

Synthesis of 3,4-Disubstituted Isoxazoles via Enamine [3+2] Cycloaddition

Qian-fa Jia,^a Pooi Ming Shurn Benjamin,^b Jiayao Huang,^b Zhiyun Du,^{*a} Xi Zheng,^a Kun Zhang,^a Allan H. Conney,^a Jian Wang^{*a,b}

^a Allan H. Conney Laboratory for Anticancer Research, Guang Dong University of Technology, Guang Dong, 510006, P. R. of China

^b Department of Chemistry, National University of Singapore, Block S15, Level 5, 3 Science Drive 3, 117543, Singapore
Fax +65(677)91691; E-mail: chmwangj@nus.edu.sg

Received: 05.11.2012; Accepted after revision: 23.11.2012

Abstract: Enamine-triggered [3+2]-cycloaddition reactions of aldehydes and *N*-hydroximidoyl chlorides in the presence of triethylamine give rise to 3,4-disubstituted isoxazoles upon oxidation of the cycloadduct 3,4,5-trisubstituted 5-(pyrrolidinyl)-4,5-dihydroisoxazoles. This offers a high yielding, regioselective and metal-free synthetic route for the synthesis of 3,4-disubstituted isoxazoles.

Key words: isoxazole, enamines, 1,3-dipoles, [3+2] cycloaddition

Since Quilico and Claisen reported their methods,^{1,2} synthetic methodologies that manipulate the synthesis of isoxazoles have progressively gained awareness in organic synthesis. As one of the prominent medicinal scaffolds, the isoxazole group is featured in a large number of pharmaceutically important compounds and natural products.³ As exemplified in Figure 1, isoxazole compounds **I–VI** exhibit some biologically and pharmacologically important properties, such as anticancer, antianaphylactic, and antitumor activity.^{3,4}

Although various synthetic methods for isoxazoles synthesis have been developed,⁵ regioselective control of isoxazole functionalization is still the main concern. Moreover, synthetic methods that are available for 3,4-disubstituted isoxazoles are currently rather scarce. Known methods either require multiple steps,⁶ metal catalyst,⁷ or give low yields.⁸ Therefore, there is an urgent need to develop an efficient method for the synthesis of 3,4-disubstituted isoxazoles under mild conditions.⁹

Our group has recently reported the use of enamines as dipolarophiles to react with azide compounds to afford substituted 1,2,3-triazole compounds with high levels of regioselectivities.¹⁰ Given that enamines formed in situ from aldehydes are regioselective, we envisioned that cycloaddition of nitrile oxides with enamines may give rise to the corresponding 3,4-disubstituted isoxazoles upon oxidation of the cycloadduct 3,4,5-trisubstituted 5-(pyrrolidinyl)-4,5-dihydroisoxazoles generated in the first step (Scheme 1). Herein, we wish to report a new metal-free strategy for the facile synthesis of 3,4-disubstituted isoxazoles that is based on this approach.

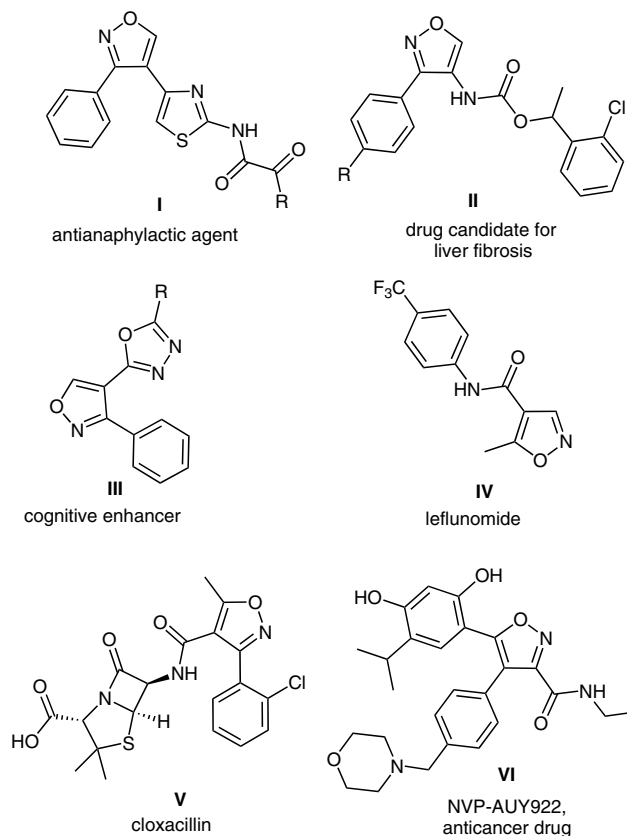
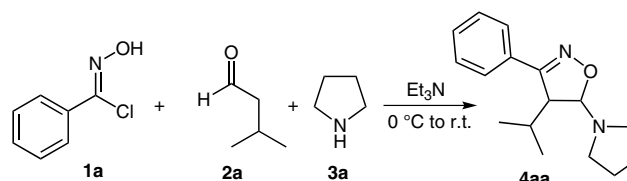


