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Cite this: *Chem. Commun.*, 2011, **47**, 3198–3200

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## COMMUNICATION

## Synthesis of isoxazoles by hypervalent iodine-induced cycloaddition of nitrile oxides to alkynes†

Anup M. Jawalekar, Erik Reubsæet, Floris P. J. T. Rutjes and Floris L. van Delft\*

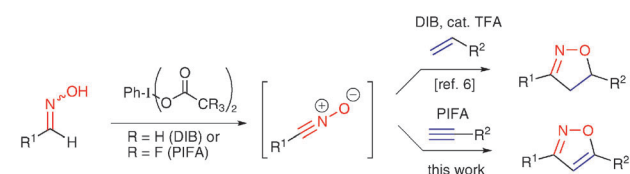
Received 27th October 2010, Accepted 6th January 2011

DOI: 10.1039/c0cc04646a

**Treatment of oximes with hypervalent iodine leads to substituted isoxazoles via rapid formation of nitrile oxides. Reaction with terminal alkynes led to a series of 3,5-disubstituted isoxazoles with complete regioselectivity and high yield, in a procedure mild enough to prepare a range of nucleoside and peptide conjugates. Exceptionally high reaction rates were found for the formation of 3,4,5-trisubstituted isoxazoles from a cyclic alkyne.**

Isoxazoles form a major class of nitrogen heterocycles that are molecular components in a variety of natural products (e.g. ibotenic acid, muscimol, isoxazole-4-carboxylic acid) and drugs (e.g. valdecoxib, leflunomide, cloxacillin).<sup>1</sup> A variety of synthetic methods has been developed for the preparation of isoxazoles,<sup>2</sup> of which the cycloaddition of nitrile oxides and alkynes is probably the most direct.<sup>3</sup> However, thermal nitrile oxide–alkyne cycloadditions typically give low yields, side-reactions and poor regioselectivity.<sup>4</sup> Copper(i) and ruthenium(ii)-induced preparation of 3,5- or 3,4-disubstituted isoxazoles has been reported,<sup>5</sup> but for many applications the use of (toxic) transition metals is undesirable if not prohibited. Therefore, there exists a clear need for metal-free, regioselective synthesis of isoxazoles.

Recently, it was reported that 3,5-disubstituted isoxazolines can be prepared by cycloaddition to olefins and nitrile oxides, generated *in situ* from oximes with (diacetoxyiodo)benzene (DIB) with catalytic TFA (Scheme 1, top).<sup>6</sup> A single example of isoxazole preparation was also given, but the methodology was not further elaborated, presumably as a consequence of



**Scheme 1** Cycloaddition of nitrile oxides to alkenes or acetylenes via hypervalent iodine-induced generation of nitrile oxide from oxime.

Institute for Molecules and Materials, Radboud University Nijmegen, Heijendaalseweg 135, NL-6525 AJ, Nijmegen, the Netherlands.  
E-mail: F.vanDelft@science.ru.nl; Fax: +31 24 3653393;  
Tel: +31 24 3652373

† Electronic supplementary information (ESI) available: Solvent screening, general synthetic procedures, structural characterisation of oximes and isoxazoles, reaction analysis by NMR and HPLC. See DOI: 10.1039/c0cc04646a

the low yield (50%) of the reaction. Herein, we report a methodology for a completely regioselective and high yielding procedure for the preparation of 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles from terminal or cyclic alkynes, respectively. Key to the strategy is near instantaneous generation of nitrile oxides from oximes by use of phenyliodine bis(trifluoroacetate) as an oxidising agent. The versatility of the procedure and applicability as a novel tool for bioconjugation is demonstrated by preparation of a range of nucleoside and peptide-containing isoxazoles.<sup>7</sup>

