Tetrahedron Letters 53 (2012) 3746–3749

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Reactivity of the ester group attached isoxazoline, benzisoxazole, and isoxazole: a facial preparation of 3-acyl-substituted these heterocycles

Kenichi Murai, Shuji Miyazaki, Hiromichi Fujioka *

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565-0871, Japan

ARTICLE INFO

Article history:
Received 18 February 2012
Revised 24 April 2012
Accepted 2 May 2012
Available online 7 May 2012

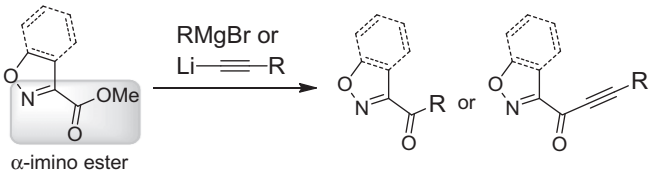
Keywords:
Heterocyclic chemistry
Ketone
Isoxazolines
Benzisoxazoles
Isoxazoles

ABSTRACT

A facile preparation of 3-acyl-substituted isoxazolines, benzisoxazoles, and isoxazoles from the corresponding 3-carboxylate esters is described. The process, involving reaction of the ester derivative of 3-carboxylic acid substituted heterocycles with Grignard or alkynyl lithium reagents, leads to direct generation of the corresponding 3-acyl heterocycle. The presence of α-imino ester moieties in the heterocyclic substrates for the reactions is thought to be a key feature governing the nature of these transformations. The synthetic utility of the new methodology is demonstrated by its application in a two-step route for the preparation of novel linked bis-heterocycles.

Isoxazolines, isoxazoles, and benzisoxazoles are important class of heterocycles in pharmaceuticals.[1] Therefore, the development of simple and practical methods for their derivatives is an important task in organic chemistry. In this communication, we describe a facile preparation of keto-derivatives of them: 3-acyl-substituted isoxazolines, benzisoxazoles, and isoxazoles are directly obtained from the corresponding 3-carboxylate esters just by a reaction with Grignard reagents or alkynyl lithium reagents (Scheme 1). This simple transformation is based on the unreported reactivity of these heterocycles. Remarkably, the developed procedure, which enables easy preparation of alkynyl ketones, provides a novel efficient strategy for bis-heterocyclic compounds, which is demonstrated by derivatization of benzisoxazoles.

In general, it is difficult to produce ketones rather than tertiary alcohols in reactions of esters with Grignard reagents and organolithium reagents.[2] Meanwhile, some α-heteroatom substituted esters are known to produce ketones directly.[3,4] For example, reactions of alkyl oxalates with Grignard reagents are often used for preparation of α-ketoesters.[3e–i] These reactions are considered to proceed via formation of a five-membered chelating hemiketal to prevent further addition of reagents. This strategy was also applied to several heterocyclic compounds.[5] However, although facile preparation of ketone substituted heterocycles from readily available esters seems to be an attractive way from a practical point of view, a kind of applicable heterocyclic compounds is not examined enough. For example, isoxazolines and benzisoxazoles have not been employed in this transformation.



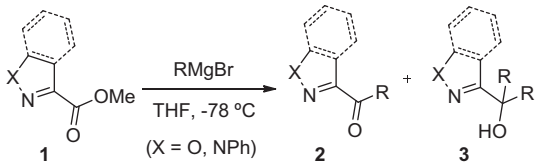
Scheme 1. This work.

