

Article

Electrophilically Activated Nitroalkanes in Double Annulation of [1,2,4]Triazolo[4,3-*a*]quinolines and 1,3,4-Oxadiazole Rings

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Abstract: Nitroalkanes activated with polyphosphoric acid could serve as efficient electrophiles in reactions with amines and hydrazines, enabling various cascade transformations toward heterocyclic systems. This strategy was developed for an innovative synthetic protocol employing simultaneous or sequential annulation of two different heterocyclic cores, affording [1,2,4]triazolo[4,3-*a*]quinolines with 1,3,4-oxadiazole substituents.

Keywords: nitroalkanes; heterocycles; annulation; cascade transformations



Citation: Aksenov, A.V.; Kirilov, N.K.; Aksenov, N.A.; Aksenov, D.A.; Sorokina, E.A.; Lower, C.; Rubin, M. Electrophilically Activated Nitroalkanes in Double Annulation of [1,2,4]Triazolo[4,3-*a*]quinolines and 1,3,4-Oxadiazole Rings. *Molecules* **2021**, *26*, 5692. <https://doi.org/10.3390/molecules26185692>

Academic Editor: Nagatoshi Nishiwaki

Received: 11 August 2021

Accepted: 17 September 2021

Published: 20 September 2021

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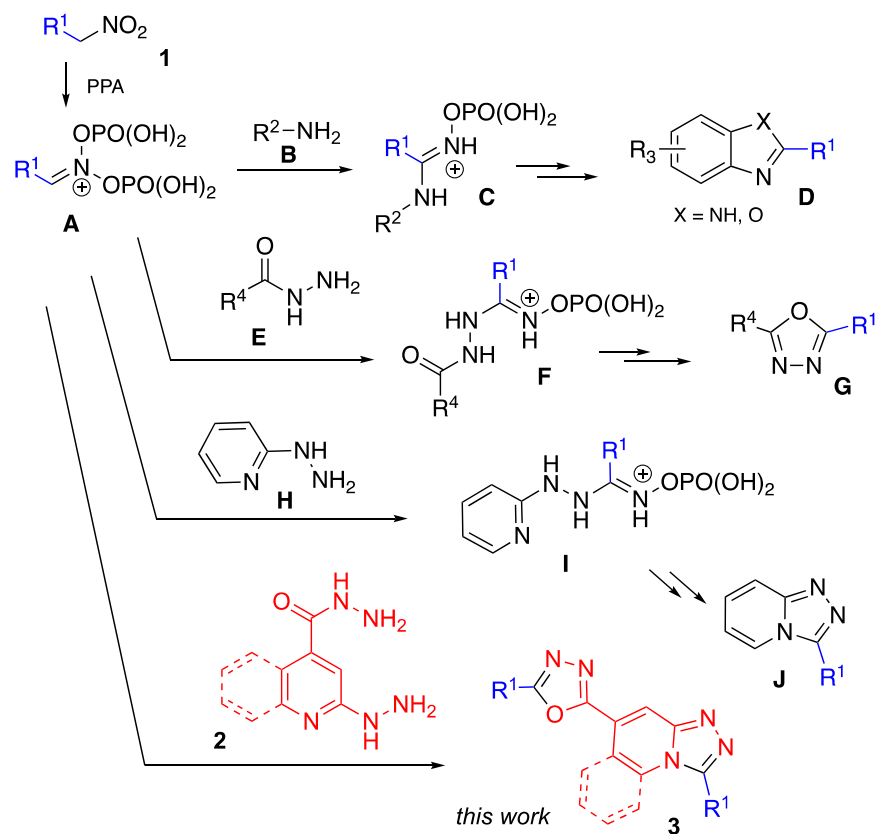
1. Introduction

There is significant emphasis on the role of [1,2,4]triazolo[4,3-*a*]quinolines in modern-day drug discovery and medicinal chemistry. This privileged scaffold was utilized in the design of potent and selective aldosterone synthase inhibitors with anti-hypertensive activity [1], as well as prospective antitumor [2,3], anticonvulsant [4–10], anti-inflammatory [11,12], and antimicrobial [13,14] agents. It was also found that an introduction of a heterocyclic substituent at C-5 could allow for the preparation of chimeric scaffolds with improved biological activities. This strategy was employed in the development of cytotoxic and antiviral agents [15], as well as analgesic and anti-inflammatory drug candidates [16]. Recently, we described the preparation of novel antitumor agents with in vitro differentiation activity against neuroblastoma cancer cell lines [2]. These compounds were assembled via an unusual annulation reaction between electrophilically activated nitroalkanes [17] and 2-hydrazinylquinolines. We also reported on the cyclocondensation of nitroalkanes with acylhydrazides furnishing 1,3,4-oxadiazole rings [18,19]. With continuous SAR studies, we had a task of building a focused library of perspective “chimeric” antitumor drug candidates possessing both [1,2,4]triazolo[4,3-*a*]quinoline and 1,3,4-oxadiazole rings. An expeditious and concise synthetic method was needed to allow for a highly efficient installation of both heterocyclic cores in a single-pot fashion. In this report, we disclosed the results of these synthetic studies.

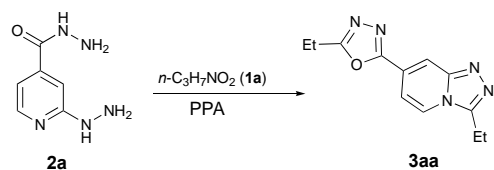
2. Results and Discussion

As we previously reported, a highly electrophilic phosphorylated nitronate species **A** is generated upon the interactions between nitroalkanes **1** and polyphosphoric acid (PPA) (Scheme 1). These entities readily react with amines **B** to afford amidinium intermediates **C**, which can be used for the highly efficient assembly of imidazoles or oxazoles (**D**) [20,21], as well as imidazolines [22] and other nitrogen-based heterocycles [23,24]. Fur-

thermore, the reaction with 2-hydrazinylpyridines **H** enacts formation of the corresponding (hydrazineyl)alkaniminium species **I**, which was found to undergo intramolecular cyclocondensations to obtain 1,2,4-triazolo[4,3-*a*]pyridines (**J**) (Scheme 1) [2]. Similarly, a mechanistically related reaction with acylhydrazides **E** proved useful for cyclization toward 1,3,4-oxadiazoles **G**. (Scheme 1) [18,19]. Remarkably, both latter reactions could be carried out under similar reaction conditions. This prompted us to pursue the idea of performing these reactions in a one-pot fashion en route to chimeric heterocyclic structures **3** (Scheme 1). To test the possibility of the simultaneous installation of these two heterocyclic moieties, we carried out the reaction of 2-hydrazineylisonicotinohydrazide (**2a**) in PPA in the presence of excess 1-nitropropane (**1a**, 4 equiv. used to compensate the loss due to evaporation). Initial tests were performed in 80% PPA (which corresponds to $H_4P_2O_7$ composition). The reaction was carried out at 130 °C for 30 min, when it notably slowed down, most likely due to the loss of relatively volatile nitroalkane (bp 132 °C). Two more equivalents of **1a** was added, and the reaction was stirred for an additional 90 min to afford the desired 2-ethyl-5-(3-ethyl-[1,2,4]triazolo [4,3-*a*]pyridin-7-yl)-1,3,4-oxadiazole (**3aa**) with a 71% yield (Table 1, entry 1). To evaluate the influence of the medium, we also performed the same reaction in 87% PPA, which corresponds to polymeric HPO_3 with lowered acidity, but enhanced anhydride activity. These parameters were modified aiming for an improved reaction performance or lowering of the reaction temperature. Indeed, even at 120 °C the yield of product **3aa** was notably higher (entry 2), and it reached 84% at 130 °C (entry 3). We also tested for the intermediate value of 85% P_2O_5 content in the reaction medium, which was found to be optimal for the featured process. With the increase in reaction temperature from 110–120 °C and then to 130 °C, the yield of **3aa** improved from 52–79% and then to 90%, respectively (entries 4–6). A further increase in temperature to 140 °C, however, was found to be detrimental, as it caused partial decomposition of the product (entry 7).



Scheme 1. Electrophilic activation of nitroalkanes in synthesis of heterocycles.

