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Improved Synthesis of Mono- and Disubstituted 2-Halonicotinonitriles from Alkylidene Malononitriles

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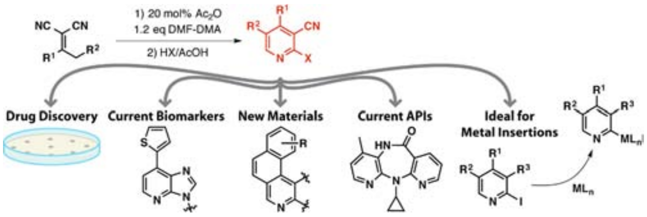
ABSTRACT



Pyridines with 2,3,4 and/or 5 substitution remain challenging to prepare. Existing strategies to form multisubstituted 2-halonicotinonitriles via enamines suffer from dimerization of the starting alkylidene malononitriles resulting in low yields. Through alteration of reaction conditions, a new high yielding method into enamines was realized by condensing DMF−DMA and alkylidene malononitriles in the presence of substoichiometric acetic anhydride. Cyclization of the resulting enamines under Pinner conditions provided 2-halonicotinonitriles in high overall yields.

Pyridines are abundant in many molecules of interest, including active pharmaceutical ingredients (APIs),[1] natural products,[2] biological probes,[3] and materials.[4] Despite many innovative approaches, high yielding syntheses of polysubstituted and fused pyridines with broad substrate applications remain elusive. These valuable multifunctional intermediates are synthesized using two major strategies: (1) modification of pyridine precursors[5] or (2) construction of the pyridine by cycloadditions or cyclizations from acyclic intermediates.[6] Complete construction of the pyridine has the promise of providing complex pyridines

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(1) For a list of current APIs, see: Mack, D. J.; Weinrich, M. L.; Vitaku, E.; Njardarson, J. Top 200 Brand Name Drugs by total US prescriptions in 2010. http://cbc.arizona.edu/njardarson/group/sites/default/files/Top%20200%20Brand-name%20Drugs%20by%20Total%20US%20Prescriptions%20in%202010sm_0.pdf (accessed July 22, 2013).

(2) (a) Aida, W.; Ohtsuki, T.; Li, X.; Ishibashi, M. *Tetrahedron* **2009**, *65*, 369. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.

(3) (a) Ishizuka, T.; Kimoto, M.; Sato, A.; Hirao, I. *Chem. Commun.* **2012**, *48*, 10835. (b) Kimoto, M.; Mitsui, T.; Yamashige, R.; Sato, A.; Yokoyama, S.; Hirao, I. *J. Am. Chem. Soc.* **2010**, *132*, 15418.

(4) (a) Lee, C. W.; Lee, J. Y. *Chem. Commun.* **2013**, *49*, 6185. (b) Luo, X.-Z.; Jia, X.-J.; Deng, J.-H.; Zhong, J.-L.; Liu, H.-J.; Wang, K.-J.; Zhong, D.-C. *J. Am. Chem. Soc.* **2013**, *135*, 11684. (c) Zhao, G.; Lu, M. *J. Phys. Org. Chem.* **2013**, *26*, 211. (d) Su, S.-J.; Sasabe, H.; Takeda, T.; Kido, J. *Chem. Mater.* **2008**, *20*, 1691. (e) Su, S.-J.; Chiba, T.; Takeda, T.; Kido, J. *Adv. Mater.* **2008**, *20*, 2125.

(5) Recent examples introducing new functionalities to pyridines: (a) Chen, Q.; du Jourdin, X. M.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958. (b) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (c) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194. (d) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.

