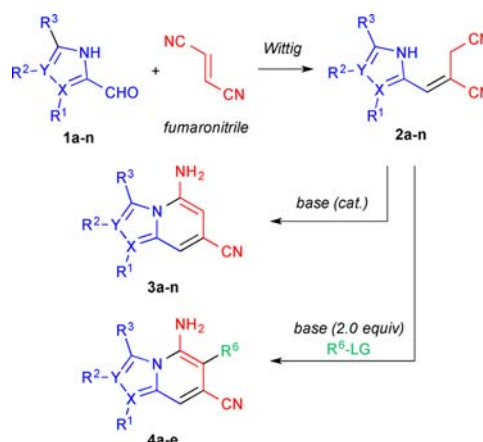
**ABSTRACT:** An efficient route to substituted *N*-fused aromatic heterocycles, including indolizines, imidazo[1,2-*a*]pyridines, and imidazo[1,5-*a*]pyridines from azole aldehydes, is reported. Wittig olefination of the aldehydes with fumaronitrile and triethylphosphine affords predominantly *E*-alkenes that undergo rapid cyclization upon treatment with a mild base. Substituent control of the 1-, 2-, and 3-positions of the resulting heteroaromatic bicycles is shown. Alternatively, the isolable *E*-alkene undergoes selective alkylation with electrophiles, followed by *in situ* annulation to indolizines additionally substituted at the 6-position.



*N*-Fused aromatic heterocycles, such as the indolizine and imidazopyridine classes, are attractive synthetic targets owing to their pharmacological potential and unique electronic properties. The wide array of biological effects elicited by members of these heteroaromatic classes has been well documented, including antimicrobial,<sup>1</sup> antiviral,<sup>2</sup> anti-inflammatory,<sup>3</sup> anti-tubercular,<sup>4</sup> anticancer,<sup>5</sup> antinociceptive,<sup>6</sup> antiprotozoal,<sup>7</sup> and hypnoselective<sup>8</sup> activities. In addition, these scaffolds, notably the imidazopyridines, have found utility as *N*-heterocyclic carbene (NHC) ligands in complexes with promising catalytic reactivity<sup>9</sup> or as inks and dyes. As a consequence of their diverse uses, several synthetic methods have been developed for their preparation. Traditional syntheses employ substituted pyridines to annulate the five-membered portion of the bicyclic system.<sup>10,11</sup> For example, the most common indolizine syntheses involve the euphonious Tschischibabin reaction or its conceptual variants and proceed by reaction of 2-alkylpyridines with  $\alpha$ -halo ketones.<sup>10a</sup> More recently, strategies have been developed to access these bicycles from their five-membered heterocyclic precursors.<sup>12</sup> Lee and Kim, for example, demonstrated the aldol-type cyclization of *N*-substituted 2-acetylpyrroles under alkaline conditions to furnish 6,8-disubstituted indolizines.<sup>12c</sup>

Despite recent developments to *N*-fused heteroaromatic bicycles, to our knowledge no routes exist that allow the direct synthesis of 5-amino-substituted indolizines. We recently reported a flexible, efficient route to highly substituted 7-aminoindoles from pyrrole-3-carboxaldehydes.<sup>13</sup> This route utilized a one-pot, three-component Wittig olefination of the aldehydes with a trialkylphosphine and fumaronitrile to afford predominantly *E*-alkenes, followed by a Lewis acid mediated intramolecular Houben–Hoesch reaction to the corresponding indoles. We envisioned a mechanistically related route to obtain the 5-aminoindolizine, 5-aminoimidazo[1,2-*a*]pyridine, and 5-aminoimidazo[1,5-*a*]pyridine classes, as shown in Scheme 1. In this case, rather than nucleophilic attack of the pyrrolic  $\alpha$ -carbon on a Lewis acid activated nitrile, we reasoned that the

## Scheme 1. Proposed Route to *N*-Fused Heterocycles



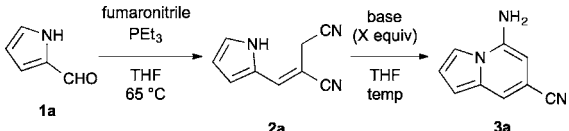
relative acidity of the azolic N–H proton would allow for facile deprotonation to a nucleophilic azolide anion followed by cycloaromatization. Alternatively, a second deprotonation could furnish an allylic dianion that could react selectively with electrophiles prior to cyclization to allow for substituent control at the 6-position.