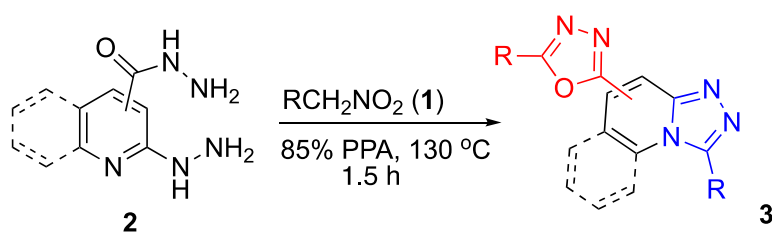
Table 1. Optimization of the reaction conditions for a one-pot double-annulation toward a chimeric product **3aa**.


	Medium ^a	T(°C)	PrNO ₂ , eq.	Yield % ^b
1	PPA, 80%	130	4 + 2	71
2	PPA, 87%	120	4 + 2	80
3	PPA, 87%	130	4 + 2	84
4	PPA, 85%	110	4 + 2	52
5	PPA, 85%	120	4 + 2	79
6	PPA, 85%	130	4 + 2	90 ^c
7	PPA, 85%	140	4 + 2	79

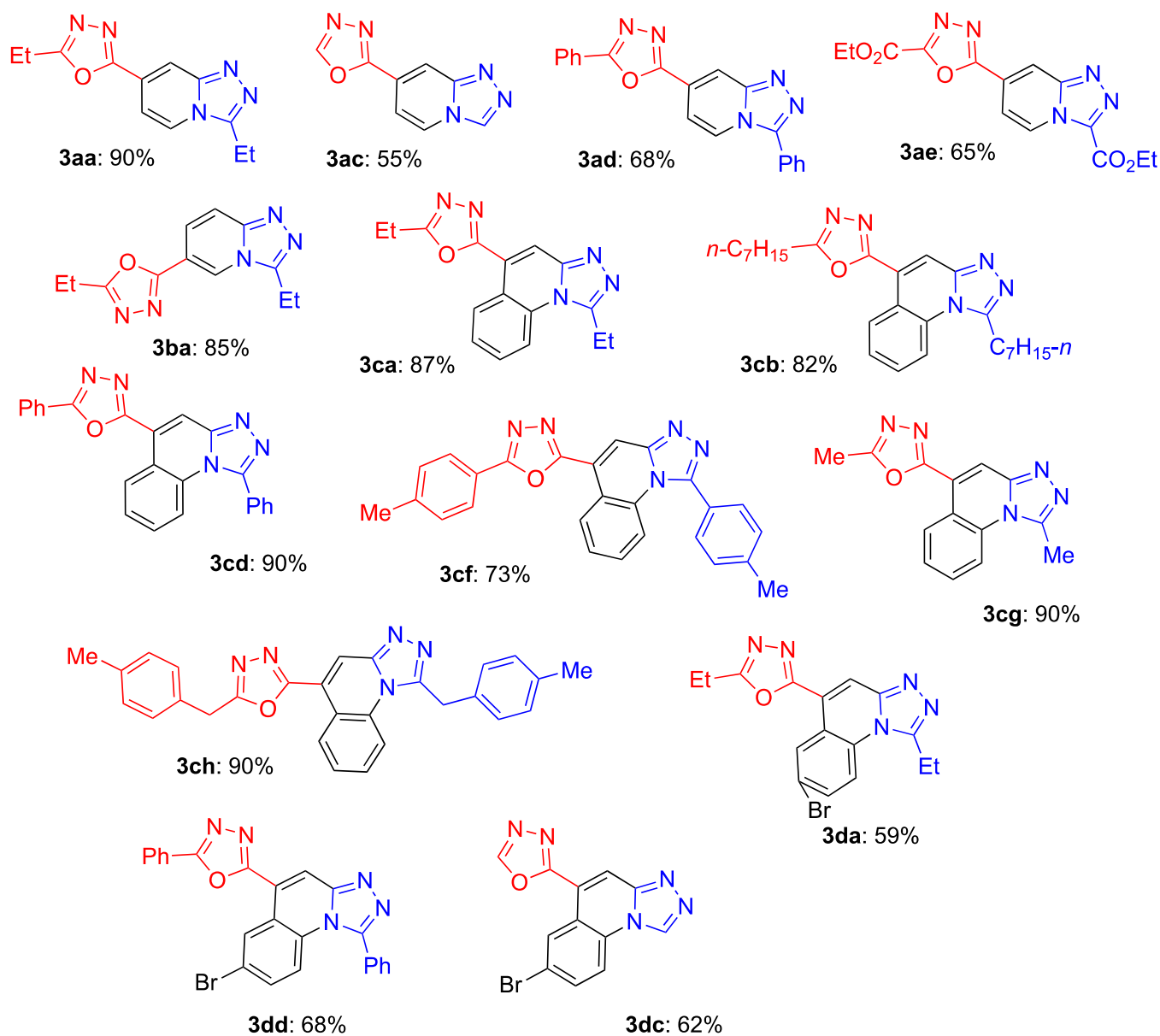
^a P₂O₅ content is shown in %; ^b NMR yields are reported unless specified otherwise; ^c isolated yield of purified product is provided.

With optimized reaction conditions in hand, we proceeded with the scope and limitation studies, the results of which are shown in Scheme 2. Nitromethane (**1c**) reacted smoothly, but the yields were somewhat lower due to partial loss of this reagent through its high volatility. The addition of nitromethane (up to 7 equivalents) to compensate for evaporation allowed for the isolation of polyheterocyclic products **3ac** and **3dc** in moderate to high yields (Scheme 2). Reactions involving three homologous nitroalkanes with higher boiling points, nitroethane (**1g**), 1-nitropropane (**1a**), and 1-nitrooctane (**1b**), proceeded much more efficiently, generally providing notably higher yields (Scheme 2). Furthermore, we managed to carry out the reaction of ethyl 2-nitroacetate, efficiently generating a bis-annulation product **3ae** with two newly introduced ester functionalities (Scheme 2). Moreover, *p*-tolyl(2-nitroethane) (**1h**) reacted smoothly, affording compound **3ch** in excellent yield (Scheme 2). A putative mechanistic rationale of the featured transformation is depicted in Scheme 3. The reaction begins with two nucleophilic attacks by both hydrazine and hydrazide groups of the substrate at two of the phosphorylated nitronate species **A**. After subsequent elimination of the two molecules of *ortho*-phosphoric acid, the resulting species **4** underwent a double-fold 5-*endo-trig* nucleophilic cyclization employing both *N*-(1-hydrazineylalkylidene)-*O*-phosphonohydroxylammonium moieties. Next, tautomeric form **5** would undergo re-protonation to produce heterocyclic intermediate **6**. The latter experiences an elimination of two equivalents of hydroxylamine *O*-phosphate to afford the aromatic final product **3** (Scheme 3).

