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An efficient route to polynitrogen-fused tricycles via a nitrene-mediated N–N bond formation under microwave irradiation

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ABSTRACT

The synthesis of unprecedented fused azaheterocyclic ring systems is described. Tricycles with either a central pyrazole or a triazole ring were obtained via a nitrene-mediated reaction of nitro bis(hetaryl) derivatives in the presence of triethylphosphite. The cyclization proceeded with complete chemoselectivity for the desired N–N bond formation and was completed within minutes under microwave activation. The key nitro bicycles were synthesized using either Stille couplings or aromatic nucleophilic substitution.

1. Introduction

Fused polyheterocycles have been the subject of numerous studies due to their pharmacological[1] and energetic properties.[2] Such compounds have mainly been prepared by amination–cyclization of heteroaryl derivatives containing a carbonyl or a halogen,[3] by cyclization of *o*-amino/*o*-heteroacetylenes,[4] or by reductive cyclization on a nitrohetaryl.[5]

Previous work from our laboratory has consisted in the synthesis of nitrogen-rich tricycles with a pyrimidin-4-one as the central core.[6] The key reaction was an N-heteroarylation under Pd-catalyzed conditions, developed in a preliminary study.[7]

In a further step toward a general route to other related fused azaheterocyclic compounds, the present communication describes the synthesis of tricycles with either a pyrazole or a 1,2,3-triazole as the central ring. The underlying strategy was based on the creation of the desired central ring via an intramolecular, nitrene-mediated N–N bond formation from a bis(hetaryl) precursor. Such a strategy pioneered by Cadogan[8] and Abramovitch[9] has been widely used on phenyl hetaryls.[10] Depending on the substrates and conditions, C–N or N–N cyclization has been observed. As a general trend, singlet nitrenes favor N–N cyclization, while triplet nitrenes favor competitive pathways (e.g., C–N cyclization, H-abstraction, dimerization, C–H insertion).[11]

Though a number of heterocyclic nitrenes have been investigated,[12] the literature is very scarce concerning the nitrene-mediated cyclization of a bis(hetaryl) systems. In a few cases, the final product was a fused tetracycle.[13] The present article demonstrates that bicyclic nitro precursors can be used to generate bicyclic hetaryl nitrenes. Such a reaction was shown to be very efficient under microwave irradiations and was found to occur with complete chemoselectivity for N–N cyclization to give a variety of new fused azaheterocyclic tricycles [Scheme 1, Ar^1=(substituted) pyrazolyl, pyridyl, or pyrimidinyl, Ar^2=(substituted) pyridyl].

Though several other methods have been recently described,[14] the most common precursors of nitrenes are azido or nitro derivatives.[10] Thermal or photo-induced decompositions of these compounds lead to intermediate nitrenoid species, known to cyclize intramolecularly with an adjacent aromatic ring. In the case of nitro precursors, a deoxygenating agent is required. Phosphites and phosphines have been used,[15,8a] triethylphosphite being the more popular reagent.

Since nitro compounds are more readily available than their azido counterparts, the present strategy was based on cyclization from a nitro bicycle. It was first envisioned that a pallado-catalyzed carbon–carbon cross-coupling would be a useful method for building the desired nitro-functionalized bis(heterocyclic)

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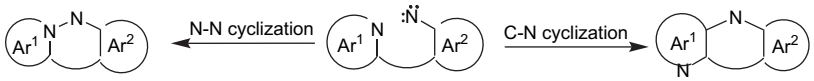


Scheme 1. Cyclization of arylnitrenes: N–N versus C–N pathway.

skeleton. Upon cyclization, tricycles with a central pyrazole ring should be produced.

2. Results and discussion

The Stille coupling between 2-tributylstannylpyridine and 2-chloro-3-nitropyridine was thus examined for the synthesis of bicycle **1a** as a model reaction (Table 1, R^1=R^2=R^3=H, X=Z=N, Y=CH). $Pd(PPh_3)_2Cl_2$ was used as the catalyst and the addition of CuI turned out to significatively improve the yields. The best results were obtained in DMF at 115 °C yielding 68% of pure isolated **1a**. Similarly, other nitro bicycles, i.e., **1b**–**1g**, were synthesized in fair yields (Table 1). The generality of the Stille coupling was demonstrated by the use of various substituted tributylstannylpyridines, a tributylstannylpyrimidine as well as a variety of chloronitropyridine derivatives. The degradation and, in some cases, a homocoupling (ca. 10%) of the tributylstannyl derivative were observed.

The cyclization conditions in the presence of triethylphosphite as a deoxygenative agent were then studied using 3-nitro-2-(pyrimidin-2-yl)pyridine **1a**. From this bicycle, the cyclization could only proceed through the formation of an N–N bond. Though classical heating proved efficient, microwave activation was preferred since reaction times could be substantially decreased with this method. At 176 °C, with an irradiating power of 300 W, the expected tricycle **2a** was obtained within 12 min in an 86% isolated yield (Table 1, entry 1). The versatility of the cyclization could be demonstrated by using different bicyclic nitro precursors (Table 1).

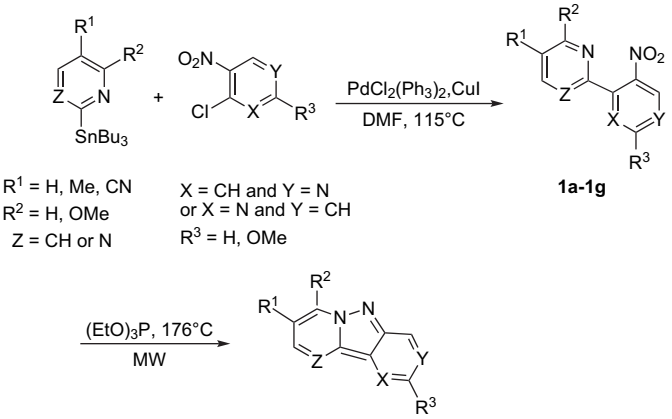
It is noteworthy that the various 3-nitro-2-(pyrid-2-yl)pyridines **1b**–**1g** cyclized with complete chemoselectivity, affording exclusively the desired tricycles from an N–N bond formation despite an available C–N cyclization site (Table 1). Moreover, the usual side products (i.e., amino, azo, azepine derivatives) were not observed.