Due to its low toxicity, ready availability and easy handling, phenyliodine bis(trifluoroacetate) (PIFA) is a useful reagent for oxidative dearomatisation, dehydromerisation and selective cyanation.<sup>8</sup> To date, however, PIFA has not been applied for the generation of nitrile oxide from oximes. We therefore investigated the reaction of phenylacetylene and benzaldoxime under the action of PIFA (ESI† and Table 1). A slow conversion was observed in MeCN, *i*-PrOH or in 1,4-dioxane/H<sub>2</sub>O (5 : 1) mixtures but in MeOH/H<sub>2</sub>O (5 : 1), a highly efficient reaction took place.<sup>9</sup> A small excess (1.5 equiv.) of oxime is required for the reaction as a result of the fact that the *in situ* formed nitrile oxide slowly homodimerizes to furoxan or 1,4-dioxo-2,5-diazine.<sup>4,10</sup> Therefore, the effect of portion-wise addition of PIFA and reaction concentration was investigated (Table 1). When benzaldoxime (1.5 equiv.) and PIFA (1.5 equiv.) were combined with phenylacetylene (0.01 M), the expected 3,5-disubstituted isoxazole was obtained in 65% yield. Addition of PIFA in two portions (total 1.5 equiv.) improved the yield to 70%. Further increasing the reaction concentration (with respect to alkyne) to 0.1 M and addition of PIFA in three portions over 2 h intervals

**Table 1** Cycloaddition of phenylacetylene and benzonitrile-*N*-oxide

Entry	Conc. <sup>a</sup> /M	Oxime (equiv.)	PIFA addition (1.5 equiv.)	Time/h	Yield (%)
1	0.01	1.5	1 portion	24	65
2	0.01	1.5	2 portions/4 h	24	70
3	0.1	1.5	3 portions/2 h	7	90

<sup>a</sup> Concentration of phenylacetylene.

(1.5 equiv. in total), gave the desired isoxazole in 90% yield after 7 h. The beneficial role of PIFA is explained by the near instantaneous formation (1 min) of nitrile oxide from *p*-methylbenzaloxime (Fig. S1, ESI<sup>†</sup>), while oxidation with DIB is sluggish and incomplete after 60 min (Fig. S2, ESI<sup>†</sup>).

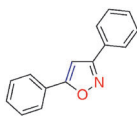
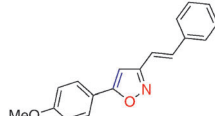
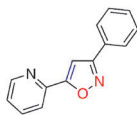
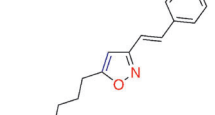
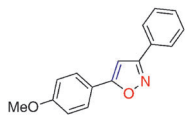
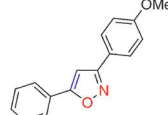
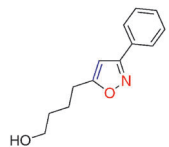
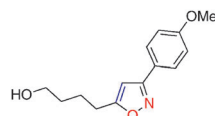
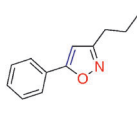
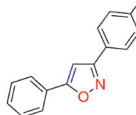
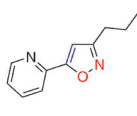
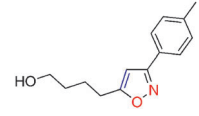
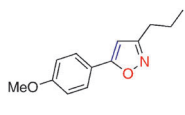
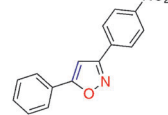
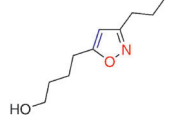
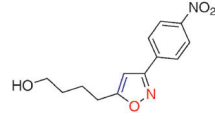
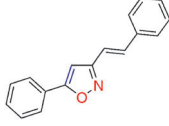
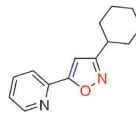
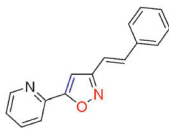
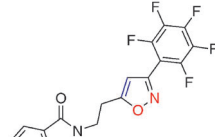
Having established optimal conditions for *in situ* generation of nitrile oxide, and cycloaddition to acetylene, the scope of isoxazole formation was evaluated for a range of substrates (Table 2). A variety of aromatic or aliphatic oximes or alkynes, with electron-deficient or electron-rich groups, was converted to 3,5-disubstituted isoxazoles in good to excellent yields. Aliphatic alkynes were less reactive than aromatic alkynes giving 55–66% product based on the oxime used. However, use of four-fold excess of oxime raised the yield to 94% (entry 16). No competitive cycloaddition of nitrile oxides to olefins was observed in case of *trans*-cinnamaloxime (entries 9–12). It must be noted that the yields obtained in our procedure compare favorably to the copper-catalysed synthesis of isoxazoles, especially in case of benzaloxime (entry 1) and 4-nitrobenzaloxime (entry 17).<sup>5a,b</sup>

