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Flow Chemistry

Multistep Flow Synthesis of 5-Amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles

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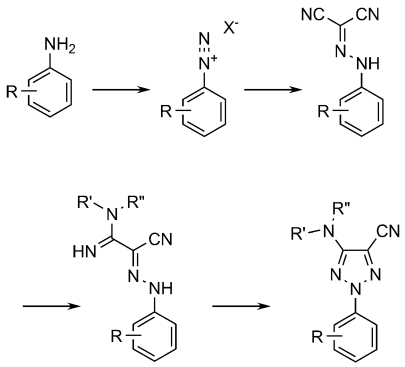
Abstract: 1,2,3-Triazole has become one of the most important heterocycles in contemporary medicinal chemistry. The development of the copper-catalyzed Huisgen cycloaddition has allowed the efficient synthesis of 1-substituted 1,2,3-triazoles. However, only a few methods are available for the selective preparation of 2-substituted 1,2,3-triazole isomers. In this context, we decided to develop an efficient flow synthesis for the preparation of various 2-aryl-1,2,3-triazoles. Our strategy involves a three-step synthesis under continuous-flow conditions that starts from the diazotization of anilines and subsequent reaction with malononitrile, followed by nucleophilic addition of amines, and finally employs a catalytic copper(II) cyclization. Potential safety hazards associated with the formation of reactive diazonium species have been addressed by inline quenching. The use of flow equipment allows reliable scale up processes with precise control of the reaction conditions. Synthesis of 2-substituted 1,2,3-triazoles has been achieved in good yields with excellent selectivities, thus providing a wide range of 1,2,3-triazoles.

Introduction

Since the discovery of the copper-catalyzed azide–alkyne cycloaddition (CuAAC), *N*-substituted 1,2,3-triazoles have become one of the most exploited heterocycles in life and materials sciences.[1] Many general synthetic methodologies have been developed for regioselective access to 1,4- and 1,5-substituted 1,2,3-triazoles.[2] In contrast, the regioselective formation of 2-substituted 1,2,3-triazoles remains challenging for triazole derivatization. 2-Aryl-1,2,3-triazoles are especially interesting derivatives because they are widely used as biologically active compounds.[2b,3] The main synthetic approaches involve condensation with arylhydrazines[4a,b] or *N*-2-arylation processes. However, arylation strategies usually face competitive *N*-1-substitution reactions, thus hampering their utility.[3b,4c] Recently, high levels of 2-selectivities have been achieved under basic conditions that start from 4,5-dibromo-1,2,3-triazole or by using copper- and palladium-based catalytic systems.[5] Nevertheless, the scope of such methodologies is limited regarding the 4- and 5-substitutions of 1,2,3-triazoles.

In terms of the biological activities of 2-substitued 1,2,3-triazoles, 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles are known as antifungal agents.[6] Thus, an improved synthetic pathway would allow further evaluation of their biological properties. The current strategy to access these compounds involves a four-step synthesis that starts from diazotization of aniline and subsequent reaction with malononitrile, followed by nucleophilic addition of an amine, and finally employs a copper(II)-mediated cyclization (Scheme 1).[6,7] A significant drawback of this methodology is the generation and isolation of highly reactive and sensitive aryl diazonium species. This issue raises significant safety concerns especially for large-scale reactions.[8]



Scheme 1. The described current strategy for the synthesis of 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitrile.

Increasing process safety has been outlined as a major asset of flow chemistry. In this regard, the development of flow chemistry as an enabling technology has been supported by both academia and industry. In addition, flow reactors offer several advantages over batch synthesis, including improved heat and mass transfer and ease of scale-up. Due to small-volume reactors in a contained environment, flow chemistry can safely generate reactive intermediates in a continuous-flow stream. For example, continuous-flow processes have enabled the efficient synthesis of aryl diazonium species with precise

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control of the reaction conditions.[9] These intermediates have been used for the continuous synthesis of azide building blocks[9a,b] and for the Sandmeyer reaction,[9c] Heck coupling,[9d] and a multistep flow synthesis of 5-amino-4-cyano-1,2,3-triazoles.[9h] To the best of our knowledge, in all the examples described in a flow mode, the aryl diazonium species have been involved as radical precursors. Herein, we describe the formation of diazonium intermediates and the subsequent nucleophilic attack of malononitrile to obtain 2-arylhydrazonomalononitriles in one flow stream. Efficiency and safety features of the process allowed us to rapidly scale up this sequence. Fully automated flow equipment enabled the production of a focused library of 2-arylhydrazonoacetamidines by the addition of various amine compounds to 2-arylhydrazonomalononitriles. Finally, 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles were obtained in good yields with excellent regioselectivities by using a new catalytic copper(II) oxidative cyclization.

Results and Discussion

Synthesis of 2-arylhydrazonomalononitriles

Our strategy to synthesize 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles started with commercially available anilines and used *tert*-butyl nitrite (*t*BuONO) as an oxidant. *t*BuONO is known as a nonexplosive stable substitute for sodium nitrite, thus allowing the formation of diazonium intermediates in batch and flow processes.[9,10] Diazonium species may decompose rapidly and uncontrollably, thus resulting in explosions and making their use hazardous in conventional batch reactors especially on a large scale.[8,11] For the synthesis of 2-arylhydrazonomalononitriles, malononitrile was solubilized with aniline to trap the diazonium species as it is formed in the flow stream, thus avoiding the accumulation and handling of explosive intermediates. In a typical experiment (Scheme 2), a solution of aniline (0.4 M) and malononitrile (0.4 M) in acetonitrile was combined with a solution of *tert*-butyl nitrite (0.52 M) in acetonitrile through a T-mixing piece and was directed to a perfluoroalkoxy (PFA) polymer tubular flow reactor maintained at room temperature to obtain 2-arylhydrazonomalononitriles in 10 minutes and in a yield of greater than 90% of the isolated product.

Interestingly, the diazonium species is generated in an organic solvent without the addition of a strong acid, such as HCl (used to obtain the more stable diazonium salt). It is also apparent that no base was needed to perform the reaction. We postulate that a diazonium intermediate is consumed rapidly upon the addition of the malononitrile nucleophile, which results from the presence of the *tert*-butanolate moiety.[12] By using these conditions, we could obtain high yields (90–99%) of the desired hydrazones **1a–f** from the corresponding anilines. It is noteworthy that similar yields were obtained with electron-donating or electron-withdrawing groups (Table 1), thus highlighting that there was no electronic effect from the C4 substituents. Finally, the optimized procedures allowed us to rapidly process various 2-arylhydrazonomalononitriles on a scale of up to 40 millimoles by using the same equipment as for the small-scale experiments (Figure 1). This outcome represents a productivity for such a process of 16.8 mmol h^{-1}.

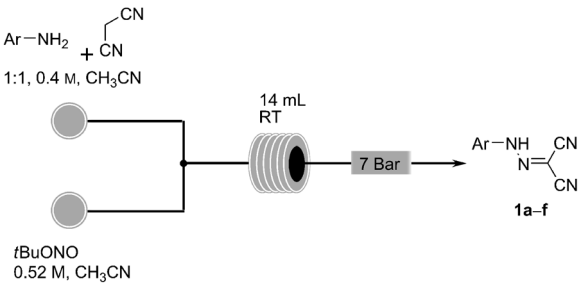
Table 1. Synthesis of 2-arylhydrazonomalononitriles **1a–f**.

Entry	Ar	Isolated product	Scale [mmol]	Yield [%][a]
1	Ph	**1a**	40	98
2	4-$MeOC_6H_4$	**1b**	40	92
3	4-MeC_6H_4	**1c**	40	98
4	4-FC_6H_4	**1d**	16	99
5	4-$NO_2C_6H_4$	**1e**	16	90
6	4-$EtO_2CC_6H_4$	**1f**	16	95

[a] Yield of the isolated product after solvent evaporation.

Synthesis of 2-arylhydrazono-2-cyanoacetamidines

We next turned our attention to the synthesis of amidines based on the direct addition of amines to nitriles. This reaction



Scheme 2. Flow synthesis of 2-arylhydrazonomalononitrile.

