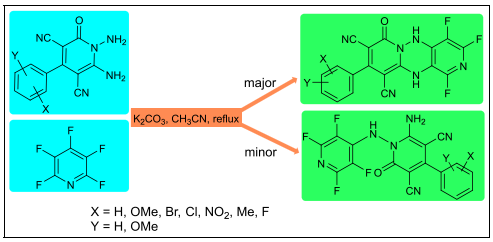
Dipyrido[1,2-b:3′,4′-e][1,2,4]triazine Scaffolds from Pentafluoropyridine

Reza Ranjbar-Karimi, Ali Darehkordi, Fahimeh Bahadornia, and Alireza Poorfreidoni*

Department of Chemistry, Faculty of Science, Vali-e-Asr University, Rafsanjan 77176, Islamic Republic of Iran
*E-mail: alireza_poorfreidoni@yahoo.com

Received April 18, 2018
DOI 10.1002/jhet.3283
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



Annelation reaction between pentafluoropyridine and diaminodihydro substituted pyridine derivatives gave dipyrido[1,2-b:3′,4′-e][1,2,4]triazine systems as major products arising from the initial nucleophilic substitution of more nucleophilic *N*-amino group of pyridone ring at 4-position of the pyridine ring followed by intramolecular cyclization at 3-position of pyridine ring. Also, 6-amino-2-oxo-1-((perfluoropyridin-4-yl) amino)-4-aryl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives were obtained as side products. The structures of all the compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy as well as elemental analysis.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

Fluor-containing heterocyclic systems are attractive synthetic scaffolds and have a wide range of applications in biochemistry, organic chemistry, and pharmaceutical chemistry [1–4]. Pentafluoropyridine is an important perfluorinated heterocycle that highly regarded in organic chemistry as an excellent scaffold for the synthesis of other heterocyclic and macrocyclic compounds [5–7]. The chemistry of pentafluoropyridine is dominated by nucleophilic substitution reactions due to the presence of five fluorine atoms attached to the pyridine ring [8,9]. Nucleophilic substitution reactions of pentafluoropyridine have been reported with various S, N, O, P, and C nucleophiles [10–14]. Regiochemistry of these reactions basically affected by the nature of the solvent, nucleophile, and reaction conditions.

Perfluorinated pyridines are useful building blocks for the synthesis of fluorinated ring-fused heterocycles on reaction with various equal and unequal bidentate nucleophiles [5,15–18]. In the last few years, we have been pursuing synthesis of ring-fused systems on the reaction of bidentate nucleophiles with perfluoropyridines [19–21]. We have shown difluorinated tetrahydropyrido[3,4-b][1,4] oxazine, thiazine, and pyrazine scaffolds, as well as imidazopyridine systems, can be readily synthesized by reaction of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl) pyridine with a variety of bidentate nucleophiles [20,21]. In another study, we have been synthesized [6,6,6] ring fused tricyclic systems on the reaction of pentafluoropyridine or 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine with difunctional nitrogen and oxygen nucleophiles attached to aromatic rings [22].

The 1,2,4-triazine systems are an important class of heterocyclic compounds, and it is well known for their biological activities such as anticancer [23], anticonvulsant [24], antimalarial [25], antitumor [26], and antiviral [27]. The most available method for the synthesis of these compounds is mainly based on the reactions of amidrazones with 1,2-diketone compounds [28,29]. Also, the multicomponent reactions of dicarbonyl compounds, hydrazides, and ammonium acetate is a pathway to the synthesis of 3,5-disubstituted 1,2,4-trizaine compounds [30].

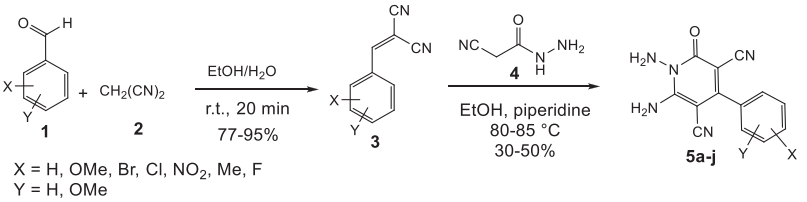
Continuing our research on synthesis fluorinated ring-fused heterocycles, we herein report the synthesis of dipyrido[1,2-b:3′,4′-e][1,2,4]triazine scaffolds from the reaction of pentafluoropyridine with diamino-dihydro substituted pyridine derivatives.

RESULTS AND DISCUSSION

Diamino-dihydro substituted pyridine derivatives were synthesized from the reaction of corresponding benzilidenmalonolnitriles **3** with 2-cyanoacetohydrazide **4** according to the literature procedure (Scheme 1) [31].

