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ARTICLE

One-pot synthesis of benzoxazoles via the metal-free *ortho*-C-H functionalization of phenols with nitroalkanes†

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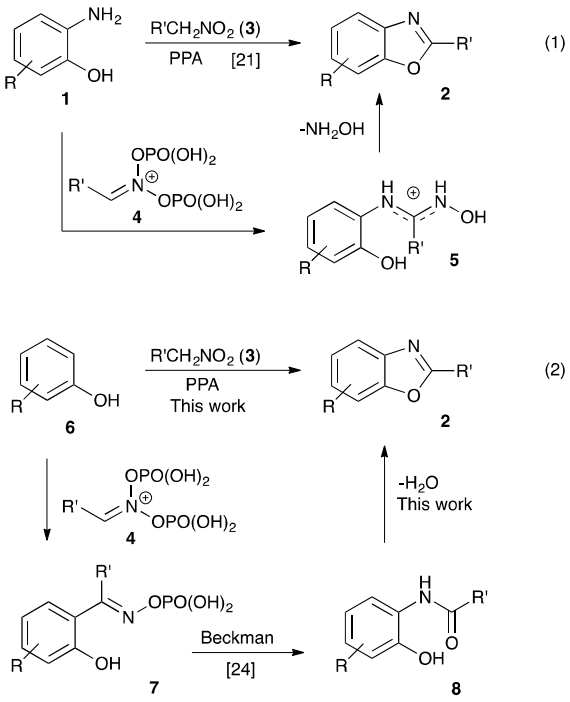
PPA-activated nitroalkanes are employed in the design of a one-pot cascade transformation involving metal-free and oxidant-free direct *ortho*-C-H functionalization, followed by Beckman rearrangment and intramolecular cyclocondensation to produce benzoxazoles and benzobisoxazoles directly from easily available phenols.

Introduction

Benzoxazole is one of the most privileged scaffolds in natural product chemistry[1] and modern drug design.[2,3] Benzoxazole derivatives are also versatile ligands for transition metal and Lewis acid catalysis.[4] Development of polybenzobisoxazoles led to the discovery of a new generation of organic polymers for electronics and novel high tensile materials.[5] Not surprisingly, vast efforts are put into the development of efficient methods for their synthesis.[6] The most straightforward approaches to benzoxazoles involve various cyclocondensations between o-aminophenols and different carbonyl derivatives: aldehydes,[7] imines,[8] carboxylic acids,[9] acyl halides,[10] esters,[11] orthoesters,[12] *N*-alkylnitrilium salts,[13] isocyanides,[14] or carbon monoxide.[15] Alternatively, benzoxazoles can be accessed by catalytic annulation of *ortho*-haloanilines with acylchlorides[16] or 1,2-dihalobenzenes with primary amides.[16] All of the above-mentioned protocols, however, require 1,2-disubstituted benzene precursors for which there are only a handful of methods that allow for the direct *ortho*-C-H functionalization of phenol derivatives. Subsequent annulation provides benzoxazole products. One of these methods involves the intramolecular Cu-catalyzed ring closure of O-aryl oximes.[17] Intermolecular approaches, involving the condensation of *N*-nitro-*O*-arylhydroxylamines[18] or aryloxenium ions[19] with nitriles and oxidative coupling of phenols with primary amines[20] or nitriles[21] were also demonstrated. Many of them, however, are rather inefficient, have limited scope, and require addition of an external oxidant, such as MnO_2, DDQ, or $K_3Fe(CN)_6$. Herein we wish to report a new, direct approach to benzoxazoles and benzobisoxazoles via the *ortho*-CH functionalization of readily available phenols with PPA-activated nitroalkanes.



Scheme 1

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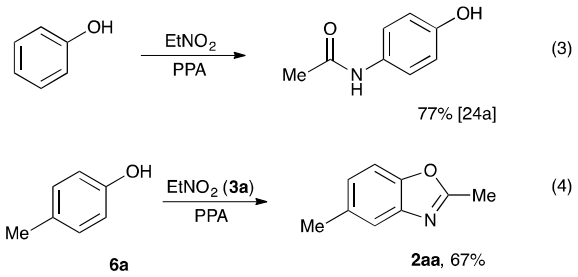
Results and discussion

Our team has been investigating the reactivity of nitro-compounds in a polyphosphoric acid (PPA) medium in application to synthesis of medicinally relevant heterocyclic compounds.[22] In the frame of this program we have previously reported the synthesis of benzoxazoles **2** proceeding via the cyclocondensation of *ortho*-aminophenols **1** with nitroalkanes **3** (Scheme 1, eq. 1).[23] The mechanism of this transformation involves umpolung of nitroalkane upon formation of a strong Lewis acid – Lewis base complex with PPA. The resulting highly electrophilic phosphorylated aci form **4** undergoes nucleophilic attack by aniline moiety in **1** to afford protonated imidamide species **5**. Subsequent acid-assisted cyclocondensation with elimination of hydroxylamine provided benzoxazole **2** (Scheme 1, eq. 1).[23] We proposed that *ortho*-aminophenols **1** can potentially be substituted with much more accessible phenols **6** to obtain the same benzoxazole products **2** by combining the described above methodology with our recent finding that unprotected phenols can undergo PPA-promoted acetamidation with nitroalkanes (Scheme 2, eq. 3).[24a] Thus, it was anticipated that aci species **4** would serve as an electrophile in the S_EAr-type reaction with electron-rich phenols to produce phosphorylated oxime **7** which, as demonstrated previously, could participate in a Beckman rearrangement to yield benzamide **8**.[24] The latter would undergo a PPA-promoted cyclocondensation into benzoxazole **2** producing water as the only by-product. It should be mentioned that acetamidation of phenol was shown to be highly *para*-selective,[24a] and this would limit the proposed transformation to substrates with substituted or sterically encumbered *para*-position to ensure the electrophilic attack at the *ortho*-position of phenols.

