Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c9ob02450f

Received 13th November 2019,
Accepted 17th December 2019

DOI: 10.1039/c9ob02450f

rsc.li/obc

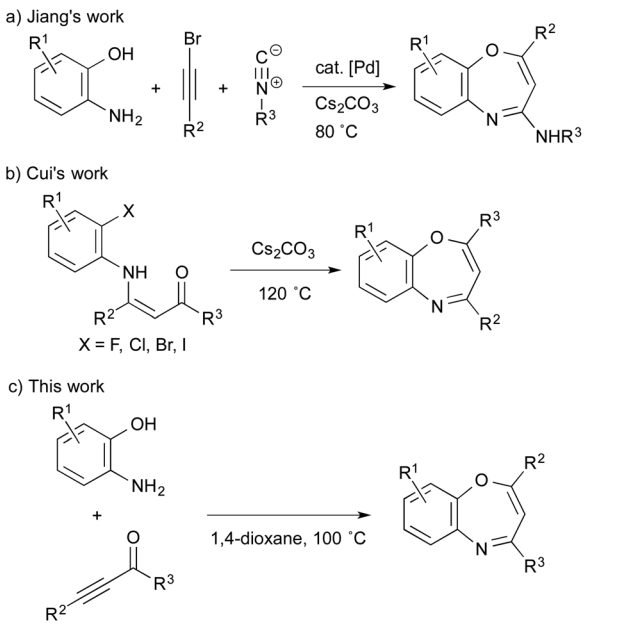
Synthesis of substituted benzo[*b*][1,4]oxazepine derivatives by the reaction of 2-aminophenols with alkynones†

Kohei Oshimoto, Biao Zhou, Hiroaki Tsuji * and Motoi Kawatsura *

We have developed a novel synthetic method accessing benzo[*b*][1,4]oxazepines that are one of the rare classes of benzoxazepine derivatives by reaction of 2-aminophenols with alkynones in 1,4-dioxane at 100 °C. A series of benzo[*b*][1,4]oxazepine derivatives can be prepared by using this synthetic protocol. Mechanistic experiments indicated that the hydroxy proton of the aminophenol could play a crucial role in the formation of an alkynylketimine intermediate that undergoes 7-*endo*-*dig* cyclization.

Benzoxazepine derivatives are one of the important seven-membered heterocycles that are known to exhibit potent pharmacological activities.[1,2] Due to their attractive features, the synthetic study of the privileged heterocyclic compounds has received a great deal of attention from the synthetic community and thus the syntheses of a wide variety of benzoxazepine derivatives, such as dibenzoxazepinones,[3] dibenzoxazepines,[4] and benzoxazepinones,[5] have been achieved in the past few decades.[6] However, there are few examples for the synthesis of the most simple benzoxazepines that consist of benzene and oxazepine rings, because the conventional synthetic methods usually rely on the aromatic nucleophilic substitution, transition metal-catalyzed coupling reaction of aromatic halides, and condensation of carboxylic acid derivatives. Given the fact that benzoxazepine analogues would exhibit potentially high biological activities, developing synthetic tools to produce such a rare class of benzoxazepines remains highly desirable. As an example for the preparation of benzoxazepines, Jiang and co-workers reported the synthesis of benzo[*b*][1,4]oxazepine derivatives, in which the three-component coupling reaction of 2-aminophenols, bromoalkynes, and isocyanides proceeded in the presence of a palladium catalyst to give the corresponding 4-amine-benzo[*b*][1,4]oxazepines in high yields (Scheme 1a).[7] Later, Cui and co-workers reported the efficient synthesis of substituted benzo[*b*][1,4]oxazepines from enaminones in the presence of Cs_2CO_3 as the promoter (Scheme 1b).[8] However, these methods require the use of a precious metal catalyst and a stoichiometric amount of base.

On the other hand, we have recently reported the synthesis of benzoxazoles *via* the copper-catalyzed hydroamination of alkynones with 2-aminophenols.[9] During the optimization of the reaction conditions of the copper catalysis, we found that the reaction of 2-aminophenols with 1.2 equivalents of alkynones in *o*-xylene at 100 °C gave benzo[*b*][1,4]oxazepines in good yields. We now report a novel synthetic method that allows easy and efficient access to benzo[*b*][1,4]oxazepines by



Scheme 1 Synthesis of substituted benzo[*b*][1,4]oxazepines. (a) Jiang's work. (b) Cui's work. (c) This work.