The reaction of diaminodihydro substituted pyridine derivatives **5a–j** with pentafluoropyridine **6** was carried out in CH_3CN in the presence of potassium carbonate at 85°C. Reaction of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **5a** with pentafluoropyridine

Scheme 1. Synthesis of diamino-dihydro substituted pyridines.

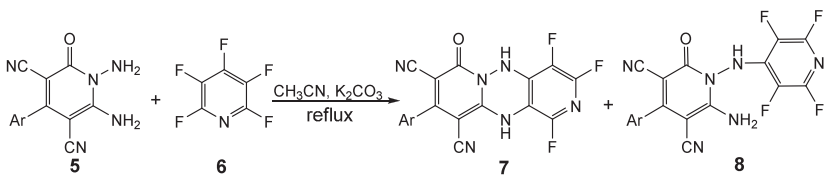


6 gave 1,3,4-trifluoro-7-oxo-9-phenyl-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7a** as major product and 6-amino-2-oxo-1-((perfluoropyridin-4-yl) amino)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **8a** as side product (Table 1, Code a) after purification using plate chromatography eluted by ethyl acetate/MeOH. Product **7a** was obtained by substitution of the amino group attached to ring nitrogen **5a** at the 4-position of the pyridine ring, followed by intramolecular ring closure at the geometrically accessible 3-position of the pyridine ring by another amino group **5a**. Product **8a** was formed by nucleophilic attack of the *N*-amino group of the compound **5a** to the 4-position of pentafluoropyridine. The chemoselectivity of nucleophilic substitution on pentafluoropyridine **6** reflected by the higher nucleophilicity of the *N*-amino group over the amino group.

The structures of **7a** and **8a** were confirmed by ^{19}F, ^{1}H, and ^{13}C NMR analysis. Three resonances by ^{19}F NMR (−93.8, −157.0, and −165.7 ppm) indicate the displacement of fluorine atoms attached to the 3-position and 4-position of the pyridine ring with 2-pyridone **5a** as a bidentate nucleophile. In ^{19}F NMR analysis of **7a**, the resonances of two ortho fluorines (F-6 and F-2) to ring nitrogen were located at δ = −157.0 and −165.7 ppm and meta fluorine (F-5) to ring nitrogen was located at δ = −93.8 ppm. ^{1}H NMR spectrum of compound **7a** showed a broad singlet peak at δ = 9.23 ppm for two NH groups. It also indicated two multiple peaks in the range of δ = 7.19–7.31 and 7.51–7.62 ppm for aromatic hydrogens. In ^{13}C NMR spectrum of compound **7a**, carbonyl group was located at δ = 161.9 ppm and other pyridone carbons were located at δ = 74.6, 86.3, 157.9, and 158.0 ppm. Aromatic carbons of benzene and pyridine rings were located in the range of δ = 128.0–135.6 ppm. Two peaks appeared at δ = 114.9 and 115.6 ppm related to cyano groups. IR spectrum **7a** showed absorption bands at 3207 and 3299 cm^{-1} for NH stretching and absorption bands at 2220 and 1692 cm^{-1} for CN and C═O stretching, respectively. In ^{19}F NMR analysis of **8a**, the resonances of meta and ortho fluorines to ring nitrogen were located at δ = −156.2 and 97.4 ppm, respectively. These two resonances indicate the displacement of fluorine atom attached to the 4-position of the pyridine ring with 2-pyridone **5a** and cyclic product not formed. ^{1}H NMR spectrum of compound **8a** showed two broad singlet peaks at δ = 5.80 and 10.34 ppm for NH and NH_2 groups, respectively. It also indicated two multiple peaks in the range of δ = 7.29–7.44 and 7.45–7.50 for aromatic hydrogens. In ^{13}C NMR spectrum of compound **8a**, peaks were located at δ = 160.2 ppm and δ = 83.5, 157.3, and 158.1 ppm attributed to carbonyl group and

Table 1

Reaction of diamino-dihydro substituted pyridines with pentafluoropyridine.



Code	Ar	**7**, Yield (%)	**8**, Yield (%)
a	C_6H_5	38	21
b	4-Me-C_6H_4	40	trace
c	4-OMe-C_6H_4	40	trace
d	2,4-di (OMe)-C_6H_3	52	trace
e	4-Cl-C_6H_4	48	trace
f	2-Br-C_6H_4	46	trace
g	2-NO_2-C_6H_4	45	trace
h	3-NO_2-C_6H_4	51	trace
i	4-NO_2-C_6H_4	33	trace
j	4-F-C_6H_4	38	trace

other carbons of pyridone ring, respectively. Also, a peak appeared at δ = 117.2 related to CN group. In IR spectrum **8a** showed an absorption band at 3416 cm^{-1} for NH stretching and absorption bands at 2215 and 1652 cm^{-1} for CN and C═O stretching, respectively.

