An improved synthesis of 1,2-benzisoxazoles: TBAF mediated 1,3-dipolar cycloaddition of nitrile oxides and benzyne†

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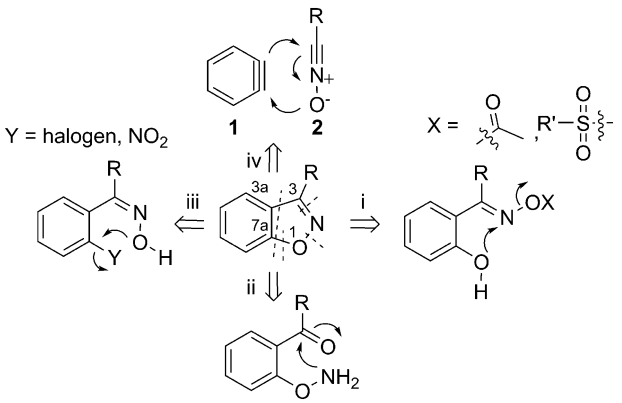
Received (in Cambridge, UK) 27th October 2009, Accepted 16th December 2009
First published as an Advance Article on the web 11th January 2010
DOI: 10.1039/b922489k

An efficient synthesis of a range of 1,2-benzisoxazoles using an improved 1,3-dipolar cycloaddition of nitrile oxides and benzyne is described. Key to the procedure is the *in situ* generation of the reactive nitrile oxide and benzyne reaction partners mediated by TBAF. Reactions are complete within 30 s, giving the target products in good to excellent yield.

Since the early pioneering work of Huisgen *et al.*, 1,3-dipolar cycloadditions have emerged as one of the most important synthetic approaches to five-membered ring heterocycles.[1] The recent advancement of the copper catalysed azide–alkyne cycloaddition, 'click' reaction (CuAAC),[2] has somewhat stimulated a demand for the discovery, or perhaps 're-investigation' of reliable and efficient 1,3-dipolar cycloadditions. In this context, there have been a number of reports focussing upon cycloadditions of 1,3-dipoles to arynes as a promising extension of "Huisgen regime", including azides,[3] diazomethane derivatives,[4] diazo compounds, azamethine imides,[5] azaallyl lithium species, pyridazine *N*-oxides, 1,2,4-triazine 1-oxides[6] and nitrones.[7] Building upon our own work in aryne cycloaddition chemistry,[3d] we were compelled to investigate the partnering of benzyne with alternative 1,3-dipoles, and were drawn towards nitrile oxides as attractive candidates for the synthesis of 1,2-benzisoxazoles. These pharmaceutically relevant structures can be found embedded in a number of biologically active compounds,[8] and therefore have immediate application.

In general, four distinct synthetic approaches to 1,2-benzisoxazoles have evolved (Scheme 1):[9] (i) cyclisation of *o*-hydroxy benzyloxime sulfonates and acetates to form the 1–2, O–N bond;[10] (ii) formation of the 2–3 double bond by intramolecular condensation with aminoxy functionality;[11] (iii) formation of the 1–7a bond, represented by the cyclisation of *o*-halo or *o*-nitrobenzyloximes;[12] and (iv) the simultaneous formation of the 1–7a and 3–3a bonds, by the 1,3-dipolar cycloaddition reaction between benzyne (**1**) and a nitrile oxide (*e.g.* **2**) (Scheme 1).[13] Each approach has limitations and drawbacks. For example, strategies i–iii involve multiple-steps and often require exposure to strong bases, sometimes leading to undesirable side products.[9] Although most attractive in terms of convergence and step-economy, there are limited examples of the synthesis of benzisoxazoles using the 1,3-dipolar cycloaddition strategy (iv, Scheme 1).[12b,13] During the early development of this chemistry, Minisci and Quilico, in 1964, reported the synthesis of 3-phenyl-1,2-benzisoxazole (**3**) in 53% yield, by reacting benzyne (**1**) generated *in situ* from anthranilic acid with preformed benzonitrile oxide.[13a] Despite almost half a century, little advance has been made towards a general and reliable method for benzisoxazole synthesis using benzyne–nitrile oxide cycloaddition chemistry. This is no doubt a consequence of the short life span of the benzyne and nitrile oxide reaction partners, both of which are known to undergo alternative side reaction pathways. Benzyne (**1**) undergoes rapid dimerisation *via* a stepwise [2 + 2] cycloaddition to yield diphenylene.[14] On the other hand, the half-life of nitrile oxides varies from seconds to days,[15] with a tendency to undergo dimerisation to furoxans.[16]