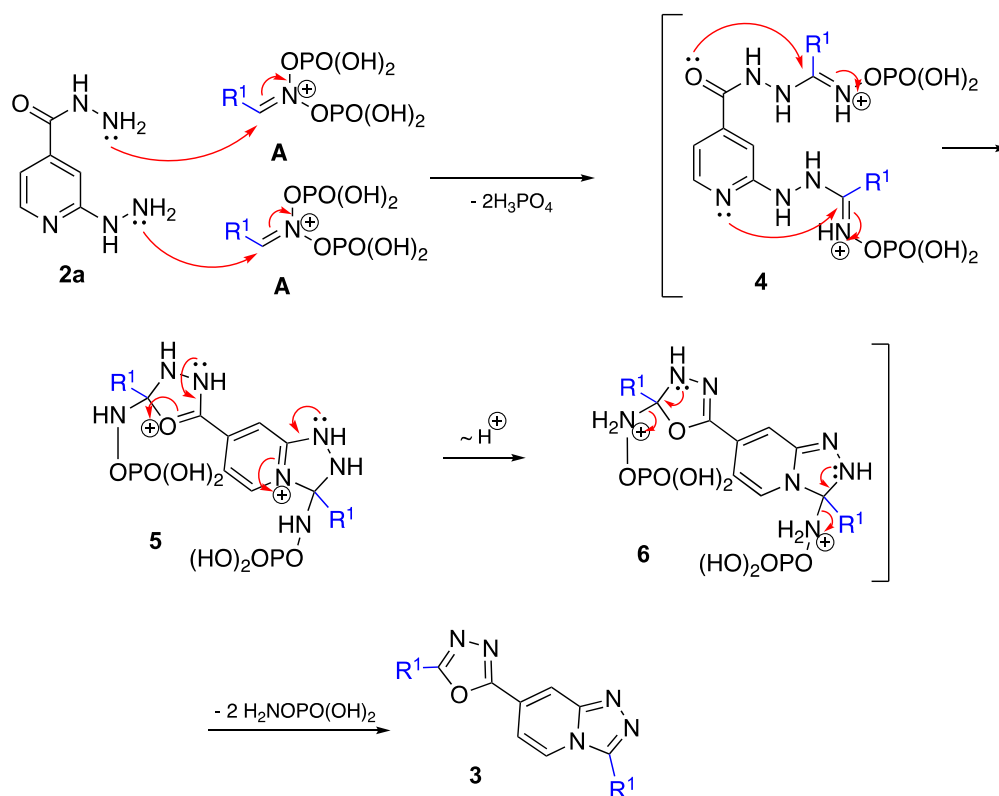
It should be pointed out that reactions involving α -nitrotoluene as a pro-electrophile proceeded sluggishly affording the corresponding bis-phenylsubstituted products (such as **3ad**) with disappointingly marginal yields (10% or below). This limitation, however, can be addressed by substituting α -nitrotoluene with α -nitroacetophenones (**1d** or **1f**, 3.0 equiv.). This tactical trick was first presented in our original report on the preparation of benzimidazoles and benzoxazoles in 2015 [20]. An updated version of this mechanistic rationale adapted for the reaction with bifunctional substrate **2a** is shown in Scheme 4. It is assumed that the initial acid-assisted double-fold interaction of **2a** with α -nitroacetophenone (**1d**) leads to the formation of bis-1-(2-nitroethylidene)hydrazin-1-ium as an intermediate **7** (Scheme 3). The electron pairs for the heteroatoms of ketone and pyridine form an intramolecular attack to afford two new five-membered rings as an intermediate **8**. The latter experiences a double-fold nucleofugal cleavage of nitromethane to produce molecule **3ad** (Scheme 4). Compounds **3cd**, **3dd**, and **3cf** were formed in a similar manner with high yields (Scheme 2).



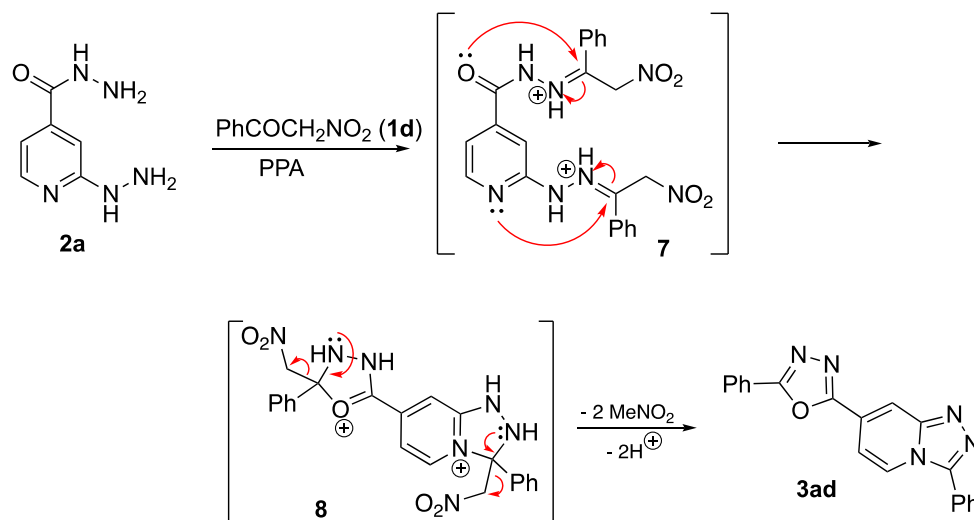
1a: R = Et; **1b:** R = *n*-C₇H₁₅; **1c:** R = H;
1d: R = PhCO; **1e:** R = CO₂Et
1f: R = 4-MeC₆H₄CO; **1g:** R = Me;
1h: R = 4-MeC₆H₄CH₂



Scheme 2. Preparation of [1,2,4]triazolo[4,3-*a*]quinolines with 1,3,4-oxadiazole rings.



Scheme 3. Mechanistic rationale involving electrophilic nitroalkanes.

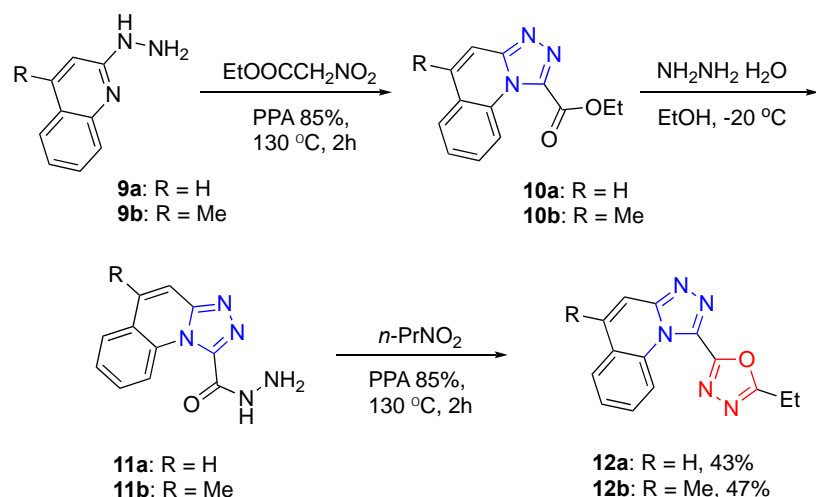


Scheme 4. Mechanistic rationale involving electrophilic nitroacetophenones.

In both discussed mechanistic rationales (Schemes 3 and 4), the initial nucleophilic attack of the hydrazine groups and subsequent annulations are occurring at two different sites. This would most likely take place independently with different kinetic rates, but for the sake of a concise depiction they are shown here to proceed in parallel.

We also decided to take advantage of the reactivity of the electrophilically activated ethyl nitroacetate (1e) to design a sequential approach for [1,2,4]triazolo[4,3-*a*]quinolines bearing 1,3,4-oxadiazole substituent at C-3 (shown in Scheme 5). To this end, 2-hydrazinylquinolines 9 were first utilized in the featured annulation to obtain triazoles 10 bearing an ester function at C-3. These compounds were taken without pu-

rification and subjected to the hydrazinolysis reaction to provide heterocyclic products **11**. The latter crude acylhydrazide moieties were transformed into 1,3,4-oxadiazole rings this time employing 1-nitropropane (**1a**) as an electrophilic component. Two compounds, **12a** and **12b**, were successfully synthesized via this approach with moderate yields (43% and 47%, respectively) (Scheme 5). In principle, the same strategy can potentially be employed for stepwise assembly of longer linear oligomeric chains with repeating 1,3,4-oxadiazole units, provided that greater annulation efficiency could be achieved at every step.



Scheme 5. Stepwise installation of [1,2,4]triazolo[4,3-*a*]quinolines and 1,3,4-oxadiazole moieties.

Formation of triazole and oxadiazole cycles in both parallel and sequential modes of the featured annulation was unambiguously confirmed by single-crystal X-ray diffraction of compounds **3ba** and **12a**, respectively (Figure 1).

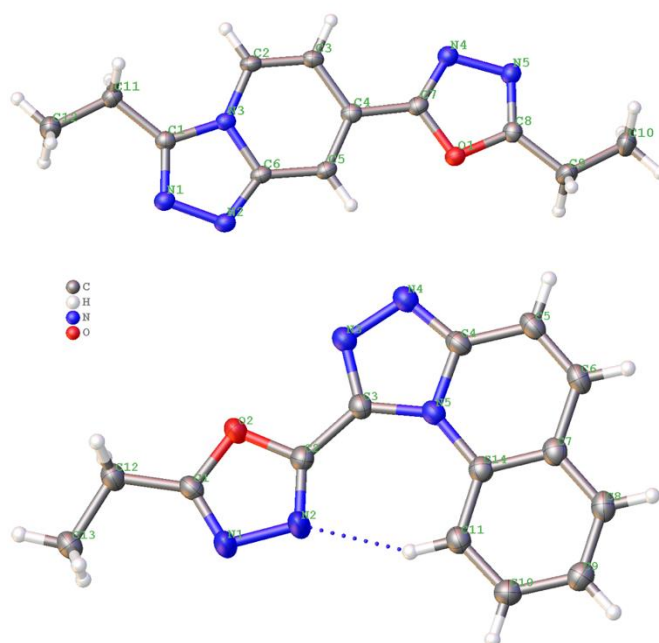


Figure 1. ORTEP drawing of X-ray structures of (2-ethyl-5-(3-ethyl-[1,2,4]triazolo[4,3-*a*]pyridin-6-yl)-1,3,4-oxadiazole) (**3ba**, CCDC #2092596) and 1-(5-ethyl-1,3,4-oxadiazol-2-yl)[1,2,4]triazolo[4,3-*a*]quinoline (**12a**, CCDC #2093198). The thermal ellipsoids are shown at 50% probability.