Similarly, the reaction of 2-pyridones **5b–j** with pentafluoropyridine gave ring-fused compounds **7b–j** as major product and uncyclized products **8b–j** (Table 1, Code b–j). In ^{19}F NMR spectra of compounds **7b–j**, F-5 of pyridine ring was located in the range of δ = (−96.3.3)–(−92.9) ppm, F-6 was located in the range of δ = (−158.8)–(−141.3) ppm, and F-2 was located in the range of δ = (−167.5)–(−163.6) ppm. ^{1}H NMR spectra showed aromatic hydrogens in the range of δ = 7.93–9.92 ppm for NH and some signals in the range of δ = 6.60–8.40 ppm for aromatic hydrogens. In ^{13}C NMR spectra, carbonyl group carbon was located in the range of δ = 159.0–165.0 ppm, cyano groups carbon was located in the range of δ = 113.2–117.6 ppm, pyridone carbons were located in the ranges of δ = 73.7–87.1 ppm and 156.0–161.7 ppm, and aromatic carbons were located in the range of δ = 113.7–159.2 ppm. Compounds **8b–j** were obtained in trace (Table 1, Code b–j). The structure of compounds **8b–j** confirmed by ^{19}F NMR. In ^{19}F NMR spectra of these compounds, ortho fluorine atoms were located in the range of δ = (−96.1)–(−98.3) ppm and meta fluorine atoms in the range of δ = (−147.3)–(−156.8) ppm.

CONCLUSION

In conclusion, we demonstrated the efficient synthesis of some dipyrido[1,2-b:3′,4′-e][1,2,4]triazine systems from the reaction of pentafluoropyridine with diaminodihydro substituted pyridine derivatives. Also, 6-amino-2-oxo-1-((perfluoropyridin-4-yl)amino)-4-aryl-1,2-dihydropyridine-3,5-dicarbonitriles formed as side product. The chemoselectivity of nucleophilic substitution on pentafluoropyridine could be concluded based on the higher nucleophilicity of the *N*-amino group due to α-effect.

EXPERIMENTAL

All the solvents and starting materials were obtained commercially (Merck). ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75 MHz, and ^{19}F NMR spectra at 282 MHz. IR spectra were recorded on a Thermo Scientific-Nicolet iS10 spectrometer in a KBr matrix. All melting points were obtained by Stuart Scientific apparatus. The elemental analyses for C, H, and N were performed using Heraeus CHN–O rapid analyzer. Thin-layer chromatography analysis was performed on silica gel thin-layer chromatography plates (Merck). Column chromatography was carried out on silica gel with mixed solvents (n-hexane/ethyl acetate).

General procedure for reaction between pentafluoropyridine and diamino dihydropyridine derivatives. Potassium carbonate (3 mmol) was added to a solution of diamino-dihydro substituted pyridine derivative **5** (1 mmol) in CH_3CN (8 mL) and the mixture was stirred at room temperature for 30 min. Then, pentafluoropyridine **6** (1 mmol) was added, and the resulting solution was refluxed for appropriate time. The reaction mixture was poured onto 10-mL water, extracted with chloroform (3 × 8 mL), and then dried with $MgSO_4$ and solvent evaporated. Purification was performed using column chromatography (EtOAc/MeOH).

1,3,4-Trifluoro-7-oxo-9-phenyl-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7a). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **5a** (0.251 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 48 h and using column chromatography (EtOAc/MeOH, 15:1), gave 1,3,4-trifluoro-7-oxo-9-phenyl-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7a** (major product): 38%; yellow solid; mp: 170–173°C. (Found: C, 56.64; H, 1.59; N, 21.90; $C_{18}H_7F_3N_6O$ requires: C, 56.85; H, 1.86; N, 22.10). IR (KBr): ν 3207 (N-H), 3299 (N-H), 2220 (CN), 1692 (C═O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.23 (bs, 2*H*, NH), 7.51–7.62 (m, 3*H*, Ar-H), 7.19–7.31 (m, 2*H*, Ar-H) ppm. ^{13}C NMR (75 MHz DMSO-d_6): δ_C 161.9 (C═O), 158.0 (pyridone-C), 157.9 (pyridone-C), 135.6 (dm, $^{1}J_{CF}$ = 265.4 Hz, C-6 py), 134.2 (Ar-C), 130.7 (Ar-CH), 128.7 (Ar-CH), 128.0 (Ar-CH), 127.9 (dm, $^{1}J_{CF}$ = 229.8 Hz, C-5 py), 115.6 (CN), 114.9 (CN), 86.3 (pyridone-C), 74.6 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −93.8 (m, 1F, F-5 py), −157.0 (m, 1F, F-6 py), −165.7 (m, 1F, F-2 py) ppm; and 6-amino-2-oxo-1-((perfluoropyridin-4-yl)amino)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **8a**; 21%; brown solid; mp: 150–153°C. IR (KBr): ν 3416 (N-H), 2215 (CN), 1652 (C═O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.34 (1*H*, NH), 7.45–7.50 (m, 3*H*, Ar-H), 7.29–7.44 (m, 2*H*, Ar-H), 5.80 (2*H*, NH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 160.2 (C═O), 158.1 (pyridone-C), 157.3 (pyridone-C), 135.5 (Ar-C), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 117.2 (CN), 83.5 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −97.4 (m, 2F, F-2,6 py), −156.2 (m, 2F, F-3,5 py) ppm.

