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Copper-catalysed amidation of 2-chloro-pyridines[†]Cite this: *RSC Advances*, 2013, **3**, 18787Received 12th June 2013,
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The simple and inexpensive *N,N*-dimethylcyclohexane-1,2-diamine/CuI catalytic system provides a versatile, easy and efficient access to an array of *N*-(2-pyridin-2-yl)-amides from 2-chloropyridine derivatives.

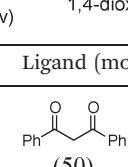
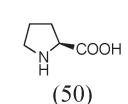
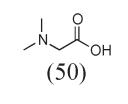
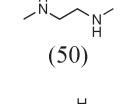
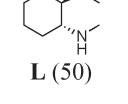
Amide formation is ubiquitous in organic chemistry as many biologically-relevant synthetic and natural products incorporate an amide moiety. Among amides, *N*-heteroaryl amides constitute one important class of pharmacophores used in medicinal chemistry and, recently, *N*-(2-pyridin-2-yl)-amide derivatives were reported to block sodium channels which are involved in neuronal regulation with potential applications in the treatment of pain, arrhythmia or epilepsy.¹ Non-catalytic amidations of 2-amino heterocycles as well as metal-catalysed amidations of aryl halides are existing to access amide derivatives.² However, despite considerable progresses in palladium- and copper-catalysed C–N bond formation,^{3–5} broadening the scope of electrophiles and nucleophiles that can be used in these reactions, only a few methods are able to achieve the amidation of aryl chlorides, and a few examples are reported for the amidation of 2-chloro-pyridine derivatives which are less reactive than their brominated counterparts.⁶ Herein, we would like to report a general method for the catalytic amidation of chloro-pyridine derivatives involving a cheap and simple catalytic system based on CuI and *trans*-*N,N*-dimethyl-cyclohexane-1,2-diamine.^{6b–c,f,7,8,9}

Initially, a catalytic amidation of 2-chloropyridine with benzamide was examined to tune up the reaction conditions (Table 1). Initial trials involving CuI (50 mol%) and 1,3-diphenylpropan-1,3-dione, proline or *N,N*-dimethylglycine as ligands (50 mol%) did not lead to any conversion of the starting

materials (Table 1, entries 1–3). However, the use of *N,N*-dimethyl-ethylenediamine as a ligand (50 mol%) provided *N*-(pyridin-2-yl)benzamide in 48% yield (Table 1, entry 4), and the yield was increased to 82% when *N,N*-dimethylcyclohexane-1,2-diamine (50 mol%) was used (Table 1, entry 5).

Having identified *N,N*-dimethylcyclohexane-1,2-diamine (**L**) as the best ligand, the optimisation of the amidation of 2-chloropyridine with benzamide was achieved (Table 2). Other copper sources such as CuO, CuBr, Cu₂O or Cu(OAc)₂·H₂O were evaluated

Table 1 Ligand screening in the amidation of 2-chloropyridine

Entry ^a	[Cu] (mol%)	Ligand (mol%)	T (°C)	Yield ^b
1	CuI (50)		100	—
2	CuI (50)		100	—
3	CuI (50)		100	—
4	CuI (50)		100	48%
5	CuI (50)		100	82%

^a *c* = 1 M. ^b Isolated yield.

^a Laboratoire de Chimie Organique, ESPCI ParisTech, UMR CNRS 7084, 10, rue Vauquelin, 75231, Paris Cedex 05, France. E-mail: janine.cossy@espci.fr; sebastien.reymond@espci.fr; Fax: (+33)140794660; Tel: (+33)140794659

^b Janssen Research & Development, a division of Janssen-Cilag, BP615- Chaussée du Vexin, 27106, Val de Reuil, France

^c Janssen Research & Development, a division of Janssen Pharmaceutica N.V. Turnhoutseweg 30, 2340, Beerse, Belgium

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Table 2 Optimisation of the catalyst for the amidation of 2-chloropyridine