Department of Chemistry, College of Humanities & Sciences, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550, Japan. E-mail: tsuji@chs.nihon-u.ac.jp, kawatsur@chs.nihon-u.ac.jp

†Electronic supplementary information (ESI) available. CCDC 1958661. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob02450f

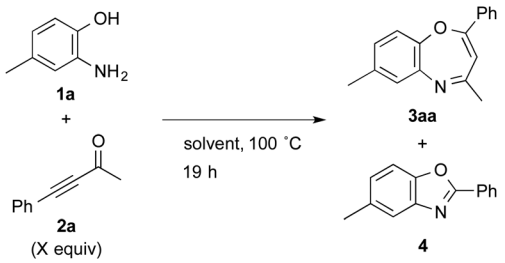
the reaction of 2-aminophenols with alkynones (Scheme 1c). In this method, the reaction can proceed without the use of additional reagents, such as a transition metal catalyst and a base, thus providing an efficient protocol for the synthesis of benzo[*b*][1,4]oxazepines that are one of the rare classes of benzoxazepine derivatives.

At the outset of our study, we examined the optimization of the reaction conditions (Table 1). We carried out the reaction of 4-methyl-2-aminophenol (**1a**) with 1.2 equivalents of alkynone **2a** in *o*-xylene at 100 °C (entry 1). We confirmed that benzo[*b*][1,4]oxazepine **3aa** was formed in 23% yield as a side product along with the formation of benzoxazole **4** in 48% yield. We speculate that the benzoxazole **4** would be obtained by the conjugate addition of **1a** to **2a**[10] and subsequent intramolecular cyclization/elimination of an acetone sequence. Motivated by this finding, we sought to develop a novel method for the synthesis of benzo[*b*][1,4]oxazepines. We initially tested various solvents (entries 2–8). As a result, the ether type solvents, such as 1,4-dioxane, CPME, and diglyme, were found to be effective for the reaction. In particular, the use of 1,4-dioxane as the solvent afforded the desired product **3aa** in 63% yield as the main product (entry 3). With the suitable solvent in hand, we next evaluated the effect of the loading amount of alkynone **2a** (entries 9–12). To our delight, the reaction of aminophenol **1a** with 1.5 equivalents of alkynone **2a** was performed in 1,4-dioxane at 100 °C to give the desired benzo[*b*][1,4]oxazepine **3aa** in 70% yield (entry 9). When 2.0 equivalents of **2a** were employed in this reaction system, the yield of **3aa** was further improved to 76% (entry 10). On the other hand, the use of 2.2 and 2.5 equivalents of **2a** led to a decrease in the yield of **3aa** (entries 11 and 12).

With the optimized reaction conditions in hand, we examined the reaction of several 2-aminophenols **1** with alkynone **2a** under the optimized reaction conditions (Scheme 2).[11] The reaction of 4-methyl-2-aminophenol (**1a**) with alkynone **2a** can be scaled up to 3 mmol scale without any loss of the reaction efficiency, providing the desired product **3aa** in 79% yield. The reaction of 2-aminophenol (**1b**) and 5-methyl-2-aminophenol (**1c**) with alkynone **2a** smoothly proceeded to give the desired benzo[*b*][1,4]oxazepines **3ba** and **3ca** in 77% and 81% yield, respectively. 2-Aminophenols **1d** and **1e** bearing methoxy and trifluoromethyl groups on their aromatic rings underwent the reaction to afford the desired products **3da** and **3ea** in moderate yields. A 5-fluoro substituent on the aromatic ring was tolerated during this transformation, giving the benzo[*b*][1,4]oxazepine **3fa** in 60% yield. On the other hand, the reaction of 2-aminophenols **1g** and **1h** bearing 5-chloro and 5-bromo substituents led to low yields of **3ga** and **3ha**. Benzo[*b*][1,4]oxazepine **3ia** having a phenyl group at the 4 position on the aromatic ring was obtained in 51% yield.