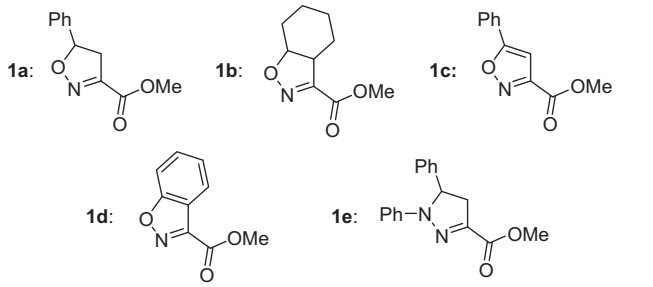
In our recent study, we reported the applicability of 3-oxazoline-4-carboxylates in this transformation: esters of them are transformed to ketones in high yields by reactions with MeMgBr and PhMgBr probably due to α-imino ester structure.[6] These observations have stimulated our interest in exploring the potential utility for the structurally related but more general five-membered heterocyclic compounds than 3-oxazoline-4-carboxylates. Therefore, to explore the applicability of the processes, we started the studies on several heterocycles including α-imino ester structure, such as isoxazolines **1a** and **1b**, isoxazole **1c**, benzisoxazole **1d**, and pyrazoline **1e**. Those heterocycles have not been studied on the describing transformation. In Table 1 the results of the reactions with methyl or phenyl magnesium bromide carried out at −78 °C are shown. The ratio of starting heterocycle **1**, ketone **2**, and tertiary alcohol **3** was determined by ^{1}H NMR spectrum of crude reaction mixtures.[7] Both isoxazolines **1a** and **1b** were found to undergo reactions with methyl magnesium bromide to give the respective methyl ketones **2aa** and **2ba** (entries 1 and 2). The temperature used for the process is important as shown by the observation that alcohol **3aa** is predominantly produced when the reaction of **1a** is

* Corresponding author. Tel.: +81 6 6879 8225; fax: +81 6 6879 8229.
E-mail address: fujioka@phs.osaka-u.ac.jp (H. Fujioka).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.006

Table 1
Screening of the reactivity trend with MeMgBr and PhMgBr[a]





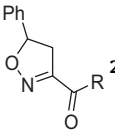
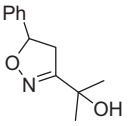
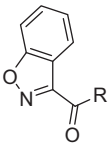
Entry	1	Reagent	Ratio (**1**:**2**:**3**) [b]
1	**1a**	MeMgBr	0:100:0 (**1a**:**2aa**:**3aa**)
2	**1b**	MeMgBr	0:100:0 (**1b**:**2ba**:**3ba**)
3	**1a**	MeMgBr (0 °C)	0:16:84 (**1a**:**2aa**:**3aa**)
4	**1a**	MeMgBr (in toluene)	0:77:23 (**1a**:**2aa**:**3aa**)
5	**1c**	MeMgBr	36:64:0 (**1c**:**2ca**:**3ca**)
6	**1d**	MeMgBr	0:100:0 (**1d**:**2da**:**3da**)
7	**1e**	MeMgBr	82:0:18 (**1e**:**2ea**:**3ea**)
8	**1a**	PhMgBr	4:85:11 (**1a**:**2ab**:**3ab**)
9	**1b**	PhMgBr	5:88:7 (**1b**:**2bb**:**3bb**)
10	**1c**	PhMgBr	21:56:24 (**1c**:**2cb**:**3cb**)
11	**1d**	PhMgBr	23:73:4 (**1d**:**2db**:**3db**)

[a] Reaction conditions: RMgBr (10 equiv) and THF (0.1 M) at −78 °C.
[b] The ratio was determined by ^{1}H NMR spectrum of crude reaction mixtures and the products were not isolated.

performed at 0 °C (entry 3). Non coordinating solvent, toluene, was found to decrease the selectivity (entry 4). Isoxazole **1c** and benzisoxazole **1d** also react with methyl magnesium bromide to give the corresponding methyl ketone derivatives (entries 5 and 6), although some starting materials remained unreacted when **1c** is the substrate. In contrast, pyrazoline **1e** reacts very slowly under these conditions to produce alcohol **3ea** as a major product, suggesting low applicability of pyrazoline **1e** (entry 7). Accordingly, the reactions of the heterocyclic esters **1a**–**1d** and PhMgBr were further conducted. Then, the similar trends were observed (entries 8–11): The esters **1a**–**1d** are selectively transformed to phenyl ketones, although the formation of corresponding alcohols was also observed in reactions of **1a** (11%), **1b** (7%), **1c** (24%), and **1d** (4%). In summary, Grignard addition reactions of 3-carboxylic acid ester substituted isoxazolines, isoxazoles, and benzisoxazoles at low temperatures yield 3-acyl-substituted heterocyclic products.[8]

