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Efficient one-step synthesis of 3-aryl-2-pyridones from 6-aryl-1,2,4-triazin-5-ones

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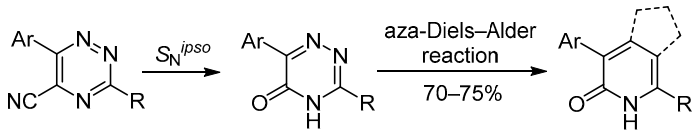


Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$; R = H, 2-Py

An efficient method for the synthesis of substituted 2-pyridones based on the aza-Diels–Alder reaction of 1,2,4-triazin-5-ones and dienophiles, 2,5-norbornadiene and 4-(cyclopent-1-en-1-yl)morpholine, is proposed.

Keywords: 2,2'-bipyridine, 2-pyridone, 1,2,4-triazin-5-one, autoclave, aza-Diels–Alder reaction, nucleophilic *ipso*-substitution.

Derivatives of 2-pyridones are of interest due to their biological activity,[1] in particular anticonvulsant (perampanel),[2] antifungal, and antimicrobial (cyclopirox)[3] properties, together with the ability to inhibit phosphodiesterase,[3] which is used in the treatment of heart failure (milrinone).[4] In addition, the 2-pyridone ring is part of natural compounds (trichodin A, B and pyridoxatin, Fig. 1), including alkaloids.[5] Derivatives of 2-pyridones are used as herbicides, insecticides,[6] and luminophores.[7] 6-(Pyridin-2-yl)-2-pyridones are of interest as ligands and fluorescent sensors of zinc cations in the composition of living cells,[8] and also have promising photophysical properties.[9]

To date, a variety of synthetic approaches to 2-pyridones are presented in the literature, summarized in several reviews.[10] However, the method based on the use of 1,2,4-triazines as dienes, well-established in the synthesis of bi- and oligopyridines,[11] is limited to only a few examples of intramolecular reactions of 1,2,4-triazines with terminal acetylene for the preparation of 2-pyridones.[12] Moreover, the formation of a mixture of products is noted in a number of cases.[13]

Earlier, we reported the possibility of synthesizing 5-aryl-2,2'-bipyridines with a methoxy, pyrrolidine,[14] or phenyl(cyano)methyl[15] substituent at position 6, as well as 8-(pyridin-2-yl)coumarins[16] *via* the aza-Diels–Alder reaction under conditions of elevated pressure and temperature in an autoclave. In the present work, 2-pyridones, including new derivatives with a pyridin-2-yl substituent at position 6 (2,2'-bipyridines), using easily accessible precursors, 1,2,4-triazin-5-ones, were obtained in a similar manner.

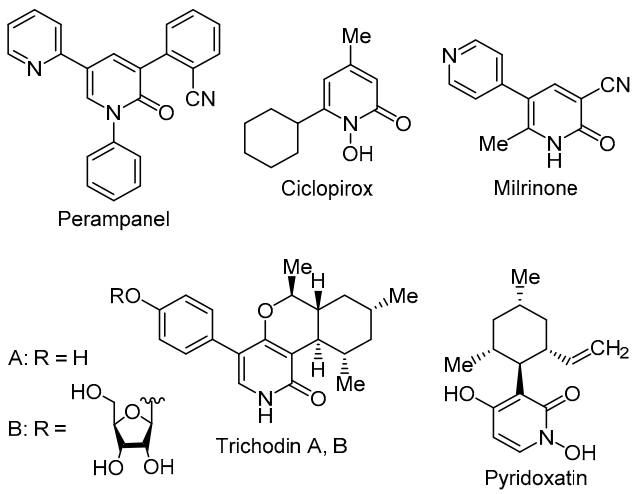
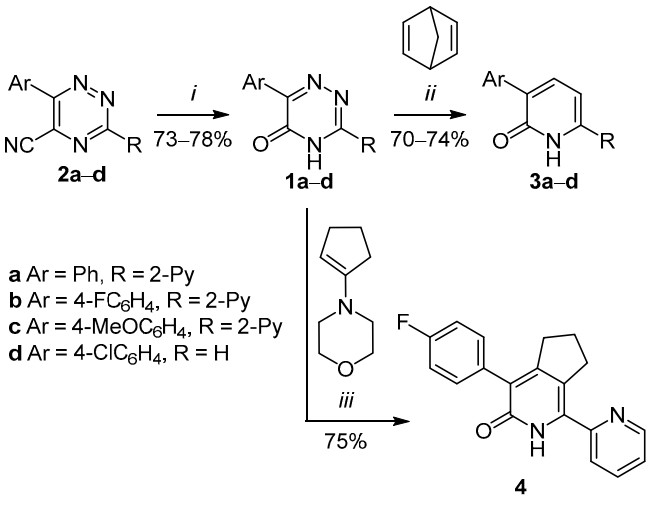


Figure 1. Structures of biologically active 2-pyridones.