Scheme 1 Synthetic approaches to 1,2-benzisoxazoles.

We reasoned that simultaneous *in situ* generation of both the reactive benzyne and nitrile oxide intermediate would be essential for reaction efficiency and practicality. Although the annulation of arynes by 1,3-dipoles is not conceptually new,[3–8,13] efforts to modernise the reaction are certainly necessary. Early examples utilising diazotised anthranilic acid as the benzyne precursors suffer from potentially dangerous reaction conditions,[14,17] and more recent examples utilising *o*-(trimethylsilyl)aryliodonium salts[18] are limited due to the availability and difficulties in the preparation of these reagents.[3a] These days, arynes are commonly accessed *in situ* by fluoride-promoted *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates,[3,19] which we considered a particularly attractive method for our studies. Base induced dehydrohalogenation of hydroximoyl

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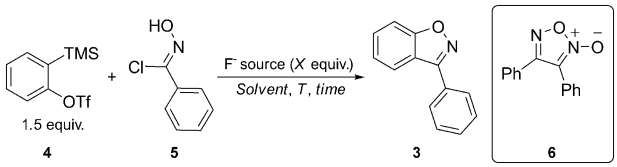
† Electronic supplementary information (ESI) available: Experimental data and procedures for the synthesis of new compounds. See DOI: 10.1039/b922489k

‡ C. S. performed the vast majority of the experimental work.

Table 1 Screening for optimal conditions



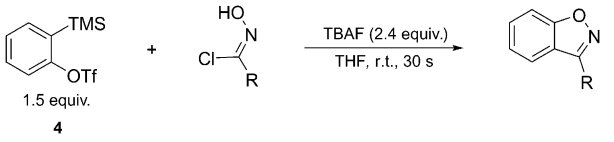
Entry[a]	F⁻ source	Equiv.	Solvent	T/°C	Time	Yield[b]/(%)
1	CsF	2.4	DCM	rt	48 h	trace
2	CsF	2.4	THF	rt	48 h	trace
3	CsF	2.4	MeCN	rt	48 h	21
4	KF	2.4	MeCN	rt	48 h	trace
5	CsF/18-C-6	2.4 : 2.4	MeCN	rt	24 h	44
6	TBAF	2.4	THF	rt	1 min	trace
7	*TBAF*	*2.4*	*THF*	*rt*	*30 s*	*75*
8	TBAF	1	THF	rt	30 s	0
9	TBAF	2	THF	rt	30 s	53
10	TBAF	3	THF	rt	30 s	75
11	TBAF	2.4	MeCN	rt	30 s	75
12	TBAF	2.4	DCM	rt	1 h	32
13	TBAF	2.4	Et_2O	rt	10 min	36
14	TBAF	2.4	THF	0	2 min	48

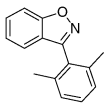
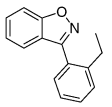
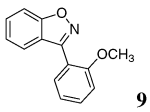
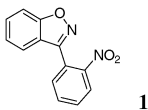
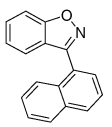
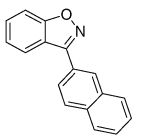
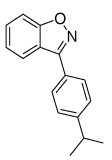
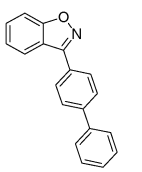
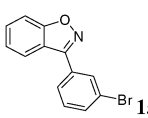
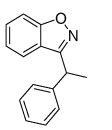
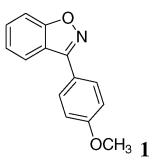
[a] Reactions were performed on 0.32 mmol scale over 24 h. [b] Isolated yields.