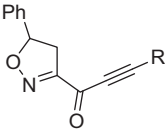
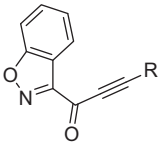
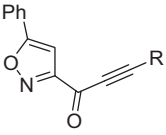
The generality of this process was subjected to further investigation (Table 2).[9,10] Unlike the reaction of isoxazoline ester **1a** with MeMgBr, which gave a methyl ketone in 96% yield (entry 1), the corresponding reaction of this substrate with alkyl Grignard reagents such as, EtMgBr and *i*PrMgCl, leads to give complex mixtures (entry 2). In contrast, phenyl, *p*MeO-phenyl, and *p*F-phenyl ketones are generated in good yields when **1a** is treated with the corresponding aryl Grignard reagents (entries 3–5). The reactivity difference between Grignard reagents and alkyl lithium reagents was of interest. We examined the reaction of **1a** and MeLi to find the generation of tertiary alcohol **3aa** in 85% yield selectively (entry 6). As for the benzisoxazole **1d**, 3-acyl benzisoxazoles were directly obtained using MeMgBr and PhMgBr in 84% and 59% isolated yields respectively (entries 7 and 8). The single step efficient preparation of 3-keto benzisoxazole **2da** was remarkable because that

Table 2
Generality 1[a]

Entry	1	Reagent	Yield[b]
1	**1a**	MeMgBr	 **2aa** (R = Me) 96% (92%)[c]
2	**1a**	EtMgBr or *i*PrMgCl	Complex mixtures
3	**1a**	PhMgBr	**2ab** (R = Ph) 84%
4	**1a**	*p*MeOPhMgBr	**2ac** (R = *p*MeOPh) 78%
5	**1a**	*p*FPhMgCl	**2ad** (R = *p*FPh) 81%
6	**1a**	MeLi	 **3aa** (R = Me) 85%
7	**1d**	MeMgBr	 **2da** (R = Me) 84%
8	**1d**	PhMgBr	**2db** (R = Ph) 59%

[a] Reaction conditions: **1** (0.1–0.2 mmol), RMgBr (5 equiv) and THF (0.2 M) at −78 °C.
[b] Isolated yield.
[c] 1.0 g (4.9 mmol) of **1a** was used.

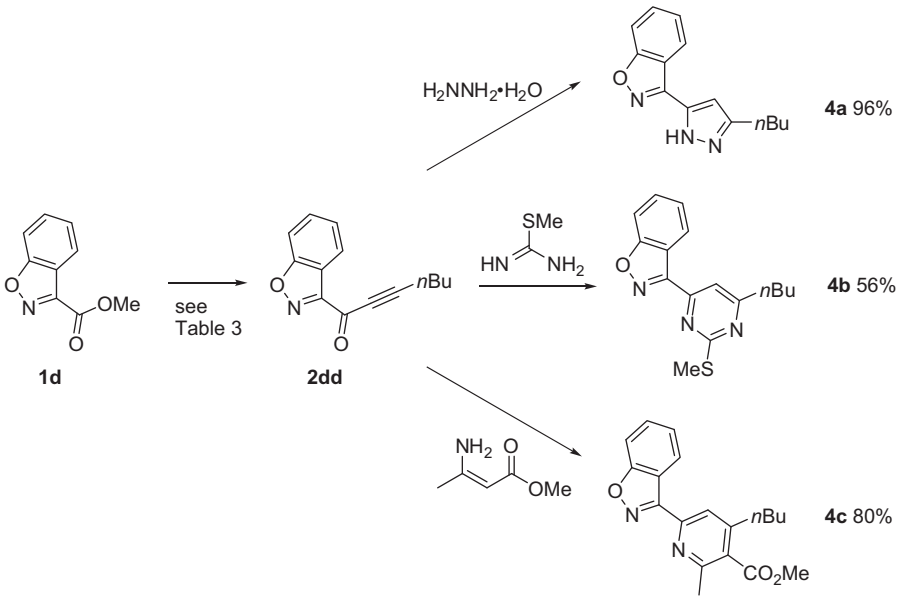
Table 3
Generality 2[a]