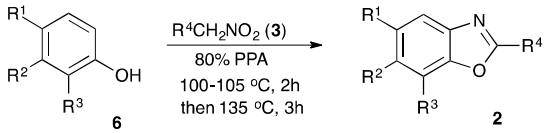
To test this idea, we attempted the reaction between *p*-cresol (**6a**) and nitroethane (**3a**), which was carried out in the 80% solution of PPA at 100-105 °C. At this temperature **6a** was completely consumed within 2 h and produced intermediate amide **8aa**, which was not isolated but further heated for 3 h at 135 °C to enable heteroannulation into benzoxazole **2aa** (Scheme 2, eq. 4; Table 1, entry 1).[25] Inspired by the successful result, we screened a few other nitroalkanes (**3b-e**) in the reaction with phenol, all of which afforded the corresponding benzoxazoles (**2ab**-**2ae**) in good yields under the same reaction conditions (entries 2-5).



Scheme 2

Analogously, other *para*-substituted phenols, *p*-ethylphenol (**6b**) and *p*-cumenol (**6c**), reacted with nitroethane to give benzoxazoles **2ba** and **2ca**, respectively (entries 6, 7). 3,4-Xylenol (**6d**) afforded trisubstituted products **2da** and **2de**, with nitroethane (**3a**) and 2-phenylnitroethane (**3e**) (entries 8-9). The structure of **2da** was unambiguously confirmed by X-ray crystallography (Figure 1). A strong M^+ *meta*-substituent, such as fluorine, also efficiently directed the S_EAr-attack *ortho* to the OH group affording benzoxazole **2ea** in reasonable yield (entry 10). Resorcinols **6f** and **6g** also reacted selectively showing a strong preference for the electrophilic attack at only one of the *ortho*-positions (C-6), governed by steric factors (entries 1-12).

Table 1



#	6	3	R^1	R^2	R^3	R^4	2	Yield, %[a]
1	**6a**	**3a**	Me	H	H	Me	**2aa**	67
2	**6a**	**3b**	Me	H	H	Et	**2ab**	74
3	**6a**	**3c**	Me	H	H	n-C_5H_{11}	**2ac**	74
4	**6a**	**3d**	Me	H	H	Ph	**2ad**	72
5	**6a**	**3e**	Me	H	H	$PhCH_2$	**2ae**	69
6	**6b**	**3a**	Et	H	H	Me	**2ba**	78
7	**6c**	**3a**	*i*-Pr	H	H	Me	**2ca**	72
8	**6d**	**3a**	Me	Me	H	Me	**2da**	76
9	**6d**	**3e**	Me	Me	H	$PhCH_2$	**2de**	71
10	**6e**	**3a**	H	F	H	Me	**2ea**	62
11	**6f**	**3a**	H	OH	H	Me	**2fa**	78
12	**6g**	**3a**	H	OH	Me	Me	**2ga**	70
13	**6h**	**3a**	OH	H	H	Me	**2ha**	34

a) Isolated yields of purified benzoxazole products

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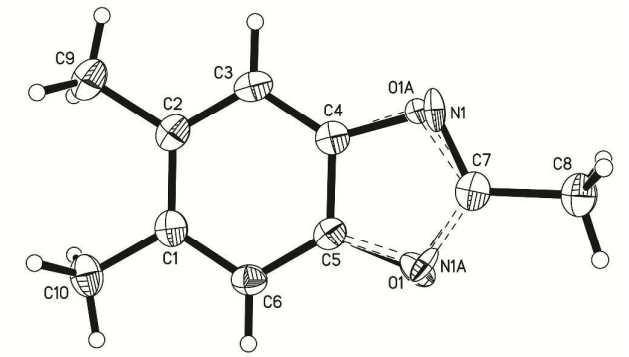
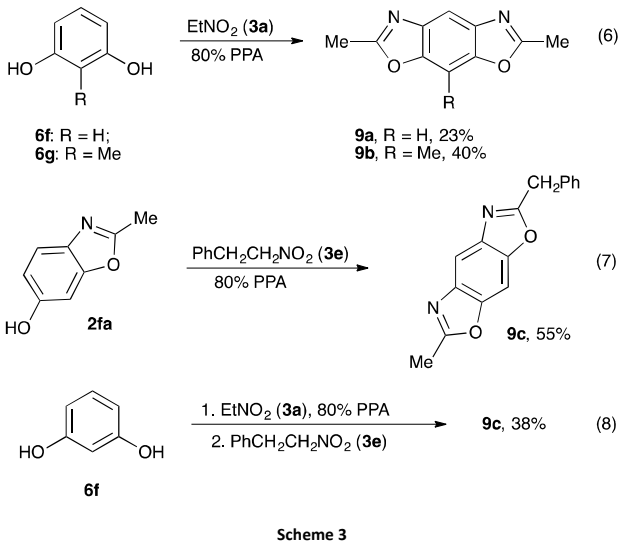


Figure 1. ORTEP drawing of 2,5,6-trimethylbenzo[d]oxazole (**2da**, CCDC 1410546) showing 50% probability amplitude displacement ellipsoids. Oxygen and nitrogen atoms are shown disordered as this planar molecule can pack in two different ways occupying practically the same space in the crystalline lattice.

