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Elemental Sulfur-Promoted Oxidative Rearranging Coupling between o-Aminophenols and Ketones: A Synthesis of 2-Alkyl benzoxazoles under Mild Conditions

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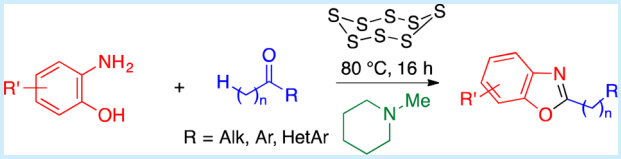
Supporting Information

ABSTRACT: In the presence of *N*-methylpiperidine, elemental sulfur was found to act as excellent oxidant in promoting oxidative rearranging coupling between *o*-aminophenols and ketones. A wide range of 2-alkylbenzoxazoles was obtained under mild conditions.

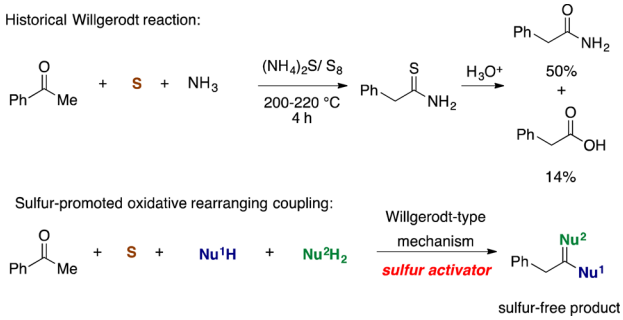


Benzoxazoles represent an important class of aza-heterocycles and have been widely used as synthetic building blocks, bioactive molecules, pharmaceuticals,[1] and functional materials.[2] There are many methods available for the synthesis of 2-substituted benzoxazoles. Traditional methods such as condensation of carboxylic acids or derivatives with *o*-aminophenols require high reaction temperatures in the presence of strong acids.[3] This approach thus suffers from side reactions on both starting materials as well as the resulting benzoxazoles. An alternative to this strategy is based on dehydrogenative or oxidative coupling reactions of *o*-aminophenol with aldehydes, alcohols, or amines.[4]

The most recent method consists of a transition metal-catalyzed C−H functionalization of 2-unsubsubstituted benzoxazoles.[5] Similar to this approach is the sequence of deprotonation by strong lithium bases/electrophilic trapping that requires cooling conditions with strong electrophiles and is, in general, incompatible with unprotected acidic or electrophilic functional groups.[6] The development of simple conditions using inexpensive reagents/starting materials provides new opportunities in the synthesis of such an important heterocyclic family.[7] In the course of our study, we identify elemental sulfur as an excellent and versatile tool for organic synthesis.[8] Herein, we show that the combination of this element with an organic base leads to the efficient oxidative coupling between *o*-aminophenols and ketones to provide 2-alkylated benzoxazoles under simple and mild conditions that tolerate a wide range of functional groups in both coupling partners.

Although relatively inactive under ambient conditions in the absence of activator, under thermal activation or in the presence of Lewis bases such as amines, ammonia, or phosphines, sulfur has been well-known to act as nucleo-electrophilic sulfuration reagent via ring opening of cyclo-octasulfur to afford nucleophilic and electrophilic species. A well-known example is the Willgerodt rearrangement[9] in which phenylthioacetamide is obtained when acetophenone is heated with a solution of elemental sulfur in aqueous ammonium sulfide (Scheme 1).

Scheme 1. Willgerodt Reaction as a New Way of C−H Functionalization



Further development of this reaction included using other nitrogen bases such as morpholine/piperidine than ammonia and allowed the reaction to occur at lower temperatures and broader scopes.[10] In this kind of reaction, if other nucleophiles are present in the reaction media, the primary thioamides will transform further into sulfur-free product via transthioamidation. The latter process requires, however, high activating energy, which results in high reaction temperatures.[11] In the case where two-fold nucleophilic attack occurs, sulfur-free product will be obtained, and the global reaction constitutes a new strategy of C−H functionalization with concomitant reorganization of oxidation degrees of the carbon chain.