Entry	1	Reagent	Yield [b]
1[c]	**1a**	PhC≡CMgBr	No reaction
2	**1a**	PhC≡CLi	 **2ae** (R = Ph) 77%
3	**1a**	*n*BuC≡CLi	**2af** (R = *n*Bu) 83%
4	**1a**	TMSC≡CLi	**2ag** (R = H) 71% [d]
5	**1d**	PhC≡CLi	 **2dc** (R = Ph) 93%
6	**1d**	*n*BuC≡CLi	**2dd** (R = *n*Bu) 97%
7	**1c**	PhC≡CLi	 **2cc** (R = Ph) 82%
8	**1c**	*n*BuC≡CLi	**2cd** (R = *n*Bu) 80%

[a] Reaction conditions: **1** (0.1–0.2 mmol), RC≡CLi (3 equiv), and THF (0.2 M) at −78 °C.
[b] Isolated yield.
[c] Reaction was performed at 0 °C.
[d] Desilylated product was obtained.

kind of methyl ketones were prepared from corresponding esters in a three-step sequence involving ester hydrolysis, Weinreb amide preparation, and Grignard addition in a patent literature.[11] Finally, the reaction is readily scalable as demonstrated by the gram scale reaction of ester **1a** with MeMgBr (entry 1, in parenthesis).

The studies on introduction of alkynyl groups were also conducted (Table 3).[12] The ready preparation of alkynyl ketones is



Scheme 2. Derivation of benzisoxazole **2dd**.

valuable from the viewpoint of divergent molecule synthesis, because these functions are useful intermediates particularly for the preparation of various heterocyclic compounds.[13] The phenylethynyl magnesium bromide was first tested, but the reaction did not proceed even at room temperature due to the lack of reactivity of alkynyl Grignard reagents (entry 1). On the other hand, alkynyl lithium reagents gave good results. They were found to react with the heterocyclic esters smoothly to produce alkynyl ketone derivatives (entries 2–8). Importantly, esters of isoxazoline **1a** and benzisoxazole **1d** along with that of the isoxazole **1c** participate efficiently in this process.

The synthetic utility of this transformation and the versatility of the alkynyl ketone moiety were demonstrated by the several transformations of alkynyl ketone **2dd** (Scheme 2). Thus, the reaction of **2dd** with hydrazine gave pyrazole derivative **4a** in good yield.[13a] Pyrimidine **4b** can also be prepared by the reaction of **2dd** with *S*-methyl isothiourea.[13a] Furthermore, the reaction of **2dd** with methyl 3-aminocrotonate leads to the formation of pyridine **4c** in a moderately high yield.[13b] As described above, the two step process, including the introduction of alkynyl group and the derivatization, is very efficient for diverse bis-heterocyclic compounds from readily available heterocyclic esters.[14]

In conclusion, we have developed a facile method for the preparation of 3-acyl-substituted isoxazolines, benzisoxazoles, and isoxazoles starting with 3-carboxylate ester derivatives of the heterocyclic substrates. It can provide a novel efficient strategy for linked bis-heterocyclic compounds. We believe the present transformation is valuable for chemist dealing with heterocyclic compounds because of simplicity and practicality. Further studies on the reactivity of a broad range of heterocycles containing α-imino ester functionality, are now in progress.

Acknowledgments

This work was financially supported by Grant-in-Aid for Scientific Research (B) and for Young Scientists (B) from the JSPS.

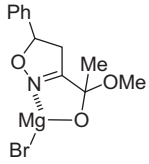
Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.006.