3. Materials and Methods

General

NMR spectra, ^1H and ^{13}C , were measured in solutions of CDCl_3 or $\text{DMSO-}d_6$ on Bruker AVANCE-III HD instrument (at 400.40 or 100.61 MHz, respectively. Bruker, Billerica, MA, USA). Residual solvent signals were used as internal standards, in $\text{DMSO-}d_6$ (2.50 ppm for ^1H , and 40.45 ppm for ^{13}C nuclei) or in CDCl_3 (7.26 ppm for ^1H , and 77.16 ppm for ^{13}C nuclei). HRMS spectra were measured on a Bruker maXis impact (electrospray ionization, in MeCN solutions, employing $\text{HCO}_2\text{Na-HCO}_2\text{H}$ for calibration). IR spectra were measured on an FT-IR spectrometer Shimadzu IRAffinity-1S equipped with an ATR sampling module. Reaction progress, purity of isolated compounds, and R_f values were monitored with TLC on Silufol UV-254 plates. Column chromatography was performed on silica gel (32–63 μm , 60 \AA pore size). Melting points were measured with Stuart SMP30 apparatus. Polyphosphoric acid samples were prepared by dissolving precisely measured amounts of P_2O_5 in 85% *ortho*-phosphoric acid. Ethyl 2-chloroquinoline-4-carboxylate, ethyl 6-bromo-2-chloroquinoline-4-carboxylate [25], ethyl 2-chloroisonicotinate [26], and ethyl 6-chloronicotinate [27] were synthesized according to the published methods. All other reagents and solvents were purchased from commercial vendors and used as received.

2-Hydrazinylpyridine-4-carbohydrazide (2a). Ethyl 2-chloroisonicotinate (740 mg, 4.00 mmol), hydrazine hydrate (88% solution in water, 2.3 mL, 40.0 mmol), and ethanol (0.7 mL) were combined in a 30 mL G30 vial and covered with a septum. The vial was placed in a Monowave 300 microwave reactor, and the mixture was heated to 160 $^\circ\text{C}$ over the course of 5 min (power did not exceed 135 watts), after which this temperature was maintained for 1.5 h (controlled by IR sensor, MW power within 10 watts, 10–15 bar pressure). The resulting mixture was poured into water (40 mL) and filtrated. The resulting precipitate was washed with water several times (2×30 mL). It was recrystallized from ethanol to afford **2a** as a pale-yellow solid, m.p. 171–172 $^\circ\text{C}$ (ethanol); yield 601 mg (3.60 mmol, 90%). R_f 0.16, EtOAc/ Et_3N (20:0.1: *v/v*). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.83 (br.s, NH, 1H), 8.03 (dd, $J = 5.3, 0.8$ Hz, 1H), 7.61 (br.s, NH, 1H), 7.07 (t, $J = 1.1$ Hz, 1H), 6.84 (dd, $J = 5.2, 1.5$ Hz, 1H), 4.51 (br.s, NH, 2H), 4.15 (br.s, NH, 2H). $^{13}\text{C-NMR}$ (101 MHz, DMSO) δ 164.9, 162.5, 147.9, 141.5, 109.4, 104.3. FTIR (ZnSe) ν (cm^{-1}): 3232, 2925, 2858, 1739, 1652, 1619, 1556, 1462, 1250, 1103, 1055, 874. HRMS (ES TOF, m/z) calculated for $\text{C}_6\text{H}_9\text{N}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 190.0694, found: 190.0699 (2.9 ppm).

2-Hydrazinylquinoline-4-carbohydrazide (2c). Ethyl 2-chloroquinoline-4-carboxylate (940 mg, 4.00 mmol), hydrazine hydrate (88% solution in water, 2.3 mL, 40.0 mmol), and ethanol (0.7 mL) were combined and refluxed for 1 h. The resulting mixture was poured into water (40 mL) and filtrated. The resulting precipitate was washed with water several times (2×30 mL). It was recrystallized from ethanol to afford **2c** as a brown solid, m.p. 219–220 $^\circ\text{C}$ (decomp.) (ethanol); yield 781 mg (3.60 mmol, 90%). R_f 0.43, EtOAc/ Et_3N (20:0.1: *v/v*). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.78 (br.s, NH, 1H), 8.24 (s, 1H), 7.84–7.76 (m, 1H), 7.59–7.49 (m, 2H), 7.18 (d, $J = 1.5$ Hz, 1H), 6.83 (br.s, NH, 1H), 4.60 (br.s, NH, 2H), 4.36 (br.s, NH, 2H). $^{13}\text{C-NMR}$ (101 MHz, DMSO) δ 166.4, 147.9, 141.7, 129.5, 125.81, 125.30, 121.7, 120.1, 109.5. FTIR (ZnSe) ν (cm^{-1}): 3691, 3253, 3183, 1775, 1612, 1511, 1245, 972, 850. HRMS (ES TOF, m/z) calculated for $\text{C}_{10}\text{H}_{11}\text{N}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 240.0848, found: 240.0856 (3.4 ppm).

6-Bromo-2-hydrazinylquinoline-4-carbohydrazide (2d). This material was obtained using the method described for preparation of compound **2a** employing ethyl 6-bromo-2-chloroquinoline-4-carboxylate (1252 mg, 4.00 mmol), and it was purified by recrystallization from ethanol to afford **2d** as a brown solid, m.p. = 215–216 $^\circ\text{C}$ (ethanol); yield 1065 g (3.60 mmol, 90%). $R_f = 0.56$, EtOAc/ Et_3N (20:0.1: *v/v*). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.86 (br.s, NH, 1H), 8.42 (s, 1H), 7.97 (d, $J = 2.3$ Hz, 1H), 7.62 (dd, $J = 8.9, 2.4$ Hz, 1H), 7.49 (d, $J = 8.9$ Hz, 1H), 6.89 (br.s, NH, 1H), 4.63 (br.s, NH, 2H), 4.40 (br.s, NH, 2H). $^{13}\text{C-NMR}$ (101 MHz, DMSO) δ 165.9, 158.9, 146.9, 140.6, 132.3, 128.0, 127.3, 121.5, 113.7, 110.5. FTIR (ZnSe) ν (cm^{-1}): 3325, 3205, 2935, 1665, 1633, 1520, 1380, 1245, 1043, 937, 756. HRMS (ES TOF, m/z) calculated for $\text{C}_{10}\text{H}_{11}\text{BrN}_5\text{O}^+$ ($[\text{M} - \text{H}]^+$): 296.0138, found: 296.0141 (1.2 ppm).

[1,2,4]Triazolo[4,3-*a*]quinoline-1-carbohydrazide (11a). Hydrazine hydrate (88% solution in water, 0.58 mL, 10.0 mmol) was added dropwise to a solution of the ethyl [1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (241 mg, 1.00 mmol) in ethanol (5 mL), cooled to $-10\text{ }^{\circ}\text{C}$. It was stirred at room temperature for 1 h, and then water (10 mL) was poured in. The precipitate was filtered off and washed with cold water ($2 \times 5\text{ mL}$). This material can be used as is for the subsequent transformation. To obtain an analytical sample, the crude material was recrystallized from ethanol to afford the titled compound as a pale-yellow solid, m.p. = $205\text{--}206\text{ }^{\circ}\text{C}$ (ethanol); yield 204 mg (90%). R_f 0.60, EtOAc/Et₃N (20:0.1: *v/v*). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 10.12 (br.s, NH, 1H), 8.41 (d, $J = 8.5\text{ Hz}$, 1H), 8.07 (dd, $J = 7.8, 1.6\text{ Hz}$, 1H), 7.93 (d, $J = 9.5\text{ Hz}$, 1H), 7.85–7.71 (m, 2H), 7.66 (td, $J = 7.6, 1.1\text{ Hz}$, 1H), 4.97 (br.s, NH, 2H). ¹³C-NMR (101 MHz, DMSO) δ 158.5, 149.0, 143.3, 131.0, 130.5, 129.9, 129.5, 126.9, 124.0, 117.8, 114.1. FTIR (ZnSe) ν (cm^{-1}): 3219, 2824, 1677, 1619, 1539, 1409, 1250, 1216, 1172, 1089, 944. HRMS (ES TOF, *m/z*) calculated for C₁₁H₉N₅NaO⁺ ([M + Na]⁺): 250.0692, found: 250.0699 (2.9 ppm).

