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Does electrophilic activation of nitroalkanes in polyphosphoric acid involve formation of nitrile oxides?†

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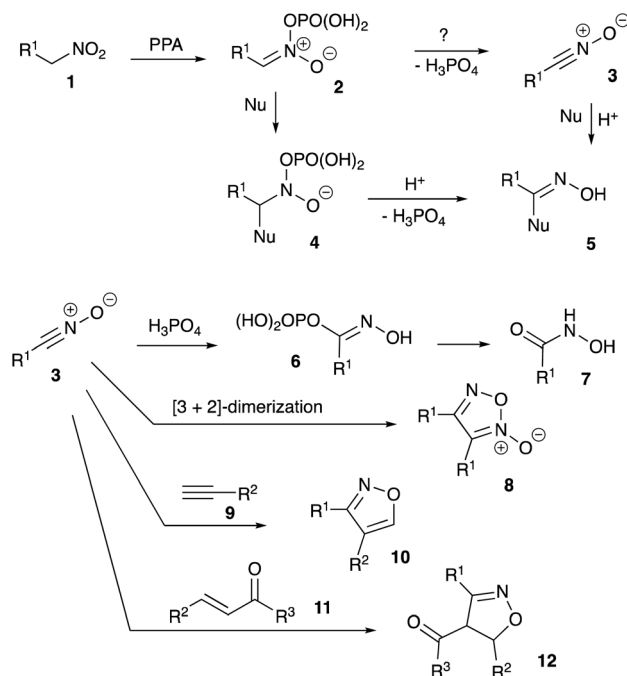
The mechanistic rationale involving activation of nitroalkanes towards interaction with nucleophilic reagents in the presence of polyphosphoric acid (PPA) was re-evaluated. Could nitrile oxide moieties be formed during this process? This experiment demonstrates that at least in some cases this could happen, as generated nitrile oxides were successfully intercepted as adducts of [3 + 2] cycloadditions.

Introduction

Nitroalkanes possessing acidic α -CH bonds are traditionally employed as versatile nucleophilic components in a variety of base-assisted C–C bond-forming reactions.^{1–8} Another mode of activation of nitroalkanes enables acid-promoted tautomerization into nitronic acid (*aci* form), which is electrophilic in nature and can interact with a number of nucleophiles. In aqueous media, facile acid-assisted reaction with water takes place, commonly known as the Nef reaction,^{9–12} resulting in the formation of aldehydes. In anhydrous media, alternative reactivity patterns are possible, involving interaction with various C- and N-based nucleophiles. Over the last decade, our group has been instrumental in the development of multistep cascade transformations triggered by initial electrophilic activation of nitroalkanes in the presence of polyphosphoric acid (PPA).^{13–17} Proposed mechanistic rationales for all these processes involve formation of a phosphorylated nitronate species as a key electrophilic intermediate. Herein, we wish to disclose our recent studies proving that formation of nitrile oxide species is also possible under the same conditions. This suggests that alternative mechanisms could be potentially considered, at least for some of the earlier described processes.

Results and discussion

As discussed above, it was previously stated that interaction of nitroalkane **1** with PPA leads to the formation of electrophilic nitronate species **2**, enabling subsequent reactions with various nucleophiles. The resulting phosphorylated *N*-hydroxy-*N*-alkyl hydroxylamine **4** may undergo further elimination of the *ortho*-phosphoric acid molecule to afford species **5** (oximes or amidines resulting from reaction with carbon or nitrogen-based nucleophiles, respectively, Scheme 1). Oximes **5** (Nu = Ar), as



Scheme 1

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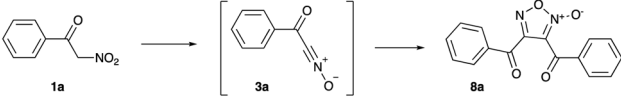
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Table 1 Optimization of the reaction conditions for generation of nitrile oxide **3a** and its subsequent dimerization into furoxan **8a**

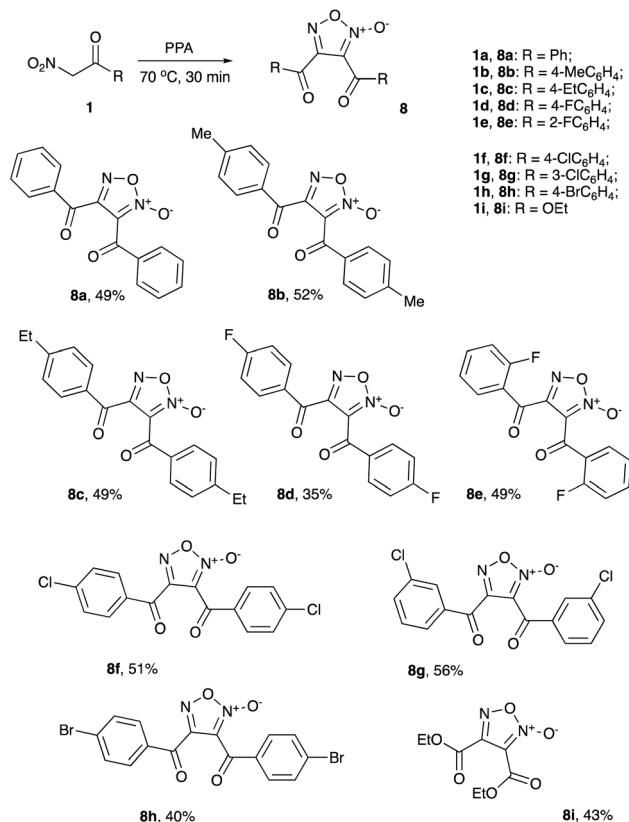
				
	Medium	m (PPA) per mmol of 1a (g)	T, °C (time, h)	Yield ^a , %
1	PPA, 80%	1.5	50 (2)	23
2		2	50 (2)	30
3	PPA, 87%	2	50 (2)	33
4		2	70 (0.5)	51
5		2	90 (0.3)	25

^a NMR yields are reported.

was previously demonstrated, may participate in Beckmann-type rearrangements, which was employed in acetamidation and carboxyamination reactions.^{18,19} Generation of amidines **5** (Nu = NHR) were utilized in design of cascade transformations leading to various heterocyclic scaffolds.^{13,20,21} We pondered if elimination of H₃PO₄ entity can take place in species **2** to form nitrile oxide **3** under the described reaction conditions.²² This species is also inherently electrophilic and reactions with nucleophiles should provide the same type of product **5** (Scheme 1).