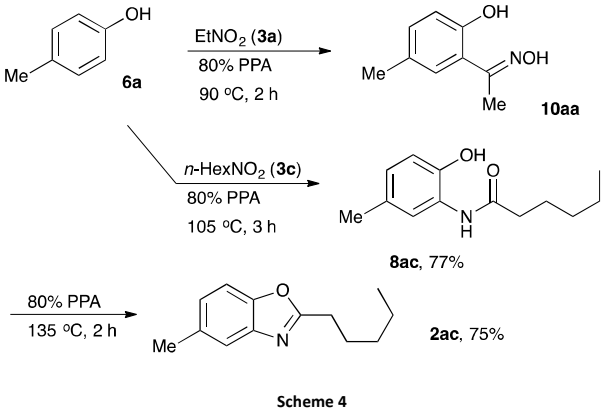
Hydroquinone (**6h**) was also considered as an illustrative substrate for the described transformations due to symmetry, which renders all possible directions for electrophilic attack identical. However, the reaction of **6h** was complicated by concurrent aerobic oxidation of the material under employed reaction conditions and only provided benzoxazole **2ha** in modest yield (entry 13).

We were also inspired by the idea of using diphenols for simultaneous or stepwise installation of two benzoxazole rings en route to benzobisoxazoles (BBOs), the key building blocks for a new generation of organic semiconducting materials.[26] The possibility to obtain BBOs in a single step from abundant and inexpensive diphenols provides clear advantages over the currently used approaches that rely on tetrasubstituted aromatic substrates.[26] To probe this idea, we carried out the reaction of resorcinols **6f**,**g** with excess nitroethane (**3a**). The initial annulation into benzoxazole (**2fa**, **2ga**) occurred uneventfully; however, subsequent cyclization required prolonged heating to afford benzobisoxazoles **9a**,**b** (Scheme 3, eq. 6). The same one-pot transformation can also be carried out with successive addition of two different nitroalkanes to resorcinol (Scheme 3, eq. 8). Alternatively, isolated benzoxazole **2fa** subjected to a second fold cyclization with 2-phenylnitroethane (**3e**) cleanly afforded non-symmetric benzobisoxazole **9c** (Scheme 3, eq. 7).

To gain additional support for the mechanism and proposed reaction intermediates (Scheme 1, eq. 2), we subjected *p*-cresol (**6a**) to the reaction with various nitroalkanes at lower temperatures. Treatment of **6a** with nitroethane at 90 °C for 2 h provided oxime **10aa** as a sole product after a standard aqueous work up. (Scheme 5). In contrast, the reaction carried out at 105 °C in the presence of 1-nitrohexane, provided the Beckman rearrangement product, amide **8ac**, in good yield. Being re-subjected to the standard reaction conditions (2 h at 135 °C), **8ac** cleanly afforded benzoxazole **2ac** (Scheme 4). It should be emphasized that, unlike other heteroannulations proceeding via C-H functionalization of arenes,[20,21] our method does not require any external oxidative agents and produces water as the only by-product.



Scheme 3



Scheme 4

This one-pot cascade transformation is made possible through the use of polyphosphoric acid, which plays an important role in each step, including: a) umpolung of nitroalkane rendering the nitro group an efficient electrophile and oxidant for the electron-rich aromatic C-H bond; b) promoting Beckman rearrangement through phosphorylation of the oxime moiety; c) facilitating the condensation step by efficient removal of water; and d) in-situ reversible protection of the phenol group at the initial stages of the reaction.

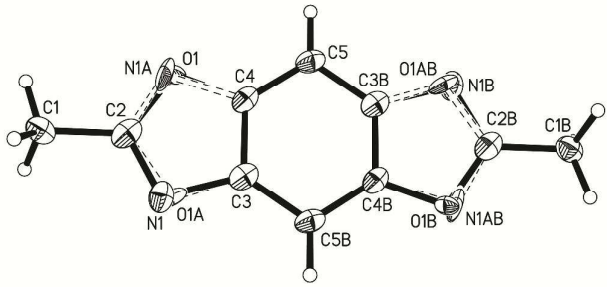


Figure 2. ORTEP drawing of 2,6-Dimethylbenzo[1,2-d:5,4-d']bis(oxazole) (**9a**, CCDC 1415173) showing 50% probability amplitude displacement ellipsoids. Oxygen and nitrogen atoms are shown disordered as this planar molecule can pack in two different ways occupying practically the same space in the crystalline lattice.

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Conclusions

We have developed a new cascade transformation combining a direct *ortho*-acetamidation of phenols and intramolecular cyclocondensation of the intermediate 2-hydroxyanilides into benzoxazoles. This reaction involves successive formation of the C-N and C-O bonds, with the former proceeding via a PPA-assisted C-H functionalization of the arene. This method offers a direct, atom-economic, metal-free, external oxidant-free, one-pot route to benzoxazoles and benzobisoxazoles from easily available phenols, producing water as the only by-product.

Experimental Part

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with BBO probe in $CDCl_3$ using TMS as internal standard. High resolution mass spectra were registered with Bruker Maxis spectrometer (electrospray ionization, in MeCN, using HCO_2Na-HCO_2H for calibration). Melting points were measured with Stuart smp30 apparatus. All reactions were performed in oven-dried drum vials open to the atmosphere employing overhead stirring. Reaction progress and purity of isolated compounds were monitored by TLC on Silufol UV-254 plates, eluting with EtOAc. Flash column chromatography was performed on Silica gel (32-63 μm, 60 Å pore size). All reagents and solvents were purchased from commercial vendors and used as received.