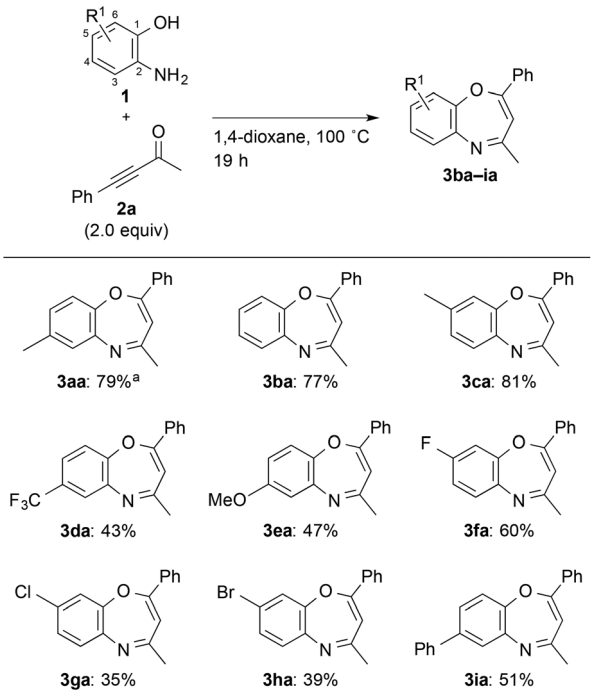
We next investigated the reaction of 2-aminophenol (**1b**) with a wide variety of alkynones **2** (Scheme 3).[11] The reaction of **1b** with alkynones bearing methyl (**2b**) and methoxy (**2c**) substituents at the *para* position on their phenyl rings took place to give benzo[*b*][1,4]oxazepines **3bb** and **3bc** in 73% and 69% yield, respectively. The structure of **3bc** was determined by X-ray crystallographic analysis as shown in Scheme 4.

Table 1 Optimization of the reaction conditions[a]

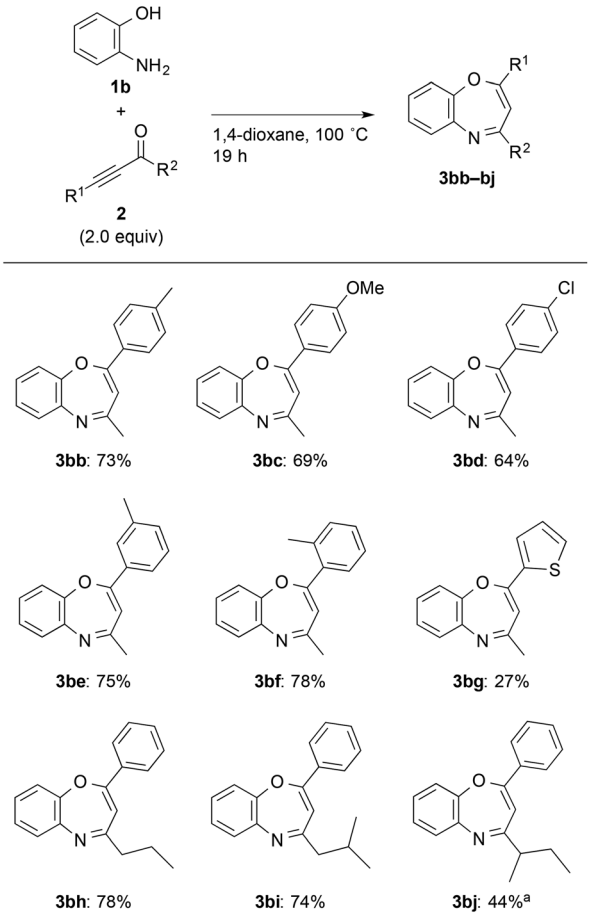


Entry	X	Solvent	Yield of **3aa**[b] (%)	Yield of **4**[b] (%)
1	1.2	*o*-Xylene	23	48
2	1.2	Toluene	21	38
3	1.2	1,4-Dioxane	63	11
4	1.2	CPME	53	24
5	1.2	Diglyme	55	15
6	1.2	DMSO	4	2
7	1.2	DMF	41	12
8	1.2	*t*AmOH	16	25
9	1.5	1,4-Dioxane	70	10
10	2.0	1,4-Dioxane	76 (77)[c]	7
11	2.2	1,4-Dioxane	74	7
12	2.5	1,4-Dioxane	69	5