Furthermore, reaction of **3** with *ortho*-phosphoric acid in the absence of other nucleophiles could be envisioned, producing *N*-hydroxyalkanimidic phosphoric anhydride **6**, which after hydrolytic cleavage, should provide hydroxamic acid **7**. It should be noted that the isomerization of nitroalkanes into hydroxamic acids taking place in the presence of PPA is well documented.²³ On the other hand, in most typical reactions nitrile oxides act as 1,3-dipoles. If nitrile oxides are indeed generated from nitroalkanes in the presence of PPA, then in the absence of external dipolarophiles, they should undergo [3 + 2]-dimerization to provide 1,2,5-oxadiazole 2-oxides (furoxans) **8** (Scheme 1). Alternatively, cross-cycloaddition reactions with alkynes **9** and chalcones **11** could be performed to generate isoxazoles **10** or 4,5-dihydroisoxazoles **12**, respectively (Scheme 1).

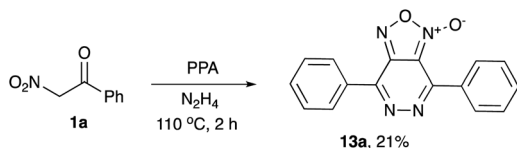
First, we attempted to conduct the experiment involving interaction of 1-nitropropane (**1**, R¹ = Et, Scheme 1) with PPA in the absence of any other reagents by targeting detection for furoxan **8** (R¹ = Et) resulting from [3 + 2]-homodimerization. However, formation of such product was not detected, as almost the entire amount of starting nitroalkane was transformed into *N*-hydroxypropionamide **7** (R¹ = Et).²⁴ Evidently, even if formed under the described reaction conditions, propionitrile oxide (**3**, R¹ = Et) is much too reactive and quickly interacts with the medium. To address this issue, we decided to test the same idea by employing 2-nitro-1-phenylethan-1-one (**1a**), producing greater concentration of *aci*-form, which should translate in higher concentration of benzoyl cyanide *N*-oxide (**3a**). Therefore, this starting material should be more prompt towards the desired dimerization reaction.



Scheme 2

Initial tests were carried out in PPA with 80% content of P₂O₅ (corresponding to diphosphoric acid, H₄P₂O₇). A mixture of **1a** (1 mmol) with PPA (1.5 g) was stirred and heated at 50 °C for 2 hours, stopping only after TLC analysis proved complete consumption of starting material. Delightfully, some nitroalkane was indeed converted into furoxan **8a**, albeit in marginal yield (Table 1, entry 1). Increasing the amount of PPA (2.0 g) improved the yield, though not significantly (entry 2). We thought that switching to 87% PPA might enhance the reaction performance, since this medium has less nominal content of water and thus less nucleophilic; however, the reaction proceeded sluggishly and at 50 °C, the yield of **8a** was essentially the same as in 80% PPA (entry 3). Further improvement was achieved upon heating to a higher temperature, which also allowed to cut down reaction time. At 70 °C, a maximum yield of 51% was obtained (entry 4) and further increases of temperature proved detrimental (entry 5). The purified product **8a** was isolated in a 46% yield (Scheme 2). With optimized reaction conditions in hand, we moved towards scope and limitation studies, the results of which are shown in Scheme 2. Generally, the reactions of substituted 2-nitro-1-phenylethan-1-ones **1b–h** proceeded smoothly, well tolerating alkyl and aromatic halide substituents and affording the corresponding furoxans in moderate yields. We also managed to execute successful transformations of ethyl 2-nitroacetate (**1i**) into furoxan **8i**, bearing two ester functions under the same reaction conditions (Scheme 2).



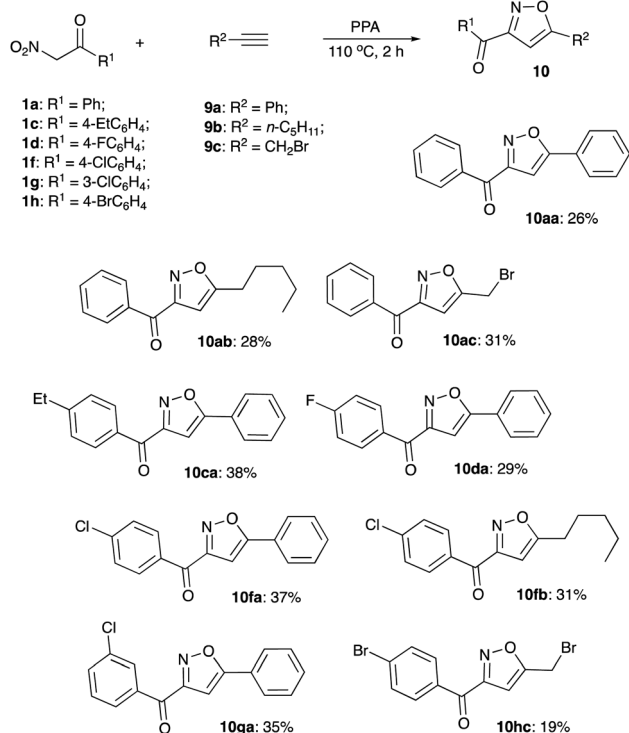


The possibility for a one-pot assembly of a bicyclic structural core, including a furoxan moiety fused to pyridazine ring, was also evaluated. To this end, nitroketone **1a** was treated with PPA in the presence of hydrazine hydrate. The bicyclic structure **13a** was formed as a sole isolable product, although in low quantities (Scheme 3).

Next, we decided to explore the possibility to intercept the nitrile oxides generated from nitroalkanes with external dipolarophiles, such as terminal acetylenes. Treatment of various nitroalkanes with PPA was carried out in the presence of phenyl acetylene (**9a**), 1-heptyne (**9b**), or propargyl bromide (**9c**) to yield the desired isoxazoles **10** (Scheme 4). Formation of isoxazole **10da** was unambiguously confirmed by single crystal X-ray crystallography (Fig. 1).