The precursors 1,2,4-triazin-5-ones **1a–d** were obtained from readily available 5-cyano-1,2,4-triazines **2a–d**.[17] Of the described procedures for performing this transformation,[17b,18] we chose the most convenient[18d] (Scheme 1). The subsequent aza-Diels–Alder reaction of the synthesized 1,2,4-triazin-5-ones **1a–d** with 2,5-norbornadiene as dienophile was carried out in an autoclave in 1,2-dichlorobenzene at 215°C for 20 h, as a result of which 2-pyridones **3a–d** were obtained with high yields. Use of 6-(4-fluorophenyl)-3-(pyridin-2-yl)-1,2,4-triazin-5(4*H*)-one (**1b**) and another dienophile, 4-(cyclopent-1-en-1-yl)-morpholine, allowed to obtain 2-pyridone **4** with an annulated cyclopentene ring in one step. This reaction was carried out also according to the previously described method[19] without solvent, but in this case it took more time to complete it. In all cases, the formation of a single product was recorded and flash chromatography was used for its final purification.

Scheme 1



i: NaOH, CH_2Cl_2–H_2O, 1:2, rt, 3 h, then concd HCl, rt, 10 min
ii: 1,2-dichlorobenzene, 215°C, 20 h, autoclave
iii: 200°C, 10 h

The structures of products **3a–d** and **4** were proved on the basis of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis data. In particular, upon conversion of 1,2,4-triazin-5-ones **1a–d** to 2-pyridones **3a–d**, the ^{1}H NMR spectra show an upfield shift of the signals of the protons of the pyridine ring and the proton of the NH group from 13.99–14.60 to 10.98–11.79 ppm. In addition, the ^{1}H NMR spectroscopy data of product **3d** correlate with previously published data when compound **3d** was obtained by an alternative method.[20] In case of product **4**, the characteristic signals of the annulated cyclopentene ring appear in the resonance region of aliphatic protons.

To conclude, we have proposed an efficient synthetic approach to novel 2-pyridones containing a pyridin-2-yl substituent using readily available precursors 5-cyano-1,2,4-triazines and 1,2,4-triazin-5-ones. The products were obtained in high yields.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded on a Bruker Daltonics MicrOTOF-Q II instrument, electrospray ionization. Elemental analysis was performed on a Perkin Elmer 2400 CHN-analyzer. Melting points were determined on a Boetius heating bench. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Sigma-Aldrich SiO_2 plates with a fluorescent indicator (254 nm). Products were purified by column chromatography on SiO_2 (230–400 mesh).

5-Cyano-1,2,4-triazines **2a–d** were synthesized according to a literature method.[17a] 1,2,4-Triazin-5-ones **1a–d** were obtained from the respective 5-cyano-1,2,4-triazines **2a–d** according to the previously described procedure for similar compounds.[18d]

6-Phenyl-3-(pyridin-2-yl)-1,2,4-triazin-5(4*H*)-one (1a). Yield 193 mg (77%), yellow crystals, mp 177–179°C (mp 174–176°C[21]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.49–7.52 (3H, m, H Ph); 7.73–7.76 (1H, m, H-5 Py); 8.11–8.17 (3H, m, H-4 Py, H Ph); 8.35 (1H, d, *J* = 8.0, H-3 Py); 8.84 (1H, d, *J* = 4.8, H-6 Py); 14.60 (1H, br. s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 251 $[M+H]^+$ (100). Found, %: C 67.09; H 3.99; N 22.31. $C_{14}H_{10}N_4O$. Calculated, %: C 67.19; H 4.03; N 22.39.