1,3,4-Trifluoro-7-oxo-9-(p-tolyl)-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7b). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-2-oxo-4-(p-tolyl)-1,2-dihydropyridine-3,5-dicarbonitrile **5b**

(0.265 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 42 h and using column chromatography (EtOAc/MeOH, 15:2), gave 1,3,4-trifluoro-7-oxo-9-(p-tolyl)-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7b**, 40%; yellow solid; mp: 176–179°C. (Found: C, 57.59; H, 2.21; N, 21.08; $C_{19}H_9F_3N_6O$ requires: C, 57.87; H, 2.30; N, 21.31). IR (KBr): ν 3207 (N-H), 3306 (N-H), 2221 (CN), 1624 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.04 (2*H*, NH), 7.46 (d, 2*H*, $^3J_{HH}$ = 8.1 Hz, Ar-H), 7.37 (d, 2*H*, $^3J_{HH}$ = 8.1 Hz, Ar-H), 2.39 (s, 3*H*, CH_3) ppm. ^{13}C NMR (75 MHz DMSO-d_6): δ_C 161.6 (C═O), 158.1 (pyridone-C), 157.8 (pyridone-C), 143.2 (dm, $^1J_{CF}$ = 235.2 Hz, C-6 py), 140.6 (Ar-C), 137.9 (m, C-2 py), 131.4 (Ar-C), 131.3 (dm, $^1J_{CF}$ = 254.9 Hz, C-5 py), 129.3 (Ar-CH), 128.1 (Ar-CH), 115.9 (CN), 115.2 (CN), 86.3 (pyridone-C), 74.5 (pyridone-C), 21.0 (CH_3) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −94.5 (m, 1F, F-5), −157.7 (m, 1F, F-6), −166.6 (m, 1F, F-2 py) ppm; and trace 6-amino-2-oxo-1-((perfluoropyridin-4-yl)amino)-4-(p-tolyl)-1,2-dihydropyridine-3,5-dicarbonitrile **8b**; brown solid; mp: 295°C. IR (KBr): ν 3448 (N-H), 2214 (CN), 1643 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −97.3 (m, 2F, F-2,6 py), −156.1 (m, 1F, F-3,5 py) ppm.

1,3,4-Trifluoro-9-(4-methoxyphenyl)-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7c). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5c** (0.281 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 42 h and using column chromatography (EtOAc/MeOH, 15:2), gave 1,3,4-trifluoro-9-(4-methoxyphenyl)-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7c**, 40%; yellow solid; mp: 220–222°C. (Found: C, 55.50; H, 2.02; N, 20.32; $C_{19}H_9F_3N_6O_2$ requires: C, 55.62; H, 2.21; N, 20.48). IR (KBr): ν 3204 (N-H), 2216 (CN), 1606 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 8.99 (2*H*, NH), 7.55 (d, 2*H*, $^3J_{HH}$ = 8.7 Hz, Ar-H), 7.12 (d, 2*H*, $^3J_{HH}$ = 8.8 Hz, Ar-H), 3.84 (s, 3*H*, OCH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 161.2 (C═O), 161.2 (pyridone-C), 158.2 (pyridone-C), 157.8 (Ar-C), 143.3 (dm, $^1J_{CF}$ = 229.4 Hz, C-6 py), 138.0 (m, C-2 py), 131.3 (dm, $^1J_{CF}$ = 264.1 Hz, C-5 py), 130.1 (Ar-CH), 126.2 (Ar-C), 116.1 (CN), 115.4 (CN), 114.1 (Ar-CH), 86.2 (pyridone-C), 74.5 (pyridone-C), 55.4 (OCH_3) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −94.6 (m, 1F, F-5 py), −157.6 (m, 1F, F-6 py), −166.6 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(4-methoxyphenyl)-2-oxo-1-((perfluoropyridin-4-yl)amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8c**, brown solid; mp:220–223°C. IR (KBr): ν 3447 (N-H), 2214 (CN), 1607 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −97.3 (m, 2F, F-2,6 py), −156.0 (m, 2F, F-3,5 py) ppm.