chlorides to nitrile oxides appeared straight forward and practical.[20] Given that fluoride is a nucleophilic base (H–F bond strength ~569 kJ mol^{-1}; *cf.* H–Cl, ~432 kJ mol^{-1}; H–O, ~428 kJ mol^{-1}; H–N, ~314 kJ mol^{-1}),[21] we considered exploiting this dual nature[22] for both benzyne and nitrile oxide generation.[23] Table 1 illustrates our findings using a range of inorganic and organic fluoride sources in a variety of solvents, with phenyl hydroximoyl chloride **5**. Using CsF, **4** and **5** reacted to furnish the corresponding 1,2-benzisoxazole **3**, albeit in low yield (entries 1, 2 and 3, Table 1). Changing the fluoride source from CsF to KF led to a decrease in yield (entry 4, Table 1) which could be attributed to its stronger ion pair. Furthermore, increasing the solubility and nucleophilicity of the fluoride ion by using a 1 : 1 mixture of CsF to 18-crown-6 gave **3** with an improved yield of 44% (entry 5, Table 1).[3c]

TBAF, known to form a weak ion pair even in organic solvents, was next chosen as a suitable nucleophilic source of fluoride.[24] Accordingly, **5** and TBAF were dissolved in THF at room temperature followed by the addition of **4** (1 : 2.4 : 1.5 equiv.) (entry 6, Table 1). The reaction was notably exothermic and resulted in full consumption of **5** (TLC), whereas **4** was faintly visible on TLC. Unfortunately, the formation of **3** could only be detected by HRMS (ESI†) of the crude reaction mixture, with furoxan dimer **6** as the only isolated product. Changing the order of reagent addition had a profound effect. Thus, when **4** and **5** were premixed in THF for 5 minutes, followed by TBAF addition, the reaction was complete within 30 s (TLC) and 1,2-benzisoxazole **3** was obtained in 75% isolated yield (entry 7, Table 1). Interestingly, when only 1.0 equiv. of TBAF was used, (entry 8, Table 1), only dimer **6** was isolated, with full recovery of **5**. This suggested that TBAF was exclusively inducing dehydrohalogenation, calling for higher quantities of fluoride. In fact a mole ratio of 1 : 2 of **5** and TBAF gave **3** in 53% (entry 9, Table 1). Increasing to 3 equiv.

Table 2 Synthesis of 1,2-benzisoxazoles



Entry[a]	Product	Yield[b]/%
1	 **7**	99
2	 **8**	93
3	 **9**	92
4	 **10**	75
5	 **11**	99
6	 **12**	85
7	 **13**	87
8	 **14**	95
9	 **15**	78
10	 **16**	50
11	 **17**	92

[a] 0.32 mmol of hydroximoyl chloride, **4** (1.5 equiv.), THF, TBAF (2.4 equiv.), rt, 30 s. [b] Isolated yields.

did not have any beneficiary effect on the yield of **3** (entry 10, Table 1). Thus, room temperature addition of 2.4 equiv. of TBAF to a premixed solution of starting materials in THF was found to be optimal.