(6) Examples for syntheses of polysubstituted pyridines including cycloadditions and cyclizations from acyclic precursers: (a) Allais, C.; Liéby-Muller, F.; Rodriguez, J.; Constantieux, T. *Eur. J. Org. Chem.* **2013**, *2013*, 4131. (b) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708. (c) Yamamoto, S.-i.; Okamoto, K.; Murakoso, M.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2012**, *14*, 3182. (d) Anderson, E. D.; Boger, D. L. *J. Am. Chem. Soc.* **2011**, *133*, 12285. (e) Rizk, T.; Bilodeau, E. J. F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8325. (f) Trost, B. M.; Gutierrez, A. C. *Org. Lett.* **2007**, *9*, 1473. (g) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.

(7) (a) Lehmann, J.; Alzieu, T.; Martin, R. E.; Britton, R. *Org. Lett.* **2013**, *15*, 3550. (b) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756. (c) Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884. (d) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (f) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (g) Winter, A.; Risch, N. *Synlett* **2003**, *2003*, 1959. (h) Katritzky, A. R.; Denisenko, A.; Arend, M. *J. Org. Chem.* **1999**, *64*, 6076.

10.1021/ol4025265

otherwise difficult to obtain. To date however, high yielding strategies into 2,3,4- or 2,3,4,5-substituted pyridines are limited.[7]

Early studies by Baldwin, Raab, and Ponticello attempted to reach 2-bromonicotinonitriles from alkylidene malononitriles using either triethyl orthoformate or *N*,*N*-dimethylformamide dimethyl acetal (DMF−DMA) as a C_1 source (Scheme 1).[8] Using triethyl orthoformate led to modest yields of the corresponding diethylacetal or enol ether but demonstrated a limited substrate scope. In addition, cyclization of the acetal or enol ether under Pinner conditions to the 2-bromonicotinonitriles was low yielding. Alternatively, when DMF−DMA was used, low yields of the corresponding enamine resulted due to dimerization of the alkylidene malononitriles.

Scheme 1. The Baldwin, Raab, and Poticello Strategy for Synthesizing Substituted 2-Bromonicotinonitriles

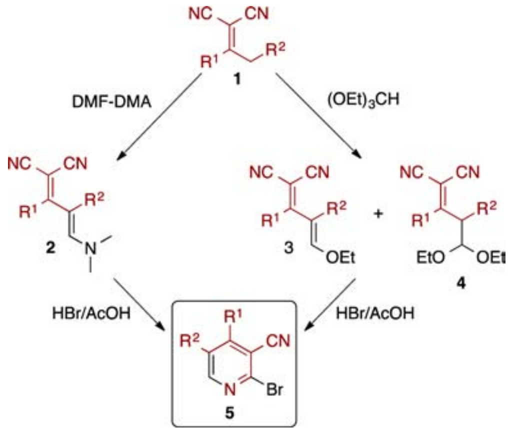
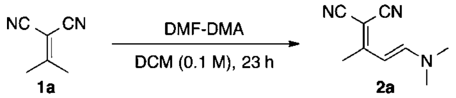


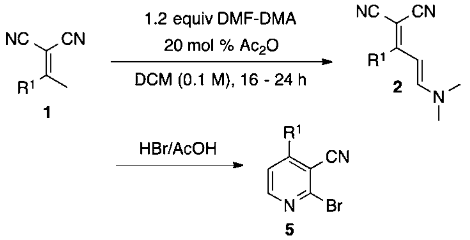
Table 1. Reducing the Addition of Ac_2O[a]

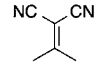
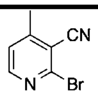
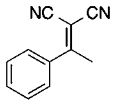
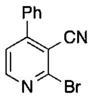
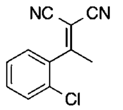
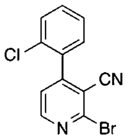
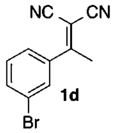
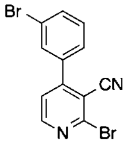
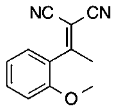
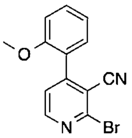
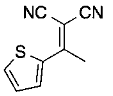


entry	Ac_2O (mol %)	DMF−DMA equiv	yield (%)[b]
1	0	1	44
2	200	1	84
3	100	1	86
4	50	1	88
5	25	1	89
6	20	1	89
7	10	1	90
8	20	1.2	>99

[a] Performed at a 0.5 mmol scale using anhydrous DCM. [b] Calibrated yields determined by GC using mesitylene as the internal standard.