9-(2,4-Dimethoxyphenyl)-1,3,4-trifluoro-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7d). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(2,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5d** (0.311 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 40 h and using column chromatography (EtOAc/MeOH, 3:1), gave 9-(2,4-dimethoxyphenyl)-1,3,4-trifluoro-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7d**, 52%; yellow solid; mp:190–193°C. (Found: C, 54.28; H, 2.41; N, 18.86; $C_{20}H_{11}F_3N_6O_3$ requires: C, 54.55; H, 2.52; N, 19.09). IR (KBr): ν 3447 (N-H), 2216 (CN), 1644 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.92, 7.94 (NH), 7.13 (d, 1*H*, $^3J_{HH}$ = 8.4 Hz, Ar-H), 6.67 (s, 1*H*, Ar-H), 6.60 (d, 1*H*, $^3J_{HH}$ = 9 Hz, Ar-H), 3.82 (s, 3*H*, OCH_3), 3.78 (s, 3*H*, OCH_3) ppm. ^{13}C NMR (75 MHz DMSO-d_6): δ_C 164.1 (C═O), 160.6 (pyridone-C), 156.1 (pyridone-C), 154.6 (Ar-C), 144.2 (dm, $^1J_{CF}$ = 223.0 Hz, C-6 py), 139.6 (m, C-2 py), 133.6 (dm, $^1J_{CF}$ = 258.3 Hz, C-5 py), 129.3 (Ar-CH), 127.5 (Ar-C), 117.6 (CN), 116.0 (CN), 113.7 (Ar-CH), 85.2 (pyridone-C), 73.7 (pyridone-C), 54.0 (OCH_3), 52.3 (OCH_3) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −93.2 (m, 1F, F-5 py), −141.7 (m, 2F, F-6 py), −164.0 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(2,4-dimethoxyphenyl)-2-oxo-1-((perfluoropyridin-4-yl) amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8d**, brown solid; mp:218–220°C. IR (KBr): ν 3440 (N-H), 2213 (CN), 1643 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −96.1 (m, 2F, F-2,6 py), −155.6 (m, 2F, F-3,5 py) ppm.

9-(4-Chlorophenyl)-1,3,4-trifluoro-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7e). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5e** (0.258 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 40 h and using column chromatography (EtOAc/MeOH, 5:1), gave 9-(4-chlorophenyl)-1,3,4-trifluoro-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7e**, 48%; yellow solid; mp: 168–170°C. (Found: C, 51.95; H, 1.25; N, 20.00; $C_{18}H_6ClF_3N_6O$ requires: C, 52.13; H, 1.46; N, 20.26). IR (KBr): ν 3447 (N-H), 2216 (CN), 1651 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.73, 7.93 (NH), 7.58 (d, 2*H*, $^3J_{HH}$ = 8.6 Hz, Ar-H), 7.46 ($^3J_{HH}$ = 8.5 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 162.3 (C═O), 159.0 (pyridone-C), 156.6 (pyridone-C), 134.7 (Ar-C), 133.9 (Ar-C), 129.9 (Ar-CH), 128.7 (Ar-CH), 116.9 (CN), 116.5 (CN), 86.9 (pyridone-C), 82.6 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −92.9 (m, 1F, F-5 py), −141.3 (m, 1F, F-6 py), −163.6 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(4-chlorophenyl)-2-oxo-1-((perfluoropyridin-4-yl)amino)-1,2-dihydropyridine-3,5-

dicarbonitrile **8e**, brown solid; mp: 210–213°C. IR (KBr): ν 3449 (N-H), 2221 (CN), 1648 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −96.6 (m, 2F, F-2,6 py), −156.2 (m, 2F, F-3,5 py) ppm.