To test the scope of this protocol several substrates were examined. The reaction was found to be tolerant of a variety of substituents on the aromatic ring of hydroximoyl chlorides, including alkyl (entries 1, 2 and 7, Table 2), electron-withdrawing (entries 4 and 9, Table 2) and electron-donating groups (entries 3, 5, 6, 8 and 11, Table 2). Excellent yields were observed for most substrates, especially those having their fulmido group sterically congested by the presence of one or two *ortho*-substituents (entries 1–5, Table 2). Even when less sterically hindered benzonitrile oxides were used, yields were high (entries 6–11, Table 2). Slightly lower yields were observed with electron deficient nitrile oxides (entries 4 and 9, Table 2). Furthermore, this improved methodology could be extended to the challenging and less stable aliphatic nitrile oxides, as exemplified by the formation of **16** in moderate yield (50%) (entry 10, Table 2). The lower yield could be attributed to self-decomposition of the unstable aliphatic hydroximoyl chloride.[25]

In summary, the present protocol describes an expedient one-pot access to 1,2-benzisoxazoles in good to excellent yields, from readily accessible starting materials. Furoxans were the only observed by-products and were easily removed by simple chromatographic techniques. The reaction demonstrates the feasibility of TBAF as an efficient reagent for nitrile oxide generation and ring annulations. The methodology surpasses those already described for its simplicity, mild reaction conditions and ease of product purification.

We thank The EPSRC, GlaxoSmithKline, Association for International Cancer Research (AICR) and The University of Nottingham for financial support.

Notes and references

1 (*a*) R. Huisgen and R. Knorr, *Naturwissenschaften*, 1961, **48**, 716; (*b*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565; (*c*) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123; (*d*) K.-R. Meier, A. Linden, G. Mlostoń and H. Heimartner, *Helv. Chim. Acta*, 1997, **80**, 1190; (*e*) A. Strauss and H.-H. Otto, *Helv. Chim. Acta*, 1997, **80**, 1823; (*f*) K. Bast, M. Behrens, T. Durst, R. Grashey, R. Huisgen, R. Schiffer and R. Temme, *Eur. J. Org. Chem.*, 1998, 379; (*g*) R. Huisgen and R. Temme, *Eur. J. Org. Chem.*, 1998, 387; (*h*) R. Huisgen and R. Temme, *Heteroat. Chem.*, 1999, **10**, 79; (*i*) R. Huisgen, I. Kalvinsch, X. Li and G. Mloston, *Eur. J. Org. Chem.*, 2000, 1685; (*j*) R. Huisgen and E. Langhals, *Heteroat. Chem.*, 2006, **17**, 433; (*k*) K. Gutsmiedl, C. T. Wirges, V. Ehmke and T. Carell, *Org. Lett.*, 2009, **11**, 2405.

2 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004; (*b*) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249.

3 (*a*) F. Shi, J. P. Waldo, Y. Chen and R. C. Larock, *Org. Lett.*, 2008, **10**, 2409; (*b*) S. Chandrasekhar, M. Seenaiah, Ch. L. Rao and Ch. R. Reddy, *Tetrahedron*, 2008, **64**, 11325; (*c*) L. Campbell-Verduyn, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx and B. L. Feringa, *Org. Biomol. Chem.*, 2008, **6**, 3461; (*d*) F. Zhang and J. E. Moses, *Org. Lett.*, 2009, **11**, 1587.

4 T. Jin and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2007, **46**, 3323.

5 T. Jin, F. Yang and Y. Yamamoto, *Collect. Czech. Chem. Commun.*, 2009, **74**, 957.

6 H. Pellissier and M. Santelli, *Tetrahedron*, 2003, **59**, 701.

7 M. Dai, Z. Wang and S. J. Danishefsky, *Tetrahedron Lett.*, 2008, **49**, 6613.

8 (*a*) J. F. Gabbert and A. J. Giannini, *Am. J. Ther.*, 1997, **4**, 159; (*b*) M. Murata, E. Horiuchi and I. Kanazawa, *Neurosci. Res.*, 2001, **41**, 397; (*c*) M. S. Malamas, E. S. Manas, R. E. McDevitt, I. Gunawan, Z. B. Xu, M. D. Collini, C. P. Miller, T. Dinh, R. A. Henderson, J. C. Keith Jr. and H. A. Harris, *J. Med. Chem.*, 2004, **47**, 5021.