Here we report our preliminary example of exploring of this strategy. A two-fold nucleophilic attack is best realized with bis-nucleophile to lower the required energy of the desulfuration step. The oxidative rearranging coupling of acetophenone **2a** with *o*-aminophenol **1a** as bis-nucleophile was chosen as a

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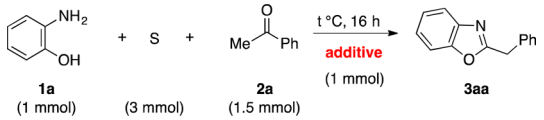
model reaction at 80 °C (Table 1). In the absence of an activator (Table 1, entry 1) or when toluene (Table 1, entry 2),

Table 1. Optimization of Reaction Conditions



1a (1 mmol) (3 mmol) **2a** (1.5 mmol) **3aa**

entry[a]	additive	t (°C)	yield (%)
1		80	0[b]
2	toluene	80	5[b]
3	pyridine	80	15[b]
4	*N*,*N*-dimethylformamide	80	20[b]
5	dimethyl sulfoxide	80	25[b]
6	*N*-methylmorpholine	80	68[c]
7	*N*-methylpiperidine	80	85[c]
8	*N*-methylpiperidine	60	72[c]

[a]Reaction conditions (unless otherwise noted): **1a** (1 mmol), S (1.5 mmol, 32 mg.mmol^{-1}, 96 mg), **2a** (2 mmol), additive (1 mmol), t °C, 16 h. [b]Conversion determined by ^{1}H NMR. [c]Isolated yield.

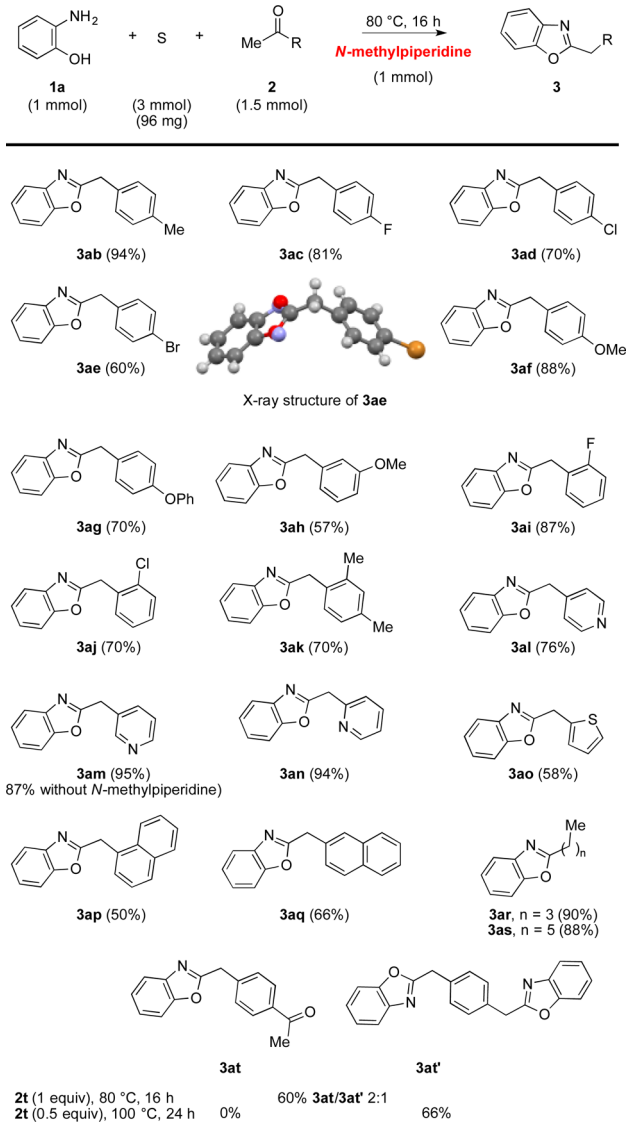
a weakly interacting compound, was used as additive, traces of the desired benzothiazole were observed. Stronger interacting additives such as pyridine, DMF, and DMSO resulted in improved conversions (Table 1, entries 3−5). In case of DMSO, parasite oxidation promoted by this additive was also observed, which led to a rather complex reaction mixture. Gratifyingly, when sulfur was activated by cyclic tertiary amines such as *N*-methylmorpholine[12] and *N*-methylpiperidine[13] (Table 1, entries 6 and 7), benzoxazole **3aa** was formed in good to excellent yields. The reaction was best performed at 80 °C (Table 1, entry 7 vs 8) in *N*-methylpiperidine as sulfur activator. It should be noted that, in contrast to classical Willgerodt-type reactions that required high temperatures,[4f,14] a temperature of 80 °C only was enough for full conversion.