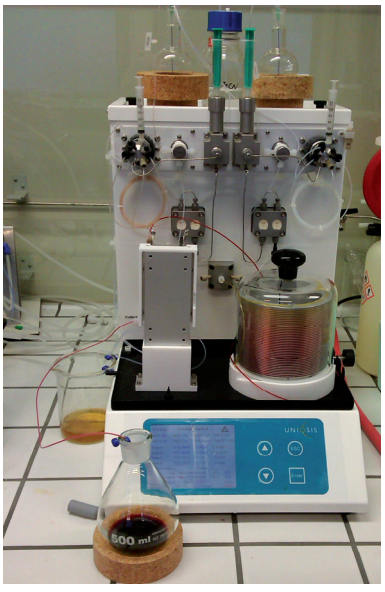
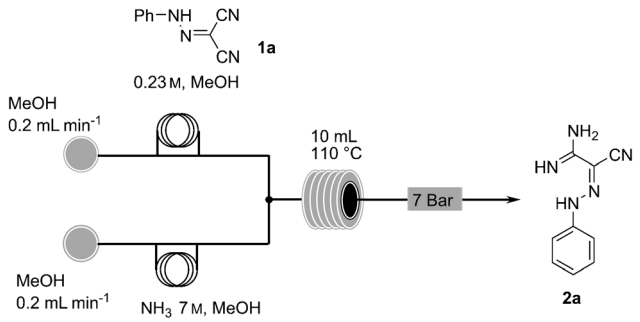


Figure 1. Uniqsis FlowSyn and setup used for the synthesis of 2-arylhydrazonomalononitrile.

is mainly driven by both the electrophilicity of the cyano group and the nucleophilicity of the amine functionality. It often requires the use of a Lewis acid or aluminum amides, high excess of the reagents, and high temperature.[13]

In our initial investigations, we examined the addition of ammonia to 2-phenylhydrazonomalononitrile (**1a**) to synthesize 3,3-diamino-2-(4-phenylazo)-acrylonitrile (**2a**; Scheme 3). As



Scheme 3. Flow synthesis of **2a**.

a gas, ammonia requires safety assessment, especially for larger-scale reactions. Although the use of gaseous ammonia has been described in continuous-flow systems,[14] we preferred to start from solutions of ammonia in methanol.[15] Furthermore ammonia in solutions at high temperature necessitates pressurization of the system. In the batch mode, sealed vessels are required for containment. Interestingly, in a continuous-flow process, simple back-pressure regulators allow immediate pressurization of the system, thus maintaining controlled solubilization of the gaseous reagent and a safer environment. The reaction was performed by using an excess of ammonia in methanol (7 M) and a back-pressure regulator of 8 bar to contain the reaction mixture as an homogeneous liquid phase. In practice, a stream containing hydrazone **1a** was mixed with a solution of ammonia in methanol (loaded through loops of 2.0 mL) in a T-mixing piece. The combined flow stream at 0.4 mL min^{-1} entered a coil reactor (10.0 mL) heated at 110 °C. High conversion (95%) into 2-arylhydrazono-2-cyanoacetamidine **2** with high purity was achieved in a residence time of 25 minutes.

The ability to perform multistep sequences in a continuous-flow stream by telescoping various reagents enhances the access to highly functionalized compounds. Such developments represent a significant challenge considering dispersion phenomena, solvent compatibility, and byproduct formation.[16] To this end, an automated system was set up to combine the synthesis of 2-arylhydrazonomalononitrile and the addition of ammonia in a continuous process (Scheme 4). A flow stream of aniline and malononitrile in acetonitrile (1:1, 0.4 M) was combined with a second flow stream of *tert*-butyl nitrite in acetonitrile (0.52 M) through a T-mixing piece (total flow rate = 0.30 mL min^{-1}). The mixed solution was passed through a PFA flow reactor at room temperature (5.0 mL). The stream containing hydrazine **1a** was telescoped with ammonia in methanol (7 M, flow rate = 0.30 mL min^{-1}), and the mixture was fed through two PFA flow reactors (10.0 mL) at 110 °C.

We were pleased to observe that this system facilitated quantitative conversion into the desired product **2a** with a high-purity profile. Finally, the system was run in a scale-up process as described for 6.25 hours at steady state. By the end of the process, 4.1 grams of product were obtained with good purity by simple evaporation of the solvents and excess of ammonia (Figure 2).

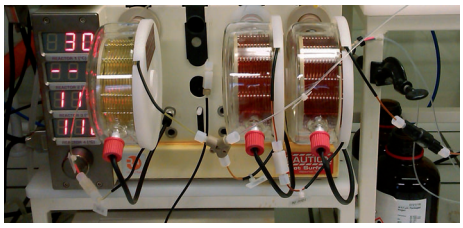
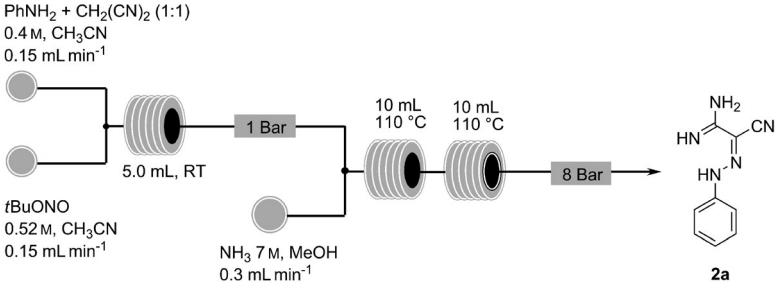


Figure 2. Reactor design for the multistep flow synthesis of **2a**.

As part of our ongoing efforts to develop automated flow processes for focused library production, we describe the use of an automated system to generate a collection of 2-arylhydrazono-2-cyanoacetamidines **2**, which are key intermediates for triazole synthesis. Various cyclic amines **3**, such as pyrrolidine **3a**, piperidine **3b**, morpholine **3c**, and piperazine **3d**, were combined with the different hydrazone derivatives **1a–f** obtained in the first step. Equimolar solutions of amines **3a–d** in ethanol and hydrazones **1a–f** in THF/ethanol mixtures were prepared and allocated positions in a Gilson liquid handler. Depending of the nature of the hydrazone, various amounts of THF were used to obtain complete dissolution of the starting material at 0.25 M. The liquid handler was used to inject feed solutions into the flow stream and to collect 2-arylhydrazonoacetamidines **2a–p**.

In a typical sequence, sample loops A and B (5 mL) were loaded with solutions of the starting materials from the auto-



Scheme 4. Multistep flow synthesis of **2a**.

sampler, switched into line, and driven with a constant stream of ethanol. After passing through a T-mixing piece, the combined flow streams were directed through a PFA-coated stainless-steel reactor (16 mL) heated at 100 °C. The resulting reaction mixture passed through a back-pressure regulator and a UV-detector to trigger collection at the liquid handler (Figure 3 and Scheme 5). In this way, 15 sequential reactions

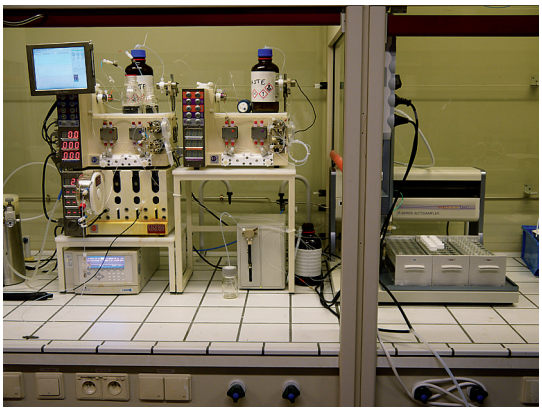
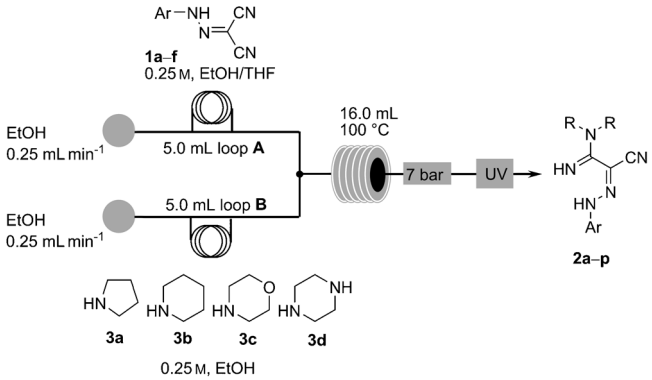


Figure 3. Automated Vapourtec system with Gilson liquid handler (the setup for the library synthesis).



Scheme 5. Automated library flow synthesis of 2-arylhydrazono-2-cyanoacetamidines **2b–p**.

were performed by the automated system without any manual input. All the products were isolated in good-to-excellent yields by parallel evaporation (Table 2). No clogging or cross-contamination were observed in any case.