Figure 1 Selected examples of bioactive isoxazole compounds



Scheme 1 Enamine-promoted [3+2] cycloaddition reaction

Initial experiments were conducted to examine various reaction parameters (Table 1). Reactions carried out in polar solvents gave low yields, whereas high yields were achieved in less polar solvent (Table 1, entries 1–4 vs. entries 5–7). The substrate ratio **1a/2a/3a** indicated that an excess of **2a** and **3a** facilitated a higher yield (Table 1, entries 12–15), probably due to a competitive self-aldol side reaction. Lowering the concentration of **1a** to 0.1 mol/L allowed higher conversion and gave the desired product in

99% yield (Table 1, entry 11). Surprisingly, only one *trans*-3,4-disubstituted diastereomer was generated.¹¹ The ¹H NMR spectrum of the crude product revealed that the diastereomeric ratio (d.r.) was more than 19:1.

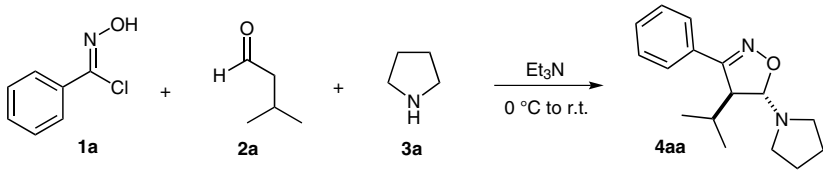
We then investigated the use of secondary amines as catalysts (Table 2). Six other secondary amines were screened and it was found that pyrrolidine **3a** gave the best yield (99%; Table 2, entry 1). Reactions with **3c**, **3e** and **3g** did not afford the desired product.

Having the optimized conditions in hand, we examined the substrate scope of the reaction (Scheme 2). Reactions between a range of acetaldehydes and *N*-hydroxyimidoyl chlorides gave good to high yields (77–99%; Scheme 2). The reaction tolerated a broad range of functional groups on both the acetaldehyde and *N*-hydroxyimidoyl chloride. Acetaldehydes bearing aliphatic and aromatic groups (Scheme 2, **2a–f** and **2i–k**) both gave high yields (82–

99%; Scheme 2, **4aa–af** and **4ai–ak**).^{12,13} Examination of a range of *N*-hydroxyimidoyl chlorides revealed that the reaction also tolerated a wide range of substituents (Scheme 2, **1a–j**), including phenyl, heterocyclic, and aliphatic groups, to give the corresponding 3,4,5-trisubstituted dihydroisoxazoles (77–98%; Scheme 2, **4bi–ii** and **4ia**).

Importantly, 3,4,5-trisubstituted 4,5-dihydroisoxazoles can undergo Cope elimination by addition of *m*-chloroperoxybenzoic acid (MCPBA) to afford 3,4-disubstituted isoxazoles in high yields [95 and 93%, respectively; Scheme 3, eq. (1) and (2)]. We then examined the feasibility of using a direct one-pot process for the synthesis of isoxazoles from **1a**, **2a** and **3a** [Scheme 3, eq. (3)] and found that **4aa** could be obtained in a yield of 83%. However, five equivalents of MCPBA were required to allow the reaction to reach completion. To this end, the develop-

