

## Copper-catalysed amidation of 2-chloropyridines†

Cite this: *RSC Advances*, 2013, 3, 18787

Received 12th June 2013,

Accepted 17th July 2013

DOI: 10.1039/c3ra43368d

www.rsc.org/advances

Lionel Nicolas,<sup>a</sup> Patrick Angibaud,<sup>b</sup> Ian Stansfield,<sup>b</sup> Lieven Meerpoel,<sup>c</sup>  
Sébastien Reymond\*<sup>a</sup> and Janine Cossy\*<sup>a</sup>

**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.**

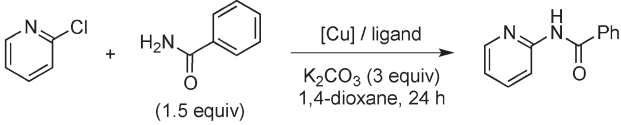
Amide formation is ubiquitous in organic chemistry as many biologically-relevant synthetic and natural products incorporate an amide moiety. Among amides, *N*-heteroaryl amides constitute one important class of pharmacophores used in medicinal chemistry and, recently, *N*-(2-pyridin-2-yl)-amide derivatives were reported to block sodium channels which are involved in neuronal regulation with potential applications in the treatment of pain, arrhythmia or epilepsy.<sup>1</sup> Non-catalytic amidations of 2-amino heterocycles as well as metal-catalysed amidations of aryl halides are existing to access amide derivatives.<sup>2</sup> However, despite considerable progresses in palladium- and copper-catalysed C–N bond formation,<sup>3–5</sup> 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.<sup>6</sup> 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.<sup>6b–c,f,7,8,9</sup>

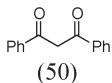
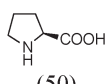
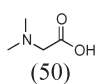
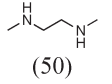
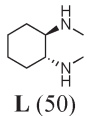
Initially, a catalytic amidation of 2-chloropyridine with benzamide was examined to tune up the reaction conditions (Table 1). Initial trials involving CuI (50 mol%) and 1,3-diphenylpropan-1,3-dione, proline or *N,N*-dimethylglycine as ligands (50 mol%) did not lead to any conversion of the starting

materials (Table 1, entries 1–3). However, the use of *N,N*-dimethylethylenediamine 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, Cu<sub>2</sub>O or Cu(OAc)<sub>2</sub>·H<sub>2</sub>O were evaluated

Table 1 Ligand screening in the amidation of 2-chloropyridine



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

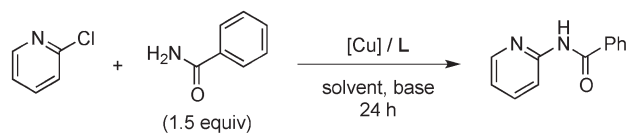
<sup>a</sup> c = 1 M. <sup>b</sup> Isolated yield.

<sup>a</sup>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

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

<sup>c</sup>Janssen Research & Development, a division of Janssen Pharmaceutica N.V. Turnhoutsweg 30, 2340, Beerse, Belgium

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and NMR spectra for amide compounds. See DOI: 10.1039/c3ra43368d

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

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

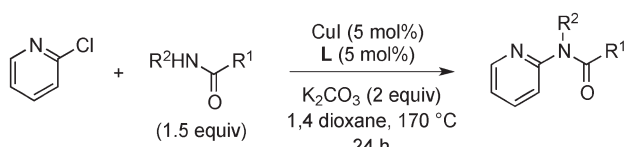
<sup>a</sup> c = 1 M. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction performed in a sealed tube. <sup>d</sup> After 60 h of reaction.