This reaction cannot be recommended as a preparative protocol towards these materials, since most amount of nitroalkanes were converted into the corresponding hydroxamic acids. Despite that, it clearly confirms that nitrile oxides were indeed generated under the described reaction conditions.

Interception of nitrile oxides with alkenes were tested as well. Reaction of **1a** in the presence of chalcone **11a** gave nearly



Scheme 4

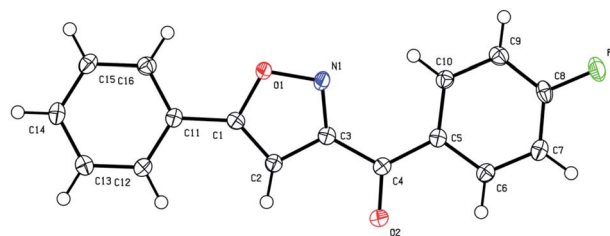
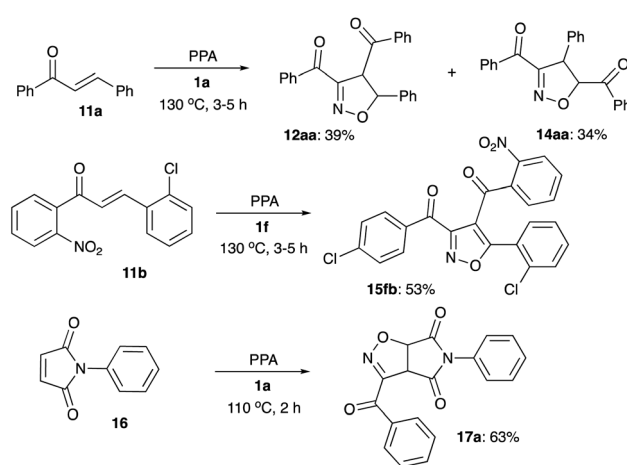


Fig. 1 ORTEP drawing of X-ray structures of (4-fluorophenyl)(5-phenylisoxazol-3-yl)methanone (**10da**, CCDC #2099762†). The thermal ellipsoids are shown at 50% probability.

an equimolar mixture of regioisomeric dihydroisoxazoles **12aa** and **14aa**, formation of which are most likely controlled by electronic and steric factors, respectively (Scheme 5). Reaction of **1f** in the presence of chalcone **11b**, with enhanced polarization of double bond, resulted in perfect electronically-controlled regiochemistry, but was accompanied by oxidative aromatization of the cycloaddition product **15fb** (Scheme 5). Finally, reaction of **1a** in the presence of malonic imide **16** proceeded smoothly, providing bicyclic imide **17a** in good yield (Scheme 5).

Since the yields obtained were quite moderate, we decided to investigate the material balance by tracing the byproducts formed in dimerization reactions towards furoxans **8** (Scheme 2). Initially we thought we will be dealing with hydroxamic acids **7**, however, benzamides **18** (sometimes in a mixture with benzoic acids **19**) were observed and isolated instead. Evidently, under the listed reaction conditions hydroxamic acids **7** undergo facile Lossen rearrangement or competing hydrolysis as shown in Scheme 6. It is believed, that *O*-phosphorylated hydroxamic acid **6** (initially formed after nucleophilic attack on nitrile oxide **2** with *ortho*-phosphoric acid as shown in Scheme 1, *vide infra*) could be re-esterified to afford NO-phosphorylated form **20**. The later would undergo Lossen rearrangement into benzoyl isocyanate **21**, which can be hydrolyzed with extrusion of isocyanic acid and formation of benzoic acid **19** (Scheme 6). More commonly, an alternative pathway was operating,



Scheme 5





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7.65 (m, 2H), 7.60–7.49 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 182.2, 180.9, 154.8, 135.9, 135.8, 134.3, 134.3, 131.0 (2C), 130.1 (2C), 129.7 (2C), 129.5 (2C), 112.1. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 1735, 1684, 1602, 1559, 1455, 1419, 1325, 1246, 1178, 1101. HRMS (ES TOF) calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 317.0533, found 317.0532 (0.4 ppm).

Benzamide (**18a**)²⁸ was also isolated from the same reaction mixture as colorless solid. Yield 53 mg (0.44 mmol, 44%). ^1H NMR (400 MHz, CDCl_3) δ 7.84 (dt, $J = 7.1, 1.4$ Hz, 2H), 7.59–7.50 (m, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 6.35 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 133.8, 132.4, 129.1 (2C), 127.8 (2C).

3,4-Bis(4-methylbenzoyl)-1,2,5-oxadiazole 2-oxide (8b). Product **8b** was obtained *via* the method described for compound **8a**, employing 2-nitro-4'-methylacetophenone **1b**²⁷ (179 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE 1 : 5). Yellow solid, mp 118–119.5 °C (EtOH), lit²⁹ mp 124 °C (EtOH); yield 83 mg (0.26 mmol, 52%). R_f 0.46, EtOAc/hexane (1 : 5, v/v). ^1H NMR (400 MHz, CDCl_3) δ 8.11 (d, $J = 8.3$ Hz, 2H), 7.76 (d, $J = 8.3$ Hz, 2H), 7.33 (dd, $J = 13.4, 8.3$ Hz, 4H), 2.45 (d, $J = 10.1$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 181.3, 180.0, 154.6, 147.0, 146.8, 131.5, 131.4, 130.7 (2C), 130.0 (2C), 129.9 (2C), 129.8 (2C), 111.9, 22.0 (2C). IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 1675, 1646, 1600, 1470, 1328, 1251, 1181, 1123, 1104. HRMS (ES TOF) calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 345.0846, found 345.0840 (1.7 ppm).

4-Methylbenzamide (**18b**)²⁸ was also isolated from the same reaction mixture as colorless solid. Yield 28 mg (0.21 mmol, 21%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.90 (s, 1H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.29 (s, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 167.8, 141.1, 131.5, 128.8 (2C), 127.6 (2C), 21.0.