2,5-Dimethylbenzo[*d*]oxazole (**2aa**)[27] (Typical procedure). Oven-dried vial was charged with *p*-cresol (108 mg, 1.00 mmol), nitroethane (85 μL, 90 mg, 1.20 mmol), and 80% polyphosphoric acid (2.0 g). The mixture was stirred at 105 °C for 2 h before all *p*-cresol was consumed. Then the temperature was raised to 135 °C and the stirring was continued for 3 h. Hot mixture was poured into solution of Na_2CO_3 (3.0 g) in cold water (27 mL), the product was extracted with petroleum ether (4 x 25 mL) (for extraction of products **2fa**, **2ha**, **2ha**, **2ia** petroleum ether should be replaced with CH_2Cl_2). Combined extracts were concentrated in vacuum and the titled compound was isolated by column chromatography (eluting with mixture petroleum ether-EtOAc, applying gradient from 10:1 to 1:1) as yellowish oil, R_f 0.71 (hexane/EtOAc 1:1). Yield 99 mg (0.67 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 7.9 Hz), 7.08 (1H, d, *J* = 7.9 Hz), 7.32 (1H, s), 2.61 (3H, s), 2.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.3, 141.6, 134.1, 125.6, 119.4, 109.7, 21.5, 14.6; IR (NaCl, film, cm^{-1}) 2926, 1616, 1580, 1489, 1435, 1261, 1118, 1044, 922, 872, 841, 798; HRMS (ES TOF) calc`d for $C_9H_{10}NO$ $(M+H)^+$: 148.0767, found 148.0767 (0.0 ppm).

2-Ethyl-5-methylbenzo[*d*]oxazole (**2ab**).[28] Prepared according to the typical procedure employing *p*-cresol (**6a**) (108 mg, 1.00 mmol) and nitropropane (**3b**) (109 μL, 107 mg, 1.20 mmol). Titled compound was isolated as yellowish oil, R_f 0.38 (hexane/EtOAc 8:1). Yield 119 mg (0.74 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.92 (q, *J* = 7.6 Hz, 2H), 2.43 (s, 3H), 1.42 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 168.3, 149.1, 141.7, 133.8, 125.5, 119.6, 109.6, 22.3, 21.5, 11.0; HRMS (ES TOF) calc`d for $C_{10}H_{12}NO$ $(M+H)^+$: 162.0919, found 162.0918 (0.6 ppm).

2-Hexyl-5-methylbenzo[*d*]oxazole (**2ac**). Prepared according to the typical procedure employing *p*-cresol (**6a**) (108 mg, 1.00 mmol) and 1-nitrohexane (**3c**) (167 μL, 157 mg, 1.20 mmol). Titled compound was isolated as yellowish oil, R_f 0.44 (hexane/EtOAc 10:1). Yield 150 mg (0.74 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 1.93-1.83 (m, 2H), 1.42-1.35 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 149.2, 141.8, 141.7, 134.0, 125.5, 119.6, 109.7, 31.5, 28.8, 26.7, 22.4, 21.6, 14.0; HRMS (ES TOF) calc`d for $C_{13}H_{18}NO$ $(M+H)^+$: 204.1388, found 204.1391 (1.5 ppm).

5-Methyl-2-phenylbenzo[*d*]oxazole (**2ad**).[29] Prepared according to the typical procedure employing *p*-cresol (**6a**) (108 mg, 1.00 mmol) and α-nitrotoluene (**3d**) (165 mg, 1.20 mmol). Titled compound was isolated as colorless crystals, mp 101-102 °C (benzene), R_f 0.69 (hexane/EtOAc 6:1). Yield 150 mg (0.72 mmol, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (dd, *J* = 7.4, 2.0 Hz, 2H), 7.67-7.56 (m, 5H), 7.23 (d, *J* = 7.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 162.3, 148.4, 141.7, 134.2, 131.8, 129.3 (2C), 127.2 (2C), 126.5, 126.5, 119.6, 110.3, 21.0; IR (NaCl, film, cm^{-1}) 3050, 2924, 1551, 1482, 1449, 1333, 1271, 1198, 1056, 1023, 924, 825, 795; HRMS (ES TOF) calc`d for $C_{14}H_{12}NO$ $(M+H)^+$: 210.0913, found 210.0916 (1.4 ppm).

2-Benzyl-5-methylbenzo[*d*]oxazole (**2ae**).[30] Prepared according to the typical procedure employing *p*-cresol (**6a**) (108 mg, 1.00 mmol) and 2-phenylnitroethane (**3e**) (162 μL, 181 mg, 1.20 mmol). Titled compound was isolated as yellowish oil, R_f 0.61 (hexane/EtOAc 4:1). Yield 154 mg (0.69 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.18-7.34 (m, 6H), 7.04 (d, *J* = 8.5 Hz, 1H), 4.20 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.4, 141.2, 134.9, 134.3, 129.1 (2C), 129.0 (2C), 127.4, 126.0, 119.7, 110.0, 35.4, 21.6; IR (NaCl, film, cm^{-1}) 3078, 1742, 1616, 1553, 1453, 1242, 1052, 742, 704; HRMS (ES TOF) calc`d for $C_{15}H_{14}NO$ $(M+H)^+$: 224.1070, found 224.1067 (1.3 ppm).

5-Ethyl-2-methylbenzo[*d*]oxazole (**2ba**).[31] Prepared according to the typical procedure employing *p*-ethylphenol (**6b**) (136 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol). Titled compound was isolated as yellowish oil, R_f 0.63 (hexane/EtOAc 4:1). Yield 126 mg (0.78 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 0.9 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.6 Hz, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 149.3, 141.7, 140.4, 124.4, 118.2, 109.6, 28.8, 16.2, 14.4. IR (NaCl, film, cm^{-1}) 2964, 2937, 2878, 1620, 1584, 1479, 1439, 1376, 1323, 1257, 1175, 1125, 1063, 1036, 914, 875, 842, 805, 756, 733, 670, 630; HRMS (ES TOF) calc`d for $C_{10}H_{12}NO$ $(M+H)^+$: 162.0913, found 162.0918 (3.1 ppm).