Table 2. Synthesis of 2-Bromonicotinonitriles from Various Alkylidene Malononitriles[a]



entry	alkylidene malononitrile	nicotinonitrile	yield (%)[b]
1	 **1a**	 **5a**	91[c]
2	 **1b**	 **5b**	94
3	 **1c**	 **5c**	87
4	 **1d**	 **5d**	97
5	 **1e**	 **5e**	87
6	 **1f**	 **5f**	94

[a] Performed at 5 mmol scale using anhydrous DCM. [b] Isolated yields from the corresponding alkylidene malononitrile. Samples contained residual AcOH (<1 wt %). [c] Performed at 20 mmol scale with alternative workup (see Supporting Information for details).

The Baldwin−Raab−Ponticello synthesis is an attractive route to substituted pyridines because the acyclic precursors can be derived from inexpensive aldehydes or ketones and malononitrile. Additionally, the 2-bromo-3,4,5-tetrasubstituted pyridines are primed for further modification.[9] Despite these positive attributes, the low overall yields of

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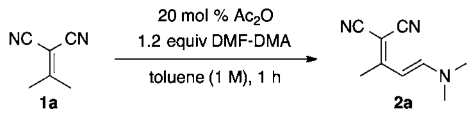
[8] Baldwin, J. J.; Raab, A. W.; Ponticello, G. S. *J. Org. Chem.* **1978**, *43*, 2529.

[9] Examples of transition metal couplings with 2-bromopyridines and quinolines: (a) Hoecker, J.; Gademann, K. *Org. Lett.* **2013**, *15*, 670. (b) Isik, M.; Tanyeli, C. *J. Org. Chem.* **2013**, *78*, 1604. (c) León, B.; Fong, J. C. N.; Peach, K. C.; Wong, W. R.; Yildiz, F. H.; Linington, R. G. *Org. Lett.* **2013**, *15*, 1234. (d) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552. (e) Kuzmina, O. M.; Steib, A. K.; Flubacher, D.; Knochel, P. *Org. Lett.* **2012**, *14*, 4818. (f) Oberli, M. A.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 4606. (g) Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. *J. Org. Chem.* **2011**, *76*, 9577.

Table 3. Temperature Screen for the Enamine Formation[a]



entry	temp (°C)	yield (%)[b]
1	rt	81
2	35	90
3	45	94
4	60	78

[a] Reactions performed at 20 mmol scale using anhydrous toluene. [b] Isolated yields.

their process have limited wide application. We hypothesized that an alternative set of conditions, using DMF−DMA, would provide a high yielding route to bifunctional enamines (**2**). Furthermore, we predicted the cyclization under Pinner conditions with these enamines would provide higher yields than those observed with the acetal or enol ether. Herein, we describe an alteration to the method that allows the corresponding enamines and 2-halonicotinonitriles to be obtained in high yield.

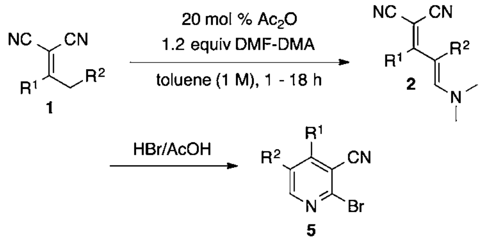
Initially, we applied the reaction conditions reported by Deng et al.[10] whereby dilute alkylidene malononitrile (**1a**; DCM) was combined with DMF−DMA. While these conditions provided the enamine (**2a**) in yields higher (44%) than those reported by Baldwin, Raab, and Ponticello (0%), ^{1}H NMR spectroscopy showed primarily dimerized **1a**. To improve the yield of **2a** further, we systematically surveyed reaction conditions that would suppress dimer formation.

