Tetrahedron Letters 51 (2010) 1030–1033

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-catalyzed cyclization of *Z*-oximes into 3-methyl-1,2-benzisoxazoles

Sandra Udd [a], Reija Jokela [a], Robert Franzén [b], Jan Tois [b,*]

[a] Faculty of Chemistry and Material Sciences, Department of Chemistry, Helsinki University of Technology, P.O. Box 6100, FIN-02015 TKK, Finland
[b] Department of Chemistry and Bioengineering, Laboratory of Chemistry, Tampere University of Technology, Korkeakoulunkatu 8, 33720 Tampere, Finland

ARTICLE INFO

Article history:
Received 29 October 2009
Revised 30 November 2009
Accepted 11 December 2009
Available online 21 December 2009

Keywords:
Cyclization
Oximes
Copper

ABSTRACT

A practical and effective room temperature copper-catalyzed cyclization of *Z*-oximes is developed. 3-Methyl-1,2-benzisoxazoles are obtained in 58–79% yields. Also, the *Z*-selective synthesis of *o*-bromo acetophenone oximes is presented for the first time.

1,2-Benzisoxazoles are motifs present in a wide range of pharmaceutically potent agents, including diuretics,[1] acetylcholinesterase inhibitors,[2] antileptics,[3] and neuroleptics.[4] As a result, several approaches have been developed to obtain these heterocycles.[5] Despite the diversity of existing methods only two are frequently used to access 3-substituted-1,2-benzisoxazoles (Fig. 1).

Route A involves formation of the N–O bond via dehydration while in route B a C–O bond is formed via nucleophilic aromatic substitution (S_NAr reaction).[6] The aforementioned strategy requires an *ortho*-hydroxy group relative to the oxime functionality and transformation of the oximino hydroxy into a good leaving group. To accomplish the dehydration, a variety of reagents have been used.[7] The latter method, route B, requires a good leaving group *ortho* relative to the oxime functionality. The deprotonated oximino hydroxy attacks the *ortho*-position and the leaving group is subsequently eliminated. It is believed that an electron-withdrawing ketoxime functionality at the *ortho*-position and the close proximity of the leaving group are the factors needed for this cyclization to occur.[8]

The effectiveness of fluoride as a leaving group in S_NAr reactions is known to be superior to other halogens and 1,2-benzisoxazole formation is not an exception.[9] Despite the higher reactivity of fluorinated starting materials, chloride,[10] bromide,[11] and nitro[12] have also been used as leaving groups. von Borsche and Schriba[13] found that an electron-donating substituent *para* relative to the leaving group diminished the reactivity when the oximes were reacted under harsh conditions. On the other hand, electron-withdrawing substituents are known to enhance the reactivity. In addition to these charge-stabilizing effects, the most limiting factor is the need for the oxime to be in *Z*-configuration, in other words, the hydroxy group needs to be *cis* to the aromatic ring.[14]

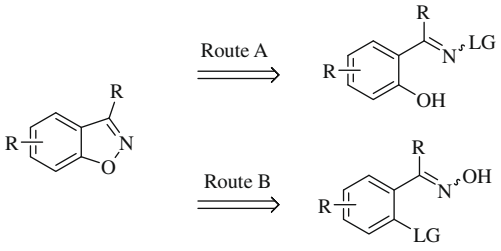
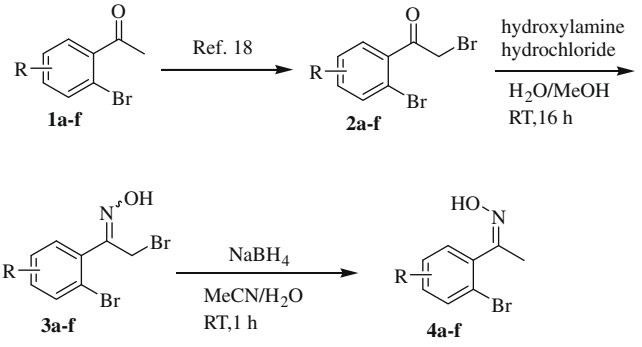


Figure 1. Synthetic routes to 1,2-benzisoxazoles.