Yields were high regardless of the nature and position of the substituents on the bis(hetaryl) derivatives. It could, however, be noticed that longer reaction times were required for compounds **1e** and **1f** to go to completion (Table 1, entries 5–6). This corroborated the observation of Suschitzky and co-workers[11] for 1-(2-nitrophenyl)pyrazoles. As a matter of fact, the electron-donating methoxy group could affect the reactivity of the intermediate electrophilic nitrenoid species derived from **1f**. In the case of **1e**, the electron-withdrawing cyano group could decrease the electron density of the pyridine ring and therefore lower the reactivity of the lone pair of the nitrogen atom of the pyridine. In view of this result, it was surprising that one of the shortest cyclization times was recorded for compound **1a** in spite of the more electron-deficient character of the pyrimidine ring (Table 2, entry 1). The cyclization also proceeded cleanly for **1g**, thus giving a tricycle with a pyrido[3,4-*c*]pyrazole moiety (Table 1, entry 7).

Compounds **2a**–**2g** represent, to the best of our knowledge, the first examples of three unprecedented ring systems, namely pyrazolo[1,5-*a*:4,3-*b*′]dipyridine, pyrazolo[1,5-*a*:3,4-*c*′]dipyridine, and pyrido[3′,2′:3,4]pyrazolo[1,5-*a*]pyrimidine. Crystals of **2a** were grown and its structure was confirmed by X-ray analysis (Fig. 1).

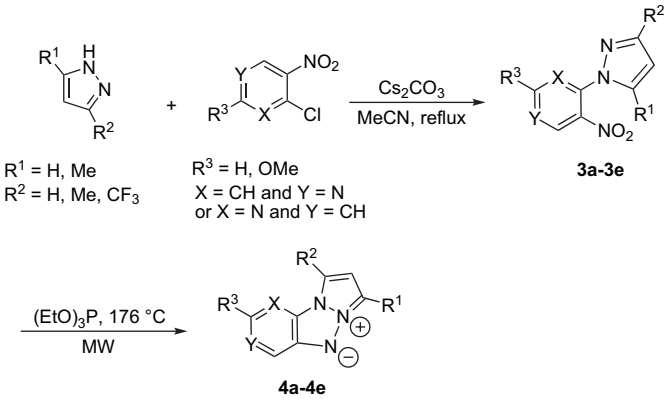
By examining these results, it was anticipated that the strategy could be further extended to access new azaheterocyclic fused compounds with a central betainic 1,2,3-triazole ring. The aromatic nucleophilic substitution of halogenopyridines by pyrazoles in the presence of bases has been well documented.[16] A variety of bases and solvents were thus screened for the reaction between 2-chloro-3-nitropyridine and pyrazole. Cesium carbonate in acetonitrile was the most efficient combination and gave rise to bicycle **3a** with

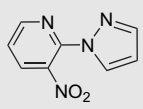
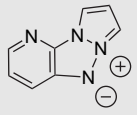
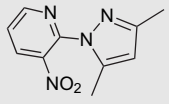
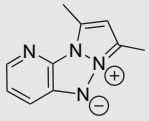
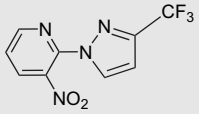
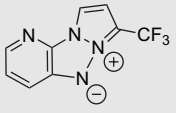
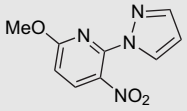
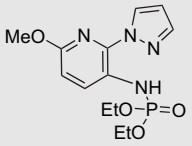
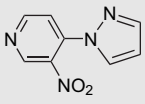
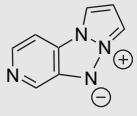
Table 1
Synthesis of nitro bishetaryls **1a**–**1g** and microwaves promoted cyclization to products **2a**–**2g**



Entry	Nitro precursors, yield	Cyclization time (min)	Tricycle, yield
1	**1a**, 68%	12	**2a**, 86%
2	**1b**, 75%	24	**2b**, 81%
3	**1c**, 59%	24	**2c**, 84%
4	**1d**, 79%	24	**2d**, 87%
5	**1e**, 47%	36	**2e**, 87%
6	**1f**, 60%	36	**2f**, 79%
7	**1g**, 71%	12	**2g**, 71%

Table 2
Synthesis of nitro bishetaryls **3a–3e** and microwaves promoted cyclization to products **4a–4g**



Entry	Bicyclic precursor, yield	Cyclization product, yield
1	 **3a**, 92%	 **4a**, 85%
2	 **3b**, 54%	 **4b**, 92%
3	 **3c**, 92%	 **4c**, 82%
4	 **3d**, 67%	 **5**, 35%
5	 **3e**, 84%	 **4e**, 20%

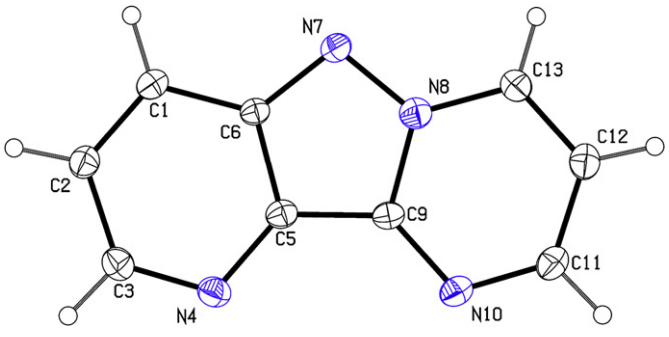


Figure 1. ORTEP view of **2a**.

a yield of 92%. These conditions allowed access to a new variety of other nitrobis(hetaryl) derivatives (Table 2). The yields ranged from 54 to 92%.