Synthesis of 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles

The oxidative cylization of 2-arylhydrazonoacetamidines **2** has been previously described with two equivalents of copper acetate in pyridine at 60 °C to form triazoles in good yields.[7] Our primary objective was to develop an efficient flow process based on the batch procedure. The reactions were performed in DMF to solubilize the starting materials, and a flow system was assembled (Scheme 6). A solution of copper acetate in

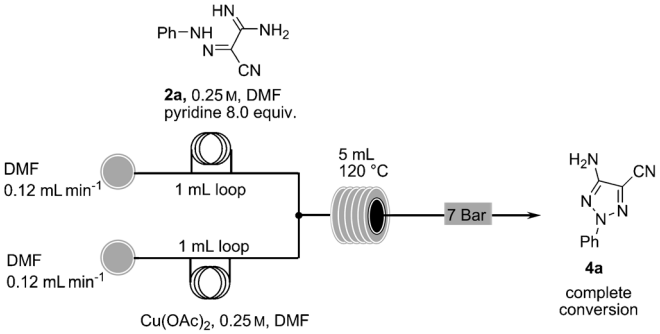
Table 2. Synthesis of **2a** and automated library synthesis of 2-arylhydrazono-2-cyanoacetamidines **2b–p**.

Entry	1	Amine	Isolated product	Yield [%][a]
1	**1a**	NH_3	**2a**	95[b]
2	**1a**	**3a**	**2b**	96
3	**1a**	**3b**	**2c**	96
4	**1a**	**3c**	**2d**	91
5	**1a**	**3d**	**2e**	98
6	**1b**	**3a**	**2f**	72
7	**1b**	**3b**	**2g**	90
8	**1b**	**3c**	**2h**	86
9	**1b**	**3d**	**2i**	88
10	**1c**	**3b**	**2j**	90
11	**1c**	**3c**	**2k**	95
12	**1c**	**3d**	**2l**	98
13	**1d**	**3a**	**2m**	89
14	**1d**	**3b**	**2n**	87
15	**1e**	**3c**	**2o**	87

Table 2. (Continued)

Entry	1	Amine	Isolated product	Yield [%][a]
16	**1f**	**3c**	**2p**	95

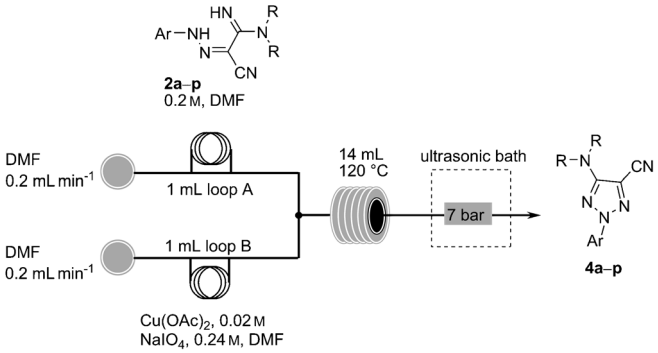
[a] All reactions were performed on a scale of 1.25 mmol. [b] The reaction was performed on scale of 0.46 mmol according to the setup described in Scheme 3; product **2a** was obtained with 90% purity (determined by LC-MS analysis).



Scheme 6. Flow synthesis of 1,2,3-triazoles adapted from the batch procedure.

DMF (0.25 M) was mixed with a solution of 3,3-diamino-2-phenylazo-acrylonitrile (**2a**; 0.25 M, 1.0 equiv) and pyridine (8 equiv) in DMF. The resulting flow stream (total flow rate = 0.24 mL min^{-1}) was delivered to a PFA coil reactor (5 mL) heated at 120 °C. We observed complete conversion of the starting material; however, isolation of product **4a** proved tedious due to the large amount of copper residues, which prompted us to evaluate the catalytic protocols.

Rapid optimization of the reactions parameters in the batch mode revealed that a catalytic amount of $Cu(OAc)_2$ (20 mol%) led to a good conversion of starting material **2a** (75%) in DMF at 80 °C in an air atmosphere. Accordingly, we explored the scope of this result with various oxidants, such as NaOCl, H_2O_2, O_2, *tert*-butyl hydroperoxide, and $NaIO_4$ (2.0 equiv). Sodium periodate ($NaIO_4$) clearly appeared to be the most effective reagent by giving a clean conversion into the desired 1,2,3-triazole product in the presence or absence of pyridine.[17] With optimal conditions in hand, we performed this critical oxidative cyclization step as a flow process (Scheme 7). Solutions of 2-arylhydrazonoacetamidine **3** in DMF (0.2 M) and solutions of DMF containing $NaIO_4$ (1.2 equiv, 0.24 mM) and $Cu(OAc)_2$ (10 mol%, 0.02 M) were separately loaded into individual loops (1.0 mL) mounted on the Uniqsis FlowSyn equipment. The solutions were combined at in a T-mixing piece connector, and the resulting flow was passed through a PFA flow coil (14 mL) heated at 120 °C. A back-pressure regulator (7 bar) was placed in a sonication bath (Scheme 7) to avoid clogging because of the precipitation of inorganic species.[18] A residence time of



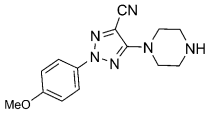
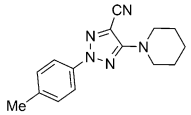
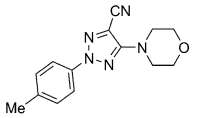
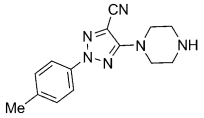
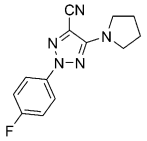
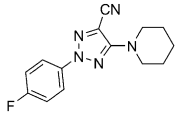
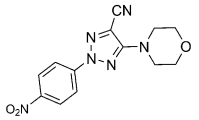
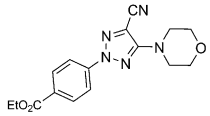
Scheme 7. Setup for the synthesis of 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles **4a–p**.

35 minutes was suitable for full consumption of the starting material. Collected solutions of the fractions were evaporated and the desired triazole products **4** could be isolated by solubilizing the crude material in dichloromethane to precipitate inorganic salts and filtration on a cartridge filled with a pad of celite and silica gel. 5-Amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles **4a–p** were thus generated in flow from 2-arylhydrazonoacetamidines **3a–p** in moderate-to-excellent yields (Table 3).

Table 3. Synthesis of 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles **4a–p**.

Entry	Acetamide	Isolated product	Yield [%][a]
1	**2a**	**4a**	50
2	**2b**	**4b**	87
3	**2c**	**4c**	95
4	**2d**	**4d**	68
5	**2e**	**4e**	48
6	**2f**	**4f**	82
7	**2g**	**4g**	98
8	**2h**	**4h**	92

Table 3. (Continued)

Entry	Acetamide	Isolated product	Yield [%][a]
9	**2i**	**4i** 	22
10	**2j**	**4j** 	80
11	**2k**	**4k** 	93
12	**2l**	**4l** 	65
13	**2m**	**4m** 	97
14	**2n**	**4n** 	77
15	**2o**	**4o** 	83
16	**2p**	**4p** 	61

[a] All reactions performed on a 0.2 mmol scale.

Conclusion

We have demonstrated that flow chemistry is a promising and powerful enabling method to facilitate and accelerate the preparation of biological relevant heterocyclic compounds. We designed a sequence of reactions to safely scale up the production of hazardous diazonium intermediates and the use of a solution of ammonia in one flow stream. An automated flow device enabled us to quickly prepare a collection of key compounds in adequate quantities for further derivatization. A novel catalytic copper oxidative cyclization in a flow mode provided a more sustainable-chemistry practice for the synthesis of 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles **4a–p**. The final compounds were obtained with excellent purities and in good yields without the need for complex downstream process. Overall, the synthetic pathway allowed the synthesis of 2-aryl-1,2,3-triazoles with complete selectivity without traces of other isomers being observed. Furthermore, such a sequence represents several improvements relative to the conventional batch-mode approach in terms of praticability, safety, and yield.

Experimental Section

General

Reagents were obtained from commercial sources and were used without purification. The removal of the solvent under reduced pressure was carried out on a standard rotary evaporator and completed by using a vacuum pump. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer with the residual solvent peak as an internal reference ([D$_6$]DMSO = 2.50 and 39.52 ppm for ^{1}H and ^{13}C NMR, respectively). ^{1}H NMR resonances are reported to the nearest 0.01 ppm. ^{13}C NMR resonances were reported to the nearest 0.1 ppm. The multiplicity of ^{1}H NMR signals are indicated as s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, or combinations of thereof. Coupling constants *J* are quoted in Hz and are reported to the nearest 0.1 Hz. Where appropriate, averages of the signals that display multiplicity were used to calculate the value of the coupling constant. IR spectra were measured of neat samples on a PerkinElmer Spectrum 2000 FTIR spectrometer by using universal attenuated total reflection (ATR) sampling accessories. LC-MS analysis was performed on a QM Waters triple quadrupole mass spectrometer. This spectrometer was equipped with an ESI source and an HPLC Waters 2795 quaternary pump with a diode-array detector (λ = 210–400 nm). Data were acquired in a full MS scan from *m/z* 50–750 in the positive and negative modes with basic elution. Gradient elution was carried out with water, acetonitrile, and ammonium formate in water (630 mg L^{-1}) + NH_4OH (30%, 500 μL L^{-1}). The *m/z* value is reported to the nearest mass unit. High-resolution mass-spectrometric analysis was performed with a Waters Micromass LCT Premier spectrometer by means of time-of-flight with positive ESI. This spectrometer was equipped with an ESI source and an UPLC Waters with diode-array detector (λ = 210–400 nm). Data were acquired in a full MS scan from *m/z* 50 to 1000 in the positive mode with an acid elution. Gradient elution was carried out with formic acid (0.5 mL L^{-1}) in acetonitrile/water (5:95) and formic acid (0.375 mL L^{-1}) in acetonitrile. All the flow reactions were performed by using etheir a Vapourtec R-series flow platform or a Uniqsis FlowSyn flow system.