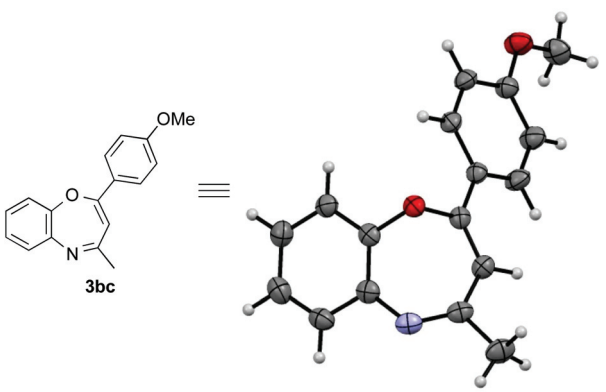
[a] Reaction conditions: **1a** (0.30 mmol) and **2a** (1.2–2.5 equiv.) in solvent (0.6 mL) at 100 °C for 19 h. [b] The yields were determined by ^{1}H NMR analyses of the crude reaction mixture using dibromomethane as an internal standard. [c] Isolated yield.



Scheme 2 Scope of 2-aminophenols **1**. Reaction conditions: **1** (0.30 mmol) and **2a** (0.60 mmol) in 1,4-dioxane (0.6 mL) at 100 °C for 19 h. [a] 3 mmol scale.



Scheme 3 Scope of alkynones **2**. Reaction conditions: **1b** (0.30 mmol) and **2** (0.60 mmol) in 1,4-dioxane at 100 °C for 19 h. [a] With a trace amount of inseparable impurities.

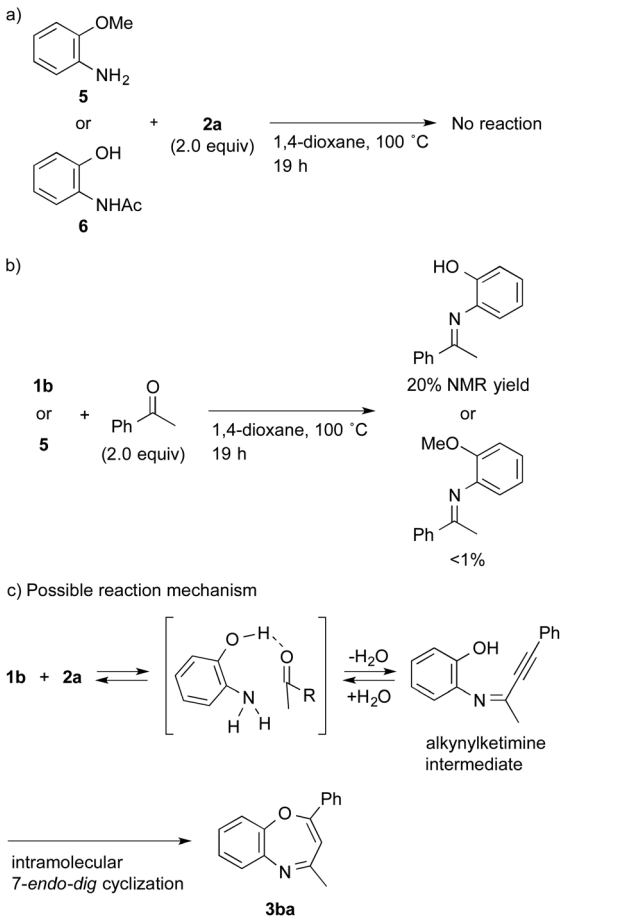


Scheme 4 X-ray crystal structure of **3bc**.

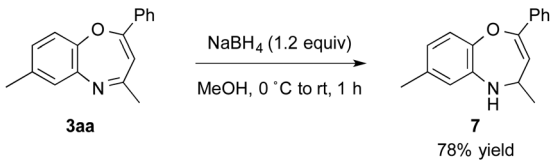
Alkynone **2d** having a chloro atom underwent the reaction to give the desired product **3bd** in 64% yield.

meta-Tolyl- and *ortho*-tolyl-substituted benzo[*b*][1,4]oxazepines **3be** and **3bf** were obtained in good yields. The use of alkynone **2g** bearing a thiophene ring led to a low yield of the desired benzo[*b*][1,4]oxazepine **3bg**. The propyl (**3bh**) and isobutyl (**3bi**) substituents can be introduced to the oxazepine skeleton instead of the methyl group in good yields. The reaction of **1b** with alkynone **2j** bearing a sterically bulky ketone consisting of a secondary butyl group also proceeded to give the desired product **3bj** in 44% yield, albeit with a mixture of a trace amount of an inseparable impurity. Unfortunately, the reaction with alkynones bearing an electron-poor aromatic ring (R^1 = 4-$CF_3C_6H_4$, R^2 = Me), aliphatic alkyne groups (R^1 = phenethyl or hexyl, R^2 = Me), and an aromatic ketone group (R^1 = Ph, R^2 = Ph) did not work well under the reaction conditions.