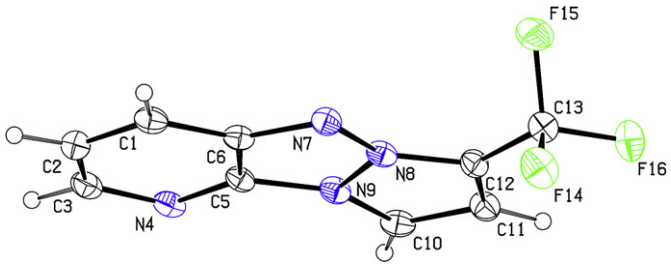


Figure 2. ORTEP view of **4c**.

As for the synthesis of tricycles **2a–2g**, the cyclization leading to **4a–4e** was performed using triethylphosphite under microwave irradiation. Again, also for this series, only the tricyclic compounds arising from an N–N bond formation between the pyrazole nitrogen and the electrophilic nitrene were isolated. Clean reactions and high yields were observed for compounds **4a–4c** despite the presence of electron-withdrawing functional groups on the pyrazole core (Table 2, entry 3). Moreover, it should be noted that in the case of 3-nitro-2-(3,5-dimethylpyrazol-1-yl)pyridine **3b**, the insertion product of the nitrene in a methyl C–H was not observed, though this could have been possible.[11a]

Nevertheless, a modification of the nitropyridine moiety substantially affected the cyclization. Thus the cyclization of **3e** (the only 4-(pyrazol-1-yl)pyridine) was sluggish and the tricycle **4e** was isolated at a yield of only 20% (Table 2, entry 5). Degradation was observed to a large extent even though the temperature was lowered to 105 °C. The introduction of an electron-donating group on the pyridine ring also proved to be detrimental to the reaction. In the case of **3d**, the expected cyclization did not occur. All that was noticed was the corresponding phosphoramidate **5** and degradation products (Table 2, entry 4). The formation of phosphoramidates in this type of reaction has been reported,[17] and they were found not to be the intermediates of the cyclized product.

Crystals suitable for X-ray analysis were obtained in the case of **4c**, and the betaine structure of the central 1,2,3-triazole ring could thus be confirmed. The recorded N–N and C–N bond lengths on the 1,2,3-triazole moiety were similar to the ones determined for the very few related structures resolved by X-ray[18] (Fig. 2).

3. Conclusion

In summary, the deoxygenation–cyclization of nitro bis(hetaryl) derivatives led to new polynitrogen-fused tricyclic compounds via a nitrenoid pathway. The reaction proceeded with complete chemoselectivity to exclusively afford products arising from an N–N bond formation. This resulted in the synthesis of derivatives of five new ring systems: pyrazolo[1,5-*a*:4,3-*b*′]dipyridine, pyrazolo[1,5-*a*:3,4-*c*′]dipyridine, pyrido[3′,2′:3,4]pyrazolo[1,5-*a*]pyrimidine, pyrazolo[1′,2′:2,3][1,2,3]triazolo[4,5-*b*]pyridine, and pyrazolo[1′,2′:1,2][1,2,3]triazolo[4,5-*c*]pyridine.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR chemical shifts were calibrated according to $CDCl_3$ signal (^{1}H: 7.27 ppm; ^{13}C: 77.23 ppm), and the ^{15}N NMR chemical shifts according to an external reference CH_3NO_2 (0 ppm) using a Bruker Avance 200 and Avance 400 WB spectrometers. Multiplicity is indicated using the following abbreviations: s for a singlet, d for a doublet, t for a triplet, q for a quadruplet. For carbon: C, CH, CH_2, CH_3 were determined according to DEPT analyses. Infrared spectra were recorded with an attenuated total

reflectance Perkin–Elmer SpectrumOne spectrometer. Melting points were determined on a Differential Scanning Calorimetry Q100, TA Instruments. Elemental analyses were performed on a ThermoFisher Scientific Flash EA1112 CHNS/O apparatus. Mass spectra were recorded on a Varian MS 1200 Quadrupole spectrometer using chemical ionization. High resolution mass spectra (HRMS) were obtained using chemical ionization (CI) and recorded on a Waters-micromass GCT Premier apparatus. Microwave-assisted reactions were performed with a CEM Discover apparatus.

Chromatographic purification of products was carried out using prepacked Analogix Superflash Si50 columns. Solid phase extraction was performed on Discovery DSC-NH_2 cartridges.

4.2. Procedure for compounds 1a–1g

5-Methyl-2-(tributylstannyl)pyridine and 2-methoxy-6-(tributylstannyl)pyridine were bought from Synthonix.

To a degassed solution of the chloronitropyridine (6 mmol, 1 equiv) and tributylstannyl derivatives (6.6 mmol, 1.1 equiv) in DMF (33 mL) were added CuI (0.6 mmol, 0.01 equiv) and $PdCl_2(PPh_3)_2$ (0.3 mmol, 0.01 equiv) under an inert atmosphere. After stirring for 18 h at 115 °C, 1 N aqueous KF (9 mL) was added, and the resulting mixture was stirred for 30 min, and then passed through a short Celite pad. The Celite was washed with Et_2O, the filtrate was concentrated, and purified by column chromatography (elution with heptane/AcOEt) to give the expected bicycle as a solid. If traces of DMF remained, further purification using an SPE cartridge (elution with dichloromethane) allowed to get the pure solid.