Table 1 Optimization of Reaction Conditions^a



Entry	Solvent	Concn (mol/L)	Ratio			Yield (%) ^{b,f}
			1a	2a	3a	
1	Toluene	0.5	1.0	4.0	2.2	98
2	Et ₂ O	0.5	1.0	4.0	2.2	97
3	THF	0.5	1.0	4.0	2.2	93
4	CH ₂ Cl ₂	0.5	1.0	4.0	2.2	98
5	MeCN	0.5	1.0	4.0	2.2	72
6	MeOH	0.5	1.0	4.0	2.2	58
7	Brine	0.5	1.0	4.0	2.2	39
8	CH ₂ Cl ₂ ^c	0.5	1.0	4.0	2.2	64
9	CH ₂ Cl ₂ ^d	0.5	1.0	4.0	2.2	80
10	CH ₂ Cl ₂	0.25	1.0	4.0	2.2	95
11	CH₂Cl₂	0.1	1.0	4.0	2.2	99
12 ^e	CH ₂ Cl ₂	0.5	1.0	4.0	2.2	90
13	CH ₂ Cl ₂	0.5	2.0	1.0	2.0	82
14	CH ₂ Cl ₂	0.5	1.0	4.0	1.2	92
15	CH ₂ Cl ₂	0.5	1.0	2.0	2.2	93

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.8 mmol, 4.0 equiv), **3a** (0.44 mmol, 2.2 equiv), Et₃N (0.2 mmol, 1.0 equiv), 0 °C (0.5 h), r.t. (1.5 h).

^b Yield of isolated product after column chromatography and diastereoisomeric ratio (all d.r. > 19:1) were determined by ¹H NMR analysis of the crude mixture.

^c *N*-Hydroxybenzimidoyl chloride added in one portion.

^d Reaction carried out at 40 °C for 1.5 h instead of room temperature.

^e Without Et₃N.

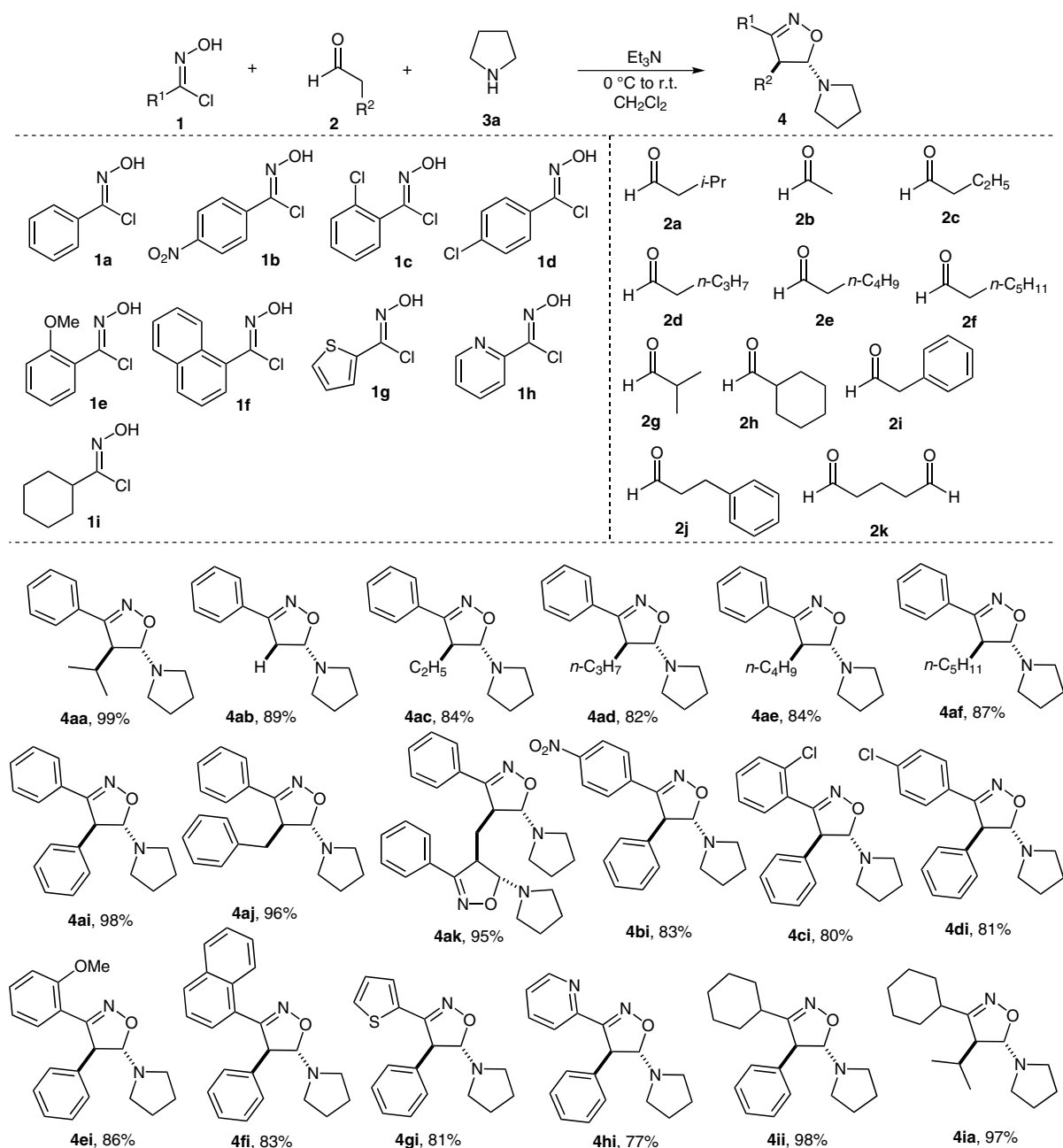
^f The relative configuration of **4aa** (*trans*-structure) was determined by X-ray crystal analysis.¹¹