5-Isopropyl-2-methylbenzo[*d*]oxazole (**2ca**). Prepared according to the typical procedure employing *p*-cumenol (**6c**) (108 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20

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mmol). Titled compound was isolated as yellowish oil, R_f 0.65 (hexane/EtOAc 4:1). Yield 126 mg (0.72 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.03-2.93 (m, 1H), 2.57 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.4, 145.2, 141.7, 123.1, 116.7, 109.6, 34.2, 24.5, 14.5 (2C); IR (NaCl, film, cm^{-1}) 2964, 2865, 1739, 1614, 1581, 1482, 1452, 1436, 1383, 1366, 1310, 1267, 1188, 1165, 1129, 1046, 921, 881, 844, 805, 733, 667, 637; HRMS calc`d for $C_{11}H_{14}NO$ (M+H)+: 176.1070, found 176.1070 (0.0 ppm).

2,5,6-Trimethylbenzo[*d*]oxazole (**2da**).[32] Prepared according to the typical procedure employing 3,4-xylenol (**6d**) (122 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol). Titled compound was isolated as colorless crystals, mp 93 °C (hexane), R_f 0.42 (hexane/EtOAc 4:1). Yield 122 mg (0.76 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.23 (s, 1H), 2.60(s, 3H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.2, 149.7, 139.5, 133.6, 132.9, 119.5, 110.7, 20.5, 20.2, 14.6; HRMS (ES TOF) calc`d for $C_{10}H_{12}NO$ $(M+H)^+$: 162.0913, found 162.0913 (0.0 ppm).

2-Benzyl-5,6-dimethylbenzo[*d*]oxazole (**2de**). Prepared according to the typical procedure employing 3,4-xylenol (**6d**) (122 mg, 1.00 mmol) and 2-phenylnitroethane (**3e**) (162 μL, 181 mg, 1.20 mmol). Titled compound was isolated as yellowish oil, R_f 0.65 (hexane/EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.39-7.30 (m, 6H), 4.26 (s, 2H), 2.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 149.7, 139.4, 135.0, 133.7, 132.8, 128.9 (2C), 128.7 (2C), 127.2, 119.7, 110.7, 35.2, 20.4, 20.1. IR (NaCl, film, cm^{-1}) 2924, 1571, 1469, 1449, 1267, 1152, 1129, 1000, 954, 868, 716; HRMS (ES TOF) calc`d for $C_{16}H_{16}NO$ $(M+H)^+$: 238.1226, found 238.1230 (1.7 ppm);

6-Fluoro-2-methylbenzo[*d*]oxazole (**2ea**).[33] Prepared according to the typical procedure employing 3-fluorophenol (**6e**) (112 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol). Titled compound was isolated as yellowish oil, R_f 0.42 (hexane/EtOAc 6:1). Yield 94 mg (0.62 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.7, 4.9 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.06-6.99 (m, 1H), 2.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (d, *J* = 3.0 Hz), 160.4 (d, *J* = 242 Hz), 151.0 (d, *J* = 14 Hz), 137.8 (d, *J* = 2 Hz), 119.7 (d, *J* = 10 Hz), 112.0 (d, *J* = 25 Hz), 98.5 (d, *J* = 28 Hz), 14.6; HRMS (ES TOF) calc`d for C_8H_7FNO $(M+H)^+$: 152.0506, found 152.0505 (0.7 ppm).

2-Methylbenzo[*d*]oxazol-6-ol (**2fa**).[34] Prepared according to the typical procedure employing resorcinol (**6f**) (110 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol). Titled compound was isolated as colorless crystals, mp 194-196 °C (acetonitrile), R_f 0.52 (hexane/EtOAc 1:1). Yield 116 mg (0.78 mmol, 78%). ^{1}H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 161.8, 155.3, 151.3, 133.6, 118.9, 112.5, 96.9, 14.0; HRMS (ES TOF) calc`d for $C_8H_8NO_2$ $(M+H)^+$: 150.0550, found 150.0560 (6.7 ppm)

2,7-Dimethylbenzo[*d*]oxazol-6-ol (**2ga**).[35] Prepared according to the typical procedure employing 2-methylresorcinol (**6g**) (124 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol). Titled compound was isolated as colorless crystals, mp 178-181 °C (benzene), R_f 0.25 (hexane/EtOAc 4:1). Yield 114 mg (0.70 mmol, 70%). ^{1}H NMR (400 MHz, DMSO) δ 8.61 (s, 1H), 6.35 (d, *J* = 8.5 Hz, 1H), 5.93 (d, *J* = 8.5 Hz, 1H), 1.65 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 152.8, 150.6, 133.2, 115.5, 111.8, 106.3, 14.1, 9.1; HRMS (ES TOF) calc`d for $C_9H_{10}NO_2$ $(M+H)^+$: 164.0706, found 164.0706 (0.0 ppm).

2-Methylbenzo[*d*]oxazol-5-ol (**2ha**).[33] Prepared according to the typical procedure employing hydroquinone (**6h**) (110 mg, 1.00 mmol) and nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol). Titled compound was isolated as colorless crystals, mp 164-165 °C (acetonitrile), R_f 0.28 (hexane/EtOAc 1:1). Yield 51 mg (0.34 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 153.8, 145.4, 141.0, 113.6, 110.8, 104.9, 14.6; HRMS (ES TOF) calc`d for $C_8H_8NO_2$ (M+H)+: 150.0550, found 150.0550 (0.0 ppm)