4.2.1. 2-(3-Nitropyridin-2-yl)pyrimidine **1a**

The title compound was isolated as a white solid in a 68% yield. Mp 102 °C; IR: ν (cm^{-1}) 3070, 1599, 1558, 1525, 1471, 1406, 1356, 1058, 860, 824, 759; ^1H NMR ($CDCl_3$) δ 7.34 (t, J=4.9 Hz, 1H), 7.54 (dd, J=4.8 and 8.2 Hz, 1H), 8.17 (dd, J=1.5 and 8.2 Hz, 1H), 8.83 (d, J=4.9 Hz, 2H), 8.88 (dd, J=1.5 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 120.9 (CH), 124.6 (CH), 132.3 (CH), 146.7 (C), 149.6 (C), 152.3 (CH), 157.6 (2CH), 162.3 (C); MS (CI^+) m/z 203 (MH^+), 173 (MH^+-NO); HRMS (CI^+) calcd for $C_9H_6N_4O_2$ (MH^+) 202.0569, found 203.0567.

4.2.2. 3-Nitro-2,2′-bipyridine **1b**

The title compound was isolated as a white solid in a 75% yield. Mp 135 °C; IR: ν (cm^{-1}) 3063, 2958, 2928, 1597, 1585, 1533, 1445, 1420, 1371, 860, 818, 753; ^1H NMR ($CDCl_3$) δ 7.29 (ddd, J=1.6, 4.9, and 7.7 Hz, 1H), 7.51 (dd, J=4.8 and 8.1 Hz, 1H), 7.90 (td, J=1.7 and 7.7 Hz, 1H), 8.07–8.12 (m, 2H), 8.62 (dd, J=1.6 and 4.8 Hz, 1H), 8.85 (dd, J=1.5 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 123.0 (CH), 123.4 (CH), 124.4 (CH), 132.1 (CH), 137.0 (CH), 146.6 (C), 149.0 (CH), 150.5 (C), 151.2 (CH), 153.8 (C); MS (CI^+) m/z 202 (MH^+), 171 (MH^+-NO); HRMS (CI^+) calcd for $C_{10}H_7N_3O_2$ (MH^+) 202.0617, found 202.0616.

4.2.3. 5′-Methyl-3-nitro-2,2′-bipyridine **1c**

The title compound was isolated as a white solid in a 59% yield. Mp 143 °C; IR: ν (cm^{-1}) 3048, 1555, 1526, 1448, 1363, 1029, 859, 848, 819, 779, 743, 659; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 7.42 (dd, J=4.8 and 8.1 Hz, 1H), 7.65 (dd, J=2.1 and 8.2 Hz, 1H), 7.95–8.03 (m, 2H), 8.41 (d, J=2.1 Hz, 1H), 8.77 (dd, J=1.5 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 122.7 (CH), 123.3 (CH), 132.1 (CH), 134.6 (C), 137.6 (CH), 146.6 (C), 149.7 (CH), 150.6 (C), 151.2 (CH), one carbon signal was not observed; MS (CI^+) m/z 244 ($M+C_2H_5^+$), 216 (MH^+), 186 (MH^+-NO); HRMS (CI^+) calcd for $C_{11}H_9N_3O_2$ (MH^+) 216.0773, found 216.0767.

4.2.4. 6′-Methoxy-3-nitro-2,2′-bipyridine **1d**

The title compound was isolated as a white solid in a 79% yield. Mp 92 °C; IR: ν (cm^{-1}) 3071, 2934, 1595, 1574, 1560, 1528, 1479, 1414, 1373, 1331, 1264, 1065, 1017, 852, 814, 763, 726; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.79 (d, J=1.0 and 8.0 Hz, 1H), 7.39 (dd, J=4.7 and 8.1 Hz, 1H), 7.71 (t, J=7.4 and 8.0 Hz, 1H), 7.81 (dd, J=1.0 and 7.4 Hz, 1H), 7.91 (dd, J=1.5 and 8.1 Hz, 1H), 8.74 (dd, J=1.5 and 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.7 (CH_3), 112.7 (CH), 115.9 (CH), 123.4 (CH), 131.8 (CH), 139.5 (CH), 146.7 (C), 149.2 (C), 150.6 (C), 150.9 (CH), 163.2 (C); MS (CI^+) m/z 260 ($M+C_2H_5^+$), 232 (MH^+), 202 (MH^+-NO). Anal. Calcd for $C_{11}H_9N_3O_3$: C 57.14%; H 3.92%; N 18.17%. Found: C 56.87%; H 4.21%; N 18.42%.

4.2.5. 3′-Nitro-2,2′-bipyridine-5-carbonitrile **1e**

The title compound was isolated as a pale yellow solid in a 47% yield. Mp 179 °C; IR: ν (cm^{-1}) 3073, 2957, 2923, 2241, 1591, 1526, 1463, 1446, 1363, 1025, 847, 829, 746, 733; ^1H NMR ($CDCl_3$) δ 7.59 (dd, J=4.7 and 8.1 Hz, 1H), 8.12–8.19 (m, 2H), 8.27 (d, J=8.1 Hz, 1H), 8.86–8.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 110.6 (C), 116.5 (C), 123.3 (CH), 124.9 (CH), 132.6 (CH), 140.6 (CH), 147.0 (C), 148.8 (C), 151.7 (CH), 151.7 (CH), 157.2 (C); MS (CI^+) m/z 227 (MH^+), 197 (MH^+-NO); HRMS (CI^-) calcd for $C_{11}H_6N_4O_2$ (M) 226.0491, found 226.0485.

