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# An alternative approach to the synthesis of [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles, their crystal structure, and DFT calculations

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New representatives of [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles were synthesized via the condensation of β-diketones or β-dialdehydes and characterized using MS spectrometry, $^{1}$H, $^{13}$C and, $^{19}$F NMR and IR spectroscopy. Crystal structures of two compounds were established using X-ray analysis and showed that title compounds are prone to the formation of planar molecules. The absence of band responsible for CN stretching vibration in trifluoromethyl-containing compounds was explained using the DFT calculations method, which also showed a significant influence of fluorines introducing on the energy gap between HOMO and LUMO.

## 1 | INTRODUCTION

The [1,2,4]triazolo[1,5-*a*]pyridine system is an interesting structural motif for the drug design.[1] Its 8-cyano derivatives possessed antibacterial,[2,3] antifungal activities,[2,4,5] and were proposed as PDE10A inhibitors,[6] immunomodulators,[7] intermediates for negative allosteric modulators of mGlu5[8] useful in treating inflammatory and autoimmune diseases.[9] 2,5,7-Triaryl[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles were patented as strong fluorescence agents.[10]

Contemporary approaches toward [1,2,4]triazolo[1,5-*a*]pyridine system, including 8-cyano derivatives have been summarized in microreview.[1] The general synthetic strategy to [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles involves the construction of a triazole ring on a pyridine compound (Scheme 1)[2,8,11–13] or annulation of pyridine core starting from triazolylacetonitriles via the cyclocondensation with β-keto esters in the presence of ammonium acetate[4,5] or functionalized acrylonitriles or their precursors, promoted by a strong base.[5,14] Simultaneous generation of the two heterocyclic rings based on hydrazine derivatives and functionalized acrylonitriles or their precursors via one-pot procedure was elaborated, as well.[10,15] [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitrile was prepared from 3-[1,2,4]triazolo[1,5-*a*]pyridine-8-yl-1,2,4-oxadiazole via the decomposition of oxazolyl moiety when heated to about 200°C (Scheme 1A).[11] 5,7-Dimethyl-2-alkyl(phenyl)[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles have been reported to obtain for the first time via the recyclization of oxadiazolopyridinium perchlorates when treated with $NH_4OH$ or $NH_4OAc$ (Scheme 1B)[16] and then upon cyclocondensation of 1-amino-4,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile with carboxamides in the presence of anhydrous $ZnCl_2$ (Scheme 1C).[12] Our work addresses the issue of construction of such compounds based on one-pot process from 2-(1*H*-1,2,4-triazol-5-yl)acetonitriles and β-diketones or β-dialdehydes.

## 2 | RESULTS AND DISCUSSION

In order to establish the limits of applicability for the reaction between 2-(1*H*-1,2,4-triazol-5-yl)acetonitriles **1a**-c and

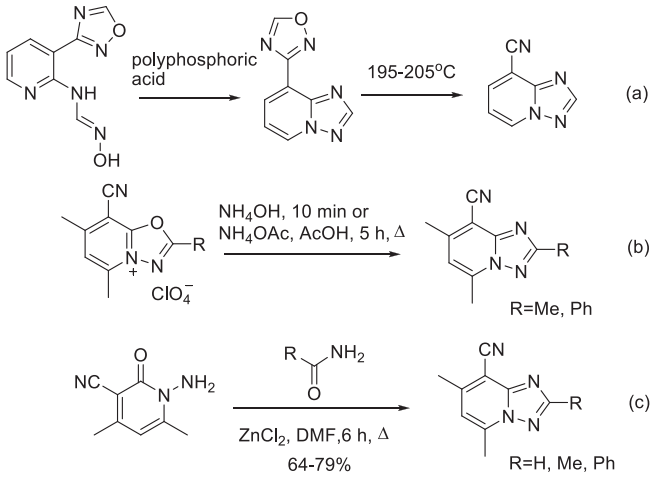
  

β-dicarbonyl compounds acetylacetone (**2**), hexafluoro acetylacetone (**3**), dibenzoylmethane, 1,1,3,3-tetrametho xypropane (**4**), and bromomalonaldehyde (**5**) were used. This reaction has the dual role of assembling the pyridine ring in the prospective [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles and providing them with the required substituents. It should be noted that the 2-(1*H*-1,2,4-triazol-5-yl)acetonitrile (**1a**) was synthesized and characterized for the first time (see Data S1). Taking into account, that this molecule is the "smallest" representative of 2-(1*H*-1,-2,4-triazol-5-yl)acetonitriles and thus could be of great interest as building-block in organic synthesis we checked the applicability of the described procedure for the multigram synthesis and showed that it could be used for the obtaining of up to 200 g of **1a** without significant influence on yield.