6-(4-Fluorophenyl)-3-(pyridin-2-yl)-1,2,4-triazin-5(4*H*)-one (1b). Yield 196 mg (73%), yellow crystals, mp 171–173°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.17–7.21 (2H, m, H Ar); 7.60–7.68 (1H, m, H-5 Py); 8.08 (1H, ddd, *J* = 7.9, *J* = 7.9, *J* = 1.0, H-4 Py); 8.31–8.42 (3H, m, H Ar, H-3 Py); 8.79 (1H, d, *J* = 4.8, H-6 Py); 14.44 (1H, br. s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 269 $[M+H]^+$ (100). Found, %: C 62.60; H 3.29; N 20.80. $C_{14}H_9FN_4O$. Calculated, %: C 62.69; H 3.38; N 20.89.

6-(4-Methoxyphenyl)-3-(pyridin-2-yl)-1,2,4-triazin-5(4*H*)-one (1c). Yield 210 mg (75%), yellow crystals, mp 183–185°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (3H, s, OCH_3); 7.05–7.08 (2H, m, H Ar); 7.71–7.75 (1H, m, H-5 Py); 8.13 (1H, ddd, *J* = 7.9, *J* = 7.9, *J* = 1.0, H-4 Py); 8.21–8.24 (2H, m, H Ar); 8.34 (1H, d, *J* = 8.0, H-3 Py); 8.83 (1H, d, *J* = 4.8, H-6 Py); 14.50 (1H, br. s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 281 $[M+H]^+$ (100). Found, %: C 64.19; H 4.28; N 19.90. $C_{15}H_{12}N_4O_2$. Calculated, %: C 64.28; H 4.32; N 19.99.

6-(4-Chlorophenyl)-1,2,4-triazin-5(4*H*)-one (1d). Yield 160 mg (78%), light-yellow crystals, mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 7.48–7.50 (2H, m, H Ar); 8.16–8.25 (2H, m, H Ar); 8.65 (1H, br. s, H-3); 13.99 (1H, br. s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 208 $[M+H]^+$ (100). Found, %: C 52.00; H 2.85; N 20.16. $C_9H_6ClN_3O$. Calculated, %: C 52.07; H 2.91; N 20.24.

Synthesis of pyridones 3a–d (General method). 2,5-Norbornadiene (0.41 ml, 4 mmol) was added to a suspension of 1,2,4-triazin-5-one **1a–d** (0.5 mmol) in 1,2-dichlorobenzene (15 ml). The resulting mixture was stirred under an argon atmosphere in an autoclave at 215°C for 20 h. The solvent was evaporated under reduced pressure, and

the residue was purified by flash chromatography (SiO_2, eluent CH_2Cl_2–EtOAc, 10:1). An analytical sample was obtained by recrystallization from MeCN.

5-Phenyl-2,2′-bipyridin-6(1*H*)-one (3a). Yield 87 mg (70%), light-yellow crystals, mp 166–168°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.23 (1H, d, *J* = 8.0, H-3); 7.31–7.35 (1H, m, H Ph); 7.37–7.43 (2H, m, H Ph); 7.46–7.48 (1H, m, H-5'); 7.73–7.81 (3H, m, H Ph, H-4); 7.95 (1H, ddd, *J* = 7.9, *J* = 7.9, *J* = 1.0, H-4'); 8.17 (1H, d, *J* = 8.0, H-3'); 8.70 (1H, d, *J* = 4.8, H-6'); 11.00 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 103.2; 119.6; 124.4; 128.0; 128.3; 128.5; 132.9; 136.3; 137.3; 138.4; 140.7; 147.9; 149.3; 161.5. Mass spectrum, *m*/*z* (I_{rel}, %): 249 $[M+H]^+$ (100). Found, %: C 77.18; H 4.73; N 11.01. $C_{16}H_{12}N_2O$. Calculated, %: C 77.40; H 4.87; N 11.28.

5-(4-Fluorophenyl)-2,2′-bipyridin-6(1*H*)-one (3b). Yield 98 mg (74%), light-yellow crystals, mp 181–183°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.09–7.13 (2H, m, H Ar); 7.18 (1H, d, *J* = 8.0, H-3); 7.41–7.44 (1H, m, H-5'); 7.72 (1H, d, *J* = 8.0, H-4); 7.80–7.84 (2H, m, H Ar); 7.91 (1H, ddd, *J* = 7.9, *J* = 7.9, *J* = 1.0, H-4'); 8.12 (1H, d, *J*-= 8.0, H-3'); 8.67 (1H, d, *J* = 4.8, H-6'); 10.98 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 103.3; 115.2 (d, *J* = 21.6); 119.6; 124.5; 130.2; 130.3; 131.9; 132.2 (d, *J* = 3.4); 137.4; 138.2; 140.6; 147.8; 149.4; 161.5; 162.6 (d, *J* = 247.8). Mass spectrum, *m*/*z* (I_{rel}, %): 267 $[M+H]^+$ (100). Found, %: C 72.08; H 4.01; N 10.45. $C_{16}H_{11}FN_2O$. Calculated, %: C 72.17; H 4.16; N 10.52.