4.2.6. 6-Methoxy-3-nitro-2,2′-bipyridine **1f**

The title compound was isolated as a yellow solid in a 60% yield. Mp 111 °C; IR: ν (cm^{-1}) 2957, 1581, 1522, 1471, 1415, 1359, 1327, 1260, 1122, 1097, 1013, 799, 762; ^1H NMR ($CDCl_3$) δ 4.05 (s, 3H), 6.83 (d, J=8.8 Hz, 1H), 7.34 (ddd, J=1.4, 4.9, and 7.5 Hz, 1H), 7.85 (td, J=1.8 and 7.5 Hz, 1H), 7.95 (d, J=7.5 Hz, 1H), 8.04 (d, J=8.8 Hz, 1H), 8.59 (d, J=4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.7 (CH_3), 110.9 (CH), 123.2 (CH), 124.4 (CH), 135.6 (CH), 137.0 (CH), 141.0 (C), 149.1 (CH), 150.1 (C), 154.5 (C), 164.2 (C); MS (CI^+) m/z 260 ($M+C_2H_5^+$), 232 (MH^+), 202 (MH^+-NO); HRMS (CI^+) calcd for $C_{11}H_9N_3O_3$ (MH^+) 232.0722, found 232.0721.

4.2.7. 3′-Nitro-2,4′-bipyridine **1g**

The title compound was isolated as an orange solid in a 71% yield. Mp 131–132 °C; IR: ν (cm^{-1}) 3045, 1603, 1585, 1525, 1462, 1434, 1369, 1187, 992, 864, 854, 796, 756, 697; ^1H NMR ($CDCl_3$) δ 7.37 (ddd, J=0.94, 4.9, and 7.7 Hz, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.58 (d, J=5.0 Hz, 1H), 7.83 (td, J=1.7 and 7.8 Hz, 1H), 8.65 (dd, J=0.9 and 4.9 Hz, 1H), 8.85 (d, J=5.0 Hz, 1H), 9.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 122.8 (CH), 124.3 (CH), 124.8 (CH), 137.3 (CH), 142.3 (C), 145.4 (CH), 145.5 (C), 150.2 (CH), 152.7 (C), 153.2 (CH); MS (CI^+) m/z 202 (MH^+), 171 (MH^+-NO); HRMS (CI^+) calcd for $C_{10}H_7N_3O_2$ (MH^+) 202.0617, found 202.0616.

4.3. Procedure for compounds 3a–3e

A suspension of the pyrazolyl compound (4.2 mmol, 1.5 equiv) and Cs_2CO_3 (4.4 mmol, 1.1 equiv) in anhydrous MeCN (16 mL) was stirred for 20 min under an inert atmosphere. The solid chloronitropyridine derivative (4 mmol, 1 equiv) was then added. After stirring under reflux for 18 h, the resulting mixture was filtered and then diluted in H_2O/AcOEt (1:1, 80 mL). The aqueous phase was extracted with AcOEt (2×15 mL). The organic layers were washed with H_2O (2×15 mL), dried over $MgSO_4$, filtered, and concentrated. The organic residue was purified by column chromatography (elution with heptane/AcOEt) to give the expected bicycle as a solid.

4.3.1. 3-Nitro-2-(1H-pyrazol-1-yl)pyridine **3a**

The title compound was isolated as a white solid in a 92% yield. Mp 95 °C; IR: ν (cm^{-1}) 3153, 1596, 1527, 1539, 1472, 1395, 1363, 938, 856, 757; ^1H NMR ($CDCl_3$) δ 6.49 (dd, J=2.6 and 1.7 Hz, 1H), 7.73 (dd, J=4.8 and 8.0 Hz, 1H), 7.73 (d, J=1.4 Hz, 1H), 8.01 (dd, J=1.6 and 8.0 Hz, 1H), 8.39(d, J=2.8 Hz, 2H), 8.57 (dd, J=1.6 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 108.7 (CH), 121.9 (CH), 128.9 (CH), 133.7 (CH), 138.6 (C), 142.5 (C), 143.6 (CH), 150.5 (CH); MS (CI^+) m/z 219 ($M+C_2H_5^+$), 191 (MH^+), 161 (MH^+-NO); HRMS (CI^-) calcd for $C_8H_6N_4O_2$ (M) 190.0491, found 190.0482.

4.3.2. 2-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-nitropyridine ***3b***

The title compound was isolated as a yellow solid in a 54% yield. Mp 108 °C; IR: ν (cm^{-1}) 3047, 2928, 1580, 1595, 1568, 1533, 1482, 1453, 1434, 1380, 1355, 813, 794, 761, 721; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.51(s, 3H), 6.04 (s, 1H), 7.39 (dd, J=4.8 and 8.0 Hz, 1H), 8.15 (dd, J=1.6 and 8.0 Hz, 1H), 8.63 (dd, J=1.6 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6 (CH_3), 13.7(CH_3), 109.2 (CH), 122.1 (CH), 133.9 (CH), 141.2 (C), 141.6 (C), 144.9 (C), 150.7 (CH), 151.8 (C); MS (CI^+) m/z 247 ($M+C_2H_5^+$), 219 (MH^+); HRMS (CI^+) calcd for $C_{10}H_{10}N_4O_2$ (MH^+) 219.0882, found 219.0881.

4.3.3. 3-Nitro-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridine ***3c***

The title compound was isolated as a red solid in a 92% yield. Mp 68 °C; IR: ν (cm^{-1}) 3168, 3147, 1541, 1465, 1393, 1368, 1277, 1154, 1133, 1113, 1046, 952, 784, 773, 755; ^1H NMR ($CDCl_3$) δ 6.75(d, J=2.7 Hz, 1H), 7.50 (dd, J=4.8 and 8.0 Hz, 1H), 8.04 (dd, J=1.5 and 8.0 Hz, 1H), 8.41 (d, J=2.7 Hz, 1H), 8.64 (dd, J=1.5 and 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 106.7 (CH), 120.6 (q, J=267.6 Hz, C, CF_3), 123.6 (CH), 130.8 (CH), 134.3 (CH), 139.1 (C), 141.9 (C), 146.0 (q, J=38.5 Hz, C, C–CF_3), 150.9 (CH); MS (CI^+) m/z 259 (MH^+), 229 (MH^+-NO); HRMS (CI^+) calcd for $C_9H_5F_3N_4O_2$ (MH^+) 259.0443, found 259.0441.