General procedure A for the synthesis 2-arylhydrazonomalononitriles 1a–f

A solution of aniline (0.4 M in MeCN) and malononitrile (1 equiv, 0.4 M) and a solution of *tert*-butyl nitrite (0.52 M) in MeCN were pumped at a flow rate of 0.7 mL min^{-1} each. The starting materials mixed in a arrowhead T-mixing piece (I.D. = 1.4 mm) and the reaction solution (combined flow rate = 1.4 mL min^{-1}) passed through a coil reactor (14 mL; I.D. = 1 mm) at room temperature and exited the flow system through a back-pressure regulator (7 bar). Crude products **1** were obtained by evaporation of the solvent.

Phenylhydrazonomalononitrile (1a): Product **1a** was obtained from aniline according to general procedure A. The reaction was performed on a scale of 40 mmol. The product was obtained as a yellow–green solid (6.66 g, 39.2 mmol, 98%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.44 (m, 4H), 7.22 ppm (t, 1H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 141.4 (C), 129.5 (2×CH), 125.8 (CH), 116.5 (2×CH), 114.4 (C), 110.0 (C), 84.5 ppm (C); FTIR (neat): $\tilde{\nu}$ = 3192, 3131, 3060, 2232, 2213, 1542, 1468, 1442, 1279, 754, 692 cm^{-1}; LC-MS: *m/z* 168.9 [*M*−H]$^-$.

(4-Methoxyphenyl)hydrazonomalononitrile (1b): Product **1b** was obtained from 4-methoxyaniline according to general procedure A. The reaction was performed on scale of 40 mmol. The product was obtained as a brown solid (7.36 g, 36.8 mmol, 92%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.42 (d, 2H, J = 9.1 Hz), 6.99 (d, 2H, J = 9.1 Hz), 3.75–3.79 ppm (m, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 157.9 (C), 135.3 (C), 118.4 (2×CH), 115.1 (2×CH), 110.6 (C), 83.2 (C), 55.8 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}$ = 3195, 3132, 3061, 2360, 2218, 1612, 1545, 1509, 1439, 1242, 1164, 1027, 825, 724 cm^{-1}; LC-MS: *m/z* 199.1 [*M*−H]$^-$.

(4-Methylphenyl)hydrazonomalonotrile (1c): Product **1c** was obtained from 4-methylaniline according to general procedure A. The reaction was performed on scale of 40 mmol. The product was obtained as a yellow–green solid (7.21 g, 39.2 mmol, 98%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.37 (d, 2H, J = 8.4 Hz), 7.23 (d, 2H, J = 8.4 Hz), 3.33–3.49 (br s, 1H), 2.30 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.5 (C), 135.8 (C), 130.3 (2×CH), 116.8 (2×CH), 114.8 (C), 110.4 (C), 84.1 (C), 20.9 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}$ = 3233, 3204, 2226, 2215, 1608, 1545, 1437, 1281, 810, 711 cm^{-1}; LC-MS: *m/z* 183.0 [*M*−H]$^-$.

(4-Fluorophenyl)hydrazonomalononitrile (1d): Product **1d** was obtained from 4-fluoroaniline according to general procedure A. The reaction was performed on scale of 16 mmol. The product was obtained as a brown solid (2.98 g, 15.84 mmol, 99%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.49 (m, 2H), 7.27 ppm (t, 2H, J = 8.7 Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 159.9 (C, J = 242.8 Hz), 138.4 (C), 118.4 (2×CH, J = 8.8 Hz), 116.3 (2×CH, J = 23.5 Hz), 114.6 (C), 110.2 (C), 84.1 ppm (C); FTIR (neat): $\tilde{\nu}$ = 3218, 3159, 3078, 2218, 1623, 1558, 1509, 1296, 1220, 832, 730 cm^{-1}; LC-MS: *m/z* 187.1 [*M*−H]$^-$.

(4-Nitrophenyl)hydrazonomalononitrile (1e): Product **1e** was obtained from 4-nitroaniline according to general procedure A. The reaction was performed on scale of 16 mmol. The product was obtained as a dark-red solid (3.01 g, 14.4 mmol, 90%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.55 (d, 2H, J = 7.5 Hz), 7.33 (t, 2H, 7.6 Hz), 7.20 (br s, 1H), 7.12 ppm (t, 1H, J = 7.3 Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 147.2 (C), 144.3 (C), 125.9 (2×CH), 117.1 (2×CH), 114.2 (C), 109.9 (C), 88.9 ppm (C); FTIR (neat): $\tilde{\nu}$ = 3223, 3092, 2225, 1560, 1508, 1459, 1339, 1279, 1109, 849, 751, 691 cm^{-1}; LC-MS: *m/z* 214.1 [*M*−H]$^-$.

(4-Carbethoxyphenyl)hydrazonomalononitrile (1f): Product **1f** was obtained from ethyl 4-aminobenzoate according to general procedure A. The reaction was performed on scale of 16 mmol. The product was obtained as a yellow solid (3.68 g, 15.1 mmol, 95%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.99 (d, 2H, J = 8.8 Hz), 7.56 (d, 2H, J = 8.8 Hz), 4.30 (q, 2H, J = 7.1 Hz), 3.21–3.57 (br s, 1H), 1.32 ppm (t, 3H, J = 7.1 Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 165.1 (C), 145.5 (C), 130.8 (2×CH), 126.3 (C), 116.3 (2×CH), 114.3 (C), 109.8 (C), 86.5 (C), 60.7 (CH$_2$), 14.2 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}$ = 3227, 3197, 3059, 2230, 1701, 1606, 1544, 1471, 1265, 1107, 854, 770, 701 cm^{-1}; LC-MS: *m/z* 241.1 [*M*−H]$^-$.

Multistep synthesis of 3,3-diamino-2-phenylazo-acrylonitrile (2a)

A stock solution of aniline (0.40 M) and malononitrile (0.40 M) in acetonitrile and a stock solution of *tert*-butyl nitrite (0.52 M) in acetonitrile were pumped at a flow rate of 0.15 mL min^{-1} (for each solution) and were combined in a T-mixing piece (I.D. = 0.5 mm). The mixed flow stream was pumped through a PFA reactor (5.0 mL, I.D. = 1 mm) at room temperature and a flow rate of 0.30 mL min^{-1}. The output stream was combined in a T-mixing piece (I.D. = 0.5 mm) with a constant stream of ammonia in methanol (7 M) pumped at a flow rate of 0.30 mL min^{-1}. The stock solution of ammonia in methanol was pressurized at 0.6 bar. The resulting stream was pumped (at 0.60 mL min^{-1}) through two consecutive coil reactors (10.0 mL, I.D. = 1 mm) heated at 110 °C (total residence time = 33 min). The output stream passed through a back-pressure regulator (8 bar). After steady state (i.e., 1 h), the stream was collected in a flask for 6.25 h. The collected fraction was evaporated and product **2a** was obtained as a black solid (4.1 g, 21.9 mmol, 97%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.55 (d, 2H, J = 8.0 Hz), 7.32 (t, 2H, J = 7.5 Hz), 7.24 (s, 3H), 7.12 ppm (t, 1H, J = 7.2 Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.3 (C), 153.0 (C), 128.6 (2×CH), 125.5 (CH), 120.3 (2×CH), 115.5 (C), 91.2 ppm (C); FTIR (neat): $\tilde{\nu}$ = 3407, 3347, 3199, 2184, 1618, 1535, 1388, 755, 697, 648 cm^{-1}; LC-MS: *m/z* 186.1 [*M*−H]$^-$; HRMS (ESI): *m/z* calcd for $C_9H_9N_5$: 188.0936; found: 188.0932.