9-(2-Bromophenyl)-1,3,4-trifluoro-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7f). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(2-bromophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5f** (0.328 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 45 h and using column chromatography (EtOAc/MeOH, 5:1), gave 9-(2-bromophenyl)-1,3,4-trifluoro-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7f**, 46%; yellow solid; mp: 214°C. (Found: C, 46.88; H, 1.05; N, 18.05; $C_{18}H_6BrF_3N_6O$ requires: C, 47.08; H, 1.32; N, 18.30). IR (KBr): 3208 (NH), 3305 (N-H), 2223 (CN), 1625 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.1 (NH), 7.83 (d, 1*H*, $^3J_{HH}$ = 7.9 Hz, Ar-H), 7.53–7.60 (m, 2*H*, Ar-H), 7.48 (t, 1*H*, $^3J_{HH}$ = 6.6 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 160.5 (C═O), 157.9 (pyridone-C), 157.4 (pyridone-C), 143.3 (dm, $^1J_{CF}$ = 231.4 Hz, C-6 py), 138.5 (m, C-2 py), 138.5 (m, C-2 py), 135.6 (Ar-C), 133.0 (Ar-CH), 131.9 (Ar-C), 130.4 (dm, $^1J_{CF}$ = 255.0 Hz, C-5 py), 129.4 (Ar-CH), 128.4 (Ar-CH), 120.2 (Ar-CH), 115.1 (CN), 114.3 (CN), 87.1 (pyridone-C), 75.2 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −95.4 (m, 1F, F-5 py), −158.4 (m, 1F, F-6 py), −166.9 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(2-bromophenyl)-2-oxo-1-((perfluoropyridin-4-yl)amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8f**, brown oil. IR (KBr): ν 3447 (N-H), 2217 (CN), 1640 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −97.6 (m, 2F, F-2,6 py), −156.0 (m, 2F, F-3,5 py) ppm.

1,3,4-Trifluoro-9-(2-nitrophenyl)-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile(7g). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5g** (0.296 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 40 h and using column chromatography (EtOAc/MeOH, 10:1), gave 1,3,4-trifluoro-9-(2-nitrophenyl)-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7g**, 45%; yellow solid; mp: 213–215°C. (Found: C, 50.59; H, 1.33; N, 22.87; $C_{18}H_6F_3N_7O_3$ requires: C, 50.84; H, 1.42; N, 23.05). IR (KBr): ν 3317 (N-H), 2224 (CN), 1627 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.16 (NH), 8.37 (d, 1*H*, $^3J_{HH}$ = 8.2 Hz, Ar-H), 8.00 (t, 1*H*, $^3J_{HH}$ = 7.5 Hz, Ar-H), 7.90 (t, 1*H*, $^3J_{HH}$ = 7.6 Hz, Ar-H), 7.80 (d, 1*H*, $^3J_{HH}$ = 7.6 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz DMSO-d_6): δ_C 159.9 (C═O), 157.8 (pyridone-C), 157.6 (pyridone-C), 146.3 (Ar-C), 143.3 (dm, $^1J_{CF}$ = 233.1 Hz, C-6 py), 137.8 (m, C-2 py), 135.3 (Ar-C), 132.2 (Ar-CH), 131.6 (dm, $^1J_{CF}$ = 252.9 Hz, C-5 py), 130.7 (Ar-CH), 129.4 (Ar-CH), 125.5 (Ar-CH), 115.1 (CN), 114.4 (CN), 86.2 (pyridone-C), 74.5 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −94.5 (m, 1F, F-5 py), −157.4 (m, 1F, F-6 py), −166.6 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(2-nitrophenyl)-2-oxo-1-((perfluoropyridin-4-yl) amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8g**, brown solid; mp: 185°C. IR (KBr): ν 3447 (N-H), 2216 (CN), 1640 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −97.0 (m, 2F, F-2,6 py), −155.8 (m, 1F, F-3,5 py) ppm.

1,3,4-Trifluoro-9-(3-nitrophenyl)-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7h). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5g** (0.296 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 40 h and using column chromatography (EtOAc/MeOH, 10:1), gave 1,3,4-trifluoro-9-(3-nitrophenyl)-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7h**, 51%; yellow solid; mp: 175–178°C. (Found: C, 50.72; H, 1.17; N, 22.82; $C_{18}H_6F_3N_7O_3$ requires: C, 50.84; H, 1.42; N, 23.05). IR (KBr): ν 3208 (NH), 3306 (N-H), 2220 (CN), 1650 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 8.21(NH), 8.35 (d, 1*H*, $^3J_{HH}$ = 8.2 Hz, Ar-H), 8.15 (s, 1*H*, Ar-H), 7.81 (t, 1*H*, $^3J_{HH}$ = 6.8 Hz, Ar-H), 7.75 (d, 1*H*, $^3J_{HH}$ = 7.4 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz DMSO-d_6): δ_C 159.8 (C═O), 156.4 (pyridone-C), 156.0 (pyridone-C), 145.8 (Ar-C), 144.1 (dm, $^1J_{CF}$ = 230.4 Hz, C-6 py), 138.2 (m, C-2 py), 134.7 (Ar-C), 132.0 (Ar-CH), 131.1 (dm, $^1J_{CF}$ = 246.2 Hz, C-5 py), 130.0 (Ar-CH), 128.6 (Ar-CH), 126.7 (Ar-CH), 115.6 (CN), 113.2 (CN), 85.7 (pyridone-C), 76.9 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −96.3 (m, 1F, F-5 py), −158.8 (m, 1F, F-6 py), −167.5 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(3-nitrophenyl)-2-oxo-1-((perfluoropyridin-4-yl)amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8h**, 7%, brown solid; mp: 130–133°C. IR (KBr): ν 3446 (N-H), 2216 (CN), 1646 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −98.3 (m, 2F, F-2,6 py), −147.3 (m, 1F, F-3,5 py) ppm.