4.3.4. 6-Methoxy-3-nitro-2-(1H-pyrazol-1-yl)pyridine ***3d***

The title compound was isolated as a yellow pale solid in a 67% yield. Mp 137–138 °C; IR: ν (cm^{-1}) 3153, 2952, 1581, 1535, 1483, 1468, 1447, 1397, 1361, 1300, 1006, 831, 765; ^1H NMR ($CDCl_3$) δ 4.04 (s, 3H), 6.49 (dd, J=1.7 and 2.7 Hz, 1H), 6.72 (d, J=8.7 Hz, 1H), 7.73 (d, J=1.7 Hz, 1H), 7.98 (d, J=8.7 Hz, 1H), 8.28 (d, J=2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.9 (CH_3), 108.5 (CH), 109.0 (CH), 128.9 (CH), 132.8 (C), 136.9 (CH), 141.9 (C), 143.4 (CH), 163,8 (C); MS (CI^+) m/z 248 ($M+C_2H_5^+$), 221 (MH^+), 190 (MH^+-NO); HRMS (CI^+) calcd for $C_9H_8N_4O_3$ (MH^+) 221.0675, found 221.0678.

4.3.5. 3-Nitro-4-(1H-pyrazol-1-yl)pyridine ***3e***

The title compound was isolated as a white solid in an 84% yield. Mp 115–116 °C; IR: ν (cm^{-1}) 3150, 3126, 1598, 1523, 1497, 1393, 1364, 1338, 1029, 935, 848, 760, 716; ^1H NMR ($CDCl_3$) δ 6.59 (dd, J=1.8 and 2.6 Hz, 1H), 7.64 (d, J=5.4 Hz, 1H), 7.84 (m, 2H), 8.84 (d, J=5.4 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.2 (CH), 117.7 (CH), 129.4 (CH), 139.1 (C), 139.4 (C), 144.1 (CH), 146.4 (CH), 153.8 (CH); MS (CI^+) m/z 190 (MH^+), 160 (MH^+-NO); HRMS (CI^+) calcd for $C_8H_6N_4O_2$ (MH^+) 191.0569, found 191.0562.

4.4. Procedure for compounds 2a–2g, 4a–4c, 4e, and 5

A suspension of bicycle (1.5 mmol, 1 equiv) in $(EtO)_3P$ (37.5 mmol, 25 equiv) was subjected to a microwave irradiation cycle at 300 W (2 min to attain 176 °C and then 10 min at 176 °C with $P_{obtained}$=1–1.3 bars for a $P_{requested}$=4 bars) unless otherwise stated. The reaction was monitored by TLC and another cycle was performed as long as the starting material remained. The resulting mixture was cooled down and concentrated under vacuum using a Kügelrohr apparatus, and then purified by column chromatography (elution with dichloromethane/MeOH) to give the expected tricycle as a solid.

In some cases, a substantial amount of tricycle precipitated on cooling to room temperature. The pure product was collected by filtration and further amounts of product were obtained after treatment of the filtrate as above.

4.4.1. Pyrido[3′,2′:3,4]pyrazolo[1,5-a]pyrimidine ***2a***

Total reaction time: 12 min. The title compound was isolated as a yellow solid in an 86% yield. Mp 173 °C; IR: ν (cm^{-1}) 305, 1626, 1548, 1521, 1402, 1387, 1333, 1211, 1117, 791, 730, 677; ^1H NMR ($CDCl_3$) δ 7.29 (dd, J=4.1 and 7.0 Hz, 1H), 7.48 (dd, J=4.1 and 8.8 Hz, 1H), 8.11(dd, J=1.3 and 7.0 Hz, 1H), 8.74 (m, 2H), 8.95 (dd, J=1.6 and 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 112.9 (CH), 124.3 (CH), 124.5 (CH), 130.2 (C), 134.5 (CH), 143.1 (C), 144.8 (CH), 146.9 (CH), 147.0 (C); ^{15}N NMR ($CDCl_3$) δ −83.8, −96.5, −133.0, −148.6; MS (CI^+) m/z 199 ($M+C_2H_5^+$), 171 (MH^+); HRMS (CI^+) calcd for $C_9H_6N_4$ (MH^+) 171.0592, found 171.0675.

4.4.2. Pyrazolo[1,5-a:4,3-b′]dipyridine ***2b***

Total reaction time: 24 min. The title compound was isolated as a yellow solid in an 81% yield. Mp 103 °C; IR: ν (cm^{-1}) 3041, 1545, 1518, 1437, 1390, 1330, 1267, 1208, 1142, 1119, 1010, 852, 795, 756, 722, 671; ^1H NMR ($CDCl_3$) δ 7.33 (td, J=1.5 and 6.9 Hz, 1H), 7.47–7.55 (m, 2H), 8.19(dd, J=1.3 and 8.7 Hz, 1H), 8.49 (d, J=8.6 Hz, 1H), 8.68 (dd, J=1.4 and 4.2 Hz, 1H), 8.81 (d, J=6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 118.0 (CH), 118.6 (CH), 123.3 (CH), 123.4.2 (CH), 123.7 (CH), 128.5 (CH), 132.9 (C), 135.4 (C), 143.0 (C), 144.9 (CH); MS (CI^+) m/z 198 ($M+C_2H_5^+$), 170 (MH^+); HRMS (CI^+) calcd for $C_{10}H_7N_3$ (MH^+) 170.0718, found 170.0712.

