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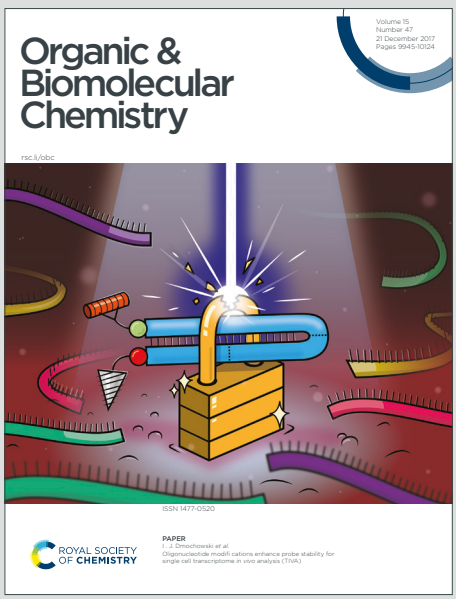

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ARTICLE

Copper-mediated oxidative [3+2]-annulation of nitroalkenes and pyridinium imines: efficient synthesis of 3-fluoro- and 3-nitro-pyrazolo[1,5-a]pyridines

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An efficient route to pyrazolo[1,5-a]pyridines by $Cu(OAc)_2$-promoted oxidative [3+2]-annulation of nitroalkenes with *in situ* generated pyridinium imines was developed. The reaction with α-fluoronitroalkenes provides the first preparative synthesis of 3-fluoro-pyrazolo[1,5-a]pyridines. The cycloaddition with α-unsubstituted nitroalkenes opens access to 3-nitro-pyrazolo[1,5-a]pyridines in excellent yields. Broad scope of transformation was demonstrated. Both electron-rich and electron-deficient nitroalkenes as well as different aminopyridinium salts can be used for the assembly of target pyrazolo[1,5-a]pyridines. The related aza-heterocycles, namely, pyrazolo[1,5-a]-pyrazines and pyrazolo[1,5-b]pyridazines were successfully prepared via the present methodology. Possible mechanism of the reaction is discussed.

Introduction

Pyrazolo[1,5-a]pyridines are medicinally relevant heterocycles[1] featuring anti-inflammatory drug Ibudilast that has found application for treatment of asthma and stroke (Figure 1). These heterocycles were shown to possess wide range of biological activity, such as antiviral (hepatitis C,[2] herpex[3]), hypnotic,[4] diuretic,[5] and antipsychotic,[6,7] Pyrazolo[1,5-a]pyridines are considered as indole bioisosteres[8] having higher metabolic stability. Therefore, their chemistry attracts a lot of attention.

The most general route for the construction of pyrazolopyridine core is the [3+2]-annulation reaction[9] between pyridine-*N*-imines and electron-deficient alkynes, bearing carbonyl or ester groups (Scheme 1).[10,11] Similar approach based on Pd-mediated oxidative cycloaddition between *N*-benzoyliminopyridines and alkenyl halides has been proposed recently to prepare 3-unsubstituted pyrazolo[1,5-a]pyridines using silver salt as an oxidant.[12] However, selectively substituted derivatives of pyrazolo[1,5-a]pyridine and especially fluorinated ones are hardly accessible via [3+2]-cycloaddition because of low stability/availability of the corresponding alkynes.[13] Recently, we have reported efficient synthesis of α-fluoronitroalkenes,[14] a promising type of monofluorinated building blocks.[15] Particularly, they behave as useful synthetic equivalents of fluoroalkynes in the synthesis of fluorinated heterocycles.[16-19]