9 For examples see: F. Gualtieri and M. Giannella, *The Chemistry of Heterocyclic Compounds: Isoxazoles, Part Two*, ed. P. Grunanger, P. Vita-Finzi, Wiley, New York, 1999, vol. 49, pp. 1–122.

10 (*a*) A. H. Blatt and L. A. Russell, *J. Am. Chem. Soc.*, 1936, **58**, 1903; (*b*) A. Villalobos, J. F. Blake, C. K. Biggers, T. W. Butler, D. S. Chapin, T. L. Chen, J. L. Ives, S. B. Jones, D. R. Liston, A. A. Nagel, D. M. Nason, J. A. Nielsen, I. A. Shalaby and W. F. White, *J. Med. Chem.*, 1994, **37**, 2721.

11 (*a*) G. M. Shutske, *J. Org. Chem.*, 1984, **49**, 180; (*b*) M. S. Malamas, E. S. Manas, R. E. McDevitt, I. Gunawan, Z. B. Xu, M. D. Collini, C. P. Miller, T. Dinh, R. A. Henderson, J. C. Keith Jr. and H. A. Harris, *J. Med. Chem.*, 2004, **47**, 5021.

12 (*a*) E. P. Kohler and W. F. Bruce, *J. Am. Chem. Soc.*, 1931, **53**, 644; (*b*) T. Yamamori, Y. Hiramatsu and I. Adachi, *J. Heterocycl. Chem.*, 1981, **18**, 347; (*c*) D. M. Fink and B. E. Kurys, *Tetrahedron Lett.*, 1996, **37**, 995; (*d*) K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya and T. Sakamoto, *Tetrahedron*, 2007, **63**, 2695.

13 (*a*) F. Minisci and A. Quilico, *Chim. Ind.*, 1964, **46**, 428; (*b*) T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 826.

14 (*a*) F. M. Logullo, A. H. Seitz and L. Friedman, *Org. Synth.*, 1968, **48**, 12; (*b*) F. M. Logullo, A. H. Seitz and L. Friedman, *Org. Synth. Coll.*, 1973, **5**, 54.

15 (*a*) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339; (*b*) C. Grundmann and S. K. Datta, *J. Org. Chem.*, 1969, **36**, 2016.

16 (*a*) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, 1960, **25**, 546; (*b*) Y. H. Chiang, *J. Org. Chem.*, 1971, **36**, 2146; (*c*) A. Gasco and A. J. Boulton, *Adv. Heterocycl. Chem.*, 1981, **29**, 251.

17 (*a*) M. Stiles and R. G. Miller, *J. Am. Chem. Soc.*, 1960, **82**, 3802; (*b*) M. Stiles, R. G. Miller and U. Burckhardt, *J. Am. Chem. Soc.*, 1963, **85**, 1792.

18 T. Kitamura, M. Todaka, I. Shin-machi and Y. Fujiwara, *Heterocycl. Commun.*, 1998, **4**, 205.

19 (*a*) Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211; (*b*) T. Jin and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2007, **46**, 3323.

20 (*a*) S. Grecian and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2008, **47**, 8285; (*b*) H. Suga, Y. Adachi, K. Fujimoto, Y. Furihata, T. Tsuchida, A. Kakehi and T. Baba, *J. Org. Chem.*, 2009, **74**, 1099.

21 J. H. Clark, *Chem. Rev.*, 1980, **80**, 429.

22 H. Yoshida, T. Kishida, M. Watanabe and J. Ohshita, *Chem. Commun.*, 2008, 5963.

23 J. Nyoung Kim, K. H. Chung and E. K. Ryu, *Heterocycles*, 1991, **32**, 477.

24 M. M. Bastos, J. P. Barbosa, A. C. Pinto, W. B. Kover, Y. Takeuchi and N. Boechat, *J. Braz. Chem. Soc.*, 2001, **12**, 417.

25 S. Kanemasa, H. Matsuda, A. Kamimura and T. Kakinami, *Tetrahedron*, 2000, **56**, 1057.