The scope of nitrile oxide–alkyne cycloaddition for bioconjugation was explored by application to a range of nucleosides and a model peptide (Fig. 1). To our delight, PIFA-induced (3 + 2) cycloaddition works well with unprotected nucleosides and a 2'-alkyl adenosine-derived<sup>11</sup> oxime, leading to adducts **21–24**, thereby tolerating various functional groups (ESI<sup>†</sup>, Fig. S3). Finally, we successfully prepared an isoxazole from a peptide with an N-terminal acetylene. To this end, freshly generated nitrile oxide from benzaloxime (3 equiv.) in MeOH (210  $\mu$ L) was added to the peptide (100  $\mu$ M in H<sub>2</sub>O), which was repeated six times over 12 h, leading to clean formation of isoxazole (>95% conversion), as confirmed by HPLC and HRMS (Fig. S4, ESI<sup>†</sup>).

Having demonstrated the viability of PIFA-induced cycloaddition of nitrile oxides and terminal alkynes, we next investigated strain-promoted reactions with cyclic alkynes, known to undergo rapid cycloadditions with azides<sup>12,13</sup> and nitrones.<sup>14</sup> We recently developed a straightforward route to a novel cyclooctyne analogue, namely bicyclo[6.1.0]nonyne (BCN), for metal-free cycloaddition reactions.<sup>15</sup> In this context, the cycloaddition of BCN with nitrile oxide could constitute another versatile metal-free ligation strategy.<sup>16</sup> Thus, a series of aromatic, aliphatic and unsaturated oximes was combined with BCN (Scheme 2) in 1 : 1 mixture of MeOH/H<sub>2</sub>O (0.1 M), before oxime and PIFA (each 1.2 equiv.) were added. As expected, the reaction was extremely fast and efficient giving 3,4,5-trisubstituted isoxazoles (compounds **26–34**, Scheme 2) in excellent yields within 2–5 min in all cases. Based on NMR experiments (ESI<sup>†</sup>), a reaction rate constant of 1.8 M<sup>-1</sup> s<sup>-1</sup> was determined for benzonitrile-*N*-oxide, a value that compares highly favourably with that of benzyl azide cycloaddition to BCN under identical conditions (0.18 M<sup>-1</sup> s<sup>-1</sup>).

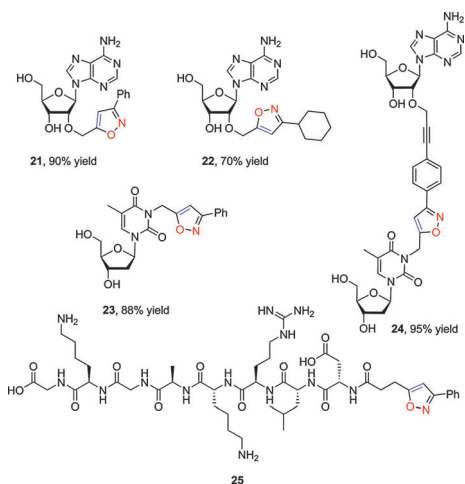
In conclusion, we have demonstrated the use of PhI(OCOCF<sub>3</sub>)<sub>2</sub> for the rapid *in situ* conversion of aldoximes into nitrile oxide and cycloaddition with alkynes. The procedure is experimentally convenient, avoiding the isolation and handling of potentially harmful and unstable hydroximoyl chlorides. The resulting nitrile oxide traps terminal and cyclic alkynes efficiently, in particular in the case of cyclic alkynes,<sup>17</sup> to give

**Table 2** Isoxazoles from terminal alkynes and nitrile oxides

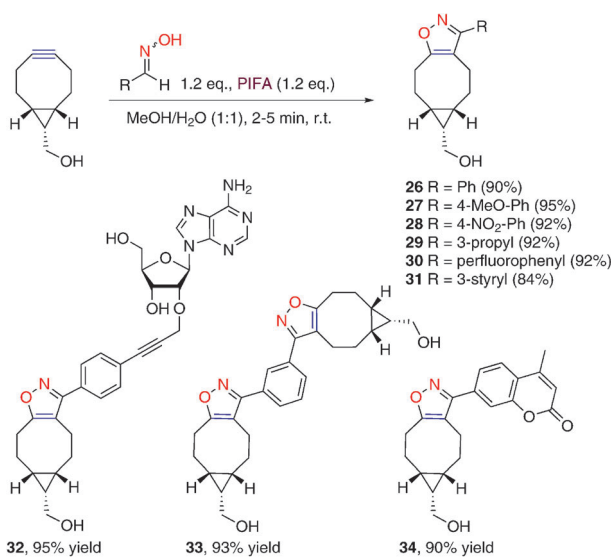
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		90	11		65
2		80	12		61 <sup>a</sup>
3		81	13		71
4		49 <sup>a</sup>	14		67 <sup>a</sup>
5		76	15		72
6		90	16		94 <sup>c</sup>
7		60	17		73
8		10 <sup>b</sup>	18		59 <sup>a</sup>
9		82	19		87
10		72	20		80