Extending the conditions established in our laboratory,<sup>14</sup> Wittig olefination of commercially available pyrrole-2-carboxaldehyde afforded alkene **2a** in excellent yield and good diastereoselectivity as shown in Table 1. To establish an optimal annulation procedure, the *E*-isomer, purified by recrystallization from the diastereomeric mixture, was then subjected to a variety of conditions. Under the Lewis acidic conditions employed previously for the Houben–Hoesch annulation to 7-aminoindoles ( $\text{BF}_3 \cdot \text{OEt}_2$ ), no desired cycliza-

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**Table 1. Optimization of Annulation of Alkene 2a to Indolizine 3a**


entry	reagent	X (equiv)	temp (°C)	time (h)	yield 3a (%) <sup>b</sup>
1	BF <sub>3</sub> ·OEt <sub>2</sub> <sup>a</sup>	2.5	90	12	0
2	LDA	1.0	-78	1	0
3	LDA	1.0	0	0.5	98
4	LDA	0.4	0	0.5	97
5	LiHMDS	1.0	0	0.5	97
6	KOH	4.0	23	0.25	97
7	KOH	0.4	23	0.25	96
8	K <sub>2</sub> CO <sub>3</sub>	4.0	70	1	86

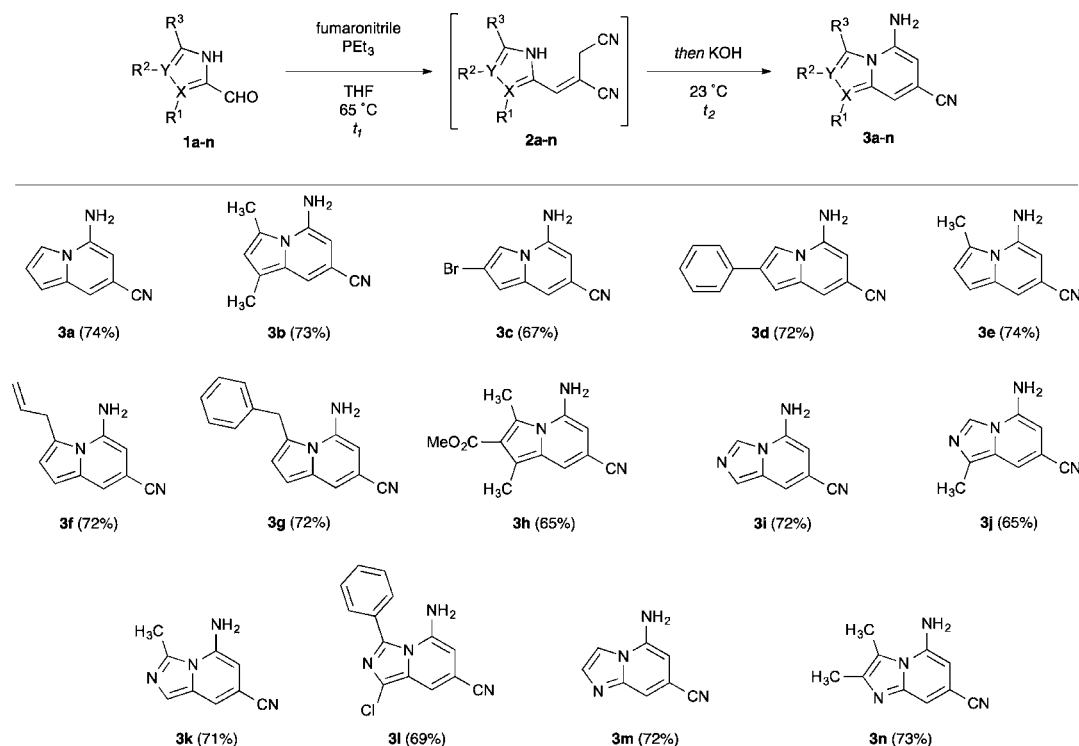
<sup>a</sup>Reaction run in 1,2-dichloroethane rather than THF. <sup>b</sup>Isolated yield.