The optimized reaction conditions were next applied to the coupling of *o*-aminophenol with other acetophenone (Scheme 2). The reaction conditions were found to tolerate a range of common substituents such as alkyl (**3ab**), halogens (**3ac**−**3ae**, **3ai**−**3aj**), and alkoxy (**3af**−**3ah**). The structure of brominated benzoxazole **3ae** was confirmed by X-ray diffraction. *o*-Substituted acetophenones **2i**−**k** by an methyl or a halogen groups proved to be good substrates for this reaction. Gratifyingly, the ketones containing important pharmacophores such as pyridines and thiophene as well as chromophore naphthalenes were also suitable substrates, which gave rise to the corresponding benzothiazoles products.

As pyridine as sulfur activator was found to be capable of promoting this reaction (Table 1, entry 3), we wondered if acetylpyridine **2m**−**o** could reaction in the same manner with *o*-aminophenol in the absence of *N*-methylpiperidine. While the reactions of 2- or 4-acetylpyridine **2l**, **2n** proceeded with extensive decomposition of these ketones, 3-acetylpyridine **2m** provided the desired product **3am** in high yield. One of the possible explanation for this difference was the basicity of 3-acetylpyridine **2m** being higher than that of its two regioisomers due to lack of conjugation between the nitrogen double bond and the carbonyl group in the first case.

The reactions with methyl alkyl ketones proceeded in the same manner and gave good yields of benzothiazoles 2-substituted by long alkyl chains. When diacetyl substrate such as *p*-diacetylbenzene **2t** was subjected to the reaction

Scheme 2. Reaction Scope of Different Methyl Ketones



conditions, a mono/di 2:1 mixture of benzoxazolated products was obtained if two organic starting substrates were used in equimolar amount. The dibenzoxazolated product **3at′** could be formed exclusively in good yield if the stoichiometry of both organic starting materials for its formation was respected upon heating at 100 °C for 24 h.

The oxidative rearranging coupling reactions between different *o*-aminophenols with acetophenone **2a** were possible under the optimized reaction conditions (Scheme 3). The variety of aryl substituents tolerated in these reactions, such as chloro, sulfamide, and sulfone, provides possibilities for further molecular elaboration.

Similar reaction conditions can be used for the oxidative rearranging coupling of other homologues of acetophenones (Scheme 4) (n = 1−3, R′ = Ph). Various α-phenyl-ω-benzoxazol-2-ylalkanes **3au**, **3bv**−**3bx** could be obtained in moderate to good yields, although the yields were lower for longer alkyl chains. The similar rearrangements were observed when alkyl phenyl ketones were heated with an aqueous solution of sulfur, ammonia, and ammonium sulfide from 160−190 °C.[15] Internal dialkyl ketones such as 3-pentanone or 4-

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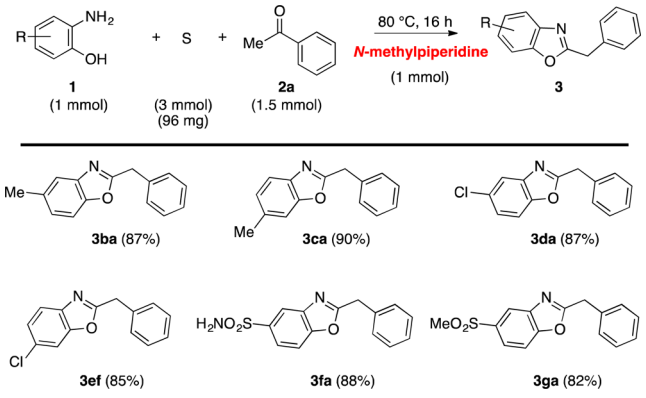
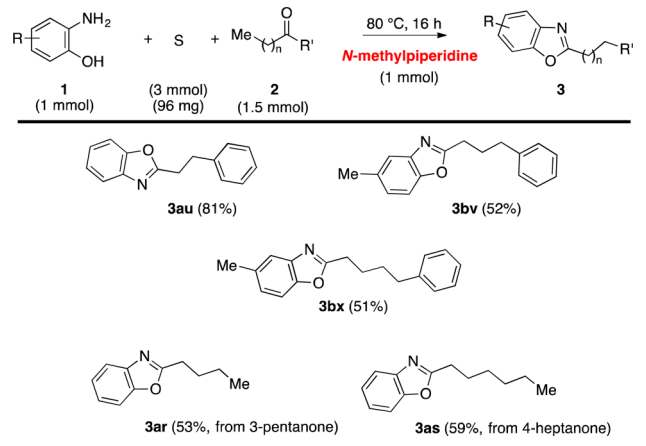
Scheme 3. Reaction Scope of Different *o*-Aminophenol