References and notes

1. For examples, see: (a) Gaonkar, S. L.; Lokanatha Rai, K. M.; Prabhuswamy, B. *Med. Chem. Res.* **2007**, *15*, 407–417; (b) Barbachyn, M. R.; Cleek, G. J.; Dolak, L. A.; Garmon, S. A.; Morris, J.; Seest, E. P.; Thomas, R. C.; Toops, D. S.; Watt, W.; Wishka, D. G.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Adams, W. J.; Friis, J. M.; Slatter, J. G.; Sams, J. P.; Oien, N. L.; Zaya, M. J.; Wienkers, L. C.; Wynalda, M. A. *J. Med. Chem.* **2002**, *46*, 284–302; (c) Quan, M. L.; Ellis, C. D.; He, M. Y.; Liauw, A. Y.; Lam, P. Y. S.; Rossi, K. A.; Knabb, R. M.; Luettgen, J. M.; Wright, M. R.; Wong, P. C.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1023–1028; (d) Taldone, T.; Sun, W.; Chiosis, G. *Bioorg. Med. Chem.* **2009**, *17*, 2225–2235; (e) Simoni, D.; Rondanin, R.; Baruchello, R.; Rizzi, M.; Grisolia, G.; Eleopra, M.; Grimaudo, S.; Cristina, A. D.; Pipitone, M. R.; Bongiorno, M. R.; Arico, M.; Invidiata, F. P.; Tolomeo, M. *J. Med. Chem.* **2008**, *51*, 4796–4803; (f) Meyers, M. J.; Arhancet, G. B.; Hockerman, S. L.; Chen, X.; Long, S. A.; Mahoney, M. W.; Rico, J. R.; Garland, D. J.; Blinn, J. R.; Collins, J. T.; Yang, S.; Huang, H.-C.; McGee, K. F.; Wendling, J. M.; Dietz, J. D.; Payne, M. A.; Homer, B. L.; Heron, M. I.; Reitz, D. B.; Hu, X. *J. Med. Chem.* **2010**, *53*, 5979–6002.
2. Additives for the direct transformations, see: (a) Huet, F.; Pellet, M.; Conia, J. M. *Tetrahedron Lett.* **1976**, *17*, 3579–3582; (b) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877–890; (c) Yamaguchi, M.; Shibato, K.; Fujiwara, S.; Hirao, I. *Synthesis* **1986**, 421–422; (d) Yim, S. J.; Kwon, C. H.; An, D. K. *Tetrahedron Lett.* **2007**, *48*, 5393–5395; (e) Yim, S. J.; Kim, M. H.; An, D. K. *Bull. Korean Chem. Soc.* **2010**, *31*, 286–290.
3. For examples, see: (a) Pégorier, L.; Petit, Y.; Mambu, A.; Larchevêque, M. *Synthesis* **1994**, 1403–1405; (b) Murata, K.; Kitazume, T. *Tetrahedron: Asymmetry* **1993**, *4*, 889–892; (c) Humptman, H.; Mader, M. *Synthesis* **1978**, 307–309; (d) Notz, W.; Hartel, C.; Waldscheck, B.; Schmidt, R. R. *J. Org. Chem.* **2001**, *66*, 4250–4260; (e) Roznyatovskiy, V.; Lynch, V.; Sessler, J. L. *Org. Lett.* **2010**, *12*, 4424–4427; (f) Evans, D. A.; Kvaerno, L.; Dunn, T. B.; Beauchemin, A.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309; (g) MaGee, D. I.; Mallais, T. C.; Eic, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3177–3181; (h) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, 564–566; (i) Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Synth. Commun.* **1981**, *11*, 943–946; (j) Béguin, C.; Andurkar, S. V.; Jin, A. Y.; Stables, J. P.; Weaver, D. F.; Kohn, H. *Bioorg. Med. Chem.* **2003**, *11*, 4275–4285.
4. Synthesis of ketones from Weinreb amides, see: (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818; (b) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967–993; (c) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340–347.
5. For examples, see: (a) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2187–2197; (b) Kang, S. H.; Jung, S.-H. *Chem. Commun.* **1998**, 1929–1930; (c) Bourland, T. C.; Carter, R. G.; Yokochi, A. F. T. *Org. Biomol. Chem.* **2004**, *2*, 1315–1329; (d) Blarer, S. *J. Tetrahedron Lett.* **1985**, *26*, 4055–4058; (e) Hasegawa, H.; Yamamoto, T.; Hatano, S.; Hagoki, T.; Katsumura, S. *Chem. Lett.* **2004**, *33*, 1592–1593; (f) Abbot, S. C.; Billedeau, R. J.; Dewdney, N. J.; Gabriel, T.; Goldstein, D. M.; McCaleb, K. L.; Soth, M.; Trejo-Martin, T. A.; Zecic, H. *Heterocycles* **2009**, *78*, 2811–2826.
6. Murai, K.; Takahara, Y.; Matsushita, T.; Komatsu, H.; Fujioka, H. *Org. Lett.* **2010**, *12*, 3456–3459.
7. For the numbering of compounds **2** and **3**, the first alphabet shows the kind of heterocycles and the second alphabet is numbered to each heterocycles in order.