tion was observed. Similarly, treatment with LDA at -78 °C resulted in the isolation of only starting material. At 0 °C, however, treatment with stoichiometric amounts of the strong base LDA or LiHMDS effected rapid and complete conversion to the indolizine 3a. The weaker bases KOH and K<sub>2</sub>CO<sub>3</sub> also exhibited the desired cyclization although higher temperatures were required. For KOH, complete conversion to the indolizine was observed at room temperature after 15 min. K<sub>2</sub>CO<sub>3</sub> was far less efficient and required reflux temperature as well as a longer reaction time and afforded lower yields. We hypothesized that the initial cyclized product, an anilide anion, could also act as a base itself thereby necessitating only a catalytic amount of base to initiate the cycle. Indeed, treatment with catalytic amounts of LDA at 0 °C or KOH at room temperature effected complete

conversion to the cyclized product. Due to the milder conditions, short reaction time, low cost, and ease of workup, we proceeded with catalytic KOH as the optimal method for annulation.

The mild and efficient cyclization conditions encouraged us to combine the Wittig olefination and cyclization steps into a tandem, one-pot synthesis of highly substituted *N*-fused heteroaromatic bicycles from azole aldehydes as shown in Scheme 2. The unadorned pyrrole-2-carboxaldehyde 1a was reacted as before with PET<sub>3</sub> and fumaronitrile at 65 °C, but for the one-pot procedure, the *E/Z* mixture was cooled to room temperature and catalytic KOH was added. The *E*-isomer was completely converted to 5-amino-7-cyanoindolizine within 30 min while the *Z*-isomer was left unreacted. The 74% yield for this reaction approaches the stoichiometric conversion of the 3:1 *E/Z* mixture. To demonstrate the scope of the olefination/cyclization sequence, a variety of substituted pyrrole and imidazole aldehydes were employed.<sup>14</sup> Under the same conditions as before, aldehydes 1b–n underwent alkene formation and cyclization to indolizines, imidazo[1,2-*a*]pyridines, and imidazo[1,5-*a*]pyridines in moderate to good yields. Like the unsubstituted pyrrole-2-aldehyde, yields approached the stoichiometric limit for the *E*-isomer present in the diastereomeric mixture of the crude Wittig reaction. The imidazole aldehydes exhibited much faster reaction rates for the Wittig reaction but much slower rates of annulation (see Supporting Information (SI) for reaction times). The additional nitrogen on the imidazole activates the aldehyde for attack by the phosphonium ylide, but the increased acidity of the imidazole stabilizes the azolide anion, thereby decreasing its nucleophilicity and slowing cyclization.

The conditions were tolerant of a range of substituents including halide, ester, and aryl functionalities, as well as alkyl

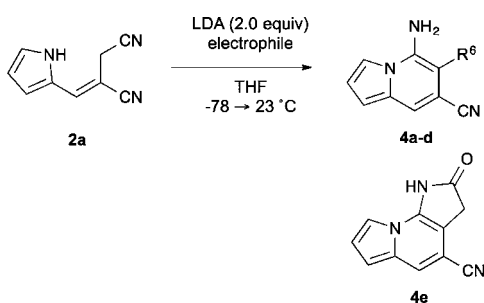
**Scheme 2. Scope of One-Pot Annulation of Azole Aldehydes<sup>a</sup>**

<sup>a</sup>See Supporting Information for reaction times.

substituents at each of the possible positions on the azole aldehydes. Deactivated azole aldehydes, for example those containing halogen and ester functionalities, showed a modest decline in yield. Aldehydes with substituents at the  $\alpha$ -position (e.g., **1b,h,l**) showed a moderate decrease in cyclization rate, potentially due to the A<sup>1,3</sup> strain present between the C-3 and C-5 substituents in the cyclized products.