***N*-(2-Hydroxy-5-methylphenyl)hexanamide** (**8ac**). Oven-dried vial was charged with *p*-cresol (108 mg, 1.00 mmol), 1-nitrohexane (**3c**) (167 μL, 157 mg, 1.20 mmol), and 80% polyphosphoric acid (2.0 g). The mixture was stirred at 105 °C for 3 h before all *p*-cresol was consumed. Then the hot mixture was poured into solution of Na_2CO_3 (3.0 g) in cold water (27 mL), the product was extracted with petroleum ether (4 x 25 mL). Combined extracts were concentrated in vacuum and the titled compound was isolated by column chromatography (eluting with mixture petroleum ether-EtOAc, applying gradient from 10:1 to 1:1) as yellowish oil, R_f 0.38 (hexane/EtOAc 8:1). Yield 170 mg (0.77 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.2 Hz, 3H), 1.43-1.32 (m, 4H), 1.58 (s, 1H), 1.68-1.59 (m, 2H), 2.29 (s, 3H), 3.44 (dd, *J* = 13.5, 6.7 Hz, 2H), 6.27 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 7.11 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 12.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.5, 135.1, 127.8, 125.3, 118.6, 114.1, 39.8, 29.4, 29.2, 22.5, 20.7, 14.1; IR (NaCl, film, cm^{-1}): 2982, 2942, 2924, 1574, 1483, 1454, 1429, 1261, 1175, 1165, 926, 833, 800, 667, 598; HRMS (ES TOF) calc`d for $C_{13}H_{20}NO_2$ $(M+H)^+$: 222.1490, found 222.1494 (1.8 ppm).

2-Hexyl-5-methylbenzo[*d*]oxazole (**2ac**) from amide **8ac**. Oven-dried vial was charged with amide **8ac** (170 mg, 0.77 mmol) and 80% polyphosphoric acid (2.0 g). The mixture was stirred at 135 °C for 2 h, and then poured into solution of Na_2CO_3 (3.0 g) in cold water (27 mL). The product was extracted with petroleum ether (4 x 25 mL). Combined extracts were concentrated in vacuum and the titled compound was isolated by column chromatography (eluting with mixture petroleum ether-EtOAc, applying gradient from 10:1 to 1:1) as colorless oil, identical to the material obtained in reaction of p-cresol and 1-nitrohexane (*vide supra*).

2,6-Dimethylbenzo[1,2-*d*:5,4-*d'*]bis(oxazole) (**9a**).[36] Oven-dried vial was charged with resorcinol (**6f**) (110 mg, 1.00 mmol), nitroethane (**3a**) (85 μL, 90 mg, 1.20 mmol), and 80% polyphosphoric acid (4.0 g). The mixture was stirred for 1 h at 100-105 °C, then for 1 h at 135 °C. The mixture was cooled down and additional amount of nitroethane (142 μL, 150 mg, 2.00 mmol) was injected. The resulting mixture was stirred at 105 °C for 2 h, and then at 135 °C for 2 h. After this the hot

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mixture was poured into solution of Na_2CO_3 (6 g) in cold water (54 mL), and the crude product was extracted with CH_2Cl_2 (4 x 25 mL). Combined organic extracts were concentrated in vacuum, and the residue was purified by column chromateogr-aphy (eluting with mixture petroleum ether-EtOAc, applying gradient from 10:1 to 1:1), and then by re-crystallization from hexane as colorless crystals, mp 128-131°C (hexane), R_f 0.23 (hexane/ EtOAc 1:1). Yield 43 mg (0.23 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.58 (s, 1H), 2.68 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.8 (2C), 148.6 (2C), 138.6 (2C), 108.8 (2C), 93.0 (2C), 14.8 (2C); IR (NaCl, film, cm^{-1}) 2931, 1620, 1429, 1386, 1267, 1247, 1145, 1109, 914, 874; HRMS (ES TOF) calc`d for $C_{10}H_9N_2O_2$ (M+H)+: 189.0659, found 189.0659 (0.0 ppm).

2,6,8-trimethylbenzo[1,2-*d*:5,4-*d'*]bis(oxazole) (**9b**). Was obtained according to procedure described for preparation of **9a**, substituting resorcinol with 2-methylresorcinol (**6g**) (124 mg, 1.00 mmol). Titled compound was isolated as colorless crystals, mp 176-177 °C (hexane), R_f 0.21 (hexane/EtOAc 1:1). Yield 85 mg (0.42 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 2.60 (s, 6H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1 (2C), 147.7 (2C), 138.2 (2C), 105.8, 103.7, 14.8 (2C), 9.5; IR (NaCl, film, cm^{-1}) 2924, 1594, 1432, 1376, 1360, 1304, 1185, 1149, 1079, 921, 845; HRMS (ES TOF) calc`d for $C_{11}H_{11}N_2O_2$ $(M+H)^+$: 203.0815, found 203.0818 (1.5 ppm).

2-Benzyl-6-methylbenzo[1,2-*d*:5,*4-d'*]bis(oxazole) (**9c**). Was obtained according to procedure described for prepar-ation of **9a**, when second portion of nitroethane (3a) was replaced with 2-phenylnitroethane (3e) (270 μL, 302 mg, 2.00 mmol). Titled compound was isolated as yellowish oil, solidif-ying upon standing to give colorless amorphous solid, R_f 0.43 (hexane/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.49 (s, 1H), 7.34-7.26 (m, 5H), 4.22 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 164.8, 148.8, 148.7, 138.9, 138.7, 134.7, 129.2 (2C), 129.0 (2C), 127.6, 109.3, 93.1, 35.5, 14.8; IR (NaCl, film, cm^{-1}) 3030, 2931, 1624, 1587, 1558, 1436, 1386, 1112, 1046, 881; HRMS calc`d for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0972, found 265.0978 (2.3 ppm);