3,4-Bis(4-ethylbenzoyl)-1,2,5-oxadiazole 2-oxide (8c). Product **8c** was obtained *via* the method described for compound **8a**, employing 2-nitro-4'-ethylacetophenone **1c** (193 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Colorless oil, R_f 0.60, EtOAc/hexane (1 : 5, v/v). Yield 86 mg (0.25 mmol, 49%). ^1H NMR (400 MHz, CDCl_3) δ 8.18–8.07 (m, 2H), 7.83–7.70 (m, 2H), 7.36 (dd, $J = 13.6, 8.1$ Hz, 4H), 2.75 (dq, $J = 9.8, 7.6$ Hz, 4H), 1.28 (q, $J = 7.8$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 181.5, 180.1, 154.7, 153.2, 152.9, 131.8, 131.7, 131.0 (2C), 130.1 (2C), 128.9 (2C), 128.7 (2C), 112.1, 29.4, 29.3, 15.1, 15.1. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 2964, 2877, 1733, 1595, 1460, 1427, 1383, 1337, 1272, 1147, 1096. HRMS (ES TOF) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 373.1159, found 373.1151 (2.0 ppm).

3,4-Bis(4-fluorobenzoyl)-1,2,5-oxadiazole 2-oxide (8d). Product **8d** was obtained *via* the method described for compound **8a**, employing 2-nitro-4'-fluoroacetophenone **1d**²⁷ (183 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Yellow oil, R_f 0.53, EtOAc/hexane (1 : 5, v/v). Yield 58 mg (0.18 mmol, 35%). ^1H NMR (400 MHz, CDCl_3) δ 8.40–8.34 (m, 2H), 8.03–7.97 (m, 2H), 7.32 (m, $J = 11.1, 8.4$ Hz, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 180.2, 178.9, 167.30 (d, $J = 259.7$ Hz), 167.28 (d, $J = 259.3$ Hz), 154.3, 133.7 (d, $J = 9.9$ Hz, 2C), 132.8 (d, $J = 10.3$ Hz, 2C), 130.3 (d, $J = 2.9$ Hz), 130.2 (d, $J = 2.9$ Hz), 116.9 (d, $J = 22.4$ Hz, 2C), 116.6 (d, $J = 22.0$ Hz, 2C), 111.7. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 1769, 1684, 1663, 1593, 1508, 1472, 1414,

1325, 1236, 1157, 1101. HRMS (ES TOF) calcd for $\text{C}_{16}\text{H}_8\text{F}_2\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 353.0344, found 353.0338 (1.7 ppm).

4-Fluorobenzamide (**18b**)²⁸ was also isolated from the same reaction mixture as colorless solid. Yield 36 mg (0.26 mmol, 26%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.01 (s, 1H), 7.97–7.87 (m, 2H), 7.41 (s, 1H), 7.32–7.19 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.0 (d, $J = 164.9$ Hz), 162.7, 130.8 (d, $J = 3.0$ Hz), 130.2 (d, $J = 9.0$ Hz, 2C), 115.2 (d, $J = 21.6$ Hz, 2C).

3,4-Bis(2-fluorobenzoyl)-1,2,5-oxadiazole 2-oxide (8e). Product **8e** was obtained *via* the method described for compound **8a**, employing 2-nitro-2'-fluoroacetophenone **1e**²⁶ (183 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE 1 : 4). Yellow oil, R_f 0.32, EtOAc/hexane (1 : 4, v/v). Yield 81 mg (0.25 mmol, 49%). ^1H NMR (400 MHz, CDCl_3) δ 7.92 (td, $J = 7.8, 1.8$ Hz, 1H), 7.82 (td, $J = 7.4, 1.8$ Hz, 1H), 7.70–7.61 (m, 2H), 7.36–7.29 (m, 2H), 7.17 (m, $J = 25.1, 11.0, 8.4, 1.2$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 180.1, 177.1, 162.0 (d, $J = 259.0$ Hz), 161.6 (d, $J = 256.4$ Hz), 154.4, 136.8 (d, $J = 7.6$ Hz), 136.7 (d, $J = 7.4$ Hz), 131.5, 131.1, 125.2 (d, $J = 3.3$ Hz), 124.8 (d, $J = 3.7$ Hz), 123.4 (d, $J = 10.3$ Hz), 123.2 (d, $J = 11.0$ Hz), 117.0 (d, $J = 21.6$ Hz), 116.6 (d, $J = 22.0$ Hz), 112.7. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 1655, 1602, 1458, 1439, 1330, 1238, 1181, 1159, 1099, 1041. HRMS (ES TOF) calcd for $\text{C}_{16}\text{H}_8\text{F}_2\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 353.0344, found 353.0334 (3.0 ppm).

3,4-Bis(4-chlorobenzoyl)-1,2,5-oxadiazole 2-oxide (8f). Product **8f** was obtained *via* the method described for compound **8a**, employing 2-nitro-4'-chloroacetophenone **1f**²⁷ (199 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE 1 : 4). Colorless solid, mp 120–121 °C (EtOH), lit³⁰ mp 124 °C; R_f 0.57, EtOAc/hexane (1 : 6, v/v). Yield 92 mg (0.25 mmol, 51%). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 8.7$ Hz, 2H), 7.80 (d, $J = 8.6$ Hz, 2H), 7.53 (m, $J = 12.0, 8.7$ Hz, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 180.5, 179.2, 154.0, 142.41, 142.39, 132.01, 132.00, 131.9 (2C), 131.0 (2C), 129.8 (2C), 129.5 (2C), 111.4. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 1773, 1682, 1610, 1586, 1472, 1405, 1323, 1243, 1176, 1089. HRMS (ES TOF) calcd for $\text{C}_{16}\text{H}_8\text{Cl}_2\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 384.9753, found 384.9760 (−1.8 ppm).