5-Methyl-[1,2,4]triazolo[4,3-*a*]quinoline-1-carbohydrazide (11b). This material was obtained by the method described for compound **2e** employing ethyl 5-methyl-[1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (255 mg, 1.00 mmol). This material can be used as is for the subsequent transformation. To obtain an analytical sample, the crude material was recrystallized from ethanol to afford the titled compound as a pale-brown solid, m.p. = $214\text{--}215\text{ }^{\circ}\text{C}$ (ethanol); yield 219 mg (91%). R_f 0.26, EtOAc/Et₃N (20:0.1: *v/v*). ¹H-NMR (400 MHz, DMSO) δ 10.47 (bs, 1H), 8.43 (dd, $J = 8.4, 1.2\text{ Hz}$, 1H), 8.09 (dd, $J = 8.1, 1.6\text{ Hz}$, 1H), 7.77 (ddd, $J = 8.6, 7.2, 1.6\text{ Hz}$, 1H), 7.72–7.66 (m, 2H), 5.00 (bs, NH, 2H), 2.64 (s, 3H). ¹³C-NMR (101 MHz, DMSO) δ 158.6, 148.9, 143.0, 138.1, 130.3, 129.9, 126.8, 126.2, 124.3, 118.0, 112.9, 19.0. FTIR (ZnSe) ν (cm^{-1}): 3296, 3209, 1674, 1522, 1414, 1375, 1303, 1248, 1168, 1091, 1036. HRMS (ES TOF, *m/z*) calculated for C₁₂H₁₁N₅NaO⁺ ([M + Na]⁺): 264.0858, found: 264.0858 (−0.8 ppm).

General method A (employing nitroalkanes). A 10 mL Erlenmeyer flask equipped with reflux condenser and magnetic stirrer was charged with 85% polyphosphoric acid (2.00 g), 2-hydrazinylisonicotinohydrazide **2** (1.00 equiv.), and nitroalkane **1** (4.00 equiv.). The mixture was placed in an oil bath that was preheated to $130\text{ }^{\circ}\text{C}$ and stirred for 30 min. Then, another 2.00 equiv. of nitro compound **1** was added, followed by stirring for an additional 1.5 h. Then, the mixture was poured into cold H₂O (5 mL), neutralized with aqueous ammonia to a pH 6–7, and extracted with EtOAc ($4 \times 5\text{ mL}$). The combined extracts were concentrated under vacuum, and the residue was purified by preparative column chromatography on silica gel, eluting with a mixture of acetone and hexane.

Method B with α -nitroacetophenone. A 10 mL Erlenmeyer flask equipped with a magnetic stirrer and a reflux condenser was charged with 2-hydrazinylisonicotinohydrazide (1.00 equiv.) **2**, polyphosphoric acid (85% P₂O₅, 2 g), and α -nitroacetophenone **1d** (3.00 equiv.). The flask was placed in an oil bath and heated to $130\text{ }^{\circ}\text{C}$ while being stirred. The mixture was heated for 1.5–2 h; when TLC analysis showed the reaction was completed, the reaction mixture was cooled. Water was added (5 mL), neutralized with 25% aqueous ammonia solution (4 mL) to pH = 8–9 and extracted with EtOAc ($4 \times 5\text{ mL}$). The combined organic phases were concentrated and the crude product was purified by preparative column chromatography eluting with acetone and hexane.

Method C with ethyl nitroacetate. In a 10 mL Erlenmeyer flask equipped with a magnetic stirrer and a reflux condenser, 2-hydrazinylisonicotinohydrazide (1.00 equiv.) **2**, PPA 85% (1 g), H₃PO₃ (1 g), and ethyl nitroacetate **1e** (3.0 equiv.) were loaded. The flask was placed in an oil bath and heated to $130\text{ }^{\circ}\text{C}$ while being stirred for 1 h. Then, another 2 equiv. of nitroacetic ether **1e** was added and heated for another hour; when TLC analysis showed the reaction was completed, the reaction mixture was cooled. Water was added (5 mL), before neutralizing with 25% aqueous ammonia solution (4 mL) to pH = 8–9 and extracting with EtOAc ($4 \times 5\text{ mL}$). The combined organic phases were concentrated, and the crude product was purified by preparative column chromatography eluting with acetone and hexane.

2-Ethyl-5-(3-ethyl-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)-1,3,4-oxadiazole (3aa): This compound was obtained via Method A employing 2-hydrazinylisonicotinohydrazide (**2a**) (167 mg, 1.00 mmol) and 1-nitropropane (**1a**) (534 mg, 6.00 mmol), purifying by silica gel column chromatography (EtOAc/hexane, gradient 1:1–2:1, *v/v*). White powder, m.p. 230–232 °C (EtOAc), R_f 0.63, acetone/hexane (2:1, *v/v*). Yield: 218 mg (0.90 mmol, 90%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.23 (q, $J = 1.4$ Hz, 1H), 8.01 (d, $J = 7.2$ Hz, 1H), 7.52 (dt, $J = 7.2, 1.8$ Hz, 1H), 3.11 (qd, $J = 7.6, 1.4$ Hz, 2H), 2.96 (qd, $J = 7.6, 1.5$ Hz, 2H), 1.50 (td, $J = 7.6, 1.6$ Hz, 3H), 1.42 (td, $J = 7.6, 1.5$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 168.9, 162.6, 149.2, 149.0, 122.8, 122.5, 115.0, 111.1, 19.3, 18.2, 10.9, 10.8. FTIR (ZnSe) ν (cm^{-1}): 3740, 2997, 1561, 1525, 1433, 1371, 1192, 1021, 951, 867. HRMS (ES TOF, m/z) calculated for $\text{C}_{12}\text{H}_{13}\text{NaN}_5\text{O}^+$ ($[\text{M} + \text{Na}]^+$): 266.1011, found: 266.1012 (0.4 ppm).

2-([1,2,4]Triazolo[4,3-*a*]pyridin-7-yl)-1,3,4-oxadiazole (3ac): This compound was obtained via Method A employing 2-hydrazinylisonicotinohydrazide (**2a**) (167 mg, 1.00 mmol) and 1-nitromethane (**1c**) (427 mg, 7.00 mmol), purifying by silica gel column chromatography (gradient acetone/hexane 1:1, *v/v*–acetone). Pale brown solid, m.p. > 300 °C (acetone), R_f 0.40, acetone. Yield: 103 mg (0.55 mmol, 55%). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.35 (s, 1H), 8.66 (dt, $J = 7.2, 1.3$ Hz, 1H), 7.94 (s, 1H), 7.55 (s, 1H), 7.38 (dt, $J = 7.3, 1.6$ Hz, 1H). $^{13}\text{C-NMR}$ (101 MHz, DMSO) δ 164.5, 155.5, 148.1, 137.3, 126.2, 123.5, 110.4, 110.1. FTIR (ZnSe) ν (cm^{-1}): 3614, 3085, 1743, 1689, 1532, 1505, 1469, 1414, 1245, 1166, 1101, 1040, 970. HRMS (ES TOF, m/z) calculated for $\text{C}_8\text{H}_5\text{N}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 210.0392, found: 210.0386 (−2.8 ppm).