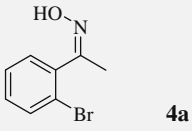
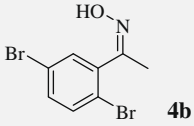
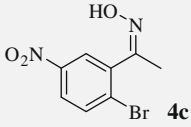
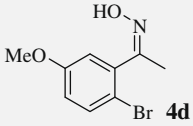
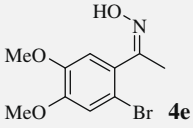
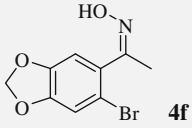


Scheme 1. *Z*-Selective synthesis of oximes.

* Corresponding author. Tel.: +358 3 31153693.
E-mail address: Jan.Tois@tut.fi (J. Tois).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.070

Table 1
Synthesized *Z*-oximes[a]

Entry	Product	Yield[b] (%)
1	 **4a**	74
2	 **4b**	75
3	 **4c**	83
4	 **4d**	89
5	 **4e**	95
6	 **4f**	91

[a] See Supplementary data for details.
[b] Isolated yield after two steps (**2a–f**→**4a–f**).

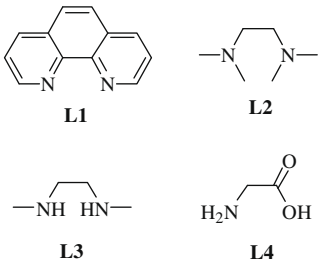


Figure 2. Structures of ligands **L1–L4**.

To avoid the forcing reaction conditions typically needed for S_NAr reactions, attempts to perform the transformation catalytically have been made.[15] So far, these trials have been restricted to the formation of 3-phenyl-1,2-benzisoxazoles, because the predominant isomer of the *o*-halogeno benzophenone oxime is in the *Z*-configuration.[16] According to our knowledge there are no catalytic methods reported for the preparation of 3-alkyl-substituted 1,2-benzisoxazoles. In this Letter, we describe the first catalytic cyclization leading to 3-methyl-1,2-benzisoxazoles.

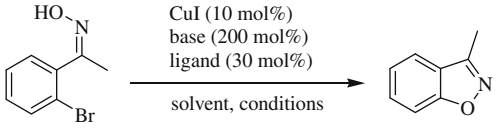
Z-Configured *o*-bromo acetophenone oximes were prepared by the seldom-utilized method, for unsubstituted acetophenone oximes, reported by Smith and Kaiser[17] (Scheme 1).

The α-bromination of *o*-bromoacetophenones **1a–f** was performed using $CuBr_2$.[18] Oximation was accomplished in the absence of base according to the method of Chaudhuri and co-workers[19] yielding a mixture of *E*- and *Z*-isomers. Finally, treatment of the mixtures of **3a–f** with sodium borohydride[17] afforded the desired *Z*-oximes **4a–f** in acceptable overall yields (Table 1).

With the *Z*-oximes in hand we next screened the copper-catalyzed cyclization conditions (Table 2).

At first, the reaction conditions of Maitra and co-workers[15b] were explored. According to TLC, the reaction was complete in

Table 2
Screening of the copper-catalyzed cyclization conditions[a]



4a **5a**

Entry	Base	Ligand	Solvent	Conditions temp (°C)/time (min)	Yield[b] (%)
1[c]	Cs_2CO_3	**L1**	Toluene	110/40	45
2	Cs_2CO_3	**L1**	Toluene	110/40	43
3	Cs_2CO_3	**L1**	Toluene	110/40	—[d]
4	Cs_2CO_3	**L1**	Toluene	23/90	—
5	Cs_2CO_3	**L1**	Toluene	60/90	—
6	Cs_2CO_3	**L1**	Toluene	80/90	17
7	*t*-BuONa	**L1**	Toluene	23/90	24
8	*t*-BuONa	**L1**	THF	23/90	35
9	*t*-BuONa	**L2**	THF	23/20	57
10	*t*-BuONa	**L3**	THF	23/5	58
11	*t*-BuONa	**L4**	THF	23/60	32
12[e]	*t*-BuONa	**L3**	THF	23/200	26
13[f]	*t*-BuONa	**L3**	THF	23/200	34
14[g]	*t*-BuONa	**L3**	THF	23/200	—
15[g]	*t*-BuONa	**L3**	THF	67/60	—

[a] See Supplementary data for experimental conditions.
[b] Isolated yield.
[c] 40 mol % Na,K-tartrate added together with the ligand.
[d] All reagents added at once.
[e] 5 mol % of CuI.
[f] 20 mol % of ligand.
[g] *E*-Oxime was used as the reactant.