With no cyclization occurring at  $-78$  °C, we hypothesized that the dianion of alkene **2a** formed at low temperatures could react with electrophiles regioselectively at the allylic position. The resulting alkylated monoanions would then cyclize *in situ* upon warming. This method would allow for selective installation of C6 substituents in the indolizine products. A set of electrophiles were chosen, and the results are summarized in Table 2. Selective addition of alkyl-, allyl-, propargyl-,

**Table 2. Tandem, One-Pot Alkylation/Cyclization Sequence to 5,6,7-Trisubstituted Indolizines 4a–e**



entry	electrophile	product	R <sup>6</sup>	yield (%) <sup>a</sup>
1	MeI	<b>4a</b>	–CH <sub>3</sub>	87
2	H <sub>2</sub> C=CHCH <sub>2</sub> Br	<b>4b</b>	–CH <sub>2</sub> CH=CH <sub>2</sub>	98
3	H <sub>2</sub> C≡CHCH <sub>2</sub> Br	<b>4c</b>	–CH <sub>2</sub> CH≡CH <sub>2</sub>	94
4	PhCH <sub>2</sub> Br	<b>4d</b>	–CH <sub>2</sub> Ph	98
5	BrCH <sub>2</sub> CO <sub>2</sub> Et	<b>4e</b>		90

<sup>a</sup>Isolated yield.

benzyl-, and  $\alpha$ -keto halides was achieved at  $-78$  °C. After 1 h of alkylation, the acetone/CO<sub>2</sub> bath was removed effecting rapid cyclization to the 5,6,7-trisubstituted indolizines **4a–e** as the reaction mixture warmed to room temperature. These tandem alkylation/cyclization reactions exhibited excellent yields. The activated electrophiles afforded slightly higher yields than the nonactivated MeI. Notably, the reaction with ethyl bromoacetate effected selective alkylation of the dianion, annulation to the indolizine, and further condensation to the  $\gamma$ -lactam **4e** in a single pot, highlighting the efficiency and synthetic potential of this method.

In conclusion, we have developed a one-pot, olefination/cyclization sequence for the synthesis of highly substituted indolizines, imidazo[1,2-*a*]pyridines, and imidazo[1,5-*a*]pyridines from pyrrole-2-, imidazole-2-, and imidazole-4-carboxaldehydes, respectively. Wittig olefination of the aldehydes with an ylide formed *in situ* from fumaronitrile and triethylphosphine affords *E*-enriched alkenes which undergo cycloaromatization when treated with catalytic and mild bases, allowing for control of the C-1, C-2, and C-3 substituents. Alternatively, the isolable *E*-isomers undergo selective dianionic alkylation at  $-78$  °C followed by spontaneous cyclization upon warming to room temperature, allowing for C-6 substituent control. The efficiency and tailorability of this method simplifies the generation of large arrays of functionalized

heteroaromatic compounds. Isosteres and nitrogen-rich homologues of indole present geometrically definable hydrogen bond donors and acceptors that greatly expand the usefulness of this privileged nucleus in medicinal chemistry. The substituents and substitution patterns readily achievable by this approach enrich and complement those available by current methods.<sup>15</sup>

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed synthetic procedures and characterization data can be found in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (a) Hazra, A.; Mondal, S.; Maity, A.; Naskar, S.; Saha, P.; Paira, R.; Sahu, K. B.; Paira, P.; Ghosh, S.; Sinha, C.; Samanta, A.; Banerjee, S.; Mondal, N. B. *Eur. J. Med. Chem.* **2011**, *46*, 2132–2140. (b) Darwish, E. S. *Molecules* **2008**, *13*, 1066–1078.
- (a) Reddy, M. V.; Rao, M. R.; Rhodes, D.; Hansen, M. S.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907. (b) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392–7399.
- (a) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636–3658. (b) Yokota, Y.; Hanasaki, K.; Ono, T.; Nakazato, H.; Kobayashi, T.; Arita, H. *Biochim. Biophys. Acta* **1999**, *1438*, 213–222.
- (a) Dannhardt, G.; Meindl, W.; Gussmann, S.; Ajili, S.; Kappe, T. *Eur. J. Med. Chem.* **1987**, *22*, 505–510. (b) Gundersen, L. L.; Negussie, A. H.; Rise, F.; Ostby, O. B. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 191–195.
- (a) Cheng, Y.; An, L. K.; Wu, N.; Wang, X. D.; Bu, X. Z.; Huang, Z. S.; Gu, L. Q. *Bioorg. Med. Chem.* **2008**, *16*, 4617–4625. (b) James, D. A.; Koya, K.; Li, H.; Liang, G.; Xia, Z.; Ying, W.; Wu, Y.; Sun, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1784–1787. (c) Shen, Y. M.; Lv, P. C.; Chen, W.; Liu, P. G.; Zhang, M. Z.; Zhu, H. L. *Eur. J. Med. Chem.* **2010**, *45*, 3184–3190. (d) Bloch, W. M.; Derwent-Smith, S. M.; Issa, F.; Morris, J. C.; Rendina, L. M.; Sumbly, C. J. *Tetrahedron* **2011**, *67*, 9368–9375.
- Vaught, J. L.; Carson, J. R.; Carmosin, R. J.; Blum, P. S.; Persico, F. J.; Hageman, W. E.; Shank, R. P.; Raffa, R. B. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1–10.
- Ismail, M. A.; Arafa, R. K.; Wenzler, T.; Brun, R.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *Bioorg. Med. Chem.* **2008**, *16*, 683–691.
- Depoortere, H.; Zivkovic, B.; Lloyd, K. G.; Sanger, D. J.; Perrault, G.; Langer, S. Z.; Bartholini, G. *J. Pharmacol. Exp. Ther.* **1986**, *237*, 649–658.
- (a) Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290–3291. (b) Klingele, J.; Kaase, D.; Hilgert, J.; Steinfeld, G.; Klingele, M. H.; Lach, J. *Dalton Trans.* **2010**, *39*, 4495–4507.