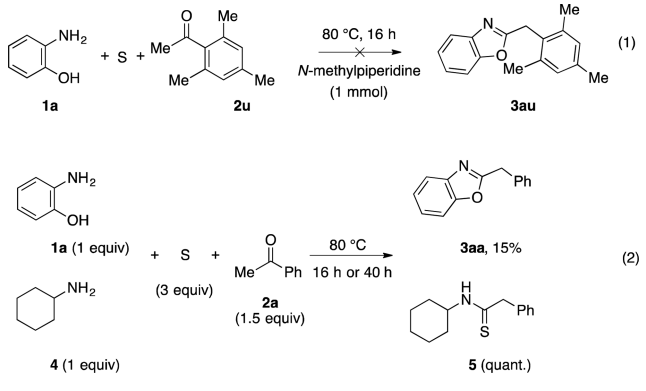
Scheme 4. Reaction Scope of Long Chain Alkyl Ketones



heptanone gave also benzoxazole **3ar**–**3as** under the present reaction conditions.

We next turned our attention to gain insight into the mechanism of this oxidative rearranging coupling (Scheme 5).

Scheme 5. Control Experiments

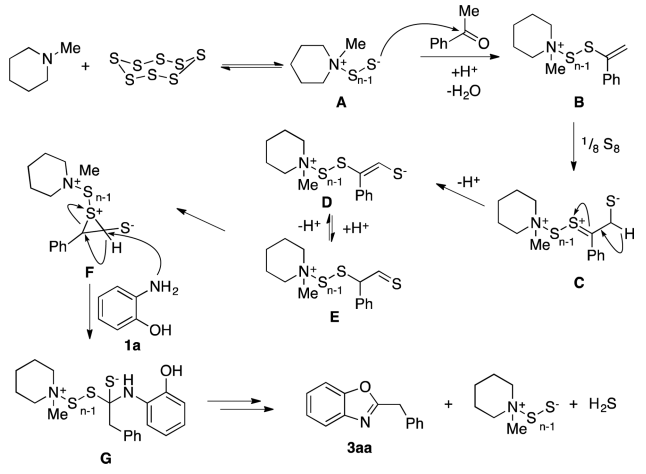


At first, in support of our working hypothesis that an attack at the carbonyl of acetophenone would initiate, we chose mesityl methyl ketone **2u** in which the carbonyl function was shielded by both *o*-methyl groups (Scheme 5, eq 1). The reaction of **2u** with **1a** did not lead to the desired benzoxazole **3au**, and starting material as well as *N*-methylpiperidine remained unchanged. This excludes the enolate species as intermediates, which are less sterically demanding.

Subsequently, to confirm the activating effect of basic nitrogen on sulfur, we performed a reaction in which a primary aliphatic amine such as cyclohexylamine **4** was used in place of *N*-methylpiperidine (Scheme 5, eq 2). The crude reaction mixture showed a total transformation of **4** into its phenylthioacetamide **5** as in a typical Willgerodt–Kindler reaction along with 15% of benzoxazole **3aa**. Further 24 h heating of the reaction mixture did not result in any conversion into **3aa**. This indicates that as long as cyclohexylamine is present in the reaction mixture, sulfur activation is maintained and acetophenone can be oxidatively condensed with **1a** to yield **3aa**.

The mechanism of this oxidative rearranging coupling reaction was proposed based on the Willgerodt reaction (Scheme 6). The first step is a ring-opening activation of S_8

Scheme 6. Proposed Reaction Mechanism



leading to highly nucleophilic polysulfide zwitterion **A**.[16] Addition of **A** to acetophenone followed by dehydration leads to styryl polysulfide **B**. Subsequence β-sulfuration of **B** followed by series of steps of double bond migration via **C** and **D** leads to α-thio thioacetaldehyde **E**. Migration of β-polysulfide chain with subsequent nucleophilic attack of **1a** provides acetamide dithioacetal **G**, which finally cyclizes to **3aa**. Other reactions pathways in which *o*-aminophenol involves in the earlier stages thanks to the nucleophilicity of its amino group are also possible. Although hydrogen sulfide is obviously the byproduct of this reactions, no pressure buildup was noticed even when the reactions were performed in closed tubes on heating. This can be explained by the formation of *N*-methylpiperidinium hydrogen sulfide, which is beneficial to avoid the emission of hydrogen sulfide gas. Moreover, the presence of hydrogen sulfide ion dissolved in the reaction mixtures may have a positive catalytic effect on ring opening of the cyclooctasulfur, an important initial step for catalytic cycle, via nucleophilic attack to form polysulfide anion similar to **A**.