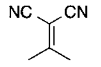
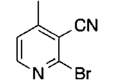
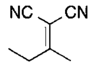
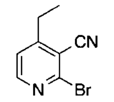
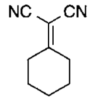
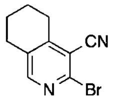
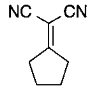
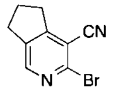
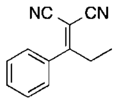
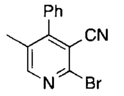
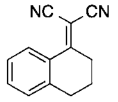
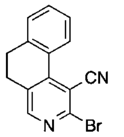
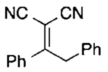
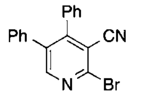
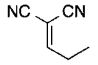
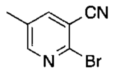
We hypothesized that the methanol released from the DMF−DMA was catalyzing the dimer formation. To test our hypothesis, we measured the yield of **2a** as as function of added MeOH scavengers: acetic anhydride, trimethylsilyl chloride (TMSCl), and molecular sieves (5 Å). Of these scavengers, only Ac_2O provided measurable quantities of the desired product.

The scavenger hypothesis was examined in more detail by analyzing the reaction mixtures by ^{1}H NMR. If the scavenger hypothesis was valid, formation of methyl acetate would be observed. To our surprise, only small quantities of methyl acetate formed prompting us to reduce the amount of Ac_2O. As shown in Table 1 (entries 4−7), Ac_2O loadings as low as 10 mol % provided improved yields.

Though 10 mol % provided significant yield improvement, a small amount of dimer remained, making purification difficult. Therefore, we elected to employ Ac_2O at the 20 mol % level. Further optimization studies demonstrated that increasing the equivalents of DMF−DMA to 1.2 gave quantitative yields of the desired enamine, prompting us to examine the cyclization and the reaction scope generally.

Table 4. Synthesis of 2-Bromonicotinonitriles at 1 M Reaction Concentration for the Enamine Formation[a]



entry	alkylidene malononitrile	nicotinonitrile	yield (%)[b]
1	 **1a**	 **5a**	76[c]
2	 **1g**	 **5g**	32[d]
3	 **1h**	 **5h**	69
4	 **1i**	 **5i**	73
5	 **1j**	 **5j**	82[e]
6	 **1k**	 **5k**	81
7	 **1l**	 **5l**	74
8	 **1m**	 **5m**	<1, 36[f]

[a] Reaction performed at 5 mmol scale using anhydrous toluene. [b] Isolated yields from the corresponding alkylidene malononitrile. Samples still contained some AcOH (< 1 wt %). [c] Yield improved to 83% upon scaling to 20 mmol. [d] Contains < 1 wt % of the 2-bromo-4,5-dimethylnicotinonitrile isomer. [e] Contains 2 wt % of starting alkylidene malononitrile. [f] Solvent DCM (0.1 M) and 1 equiv of Ac_2O was used.

We proceeded to focus on enamine cyclization under Pinner conditions. We hypothesized that the enamines would provide high yields of the desired pyradines compared to similar acetals or enol ethers, because HBr reacts with acetals and enol ethers through multiple manifolds, whereas enamines can only cyclize. To our gratification, we were able to synthesize 2-bromo-4-methylnicotinonitrile (**5a**) in 91% yield in two steps (Table 2, entry 1). The method

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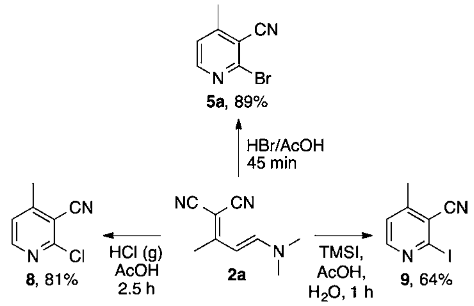
(10) (a) Xue, D.; Li, J.; Zhang, Z.-T.; Deng, J.-G. *J. Org. Chem.* **2007**, *72*, 5443. (b) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293.