4-Chlorobenzamide (**18f**)²⁸ and 4-chlorobenzoic acid (**19f**)³¹ were also isolated from the same reaction mixture as colorless solid. **18f**: yield 25 mg (0.16 mmol, 16%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.06 (br. s, 1H), 7.93–7.84 (m, 2H), 7.55–7.50 (m, 2H), 7.49 (br. s, 1H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 166.9, 136.1, 133.1, 129.5 (2C), 128.4 (2C). **19f**: yield 41 mg (0.26 mmol, 26%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.19 (br. s, 1H), 7.93 (d, $J = 8.6$ Hz, 2H), 7.55 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 166.5, 137.8, 131.2 (2C), 129.7, 128.8 (2C).

3,4-Bis(3-chlorobenzoyl)-1,2,5-oxadiazole 2-oxide (8g). Product **8g** was obtained *via* the method described for compound **8a**, employing 2-nitro-3'-chloroacetophenone **1g**²⁷ (199 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Yellow oil; R_f 0.49, EtOAc/hexane (1 : 4, v/v). Yield 102 mg (0.28 mmol, 56%). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (m, $J = 1.9$ Hz, 1H), 8.12 (m, $J = 7.8, 1.4$ Hz, 1H), 7.84 (m, $J = 1.9$ Hz, 1H), 7.73–7.64 (m, 3H), 7.50 (m, $J = 15.8, 7.9$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 180.5, 179.2, 153.8, 135.8, 135.50, 135.46, 135.3, 135.2, 135.11, 130.6, 130.4, 130.3, 129.4, 128.7, 127.8, 111.1. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 1754, 1687, 1614, 1571, 1467, 1419,

1323, 1236, 1079. HRMS (ES TOF) calcd for $C_{16}H_8Cl_2N_2NaO_4$ ($[M + Na]^+$): 384.9753, found 384.9762 (−2.2 ppm).

3,4-Bis(4-bromobenzoyl)-1,2,5-oxadiazole 2-oxide (8h). Product **8h** was obtained *via* the method described for compound **8a**, employing 2-nitro-4'-bromoacetophenone **1h**²⁷ (244 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Yellowish solid, mp 135.9–136.7 °C (EtOAc), R_f 0.57, EtOAc/hexane (1 : 4, v/v). Yield 90 mg (0.20 mmol, 40%). ¹H NMR (400 MHz, CDCl₃) δ 8.12–8.05 (m, 2H), 7.76–7.64 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 180.7, 179.4, 154.0, 132.7 (2C), 132.5 (2C), 132.4 (2C), 131.9 (2C), 131.3 (2C), 131.0 (2C), 111.3. IR, ν_{max}/cm^{-1} : 928, 1012, 1067, 1173, 1212, 1251, 1325, 1395, 1467, 1581, 1612, 1655, 1689, 3089. HRMS (ES TOF) calcd for $C_{16}H_8Br_2N_2NaO_4$ ($[M + Na]^+$): 472.8743, found 472.8741 (0.4 ppm).

4-Bromobenzamide (18h)²⁸ was also isolated from the same reaction mixture as colorless solid. Yield 56 mg (0.28 mmol, 28%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (s, 1H), 7.84–7.78 (m, 2H), 7.70–7.63 (m, 2H), 7.48 (s, 1H). ¹³C NMR (101 MHz, DMSO) δ 167.4, 133.8, 131.7 (2C), 130.1 (2C), 125.5.

3,4-Bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-oxide (8i). Product **8i** was obtained *via* the method described for compound **8a**, employing ethyl nitroacetate (133 mg, 1.00 mmol), and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Colorless oil, R_f 0.46, EtOAc/hexane (1 : 4, v/v). Yield 49 mg (0.21 mmol, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.45 (qd, $J = 7.1$, 1.0 Hz, 2H), 4.36 (qd, $J = 7.1$, 1.1 Hz, 2H), 1.33 (td, $J = 7.1$, 1.0 Hz, 3H), 1.27 (td, $J = 7.1$, 1.1 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 156.5, 154.8, 148.8, 107.4, 63.5, 63.1, 13.72, 13.7. IR, ν_{max}/cm^{-1} : 2988, 1742, 1619, 1472, 1373, 1335, 1246, 1195, 1063, 1022. HRMS (ES TOF) calcd for $C_8H_{10}N_2NaO_6$ ($[M + Na]^+$): 253.0431, found 253.0426 (2.1 ppm).

Procedure for preparation of cyclization products of hydrazine hydrate with 2-nitroethan-1-one, 4,7-diphenyl-[1,2,5]oxadiazolo[3,4-*d*]pyridazine-1-oxide (13a). 2-Nitroacetophenone **1a** (165 mg, 1.00 mmol), hydrazine monohydrate (65% solution in water, 154 mg, 150 μ L, 2.00 mmol) were added to 2 g of 87% polyphosphoric acid. The mixture was stirred at 110 °C for 2 h and then diluted with water (40 mL) and quenched with aqueous ammonia (20% solution in H₂O, 15 mL). Reaction mixture was extracted with ethyl acetate (4 \times 15 mL). Combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: EtOAc : PE, 1 : 4 v/v) affording the titled product as orange solid, mp 199–201 °C (EtOAc), lit³⁰ mp 210 °C; R_f 0.44, EtOAc/hexane (1 : 4, v/v). Yield 31 mg (0.11 mmol, 21%). ¹H NMR (400 MHz, CDCl₃) δ 8.68–8.60 (m, 2H), 8.00–7.90 (m, 2H), 7.68–7.56 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 150.4, 148.3, 145.1, 132.6, 131.9, 131.8, 130.3, 129.6 (2C), 129.3 (2C), 129.2 (2C), 128.7 (2C), 106.9. IR, ν_{max}/cm^{-1} : 2974, 2882, 1600, 1508, 1460, 1429, 1388, 1263, 1147, 1089, 1048. HRMS (ES TOF) calcd for $C_{16}H_{10}N_4NaO_2$ ($[M + Na]^+$): 313.0696, found 313.0691 (1.7 ppm).