ment of a more efficient and concise one-pot synthetic method is in progress in our laboratory.

To illustrate the broad synthetic utility of our developed methodology, we undertook the formal synthesis of herpes virus replication inhibitor **7**.¹⁴ Intermediate **4bi** was easily transformed into **5bi** through a Cope elimination step (93%; Scheme 4). Compound **5bi** was efficiently reduced to **6bi** in the presence of tin(II) chloride (98%; Scheme 4), and **6bi** could be converted into the reported herpes virus replication inhibitor **7** following known methods.¹⁰ Consequently, the presented method provides a convenient and high-yielding process for the synthesis of 3,4-disubstituted isoxazoles, which are useful intermediates for drug design and synthesis. Notably, 3,4-disub-

stituted isoxazoles that were previously accessed through either low-yielding methods or required transition-metal catalysis can now be made through a metal-free, high-yielding reaction under mild conditions.

Mechanistically, we propose that nitrile oxide **D** will be generated from *N*-hydroxyimidoyl chloride **A** upon treatment with base (Scheme 5). Enamine **E** is rapidly generated in situ when acetaldehyde **B** reacts with secondary amine **C**. Subsequently, **D** will undergo an inverse-electron-demand [3+2]-cycloaddition reaction with **E**, which behaves as a dipolarophile, to form the cycloadduct **F**. The latter undergoes oxidation to form amine oxide **G**. Finally, intermediate **G** will convert into target isoxazole **H** through subsequent elimination (Scheme 5).



Scheme 2 Substrate scope. ^a Unless specified, see the experimental section for reaction conditions. ^b All d.r. > 19:1.