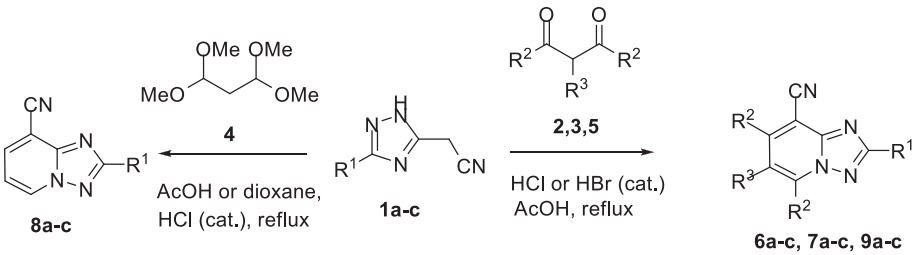
The reaction of **1a-c** with **2** proceeded smoothly in the presence of catalytic amount of HCl in acetic acid under reflux to furnish 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*] pyridine-8-carbonitriles **6a-c** in 57% to 72% yields (Scheme 2). The proposed protocol proved to be efficient and works well also for compounds **1a-c** and **3**, leading to 5,7-di(triflluoromethyl)-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles **7a-c** in 77% to 85% yields. Unfortunately using dibenzoylmethane in this reaction has not resulted in the desired heterocyclic system. As to the reaction with β-dialdehydes or their acetals, the interaction of compounds **1a-c** and 1,1,3,3-tetramethoxypropane (**4**) or bromomalonaldehyde (**5**) proceeded in 15 minutes compared with 1 to 4 hours for compounds **6** and **7**. However, the yields of compounds **8** and **9** were lower (23-79%) than those of compounds **6** or **7** (57-85%) due to the self-condensation of dialdehydes. Prolonged boiling of compounds **1** and **4** or **5** in AcOH led to the resinification of the products and, as a result, to lower yields of the target products. Replacing AcOH with dioxane in the case of product **8b** promoted increasing the yield. It should be noted that the products of the interaction of compounds **1** and **5** in the presence of HCl contained 10% impurities of 6-chloro[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles. Carrying out the reaction in the presence of HBr avoided this drawback.

The formation of compounds **6-9** was supported by MS spectrometry, $^{1}$H, $^{13}$C, and $^{19}$F NMR and IR spectroscopy. Solid-state structures of **7c** and **9c** were proved by means of X-ray analysis. The $^{1}$H NMR spectra of **6a-c** revealed the signal corresponding to the H6 proton at 7.13 to 7.24 ppm. A marked downfield chemical shift of the H6 proton (up to 1.11 ppm) in $^{1}$H NMR spectra of **7a-c** was consistent with the electron withdrawing $CF_3$ groups. The H7 (8.61-8.67 ppm) and H5 (9.64-9.77 ppm) proton resonances of **9a-c** were downfield of the corresponding signals of the **8a-c** up to 0.3 and 0.45 ppm, respectively, which is due to the electron withdrawing Br substituent. Product yields and melting points are summarized in Table 1.

The IR spectra of **6**, **8**, and **9a-c** exhibited a strong absorption peak at 2224 to 2241 cm$^{-1}$ attributed to a cyano-group. The interesting peculiarity of compounds **7a-c** is decrease in the signal intensity of the CN-group up to its disappearance in some cases. These could be due to the introducing of an electron-withdrawing trifluoromethyl group into the pyridine ring in *p*-position to nitrile function, which reduces dipole moment of the molecule during




**SCHEME 1** Known approaches to [1,2,4]triazolo[1,5-*a*] pyridine-8-carbonitriles




**1,6-9** $R^1$=H (**a**), Me (**b**), Ph (**c**)

**2,6** $R^2$=Me, $R^3$=H; **3,7** $R^2$=$CF_3$, $R^3$=H; **5,9** $R^2$=H, $R^3$=Br

**SCHEME 2** The synthesis of [1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles **6-9**

**TABLE 1** Yield and melting point of [1,2,4]triazolo[1,5-*a*] pyridine-8-carbonitriles

| Compound | $R^1$ | $R^2$ | $R^3$ | m.p. (°C) | Yield (%) |
|---|---|---|---|---|---|
| **6a** | H | $CH_3$ | H | 186-187 | 62 |
| **7a** | H | $CF_3$ | H | 117-118 | 81 |
| **8a** | H | H | H | 193-194 | 85 |
| **9a** | H | H | Br | 218-219 | 37 |
| — | H | Ph | H | — | 0 |
| **6b** | $CH_3$ | $CH_3$ | H | 203-204 | 57 |
| **7b** | $CH_3$ | $CF_3$ | H | 97-98 | 85 |
| **8b** | $CH_3$ | H | H | 181-182 | 48 |
| **9b** | $CH_3$ | H | Br | 215-216 | 23 |
| — | $CH_3$ | Ph | H | — | 0 |
| **6c** | Ph | $CH_3$ | H | 211-212 | 72 |
| **7c** | Ph | $CF_3$ | H | 133-134 | 77 |
| **8c** | Ph | H | H | 222-223 | 79 |
| **9c** | Ph | H | Br | 234-235 | 50 |
| — | Ph | Ph | H | — | 0 |