Entry	[Cu] (mol%)	L (mol%)	Base (equiv.)	Solvent ^a	T (°C)	Yield ^b
1	CuO (50)	(50)	K ₂ CO ₃ (3)	1,4-dioxane	100	11%
2	CuBr (50)	(50)	K ₂ CO ₃ (3)	1,4-dioxane	100	23%
3	Cu ₂ O (50)	(50)	K ₂ CO ₃ (3)	1,4-dioxane	100	38%
4	Cu(OAc) ₂ ·H ₂ O (50)	(50)	K ₂ CO ₃ (3)	1,4-dioxane	100	26%
5	CuI (50)	(50)	K ₃ PO ₄ (3)	1,4-dioxane	100	74%
6	CuI (50)	(50)	Cs ₂ CO ₃ (3)	1,4-dioxane	100	36%
7	CuI (50)	(50)	K ₂ CO ₃ (3)	DMF	150	38%
8	CuI (50)	(50)	K ₂ CO ₃ (3)	DME	85	85%
9	CuI (25)	(25)	K ₂ CO ₃ (3)	1,4-dioxane	100	71%
10	CuI (10)	(10)	K ₂ CO ₃ (3)	1,4-dioxane	100	28%
11	CuI (10)	(10)	K ₂ CO ₃ (2)	1,4-dioxane	170 ^c	81%
12	CuI (5)	(5)	K ₂ CO ₃ (2)	1,4-dioxane	170 ^c	69%
13	CuI (2)	(2)	K ₂ CO ₃ (2)	1,4-dioxane	170 ^c	60% ^d
14	—	—	K ₂ CO ₃ (2)	1,4-dioxane	170 ^c	—
15	CuI (10)	—	K ₂ CO ₃ (2)	1,4-dioxane	170 ^c	—
16	—	(10)	K ₂ CO ₃ (2)	1,4-dioxane	170 ^c	—

^a c = 1 M. ^b Isolated yield. ^c Reaction performed in a sealed tube. ^d After 60 h of reaction.

(Table 2, entries 1–4), however they displayed lower catalytic activities than CuI (Table 1, entry 5). The use of K₃PO₄ as a base, instead of K₂CO₃, led to a slightly decreased yield (74%) whereas the use of Cs₂CO₃ lowered the yield to 36% (Table 2, entries 5–6). When DMF was used as the solvent, *N*-(pyridin-2-yl)benzamide was isolated in 48% yield, and when DME was utilised, the yield was similar to the one obtained with 1,4-dioxane (85%) (Table 2, entries 7–8). A decrease of the catalytic loading in both CuI and ligand **L** from 50 mol% to 10 mol% dramatically decreased the yield in the cross-coupling; *N*-(pyridin-2-yl)benzamide was isolated in 71% yield with 25 mol%, and in 28% yield with a 10 mol% catalytic loading (Table 2, entries 9–10). Gratifyingly, when the reaction was performed with 10 mol% CuI and 10 mol% **L** in 1,4-dioxane in a sealed tube at 170 °C, *N*-(pyridin-2-yl)benzamide was isolated in 81% yield (Table 2, entry 11) and, at this temperature, the amount of K₂CO₃ could be reduced to 2 equivalents. It was possible to decrease the catalytic charge to 5 mol% of CuI and 5 mol% of **L** as *N*-(pyridin-2-yl)benzamide was still obtained in good yield (69%) (Table 2, entry 12). With 2 mol% of CuI and 2 mol% of **L**, the yield was 60% however, after 60 h of reaction (Table 2, entry 13). We have to point out that in the absence of either CuI or **L**, no conversion of the starting material was observed under the reaction conditions (Table 2, entries 14–16).¹⁰

Having obtained optimized conditions for the cross-coupling of 2-chloropyridine with benzamide (5 mol% CuI and 5 mol% **L**, 2 equiv., K₂CO₃, 170 °C, 1,4-dioxane, 24 h), the reaction of 2-chloropyridine was evaluated with several aromatic, heteroaromatic and aliphatic amides, and the results are reported in Table 3. Aromatic amides such as 4-methoxybenzamide, 4-methylbenzamide or 4-nitrobenzamide provided the corresponding cross-coupling products in 72–57% yield (Table 3, entries 1–3),

the electron-poor 4-nitrobenzamide leading to the lowest yield (57%) (Table 3, entry 3). When 3,4-dichlorobenzamide was engaged in the amidation of 2-chloropyridine, the cross-coupling was chemoselective and the expected amide was obtained in 69% yield (Table 3, entry 4). Heteroaromatic amides such as nicotinamide or thiophene-2-carboxamide are suitable in the cross-coupling with 2-chloropyridine as the corresponding amides were isolated with good yields of 83% and 75% respectively (Table 3, entries 5 and 6). Aliphatic amides such as a primary amide, butyramide, or a secondary amide, piperidin-2-one, provided the expected *N*-(pyridin-2-yl)amides in 96% and 78% yields respectively (Table 3, entries 7–8).