General procedure B for the synthesis of 2-arylhydrazono-2-cyanoacetamidines (2b–p)

Sample loop A (5.0 mL) was filled with a stock solution of arylhydrazonomalononitrile **1a–f** (1.25 mmol, 0.25 M) in EtOH/THF mixtures and sample loop B (5.0 mL) was filled with a stock solution of amine **3a–d** (pyrrolidine, piperidine, morpholine, or piperazine; 1.25 mmol, 0.25 M) in EtOH. The two sample loops were simultaneously switched into line and the starting material solutions were pumped through the system at a flow rate of 0.25 mL min^{-1} each, driven by pumps with a constant stream of EtOH. The starting materials were mixed in a T-mixing piece (I.D. = 0.5 mm), and the reaction solution (combined flow rate = 0.50 mL min^{-1}) passed through a PFA-coated stainless-steel reactor (16.0 mL, I.D. = 2.1 mm) heated at 100 °C (residence time = 33 min) and exited the flow system through a back-pressure regulator (7 bar). The output stream was collected on the Gilson platform in a tube and products **2b–p** were obtained by evaporation of the solvent.

2-Phenylhydrazono-2-cyano-*N*,*N*-butylmethylen-acetamidine (2b): Product **2b** was obtained from product **1a** and pyrrolidine **3a** according to general procedure B. Compound **1a** was dissolved in an EtOH/THF mixture (95:5, v/v). Product **2b** was obtained as an orange solid (290 mg, 1.20 mmol, 96%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.48 (d, 2H, J = 7.6 Hz), 7.32 (t, 2H, J = 7.5 Hz), 7.22–7.28 (m, 2H), 7.10 (t, 1H, J = 7.2 Hz), 3.58–3.70 (m, 4H), 1.94 ppm (t, 4H, J = 6.3 Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 158.3 (C), 153.6 (C), 128.7 (2×CH), 125.2 (CH), 120.4 (2×CH), 117.1 (C), 92.4 (C), 49.7 (2×CH$_2$), 24.8 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3383, 3302, 3212, 2980, 2181, 1560, 1478, 1376, 1357, 1305, 1220, 761, 697 cm^{-1}; LC-MS: *m/z* 242.18 [*M*+H]$^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{15}N_5$: 242.1405; found: 242.1411.

2-Phenylhydrazono-2-cyano-*N*,*N*-pentamethylen-acetamidine (2c): Product **2c** was obtained from product **1a** and piperidine **3b** according to general procedure B. Compound **1a** was dissolved in an EtOH/THF mixture (95:5, v/v). Product **2c** was obtained as a brown solid (306 mg, 1.20 mmol, 96%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.54–7.61 (br s,1H), 7.49 (d, 2H, J = 7.5 Hz), 7.32 (t, 2H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.2 Hz), 3.51–3.63 (m, 4H), 1.59–1.70 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.1 (C), 153.6 (C), 128.6 (2×CH), 125.3 (CH), 120.4 (2×CH), 117.0 (C), 92.7 (C), 49.3 (2×CH$_2$), 25.6 (2×CH$_2$), 23.6 ppm (CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3297, 3203, 2933, 2184, 1619, 1560, 1478, 1379, 1313, 1204, 992, 764, 694 cm^{-1}; LC-MS: *m/z* 256.24 [*M*+H]$^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{17}N_5$: 256.1562; found: 256.1554.

2-Phenylhydrazono-2-cyano-*N*,*N*-(3-oxopentamethylen)-acetamidine (2d): Product **2d** was obtained from product **1a** and morpholine **3c** according to general procedure B. Compound **1a** was dissolved in an EtOH/THF mixture (95:5, v/v). The product **2d** was

obtained as an orange solid (292 mg, 1.14 mmol, 91%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.72 (br s, 1H), 7.51 (d, 2H, J = 7.5 Hz), 7.34 (t, 2H, J = 7.5 Hz), 7.14 (t, 1H, J = 7.2 Hz), 3.71 (m, 4H), 3.62 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.5 (C), 153.4 (C), 128.7 (2×CH$_2$), 125.7 (CH), 120.5 (2×CH$_2$), 116.9 (C), 92.7 (C), 66.0 (2×CH$_2$), 48.7 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3428, 3275, 3079, 2973, 2892, 2852, 2194, 1626, 1552, 1490, 1356, 1314, 1219, 1119, 1007, 762, 686 cm^{-1}; LC-MS: m/z 258.20 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{13}H_{15}N_5O$: 258.1355; found: 258.1346.

2-Phenylhydrazono-2-cyano-*N*,*N*-(3-nitrosopentamethylen)-acetamidine (2e): Product **2e** was obtained from **1a** and piperazine **3d** according to general procedure B. Compound **1a** was dissolved in an EtOH/THF mixture (95:5, v/v). Product **2e** was obtained as a red solid (314 mg, 1.23 mmol, 98%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.49 (d, 2H, J = 7.6 Hz), 7.32 (t, 2H, J = 7.6 Hz), 7.11 (t, 1H, J = 7.2 Hz), 3.52 (m, 4H), 2.79 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.4 (C), 153.6 (C), 128.6 (2×CH), 125.4 (CH), 120.4 (2×CH), 117.0 (C), 92.8 (C), 49.8 (2×CH$_2$), 45.6 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3309, 2180, 1542, 1475, 1364, 1305, 1210, 1097, 993, 763, 692 cm^{-1}; LC-MS: m/z 257.10 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{13}H_{16}N_6$: 257.1515; found: 257.1505.

2-(4-Methoxyphenylhydrazono)-2-cyano-*N*,*N*-butylmethylen-acetamidine (2f): Product **2f** was obtained from **1b** and pyrrolidine **3a** according to general procedure B. Compound **1b** was dissolved in an EtOH/THF mixture (67:33, v/v). Product **2f** was obtained as a dark-green solid (244 mg, 0.90 mmol, 72%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.47 (d, 2H, J = 8.7 Hz), 7.13 (br s, 1H), 6.89 (d, 2H, J = 8.8 Hz), 3.76 (s, 3H), 3.63 (m, 4H), 1.94 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 158.3 (C), 157.4 (C), 121.5 (2×CH), 117.5 (C), 113.9 (2×CH), 105.5 (C), 91.5 (C), 55.2 (CH$_3$), 49.5 (2×CH$_2$), 24.9 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3457, 3321, 2972, 2182, 1603, 1557, 1478, 1379, 1357, 1225, 1173, 1104, 1027, 828 cm^{-1}; LC-MS: m/z 272.20 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{14}H_{17}N_5O$: 272.1511; found: 272.1512.

2-(4-Methoxyphenylhydrazono)-2-cyano-*N*,*N*-pentamethylen-acetamidine (2g): Product **2g** was obtained from **1b** and piperidine **3b** according to general procedure B. Compound **1b** was dissolved in an EtOH/THF mixture (67:33, v/v). Product **2g** was obtained as a black solid (322 mg, 1.13 mmol, 90%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.47 (d, 2H, J = 8.9 Hz), 7.43 (br s, 1H), 6.90 (d, 2H, J = 8.9 Hz), 3.75 (s, 3H), 3.54 (m, 4H), 1.59 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.6 (C), 157.9 (C), 148.0 (C), 121.9 (2×CH), 117.7 (C), 114.3 (2×CH), 92.4 (C), 55.6 (CH$_3$), 49.7 (2×CH$_2$), 26.1 (2×CH$_2$), 24.1 ppm (CH$_2$); FTIR (neat): $\tilde{\nu}$ = 2925, 2185, 1601, 1541, 1508, 1236, 1025, 832 cm^{-1}; LC-MS: m/z 286.20 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{15}H_{19}N_5O$: 286.1668; found: 286.1673.

2-(4-Methoxyphenylhydrazono)-2-cyano-*N*,*N*-(3-oxopentamethylen)-acetamidine (2h): Product **2h** was obtained from **1b** and morpholine **3c** according to general procedure B. Compound **1b** was dissolved in an EtOH/THF mixture (67:33, v/v). Product **2h** was obtained as a black solid (308 mg, 1.07 mmol, 86%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.56 (s, 1H), 7.48 (d, 2H, J = 8.8 Hz), 6.91 (d, 2H, J = 8.8 Hz), 3.76 (s, 3H), 3.69 (m, 4H), 3.59 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.5 (C), 157.7 (C), 147.5 (C), 121.7 (2×CH), 117.2 (C), 113.9 (2×CH), 92.1 (C), 66.0 (2×CH$_2$), 55.2 (CH$_3$), 48.7 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3282, 3199, 2912, 2858, 2174, 1599, 1544, 1388, 1314, 1238, 1103, 1020, 996, 830 cm^{-1}; LC-MS: m/z 288.17 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{14}H_{17}N_5O_2$: 288.146; found: 288.1451.