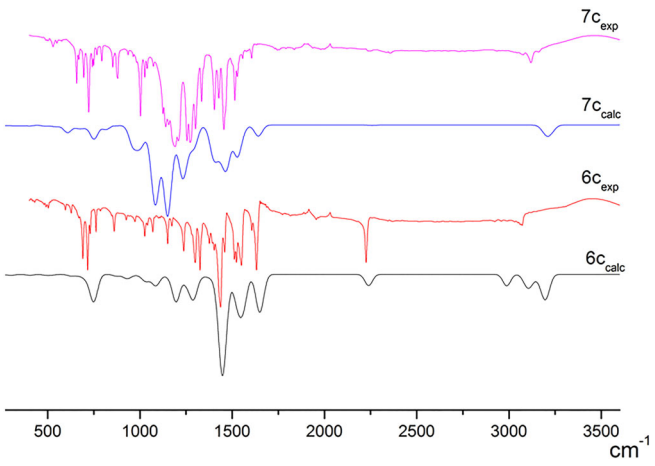



**FIGURE 1** Experimental and calculated IR spectra for **6c** and **7c**

stretching vibration of CN-group. This statement was proved using theoretical calculations (Figure 1), which also showed a significant difference (~90 °) of dipole moment direction (Figure S43) between **6**c and **7c**.

The X-ray diffraction study (see Data S1) of **7c** and **9c** provided a convincing evidence that the reaction products had the proposed structure **6a-c-9a-c**. Compounds **7c** and **9c** crystallize in triclinic space group *P*-1. The results of single crystal X-ray investigation are shown in Figure 2, while the bond distances and angles—in Tables S1 and S2. The triazolo-pyridine ring system and phenyl ring are almost co-planar for both compounds with the dihedral angle of 2.35(7)° and 4.91(1)° for **7c** and **9c**, respectively.

Despite the nature and the positions of substituents, of **7c** and **9c**, the main crystal structure motif for both compounds is determined by the presence of numerous π···π stacking interactions. The centroid-to-centroid distances are in the range of 3.577(1) ÷ 3.727(1) Å and 3.740 (2) ÷ 3.809(2) Å, for **7c** and **9c**, respectively. Thus, the crystal structures of two compounds are characterized as a parallel packing of discrete weakly interacting columns, as shown in Figure 3.

The ground state geometries of the **6c** and **7c** were optimized in the singlet state by the DFT method using the B3LYP functional with SBKJC basis sets. The calculation of the structure of the ground state for **7c** showed that the calculated geometry is in good agreement with the experimental data of X-ray diffraction analysis.

It is known that HOMO energy describes electron-donor properties, while LUMO describes electron-acceptor properties. The isodensity surfaces for these orbitals are visualized in Figure 4. It can be seen that the electron density of the HOMO in **6c** and **7c** is localized on the phenyl and triazole rings, partially on the cyano-group. In the case of the LUMO, the orbitals are located on the C═C and C═N bonds (pyridine ring), cyano-group, and partially on the carbon atoms of the phenyl ring in the *o*- and *p*-positions. In contrast to the shape of the orbitals, the introducing of fluorines in **7c** leads to significant decrease (1.01 eV) of the energy gap between HOMO and LUMO (Figure 4).

## 3 | CONCLUSION

The proposed synthetic methodology shows broad utility and functional group tolerance and provides a straightforward approach to the preparation of [1,2,4]triazolo [1,5-*a*]pyridine-8-carbonitriles. Latter due to their high planarity and presence of donating atoms could be potentially used as chelators in coordination chemistry. On the other hand, theoretical calculations showed that the electronic structure of the title compounds was significantly influenced by the nature of substituents in pyridine ring and thus could be varied, depending on purposes.

