# ORGANIC CHEMISTRY

# **RESEARCH ARTICLE**



View Article Online View Journal | View Issue

**Cite this:** Org. Chem. Front., 2014, **1**, 148

# Access to pyridines via DMAP-catalyzed activation of $\alpha$ -chloro acetic ester to react with unsaturated imines<sup>+</sup>

Lin Hao,<sup>‡a</sup> Xingkuan Chen,<sup>‡a</sup> Shaojin Chen,<sup>a</sup> Ke Jiang,<sup>b</sup> Jaume Torres<sup>b</sup> and Yonggui Robin Chi<sup>\*a</sup>

Received 20th November 2013, Accepted 26th December 2013 DOI: 10.1039/c3qo00045a rsc.li/frontiers-organic

Facile access to trisubstituted pyridines from  $\alpha$ -chloro acetic ester and unsaturated imines is achieved. DMAP-catalyzed activation of ester to form an enolate intermediate constitutes a key reaction step. On the application side, the wide availability and low cost of the substrates and catalysts make this method very attractive.

(a) examples of bioactive pyridines

Functionalized pyridines are important building blocks and subunits of natural products and synthetic pharmaceuticals (Fig. 1a).<sup>1</sup> Effective catalytic access to pyridines is therefore of considerable research interest. Transition metal-mediated cycloaddition reactions constitute a major effort for the assembly of substituted pyridines.<sup>2</sup> Typically, relatively high reaction temperatures are necessary and the residual transition metal left with products may not be desirable in these otherwise very successful metal-based approaches. Organocatalytic methods for pyridine synthesis have recently emerged. The mild reaction conditions and non-toxic nature of the organocatalysts make this approach highly promising, especially for the synthesis of pyridines bearing functional groups or for medical uses. Loh and co-workers reported amine-catalyzed aza-Rauhut-Currier reaction of allenoates and a, p-unsaturated imines (1-azadienes) to generate functionalized pyridines.<sup>3</sup> Smith recently reported isothiourea-catalyzed pyridine synthesis by reacting anhydrides with 1-azadienes.<sup>4</sup>

We are interested in the organocatalytic activation of readily available carboxylic esters for facile access to useful molecules.<sup>5</sup> We have recently developed N-heterocyclic carbene (NHC)-catalyzed activation of esters<sup>5*a*-*e*</sup> and unsaturated esters,<sup>5*f*,*g*</sup> including unusual  $\beta$ -sp<sup>3</sup> carbon activation<sup>5*e*</sup> of saturated esters. Herein, we report an organocatalytic activation of esters to form enolate intermediates by using DMAP as an organocatalyst (Fig. 1b). The reaction of  $\alpha$ -chloro acetic ester

Caerulomycin C Nicotine (antifungal) Noranabasamine Nemertelline (nAChRs) (nAChRs and ion channels) (Neurotoxin) (b) our proposed pyridine synthesis via DMAP-catalyzed ester activation ш heat DMAP cat. 3 ester 1 (c) our organocatalytic pyridine synthesis-the overall reaction OrganoCat. (DMAP) OΔ. ester unsaturated imine pyridine

Fig. 1 Examples of bioactive pyridines and our organocatalytic approach for pyridine synthesis.

with unsaturated imines effectively forms substituted pyridines (Fig. 1c). The ester and imine substrates can be easily prepared, and the DMAP organocatalyst is commercially available at low cost (\$ 0.05 per gram from Alibaba).

<sup>&</sup>lt;sup>a</sup>Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg

E-mail: Tobineni@niu.eau.sg

<sup>&</sup>lt;sup>b</sup>School of Biological Sciences, Nanyang Technological University, Singapore 637551, Singapore

<sup>†</sup>Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/c3q000045a

<sup>‡</sup>These authors contributed equally to this work.

Experimentally, ester 1a prepared from inexpensive and commercially available  $\alpha$ -chloro acetic acid (\$ 0.73 per kg from Alibaba) was chosen as our substrate to react with 2a as a model unsaturated imine. No formation of pyridine product 3a was observed when bases (such as Cs<sub>2</sub>CO<sub>3</sub>, DIPEA, etc.; in the absence of DMAP) were used for a direct  $\alpha$ -CH deprotonation of ester 1a to react with 2a (Table 1, entry 1). N-heterocyclic carbene (NHC) organocatalysts, found effective in our earlier studies on ester activation,<sup>5</sup> were then evaluated. The use of triazolium-based NHC catalysts A-D led to 3a with low to moderate yields (entries 2-5). Although further development of NHC catalysts could likely lead to effective reactions, we decided to move towards a different direction in search of a cheaper organocatalyst. At last, we found that by using DMAP<sup>6</sup> as an ester-activating catalyst and triethylamine (TEA) as a base, pyridine 3a could be obtained in 54% isolated yield for a reaction carried out in CH2Cl2 at room temperature and 24 hours (entry 6). An improved yield (66%) could be obtained when the reaction time was prolonged to 48 hours (entry 7). A switch of solvent from CH<sub>2</sub>Cl<sub>2</sub> to (CH<sub>2</sub>Cl)<sub>2</sub> led to 3a with 75% yield (entry 8). Increasing the reaction temperature led to a decreased yield (entry 9).