We next demonstrated the mechanistic consideration of the transformation (Scheme 5). We initially examined the mechanistic experiments as shown in Schemes 5a and b. We confirmed that the reaction of *o*-anisidine **5** or *o*-hydroxyacetanilide **6** with 2.0 equivalents of alkynone **2a** under the reaction conditions did not proceed at all (Scheme 5a). Furthermore, while the reaction of aminophenol **1b** with 2.0 equivalents of acetophenone under the reaction conditions afforded the corresponding ketimine in a 20% NMR yield, no ketimine product was observed in the reaction with *o*-anisidine **5** (Scheme 5b). These results indicated that the presence of a phenolic proton might be necessary for the formation of an



Scheme 5 Mechanistic consideration.



Scheme 6 Transformation of benzo[*b*][1,4]oxazepine **3aa**.

alkynylketimine intermediate. Based on these results, we proposed the possible reaction mechanism as shown in Scheme 5c. Initially, the reaction of aminophenol **1b** with alkynone **2a** would occur to produce an alkynylketimine intermediate. We surmised that this process would be accelerated by the hydrogen bonding interaction between the carbonyl group of alkynone **2a** and the phenolic proton of aminophenol **1b**.[12] The alkynylketimine intermediate would undergo intramolecular 7-*endo-dig* cyclization to give the desired benzoxazepine **3ba**.[13]

Next, we attempted to examine the transformation of benzo[*b*][1,4]oxazepine **3aa** (Scheme 6). Benzo[*b*][1,4]oxazepine **3aa** was converted into 4,5-dihydrobenzo[*b*][1,4]oxazepine derivative **7** in 78% yield by reduction with $NaBH_4$ in MeOH.

Conclusions

In conclusion, we have achieved the efficient synthesis of benzo[*b*][1,4]oxazepines that belong to one of the rare classes of benzoxazepine derivatives by the reaction of 2-aminophenols with alkynones. A series of benzo[*b*][1,4]oxazepines were obtained in good yields using the novel synthetic method. Mechanistic experiments indicated that the phenolic proton on the aminophenols might be involved in the formation of the alkynylketimine intermediate that would undergo intramolecular 7-*endo-dig* cyclization to produce benzo[*b*][1,4]oxazepines. The extension of the substrate scope and the detailed mechanistic study are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (17K05794). We thank Mr Yoshiyuki Takahashi for his experimental support.

References

1 For a review, see: J. N. Sangshetti, A. Altamash Shakeel Ahmad, F. A. Kalam Khan and Z. Zaheer, *Mini-Rev. Org. Chem.*, 2015, **12**, 345–354.

2 For examples of pharmacologically active benzoxazepine derivatives, see: (*a*) Y. Nagai, A. Irie, H. Nakamura, K. Hino, H. Uno and H. Nishimura, *J. Med. Chem.*, 1982, **25**, 1065–1070; (*b*) J. M. Klunder, K. D. Hargrave, M. West, E. Cullen, K. Pal, M. L. Behnke, S. R. Kapadia, D. W. McNeil, J. C. Wu, G. C. Chow and J. Adams, *J. Med. Chem.*, 1992, **35**, 1887–1897; (*c*) Y. Liao, B. J. Venhuis, N. Rodenhuis, W. Timmerman and H. Wikström, *J. Med. Chem.*, 1999, **42**, 2235–2244; (*d*) T. Miki, M. Kori, H. Mabuchi, R. Tozawa, T. Nishimoto, Y. Sugiyama, K. Teshima and H. Yukimasa, *J. Med. Chem.*, 2002, **45**, 4571–4580; (*e*) R. A. Smits, H. D. Lim, B. Stegink, R. A. Bakker, I. J. P. de Esch and R. Leurs, *J. Med. Chem.*, 2006, **49**, 4512–4516.