In conclusion, we have developed a general, inexpensive, and versatile method for the synthesis of alkylated benzoxazoles, which are important heterocyclic molecules and materials. The chemistry is based on the Willgerodt-type rearrangement using *o*-aminophenols as weak bis-nucleophiles. The *N*-methylpiperidine/sulfur combination enables the oxidative rearranging coupling of both aliphatic and aromatic ketones under mild conditions. Consequently, this strategy is capable of providing a wide range of 2-alkylated benzoxazoles, which is difficult to

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obtain using other synthetic procedures, from readily available *o*-aminophenols and ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01775.

Experimental procedures, copies of NMR spectra (PDF)
Crystallographic data of benzoxazole **3ae** (CIF)

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For selected examples, see: (a) Arakawa, K.; Inamasu, M.; Matsumoto, M.; Okumura, K.; Yasuda, K.; Akatsuka, H.; Kawanami, S.; Watanabe, A.; Homma, K.; Saiga, Y.; Ozeki, M.; Iijima, I. *Chem. Pharm. Bull.* **1997**, *45*, 1984. (b) Tekiner-Gulbas, B.; Temiz-Arpaci, O.; Yildiz, I.; Altanlar, N. *Eur. J. Med. Chem.* **2007**, *42*, 1293. (c) Oeren, I.; Temiz, O.; Yalcin, I.; Sener, E.; Akin, A.; Ucartuerk, N. *Drug Res.* **1997**, *47*, 1393. (d) Verma, M.; Tripathi, M.; Saxena, A. K.; Shanker, K. *Eur. J. Med. Chem.* **1994**, *29*, 941. (e) Oksuzoglu, E.; Temiz-Arpaci, O.; Tekiner-Gulbas, B.; Eroglu, H.; Sen, G.; Alper, S.; Yildiz, I.; Diril, N.; Aki-Sener, E.; Yalcin, I. *Med. Chem. Res.* **2008**, *16*, 1. (f) Chancellor, D. R.; Davies, K. E.; De Moor, O.; Dorgan, C. R.; Johnson, P. D.; Lambert, A. G.; Lawrence, D.; Lecci, C.; Maillol, C.; Middleton, P. J.; Nugent, G.; Poignant, S. D.; Potter, A. C.; Price, P. D.; Pye, R. J.; Storer, R.; Tinsley, J. M.; Van Well, R.; Vickers, R.; Vile, J.; Wilkes, F. J.; Wilson, F. X.; Wren, S. P.; Wynne, G. M. *J. Med. Chem.* **2011**, *54*, 3241.

(2) Rajasekhar, S.; Maiti, B.; Chanda, K. *Synlett* **2017**, *28*, 521.

(3) For selected examples, see: (a) Seijas, J. A.; Vazquez-Tato, M. P.; Carballido-Reboredo, M. R.; Crecente-Campo, J.; Romar-Lopez, L. *Synlett* **2007**, *2007*, 313. (b) Wen, X.; Bakali, J. E.; Deprez-Poulain, R.; Deprez, B. *Tetrahedron Lett.* **2012**, *53*, 2440. (c) Wang, Y.; Wu, C.; Nie, S.; Xu, D.; Yu, M.; Yao, X. *Tetrahedron Lett.* **2015**, *56* (49), 6827. (d) Huang, L.; Zhang, W.; Zhang, X.; Yin, L.; Chen, B.; Song, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5299. (e) Bhumgara, S. K.; Seshadri, S. *Indian J. Chem. B* **1987**, *26*, 171. (f) Terashima, M.; Ishii, M.; Kanaoka, Y. *Synthesis* **1982**, *6*, 484. (g) Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823. (h) Bastug, G.; Eviolitte, C.; Markó, I. E. *Org. Lett.* **2012**, *14*, 3502. (i) Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *J. Org. Chem.* **2014**, *79*, 6310. (j) Tan, H.; Pan, C.; Xu, Y.; Wang, H.; Pan, Y. *J. Chem. Res.* **2012**, *36*, 370.