<sup>a</sup> Based on oxime. <sup>b</sup> Volatile. <sup>c</sup> 4 equiv. oxime used.

3,5-disubstituted and 3,4,5-trisubstituted isoxazoles in high yield. Because no transition metal catalyst is needed and a wide variety of functional groups are tolerated, we foresee high usefulness of



**Fig. 1** Nucleoside and peptide-isoxazole conjugates.



**Scheme 2** Nitrile oxide cycloaddition to ring-strained BCN.

our PIFA-mediated synthesis of isoxazoles.<sup>18</sup> Currently, we are making progress on the application of our approach for labeling of oligonucleotides<sup>7b-d</sup> and for nitrile oxide-acetylene cycloaddition to proteins, which may unveil unprecedented ways for metal-free conjugation of proteins containing acetylenes.<sup>19</sup>

We gratefully acknowledge the Netherlands Organisation for Scientific Research (NWO) for financial support (ECHO 07.BM3.038). We thank MSc Morten B. Hansen for his help on the peptide synthesizer and Jan Dommerholt for determination of reaction rate constants.

## Notes and references

- (a) J. Sperry and D. Wright, *Curr. Opin. Drug Discovery Dev.*, 2005, **8**, 723; (b) K. D. Shin, M.-Y. Lee, D.-S. Shin, S. Lee, K.-H. Son, S. Koh, Y.-K. Paik, B.-M. Kwon and D. C. Han, *J. Biol. Chem.*, 2005, **50**, 41439; (c) Y.-S. Lee, S. M. Park and B. H. Kim, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1126; (d) B. Rozman, S. Praprotnik, D. Logar, M. Tomsic, M. Hijnik, M. Kos-Golja and P. Dolenc, *Ann. Rheum. Dis.*, 2002, **61**, 567; (e) S. L. Lawrence, V. Roth, R. Slinger, B. Toye, I. Gaboury and B. Lemyre, *BMC Pediatrics*, 2005, **5**, 49; (f) K. Kobinata, S. Sekido, M. Uramoto, M. Ubukato, H. Osada, I. Yamaguchi and K. Isono, *Agric. Biol. Chem.*, 1991, **55**, 1416.
- (a) L. Claisen and O. E. Lowman, *Ber. Dtsch. Chem. Ges.*, 1888, **21**, 784; (b) A. Kumar, R. A. Maruya, S. Sharma, P. Ahmad, A. B. Singh, A. K. Tamrakar and A. K. Srivastava, *Bioorg. Med. Chem.*, 2009, **17**, 5285; (c) Y.-G. Wang, W.-M. Xu and X. Huang, *Synthesis*, 2007, 28; (d) C. Praveen, A. Kalyanasundaram and P. T. Perumal, *Synlett*, 2010, 777; (e) M. Mazzei, A. Balbi, E. Sottofattori, R. Garzoglio, A. D. Montis, S. Corrias and P. L. Colla, *Eur. J. Med. Chem.*, 1993, **28**, 669; (f) M. Yokoyama, K. Tsuji and M. Kushida, *J. Chem. Soc., Perkin Trans. 1*, 1986, 67; (g) S. Zen, K. Harada, H. Nakamura and Y. Iitaka, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2881; (h) S. Tang, J. He, Y. Sun, L. He and X. She, *Org. Lett.*, 2009, **11**, 3982; (i) J. P. Waldo and R. C. Larock, *Org. Lett.*, 2005, **7**, 5203; (j) J. P. Waldo and R. C. Larock, *Org. Lett.*, 2007, **72**, 9643.
- (a) R. Huisgen, *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 1, p. 1; (b) V. Jaeger and P. A. Colinas, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*, ed. A. Padwa, Wiley, Hoboken, 2002, vol. 59, p. 361; (c) S. Dadiboyena, J. Xu and A. T. Hamme II, *Tetrahedron Lett.*, 2007, **48**, 1295; (d) S. Beha, D. Giguere, R. Patnam and R. Roy, *Synlett*, 2006, 1739; (e) N. Maugein, A. Wagner and C. Mioskowski, *Tetrahedron Lett.*, 1997, **38**, 1547; (f) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339.