5-(4-Methoxyphenyl)-2,2′-bipyridin-6(1*H*)-one (3c). Yield 100 mg (72%), light-yellow crystals, mp 199–201°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.86 (3H, s, OCH_3); 7.03–7.06 (2H, m, H Ar); 7.24–7.26 (1H, m, H-3); 7.54–7.58 (1H, m, H-5'); 7.84–7.87 (3H, m, H-4, H Ar); 8.04 (1H, ddd, *J* = 7.9, *J* = 7.9, *J* = 1.0, H-4'); 8.23 (1H, d, *J* = 8.0, H-3'); 8.77 (1H, d, *J* = 4.8, H-6'); 11.18 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 55.4; 117.5; 125.6; 126.9; 127.4; 127.8; 129.0; 129.3; 129.4; 130.0; 130.3; 131.5; 133.7; 135.8; 139.0; 141.0; 154.5. Mass spectrum, *m*/*z* (I_{rel}, %): 279 $[M+H]^+$ (100). Found, %: C 73.30; H 4.99; N 10.01. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.37; H 5.07; N 10.07.

3-(4-Chlorophenyl)pyridin-2(1*H*)-one (3d). Yield 76 mg (74%), light-yellow crystals, mp 177–179 °C (mp 182–184°C[20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.22 (1H, dd, *J* = 6.6, *J* = 6.6, H-5); 7.28–7.34 (3H, m, H Ar, H-4); 7.56 (1H, dd, *J* = 6.6, *J* = 2.0, H-6); 7.71–7.73 (2H, m, H Ar); 11.79 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 107.2; 128.5; 129.9; 130.4; 133.8; 134.3; 134.9; 139.8; 164.0. Mass spectrum, *m*/*z* (I_{rel}, %): 206 $[M+H]^+$ (100). Found, %: C 64.16; H 3.85; N 6.72. $C_{11}H_8ClNO$. Calculated, %: C 64.25; H 3.92; N 6.81.

4-(4-Fluorophenyl)-1-(pyridin-2-yl)-2,5,6,7-tetrahydro-3*H*-cyclopenta[*c*]pyridin-3-one (4). A mixture of 1,2,4-triazin-5-one **1b** (200 mg, 0.75 mmol) and 4-(cyclopent-1-en-1-yl)morpholine (0.6 ml, 3.75 mmol) was stirred under an argon atmosphere at 200°C for 10 h. The product was isolated from the reaction mixture by column chromatography (SiO_2, eluent CH_2Cl_2–EtOAc, 10:1). The solvent was evaporated under reduced pressure from the combined fractions containing product **4**, and the residue was treated with EtOH (20 ml). The formed precipitate was filtered off, washed with EtOH (20 ml), and dried. Yield 172 mg (75%), light-yellow crystals, mp 124–126°C (MeCN), R_f 0.40 (CH_2Cl_2–EtOAc, 10:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02–2.05 (2H, m, 6-CH_2); 2.80 (2H, t, *J* = 7.6, 7-CH_2); 3.11 (2H, t, *J* = 7.6, 5-CH_2); 7.08–7.12 (2H, m, H Ar); 7.43–7.47 (3H, m, H-5 Py, H Ar); 7.86 (1H, d, *J* = 7.6, H-3 Py); 7.93 (1H, ddd, *J* = 7.9, *J* = 7.9, *J* = 1.0, H-4 Py); 8.71 (1H, d, *J* = 4.8, H-6 Py); 10.60 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 26.3; 31.8; 33.0; 115.0 (d, *J* = 21.8); 121.9; 122.3; 123.8; 127.1; 131.3 (d, *J* = 3.2); 131.5; 134.0; 137.1; 148.8; 149.5; 158.2; 161.8; 162.1 (d, *J* = 246.4). Mass spectrum, *m*/*z* (I_{rel}, %): 307 $[M+H]^+$ (100). Found, %: C 74.42; H 4.89; N 9.05. $C_{19}H_{15}FN_2O$. Calculated, %: C 74.50; H 4.94; N 9.14.

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