At this stage, the amidation of other pyridyl halides with benzamide was examined, under the optimized conditions (5 mol% CuI and 5 mol% **L**, 2 equiv. K₂CO₃, 170 °C, 1,4-dioxane, 24 h), and the results are reported in Table 4. When 2-chloro-5-methoxypyridine was used, *N*-(5-methoxy-2-pyridyl)benzamide was obtained in 92% yield (Table 4, entry 1), whereas with 2-chloro-3-methoxy-2-pyridine, no cross-coupling product was isolated and the starting material was recovered (Table 4, entry 2). The reaction of 2-chloro-5-chloropyridine was chemoselective and the expected mono-amide was obtained selectively, however in 45% isolated yield for 75% conversion of the starting dihalopyridine (Table 3, entry 3). When 2,4-dichloropyridine was used, the corresponding mono-amide was obtained chemoselectively and, in this case, the isolated yield was 32%, for 72% conversion of the starting 2,4-dichloro-pyridine (Table 3, entry 4). In contrast, the use of 2-chloro-4-iodopyridine led to the expected diamide in 32% yield and only traces of the mono-amide were observed (Table 3, entry 5). Concerning 2-chloro-4-bromopyridine, the diamide product was isolated in only 21% yield, and only traces of the mono-amide were

Table 3 Amidation of 2-chloropyridine with various amides

Entry ^{a,b}	Amide	Product	Yield ^c
1			72%
2			66%
3			57%
4			69%
5			83%
6			75%
7			96%
8			78%

^a *c* = 1 M. ^b Reaction performed in a sealed tube. ^c Isolated yield.

observed (Table 3, entry 6). Worthy of note is the reaction of 3-chloropyridine which was unreactive under the reaction conditions (Table 3, entry 7). Finally, 2-chloropyrazine and 2-chloroquinoline successfully reacted with benzamide, and the corresponding amides were produced in 67% and 88% yield respectively (Table 3, entries 8–9).

Table 4 Amidation of various halogeno-heteroaromatics

Entry ^{a,b}	Halogeno pyridine	Product	Yield ^c
1			92%
2		—	—
3			45% ^d
4			32% ^e
5			32% ^f
6			21% ^f
7		—	—
8			67%
9			88%

^a *c* = 1 M. ^b Reaction performed in a sealed tube. ^c Isolated yield.

^d 25% of starting material recovered. ^e 28% of starting material recovered. ^f Only traces of mono-amide product were observed.

Conclusions

In summary, we have described a straightforward method for the amidation of 2-chloropyridine derivatives with a cheap and convenient *CuI/N,N*-dimethylcyclohexane-1,2-diamine catalytic sys-

tem, which constitutes an interesting alternative to both the reported Pd-centered methods and Cu-catalysed amidation of 2-bromo-pyridine derivatives. This C–N bond formation is general and can involve aromatic, heteroaromatic or aliphatic amides, and various pyridine derivatives such as 2-chloropyridines, as well as 2-chloropyrazine and 2-chloroquinoline.