5-Phenyl-3-benzoylisoxazole. General method for synthesis of isoxazoles (10aa). 2-Nitroacetophenone **1a**²⁷ (165 mg, 1.00 mmol) and phenylacetylene **9a** (102 mg, 1.00 mmol) were added to 2.0 g of 87% polyphosphoric acid. The mixture was stirred at

110 °C for 2 h and then diluted with water (40 mL) and quenched with aqueous ammonia (20% solution in H₂O, 15 mL). Reaction mixture was extracted with ethyl acetate (4 \times 15 mL). Combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: benzene/hexane, 1 : 2 v/v) to afford the titled compound as yellowish solid, mp 85.4–86 °C (EtOH), lit³² mp 88–90 °C, R_f 0.46, benzene/hexane (1 : 2, v/v). Yield 65 mg (0.26 mmol, 26%). ¹H NMR (400 MHz, CDCl₃) δ 8.38–8.32 (m, 2H), 7.86 (m, $J = 7.8$, 1.9 Hz, 2H), 7.67 (m, $J = 7.4$ Hz, 1H), 7.53 (m, $J = 17.5$, 7.9 Hz, 5H), 7.06 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 185.9, 170.8, 162.4, 135.8, 134.1, 130.8, 130.7 (2C), 129.2 (2C), 128.6 (2C), 126.7, 126.0 (2C), 100.3. IR, ν_{max}/cm^{-1} : 1655, 1598, 1573, 1451, 1426, 1236, 1181, 1147, 1101, 1075. HRMS (ES TOF) calcd for $C_{16}H_{11}NNaO_2$ ($[M + Na]^+$): 272.0682, found 272.0678 (1.3 ppm).

5-Pentyl-3-benzoylisoxazole (10ab). Product **10ab** was obtained *via* the method described for compound **10aa**, employing 2-nitroacetophenone **1a**²⁷ (165 mg, 1.00 mmol) and hept-1-yne **9b** (96 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc/PE 1 : 4). Colorless oil; R_f 0.72, EtOAc/hexane (1 : 4, v/v). Yield 68 mg (0.28 mmol, 28%). ¹H NMR (400 MHz, CDCl₃) δ 8.33–8.26 (m, 2H), 7.67–7.61 (m, 1H), 7.54–7.48 (m, 2H), 6.52 (s, 1H), 2.86–2.80 (m, 2H), 1.80–1.71 (m, 2H), 1.42–1.34 (m, 4H), 0.95–0.89 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 185.2, 173.8, 160.8, 134.9, 132.9, 129.6 (2C), 127.5 (2C), 100.6, 30.1, 26.1, 25.6, 21.3, 12.9. IR, ν_{max}/cm^{-1} : 2930, 1774, 1660, 1602, 1455, 1434, 1258, 1239, 1181, 1104. HRMS (ES TOF) calcd for $C_{15}H_{17}NNaO_2$ ($[M + Na]^+$): 266.1151, found 266.1145 (2.6 ppm).

5-(Bromomethyl)-3-benzoylisoxazole (10ac). Product **10ac** was obtained *via* the method described for compound **10aa**, employing 2-nitroacetophenone **1a**²⁷ (165 mg, 1.00 mmol) and propargyl bromide **9c** (119 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc/PE 1 : 4). Yellow solid, mp 62–65 °C; R_f 0.73, EtOAc/hexane (1 : 4, v/v). Yield 82 mg (0.31 mmol, 31%). ¹H NMR (400 MHz, CDCl₃) δ 8.31–8.28 (m, 2H), 7.68–7.63 (m, 1H), 7.55–7.50 (m, 2H), 6.85 (d, $J = 0.6$ Hz, 1H), 4.54 (d, $J = 0.6$ Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 185.3, 168.5, 162.3, 135.6, 134.4, 130.8 (2C), 128.8 (2C), 104.9, 18.1. IR, ν_{max}/cm^{-1} : 3152, 2959, 1766, 1645, 1599, 1578, 1452, 1291, 1224, 1187, 999. HRMS (ES TOF) calcd for $C_{11}H_8BrNaNO_2$ ($[M + Na]^+$): 287.9631, found 287.9624 (2.2 ppm).

3-(4-Ethylbenzoyl)-5-phenylisoxazole (10ca). Product **10ca** was obtained *via* the method described for compound **10aa**, employing 2-nitro-4'-ethylacetophenone **1c** (193 mg, 1.00 mmol) and phenylacetylene **9a** (102 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc : PE 1 : 4). White solid, mp 84–85 °C (EtOH), R_f 0.49, benzene/hexane (1 : 2, v/v). Yield 105 mg (0.38 mmol, 38%). ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, $J = 8.3$ Hz, 2H), 7.85 (dd, $J = 7.8$, 1.8 Hz, 2H), 7.55–7.47 (m, 3H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.04 (s, 1H), 2.75 (q, $J = 7.6$ Hz, 2H), 1.29 (t, $J = 7.6$ Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 184.4, 169.6, 161.6, 150.3, 132.4, 129.9 (2C), 129.7, 128.1 (2C), 127.2 (2C), 125.8, 125.0 (2C), 99.3, 28.1, 14.1. IR, ν_{max}/cm^{-1} : 2964, 1653, 1602, 1566, 1439, 1296, 1255, 1183, 1151, 1046. HRMS (ES TOF)



calcd for $C_{18}H_{15}NNaO_2$ ($[M + Na]^+$): 300.0995, found 300.0997 (−0.6 ppm).

3-(4-Fluorobenzoyl)-5-phenylisoxazole (10da). Product **10da** was obtained *via* the method described for compound **10aa**, employing 2-nitro-4'-fluoroacetophenone **1d**²⁷ (183 mg, 1.00 mmol) and phenylacetylene **9a** (102 mg, 1.00 mmol) and purified by column chromatography (eluent benzene/hexane, 1 : 2 v/v). White solid, mp 111–113 °C (EtOH), lit³² mp 112–114 °C; yield 77 mg (0.29 mmol, 29%). R_f 0.49, benzene/hexane (1 : 2, v/v). 1H NMR (400 MHz, $CDCl_3$) δ 8.48–8.39 (m, 2H), 7.89–7.82 (m, 2H), 7.55–7.48 (m, 3H), 7.25–7.18 (m, 2H), 7.05 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0, 169.9, 165.4 (d, J = 256.8 Hz), 161.4, 132.5 (d, J = 9.5 Hz, 2C), 131.1 (d, J = 2.8 Hz), 129.8, 128.2, 125.6, 125.0, 114.8 (d, J = 21.6 Hz, 2C), 99.2. IR, ν_{max}/cm^{-1} : 3133, 1655, 1600, 1506, 1441, 1296, 1251, 1231, 1147, 1104. HRMS (ES TOF) calcd for $C_{16}H_{10}FNNaO_2$ ($[M + Na]^+$): 290.0588, found 290.0582 (1.9 ppm).