1,3,4-Trifluoro-9-(4-nitrophenyl)-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7i). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5i** (0.296 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 40 h and using column chromatography (EtOAc/MeOH, 10:1), gave 1,3,4-trifluoro-9-(4-nitrophenyl)-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7i**, 33%; yellow solid; mp: 226–229°C. (Found: C, 50.60; H, 1.36; N, 22.90; $C_{18}H_6F_3N_7O_3$ requires: C, 50.84; H, 1.42; N, 23.05). IR (KBr): ν 3212 (NH), 3306 (N-H), 2223 (CN), 1630 (C═O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 9.50 (NH), 8.40 (d, 2*H*, $^3J_{HH}$ = 8.6 Hz, Ar-H), 7.90 (d, 2*H*,

$^3J_{HH}$ = 8.6 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 159.0 (C═O), 157.8 (pyridone-C), 157.4 (pyridone-C), 148.7 (Ar-C), 140.6 (Ar-C), 130.0 (Ar-CH), 123.9 (Ar-CH), 115.5 (CN), 114.8 (CN), 86.3 (pyridone-C), 74.3 (pyridone-C) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −95.6 (m, 1F, F-53 py), −158.2 (m, 1F, F-6 py), −167.2 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(4-nitrophenyl)-2-oxo-1-((perfluoropyridin-4-yl)amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8i**, brown solid; mp: 203°C. IR (KBr): ν 3447 (N-H), 2217 (CN), 1640 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F –97.1 (m, 2F, F-2,6 py), −156.0 (m, 2F, F-3,5 py) ppm.

1,3,4-Trifluoro-9-(4-fluorophenyl)-7-oxo-7,11-dihydro-5H-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile (7j). Potassium carbonate (0.414 g, 3 mmol), 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **5j** (0.269 g, 1 mmol), pentafluoropyridine **6** (0.169 g, 1 mmol), and CH_3CN (8 mL), after refluxing for 45 h and using column chromatography (EtOAc/MeOH, 10:1), gave 1,3,4-trifluoro-9-(4-fluorophenyl)-7-oxo-7,11-dihydro-5*H*-dipyrido[1,2-b:3′,4′-e][1,2,4]triazine-8,10-dicarbonitrile **7j**, 38%; yellow solid; mp: 227–230°C. (Found: C, 54.08; H, 1.39; N, 20.85; $C_{18}H_6F_4N_6O$ requires: C, 54.28; H, 1.52; N, 21.10). IR (KBr): ν 3424 (NH), 2230 (CN), 1625 (C═O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.1 (NH), 7.62–7.68 (m, 2*H*, Ar-H), 7.38–7.45 (m, 2*H*, Ar-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 165.0 (C═O), 161.7 (pyridone-C), 159.2 (d, $^1J_{CF}$ = 173.6 Hz, Ar-C), 157.6 (pyridone-C), 143.3 (dm, $^1J_{CF}$ = 235.2 Hz, C-6 py), 138.4 (m, C-2 py), 131.4 (dm, $^1J_{CF}$ = 246.7 Hz, C-5 py), 130.8 (d, $^3J_{CF}$ = 8.85 Hz, Ar-CH), 130.7 (d, $^4J_{CF}$ = 3.2 Hz, Ar-C), 116.0 (CN), 115.7 (CN), 115.5 (d, $^2J_{CF}$ = 51.2 Hz, Ar-CH), 86.5 (pyridone-C), 74.7 (pyridone-C) pm. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F −95.1 (m, 1F, F-5 py), −110.0 (1F, Ar-CF), −157.8 (m, 1F, F-6 py), −166.7 (m, 1F, F-2 py) ppm; and trace 6-amino-4-(4-fluorophenyl)-2-oxo-1-((perfluoropyridin-4-yl)amino)-1,2-dihydropyridine-3,5-dicarbonitrile **8j**, brown solid; mp: 200–202°C. IR (KBr): ν 3441 (N-H), 2215 (CN), 1651 (C═O) cm^{-1}. ^{19}F NMR (282 MHz, DMSO-d_6): δ_F –97.6 (m, 2F, F-2,6 py), −110.8 (1F, Ar-CF) −156.8 (m, 2F, F-3,5 py) ppm.