## 4 | EXPERIMENTAL

### 4.1 | Instrumentation

Elemental analyses were carried out with Perkin-Elmer 2400 CHN Analyzer. Melting points (°C, uncorrected) were measured with OptiMelt

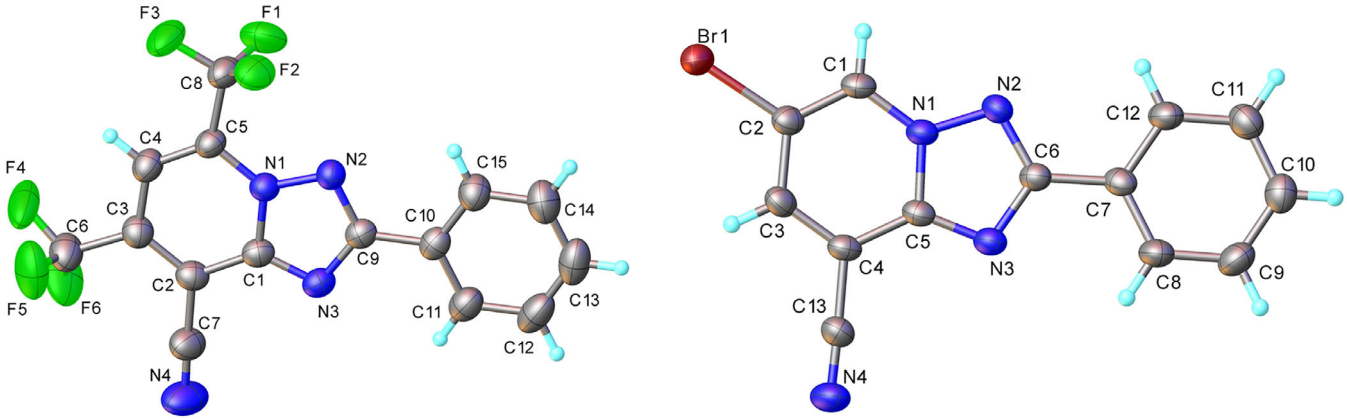



**FIGURE 2** X-ray molecular structure with atom labeling and thermal ellipsoids at 50% level of **7c** (left) and **9c** (right)

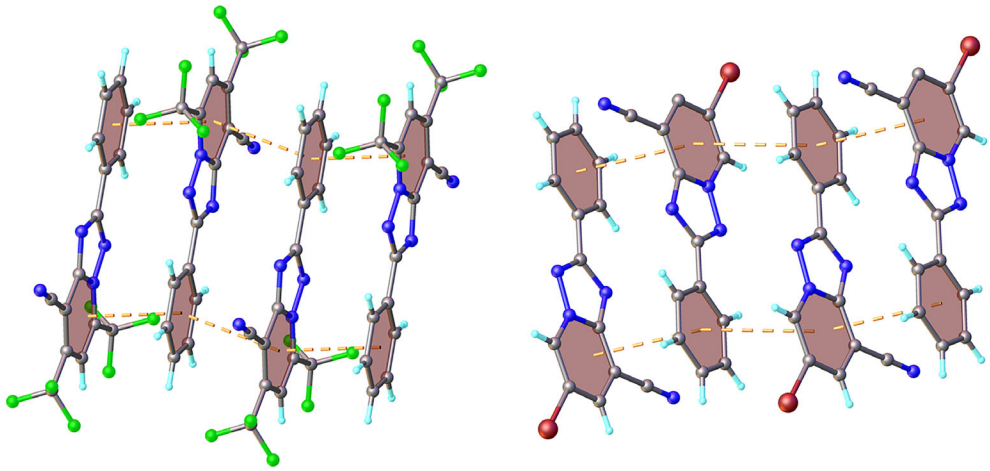


**FIGURE 3** The intermolecular π-π stacking interactions in the crystal structure of **7c** (left) and **9c** (right)

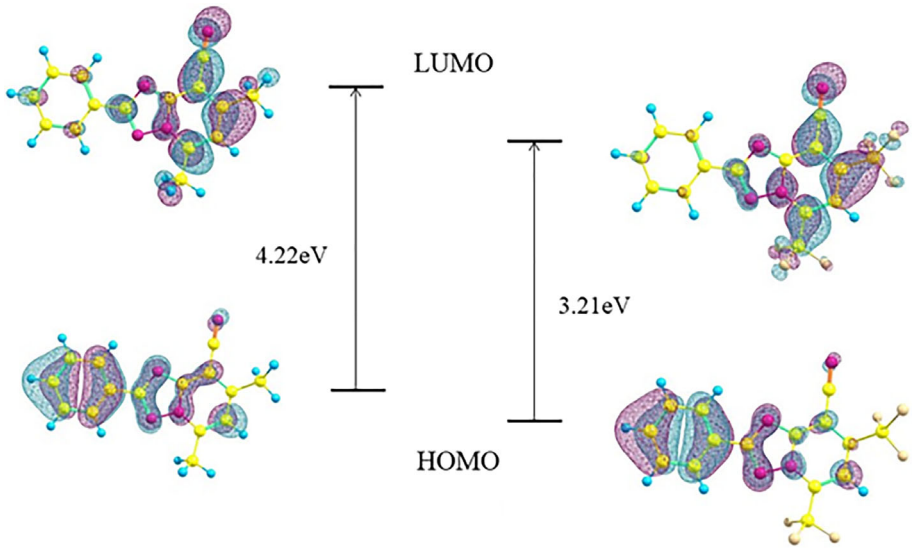



**FIGURE 4** Calculated HOMO and LUMO energies (B3LYP/SBKJC) for **6c** (left) and **7c** (right)

Automated Melting Point System (MPA 100). The IR spectra (KBr, pellet) were recorded with Spektrum BX Perkin Elmer spectrometer. The mass spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MSD SL mass selective detector; the ionization method is atmospheric-pressure chemical ionization (APCI).