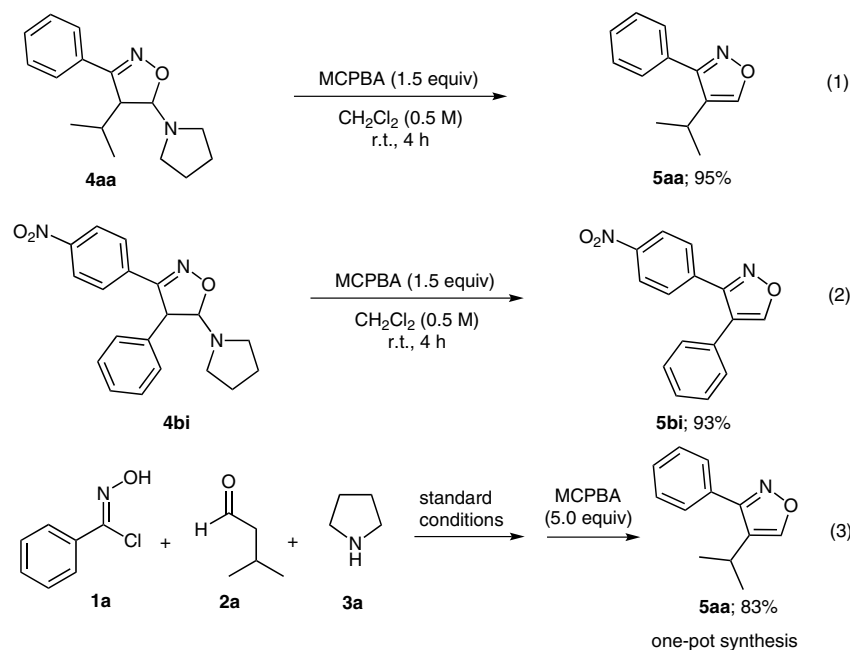
Table 2 Effect of the Secondary Amine^a

Entry	Amine	Yield (%) ^b	Entry	Amine	Yield (%) ^b
1	3a	99	5	3e	— ^c
2	3b	76	6	3f	37
3	3c	— ^c	7	3g	— ^c
4	3d	75			

^a Unless specified, see the experimental section for reaction conditions.

^b Yield of isolated product after column chromatography; diastereoisomeric ratio > 19:1.

^c No reaction.

**Scheme 3**

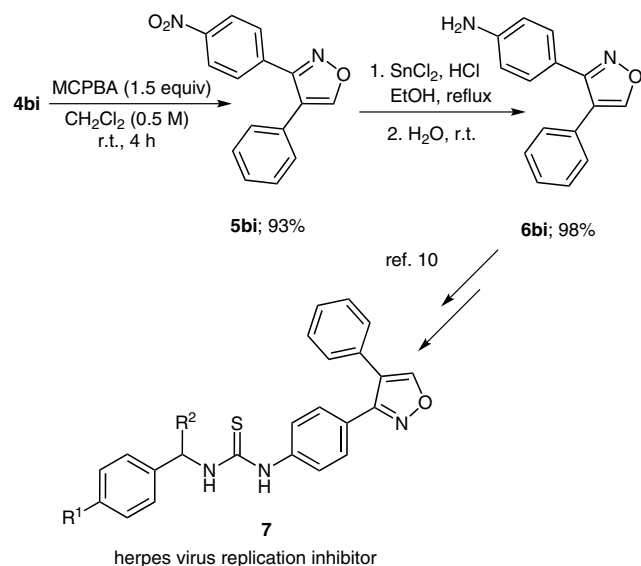
Notably, this methodology provides a regioselective route to 3,4-disubstituted isoxazoles. Due to the regiospecific formation of the enamine from acetaldehyde, only one regioisomer is finally formed in the 1,3-dipolar cycloaddition process.

In conclusion, we have described a new synthetic route to 3,4,5-trisubstituted dihydroisoxazole through an enamine-promoted [3+2]-cycloaddition reaction under mild conditions and high regioselectivities. These 3,4,5-trisubstituted dihydroisoxazoles can be rapidly converted into 3,4-disubstituted isoxazoles through a high-yielding Cope

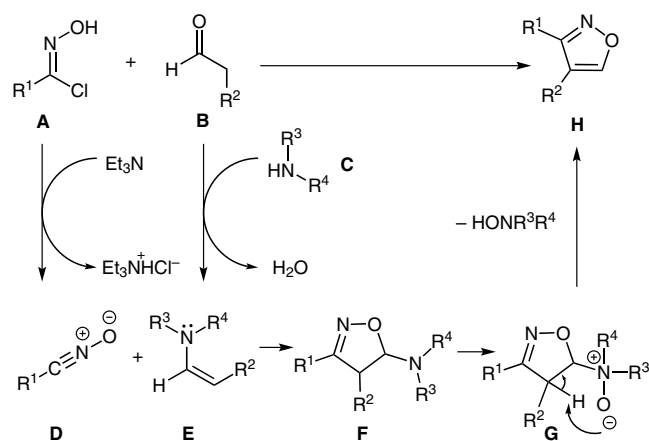
elimination step. Further investigations into the applications of this enamine-promoted [3+2] strategy for the synthesis of other important biological scaffolds are underway.