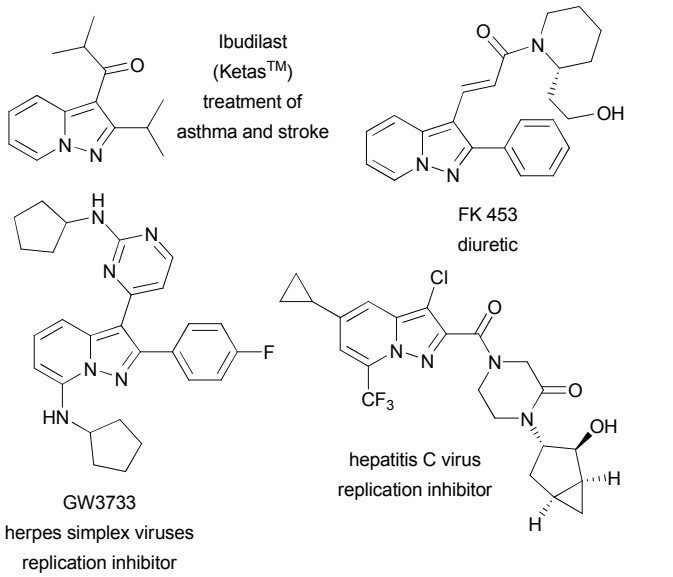

Figure 1. Bioactive pyrazolo[1,5-a]pyridines.

Nowadays, organofluorine chemistry is one of the most important fields of organic chemistry.[20] Unique properties of fluorinated compounds made them intensively exploited in pursuit of new construction materials, components of liquid crystalline compositions, agrochemicals and pharmaceuticals. About 20-25% of currently used drugs and agrochemicals contain at least one fluorine atom.[21] Fluorinated heterocycles are of special interest for medicinal chemistry and drug

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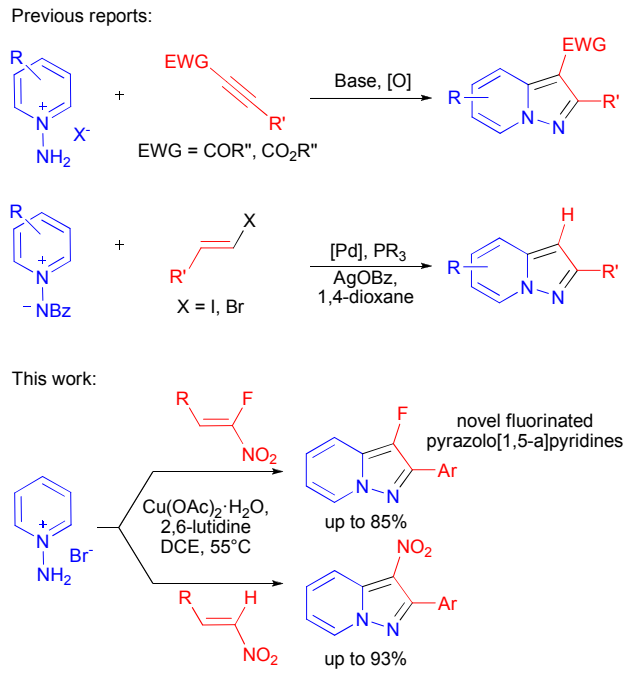


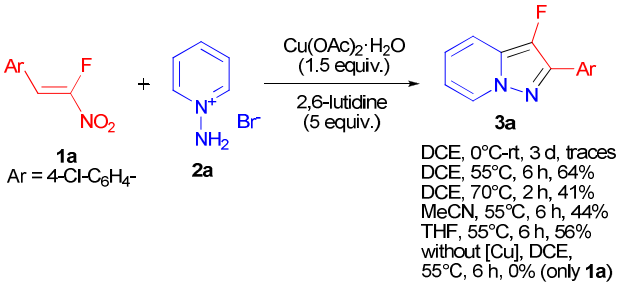
Scheme 1 Approaches to the synthesis of various pyrazolo[1,5-a]pyridines *via* [3+2]-annulation

design.[22] However, despite pharmaceutical attractiveness of 3-fluoro-pyrazolo[1,5-a]pyridines, currently only very rare examples of synthesis of these compounds can be found in patent literature. Direct fluorination of some pyrazolo[1,5-a]pyridines by Selectfluor has been used for this aim, however only low yields were demonstrated.[23] As a result, new efficient methods for the preparation of fluorinated pyrazolo[1,5-a]pyridines are highly demanding since the direct fluorination has a significant drawback of functional group tolerance.