3 For examples see: (*a*) S.-M. Lu and H. Alper, *J. Am. Chem. Soc.*, 2005, **127**, 14776–14784; (*b*) R. A. Bunce and J. E. Schammerhorn, *J. Heterocycl. Chem.*, 2006, **43**, 1031–1035; (*c*) Q. Yang, H. Cao, A. Robertson and H. Alper, *J. Org. Chem.*, 2010, **75**, 6297–6299; (*d*) Y. Liu, C. Chu, A. Huang, C. Zhan, Y. Ma and C. Ma, *ACS Comb. Sci.*, 2011, **13**, 547–553; (*e*) M. O. Kitching, T. E. Hurst and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 2925–2929; (*f*) N. C. Ganguly, P. Mondal, S. Roy and P. Mitra, *RSC Adv.*, 2014, **4**, 55640–55648; (*g*) C. Shen, H. Neumann and X.-F. Wu, *Green Chem.*, 2015, **17**, 2994–2999; (*h*) S. Liu, Y. Hu, P. Qian, Y. Hu, G. Ao, S. Chen, S. Zhang and Y. Zhang, *Tetrahedron Lett.*, 2015, **56**, 2211–2213; (*i*) T. E. Hurst, M. O. Kitching, L. C. R. M. da Frota, K. G. Guimarães, M. E. Dalziel and V. Snieckus, *Synlett*, 2015, **26**, 1455–1460; (*j*) C. Shen and X.-F. Wu, *Catal. Sci. Technol.*, 2015, **5**, 4433–4443; (*k*) X. Guo, D. Zhang-Negrerie and Y. Du, *RSC Adv.*, 2015, **5**, 94732–94736; (*l*) E. Zhang, X. Zhang, W. Wei, D. Wang, Y. Cai, T. Xu, M. Yan and Y. Zou, *RSC Adv.*, 2015, **5**, 5288–5294; (*m*) Y. Zhou, J. Zhu, B. Li, Y. Zhang, J. Feng, A. Hall, J. Shi and W. Zhu, *Org. Lett.*, 2016, **18**, 380–383; (*n*) J. Shi, J. Wu, C. Cui and W.-M. Dai, *J. Org. Chem.*, 2016, **81**, 10392–10403 and also see ref. 2*a* and *b*.

4 (*a*) A. V. Konstantinova, T. N. Gerasimova, M. M. Kozlova and N. I. Petrenko, *Chem. Heterocycl. Compd.*, 1989, **25**, 451–454; (*b*) D. Tsvelikhovsky and S. L. Buchwald, *J. Am. Chem. Soc.*, 2011, **133**, 14228–14231; (*c*) J.-B. Feng and X.-F. Wu, *Green Chem.*, 2015, **17**, 4522–4526; (*d*) F. Hu, H. Liu, J. Jia and C. Ma, *Org. Biomol. Chem.*, 2016, **14**, 11076–11079; (*e*) V. Jamsheena, C. K. Mahesha, M. N. Joy and R. S. Lankalapalli, *Org. Lett.*, 2017, **19**, 6614–6617; (*f*) X.-Y. Chen, Z.-H. Li, J.-Q. Liu and X.-S. Wang, *Synthesis*, 2019, **51**, 1662–1668; (*g*) W. Hu, F. Teng, H. Hu, S. Luo and Q. Zhu, *J. Org. Chem.*, 2019, **84**, 6524–6535, and also see ref. 2*c* and *e*.

5 (*a*) A. D. Cale, Jr., T. W. Gero, K. R. Walker, Y. S. Lo, W. J. Welstead, Jr., L. W. Jaques, A. F. Johnson, C. A. Leonard, J. C. Nolan and D. N. Johnson, *J. Med. Chem.*, 1989, **32**, 2178–2199; (*b*) K. Kamei, N. Maeda, R. Ogino, M. Koyama, M. Nakajima, T. Tatsuoka, T. Ohno and T. Inoue, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 595–598; (*c*) K. Kamei, N. Maeda, K. Nomura, M. Shibata, R. Katsuragi-Ogino, M. Koyama, M. Nakajima, T. Inoue,