(4) For selected examples of dehydrogenative or oxidative coupling reactions, see: (a) Kondo, T.; Yang, S.; Huh, K.; Kobayashi, M.; Kotachi, S.; Watanabe, Y. *Chem. Lett.* **1991**, *20*, 1275. (b) Pizzetti, M.; De Luca, E.; Petricci, E.; Taddei, M.; Porcheddu, A. *Adv. Synth. Catal.* **2012**, *354*, 2453. (c) Khalafi-Nezhad, A.; Panahi, F. *ACS Catal.* **2014**, *4*, 1686. (d) Cho, Y.; Lee, C.; Cheon, C. *Tetrahedron* **2013**, *69*, 6565. (e) Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 6106. (f) Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948. (g) Endo, Y.; Bäckvall, J. E. *Chem. - Eur. J.* **2012**, *18*, 13609. For representative examples of redox condensation of *o*-nitrophenols with alcohols, see: (h) Tang, L.; Guo, X.; Yang, Yu; Zha, Z.; Wang, Z. *Chem. Commun.* **2014**, *50*, 6145. (i) Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G. *Org. Lett.* **2012**, *14*, 2722. (j) Yu, C.; Guo, X.; Xi, Z.; Muzzio, M.; Yin, Z.; Shen, B.; Li, J.; Seto, C. T.; Sun, S. *J. Am. Chem. Soc.* **2017**, *139*, 5712.

(5) (a) Li, Y.; Wang, M.; Fan, W.; Qian, F.; Li, G.; Lu, H. *J. Org. Chem.* **2016**, *81*, 11743. (b) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. (c) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748. Ackermann, L.; Barfuesser, S.; Kornhaass, C.; Kapdi, A. R. *Org. Lett.* **2011**, *13*, 3082. (e) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061. (f) Lee, W.; Wang, C.; Lin, Y.; Shih, W.; Ong, T. *Org. Lett.* **2013**, *15*, 5358. (g) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 12307. (h) Shibahara, F.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2011**, *76*, 2680. (i) Do, H.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129* (41), 12404. (j) Xie, P.; Huang, H.; Xie, Y.; Guo, S.; Xia, C. *Adv. Synth. Catal.* **2012**, *354*, 1692. (k) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (l) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329.

(6) (a) Ji, Y.; Zhang, Y.; Hu, Y.; Shao, L. *Tetrahedron* **2015**, *71*, 6818. (b) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (c) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

(7) For miscellaneous methods, see the following. Cyclization of *o*-haloanilides: (a) Jadhav, J.; Gaikwad, V.; Kurane, R.; Salunkhe, R.; Rashinkar, G. *Tetrahedron* **2013**, *69*, 2920. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. Benzylic C−H bond functionalization of 2-alkylbenzoxazoles: (d) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706. (e) Obora, Y.; Ogawa, S.; Yamamoto, N. *J. Org. Chem.* **2012**, *77*, 9429. (f) Saari, W. S.; Hoffman, J. M.; Wai, J. S.; Fisher, J. E.; Rooney, C. S.; Smith, A. M.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A. *J. Med. Chem.* **1991**, *34*, 2922. C−N and C−O cross-coupling from primary amides: (g) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661.

(8) (a) Nguyen, T. B. *Adv. Synth. Catal.* **2017**, *359*, 1066. (b) Nguyen, T. B. *Asian J. Org. Chem.* **2017**, *6*, 477.

(9) Willgerodt, C. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 534.

(10) (a) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187. (b) DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* **1946**, *68*, 2025. For selected reviews, see: (c) Carmack, M.; Spielman, M. A. *Org. React.* **1946**, 3. (d) Priebbenow, D. L.; Bolm, C. *Chem. Soc. Rev.* **2013**, *42*, 7870. (e) Brown, E. V. *Synthesis* **1975**, *1975*, 358.

(11) Yutilov, Yu. M.; Shcherbina, L. I.; Stetsenko, L. B. *Russian J. Org. Chem.* **1994**, *30*, 495.

(12) Nguyen, T. B.; Pasturaud, K.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2015**, *17*, 2562.

(13) Nguyen, T. B.; Ermolenko, L.; Corbin, M.; Al-Mourabit, A. *Org. Chem. Front.* **2014**, *1*, 1157.

(14) (a) Sulfur-promoted decarboxylative coupling between *o*-aminophenol with acid phenylpropiolic at 130 °C in the presence of *N*-methylmorpholine to provide 2-benzylbenzoxazole: Guntreddi, T.; Vanjari, R.; Kumar, S.; Singh, R.; Singh, N.; Kumar, P.; Singh, K. N. *RSC Adv.* **2016**, *6*, 81013.

(15) DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* **1946**, *68*, 2025.

(16) Hodgson, W. G.; Buckler, S. A.; Peters, G. *J. Am. Chem. Soc.* **1963**, *85*, 543.

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