2-(4-Methoxyphenylhydrazono)-2-cyano-*N*,*N*-(3-nitrosopentamethylen)-acetamidine (2i): Product **2i** was obtained from **1b** and piperazine **3d** according to general procedure B. Compound **1b** was dissolved in an EtOH/THF mixture (67:33, v/v). Product **2i** was obtained as a brown solid (315 mg, 1.10 mmol, 88%; mixture of isomers 1 and 2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): isomer 1: δ = 7.47 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.6 Hz), 3.76 (s, 3H), 3.60 (m, 4H), 2.88 ppm (m, 4H); isomer 2: δ = 7.47 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.6 Hz), 3.76 (s, 3H), 3.51 (m, 4H), 2.81 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 157.6 (C), 147.6 (C), 132.7 (C), 121.6 (2×CH), 113.9 (2×CH), 99.7 (C), 92.0 (C), 55.2 (2×CH$_3$), 49.5 (2×CH$_2$), 45.5 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 2911, 2179, 1541, 1490, 1375, 1313, 1240, 1000, 832 cm^{-1}; LC-MS: m/z 287.18 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{14}H_{18}N_6O$: 287.162; found: 287.1614.

2-(4-Methylphenylhydrazono)-2-cyano-*N*,*N*-pentamethylen-acetamidine (2j): Product **2j** was obtained from **1c** and piperidine **3b** according to general procedure B. Compound **1c** was dissolved in an EtOH/THF mixture (56:44, v/v). Product **2j** was obtained as a brown solid (302 mg, 1.12 mmol, 90%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.46–7.53 (br s, 1H), 7.40 (d, 2H, J = 8.1 Hz), 7.13 (d, 2H, J = 8.1 Hz), 3.49–3.59 (m, 4H), 2.29 (s, 3H), 1.53–1.71 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.2 (C), 151.5 (C), 134.6 (C), 129.2 (2×CH), 120.3 (2×CH), 117.2 (C), 92.3 (C), 49.3 (2×CH$_2$), 25.6 (2×CH$_2$), 23.7, 20.7 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}$ = 3358, 2927, 2852, 2187, 1627, 1535, 1482, 1365, 1310, 1207, 1084, 992, 816 cm^{-1}; LC-MS: m/z 270.23 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{15}H_{19}N_5$: 270.1718; found: 270.1715.

2-(4-Methylphenylhydrazono)-2-cyano-*N*,*N*-(3-oxopentamethylen)-acetamidine (2k): Product **2k** was obtained from **1c** and morpholine **3c** according to general procedure B. Compound **1c** was dissolved in an EtOH/THF mixture (56:44, v/v). Product **2k** was obtained as a yellow solid (322 mg, 1.19 mmol, 95%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.63 (br s, 1H), 7.41 (d, 2H, J = 8.2 Hz), 7.14 (d, 2H, J = 8.2 Hz), 3.70 (m, 4H), 3.60 (m, 4H), 2.29 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.5 (C), 151.4 (C), 135.0 (C), 129.2 (2×CH), 120.4 (2×CH), 117.1 (C), 92.4 (C), 66.0 (2×CH$_2$), 48.7 (2×CH$_2$), 20.7 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}$ = 3407, 3300, 3212, 2859, 2183, 1648, 1622, 1541, 1488, 1376, 1316, 1206, 1099, 993, 821 cm^{-1}; LC-MS: m/z 272.20 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{14}H_{17}N_5O$: 272.1511; found: 272.152.

2-(4-Methylphenylhydrazono)-2-cyano-*N*,*N*-(3-nitrosopentamethylen)-acetamidine (2l): Product **2l** was obtained from **1c** and piperazine **3d** according to general procedure B. Compound **1c** was dissolved in an EtOH/THF mixture (56:44, v/v). Product **2l** was obtained as a brown solid (331 mg, 1.23 mmol, 98%; mixture of isomers 1 and 2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): isomer 1: δ = 7.53 (s, 1H), 7.40 (d, 2H, J = 8.2 Hz), 7.13 (d, 2H, J = 8.1 Hz), 3.80 (m, 4H), 2.69 (m, 4H), 2.29 ppm (s, 3H); isomer 2: δ = 7.53 (s, 1H), 7.40 (d, 2H, J = 8.2 Hz), 7.13 (d, 2H, J = 8.1 Hz), 3.49 (m, 4H), 2.78 (m, 4H), 2.29 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.4 (C), 151.5 (C), 134.7 (C), 129.2 (2×CH), 120.3 (2×CH), 117.2 (C), 92.3 (C), 49.8 (2×CH$_2$), 45.6 (2×CH$_2$), 20.7 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}$ = 3298, 3198, 2188, 1619, 1550, 1487, 1376, 1305, 1120, 1001, 823 cm^{-1}; LC-MS: m/z 271.21 [M+H]$^+$; HRMS (ESI): m/z calcd for $C_{14}H_{18}N_6$: 271.1671; found: 271.1668.

2-(4-Fluorophenylhydrazono)-2-cyano-*N*,*N*-butylmethylen-acetamidine (2m): Product **2m** was obtained from **1c** and pyrrolidine **3a** according to general procedure B. Compound **1d** was dissolved in an EtOH/THF mixture (67:33, v/v). Product **2m** was obtained as a dark-green solid (288 mg, 1.11 mmol, 89%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.52 (m, 2H), 7.25–7.30 (br s, 1H), 7.14 (t, 2H, J = 8.6 Hz), 3.57–3.68 (m, 4H), 1.89–1.98 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.0 (d, C, J = 242 Hz), 158.3 (C), 150.4 (C), 121.8 (d, 2 CH, J = 8 Hz), 117.1 (C), 115.3 (d, 2 CH, J = 22 Hz), 92.2 (C), 49.7 (2×CH$_2$), 24.8 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}$ = 3387,

3301, 3206, 2972, 2187, 1596, 1551, 1477, 1375, 1355, 1210, 837 cm^{-1}; LC-MS: *m/z* 260.18 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}FN_5$: 260.1311; found: 260.1316.

2-(4-Fluorophenylhydrazono)-2-cyano-*N*,*N*-pentamethylen-acetamidine (2n): Product **2n** was obtained from **1d** and piperidine **3b** according to general procedure B. Compound **1d** was dissolved in an EtOH/THF mixture (67:33, v/v). Product **2n** was obtained as a dark-green solid (297 mg, 1.08 mmol, 87%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.59$ (br s, 1H), 7.52 (dd, 2H, $J=8.9$, 5.4 Hz), 7.14 (t, 2H, $J=8.8$ Hz), 3.57 (m, 4H), 1.64 ppm (s, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=162.2$ (C), 161.5 (d, C, $J=214.9$ Hz), 150.4 (C), 121.8 (d, 2 CH, $J=8.1$ Hz), 117.0 (C), 115.3 (d, 2 CH, $J=22.7$ Hz), 92.6 (C), 49.3 (2×CH$_2$), 25.6 (2×CH$_2$), 23.6 ppm (CH$_2$); FTIR (neat): $\tilde{\nu}=3395$, 3298, 3203, 2933, 2184, 1619, 1560, 1478, 1379, 1360, 1313, 1195, 1089, 994, 842 cm^{-1}; LC-MS: *m/z* 274.23 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}FN_5$: 274.1468; found: 274.1465.

2-(4-Nitrophenylhydrazono)-2-cyano-*N*,*N*-(3-oxopentamethylen)-acetamidine (2o): Product **2o** was obtained from **1e** and morpholine **3c** according to general procedure B. Compound **1e** was dissolved in THF. Product **2o** was obtained as a red solid (328 mg, 1.08 mmol, 87%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=8.16$ (d, 2H, $J=9.0$ Hz), 8.09 (br s, 1H), 7.61 (d, 2H, $J=9.0$ Hz), 3.73 (d, 4H, $J=4.6$ Hz), 3.67 ppm (d, 4H, $J=4.5$ Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=161.8$ (C), 158.8 (C), 143.2 (C), 124.8 (2×CH), 120.3 (2×CH), 115.7 (C), 96.4 (C), 65.9 (2×CH$_2$), 48.9 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=$ 3415, 3373, 3277, 3181, 2198, 1558, 1490, 1307, 1093, 1018, 1000, 845 cm^{-1}; LC-MS: *m/z* 303.15 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}N_6O_3$: 303.1205; found: 303.1207.

2-(4-Carbethoxyhydrazono)-2-cyano-*N*,*N*-(3-oxopentamethylen)-acetamidine (2p): Product **2p** was obtained from **1f** and morpholine **3c** according to general procedure B. Compound **1f** was dissolved in an EtOH/THF mixture (75:25, v/v). Product **2p** was obtained as a dark-red solid (391 mg, 1.18 mmol, 95%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.96$ (br s, 1H), 7.91 (d, 2H, $J=8.5$ Hz), 7.56 (d, 2H, $J=8.5$ Hz), 4.29 (q, 2H, $J=7.1$ Hz), 3.72 (m, 4H), 3.63 (m, 4H), 1.33 ppm (t, 3H, $J=7.1$ Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=165.6$ (C), 162.2 (C), 157.0 (C), 130.0 (2×CH), 125.7 (C), 120.2 (2×CH), 116.2 (C), 94.5 (C), 65.9 (2×CH$_2$), 60.4 (CH$_2$), 48.8 (2×CH$_2$), 14.2 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}=3310$, 3198, 2974, 2185, 1698, 1542, 1355, 1266, 1212, 1095, 998, 857, 772 cm^{-1}; LC-MS: *m/z* 330.18 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{19}N_5O_3$: 330.1566; found: 330.1581.