2-Phenyl-5-(3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)-1,3,4-oxadiazole (3ad): This compound was obtained via Method B employing 2-hydrazinylisonicotinohydrazide (**2a**) (167 mg, 1.00 mmol) and α -nitroacetophenone (**1d**) (495 mg, 3.00 mmol), purifying by silica gel column chromatography (benzene/ Et_3N , 20:1, *v/v*). Light-green solid, m.p. 225–226 °C (EtOAc), R_f 0.63, acetone/hexane (1:1, *v/v*). Yield: 298 mg, 88%. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 9.04 (dd, $J = 7.5, 0.8$ Hz, 1H), 8.49 (dd, $J = 1.8, 0.8$ Hz, 1H), 8.48–8.42 (m, 2H), 8.23–8.19 (m, 2H), 7.93 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.65–7.59 (m, 3H), 7.55–7.52 (m, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 165.8, 162.4, 149.9, 147.2, 132.6, 131.0, 129.7 (2C), 129.5 (2C), 128.5 (2C), 127.4 (2C), 125.9, 123.7, 123.3, 123.2, 115.3, 112.2. FTIR (ZnSe) ν (cm^{-1}): 3315, 3070, 1672, 1657, 1604, 1578, 1549, 1455, 1383, 1281, 1180, 1077, 1028, 930. HRMS (ES TOF, m/z) calculated for $\text{C}_{20}\text{H}_{13}\text{NaN}_5\text{O}^+$ ($[\text{M} + \text{Na}]^+$): 362.1003, found: 362.1012 (2.6 ppm).

2-Ethyl-5-(3-ethyl-[1,2,4]triazolo[4,3-*a*]pyridin-6-yl)-1,3,4-oxadiazole (3ba): This compound was obtained via Method A employing 6-hydrazinylisonicotinohydrazide (**2b**) (167 mg, 1.00 mmol) and 1-nitropropane (**1a**) (534 mg, 6.00 mmol), purifying by silica gel column chromatography (gradient acetone/hexane, 1:1, *v/v*–acetone). Pale-brown solid, m.p. 116–117 °C (EtOAc), R_f 0.23, acetone/hexane (1:1, *v/v*). Yield: 298 mg (0.88 mmol, 88%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.60 (d, $J = 1.5$ Hz, 1H), 7.82 (dd, $J = 4.1, 1.3$ Hz, 2H), 3.15 (q, $J = 7.5$ Hz, 2H), 2.96 (q, $J = 7.6$ Hz, 2H), 1.53 (t, $J = 7.5$ Hz, 3H), 1.43 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 172.0, 168.2, 161.7, 149.1, 124.4, 121.7, 117.5, 112.4, 19.3, 18.3, 10.91, 10.85. FTIR (ZnSe) ν (cm^{-1}): 3325, 3205, 2935, 1665, 1633, 1520, 138, 1245, 1043, 937. HRMS (ES TOF, m/z) calculated for $\text{C}_{12}\text{H}_{13}\text{NaN}_5\text{O}^+$ ($[\text{M} + \text{Na}]^+$): 266.1004, found: 266.1014 (2.9 ppm).

1-Ethyl-5-(5-ethyl-1,3,4-oxadiazol-2-yl)[1,2,4]triazolo[4,3-*a*]quinoline (3ca): This compound was obtained via Method A employing 2-hydrazinylquinoline-4-carbohydrazide (**2c**) (217 mg, 1.00 mmol) and 1-nitropropane (**1a**) (534 mg, 6.00 mmol), purifying by silica gel column chromatography (acetone/hexane, gradient 1:2–1:1–2:1, *v/v*). Colorless powder, m.p. 235–236 °C (acetone), R_f 0.50, acetone/hexane (1:1, *v/v*). Yield: 254 mg (0.87 mmol, 87%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 9.47 (dd, $J = 8.3, 1.6$ Hz, 1H), 8.35 (s, 1H), 8.28 (dd, $J = 8.6, 1.2$ Hz, 1H), 7.79 (ddd, $J = 8.6, 7.2, 1.5$ Hz, 1H), 7.68 (ddd, $J = 8.4, 7.2, 1.2$ Hz, 1H), 3.55 (q, $J = 7.4$ Hz, 2H), 3.05 (q, $J = 7.6$ Hz, 2H), 1.69 (t, $J = 7.3$ Hz, 3H), 1.50 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 168.2, 162.5, 152.0, 148.9, 132.6, 130.3, 129.3, 126.8, 122.0, 121.7, 117.6, 116.4, 23.5, 19.3, 11.5, 10.9. FTIR (ZnSe) ν (cm^{-1}): 2930, 2862, 1737, 1657, 1561, 1440, 1380, 1240, 1180, 1055, 997, 879. HRMS (ES TOF, m/z) calculated for $\text{C}_{16}\text{H}_{15}\text{NaN}_5\text{O}^+$ ($[\text{M} + \text{Na}]^+$): 316.1166, found: 316.1169 (1.0 ppm).

2-Heptyl-5-(1-heptyl-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-1,3,4-oxadiazole (3cb): This compound was obtained via Method A employing 2-hydrazinylquinoline-4-carbohydrazide (**2c**) (217 mg, 1.00 mmol) and 1-nitrooctane (**1b**) (636 mg, 4.00 mmol), purifying by silica gel column chromatography (EtOAc/hexane, gradient 1:3–1:2–1:1, *v/v*). Dark brown solid, m.p. 198–200 °C (EtOAc), *R_f* 0.73, acetone/hexane (2:1, *v/v*). Yield: 355 mg (0.82 mmol, 82%). ¹H-NMR (400 MHz, CDCl₃-*d*) δ 9.48 (d, *J* = 8.1 Hz, 1H), 8.33 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 3.50 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.08 (quint, *J* = 7.7 Hz, 2H), 1.91 (quint, *J* = 7.4 Hz, 2H), 1.62–1.54 (m, 3H), 1.32 (ddt, *J* = 10.4, 7.4, 3.6 Hz, 13H), 0.89 (t, *J* = 6.7 Hz, 6H). ¹³C-NMR (101 MHz, CDCl₃) δ 167.5, 162.5, 151.1, 148.9, 132.7, 130.3, 129.3, 126.8, 121.9, 120.8, 117.7, 116.4, 31.8, 31.7, 29.8, 29.5, 29.2, 29.1, 28.9, 26.8, 26.7, 25.53, 22.8, 22.7, 14.22, 14.19. FTIR (ZnSe) *ν* (cm⁻¹): 3026, 2935, 2848, 1869, 1727, 1566, 1469, 1399, 1243, 1166, 997, 946. HRMS (ES TOF, *m/z*) calcd for C₂₆H₃₅NaN₅O⁺ ([M + Na]⁺): 456.2728, found: 456.2734 (1.4 ppm).

2-Phenyl-5-(1-phenyl-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-1,3,4-oxadiazole (3cd): This compound was obtained via Method B employing 2-hydrazinylquinoline-4-carbohydrazide (**2c**) (217 mg, 1.00 mmol) and α -nitroacetophenone (**1d**) (495 mg, 3.00 mmol), purifying by silica gel column chromatography (EtOAc/hexane, gradient 1:1–3:1, *v/v*). Pale-brown solid, m.p. 243–245 °C (acetone), *R_f* 0.53, EtOAc/hexane (3:1, *v/v*). Yield: 350 mg (0.90 mmol, 90%). ¹H-NMR (400 MHz, CDCl₃) δ 9.57 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.68 (s, 1H), 8.28–8.21 (m, 2H), 7.75 (dd, *J* = 8.1, 1.5 Hz, 3H), 7.72–7.58 (m, 7H), 7.54–7.49 (m, 1H). ¹³C-NMR (101 MHz, CDCl₃) δ 165.0, 162.2, 149.9, 148.3, 137.0, 132.7, 132.0, 131.3, 130.3, 130.11 (2C), 129.52 (4C), 129.4, 128.7, 127.52 (3C), 123.3, 120.9, 117.3, 116.8. FTIR (ZnSe) *ν* (cm⁻¹): 3335, 3195, 2988, 1783, 1761, 1655, 1554, 1375, 1243, 1050, 937. HRMS (ES TOF, *m/z*) calculated for C₂₄H₁₅NaN₅O⁺ ([M + Na]⁺): 412.1177, found: 412.1169 (−2.1 ppm).