Herein we report new convenient method for the synthesis of 3-fluoro-pyrazolo[1,5-a]pyridines *via* copper-mediated oxidative [3+2]-annulation strategy and study of applicability of this approach to the synthesis of 3-nitro-pyrazolo[1,5-a]pyridines.

Results and discussion

Copper(II)-mediated oxidative annulation reactions are useful tool for the preparation of indolizines and related pyridine-annulated heterocycles.[24] Recently we have described a method for the synthesis of indolizines based on oxidative annulation between nitroalkenes and pyridinium ylides mediated by the mild copper diacetate/lutidine system.[17] We expected that annulation of nitroalkenes with pyridine-*N*-imines can proceed in a similar manner under these conditions. We initiated our study with the model reaction between fluoronitroalkene **1a** and aminopyridinium salt **2a**. However, target pyrazolo[1,5-a]pyridine **3a** was obtained in only 3% yield when the conditions we previously described for indolizine synthesis (DCE, $Cu(OAc)_2 \cdot H_2O$, 2,6-lutidine, 0°C-rt) were used. It was found that the reaction proceeds much more slowly and main amount of the starting nitroalkene **1a** was unchanged. To our delight, simple heating the reaction mixture up to 55°C was sufficient to obtain complete conversion. Under these conditions high yield of target product **3a** was detected after 6 h of reaction (Scheme 2). Other solvents studied gave lower yields. Application of higher temperature (70°C) resulted in acceleration of the process, however, yield of **3a** dropped down to 41%. In the absence of copper salt no consumption of starting nitroalkene **1a** was observed indicating its necessity for the reaction.



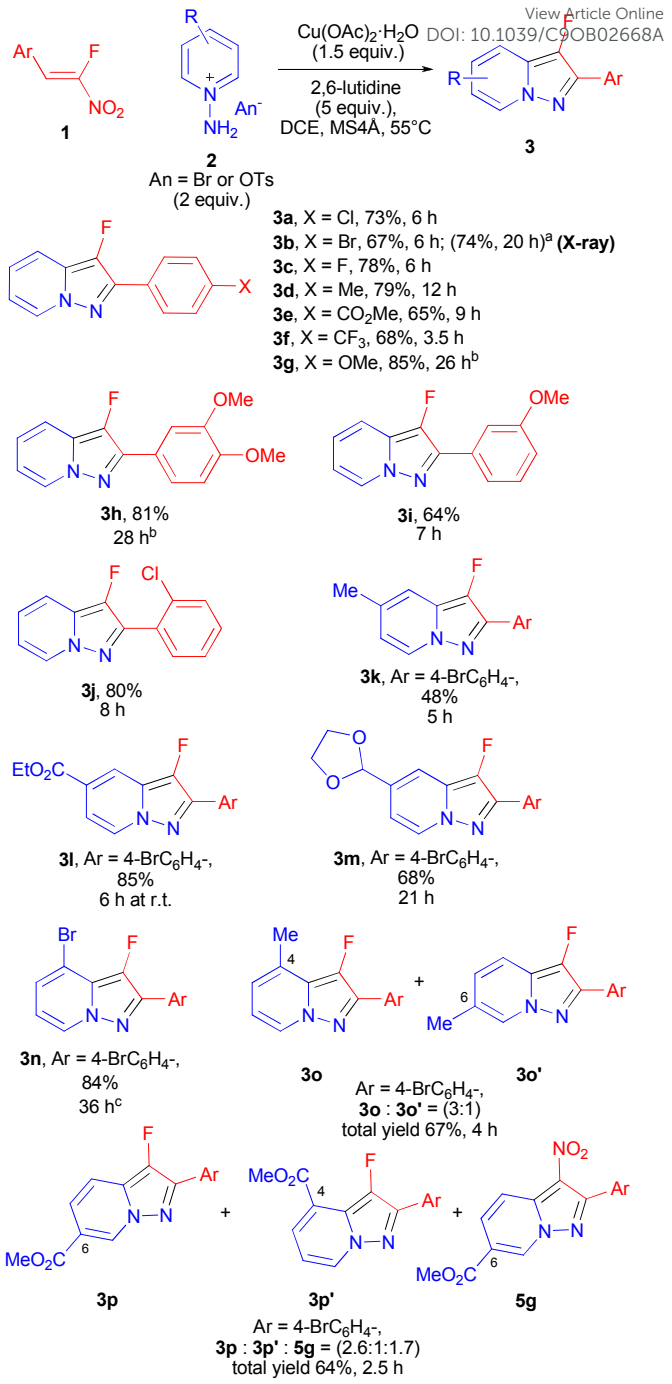
Scheme 2 Initial findings and screening of the reaction conditions. Yields were determined by ^{19}F NMR with internal standard (C_6F_6).