NMR spectra $^{1}H$, $^{19}F$, and $^{13}C$ NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500.1, 470.6, and 125.8 MHz for $^{1}H$, $^{19}F$, and $^{13}C$ nuclei, respectively), Varian Unity Plus 400 spectrometer (at 400.4, 376.5, and 100.7 MHz for $^{1}H$, $^{19}F$, and $^{13}C$ nuclei, respectively) and Agilent ProPulse 600 spectrometer (at 600 MHz for $^{1}H$ NMR and 151 MHz for $^{13}C$ NMR. Internal standard – signal of residual solvent protons (DMSO-*d*6—2.50 ppm) and carbons (DMSO-$d_6$—39.5 ppm). Hexafluorobenzene was used as an internal standard for $^{19}F$ NMR-spectra. Some of the signals in $^{13}C$ spectra of initial compounds are significantly broadened due to superposition from several tautomeric forms and transition states, which makes impossible their determination.

X-ray diffraction data were collected with an Oxford-Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated Mo *K*α radiation. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction.[17] The structures were solved by direct methods using Olex2[18] software with the SHELXS structure solution program and refined by full-matrix least-squares on $F^2$ with SHELXL-97.[19] Hydrogen atoms attached to carbon were placed in fixed, idealized positions and refined as rigidly bonded to the corresponding nonhydrogen atoms with $U_{iso}$(H) set to 1.2$U_{eq}$(C). CCDC—2,010,819 (**7c**), CCDC—2,010,818 (**9c**).

Structure optimization calculations of (**6c**) and (**7c**) were carried out with Firefly v.8.1.1 software[20] using the DFT[21] with B3LYP functional[22–24] with SBKJC[25–27] basis sets to compare the molecular (experimental and calculated) structure and vibrational wave numbers. A comparison between the experimental and the DFT calculated geometric parameters of (**6c**) and (**7c**) afforded good agreement.

## 4.2 | Synthetic procedures

The solvents were purified according to the standard procedures. All the starting materials were obtained from Enamine Ltd. and UORSY. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel Merck 60 (230-400 mesh) as the stationary phase. **1a-c** were prepared by procedures described in Data S1.

### 4.2.1 | Typical procedure for preparation of 2-R$^1$-5,7-dimethyl-[1,2,4]triazolo[1,5-a] pyridine-8-carbonitrile (6a-c)

1 drop of HCl was added to solution of 2-(3-R$^1$-1H-1,-2,4-triazol-5-yl)acetonitrile (**1a-c**) (2 mmol) and acetylacetone (**2**) (0.6 g, 6 mmol) in acetic acid (1 mL). The reaction mixture was refluxed (118°C) for 3 to 4 hours and carried out at room temperature for 12 hours. Precipitated products **6a-c** were filtered off, dried on air, and recrystallized from acetic acid.

### 4.2.2 | 5,7-Dimethyl[1,2,4]triazolo[1,5-a] pyridine-8-carbonitrile (6a)

Yield: 62%, mp 186°C to 187°C; $^{1}H$ NMR (500 MHz, DMSO-$d_6$) δ 2.62 (s, 3H, 7-$CH_3$), 2.77 (s, 3H, 5-$CH_3$), 7.24 (s, 1H, H6), 8.62 (s, 1H, H2) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ 17.24, 20.16, 96.45, 114.19, 115.65, 143.17, 148.85, 149.17, 154.36 ppm. IR (KBr, cm$^{-1}$): 3086, 2924, 2851, 2252, 1748, 1519, 1466, 1401, 1362, 1262, 1214, 1169, 1083, 973, 939, 895, 879, 688, 638. MS (*m/z*, CI) 173 $[M + H]^+$. Anal. Calcd. for $C_9H_8N_4$: C 62.78; H 4.68; N 32.54. Found: C 62.33; H 4.65; N 32.35.

### 4.2.3 | 2,5,7-Trimethyl[1,2,4]triazolo [1,5-a]pyridine-8-carbonitrile (6b)

Yield: 57%, mp 203°C to 204°C (Reference [16] 203.5°C to 204°C); $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 2.51 (s, 3H, 2-$CH_3$), 2.58 (s, 3H, 7-$CH_3$), 2.72 (s, 3H, 5-$CH_3$), 7.13 (s, 1H, H6), ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 14.19, 17.30, 20.09, 95.39, 114.32, 114.90, 142.67, 148.26, 149.85, 163.90 ppm. IR (KBr, cm$^{-1}$): 3048, 2964, 2218, 1631, 1550, 1432, 1317, 1231, 1136, 999, 864, 761. MS (*m/z*, CI): 187 $[M + H]^+$. Anal. Calcd. for $C_{10}H_{10}N_4$: C 64.50; H 5.41; N 30.09. Found: C 64.77; H 5.35; N 29.77.