T. Ohno and T. Tatsuoka, *Bioorg. Med. Chem.*, 2006, **14**, 1978–1992; (*d*) L. Banfi, A. B. G. Guanti, P. Lecinska and R. Riva, *Org. Biomol. Chem.*, 2006, **4**, 4236–4240; (*e*) G. Chouhan and H. Alper, *Org. Lett.*, 2010, **12**, 192–195; (*f*) Y. Liu, Y. Ma, C. Zhan, A. Huang and C. Ma, *Synlett*, 2012, **23**, 255–258; (*g*) S. Pandey, S. V. Kumar, R. Kant and P. M. S. Chauhan, *Org. Biomol. Chem.*, 2014, **12**, 5346–5350; (*h*) K. Singh, B. K. Malviya, T. K. Roy, V. S. Mithu, V. K. Bhardwaj, V. P. Verma, S. S. Chimni and S. Sharma, *J. Org. Chem.*, 2018, **83**, 57–68 and also see ref. 2*d*.

6 For other related examples, see: (*a*) F. Ji, M.-F. Lv, W.-B. Yi and C. Cai, *Adv. Synth. Catal.*, 2013, **355**, 3401–3406; (*b*) C. K. Shahi, A. Bhattacharyya, Y. Nanaji and M. K. Ghorai, *J. Org. Chem.*, 2017, **82**, 37–47; (*c*) V. Srinivasulu, I. Shehadeh, M. A. Khanfar, O. G. Malik, H. Tarazi, I. A. Abu-Yousef, A. Sebastian, N. Baniowda, M. J. O'Connor and T. H. Al-Tel, *J. Org. Chem.*, 2019, **84**, 934–948.

7 B. Liu, Y. Li, M. Yin, W. Wu and H. Jiang, *Chem. Commun.*, 2012, **48**, 11446–11448.

8 J. Shen, L. Xue, X. Lin, G. Cheng and X. Cui, *Chem. Commun.*, 2016, **52**, 3292–3295.

9 K. Oshimoto, H. Tsuji and M. Kawatsura, *Org. Biomol. Chem.*, 2019, **17**, 4225–4229.

10 (*a*) V. K. Tripathi, P. S. Venkataramani and G. Mehta, *J. Chem. Soc., Perkin Trans. 1*, 1979, 36–41; (*b*) T. Sakamoto, T. Nagano, Y. Kondo and H. Yamanaka, *Synthesis*, 1990, 215–218; (*c*) S. M. Bromidge, D. A. Entwistle, J. Goldstein and B. S. Orlek, *Synth. Commun.*, 1993, **23**, 487–494; (*d*) W. Liu, C. Chen and Q. Zhang, *Org. Biomol. Chem.*, 2011, **9**, 6484–6486; (*e*) S. Roy, M. P. Davydova, R. Pal, K. Gilmore, G. A. Tolstikov, S. F. Vasilevsky and I. V. Alabugin, *J. Org. Chem.*, 2011, **76**, 7482–7490; (*f*) J. Shao, X. Huang, X. Hong, B. Liu and B. Xu, *Synthesis*, 2012, **44**, 1798–1805; (*g*) G. Cheng, X. Zeng, J. Shen, X. Wang and X. Cui, *Angew. Chem., Int. Ed.*, 2013, **52**, 13265–13268.

11 We confirmed the formation of small amounts of the corresponding benzoxazoles in the reaction of 2-aminophenols **1** and alkynones **2**.

12 Examples of the reaction involving the intermolecular phenolic hydrogen bonding interaction with the carbonyl group, see: (*a*) Y. M. A. Yamada and S. Ikegami, *Tetrahedron Lett.*, 2000, **41**, 2165–2169; (*b*) D. C. Braddock, I. D. MacGilp and B. G. Perry, *Synlett*, 2003, 1121–1124; (*c*) N. T. McDougal and S. E. Schaus, *J. Am. Chem. Soc.*, 2003, **125**, 12094–12095; (*d*) Y. E. Türkmen and V. H. Rawal, *J. Org. Chem.*, 2013, **78**, 8340–8353.

13 Related 7-*endo-dig* cyclization of alkynone derivatives, see: (*a*) Y. Chen, X. Liu, M. Lee, C. Huang, I. Inoyatov, Z. Chen, A. C. Perl and W. H. Hersh, *Chem. – Eur. J.*, 2013, **19**, 9795–9799; (*b*) Y. Chen, C. Huang, X. Liu, E. Perl, Z. Chen, J. Namgung, G. Subramaniam, G. Zhang and W. H. Hersh, *J. Org. Chem.*, 2014, **79**, 3452–3464 and also see ref. 5*h*.