General procedure C for the synthesis of 5-amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles 4a–p

Sample loop A (1.0 mL) was filled with a solution of acetamidine derivatives **2a–p** (0.20 mmol, 0.20 M) in DMF and sample loop B (1.0 mL) was filled with a solution containing copper acetate (0.02 mmol, 0.02 M) and sodium periodate (0.24 mmol, 0.24 M) in DMF. The two sample loops were simultaneously switched into line and the starting materials were pumped through the system with DMF as a solvent at a flow rate of 0.20 mL min^{-1} (for each line). The starting solutions were mixed by using an arrowhead T-mixing piece (I.D. = 1.4 mm) and pumped (combined flow rate = 0.40 mL min^{-1}) through a PFA coil reactor (14.0 mL, I.D. = 1.0 mm; residence time = 35 min) heated at 120 °C. The reaction mixture passed through a back-pressure regulator (4 bar) before exiting the system. The back-pressure regulator was located in a sonicator bath due to precipitation inside the reactor. Sonication was periodically switch on (20 s every 1 min) to avoid clogging of the system. The collected fractions were evaporated to dryness, and the crude material was suspended in dichloromethane (2.0 mL) and passed through a two-layer pad of celite and silica gel. The pad was washed with dichloromethane (2×5.0 mL). Evaporation of the filtrate was performed to obtain triazole compounds **4a–o**.

2-Phenyl-4-cyano-5-amino-2*H*-[1,2,3]-triazole (4a): Product **4a** was obtained from **2a** according to general procedure C as an off-white solid (18.5 mg, 1.00 mmol, 50%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.90$ (d, 2H, $J=8.0$ Hz), 7.56 (t, 2H, $J=7.6$ Hz), 7.44 (t, 1H, $J=7.4$ Hz), 6.61 ppm (s, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=156.8$ (C), 138.6 (C), 129.6 (2×CH), 128.2 (CH), 118.5 (2×CH), 112.2 (C), 107.8 ppm (C); FTIR (neat): $\tilde{\nu}=3395$, 3329, 2922, 2852, 2235, 1637, 1560, 1488, 1333, 1322, 963, 763, 647 cm^{-1}; LC-MS: *m/z* 186.1 $[M+H]^+$.

2-Phenyl-4-cyano-5-pyrrolidin-1-yl-2*H*-[1,2,3]-triazole (4b): Product **4b** was obtained from **2b** according to general procedure C as an orange solid (42 mg, 0.176 mmol, 87%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.94$ (d, 2H, $J=7.8$ Hz), 7.57 (t, 2H, $J=7.8$ Hz), 7.45 (t, 1H, $J=7.3$ Hz), 3.51 (t, 4H, $J=6.4$ Hz), 1.97 ppm (t, 4H, $J=6.4$ Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=155.7$ (C), 138.3 (C), 129.8 (2×CH), 128.4 (CH), 118.4 (2×CH), 113.8 (C), 105.8 (C), 48.2 (2×CH$_2$), 25.0 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2923$, 2873, 2224, 1583, 1496, 1458, 961, 759, 689 cm^{-1}; LC-MS: *m/z* 240.3 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_5$: 240.1249; found: 240.1244.

2-Phenyl-4-cyano-5-piperidin-1-yl-2*H*-[1,2,3]-triazole (4c): Product **4c** was obtained from **2c** according to general procedure C as an off-white solid (48 mg, 0.190 mmol, 95%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.95$ (d, 2H, $J=7.8$ Hz), 7.58 (t, 2H, $J=7.8$ Hz), 7.47 (t, 4H, $J=7.4$ Hz), 3.46–3.52 (m, 4H), 1.55–1.70 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=157.9$ (C), 138.2 (C), 129.8 (2×CH), 128.6 (CH), 118.5 (2×CH), 113.6 (C), 107.0 (C), 48.0 (2×CH$_2$), 24.3 (2×CH$_2$), 23.3 ppm (CH$_2$); FTIR (neat): $\tilde{\nu}=2924$, 2852, 2228, 1542, 1241, 966, 760, 722, 688, 649 cm^{-1}; LC-MS: *m/z* 254.3 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}N_5$: 254.1405; found: 254.1384.

2-Phenyl-4-cyano-5-morpholino-1-yl-2*H*-[1,2,3]-triazole (4d): Product **4d** was obtained from **2d** according to general procedure C as a yellow solid (35 mg, 0.137 mmol, 68%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.95$ (d, 2H, $J=7.8$ Hz), 7.58 (t, 2H, $J=7.5$ Hz), 7.48 (t, 1H, $J=7.5$ Hz), 3.77 (m, 4H), 3.46 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=157.9$ (C), 138.2 (C), 129.8 (2×CH), 128.8 (CH), 118.6 (2×CH), 113.3 (C), 107.3 (C), 65.2 (2×CH$_2$), 47.1 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2924$, 2855, 2233, 1542, 1498, 1454, 1373, 1265, 1229, 1116, 927, 753, 680 cm^{-1}; LC-MS: *m/z* 256.17 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_5O$: 256.1198; found: 256.1192.

2-Phenyl-4-cyano-5-piperazin-1-yl-2*H*-[1,2,3]-triazole (4e): Product **4e** was obtained from **2e** according to general procedure C as an off-white solid (24 mg, 0.094 mmol, 48%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=9.09$ (br s, 1H), 7.97 (d, 2H, $J=8.0$ Hz), 7.60 (t, 2H, $J=7.6$ Hz), 7.50 (m, 1H), 3.68 (m, 4H), 3.48 (br s, 1H), 3.32 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=157.0$ (C), 138.2 (C), 129.9 (2×CH), 128.9 (CH), 118.6 (2×CH), 112.9 (C), 107.9 (C), 44.2 (2×CH$_2$), 41.8 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2704$, 2492, 2232, 1672, 1535, 1184, 1119, 968, 831, 722 cm^{-1}; LC-MS: *m/z* 255.37 $[M+H]^+$.

2-(4-Methoxyphenyl)-4-cyano-5-pyrrolidin-1-yl-2*H*-[1,2,3]-triazole (4f): Product **4f** was obtained from **2f** according to general procedure C as an off-white solid (44 mg, 0.163 mmol, 82%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.85$ (d, 2H, $J=8.9$ Hz), 7.10 (d, 2H, $J=8.9$ Hz), 3.81 (s, 3H), 3.45–3.53 (m, 4H), 1.93–2.01 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=159.2$ (C), 155.7 (C), 132.0 (C), 120.1 (2×CH), 114.8 (2×CH), 113.9 (C), 104.8 (C), 55.6 (CH$_3$), 48.2 (2×CH$_2$), 25.0 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2924$, 2225, 1591, 1516, 1028, 966, 825, 798 cm^{-1}; LC-MS: *m/z* 270.23 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}N_5O$: 270.1355; found: 270.1342.

2-(4-Methoxyphenyl)-4-cyano-5-piperidin-1-yl-2*H*-[1,2,3]-triazole (4g): Product **4g** was obtained from **2g** according to general procedure C as an off-white solid (55 mg, 0.194 mmol, 98%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.87$ (d, 2H, $J=9.1$ Hz), 7.11 (d, 2H, $J=9.1$ Hz), 3.82 (s, 3H), 3.43–3.50 (m, 4H), 1.58–1.69 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=159.7$ (C), 158.3 (C), 132.3 (C), 120.6 (2×CH), 115.2 (2×CH), 114.2 (C), 106.5 (C), 56.0 (CH$_3$), 48.4 (2×CH$_2$), 24.8 (2×CH$_2$), 23.7 ppm (CH$_2$); FTIR (neat): $\tilde{\nu}=2923$, 2852, 2225, 1542, 1512, 1238, 1029, 968, 826 cm^{-1}; LC-MS: *m/z* 284.2 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{15}H_{17}N_5O$: 284.1511; found: 284.1499.