### 4.2.4 | 5,7-Dimethyl-2-phenyl[1,2,4] triazolo[1,5-a]pyridine-8-carbonitrile (6c)

Yield: 72%, mp 211°C to 212°C (Reference [16] 211.5°C to 212°C); $^{1}H$ NMR (500 MHz, DMSO-$d_6$) δ 2.60 (s, 3H, 7-$CH_3$), 2.79 (s, 3H, 5-$CH_3$), 7.19 (s, 1H, H6), 7.54 (s, 3H, H3′ + H4′ + H5′), 8.20 (s, 2H, H2′ + H6′) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ 17.32, 20.18, 96.04, 114.33, 115.64, 127.04, 128.95, 129.80, 130.60, 143.06, 148.78, 150.41, 163.40 ppm. IR (KBr, cm$^{-1}$): 3070, 2234, 1631, 1550, 1522, 1435, 1326, 1298, 1236, 716, 688. MS (*m/z*, CI) 249 $[M + H]^+$. Anal. Calcd. for $C_{15}H_{12}N_4$: C 72.56; H 4.87; N 22.57. Found: C 72.93; H 4.76; N 22.40.

### 4.2.5 | Typical procedure for preparation of 2-R$^1$-5,7-bis(trifluoromethyl)-[1,2,4] triazolo[1,5-a]pyridine-8-carbonitrile (7a-c)

1 drop of HCl was added to solution of 2-(3-R$^1$-1H-1,-2,4-triazol-5-yl)acetonitrile (**1a-c**) (2 mmol) and

hexafluoroacetylacetone (**3**) (1.2 g, 6 mmol) in acetic acid (1 mL). The reaction mixture was refluxed (118°C) for 1 hours. Precipitated product **7c** was filtered off, after cooling of the reaction mixture. In the case of **7b** the reaction mixture was diluted with water (20 mL), which resulted in the formation of white precipitate. The crude product was filtered off, dried on air, and recrystallized from acetic acid.

### 4.2.6 | 5,7-Di(triflluoromethyl)[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile (7a)

Yield: 81%, mp. 117°C to 118°C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.35 (s, 1H, H6), 9.12 (s, 1H, H2) ppm. $^{19}$F NMR (470 5 Hz, DMSO-$d_6$) δ −62.63 (s, $CF_3$), −68.84 (s, $CF_3$) ppm. $^{13}$C{$^{19}$F} NMR (151 MHz, DMSO-$d_6$) δ 103.66 (s), 110.91 (s), 111.00 (m), 118.72 (q, J = 274 Hz), 121.12 (q, J = 275 Hz), 130.91 (q, J = 37 Hz), 134.54 (q, J = 34 Hz), 150.41 (s), 156.76 (s) ppm. IR (KBr, cm$^{-1}$): 3059, 2028, 1910, 1891, 1527, 1317, 1270, 1208, 1152, 993, 648. MS (*m/z*, CI): 281 $[M + H]^+$. Anal. Calcd. for $C_9H_2F_6N_4$: C 38.59; H 0.72; N 20.00. Found: C 38.40; H 0.89; N 20.12.

### 4.2.7 | 2-Methyl-5,7-di(triflluoromethyl)[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile (7b)

Yield: 85%, mp. 97°C to 98°C; $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 2.69 (s, 1H, $CH_3$), 8.24 (s, 1H, H6) ppm. $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ −62.63 (s, $CF_3$), −68.84 (s, $CF_3$) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 14.25 (s), 102.17 (s), 110.20 (m), 111.00 (s), 118.71 (q, J = 275 Hz), 121.18 (q, J = 275 Hz), 130.24 (q, J = 38 Hz), 133.99 (q, J = 34 Hz), 150.97 (s), 167.02 (s) ppm. IR (KBr, cm$^{-1}$): 3109, 2230, 1524, 1480, 1401, 1320, 1276, 1178, 1147, 878, 655. MS (*m/z*, CI) 295 $[M + H]^+$. Anal. Calcd. for $C_{10}H_4F_6N_4$ Calculated, %: C 40.83; H 1.37; N 19.05. Found: C 40.98; H 1.39; N 18.98.