Mechanistically (as illustrated in Fig. 1b), the reaction of substrate ester 1 and imine 2 initially formed a lactam IV (unstable, not isolable) that underwent *E*2-elimination to afford adduct V (isolable). *N*- to *O*-tosyl transfer<sup>7</sup> of V effectively led to pyridine 3a at an elevated temperature. All the

transformations from **1a** and **2a** to pyridine **3a** were performed in a "single-step" operation. Notably, when only a base catalyst (a weak base such as TEA or a strong base such as DBU or NaOCH<sub>3</sub>) was used, no pyridine product could be formed. The addition of a DMAP organocatalyst to the ester substrate (to form intermediate **I**) and subsequent formation of DMAPbound ester enolate intermediate **II** are necessary for this reaction. In other words, the DMAP catalyst not only facilitates ester  $\alpha$ -CH deprotonation but also helps to modulate the reactivity of the DMAP-bound enolate intermediate in this reaction.

Examples of the unsaturated imine substrates that worked well under the optimal conditions (Table 1, entry 8) are shown in Scheme 1. When the R and/or R' groups on the imines bear electron-donating substituents, the corresponding pyridine products (**3b–e**) were obtained with moderate to good yields. Replacing the phenyl group by a bulkier napthyl substituent was tolerated (**3f**, **3g**). The use of electron-deficient imines bearing electron-withdrawing substituents afforded products with higher yields (**3h–j**). The imines containing heterocyclic rings (**3k–n**) such as furanyl or pyridinyl units were also suitable substrates. The pyridine products (**3k–n**) that resulted from these imines are amenable to further transformations such as Suzuki couplings to prepare terpyridine derivatives.<sup>8</sup> The sulfonyl tosyl group on the imine nitrogen can be replaced by a methyl (**3p**) or *p*-methoxybenzenesulfonyl (**3q**) unit. As a



<sup>*a*</sup> General conditions (unless otherwise specified): **1a** (0.20 mmol), **2a** (0.10 mmol), solvent (0.40 mL), reacted at room temperature for 48 h and then at 60 °C for 6 h. In all the above cases, the conversion of ester **1a** was >90%. <sup>*b*</sup> Isolated yield (except entries 1–3, which were estimated *via* <sup>1</sup>H NMR analysis). <sup>*c*</sup> Bases such as DIPEA (5 eq.), DBU (2 eq.), TBD (2 eq.), Cs<sub>2</sub>CO<sub>3</sub> (2 eq.) and K<sub>2</sub>CO<sub>3</sub> (2 eq.) were tested. DIPEA = *N*,*N*-diisopropylethylamine, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, TBD = 1,5,7-triazabicyclo-[4.4.0]dec-5-ene, TEA = triethyl amine.



Scheme 1 Substrate scope.

#### **Research Article**

note, the use of chloro acetic esters with an  $\alpha$ -alkyl substituent (*e.g.* ethyl or benzyl unit) led to no pyridine products under current conditions.



The tosylate unit in the pyridine products (**3a–o**) is a versatile reactive group in cross-coupling reactions such as Suzuki couplings,<sup>9</sup> Heck couplings,<sup>10</sup> Kumada couplings<sup>11</sup> and metalcatalyzed amination reactions.<sup>12</sup> For example, amino pyridine **4a**, a selective 5-HT<sub>2A</sub>/5-HT<sub>1A</sub> receptor ligand,<sup>13</sup> could be readily prepared by coupling **3a** with *N*-methylpiperazine (eqn (1)).

### Conclusions

In summary, we have developed a DMAP-catalyzed synthesis of trisubstituted pyridines. Activation of the ester substrate by DMAP to form a DMAP-bound enolate intermediate is a key step in this process. A readily available and inexpensive organocatalyst and an ester substrate were used. The pyridine adducts obtained with our methods are amenable to effective transformations to bioactive molecules. Further development in activating readily available raw materials such as esters and acids as chemical feedstock is being pursued in our laboratory. In addition, this study is expected to encourage exploration of DMAP and its analogs as organocatalysts for the activation of carboxylic esters and their derivatives.

## Acknowledgements

We thank the Singapore National Research Foundation (NRF), Singapore Economic Development Board (EDB), GlaxoSmith-Kline (GSK) and Nanyang Technological University (NTU) for generous financial support. Torres acknowledges funding of the National Research Foundation grant NRF-CRP4-2008-02.