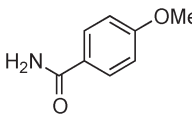
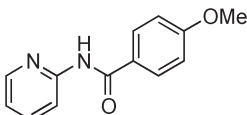
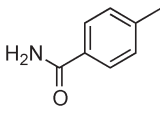
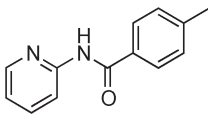
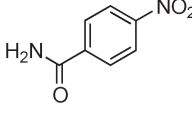
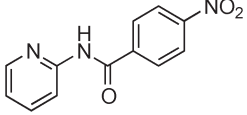
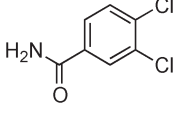
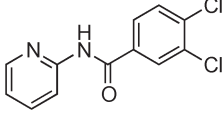
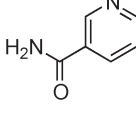
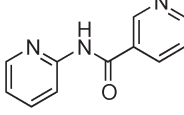
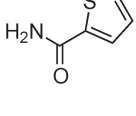
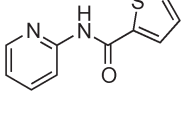
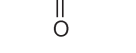
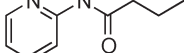
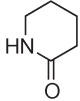
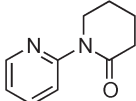
(Table 2, entries 1–4), however they displayed lower catalytic activities than CuI (Table 1, entry 5). The use of K<sub>3</sub>PO<sub>4</sub> as a base, instead of K<sub>2</sub>CO<sub>3</sub>, led to a slightly decreased yield (74%) whereas the use of CS<sub>2</sub>CO<sub>3</sub> lowered the yield to 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 K<sub>2</sub>CO<sub>3</sub> 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).<sup>10</sup>

Having obtained optimized conditions for the cross-coupling of 2-chloropyridine with benzamide (5 mol% CuI and 5 mol% L, 2 equiv., K<sub>2</sub>CO<sub>3</sub>, 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).

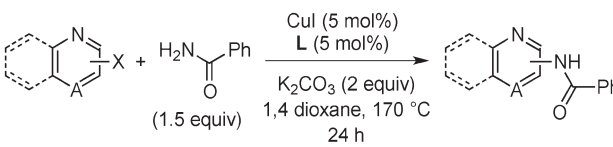
At this stage, the amidation of other pyridyl halides with benzamide was examined, under the optimized conditions (5 mol% CuI and 5 mol% L, 2 equiv. K<sub>2</sub>CO<sub>3</sub>, 170 °C, 1,4-dioxane, 24 h), and the results are reported in Table 4. When 2-chloro-5-methoxypyridine was used, *N*-(5-methoxypyridin-2-yl)benzamide was obtained in 92% yield (Table 4, entry 1), whereas with 2-chloro-3-methoxypyridine, 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-dichloropyridine (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

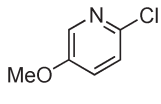
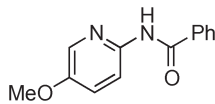
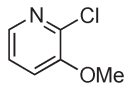
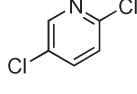
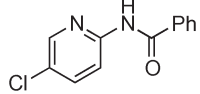
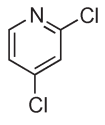
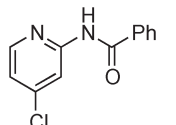
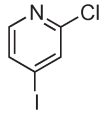
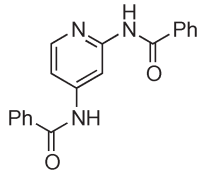
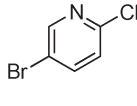
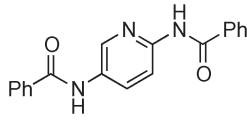
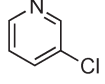
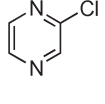
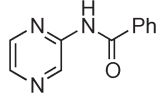
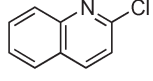
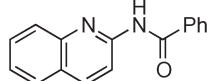
**Table 3** Amidation of 2-chloropyridine with various amides


Entry <sup>a,b</sup>	Amide	Product	Yield <sup>c</sup>
1			72%
2			66%
3			57%
4			69%
5			83%
6			75%
7			96%
8			78%

<sup>a</sup> *c* = 1 M. <sup>b</sup> Reaction performed in a sealed tube. <sup>c</sup> 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-chloropyridine 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 <sup>a,b</sup>	Halogeno pyridine	Product	Yield <sup>c</sup>
1			92%
2		—	—
3			45% <sup>d</sup>
4			32% <sup>e</sup>
5			32% <sup>f</sup>
6			21% <sup>f</sup>
7		—	—
8			67%
9			88%

<sup>a</sup> *c* = 1 M. <sup>b</sup> Reaction performed in a sealed tube. <sup>c</sup> Isolated yield. <sup>d</sup> 25% of starting material recovered. <sup>e</sup> 28% of starting material recovered. <sup>f</sup> 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

Janssen Research & Development, a Division of Janssen-Cilag, is gratefully acknowledged for financial support.

## 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(sp<sup>2</sup>)-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. Broggin, 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. Kuhen, T. Ngoc Nguyen, D. Ellis, B. Anaclerio, 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. Zhanga, 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. Tlili, 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-acetamidoquinoline 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. Kórodi, *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.