2-(*p*-Tolyl)-5-(1-(*p*-tolyl)-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-1,3,4-oxadiazole (3cf): This compound was obtained via Method B employing 2-hydrazinylquinoline-4-carbohydrazide (**2c**) (217 mg, 1.00 mmol) and 1-(4-methylphenyl)-2-nitroethan-1-one (**1f**) [28] (394 mg, 2.2 mmol), purifying by silica gel column chromatography (ACETONE/hexane, gradient 1:3–1:2, *v/v*). Pale-brown solid, m.p. 190–191 °C (acetone), *R_f* 0.53, acetone/hexane (1:1, *v/v*). Yield: 304 mg (0.73 mmol, 73%). ¹H-NMR (400 MHz, CDCl₃) δ 9.50 (d, *J* = 9.3 Hz, 1H), 8.56 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 2H), 7.79–7.76 (m, 1H), 7.62 (d, *J* = 8.1 Hz, 3H), 7.50–7.46 (m, 1H), 7.42 (dd, *J* = 13.7, 7.9 Hz, 4H), 2.53 (s, 3H), 2.48 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ 165.0, 162.1, 150.2, 148.8, 143.3, 141.3, 132.2, 130.2 (2C), 130.1 (2C), 129.90 (2C), 129.88, 129.2, 127.4 (2C), 127.1, 126.1, 122.4, 120.8, 120.5, 117.4, 117.2, 21.9, 21.8. FTIR (ZnSe) *ν* (cm⁻¹): 2920, 2858, 1713, 1614, 1554, 1513, 1465, 1380, 1250, 1180, 1016, 951. HRMS (ES TOF, *m/z*) calculated for C₂₆H₁₉NaN₅O⁺ ([M + Na]⁺): 440.1470, found: 440.1482 (−2.7 ppm).

2-Methyl-5-(1-methyl-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-1,3,4-oxadiazole (3cg): This compound was obtained via Method B employing 2-hydrazinylquinoline-4-carbohydrazide (**2c**) (217 mg, 1.00 mmol) and nitroethane (**1g**) (225 mg, 3.00 mmol), purifying by silica gel column chromatography (acetone/hexane, gradient 1:1–acetone, *v/v*). White solid, m.p. 250–251 °C (acetone), *R_f* 0.29, acetone. Yield: 219 mg (0.83 mmol, 83%). ¹H-NMR (400 MHz, CDCl₃) δ 9.46 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.32 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.29 (s, 1H), 7.78 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 3.21 (s, 3H), 2.72 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ 164.1, 162.7, 148.8, 147.3, 132.7, 130.4, 129.3, 126.9, 121.9, 120.6, 117.5, 116.1, 16.4, 11.3. FTIR (ZnSe) *ν* (cm⁻¹): 2925, 2853, 1703, 1652, 1614, 1578, 1508, 1472, 1395, 12540, 1180, 1161, 1055, 939. HRMS (ES TOF, *m/z*) calculated for C₁₄H₁₁NaN₅O⁺ ([M + Na]⁺): 288.0849, found: 288.0856 (2.5 ppm).

2-(4-Methylbenzyl)-5-(1-(4-methylbenzyl)-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-1,3,4-oxadiazole (3ch): This compound was obtained via Method B employing 2-hydrazinylquinoline-4-carbohydrazide (**2c**) (217 mg, 1.00 mmol) and 1-methyl-4-(2-nitroethyl)benzene (**1h**) [29] (330 mg, 2.00 mmol), purifying by silica gel column chromatography (acetone/hexane, gradient 1:3–1:2, *v/v*). White solid, m.p. 214–215 °C (acetone), *R_f* 0.49, acetone/hexane (1:2, *v/v*). Yield: 187 mg (0.42 mmol, 42%). ¹H-NMR (400 MHz, CDCl₃) δ 9.38 (dd, *J* = 6.4, 3.5 Hz, 1H), 8.30 (s, 1H), 8.10 (dd, *J* = 6.4, 3.4 Hz, 1H), 7.58 (dd, *J* = 6.4, 3.4 Hz, 2H), 7.31–7.28

(m, 2H), 7.20 (d, $J = 7.8$ Hz, 2H), 7.13–7.06 (m, 4H), 4.90 (s, 2H), 4.32 (s, 2H), 2.36 (s, 3H), 2.29 (s, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ 165.9, 162.9, 149.2, 149.1, 137.8, 137.3, 132.0, 131.7, 130.4, 130.3, 130.0 (3C), 130.0, 129.0 (3C), 128.1 (2C), 126.9, 122.1, 120.5, 117.7, 117.1, 34.5, 31.6, 21.3, 21.2. FTIR (ZnSe) ν (cm^{-1}): 3672, 2930, 2858, 1744, 1718, 1684, 1652, 1558, 1508, 1457, 1428, 1243, 1168, 1055, 992. HRMS (ES TOF, m/z) calculated for $\text{C}_{28}\text{H}_{23}\text{NaN}_5\text{O}^+$ ($[\text{M} + \text{Na}]^+$): 468.1802, found: 468.1795 (−1.6 ppm).

2-(7-Bromo-1-ethyl-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-5-ethyl-1,3,4-oxadiazole (3da): This compound was obtained via Method A employing 6-bromo-2-hydrazinylquinoline-4-carbohydrazide (**2d**) (295 mg, 1.00 mmol) and 1-nitropropane (**1a**) (534 mg, 6.00 mmol), purifying by silica gel column chromatography (gradient acetone/hexane 1:1, v/v -acetone). Light-brown solid, m.p. 320–322 °C (acetone), R_f 0.66, acetone. Yield: 218 mg (0.59 mmol, 59%). ^1H -NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.65 (d, $J = 1.3$ Hz, 1H), 10.09 (d, $J = 1.3$ Hz, 1H), 8.47 (d, $J = 2.3$ Hz, 1H), 8.34 (d, $J = 9.2$ Hz, 1H), 7.98 (dd, $J = 9.1, 2.4$ Hz, 1H), 7.83 (s, 1H), 3.49 (q, $J = 7.3$ Hz, 2H), 2.26 (q, $J = 7.6$ Hz, 2H), 1.50 (t, $J = 7.3$ Hz, 3H), 1.11 (t, $J = 7.6$ Hz, 3H). ^{13}C -NMR (101 MHz, $\text{DMSO-}d_6$) δ 173.0, 165.5, 152.1, 148.2, 133.1, 132.7, 131.6, 129.7, 123.6, 119.9, 119.1, 116.0, 27.0, 22.7, 11.5, 10.1. FTIR (ZnSe) ν (cm^{-1}): 3301, 3205, 2992, 2906, 2848, 1775, 1669, 1534, 1457, 1375, 1243, 1166, 1048, 932. HRMS (ES TOF, m/z) calculated for $\text{C}_{16}\text{H}_{14}\text{BrNaN}_5\text{O}^+$ ($[\text{M} + \text{Na}]^+$): 394.0270, found: 394.0274 (0.9 ppm).

2-(7-Bromo-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-1,3,4-oxadiazole (3dc): This compound was obtained via Method A employing 6-bromo-2-hydrazinylquinoline-4-carbohydrazide (**2d**) (295 mg, 1.00 mmol) and 1-nitromethane (**1c**) (427 mg, 7.00 mmol), purifying by silica gel column chromatography (gradient acetone/hexane, 2:1, v/v -acetone). Colorless solid, m.p. 311–312 °C (acetone), R_f 0.67, acetone. Yield: 195 mg, 62%. ^1H -NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.17 (d, $J = 0.8$ Hz, 1H), 9.59 (s, 1H), 9.36 (d, $J = 2.2$ Hz, 1H), 8.57 (d, $J = 8.9$ Hz, 1H), 8.51 (d, $J = 0.8$ Hz, 1H), 8.15 (dd, $J = 8.9, 2.2$ Hz, 1H). ^{13}C -NMR (101 MHz, DMSO) δ 161.5, 154.8, 146.1, 137.6, 133.4 (2C), 129.9, 129.8, 120.8, 120.4, 119.5, 118.3. FTIR (ZnSe) ν (cm^{-1}): 3629, 3099, 1746, 1705, 1684, 1532, 1505, 1469, 1414, 1245, 1166, 1101, 1040, 970. HRMS (ES TOF, m/z) calculated for $\text{C}_{12}\text{H}_6\text{BrN}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 337.9652, found: 337.964 (−1.3 ppm).