With these reaction conditions in hand, the scope of this new reaction was investigated (Scheme 3). First, the influence of the nature of fluoronitrostyrenes **1** was studied. Thus, a number of alkenes **1** possessing electronically different substituents was tested in the reaction with *N*-aminopyridinium bromide **2a** (Scheme 3). Gratifyingly, the reaction appeared to be very general working perfectly with nitrostyrenes having either electron rich- or electron poor aryl ring to produce the desired products in high isolated yields up to 85%. Electron-neutral substrates (4-chlorophenyl-, 4-bromophenyl-, 4-fluorophenyl and *p*-tolyl-substituted examples) gave the corresponding pyrazolopyridines **3a-3d** in good yields after 6-12 hours at 55°C. Electron-deficient 4-methoxycarbonyl- and 4-CF_3-substituted fluoronitroalkenes **1e,f** afforded the products **3e**,**f** in shorter time albeit in slightly lower yields. On the contrary, electron-rich 4-methoxyphenyl and 3,4-dimethoxyphenyl-substituted nitroalkenes afforded the products **3g**,**h** after prolonged heating (26-28 hours), however, excellent yields were obtained. Meta- as well as sterically hindered ortho-substituted nitroalkenes also gave corresponding products **3i,j** in good yields. The synthesis of pyrazolopyridines is scalable as was demonstrated for 3 mmol (0.5 gram) of **3b** with no loss in yield.

Next, the scope of aminopyridinium salts **2** was studied. 4-Methyl-aminopyridinium bromide afforded the corresponding 5-substituted pyrazolopyridine **3k** in 48% yield. Godd yields were also achieved for ester (**3l**) and 1,3-dioxolan-2-yl- (**3m**) substituted substrates. Moreover, isonicotinate derivative **3l** did not require elevated temperature for the preparation. Various regioselectivitites were observed for 3-substituted pyridinium salts. In the case of 3-bromo-substituted pyridinium salt the product **3n** was obtained in high yield, though prolonged heating at 65°C was necessary to achieve complete conversion. It was found that the reaction proceeds regioselectively to give 4-substituted isomer **3n** with

minor amonts (12%) of 6-substituted isomer. We believe that electronic factors rather than steric hindrance determine the regioselectivity of cyclization in this case similarly to the synthesis of indolizines.[17,25] The reaction with 3-methyl-1-aminopyridinium bromide afforded mixture of two regioisomeric pyrazolopyridines **3o/3o'** in 3:1 ratio, with the preference of formation of 4-substituted isomer **3o** similar to previously described synthesis of indolizines.[17] In contrast, electron withdrawing ester group in *m*-position gave 6-substituted pyrazolo[1,5-a]pyridine **3p** as major product. Additionally in this cases diminished chemoselectivity was observed as corresponding 3-nitro-substituted product **5g** was isolated in substantial yield of 20% (see also discussion of mechanism). Unfortunately, amino-substituted pyridinium salts (*p*-Me_2N, *p*-BocNH, *m*-CH_2NHAc) failed to give desired products **3**. Also, the attempts to prepare 8-substituted pyrazolo[1,5-a]pyridines from 2-substituted aminopyridinium salts were unsuccessful, as these salts were found unreactive even at 80°C.