4.4.3. 8-Methylpyrazolo[1,5-a:4,3-b′]dipyridine ***2c***

Total reaction time: 24 min. The title compound was isolated as a yellow solid in an 84% yield. Mp 148 °C; IR: ν (cm^{-1}) 3049, 2914, 1518, 1417, 1381, 1359, 1325, 1272, 1250, 1036, 799, 765, 723, 671; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 7.18 (dd, J=1.0 and 8.8 Hz, 1H), 7.35 (dd, J=4.2 and 8.7 Hz, 1H), 8.04 (dd, J=1.3 and 8.7 Hz, 1H), 8.20 (d, J=8.8 Hz, 1H), 8.46 (d, J=1.0 Hz, 1H), 8.54 (dd, J=1.3 and 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_3), 117.5 (CH), 123.9 (CH), 123.2 (CH), 125.9 (CH), 126.5 (CH), 128.3 (C), 133.0 (C), 133.5 (C), 142.6 (C), 144.4 (CH); MS (CI^+) m/z 212 ($M+C_2H_5^+$), 184 (MH^+); HRMS (CI^+) calcd for $C_{11}H_9N_3$ (MH^+) 184.0875, found 184.0868.

4.4.4. 7-Methoxypyrazolo[1,5-a:4,3-b′]dipyridine ***2d***

Total reaction time: 24 min. The title compound was isolated as a yellow solid in an 87% yield. Mp 112–113 °C; IR: ν (cm^{-1}) 3386, 3072, 1637, 1586, 1553, 1526, 1543, 1408, 1328, 1310, 1283, 1119, 1024, 848, 793, 748; ^1H NMR ($CDCl_3$) δ 4.20 (s, 3H), 6.58 (dd, J=1.0 and 7.7 Hz, 1H), 7.36–7.44 (m, 2H), 8.02 (dd, J=1.0 and 8.6 Hz, 1H), 8.15 (dd, J=1.3 and 8.7 Hz, 1H), 8.57 (dd, J=1.3 and 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 57.2 (CH_3), 95.1 (CH), 110.2 (CH), 123.6 (CH), 124.0 (CH), 124.8 (CH), 132.8 (C), 136.8 (C), 139.0 (C), 143.1 (C), 144.8 (CH), 150.7 (C); MS (CI^+) m/z 228 ($M+C_2H_5^+$), 200 (MH^+); HRMS (CI^+) calcd for $C_{11}H_9N_3O$ (MH^+) 200.0824, found 200.0822.

4.4.5. Pyrazolo[1,5-a:4,3-b′]dipyridine-8-carbonitrile ***2e***

Total reaction time: 36 min. The title compound was isolated as a yellow solid in an 87% yield. Mp 288 °C; IR: ν (cm^{-1}) 3032, 2234, 1639, 1380, 1336, 1321, 1277, 897, 834,816, 798, 771, 731, 719; ^1H NMR ($CDCl_3$) δ 7.61 (m, 2H), 8.29 (dd, J=1.3 and 8.8 Hz, 1H), 8.61 (d, J=8.9 Hz, 1H), 8.79 (dd, J=1.3 and 4.2 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 104.5 (CN), 120.1 (CH), 124.5 (CH), 125.6 (CH), 125.9 (CH), 134.6 (CH), 136.2 (C), 145.3 (C), 145.4 (CH), two carbon signals were not observed; MS (CI^+) m/z 223 ($M+C_2H_5^+$), 195 (MH^+); HRMS (CI^-) calcd for $C_{11}H_6N_4$ (M) 194.0592, found 194.0584.

4.4.6. 2-Methoxypyrazolo[1,5-a:4,3-b′]dipyridine ***2f***

Total reaction time: 36 min. The title compound was isolated as a yellow solid in a 79% yield. Mp 116 °C; IR: ν (cm^{-1}) 3000, 2986, 1594, 1557, 1527, 1469, 1435, 1396, 1318, 1288, 1269, 1211, 1013, 821, 731; ^1H NMR ($CDCl_3$) δ 4.07 (s, 3H), 7.01 (d, J=6.2 Hz, 1H), 7.07 (ddd, J=2.4, 6.9, and 6.9 Hz, 1H), 7.27(ddd, J=0.9, 6.9, and 8.7 Hz, 1H), 8.04 (d, J=9.2 Hz, 1H), 8.19 (d, J=8.7 Hz, 1H), 8.64 (d, J=6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.70 (CH_3), 115.8 (CH), 116.1 (CH), 118.3 (CH), 127.3 (CH), 128.3 (CH), 128.6 (C), 133.9 (C), 140.5 (C), 160.2 (CH); MS (CI^+) m/z 228 ($M+C_2H_5^+$), 200 (MH^+); HRMS (CI^+) calcd for $C_{11}H_9N_3O$ (MH^+) 200.0824, found 200.0824.

4.4.7. Pyrazolo[1,5-a:3,4-c′]dipyridine **2g**

Total reaction time: 12 min. The title compound was isolated as a rust solid in a 71% yield. Mp 140 °C; IR: ν (cm^{-1}) 3038, 2983, 1588, 1458, 1339, 1285, 1220, 1141, 1023, 805, 779, 747, 725, 680; ^{1}H NMR ($CDCl_3$) δ 7.28–7.47 (m, 2H), 7.89 (dd, J=1.2 and 5.7 Hz, 1H), 8.16 (d, J=8.6 Hz, 1H), 8.36 (d, J=5.7 Hz, 1H), 8.82 (d, J=6.8 Hz, 1H), 9.38 (d, J=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 113.5 (CH), 118.4 (C), 118.6 (CH), 119.4 (CH), 123.0 (CH), 128.8 (CH), 134.9 (C), 137.1 (CH), 142.1 (CH), 145.7 (C); MS (CI^+) m/z 198 ($M+C_2H_5^+$), 170 (MH^+); HRMS (CI^+) calcd for $C_{10}H_7N_3$ (MH^+) 170.0718, found 170.0714.