2-(7-Bromo-1-phenyl-[1,2,4]triazolo[4,3-*a*]quinolin-5-yl)-5-phenyl-1,3,4-oxadiazole (3dd): This compound was obtained via Method B employing 6-bromo-2-hydrazinylquinoline-4-carbohydrazide (**2d**) (295 mg, 1.00 mmol) and α -nitroacetophenone (**1d**) (495 mg, 3.00 mmol), purifying by silica gel column chromatography (gradient acetone/hexane, 1:1, v/v -acetone). Brown solid, m.p. 247–248 °C (acetone), R_f 0.51 (acetone/hexane, 1:1, v/v). Yield: 378 mg (0.68 mmol, 68%). ^1H -NMR (400 MHz, chloroform-*d*) δ 9.78 (t, $J = 1.3$ Hz, 1H), 8.64 (s, 1H), 8.24–8.21 (m, 2H), 7.74–7.62 (m, 8H), 7.59 (d, $J = 1.3$ Hz, 2H). ^{13}C -NMR (101 MHz, DMSO) δ 133.3, 132.8, 131.85, 131.4, 130.0 (5C), 129.7 (3C), 129.6 (5C), 127.5 (4C), 118.6, 117.91, 117.90. FTIR (ZnSe) ν (cm^{-1}): 3613, 3080, 1747, 1675, 1601, 1568, 1557, 1457, 1373, 1282, 1114, 1077, 945. HRMS (ES TOF, m/z) calculated for $\text{C}_{24}\text{H}_{14}\text{BrN}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 490.0258, found: 490.0274 (3.3 ppm).

Ethyl 5-(3-(ethoxycarbonyl)-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)-1,3,4-oxadiazole-2-carboxylate (3ae): This compound was obtained via Method C employing 2-hydrazinylisonicotinohydrazide (**2a**) (167 mg, 1.00 mmol) and ethyl 2-nitroacetate (**1e**) (400 mg, 3.00 mmol), purifying by silica gel column chromatography (acetone/hexane 1:4, v/v). Colorless powder, m.p. 199–200 °C (acetone), R_f 0.37, acetone/hexane (1:1, v/v). Yield: 215 mg, 65%. ^1H -NMR (400 MHz, CDCl_3) δ 9.33 (dd, $J = 7.3, 1.1$ Hz, 1H), 8.80–8.62 (m, 1H), 7.88 (dd, $J = 7.3, 1.6$ Hz, 1H), 4.61 (dq, $J = 11.1, 7.1$ Hz, 4H), 1.52 (dt, $J = 10.6, 7.1$ Hz, 6H). ^{13}C -NMR (101 MHz, CDCl_3) δ 163.6, 158.1, 157.3, 153.9, 150.5, 138.6, 127.0, 123.5, 116.4, 113.3, 64.1, 63.0, 14.3, 14.1. FTIR (ZnSe) ν (cm^{-1}): 2925, 2848, 1739, 1698, 1563, 1532, 1462, 1387, 1313, 1255, 1187, 157, 1011, 934, 848. HRMS (ES TOF, m/z) calculated for $\text{C}_{14}\text{H}_{13}\text{N}_5\text{NaO}_5^+$ ($[\text{M} + \text{Na}]^+$): 354.0797, found: 354.0809 (3.4 ppm).

Ethyl [1,2,4]triazolo[4,3-*a*]quinoline-1-carboxylate (10a). This compound was obtained via Method C (only PPA) employing 2-hydrazinylquinoline (159 mg, 1.00 mmol) and ethyl 2-nitroacetate (**2e**) (400 mg, 3.00 mmol). This material can be used in the subsequent transformation in crude form. The sample for analytical purposes was purified by

silica gel column chromatography (acetone/hexane 1:2, *v/v*) to obtain a pale-yellow solid, m.p. 145–146 °C (acetone); yield: 140 mg, 58%. R_f 0.33, acetone/hexane (1:1, *v/v*). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.85 (dq, $J = 8.7, 0.8$ Hz, 1H), 7.84 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.77–7.68 (m, 3H), 7.59 (ddd, $J = 8.2, 7.3, 1.1$ Hz, 1H), 4.64 (q, $J = 7.1$ Hz, 2H), 1.55 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 159.9, 151.2, 142.0, 132.0, 131.6, 129.9, 129.4, 127.3, 124.9, 119.4, 114.6, 63.4, 14.3. FTIR (ZnSe) ν (cm^{-1}): 3325, 3243, 3002, 1761, 1677, 1527, 1443, 1375, 1248, 1091, 1055, 949. HRMS (ES TOF, m/z) calculated for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{NaO}_2^+$ ($[\text{M} + \text{Na}]^+$): 264.0739, found: 264.0743 (1.9 ppm).

1-(5-Ethyl-1,3,4-oxadiazol-2-yl)[1,2,4]triazolo[4,3-*a*]quinoline (12a). This compound was obtained via Method A employing [1,2,4]triazolo[4,3-*a*]quinoline-1-carbohydrazide (**11a**) (227 mg, 1.00 mmol) and 1-nitropropane (**1a**) (267 mg, 3.00 mmol), purifying by silica gel column chromatography (acetone/hexane 1:2–1:1, *v/v*). Pale-brown solid, m.p. 160–161 °C (acetone); yield: 140 mg, 43%. R_f 0.37, acetone/hexane (1:1, *v/v*). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 9.56 (dq, $J = 8.6, 0.8$ Hz, 1H), 7.88 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.82–7.72 (m, 3H), 7.63 (ddd, $J = 8.2, 7.3, 1.1$ Hz, 1H), 3.11 (q, $J = 7.6$ Hz, 2H), 1.54 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 169.7, 157.2, 151.4, 136.8, 132.0, 131.8, 130.3, 129.4, 127.6, 124.9, 119.3, 114.6, 19.5, 10.9. FTIR (ZnSe) ν (cm^{-1}): 3320, 3234, 2992, 1763, 1679, 1554, 1378, 1250, 1052, 937. HRMS (ES TOF, m/z) calculated for $\text{C}_{14}\text{H}_{11}\text{N}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 288.0847, found: 288.0856 (3.1 ppm).

2-Ethyl-5-(5-methyl-[1,2,4]triazolo[4,3-*a*]quinolin-1-yl)-1,3,4-oxadiazole (12b). This compound was obtained via Method A employing 5-methyl-[1,2,4]triazolo[4,3-*a*]quinoline-1-carbohydrazide (**11b**) (241 mg, 1.00 mmol) and 1-nitropropane (**1a**) (267 mg, 3.00 mmol), purifying by silica gel column chromatography (acetone/hexane 1:2–1:1, *v/v*). Pale-yellow solid, m.p. 147–149 °C (acetone); yield: 127 mg, 47%. R_f 0.40, acetone/hexane (1:1, *v/v*). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 9.59 (d, $J = 8.5$ Hz, 1H), 8.00 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.75 (ddd, $J = 8.7, 7.3, 1.5$ Hz, 1H), 7.70–7.62 (m, 2H), 3.10 (q, $J = 7.6$ Hz, 2H), 2.71 (s, 3H), 1.53 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 169.3, 157.9, 150.9, 139.3, 136.8, 132.0, 130.0, 127.5, 125.9, 125.4, 119.4, 113.7, 19.95, 19.4, 10.9. FTIR (ZnSe) ν (cm^{-1}): 2930, 2858, 1746, 1648, 1566, 1460, 1385, 1243, 1163, 1115, 1062, 966, 848, 807. HRMS (ES TOF, m/z) calculated for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{NaO}^+$ ($[\text{M} + \text{Na}]^+$): 302.1003, found: 302.1012 (3.1 ppm).

4. Conclusions

In conclusion, an efficient protocol for simultaneous parallel cyclization of [1,2,4]triazolo[4,3-*a*]quinoline and 1,3,4-oxadiazole heterocyclic rings was developed. The featured transformation involved an unprecedented double-fold nucleophilic attack by two different hydrazine moieties of 2-hydrazineylpyridinecarbohydrazide substrates on nitroalkanes electrophilically activated in a polyphosphoric acid medium. The method provides an expeditious and direct access to [1,2,4]triazolo[4,3-*a*]quinolines bearing a 1,3,4-oxadiazole substituent, which might be of interest for medicinal chemistry. Furthermore, this research paves the road for development of other acid-mediated cascade transformations for preparation of complex heterocyclic compounds. Synthesis of a focused library for biological studies is currently underway in our laboratories.

Supplementary Materials: Supporting Information data include NMR and HRMS spectral charts and X-ray crystallography data.

Author Contributions: Conceptualization, A.V.A. and M.R.; methodology, N.A.A.; formal analysis, N.A.A., E.A.S. and C.L.; investigation, N.K.K., D.A.A. and E.A.S.; writing, C.L. and M.R.; supervision, A.V.A. and M.R.; funding acquisition, A.V.A. and N.A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Russian Foundation for Basic Research (grant #20–33–90026) and the Ministry of Education and Science of the Russian Federation (grant #0795–2020–0031).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Supplementary Materials include NMR and HRMS spectral charts and X-ray crystallography data.

Conflicts of Interest: The authors declare no conflict of interest.

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