- (a) T. M. V. D. Pinho e Melo, *Curr. Org. Chem.*, 2005, **9**, 925; (b) L. I. Belen'kii, in *Nitrile oxides, nitrones and nitronates in organic synthesis*, ed. H. Feuer, Wiley, Hoboken, NJ, USA, 2nd edn., 2008.
- (a) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovstev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2004, **127**, 210; (b) T. V. Hansen, W. Peng and V. V. Fokin, *J. Org. Chem.*, 2005, **70**, 7761; (c) S. Grecian and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2008, **47**, 8285.
- B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh and M. A. Ciufolini, *Org. Lett.*, 2009, **11**, 1539.
- (a) A. Dondoni, P. P. Giovannini and A. Massi, *Org. Lett.*, 2004, **17**, 2929; (b) I. Singh, S. J. Vyle and F. Heaney, *Chem. Commun.*, 2009, 3276; (c) K. Gutmiedel, C. T. Wirges, V. Ehmke and T. Carell, *Org. Lett.*, 2009, **11**, 2405; (d) V. Algay, I. Singh and F. Heaney, *Org. Biomol. Chem.*, 2010, **8**, 391; (e) I. Singh and F. Heaney, *Org. Biomol. Chem.*, 2010, **8**, 451.
- X.-Y. Han, *Synlett*, 2006, 2851.
- The protic solvent(s) may be key in rate enhancement, although opposing effects (hydrophobic, H-bonding, and solvent polarity) make it difficult to denote exactly how. See also: T. Rispens and J. B. F. N. Engberts, *J. Phys. Org. Chem.*, 2005, **18**, 908.
- (a) Z.-X. Yu, P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, 2003, **125**, 15420; (b) D. R. Kelly, S. C. Baker, D. S. King, D. S. de Silva, G. Lord and J. P. Taylor, *Org. Biomol. Chem.*, 2008, **6**, 787.
- A. M. Jawalekar, N. Meeuwenoord, J. S.-G. O. Cremers, H. S. Overkleeft, G. A. van der Marel, F. P. J. T. Rutjes and F. L. van Delft, *J. Org. Chem.*, 2008, **73**, 287.
- (a) N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2004, **126**, 15046; (b) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 16793; (c) X. Ning, J. Guo, M. A. Wolfert and G.-J. Boons, *Angew. Chem., Int. Ed.*, 2008, **47**, 2253.
- M. F. Debets, S. S. van Berkel, S. Schoffelen, F. P. J. T. Rutjes, J. C. M. van Hest and F. L. van Delft, *Chem. Commun.*, 2010, **46**, 97.
- X. Ning, R. P. Temming, J. Dommerholt, J. Guo, D. B. Ania, M. F. Debets, M. A. Wolfert, G. J. Boons and F. L. van Delft, *Angew. Chem., Int. Ed.*, 2010, **49**, 3065.
- J. Dommerholt, S. Schmidt, R. Temming, L. J. A. Hendriks, F. P. J. T. Rutjes, J. C. M. van Hest, D. J. Lefeber, P. Friedl and F. L. van Delft, *Angew. Chem., Int. Ed.*, 2010, **49**, 9422.
- P. König, J. Zountsas, K. Bleckman and H. Meier, *Chem. Ber.*, 1983, **116**, 3580.
- Reaction of benzonitrile-*N*-oxide (4 equiv.) with acyclic alkynes (diphenylacetylene, 2-butyn-1,4-diol) led to only ~10% isoxazole.
- Other applications include reaction with alkylnitride, see: J. A. Crossley and D. L. Browne, *J. Org. Chem.*, 2010, **75**, 5414 or to benzyne, see: A. V. Dubrovskiy and R. C. Larock, *Org. Lett.*, 2010, **12**, 1180.
- (a) E. M. Brustad, E. A. Lemke, P. G. Schultz and A. A. Deniz, *J. Am. Chem. Soc.*, 2008, **130**, 17664; (b) A. J. Link and D. A. Tirrell, *J. Am. Chem. Soc.*, 2003, **125**, 11164.