Acknowledgment

The authors acknowledge financial support from the Ministry of Education and National Research Foundation (Singapore) (MOE R143000443112, R143000480112 and NRF-CRP7-2010-03).



Scheme 4 Synthesis of herpes virus replication inhibitor 7



Scheme 5 Proposed mechanism

References and Notes

- (1) Claisen, L.; Lowman, O. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 1149.
- (2) Quilico, A.; Stagno D'Alcontres, G.; Grunarger, P. *Nature* **1950**, *166*, 226.
- (3) For reviews on drug developments and natural product synthesis involving isoxazoles, see: (a) Kotyatkina, A. I.; Zhabinsky, V. N.; Khripach, V. A. *Russ. Chem. Rev.* **2007**, *70*, 641. (b) Behrens, F.; Koehm, M.; Burkhardt, H. *Current Opinion in Rheumatology* **2011**, *23*, 282. (c) Peter-Getzlaff, S.; Polsfuss, S.; Poledica, M.; Hombach, M.; Giger, J.; Bottger, E. C.; Zbinden, R.; Bloemberg, G. V. *J. Clin. Microbiol.* **2011**, *49*, 2924. (d) Brough, P. A.; Aherne, W.; Barril, X.; Borgognoni, J.; Boxall, K.; Cansfield, J. E.; Cheung, K.-M. J.; Collins, I.; Davies, N. G. M.; Drysdale, M. J.; Dymock, B.; Eccles, S. A.; Finch, H.; Fink, A.; Hayes, A.; Howes, R.; Hubbard, R. E.; James, K.; Jordan, A. M.; Lockie, A.; Martins, V.; Massey, A.; Matthews, T. P.; McDonald, E.; Northfield, C. J.; Pearl, L. H.; Prodromou, C.; Ray, S.; Raynaud, F. I.; Roughley, S. D.; Sharp, S. Y.; Surgenor, A.; Walmsley, D. L.; Webb, P.; Wood, M.; Workman, P.; Wright, L. *J. Med. Chem.* **2008**, *51*, 196.
- (4) Chiarino, D.; Grancini, G.; Frigeni, V.; Biasini, I.; Careni, A. *J. Med. Chem.* **1991**, *34*, 600. (f) Yamamoto, T.; Fujita, K.; Asari, S.; Chiba, A.; Kataba, Y.; Ohsumi, K.; Ohmura, N.; Iida, Y.; Ijichi, C.; Iwayama, S.; Fukuchi, N.; Shoji, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3736.
- (5) For reviews on isoxazole chemistry and its role in synthetic chemistry, see: (a) Cicchi, S.; Cordero, F. M.; Giomi, D. *Five-Membered Ring Systems with O and N Atoms*, In *Progress in Heterocyclic Chemistry*; 1st ed., Vol. 23; Elsevier: Amsterdam, **2011**, 303–327. (b) Altuğ, C.; Dürüst, Y.; Elliott, M. C. *Tetrahedron Lett.* **2009**, *50*, 7392. (c) Wakefield, B. I.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147. (d) Melo, T. M. V. D. P. E. *Curr. Org. Chem.* **2005**, *9*, 925.
- (6) For selected examples of 3,5-disubstituted isoxazole synthesis, see: (a) Vieira, A. A.; Bryk, F. R.; Conte, G.; Bortoluzzi, A. J.; Gallardo, H. *Tetrahedron Lett.* **2009**, *50*, 905. (b) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210. (c) Chen, S.; Ren, J.; Wang, Z. *Tetrahedron* **2009**, *65*, 9146. (d) Mabrou, M.; Bougrin, K.; Benhida, R.; Loupy, A.; Soufiaoui, M. *Tetrahedron Lett.* **2007**, *48*, 443. (e) Xu, J.; Hamme, A. II. *Synlett* **2008**, 919. (f) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966. (g) Willy, B.; Rominger, F.; Müller, T. J. J. *Synthesis* **2008**, 293.
- (7) Kim, H. J.; Lee, J. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6513.
- (8) (a) Grecian, S.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 8285. (b) Dissanayake, A. A.; Odom, A. L. *Tetrahedron* **2012**, *68*, 807.
- (9) Schmitt, D. C.; Lam, L.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 5136.
- (10) For other synthetic methods of isoxazolines and isoxazoles, see: (a) Perez, C.; Janin, Y. L.; Adams, D. R.; Monneret, C.; Grierson, D. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 901. (b) Caramella, P.; Bianchessi, P. *Tetrahedron* **1970**, *26*, 5773. (c) Ballabio, M.; Destro, R.; Franzoi, L.; Gelmi, M. L.; Pocar, D.; Trimarco, P. *Chem. Ber.* **1987**, *120*, 1797. (d) Bujak, P.; Krompiec, S.; Malarz, J.; Krompiec, M.; Filapek, M.; Danikiewicz, W.; Kania, M.; Gębarowska, K.; Grudzka, I. *Tetrahedron* **2010**, *66*, 5972. (e) de Almeida, V. M.; dos Santos, R. J.; da Silva Góes, A. J.; de Lima, J. G.; Correia, C. R. D.; de Faria, A. R. *Tetrahedron Lett.* **2009**, *50*, 684. (f) Krompiec, S.; Bujak, P.; Szczepankiewicz, W. *Tetrahedron Lett.* **2008**, *49*, 6071. (g) Brooking, P.; Crawshaw, M.; Hird, N. W.; Jones, C.; MacLachlan, W. S.; Readshaw, S. A.; Wilding, S. W. *Synthesis* **1999**, 1986. (h) Kim, J. N.; Ryu, E. K. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 941. (i) Pocar, D.; Rossi, L. M.; Trimarco, P.; Vago, L. *J. Heterocycl. Chem.* **1980**, *17*, 881. (j) Caramella, P.; Coda Corsico, A.; Corsaro, A.; Del Monte, D.; Marinone Albini, F. *Tetrahedron* **1982**, *38*, 173. (k) Reddy, A. R.; Goverdhan, G.; Sampath, A.; Mukkanti, K.; Reddy, P. P.; Bandichhor, R. *Synth. Commun.* **2012**, *42*, 639.
- (11) (a) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J.* **2011**, *17*, 3584. (b) Wang, L.; Peng, S. Y.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem. Eur. J.* **2012**, *18*, 6088.
- (12) CCDC-876696 (4aa) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- (13) **Synthesis of 4aa–ia; General Procedure:** Pyrrolidine **3a** (74.5 μL , 0.88 mmol) and Et₃N (53.9 μL , 0.4 mmol) was dissolved in CH₂Cl₂ (4 mL), the mixture was cooled to 0 °C