### 4.2.8 | 2-Phenyl-5,7-di(triflluoromethyl)[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile (7c)

Yield: 77%, mp. 133°C to 134°C $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.63 (s, 3H, H3′ + H4′ + H5′), 8.30 (s, 3H, H2′ + H6′ + H6) ppm. $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ −62.65 (s, $CF_3$), −68.75 (s, $CF_3$) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 102.67 (s), 110.82 (m), 111.05, 118.76 (q, J = 275 Hz), 121.16 (q, J = 275 Hz), 127.53, 128.28, 129.37, 130.61 (q, J = 38 Hz), 131.83, 134.29 (q, J = 35 Hz), 151.74, 165.92 ppm. IR (KBr, cm$^{-1}$): 3120, 1508, 1455, 1404, 1267, 1183, 1001, 719, 655. MS (*m/z*, CI) 357 $[M + H]^+$. Anal. Calcd. For $C_{15}H_6F_6N_4$: C 50.58; H 1.70; N 15.73. Found: C 51.07; H 1.66; N 15.38. Crystal data: $C_{15}H_6F_6N_4$, Mr = 356.24 g mol$^{-1}$, size 0.5 × 0.4 × 0.15 mm$^3$, triclinic, space group P-1, a = 7.1943(5) Å, b = 8.2057(8) Å, c = 13.1584(11) Å, α = 100.000(8)°, β = 95.612(6)°, γ = 100.304(7)°, V = 745.97 (11) Å$^3$, Z = 2, $\rho_{calcd}$ = 1.586 g cm$^{-3}$, μ(MoKα) = 0.151 mm$^{-1}$, F(000) = 356, 4852 reflections in h (−8/8), k(−7/9), l(−15/11), measured in the range 3.172 ≤ 2Θ ≤ 50.05, T = 293 K, completeness $\Theta_{max}$ = 99.95%, 2639 independent reflections, $R_{int}$ = 0.0187, 254 parameters, 0 restraints, $R_{1obs}$ = 0.0416, $wR_{2obs}$ = 0.0890, $R_{1all}$ = 0.0624, $wR_{2all}$ = 0.1011, GoF = 1.042, largest difference peak and hole: 0.13/−0.16 e A$^{-3}$.

### 4.2.9 | Typical procedure for preparation of 2-R$^1$-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile (8a-c)

1 drop of HCl was added to solution of 2-(3-R$^1$-1H-1,-2,4-triazol-5-yl)acetonitrile (**1a-c**) (2 mmol) and 1,1,3,3-tetramethoxypropane (**4**) (0.33 g, 2 mmol) in dioxane (101°C) (2 mL) for **8a,b** or acetic acid (118°C) (1 mL) for **8c**.. The reaction mixture was refluxed for 40 minutes. Precipitated product **8c** was filtered off, after cooling of the reaction mixture, dried on air, and recrystallized from dioxane. In the case of **8a,b** dioxane was removed under vacuo and the residue was recrystallized from methanol.

### 4.2.10 | [1,2,4]Triazolo[1,5-a]pyridine-8-carbonitrile (8a)

Yield: 65%, mp. 193°C to 194°C (lit. [11] 193°C to 195°C); $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.38 (s, 1H, H6), 8.39 (s, 1H, H7), 8. 72 (s, 1H, H2), 9.32 (s, 1H, H5) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 100.07, 113.97, 114.55, 134.17, 137.91, 148.73, 154.82 ppm. IR (KBr, cm$^{-1}$): 3092, 2224, 1620, 1505, 1312, 1192, 755. MS (*m/z*, CI) 145 $[M + H]^+$. Anal. Calcd. for $C_7H_4N_4$: C 58.33; H 2.80; N 38.87. Found: C 58.15; H 2.53; N 38.65.

### 4.2.11 | 2-Methyl[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile (8b)

Yield: 48%, mp. 181°C to 182°C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 2.52 (s, 3H, $CH_3$), 7.27 (t, J = 8.0, 1H, H6), 8.30 (d, J = 8.0, 1H, H7), 9.17 (d, J = 8.0, 1H, H5) ppm.

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 14.07, 98.86, 113.18, 114.67, 133.53, 137.37, 140.39, 164.48 ppm. IR (KBr, $cm^{-1}$): 3087, 3036, 2224, 1620, 1508, 1477, 1429, 1387, 1303, 797, 755. MS (*m/z*, CI) 159 $[M + H]^+$. Anal. Calcd. for $C_8H_6N_4$: C 60.75; H 3.82; N 35.42. Found: C 60.82; H 3.53; N 35.11.