1-(2-Hydroxy-5-methylphenyl)ethan-1-one oxime (**10aa**) R_f 0.63 (hexane/AcOEt 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (br. s, 1H), 8.13 (br. s, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.89 (d, *J* = 8.0 HZ, 1H), 2.34 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.2, 131.6, 128.4, 128.0, 118.4, 117.1, 20.8, 10.9; IR (NaCl, film, cm^{-1}) 3327, 1636, 1503, 1391, 1369, 1321, 1285, 1252, 1036, 816, 783, 743, 669; HRMS calc`d for $C_9H_{12}NO_2$ $(M+H)^+$ 166.0863, found 166.0857 (3.6 ppm);

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Notes and references

1 See, for example: (a) G. Daletos, N. J. de Voogd, W. E. G. Mueller, V. Wray, W. Lin, D. Feger, M. Kubbutat, A. H. Aly, Amal H.; P. Proksch, *J. Nat. Prod.* 2014, **77**, 218. (b) G. Genta-Jouve, N. Francezon, A. Puissant, P. Auberger, J. Vacelet, T. Perez, A. Fontana, A. Al Mourabit, O. P. Thomas, *Magn. Reson. Chem.* 2011, **49**, 533. (c) S. P. B. Ovenden, J. L. Nielson, C. H. Liptrot, R. H. Willis, D. M. Tapiolas, A. D. Wright, C. A. Motti, *J. Nat. Prod.* 2011, **74**, 65. (d) C. Hohmann, K. Schneider, C. Bruntner, E. Irran, G. Nicholson, A. T. Bull, A. L. Jones, R. Brown, J. E. M. Stach, M. Goodfellow, W. Beil, M. Krämer, J. F. Imhoff, R. D Süssmuth, H.-P. Fiedler, *J. Antibiot.* 2009, **62**, 99. (e) I. I. Rodriguez, A. D. Rodriguez, Y. Wang, S. G. Franzblau, *Tetrahedron Lett.* 2006, **47**, 3229.

2 For recent reviews, see: (a) C. S. Demmer, L. Bunch, *Eur. J. Med. Chem.* 2015, **97**, 778. (b) M. K. Gautam, Sonal, N. K. Sharma, Priyanka, K. K. Jha, *Int. J. ChemTech Res.* 2012, **4**, 640. (c) B. Shrivastava, V. Sharma, P. Lokwani, *Pharmacologyonline* 2011, 236.

3 See, for most recent reports: (a) C. Yang, X. Zhi, H. Xu, *Bioorg. Med. Chem. Lett.* 2015, **25**, 2217. (b) P. Anusha, J. V. Rao, *Int. J. Pharm. Biol. Sci*. 2014, **4**, 83. (c) A. Kaur, S. Wakode, D. P. Pathak, *Int. J. Pharm. Pharm. Sci.* 2015, **7**, 16. (d) C. Yang, X. Zhi, H. Xu, *Bioorg. Med. Chem. Lett.* 2015, **25**, 2217. (e) A. Srivastava, L. Aggarwal, N. Jain, *ACS Comb. Sci*. 2015, **17**, 39.

4 L. Fu, *Top. Heterocycl. Chem.* 2012, **29**, 103.

5 (a) K. Fukukawa, M. Ueda, *J. Photopol. Sci. Technol.* 2009, **22**, 761. (b) G. A. Holmes, K. Rice, C. R. Snyder, *J. Mater. Sci.* 2006, **41**, 4105.

6 For selected reviews, see: (a) G. V. Boyd, *Science of Synthesis* 2002, **11**, 481. (b) R. V. Kumar, *Asian J. Chem.* 2004, **16**, 1241. (c) M. Schnurch, J. Hammerle, P. Stanetty, *Science of Synthesis, Knowledge Updates* 2010, 153.

7 (a) Y.-X. Chen, L.-F. Qian, W. Zhang, B. Han, *Angew. Chem., Int. Ed.* 2008, **47**, 9330. (b) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi, J. M. J. Williams, *Org. Lett.* 2009, **11**, 2039.

8 F. Su, S. C. Mathew, L. Möhlmann, M. Antonietti, X. Wang, S. Blechert, Angew. Chem., Int. Ed. 2011, **50**, 657.

9 (a) Y. Wang, K. Sarris, D. R. Sauer, S. W. Djuric, *Tetrahedron Lett*. 2006, **47**, 4823. (b) M. Terashima, M. Ishii, Y. Kanaoka, *Synthesis* 1982, 484. (c) J. A. Seijas, M. P. Vazquez-Tato, M. R. Carballido-Reboredo, J. Crecente-Campo, L. Romar-Lopez, *Synlett* 2007, 313. (d) C. O. Kangani, D. E. Kelley, B. W. Day, *Tetrahedron Lett.* 2006, **47**, 6497. (e) D. Kumar, S. Rudrawar, A. K. Chakraborti, *Austral. J. Chem.* 2008, **61**, 881.

10 C. Chen, Y.-J. Chen, *Tetrahedron Lett*. 2004, **45**, 113.

11 (a) H. J. Lim, D. Myung, I. Y. C. Lee, M. H. Jung, *J. Comb. Chem.* 2008, **10**, 501. (b) R. Kumar, C. Selvam, G. Kaur, A. K. Chakraborti, *Synlett* 2005, 1401.

12 (a) C. L. Cioffi, J. J. Lansing, H. Yuksel, *J. Org. Chem*. 2010, **75**, 7942. (b) G. Bastug, C. Eviolitte, I. E. Marko, *Org. Lett*. 2012, **14**, 3502.