40 min and **5a** was isolated in 45% yield after chromatography (entry 1). The reaction was repeated in the absence of Na,K-tartrate to afford a similar result (entry 2).[20] When the reagents were added simultaneously to the flask followed by the solvent, a complex mixture was obtained. ^{1}H NMR analysis of the crude reaction mixture indicated that formation of **5a** had not occurred. When the reaction was repeated at room temperature (entry 4) or at 60 °C (entry 5) only starting material was detected by TLC. When the reaction temperature was 80 °C (entry 6) the desired compound **5a** was obtained after purification in 17% yield. During the experiment there was a color change from colorless to yellow after the addition of base, which is probably due to deprotonation. This indicates that the oxime hydroxy group needs to be deprotonated before addition of the ligand and catalyst. We decided to use a stronger base, *t*-BuONa, and to our delight the reaction took place at room temperature (entry 7). However, the reaction did not proceed toward completion, but there was no formation of side products either. We concluded that the poor solubility of **4a** in toluene at room temperature might explain the incomplete reaction. Toluene was replaced by THF and **5a** was isolated in 35% yield (entry 8). In this case also the reaction never went to completion. Next, we decided to screen several readily available ligands (Fig. 2) which have been utilized in copper-catalyzed C–O bond-forming reactions.[21]

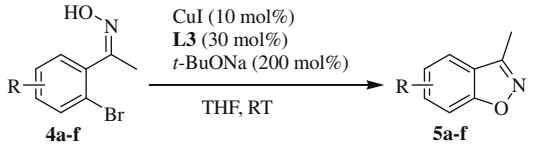
When **L2** was utilized as the ligand, the reaction was complete in 20 min at room temperature according to TLC. After aqueous work-up, compound **5a** was obtained in 57% yield (entry 9). When TMEDA was replaced by DMEDA (**L3**), the reaction was even faster and the target molecule was formed in five minutes in comparable yield (entry 10). Also in this case, there was no need for chromatographic purification. The N,O-chelating ligand (**L4**) was not as effective and side products were observed (entry 11).

Decreasing the amount of copper or ligand led to incomplete reactions, thus indicating that 10 mol % of CuI and 30 mol % of ligand were needed for successful cyclizations (entries 12 and 13). When an *E*-configured oxime was subjected to the optimized conditions only a mixture of side products was obtained (entries 14 and 15). Under these conditions no isomerization[22] (*E*→*Z*) was observed and the side reactions became dominant. To confirm that the reaction proceeded catalytically and not via a S_NAr mechanism, a control reaction was performed. The *Z*-oxime **4a** was stirred with *t*-BuONa in THF and the reaction was monitored by TLC. After 90 min no formation of **5a** was detected. Ligand **L3** was added and the reaction was further stirred for 60 min without formation of **5a**. When CuI was added, the cyclization occurred immediately, clearly demonstrating that the reaction is catalytic. To explore the scope of the reaction, *Z*-oximes **4b–f** were subjected to the reaction conditions and the results are shown in Table 3.

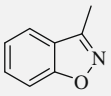
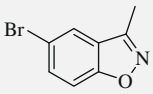
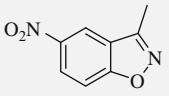
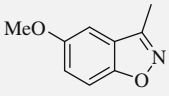
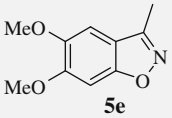
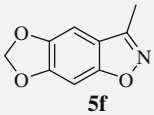
When an electron-donating methoxy group was present *para* to the bromo-substituent, the reaction time was 60 min (entry 4). As expected, the electron-withdrawing NO_2-substituent activated the system to such an extent that **4c** cyclized without addition of the ligand and catalyst via a S_NAr mechanism (entry 3).