3-(4-Chlorobenzoyl)-5-phenylisoxazole (10fa). Product **10fa** was obtained *via* the method described for compound **10aa**, employing 2-nitro-4'-chloroacetophenone **1f**²⁷ (199 mg, 1.00 mmol) and phenylacetylene **9a** (102 mg, 1.00 mmol) and purified by column chromatography (eluent benzene/hexane, 1 : 2 v/v). Yellowish solid, mp 139–141 °C (EtOH), lit³² mp 143–145 °C; R_f 0.49, benzene/hexane (1 : 2, v/v). Yield 105 mg (0.37 mmol, 37%). 1H NMR (400 MHz, $CDCl_3$) δ 8.38–8.30 (d, 2H), 7.85 (dd, J = 7.6, 2.0 Hz, 2H), 7.51 (m, J = 8.4, 2.0 Hz, 5H), 7.05 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.4, 169.9, 161.3, 139.7, 133.0, 131.1 (2C), 129.8, 128.2 (2C), 127.9 (2C), 125.6, 125.0 (2C), 99.2. IR, ν_{max}/cm^{-1} : 3133, 3060, 1930, 1884, 1648, 1588, 1443, 1395, 1251, 1181, 1089. HRMS (ES TOF) calcd for $C_{16}H_{10}ClNNaO_2$ ($[M + Na]^+$): 306.0292, found 306.0295 (−0.9 ppm).

3-(4-Chlorobenzoyl)-5-pentylisoxazole (10fb). Product **10fb** was obtained *via* the method described for compound **10aa**, employing 2-nitro-4'-chloroacetophenone **1f**²⁷ (199 mg, 1.00 mmol) and hept-1-yne **9b** (96 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Colorless oil; R_f 0.74, EtOAc/hexane (1 : 4, v/v). Yield 86 mg (0.31 mmol, 31%). 1H NMR (400 MHz, $CDCl_3$) δ 8.33–8.28 (m, 2H), 7.53–7.47 (m, 2H), 6.55 (s, 1H), 2.86 (t, J = 7.6 Hz, 2H), 1.83–1.75 (m, 2H), 1.44–1.35 (m, 4H), 0.95–0.92 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 175.1, 161.9, 140.7, 134.3, 132.2 (2C), 129.0 (2C), 101.8, 31.3, 27.3, 26.7, 22.4, 14.0. IR, ν_{max}/cm^{-1} : 2935, 2853, 1923, 1665, 1590, 1455, 1400, 1255, 1210, 1178, 1096. HRMS (ES TOF) calcd for $C_{15}H_{16}ClNNaO_2$ ($[M + Na]^+$): 300.0762, found 300.0760 (0.7 ppm).

3-(3-Chlorobenzoyl)-5-phenylisoxazole (10ga). Product **10ga** was obtained *via* the method described for compound **10aa**, employing 2-nitro-3'-chloroacetophenone **1g**²⁷ (199 mg, 1.00 mmol) and phenylacetylene **9a** (102 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc/PE 1 : 4). Colorless solid, mp 117–117.5 °C (EtOH); R_f 0.46, benzene/hexane (1 : 2, v/v). Yield 99 mg (0.35 mmol, 35%). 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (t, J = 2.0 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.85 (m, J = 7.8, 2.0 Hz, 2H), 7.63 (m, J = 8.1, 2.2, 1.1 Hz, 1H), 7.54–7.48 (m, 4H), 7.06 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.5, 171.1, 162.2, 137.2, 134.9, 134.0, 130.9, 130.6, 129.9, 129.2 (2C), 128.9, 126.6, 126.0 (2C), 100.2. IR, ν_{max}/cm^{-1} : 1959, 1896, 1761, 1655,

1571, 1436, 1236, 1159, 1082, 1046. HRMS (ES TOF) calcd for $C_{16}H_{10}ClNNaO_2$ ($[M + Na]^+$): 306.0292, found 306.0285 (2.2 ppm).

5-(Bromomethyl)-3-(4-bromobenzoyl)isoxazole (10hc).

Product **10hc** was obtained *via* the method described for compound **10aa**, employing 2-nitro-4'-bromoacetophenone **1h**²⁷ (244 mg, 1.00 mmol) and propargyl bromide **9c** (119 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Brown solid, mp 83–85 °C; R_f 0.40, EtOAc/hexane (1 : 4, v/v). Yield 66 mg (0.19 mmol, 19%). 1H NMR (400 MHz, $CDCl_3$) δ 8.22–8.18 (m, 2H), 7.69–7.66 (m, 2H), 6.85 (d, J = 0.6 Hz, 1H), 4.54 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 168.6, 162.1, 134.1, 132.2 (2C), 132.0 (2C), 129.8, 104.7, 17.9. IR, ν_{max}/cm^{-1} : 3147, 2920, 2853, 1934, 1652, 1585, 1448, 1397, 1295, 1224, 1178, 932. HRMS (ES TOF) calcd for $C_{11}H_7Br_2NaNO_2$ ($[M + Na]^+$): 365.8736, found 365.8727 (2.4 ppm).

3,4-Dibenzoyl-5-phenyl-4,5-dihydroisoxazole (12aa) and 3,5-dibenzoyl-4-phenyl-4,5-dihydroisoxazole (14aa).

2-Nitroacetophenone **1a**²⁷ (165 mg, 1.00 mmol) and *trans*-chalcone **11a** (312 mg, 1.5 mmol) were combined with to 2.0 g of polyphosphoric acid (80 wt% of P_2O_5). The reaction mixture was stirred at 130 °C for 3–5 h (TLC control). Reaction mixture was diluted with water and extracted with ethyl acetate (4 × 15 mL). Combined organic layers were washed with brine, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: EtOAc/PE, 1 : 4 v/v) to obtain two regioisomeric products **12aa** and **14aa**.