(10) For pyridine-based indolizine syntheses, see: (a) Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1607–1610. (b) Behnisch, R. *Houben-Weyl, Methoden der Organischen Chemie*; Thieme: Stuttgart, 1994; *E6b1*, pp 323–450. (c) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209–236. (d) Katritzky, A. R.; Qui, G.; Yang, B.; He, H.-Y. *J. Org. Chem.* **1999**, *64*, 7618–7621. (e) Kostik, E. I.; Abiko, A.; Oku, A. *J. Org. Chem.* **2001**, *66*, 2618–2623. (f) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169–1171. (g) Basavaiah, D.; Devendar, B.; Lenin, D.; Satyanarayana, T. *Synlett* **2009**, 411–416.

(11) For pyridine-based imidazopyridine syntheses, see: (a) Barun, O.; Ila, H.; Junjappa, H.; Singh, O. M. *J. Org. Chem.* **2000**, *65*, 1583–1587. (b) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260–264. (c) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743–2746. (d) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433–3436. (e) Katritzky, A. R.; Xu, Y.-J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935–4937. (f) Masquelin, T.; Bui, H.; Brickley, B.; Stephenson, G.; Schwerkeroske, J.; Hulme, C. *Tetrahedron Lett.* **2006**, *47*, 2989–2991.

(12) For syntheses originating from five-membered ring, see: (a) Kim, M.; Vedejs, E. *J. Org. Chem.* **2004**, *69*, 6945–6948. (b) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792–2794. (c) Lee, J. H.; Kim, I. *J. Org. Chem.* **2013**, *78*, 1283–1288. (d) Kucukdisli, M.; Opatz, T. *J. Org. Chem.* **2013**, *78*, 6670–6676. (e) Galons, H.; Bergerat, I.; Combet Farnoux, C.; Miocque, M. *Synthesis* **1982**, 1103–1105. (f) Knölker, H. J.; Hitzemann, R.; Boese, R. *Chem. Ber.* **1990**, *123*, 327–339. (g) Virieux, D.; Guillouzic, A.-F.; Cristau, H.-J. *Tetrahedron* **2006**, *62*, 3710–3720.

(13) Outlaw, V. K.; Townsend, C. A. *Org. Lett.* **2014**, *16*, 6334–6337.

(14) For preparation of known substituted pyrrole-2-aldehydes shown in SI, see: (a) Krayner, M.; Balasubramanian, T.; Ruzié, C.; Ptaszek, M.; Cramer, D. L.; Taniguchi, M.; Lindsey, J. S. *J. Porphyr. Phthalocyanines* **2009**, *13*, 1098–1110. (b) Bergauer, M.; Gmeiner, P. *Synthesis* **2002**, *2*, 0274–0278. (c) Muchowski, J. M.; Hess, P. *Tetrahedron Lett.* **1988**, *29*, 777–780.

(15) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237–5257.