In summary, we have developed an efficient copper-catalyzed method for the preparation of 3-methyl-1,2-benzisoxazoles. The catalytic reaction is rapid, selective, and no heating is required. The obtained products are pure and therefore chromatographic purification can be omitted. For cyclization to occur under the catalytic conditions employed here, it is vital that the acetophenone oxime is of *Z*-configuration and thus a synthetic pathway for *o*-bromo acetophenones was developed. Further investigations to extend this strategy to other alkyl substituents and to utilize this method for more complex molecules are currently underway in our laboratory.

Table 3
Products, yields, and reaction times for the cyclization of *Z*-oximes



4a-f 5a-f

Entry	Product	Time[a] (min)	Yield[b] (%)
1	 **5a**	5	58
2	 **5b**	5	66
3	 **5c**	5[c]	63
4	 **5d**	60	79
5	 **5e**	35	68
6	 **5f**	45	70

[a] The reaction time refers to the time after addition of catalyst.
[b] Isolated yield of pure compound.
[c] The reaction occurs without addition of ligand or catalyst.

Acknowledgments

We thank Orionpharma Corporation for financial support, and Mrs. Mia Malmström and Dr. Marko Ahlmark for valuable assistance with NMR spectrometry.

Supplementary data

Supplementary data (experimental procedures and data for compounds **4a–f** and **5b–f**) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.070.

References and notes

1. Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis, L.; Effland, R. C.; Ranbom, K.; Kitzen, J. M.; Wilker, J. C.; Novick, W. J., Jr. *J. Med. Chem.* **1982**, *25*, 36–44.
2. Rangappa, K. S.; Basappa, S. *J. Phys. Org. Chem.* **2005**, *18*, 773–778.
3. Veera Reddy, A.; Rajendiran, C.; Vaishali, N. Improved Process for the Preparation of Intermediates Useful for the Preparation of Zonisamide. WO 2005/030738, Sep 29, 2003; *Chem. Abstr.* **2005**, *142*, 33849.
4. Struczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Glamkovski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, *28*, 761–769.
5. Smalley, R. K.. *Methoden der organischen Chemie, Band E 8 a Hetarene III-Teil 1*; Georg Thieme, 1993. p 226–348.
6. Throughout this Letter the addition–elimination mechanism is referred to as S_NAr.
7. (a) von Lindemann, H.; Thiele, H. *Justus Liebigs Ann. Chem.* **1926**, *449*, 63–81; (b) Thakar, K. A.; Goswami, D. D.; Bhawal, B. M. *Indian J. Chem.* **1977**, *15B*, 1058–1059; (c) Liu, K.; Xu, L.; Berger, J. P.; MacNaul, L. L.; Zhou, G.; Doebbler, T. W.;

Forrst, M. J.; Moller, D. E.; Jones, A. B. *J. Med. Chem.* **2005**, *48*, 2262–2265; (d) Roman, G.; Comanita, E.; Comanita, B. *Tetrahedron* **2002**, *58*, 1617–1622; (e) Jain, M.; Kwon, C. *J. Med. Chem.* **2003**, *46*, 5428–5436; (f) Stakker, G. *J. Org. Chem.* **1983**, *48*, 2613–2615; (g) Kalkote, U. R.; Goswami, D. D. *Aust. J. Chem.* **1977**, *30*, 1847–1850; (h) Cvetovich, R. J.; Chung, J. Y. L.; Kress, M. H.; Amato, J. S.; Matty, L.; Weingarten, M. D.; Tsay, F.-R.; Li, Z.; Zhou, G. *J. Org. Chem.* **2005**, *70*, 8560–8563; (i) Blatt, A. H. *J. Org. Chem.* **1955**, *20*, 591–602; (j) Crabbé, P.; Maldonaldo, L. A.; Sánchez, I. *Tetrahedron* **1971**, *27*, 711–725; (k) Mantegani, S.; Traquandi, G.; Varasi, M. *J. Heterocycl. Chem.* **2001**, *38*, 759–763; (l) Poissonnet, G. *Synth. Commun.* **1997**, *27*, 3839–3846; (m) Malamas, M. S.; Manas, E. S.; McDewitt, R. E.; Gunawan, I.; Xu, Z. B.; Collini, M. D.; Miller, C. P.; Dinh, T.; Henderson, R. A.; Keith, ; Jr, J. C.; Harris, H. A. *J. Med. Chem.* **2004**, *47*, 5021–5040; (n) Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron Lett.* **2006**, *47*, 8247–8250.