Acknowledgements

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References

- 1 C. Ni, M. Park, B. Shao, L. Tafesse, J. Yao, M. Youngman and X. Zhou, *WO 2012/085650 A1*, 2012.
- 2 The stoichiometric amidation of 2-amino heterocycles is not always an obvious reaction because of their low nucleophilicity. For examples, see (a) A. R. Katritzky, H.-Y. He and K. Suzuki, *J. Org. Chem.*, 2000, **65**, 8210; (b) A. R. Katritzky, B. El-Dien, M. El-Gendy, E. Todadze and A. A. A. Abdel-Fattah, *J. Org. Chem.*, 2008, **73**, 5442; (c) K. Kim and K. Le, *Synlett*, 1999, 1957.
- 3 (a) A. Correa and C. Bolm, *Topics in Organometallic Chemistry, Metal-catalyzed C(sp²)-N bond Formation*, Springer, Berlin, Heidelberg, 2013; (b) Y. Jiang and D. Ma, *Topics in Organometallic Chemistry, Assembly of N-Containing Heterocycles via Pd- and Cu-Catalyzed C–N Bond Formation Reactions*, Springer, Berlin, Heidelberg, 2013; (c) I. P. Beletskaya and A. V. Cheprakov, *Organometallics*, 2012, **31**, 7753.
- 4 For reviews on Pd-catalysed C–N bond formations, see (a) J. F. Hartwig, *Nature*, 2008, **455**, 314–322; (b) *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004, vol. 1, ch. 13, p. 699; (c) R. J. Lundgren and M. Stradiotto, *Chem.–Eur. J.*, 2012, **18**, 9758; (d) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318.
- 5 For reviews on Cu-catalysed C–N bond formations, see (a) G. Evano, N. Blanchard and T. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (b) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (c) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954.
- 6 For some examples, see (a) Q. Shen, S. Shekhar, J. P. Stambuli and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2005, **44**, 1371; (b) F. Halley, Y. El-Ahmad, V. Certal, C. Venot, A. Dagallier, H. Strobel, K. Ritter and S. Ruf, *US 2009/0082329 A1*, 2009; (c) N. R. Irlapati, G. K. Deshmukh, V. P. Karche, S. M. Jachak, N. Sinha, V. P. Palle and R. K. Kamboj, *WO 2012/056478 A1*, 2012; (d) S. Guo, Y. Wang, C. Sun, J. Li, D. Zhou, Y. Wu and Y. Wu, *Tetrahedron Lett.*, 2013, **54**, 3233; (e) H. Kakuta, X. Zheng, H. Oda, S. Harada, Y. Sugimoto, K. Sasaki and A. Tai, *J. Med. Chem.*, 2008, **51**, 2400; (f) B. Wu, K. Kuhnen, T. Ngoc Nguyen, D. Ellis, B. Anacleto, X. He, K. Yang, D. Karanewsky, H. Yin, K. Wolff, K. Bieza, J. Caldwell and Y. He, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3430; (g) G. B. W. L. Lighthart, H. Ohkawa, R. P. Sijbesma and E. W. Meijer, *J. Org. Chem.*, 2006, **71**, 375; (h) D. Doller, G. Li, G. Ma and H. Zhou, *US 2011/0098299 A1*, 2011; (i) P.-S. Wang, C.-K. Liang and M.-k. Leung, *Tetrahedron*, 2005, **61**, 2931.
- 7 For examples of Cu-catalysed amidation of aryl halides, see (a) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727; (b) K. R. Crawford and A. Padwa, *Tetrahedron Lett.*, 2002, **43**, 7365; (c) S. K. Kang, D. H. Kim and J. N. Park, *Synlett*, 2002, 427; (d) A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421; (e) W. Deng, Y.-F. Wang, Y. Zou, L. Liu and Q.-X. Guo, *Tetrahedron Lett.*, 2004, **45**, 2311; (f) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120; (g) W. Chen, J. Li, D. Fang, C. Feng and C. Zhang, *Org. Lett.*, 2008, **10**, 4565; (h) E. R. Strieter, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 78; (i) P. F. Larsson, A. Correa, M. Carril, P. O. Norrby and C. Bolm, *Angew. Chem., Int. Ed.*, 2009, **48**, 5691; (j) S. Jammi, S. Krishnamoorthy, P. Saha, D. S. Kundu, S. Sakthivel, M. A. Ali, R. Paul and T. Punniyamurthy, *Synlett*, 2009, 3323; (k) Y. Zijian and W. Xianwen, *Chin. J. Chem.*, 2010, **28**, 2260; (l) H. C. Ma, X. Z. Jiang, X. Ma and Z. Jiang, *Synlett*, 2008, 1335; (m) C. Wang, L. Liu, W. Wang, D.-S. Ma and H. Zhang, *Molecules*, 2010, **15**, 1154; (n) W. Mangang, Y. Hua, Y. Xinwen, W. Jun and S. Zhicai, *Chin. J. Chem.*, 2012, **30**, 2356; (o) H. Xu and C. Wolf, *Chem. Commun.*, 2009, 1715.
- 8 For selected examples involving the Cu-catalysed amidation of 2-bromo-pyridine, see (a) I. M. Bella, R. A. Bednarb, J. F. Fayb, S. N. Gallicchio, J. H. Hochmanc, D. R. McMastersd, C. Miller-Steinc, E. L. Mooreb, S. D. Mosserb, N. T. Pudvahc, A. G. Quigleya, C. A. Salvatoreb, C. A. Stumpa, C. R. Thebergea, B. K. Wongc, C. B. Zartmana, X.-F. Zhang, S. A. Kaneb, S. L. Grahama, J. P. Vaccaa and T. M. Williamsa, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6165; (b) J. Li, Y. Zhang and D. Ma, *Tetrahedron Lett.*, 2012, **53**, 3981; (c) T. Hafner and D. Kunz, *Synlett*, 2007, 1403; (d) C.-C. Lee, P.-S. Wang, M. B. Viswanath and M.-k. Leung, *Synthesis*, 2008, 1359; (e) X. Lv and W. Bao, *J. Org. Chem.*, 2007, **72**, 3863.
- 9 For references concerning mechanistic features of Cu-catalysed C–N bond forming reactions, see ref. 3c, 6f, 6h and G. Lefèvre, G. Franc, A. Thili, C. Adamo, M. Taillefer, I. Ciofini and A. Jutand, *Organometallics*, 2012, **31**, 7694.
- 10 The use of a large excess of primary amides such as benzamide was shown to convert 2-chloroquinolines and some halogenated quinolines, pyrazines and pyridines into the corresponding amino derivatives. With a large excess of acetamide (ca. 80 equiv.) it is possible to isolate the corresponding 2-acetamido-quinoline derivatives, however in modest yields. See (a) T. Watanabe, E. Kikuchi, W. Tamura, Y. Akita, M. Tsutsui and A. Ohta, *Heterocycles*, 1980, **14**, 287; (b) F. Kóródi, *Synth. Commun.*, 1991, **21**, 1841; (c) S. Inglis, R. Jones, D. Fritz, C. Stojkoski, G. Booker and S. Pyke, *Org. Biomol. Chem.*, 2005, **3**, 2543.