2-(4-Methoxyphenyl)-4-cyano-5-morpholino-1-yl-2*H*-[1,2,3]-triazole (4h): Product **4h** was obtained from **2h** according to general procedure C as a brown solid (52 mg, 0.182 mmol, 92%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.87$ (d, 2H, $J=8.7$ Hz), 7.11 (d, 2H, $J=8.7$ Hz), 3.83 (s, 3H), 3.77 (m, 4H), 3.44 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=159.4$ (C), 157.9 (C), 131.9 (C), 120.3 (2×CH), 114.8 (2×CH), 113.5 (C), 106.4 (C), 65.2 (2×CH$_2$), 55.6 (CH$_3$), 47.2 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2921$, 2852, 2229, 1541, 1515, 1458, 1255, 1120, 1031, 827, 654 cm^{-1}; FTIR (neat): $\tilde{\nu}=2920$, 2851, 2229, 1541, 1512, 1458, 1255, 1121, 1032, 967, 925, 828, 653 cm^{-1}; LC-MS: *m/z* 286.2 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}N_5O_2$: 286.1304; found: 286.1292.

2-(4-Methoxyphenyl)-4-cyano-5-piperazin-1-yl-2*H*-[1,2,3]-triazole (4i): Product **4i** was obtained from **2i** according to general procedure C as an off-white solid (12 mg, 0.042 mmol, 22%); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=9.12$ (br s, 1H), 7.89 (d, 2H, $J=9.0$ Hz), 7.13 (d, 2H, $J=9.0$ Hz), 3.83 (s, 3H), 3.69 (t, 4H, $J=4.6$ Hz), 3.32 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=159.5$ (C), 157.0 (C), 131.8 (C), 120.3 (2×CH), 114.9 (2×CH), 113.1 (C), 107.0 (C), 55.6 (CH$_3$), 44.3 (2×CH$_2$), 41.8 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=$ 2973, 2731, 2237, 1669, 1540, 1509, 1250, 1169, 1125, 1020, 967, 835, 827, 721 cm^{-1}; LC-MS: *m/z* 285.21 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N_6O$: 285.1464; found: 285.1483.

2-(4-Methylphenyl)-4-cyano-5-piperidin-1-yl-2*H*-[1,2,3]-triazole (4j): Product **4j** was obtained from **2j** according to general procedure C as an off-white solid (43 mg, 0.161 mmol, 80%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.82$ (d, 2H, $J=8.4$ Hz), 7.36 (d, 2H, $J=8.4$ Hz), 3.43–3.50 (m, 4H), 2.36 (s, 3H), 1.54–1.69 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=157.9$ (C), 138.4 (C), 136.2 (C), 130.1 (2×CH), 118.5 (2×CH), 113.7 (C), 106.6 (C), 48.0 (2×CH$_2$), 24.3 (2×CH$_2$), 23.3 (CH$_2$), 20.6 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}=2936$, 2857, 2225, 1542, 1513, 1452, 1239, 969, 818 cm^{-1}; LC-MS: *m/z* 268.3 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{15}H_{17}N_5$: 268.1562; found: 268.1549.

2-(4-Methylphenyl)-4-cyano-5-morpholino-1-yl-2*H*-[1,2,3]-triazole (4k): Product **4k** was obtained from **2k** according to general procedure C as an off-white solid (50 mg, 0.186 mmol, 93%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.84$ (d, 2H, $J=8.4$ Hz), 7.38 (d, 2H, $J=8.4$ Hz), 3.77 (m, 4H), 3.45 (m, 4H), 2.37 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=158.3$ (C), 138.9 (C), 136.5 (C), 130.6 (2×CH), 118.9 (2×CH), 113.8 (C), 107.2 (C), 65.6 (2×CH$_2$), 47.5 (2×CH$_2$), 21.0 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}=2922$, 2857, 2232, 1541, 1120, 969, 938, 924, 811 cm^{-1}; LC-MS: *m/z* 270.20 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}N_5O$: 270.1355; found: 270.1342.

2-(4-Methylphenyl)-4-cyano-5-piperazin-1-yl-2*H*-[1,2,3]-triazole (4l): Product **4l** was obtained from **2l** according to general procedure C as a brown solid (35 mg, 0.131 mmol, 65%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=8.95$ (br s, 1H), 7.86 (d, 2H, $J=8.5$ Hz), 7.40 (d, 2H, $J=8.5$ Hz), 3.69 (t, 4H, $J=4.8$ Hz), 3.30 (m, 4H), 2.38 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=157.0$ (C), 138.8 (C), 136.0 (C), 130.2 (2×CH), 118.6 (2×CH), 113.0 (C), 107.5 (C), 44.2 (2×CH$_2$), 41.8 (2×CH$_2$), 20.6 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}=$ 2989, 2496, 2236, 1669, 1540, 1508, 1175, 1116, 966, 835, 817, 795, 722 cm^{-1}; LC-MS: *m/z* 269.18 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N_6$: 269.1515; found: 269.1501.

2-(4-Fluorophenyl)-4-cyano-5-pyrrolidin-1-yl-2*H*-[1,2,3]-triazole (4m): Product **4m** was obtained from **2m** according to general procedure C as a brown solid (50 mg, 0.195 mmol, 97%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.95$ (m, 2H), 7.41 (t, 2H, $J=8.7$ Hz), 3.50 (t, 4H, $J=6.4$ Hz), 1.97 ppm (t, 4H, $J=6.4$ Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=161.8$ (d, C, $J=245.5$ Hz), 156.1 (C), 135.3 (C), 121.1 (d, 2 CH, $J=9.2$ Hz), 117.1 (d, 2 CH, $J=23.7$ Hz), 114.1 (C), 106.2 (C), 48.6 (2×CH$_2$), 25.4 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2923$, 2227, 1589, 1507, 1458, 1216, 1096, 961, 837, 669 cm^{-1}; LC-MS: *m/z* 258.21 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}FN_5$: 258.1155; found: 258.1154.

2-(4-Fluorophenyl)-4-cyano-5-piperidin-1-yl-2*H*-[1,2,3]-triazole (4n): Product **4n** was obtained from **2n** according to general procedure C as an off-white solid (42 mg, 0.155 mmol, 77%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=8.00$ (m, 2H), 7.43 (t, 2H, $J=8.8$ Hz), 3.48 (m, 4H), 1.56–1.69 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=165.1$ (d, C, $J=377.1$ Hz), 158.4 (C), 135.2 (C), 121.3 (d, 2 CH, $J=9.2$ Hz), 117.1 (d, 2 CH, $J=22.9$ Hz), 114.0 (C), 107.5 (C), 48.4 (2×CH$_2$), 24.7 (2×CH$_2$), 23.7 ppm (CH$_2$); FTIR (neat): $\tilde{\nu}=2952$, 2931, 2856, 2229, 1545, 1508, 1221, 967, 835 cm^{-1}; LC-MS: *m/z* 272.20 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}FN_5$: 272.1311; found: 272.1321.

2-(4-Nitrophenyl)-4-cyano-5-morpholino-1-yl-2*H*-[1,2,3]-triazole (4o): Product **4o** was obtained from **2o** according to general procedure C as a brown solid (50 mg, 0.167 mmol, 83%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=8.43$ (d, 2H, $J=9.2$ Hz), 8.18 (d, 2H, $J=9.2$ Hz), 3.79 (m, 4H), 3.50 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=158.4$ (C), 146.9 (C), 142.3 (C), 126.0 (2×CH), 119.7 (2×CH), 113.3 (C), 109.9 (C), 65.6 (2×CH$_2$), 47.4 ppm (2×CH$_2$); FTIR (neat): $\tilde{\nu}=2922$, 2235, 1569, 1541, 1524, 1350, 1337, 1320, 1261, 1222, 1109, 965, 835, 748 cm^{-1}; LC-MS: *m/z* 301.2 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}N_6O_3$: 301.1049; found: 301.1064.

2-(4-Carbethoxyphenyl)-4-cyano-5-morpholino-1-yl-2*H*-[1,2,3]-triazole (4p): Product **4p** was obtained from **2p** according to general procedure C as a brown solid (40 mg, 0.122 mmol, 61%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=8.14$ (d, 2H, $J=8.8$ Hz), 8.08 (d, 2H, $J=8.8$ Hz), 4.35 (q, 2H, $J=7.1$ Hz), 3.78 (m, 4H), 3.48 (m, 4H), 1.34 ppm (t, 3H, $J=7.1$ Hz); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=$ 164.8 (C), 158.0 (C), 141.0 (C), 130.9 (2×CH), 129.5 (C), 118.6 (2×CH), 113.0 (C), 108.5 (C), 65.2 (2×CH$_2$), 61.1 (CH$_2$), 47.0 (2×CH$_2$), 14.1 ppm (CH$_3$); FTIR (neat): $\tilde{\nu}=2923$, 2236, 1715, 1542, 1265, 1051, 963, 852, 766 cm^{-1}; LC-MS: *m/z* 328.20 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}N_5O_3$, 328.141; found: 328.1395.

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