13 B. L. Booth, K. O. Jibodu, M. F. Proenca, *J. Chem. Soc., Chem. Commun.* 1980, 1151.

14 P. J. Boissarie, Z. E. Hamilton, S. Lang, J. A. Murphy, C. J. Suckling, *Org. Lett*. 2011, **13**, 6256.

15 K. T. Neumann, A. T. Lindhardt, B. Bang-Andersen, T. Skrydstrup, *Org. Lett.* 2015, **17**, 2094.

16 R. D. Viirre, G. Evindar, R. A. Batey, *J. Org. Chem.* 2008, **73**, 3452.

View Article Online
DOI: 10.1039/C5RA15128G

17 (a) M. M. Guru, M. A. Ali, T. Punniyamurthy, *Org. Lett*. 2011, **13**, 1194. (b) M. M. Guru, M. A. Ali, T. Punniyamurthy, *J. Org. Chem.* 2011, **76**, 5295.
18 M. S. Klenov, A. M. Churakov, Yu. A. Strelenko, V. A. Tartakovsky, *Russ. Chem. Bull*. 2011, **60**, 2429.
19 R. A. Abramovitch, G. Alvernhe, M. N. Inbasekaran, *Tetrahedron Lett*. 1977, **18**, 1113.
20 (a) D. L. Boger, L. R. Cerbone, D. Yohannes, J. Org. Chem. 1988, **53**, 5163. (b) S. Archer, B. S. Ross, L. Pica-Mattoccia, D. Cioli, *J. Med. Chem*. 1987, **30**, 1204. (c) R. Sundaramoorthi, V. K. Kansal, B. C. Das, P. Potier, *J. Chem. Soc., Chem. Commun.* 1986, 371. (d) Y. Girard, P. Hamel, M. Therien, J. P. Springer, J. Hirshfield, *J. Org. Chem.* 1987, **52**, 4000. (e) V. K. Kansal, R. Sundaramoorthi, B. C. Das, P. Potier, *Tetrahedron Lett.* 1985, **26**, 4933.
21 (a) Y. Yamagishi, H. Ashigai, Y. Goto, H. Murakami, H. Suga, *ChemBioChem* 2009, **10**, 1469. (b) Abdelghani, Essam; A. Abd El-Aal, W. Shehab, M. El-Mobayed, *Synthesis* 2003, 1373.
22 (a) A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, I. V. Aksenova, L. V. Frolova, A. Kornienko, I. V. Magedov, M. Rubin, *Chem. Commun.* 2013, **49**, 9305. (b) A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, I. V. Aksenova, A. S. Bijieva, M. Rubin, *Org. Biomol. Chem.* 2014, **12**, 9786. (c) A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, I. V. Aksenova, J. P. Matheny, M. Rubin, *RSC Adv.* 2015, **5**, 8647. (d) A. V. Aksenov, A. N. Smirnov, I. V. Magedov, M. R. Reisenauer, N. A. Aksenov, I. V. Aksenova, A. L. Pendleton, G. Nguyen, R. K. Johnston, M. Rubin, A. De Carvalho, R. Kiss, V. Mathieu, F. Lefranc, J. Correa, D. A. Cavazos, A. J. Brenner, B. A. Bryan, S. Rogelj, A. Kornienko, L. Frolova, *J. Med. Chem*. 2015, **58**, 2206.
23 A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, A. S. Bijieva, I. V. Aksenova, M. Rubin, *Org. Biomol. Chem.* 2015, **13**, 4289.
24 (a) A. V. Aksenov, N. A. Aksenov, O. N. Nadein, I. V. Aksenova, *Synlett* 2010, 2628. (b) A. V. Aksenov, N. A. Aksenov, O. N. Nadein, I. V. Aksenova, *Chem. Heterocycl. Comp.* 2011, **46**, 1405.
25 Such stepwise increase of temperature was necessary to ensure high reaction efficiency. Several attempts to carry out the process maintaining 135 ^{o}C throughout the whole period of the transformation resulted in notably lower yields of the target heterocyclic products.
26 For recent reviews, see: M. A. Saeed, H. T. M. Le, O. S. Miljanic, *Acc. Chem. Res.* 2014, **47**, 2074. (b) A. Facchetti, *Chem. Mater.* 2011, **23**, 733.
27 J. J. Lee, J. Kim, Y. M. Jun, B. M. Lee, B. H. Kim, *Tetrahedron* 2009, **65**, 8821.
28 M. Anand, A. Ranjitha, M. Himaja, *Int. Res. J. Pharm.* 2011, **2**, 211.
29 S. Ueda, H. Nagasawa, *Angew. Chem., Int. Ed.* 2008, **47**, 6411.
30 L. Ackermann, S. Barfuesser, J. Pospech, *Org. Lett.* 2010, **12**, 724.
31 M. Lozynski, E. Krzyzanowska, D. Matecka, *Pol. J. Chem.* 1990, **64**, 93.
32 P. V. Guerra, V. A. Yaylayan, *Food Chem.* 2013, **141**, 4391.
33 T. Fujimoto, T. Ritter, *Org. Lett.* 2015, **17**, 544.
34 S. Fujita, K. Koyama, Y. Inagaki, *Synthesis* 1982, 68.
35 J.-L. Pozzo, V. A. Lokshin, R. Guglielmetti, *J. Chem. Soc., Perkin Trans. 1* 1994, 2591.
36 J. F. Mike, A. J. Makowski, M. Jeffries-El, *Org. Lett.* 2008, **10**, 4915.

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One-pot synthesis of benzoxazoles via the metal-free *ortho*-C-H functionalization of phenols with nitroalkanes†

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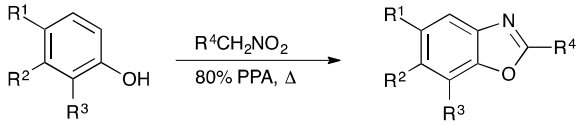
Graphical Abstract



Abstract: PPA-activated nitroalkanes are employed in the design of a one-pot cascade transformation involving ortho-C-H functionalization, by Beckman rearrangment, and condensation to produce benzoxazoles and benzobisoxazoles directly from easily available phenols.