### 4.2.12 | 2-Phenyl[1,2,4]triazolo[1,5-a] pyridine-8-carbonitrile (8c)

Yield:79%, mp. 222°C to 223°C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.36 (s, 1H, H6), 7.56 (s, 3H, H3′ + H4′ + H5′), 8.23 (s, 2H, H2′ + H6′), 8.37 (s, 1H, H7), 9.32 (s, 1H, H5) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 99.55, 113.90, 114.70, 127.07, 129.00, 129.52, 130.77, 133.97, 137.86, 149.97, 163.93 ppm. IR (KBr, $cm^{-1}$): 3087, 2224, 1625, 1499, 1452, 1427, 1306, 1234, 750, 716. MS (*m/z*, CI) 221 $[M + H]^+$. Anal. Calcd. for $C_{13}H_8N_4$: C 70.90; H 3.66; N 25.44. Found: C 70.55; H 3.53; N 25.48.

### 4.2.13 | Typical procedure for preparation of 6-bromo-2-R$^1$-[1,2,4]triazolo [1,5-a]pyridine-8-carbonitrile (9a-c)

1 drop of HBr was added to solution of 2-(3-R$^1$-1H-1,-2,4-triazol-5-yl)acetonitrile (**1a-c**) (2 mmol) and 2-bromomallonaldehyde (**5**) (0.3 g, 2 mmol) in acetic acid (1 mL). The reaction mixture was refluxed (118°C) for 15 minutes. Precipitated products were filtered off, after cooling of the reaction mixture, dried on air, and recrystallized from DMF.

### 4.2.14 | 6-Bromo[1,2,4]triazolo[1,5-a] pyridine-8-carbonitrile (9a)

Yield: 37%, mp. 218°C to 219°C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.69 (s, 1H, H7), 8.72 (s, 1H, H2), 9.77 (s, 1H, H5) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 100.87, 106.50, 113.58, 134.70, 140.23, 147.97, 155.13 ppm. IR (KBr, $cm^{-1}$): 3098, 3042, 2230, 1620, 1494, 1312, 1248, 1178, 775. MS (*m/z*, CI) 223 $[M + H]^+$. Anal. Calcd. for $C_7H_4N_4$: C 37.70; H 1.36; N 25.12. Found: C 38.07; H 0.94; N 25.24.

### 4.2.15 | Spectroscopic data for 6-bromo-2-methyl[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile (9b)

Yield: 23%, mp. 215°C to 216°C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.53 (s, 3H, $CH_3$), 8.61 (s, 1H, H7), 9.64 (s, 1H, H5) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 14.06, 99.66, 105.54, 113.67, 134.05, 139.60, 148.58, 164.89 ppm. IR (KBr, $cm^{-1}$): 3053, 2359, 2224, 1614, 1499, 1357, 1306, 887. MS (*m/z*, CI) 237 $[M]^+$. Anal. Calcd. for $C_8H_5BrN_4$: C 40.53; H 2.13; N 23.63. Found: C 40.90; H 1.83; N 23.27.

### 4.2.16 | 6-Bromo-2-phenyl[1,2,4]triazolo [1,5-a]pyridine-8-carbonitrile (9c)

Yield: 50%, mp. 234°C to 235°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.56 (s, 3H, H3′ + H4′ + H5′), 8.24 (s, 2H, H2′ + H6′), 8.67 (s, 1H, H7), 9.77 (s, 1H, H5) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 100.31, 106.25, 113.71, 127.07, 129.06, 129.21, 130.95, 134.46, 140.08, 149.19, 164.18 ppm. IR (KBr, $cm^{-1}$): 3064, 2364, 2241, 1617, 1491, 1446, 1320, 1303, 794, 716. MS (*m/z*, CI) 299 $[M + H]^+$. Anal. Calcd. for $C_{13}H_7BrN_4$: C 52.20; H 2.36; N 18.73. Found: C 52.32; H 1.88; N 18.55. Crystal data: $C_{13}H_7BrN_4$, Mr = 299.14 g $mol^{-1}$, size 0.25 × 0.2 × 0.15 $mm^3$, triclinic, space group P-1, a = 6.8636(7) Å, b = 7.4948(11) Å, c = 11.8459(12) Å, α = 76.446(10)°, β = 83.714(8)°, γ = 80.735(10)°, V = 583.03(12) Å$^3$, Z = 2, $\rho_{calcd}$ = 1.704 g $cm^{-3}$, μ(MoKα) = 3.510 $mm^{-1}$, F(000) = 296, 3956 reflections in h(−8/7), k(−8/8), l(−14/14), measured in the range 3.546 ≤ 2Θ ≤ 50.048, T = 293 K, completeness $\Theta_{max}$ = 99.95%, 2041 independent reflections, $R_{int}$ = 0.0310, 163 parameters, 0 restraints, $R_{1obs}$ = 0.0410, $wR_{2obs}$ = 0.0849, $R_{1all}$ = 0.0531, $wR_{2all}$ = 0.0917, GoF = 1.069, largest difference peak and hole: 0.49/−0.49 e A$^{-3}$.

## DATA AVAILABILITY STATEMENT

Data available in article supplementary material.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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