## Notes and references

For reviews, see: (a) F. W. Bergstrom, Chem. Rev., 1944, 35, 77; (b) G. Desimoni, G. Faita and P. Quadrelli, Chem. Rev., 2003, 103, 3119; (c) V. C. Gibson, C. Redshaw and G. A. Solan, Chem. Rev., 2007, 107, 1745; For selected examples, see: (d) R. B. Martin and J. A. Lissfelt, J. Am. Chem. Soc., 1956, 78, 938; (e) T. Tokuyama and J. W. Daly, Tetrahedron, 1983, 39, 41; (f) M. P. Cruskie Jr., J. A. Zoltewicz and K. A. Abboud, J. Org. Chem., 1995, 60, 7491; (g) F. Trécourt, B. Gervais, M. Mallet and G. Quéguiner, J. Org. Chem., 1996, 61, 1673;

(*h*) T. T. Denton, X. Zhang and J. R. Cashman, *Biochem. Pharmacol.*, 2004, **67**, 751.

- 2 (a) J. A. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787;
  (b) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644;
  (c) B. Heller and M. Hapke, *Chem. Soc. Rev.*, 2007, **36**, 1085;
  (d) M. D. Hill, *Chem.-Eur. J.*, 2010, **16**, 12052.
- 3 Z. Shi and T.-P. Loh, Angew. Chem., Int. Ed., 2013, 52, 8584.
- 4 D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan and A. D. Smith, *Angew. Chem., Int. Ed.*, 2013, **52**, 11642.
- 5 (a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao and Y. R. Chi, Org. Lett., 2012, 14, 2154; (b) L. Hao, C. Chuen, R. Ganguly and Y. R. Chi, Synlett, 2013, 1197; (c) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim and Y. R. Chi, Org. Lett., 2013, 15, 4956; (d) S. Chen, L. Hao, Y. Zhang, B. Tiwari and Y. R. Chi, Org. Lett., 2013, 15, 5822; (e) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong and Y. R. Chi, Nature Chem., 2013, 5, 835; (f) J. Cheng, Z. Huang and Y. R. Chi, Angew. Chem., Int. Ed., 2013, 52, 8592; (g) J. Xu, Z. Jin and Y. R. Chi, Org. Lett., 2013, 15, 5028.
- 6 (*a*) U. Ragnarsson and L. Grehn, *Acc. Chem. Res.*, 1998, **31**, 494; (*b*) R. Murugan and E. F. V. Scriven, *Aldrichimica Acta*, 2003, **36**, 21; (*c*) G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542.
- 7 (a) M. Hamer and E. P. Lira, J. Heterocycl. Chem., 1972, 9, 215; (b) K. Afarinkia and F. Mahmood, Tetrahedron Lett., 1998, 39, 493; (c) A. Perry, A. Nelson, R. Hodgson and A. Kennedy, Synlett, 2007, 1043.
- For selected reviews, see: (a) E. Baranoff, J.-P. Collin, L. Flamigni and J.-P. Sauvage, Chem. Soc. Rev., 2004, 33, 147; (b) E. C. Constable, Chem. Soc. Rev., 2007, 36, 246; (c) I. Eryazici, C. N. Moorefield and G. R. Newkome, Chem. Rev., 2008, 108, 1834; (d) L. Flamigni, J.-P. Collin and J.-P. Sauvage, Acc. Chem. Res., 2008, 41, 857; (e) S. Hayami, Y. Komatsu, T. Shimizu, H. Kamihata and Y. H. Lee, Coord. Chem. Rev., 2011, 255, 1981; (f) J. Husson and M. Knorr, Beilstein J. Org. Chem., 2012, 8, 379; (g) J. Husson and M. Knorr, J. Heterocycl. Chem., 2012, 49, 453.
- 9 J. Yang, S. Liu, J.-F. Zheng and J. S. Zhou, *Eur. J. Org. Chem.*, 2012, 6248.
- 10 (a) S. b. Noël, C. Pinel and L. Djakovitch, Org. Biomol. Chem., 2006, 4, 3760; (b) T. M. Gøgsig, A. T. Lindhardt, M. Dekhane, J. Grouleff and T. Skrydstrup, Chem.-Eur. J., 2009, 15, 5950; (c) T. M. Gogsig, J. Kleimark, S. O. N. Lill, S. Korsager, A. T. Lindhardt, P. O. Norrby and T. Skrydstrup, J. Am. Chem. Soc., 2012, 134, 443; (d) L. Qin, X. Ren, Y. Lu, Y. Li and J. S. Zhou, Angew. Chem., Int. Ed., 2012, 51, 5915.
- 11 A. H. Roy and J. F. Hartwig, J. Am. Chem. Soc., 2003, 125, 8704.
- 12 C.-Y. Gao and L.-M. Yang, J. Org. Chem., 2008, 73, 1624.
- M. H. Paluchowska, A. J. Bojarski, R. Bugno, S. Charakchieva-Minol and A. Wesolowska, *Arch. Pharm.*, 2003, 336, 104.