8. Wünsch, K.-H.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1967**, *8*, 277–302.
9. For some recent examples in which fluoride is utilized as a leaving group, see: (a) Bunnett, J. F.; Yih, S. Y. *J. Am. Chem. Soc.* **1961**, *83*, 3805–3807; (b) Kunz, R. K.; Rumfelt, S.; Chen, N.; Zhang, D.; Tasker, A. S.; Bürli, R.; Hungate, R.; Yu, V.; Nguyen, Y.; Whittington, D. A.; Meagher, K. L.; Plant, M.; Tudor, Y.; Schrag, M.; Xu, Y.; Ng, G. Y.; Hu, E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5115–5117; (c) Gopalsamy, A.; Shi, M.; Golas, J.; Vogan, E.; Jacob, J.; Johnson, M.; Lee, F.; Nilakantan, R.; Petersen, R.; Svenson, K.; Chopra, R.; Tam, M. S.; Wen, Y.; Ellingboe, J.; Arndt, K.; Boschelli, F. *J. Med. Chem.* **2008**, *51*, 373–375.
10. For some recent examples in which chloride is utilized as a leaving group, see: (a) King, J. F.; Durst, T. *Can. J. Chem.* **1962**, *40*, 882–889; (b) Villani, F. *J. Org. Chem.* **1975**, *40*, 1734–1737; (c) Sato, H.; Dan, T.; Onuma, E.; Haruko, A.; Bunya, K. *Chem. Pharm. Bull.* **1991**, *39*, 1760–1772.
11. For some recent examples in which bromide is utilized as a leaving group, see: (a) Tidwell, R. R.; Geratz *J. Med. Chem.* **1978**, *21*, 613–623; (b) De Sousa, B. F. S. E.; Siegrist, A. E. *Helv. Chim. Acta* **1978**, *61*, 2904–2940.
12. For some recent examples in which a nitro group is utilized as a leaving group, see: (a) Kemp, D. S.; Paul, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 7305–7312; (b) Hrib, N. J.; Jurcak, J. G.; Burgher, K. L.; Conway, P. G.; Hartman, H. B.; Kerman, L. L.; Roehr, J. E.; Woods, A. T. *J. Med. Chem.* **1994**, *37*, 2308–2314.
13. von Borsche, W.; Schriba, W. *Justus Liebigs Ann. Chem.* **1939**, *541*, 283–292.
14. Wünsch, K.-H.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1967**, *9*, 277–302.
15. (a) Coffen, D. L.; Schaer, B.; Bizzarro, F. T.; Cheung, J. B. *J. Org. Chem.* **1984**, *49*, 296–300; (b) Nonappa, P. D.; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, *9*, 2767–2770; (c) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695–2711.
16. Cathcart, W. R., Jr.; Meyer, V. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 3291–3297.
17. Smith, J. H.; Kaiser, E. T. *J. Org. Chem.* **1974**, *39*, 728–730.
18. King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459–3461.
19. Pavlischchuk, V.; Birkelbach, F.; Weyhermüller, T.; Wieghardt, K.; Chaudhuri, P. *Inorg. Chem.* **2002**, *41*, 4405–4416.
20. Maitra reported that Na,K-tartrate was needed to prevent the Cu(II)-catalyzed deoximation, for details see: Ref. 15b.
21. For copper-catalyzed formation of C–O-bonds, see: (a) Chem, C.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964–6967; (b) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467–1470; (c) Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Tetrahedron Lett.* **2007**, *48*, 7578–7581; (d) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661–1664; (e) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808; (f) Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2007**, *63*, 10425–10432; (g) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452–3459; (h) Fagan, P. J.; Hauptmann, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051; (i) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427–6431.
22. Heating may induce isomerization under basic conditions. For details, see: Smith, N. H. P. *J. Chem. Soc.* **1961**, 4209–4211.