Product 12aa. Brown solid, mp 105–107 °C; R_f 0.30, EtOAc/hexane (1 : 4, v/v). Yield 138 mg (0.39 mmol, 39%). 1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dt, J = 8.3, 1.3 Hz, 2H), 7.90–7.85 (m, 2H), 7.62 (dddd, J = 7.5, 5.2, 3.9, 1.9 Hz, 2H), 7.52–7.41 (m, 7H), 7.33 (dd, J = 6.3, 2.6 Hz, 2H), 5.78 (d, J = 8.2 Hz, 1H), 5.58 (dd, J = 8.3, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 185.8, 157.1, 138.3, 135.6, 135.5, 134.4, 134.1, 130.7 (2C), 129.5, 129.4 (2C), 129.3 (2C), 129.1 (2C), 128.6 (2C), 126.4 (2C), 89.5, 63.1. IR, ν_{max}/cm^{-1} : 3060, 2925, 1684, 1643, 1578, 1448, 1366, 1277, 1195, 1016, 932. HRMS (ES TOF) calcd for $C_{23}H_{17}NaNO_3$ ($[M + Na]^+$): 378.1101, found 378.1091 (2.6 ppm).

Product 14aa. Yellow viscous oil; R_f 0.29, EtOAc/hexane (1 : 4, v/v). Yield 121 mg (0.34 mmol, 34%). 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (dt, J = 8.5, 1.2 Hz, 2H), 8.01 (dt, J = 8.5, 1.2 Hz, 2H), 7.66–7.56 (m, 2H), 7.53–7.32 (m, 9H), 5.86 (dd, J = 5.4, 1.0 Hz, 1H), 5.37 (dd, J = 5.4, 1.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 184.9, 159.1, 137.6, 135.9, 134.4, 134.0, 133.8, 130.5 (2C), 129.6 (2C), 129.6 (2C), 129.1 (2C), 128.5 (2C), 128.47, 127.8 (2C), 90.6, 55.4. IR, ν_{max}/cm^{-1} : 3062, 2927, 1686, 1645, 1579, 1448, 1369, 1279, 1196, 1026, 932. HRMS (ES TOF) calcd for $C_{23}H_{17}NaNO_3$ ($[M + Na]^+$): 378.1101, found 378.1092 (2.3 ppm).

3-(4-Chlorobenzoyl)-4-(2-nitrobenzoyl)-5-(2-chlorophenyl)isoxazole (15fb). Product **15gb** was obtained *via* the method described for compound **12aa**, employing 2-nitro-4'-chloroacetophenone **1f** (199 mg, 1.00 mmol), and (*E*)-2-chloro-2'-nitrochalcone **11b**²⁵ (431 mg, 1.5 mmol) and purified by column chromatography (eluent EtOAc/PE, 1 : 4). Brown viscous oil; R_f = 0.41, benzene. Yield 248 mg (0.53 mmol, 53%). 1H NMR (400 MHz, $CDCl_3$) δ 8.05–7.92 (m, 2H), 7.77 (dd, J = 8.5, 1.2 Hz, 1H), 7.56–7.49 (m, 3H), 7.41–7.16 (m, 6H). ^{13}C NMR (101 MHz,



CDCl_3) δ 185.0, 184.3, 171.0, 160.2, 145.8, 141.6, 134.3, 134.1, 133.9, 133.9, 132.7, 131.5 (2C), 131.4, 131.3, 129.9, 129.4 (2C), 129.1, 126.8, 125.0, 123.9, 118.6. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 3089, 2925, 1732, 1674, 1587, 1522, 1346, 1224, 1084, 1014, 930. HRMS (ES TOF) calcd for $\text{C}_{23}\text{H}_{12}\text{Cl}_2\text{N}_2\text{NaO}_5$ ($[\text{M} + \text{Na}]^+$): 489.0015, found 489.0013 (0.6 ppm).

3-Benzoyl-5-phenyl-3a,6a-dihydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5H)-dione (17a). Product 17a was obtained *via* the method described for compound 10aa, employing 2-nitroacetophenone 1a²⁷ (165 mg, 1.00 mmol) and *N*-phenylmaleimide 16 (173 mg, 1.00 mmol) and purified by column chromatography (eluent EtOAc/PE 1 : 4). Colorless solid, mp 147–150 °C, lit³³ mp 100–102 °C (EtOAc); R_f 0.16, EtOAc/hexane (1 : 4, v/v). Yield 201 mg (0.63 mmol, 63%). ¹H NMR (400 MHz, CDCl_3) δ 8.27–8.17 (m, 2H), 7.68–7.62 (m, 1H), 7.54–7.42 (m, 5H), 7.31–7.26 (m, 2H), 5.70 (d, J = 9.8 Hz, 1H), 5.24 (d, J = 9.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl_3) δ 183.4, 170.0, 168.8, 153.2, 134.9, 134.7, 130.8, 130.6 (2C), 129.5 (2C), 129.4, 128.8 (2C), 126.2 (2C), 81.2, 54.9. IR, $\nu_{\text{max}}/\text{cm}^{-1}$: 3065, 1901, 1713, 1651, 1598, 1501, 1448, 1381, 1279, 1200, 1070, 1024. HRMS (ES TOF) calcd for $\text{C}_{18}\text{H}_{12}\text{N}_2\text{NaO}_4$ ($[\text{M} + \text{Na}]^+$): 343.0689, found 343.0679 (2.9 ppm).

Author contributions

A. V. Aksenov – conceptualization, supervision, funding acquisition; N. A. Aksenov – methodology, formal analysis, funding acquisition; N. K. Kirilov – investigation; A. A. Skomorokhov – investigation; D. A. Aksenov – investigation; I. A. Kurenkov – investigation; E. A. Sorokina – investigation, formal analysis; M. A. Nobi – formal analysis, writing (review and editing); M. Rubin – conceptualization, supervision, writing (original draft, review, and editing).

Conflicts of interest

There are no conflicts to declare.

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