Acknowledgment. The authors wish to thank Vali-e-Asr University of Rafsanjan for partially funding this work.

REFERENCES AND NOTES

[1] Halpern, D. F.; Vernice, G. G. Chemistry of Organic Fluorine Compounds II; American Chemical Society: Washington, DC, 1995, p. 172.

[2] Filler, R.; Kobayashi, Y.; Yagulpolskii, Y. L. Organo-fluorine Compound in Medicinal Chemistry and Biomedical Applications; Elsevier: Amsterdam, 1993, pp. 1–380.

[3] Welch, J. T. Tetrahedron 1987, 43, 3123.

[4] Smart, B. E. J Fluor Chem 2001, 109, 3.

[5] Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. J Org Chem 2005, 70, 7208.

[6] Chambers, R. D.; Khalil, A.; Murray, C. B.; Sandford, G.; Batsanov, A. S.; Howard, J. A. K. J Fluor Chem 2005, 126, 1002.

[7] Ranjbar-Karimi, R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. J Fluor Chem 2008, 129, 307.

[8] Brooke, G. M. J Fluor Chem 1997, 86, 1.

[9] Chambers, R. D.; Sargent, C. R. Adv Heterocycl Chem 1981, 28, 1.

[10] Banks, R. E.; Haszeldine, R. N.; Philips, E.; Young, I. M. J Chem Soc C 1967 2091.

[11] Banks, R. E.; Burgess, J. E.; Cheng, W. M.; Haszeldine, R. N. J Chem Soc 1965 575.

[12] Banks, R. E.; Haszeldine, R. N.; Karsa, D. R.; Rickett, F. E.; Young, I. M. J Chem Soc C 1969 1660.

[13] Nguyen, B. V.; Burton, D. J. J Fluor Chem 2012, 135, 144.

[14] Chambers, R. D.; Iddon, B.; Musgrave, W. K. R. Tetrahedron 1968, 24, 877.

[15] Baron, A.; Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. J Org Chem 2005, 70, 9377.

[16] Hargreaves, C. A.; Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. Tetrahedron 2007, 63, 5204.

[17] Cartwright, M. W.; Convery, L.; Kraynck, T.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. Tetrahedron 2010, 66, 519.

[18] Cartwright, M. W.; Sandford, G.; Bousbaa, J.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. Tetrahedron 2007, 63, 7027.

[19] Ranjbar-Karimi, R.; Heidari, E. J Fluor Chem 2013, 154, 47.

[20] Ranjbar-Karimi, R.; Mousavi, M. J Fluor Chem 2010, 131, 587.

[21] Poorfreidoni, A.; Ranjbar-Karimi, R. Tetrahedron Lett 2016, 57, 5781.

[22] Ranjbar-Karimi, R.; Hashemi-Uderji, S.; Danesteh, R. J Iran Chem Soc 2012, 9, 747.

[23] Anjomshoa, M.; Hadadzadeh, H.; Torkzadeh-Mahani, M.; Fatemi, S. J.; Adeli-Sardou, M.; Rudbari, H. A.; Nardo, V. M. Eur J Med Chem 2015, 96, 66.

[24] Ahuja, P.; Siddiqui, N. Eur J Med Chem 2014, 80, 509.

[25] Agarwal, A.; Srivastava, K.; Puri, S. K.; Chauhan, P. M. S. Bioorg Med Chem Lett 2005, 15, 531.

[26] Yurttas, L.; Demirayak, S.; Ilgin, S.; Atli, O. Bioorg Med Chem 2014, 22, 6313.

[27] Rusinov, V. L.; Egorov, I. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Serova, O. A. Pharm Chem J 2012, 45, 655.

[28] Pabst, G. R.; Sauer, J. Tetrahedron Lett 1998, 39, 6687.

[29] Altuna-Urquijo, M.; Stanforth, S. P.; Tarbitb, B. Tetrahedron Lett 2005, 46, 6111.

[30] Ghorbani-Vaghei, R.; Shahriari, A.; Salimia, Z.; Hajinazari, S. RSC Adv 2015, 5, 3665.

[31] Ghosh, P. S.; Manna, K.; Banik, U.; Das, M.; Sarkar, P. Int J Pharm Sci 2014, 6, 975.

SUPPORTING INFORMATION

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