and isovaleraldehyde **2a-i** (173.9 μ L, 1.6 mmol) was added. Immediately afterwards, *N*-hydroxybenzimidoyl chloride **1a** (62.2 mg, 0.4 mmol) in CH_2Cl_2 (0.2 mL) was added in five portions in five-minute intervals. After complete addition of *N*-hydroxybenzimidoyl chloride, the reaction mixture was stirred for a further 10 min at 0 $^\circ\text{C}$, after which, it was allowed to warm to r.t. slowly and stirred for another 1.5 h. The reaction was then stopped and the product was purified by flash column chromatography with silica gel (EtOAc–hexane, 10%) to afford **4aa-ia**.

- (13) **3-Phenyl-4-isopropyl-5-(pyrrolidin-1-yl)-4,5-dihydroisoxazoles (4aa)**: Yellow crystals. ^1H NMR (300

MHz, CDCl_3): δ = 7.75–7.69 (m, 2 H), 7.48–7.41 (m, 3 H), 5.41 (d, J = 2.7 Hz, 1 H), 3.40 (dd, J = 3.5, 2.8 Hz, 1 H), 2.91–2.68 (m, 4 H), 2.22–2.13 (m, 1 H), 1.83–1.78 (m, 4 H), 1.10 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 157.2, 129.6, 128.8, 126.8, 95.3, 56.2, 46.9, 28.1, 23.8, 20.6, 17.1; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}$: 259.1805; found: 259.1812.

- (14) (a) Bloom, J. D. U. S. Patent 157900, **2004**. (b) Di Grandi, M. J.; Curran, K. J.; Feigelson, G.; Prashad, A.; Ross, A. A.; Visalli, R.; Fairhurst, J.; Feld, B.; Bloom, J. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4157.