The structures of obtained products were supported by ^{1}H and ^{13}C NMR spectra (including 2D) as well as by HRMS data. For the *p*-bromophenyl derivative **3b** single crystal X-ray analysis was also performed (Figure 2).[26]



Scheme 3 Synthesis of 3-fluoro-pyrazolo[1,5-a]pyridines **3** from different fluoronitroalkenes **1** (0.08-0.25 mmol) and aminopyridinium salts **2**. Yields refer to isolated products **3**. [a]Yield for the reaction on 3 mmol scale in brackets. [b] 2.3 equiv. of **2** was used. [c] Reaction at 65°C .

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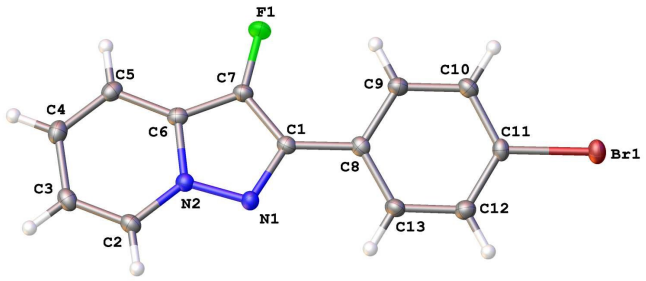
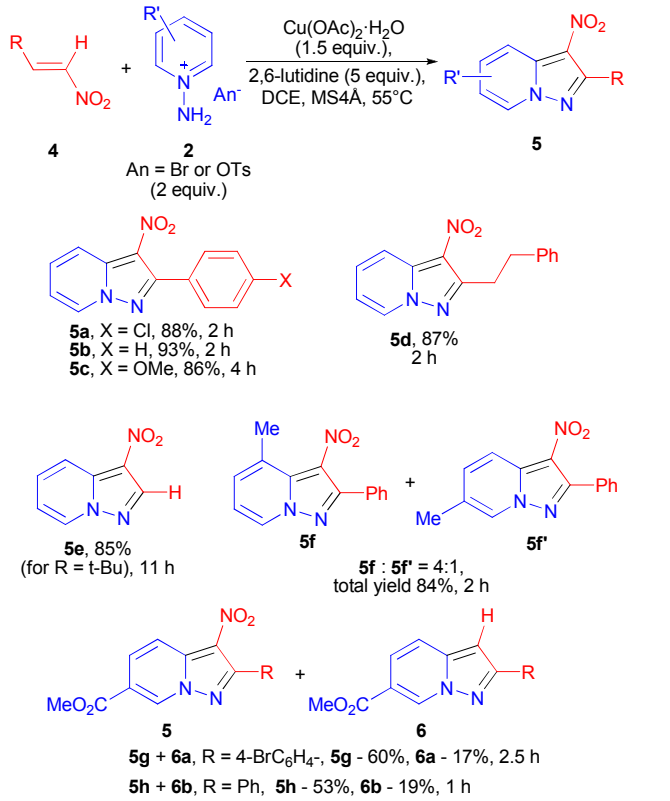


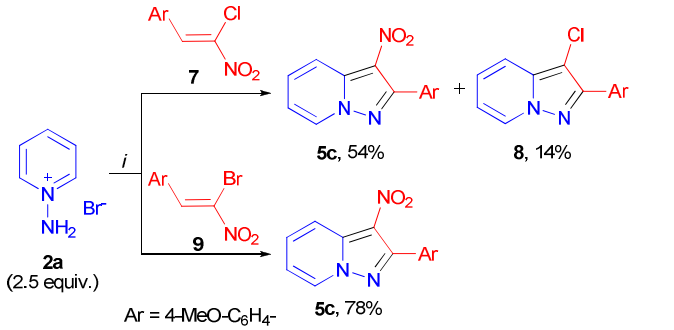
Figure 2 General view of the compound **3b** in representation of atoms *via* thermal ellipsoids at 50% probability level.



Scheme 4 Synthesis of 3-nitro-pyrazolo[1,5-a]pyridines **5** from nitroalkenes **4** and aminopyridinium salts **2**. Yields refer to isolated products **5**.