4.4.8. Pyrazolo[1′,2′:2,3][1,2,3]triazolo[4,5-b]pyridin-6-ium-5-ide **4a**

Total reaction time: 12 min. The title compound was isolated as a yellow solid in an 85% yield. Mp 162 °C; IR: ν (cm^{-1}) 3109, 1582, 1518, 1481, 1384, 1313, 1266, 1233, 780, 745, 702; ^{1}H NMR ($CDCl_3$) δ 6.83 (t, J=3.0 Hz, 1H), 7.29 (dd, J=4.6 and 8.4 Hz, 1H), 7.65 (d, J=2.6 Hz, 1H), 7.69 (dd, J=1.2 and 8.4 Hz, 1H), 7.93 (d, J=3.2 Hz, 1H), 8.00 (dd, J=1.2 and 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 105.7 (CH), 106.4 (CH), 109.7 (CH), 119.5 (CH), 122.2 (CH), 134.4 (C), 136.6 (CH), 140.4 (C); ^{15}N NMR ($CDCl_3$) δ −122.1, −122.4, −162.97, −172.0; MS (CI^+) m/z 159 (MH^+), 132 (MH^+-N_2); HRMS (CI^+) calcd for $C_8H_6N_4$ (MH^+) 159.0671, found 159.0667.

4.4.9. 7,9-Dimethylpyrazolo[1′,2′:2,3][1,2,3]triazolo[4,5-b]-pyridin-6-ium-5-ide **4b**

Total reaction time: 12 min. The title compound was isolated as a yellow solid in a 92% yield. Mp 83 °C; IR: ν (cm^{-1}) 1583, 1505, 1470, 1343, 1305, 1258, 1032, 845, 768, 743, 675; ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 2.91(s, 3H), 6.46 (s, 1H), 7.39 (dd, J=4.8 Hz and J=8.2 Hz, 1H), 7.83 (d, J=8.2 Hz, 1H), 8.17 (d, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.3 (CH_3), 11.3 (CH_3), 108.2 (CH), 115.7 (C), 117.4 (CH), 120.0 (C), 121.6 (CH), 134.9 (CH), 136.7 (C), 141.1 (C); MS (CI^+) m/z 214 ($M+C_2H_5^+$), 187 (MH^+); HRMS (CI^+) calcd for $C_{10}H_{10}N_4$ (MH^+) 187.0984, found 187.0990.

4.4.10. 7-(Trifluoromethyl)pyrazolo[1′,2′:2,3][1,2,3]triazolo-[4,5-b]pyridin-6-ium-5-ide **4c**

Total reaction time: 12 min. The title compound was isolated as an ivory solid in an 82% yield. Mp 209 °C; IR: ν (cm^{-1}) 3117, 1529, 1388, 1294, 1261, 1198, 1105, 1081, 961, 817, 791, 750, 721, 712, 656; ^{1}H NMR ($CDCl_3$) δ 7.12 (d, J=3.5 Hz, 1H), 7.43 (dd, J=4.6 and 8.5 Hz, 1H), 7.94 (m, 2H), 8.22 (dd, J=4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 105.7 (CH), 107.1 (q, J=47.3 Hz, C, C–CF_3), 109.1 (CH), 120.4 (q, J=265 Hz, C, CF_3), 122.2 (CH), 122.9 (CH), 134.1 (C), 139.8 (C), 139.9 (CH); MS (CI^-) m/z 226 (M). Anal. Calcd for $C_9H_5F_3N_4$: C 47.80%; H 2.23%; N 24.77%. Found: C 47.66%; H 2.71%; N 24.78%.

4.4.11. Pyrazolo[1′,2′:1,2][1,2,3]triazolo[4,5-c]pyridin-9-ium-10-ide **4e**

Total reaction time: 50 min at 105 °C. The title compound was isolated as an orange solid in a 20% yield. Mp 161 °C; IR: ν (cm^{-1}) 3139, 1571, 1524, 1439, 1376, 1322, 1291, 1247, 1025, 782, 702; ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, J=2.8 and 3.1 Hz, 1H), 7.63 (d, J=5.5 Hz, 1H), 7.73 (d, J=2.8 Hz, 1H), 7.80 (d, J=3.1 Hz, 1H), 8.22 (d, J=5.5 Hz, 1H), 8.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 104.8 (CH), 105.2 (CH), 106.7 (CH), 110.8 (CH), 123.5 (C), 134.5 (CH), 135.9 (CH), 143.8 (C); MS (CI^-) m/z 159 (M); HRMS (CI^+) calcd for $C_8H_6N_4$ (MH^+) 159,0671, found 159.0669.

4.4.12. Diethyl [6-methoxy-2-(1H-pyrazol-1-yl)pyridin-3-yl]-amidophosphate **5**

Total reaction time: 24 min. The title compound was isolated as a brown oil in a 35% yield. IR: ν (cm^{-1}) 2984, 1490, 1439, 1402, 1256, 1017, 965, 916, 797, 762; ^{1}H NMR ($CDCl_3$) δ 1.24–1.34 (m, 6H), 3.88 (s, 3H), 4.00–4.15 (m, 4H), 6.42 (dd, J=1.8 and 2.6 Hz, 1H), 6.59 (d, J=8.8 Hz, 1H), 7.68 (d, J=1.8 Hz, 1H), 7.78 (d, J=8.8 Hz, 1H), 8.53 (d, J=2.6 Hz, 1H), 9.64 (d, J=9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2 (CH_3), 16.3 (CH_3), 53.66 (OCH_3), 63.0 (CH_2), 63.1 (CH_2), 63.7 (CH_2), 63.8 (CH_2), 106.4 (CH), 108.8 (CH), 121.0 (C), 128.5 (CH), 132.0 (CH), 134.3 (C), 140.4 (CH), 156.7 (C); MS (CI^+) m/z 355 ($M+C_2H_5^+$), 327 (MH^+); HRMS (CI^+) calcd for (MH^+) 327.1226, found 327.1226.

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Supplementary data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) nos. 679154 and 679155 for compound **2a** and **4c**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). The crystallographic data is available free of charge in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.055.

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