8. The reaction of ketone **2aa** and MeMgBr at −78 °C produced alcohol **3aa**. Then, in situ generation of unreactive 5-membered chelation intermediates, such as A, is plausible in these transformations.



A

9. For examples of the reports on synthesis of 3-methyl keto and aryl keto isoxazolines and benzisoxazolines, see: (a) Jen, T.; Mendelsohn, B. A.; Ciufolini, M. A. *J. Org. Chem.* **2011**, *76*, 728–731; (b) Cecchi, L.; De, S. F.; Machetti, F. *Chem. Eur. J.* **2008**, *14*, 7903–7912; (c) Itoh, K.; Sakamaki, H.; Nakazato, N.; Horiuchi, A.; Horn, E.; Horiuchi, A. *Synthesis* **2005**, 3541–3548; (d) Kai, H.; Tomida, M.; Nakai, T.; Takase, A. *Heterocycles* **2002**, *57*, 2299–2308; (e) Arai, N.; Iwakoshi, M.; Tanabe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2277–2285; (f) Wade, P. A.; Amin, N. V.; Yen, H. K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595–4601; (g) Yamamori, T.; Hiramatsu, Y.; Adachi, I. *J. Heterocycl. Chem.* **1981**, *18*, 347–350.

10. The synthesis of 3-alkynyl keto isoxazolines and benzisoxazolines was previously unknown.

11. Cohen, F.; Tsui, V. H.-W.; Ly, C.; Flygare, J. A. (Genentech, Inc.) WO2006069063A1, 2006.

12. Among heterocyclic compounds, only 4-methoxycarbonyloxazolidinone is employed to introduction of alkynyl groups, see: (a) Hakogi, T.; Shigenari, T.; Katsumura, S.; Sano, T.; Kohno, T.; Igarashi, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 661–664; (b) Asana, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun.* **1999**, 41–42. Ref. 5e.

13. For examples, see: (a) Adamo, M. F. A.; Adlington, R. M.; Baldwin, J. E.; Prichard, G. J.; Rathmell, R. E. *Tetrahedron* **2003**, *59*, 2197–2205; (b) Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149–1151; (c) Linderman, R. J.; Kirollos, K. S. *Tetrahedron Lett.* **1989**, *30*, 2049–2052; (d) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis.* **2004**, 2015–2025.

14. For examples of synthesis and biological activity of benzisoxazoline containing bis-heterocyclic compounds, see: (a) Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis, L.; Effland, R. C.; Ranbom, K. J. *Med. Chem.* **1982**, *25*, 36–44; (b) Sabat, M.; VanRens, J. C.; Laufersweiler, M. J.; Brugel, T. A.; Maier, J.; Golebiowski, A.; De, B.; Easwaran, V.; Hsieh, L. C.; Walter, R. L.; Mekel, M. J.; Evdokimov, A.; Janusz, M. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5973–5977.