Scheme 2. Synthesis of 2-Bromo, 2-Chloro, and 2-Iodo-4-methylonicotinonitriles[a]



[a] Yields of isolated product. See Supporting Information for details.

was then applied to several substrates obtained from acetophenone and acetophenone derivatives (entries 2−6).

Although this initial process provided high overall yields (> 87%), we sought to refine the route by removing the use of DCM while increasing the overall concentration. Of the solvents we examined, toluene was the most attractive because pure enamine product (**2a**) precipitated from the reaction and also enabled a 10-fold increase in concentration. Product precipitation drives the reaction forward and simplifies workup to merely filtration. Despite these benefits, the reaction at room temperature produced **2a** in only 81% yield (Table 3, entry 1). Further optimization revealed heating to 45 °C improved the yield (Table 3, entry 3). Temperatures higher than 45 °C led to lower yields (Table 3, entry 4).

We applied the improved method to various substrates with the goal of producing both 2-bromo-4-substituted and 2-bromo-4,5-disubstituted nicotinonitriles. The method works well with substrates derived from ketones, including substrates leading to bi- and tricyclic compounds (**5h**, **5i**, **5k**) (Table 4). These compounds can potentially be transformed into different isoquinoline, 2-azaphenanthrene, and other fused pyridine derivatives after functionalizing the nitrile and/or halogen that followed upon oxidation or halogenation followed by elimination.[11] Furthermore, yields improve upon scaling as shown with substrate **5a** (entry 1; 5 to 20 mmol scale).

The substrate **1g**, despite its similarity to **1a**, is not high yielding (entry 2) because the 2-bromo-4,5-dimethylnicotinonitrile isomer is also produced (structure not shown). The reaction conditions do not work well with substrates formed from aldehydes (**1m**) (entry 8). Using the alternative dilute conditions with DCM and a higher concentration of Ac_2O improved the yield of **1m** to 36% (see Supporting Information for details).

Finally, to further expand the access to alternative 2-halonicotinonitriles, we investigated synthesizing both 2-chloro and 2-iodo dervatives from the enamine (**2a**) (Scheme 2). Upon treatment with HCl (*g*), the slurry of enamine **2a** in AcOH was transformed into 2-chloro-4-methylnicotinonitrile (**8**), the precursor to a starting material to nevirapine,[12] 2-chloro-3-amino-4-picoline (CAPIC). In addition, the enamine (**2a**) slurry treated with trimethylsilyl iodide (TMSI) and water to produce HI *in situ* produced 2-iodo-4-methylnicotinonitrile, an ideal substrate for difficult metal insertions.

In conclusion, we have developed an efficient method to produce 4-substituted and 4,5-disubstituted 2-halonicotinonitriles. The substoichiometric addition of Ac_2O has a major impact on the viability of this approach, allowing access to 4-substituted and 4,5-disubstituted 2-halonicotinonitriles. However, the role of the acetic anhydride has yet to be determined. Rate enhancement occurs upon addition of Ac_2O, but the dependency of Ac_2O appears complex.[13] This process provides a window of opportunity for chemists to reach a variety of multisubstituted pyridines that were previously either unattainable or only attainable in low yields.

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Supporting Information Available. Experimental procedures, characterization, and prelimary kinetic data of reaction products. This information is available free of charge via the Internet at http://pubs.acs.org.

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(13) For preliminary kinetic data, see Supporting Information.

The authors declare no competing financial interest.