Next, we decided to study applicability of the present method to other nitroalkenes. It was found that the approach is very general and can be used for the synthesis of other pyrazolopyridines as well. First, the reaction of α-unsubstituted nitroalkenes **4** with aminopyridinium salts **2** was studied. It was found to proceed smoothly under the same conditions to afford 3-nitro-pyrazolo[1,5-a]pyridines **5** in excellent yields (Scheme 4). In this case the reaction was complete after 2-4 hours of heating at 55°C for the neutral (**5a,b**) and electron-rich (**5c**) substrates. It is important to note that aliphatic nitroalkene **4d** was tolerated under the reaction conditions to provide the corresponding product **5d** in excellent yield. Regioselectivity of the preparation of 3-nitro derivatives is similar to fluorinated ones. The reaction with 3-methyl-1-aminopyridinium bromide afforded the mixture of nitro-substituted products **5f/5f'** in the 4:1 ratio. An unexpected result was obtained for the reaction with *tert*-butyl-substituted nitroalkene **4e**, where 2-unsubstituted 3-nitro-pyrazolopyridine **5e** was isolated in 85% yield. Apparently, the loss of *tert*-butyl group took place. The mechanism of this transformation was not studied in detail, however most probably elimination of *t*-Bu cation takes place and this observation is in agreement with the mechanism discussed below. Another peculiarity was observed for nicotinic ester-derived products **5g,h**. While the regiochemical outcome was similar to products **3p** providing 6-carbmethoxy products **5**, the chemoselectivity was diminished due to denitration and formation of 3-unsubstituted derivatives **6a,b**.

Annulation of α-chloronitroalkenes with pyridinium imines is of special interest. Elimination of either HCl or HNO_2 may be expected affording nitro- or chloro-substituted heterocycles, respectively.[27] It was found that the reaction of nitroalkene **7** with the salt **2a** afforded mixture of nitrated pyrazolopyridines **5c** with minor amount of 3-chloro-pyrazolopyridine **8** (Scheme 5). Therefore, elimination of HCl proceeds preferably. We decided to demonstrate importance of leaving group for the reaction using bromo-substituted substrate. As expected, the reaction with α-bromonitroalkene **9** proceeded 100% chemoselectively to form nitro-derivative **5c** as single product.[28]

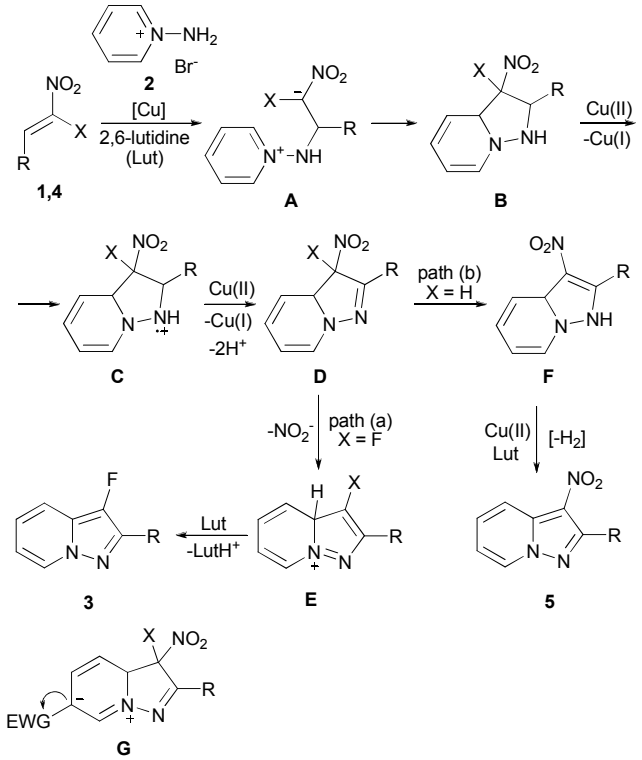


Scheme 5 Oxidative annulation of pyridinium imines with α-chloro- and α-bromonitroalkenes. *i*: $Cu(OAc)_2·H_2O$ (1.5 equiv.), 2,6-lutidine (5-equiv.) DCE, MS 4Å, 55°C, 24 h.

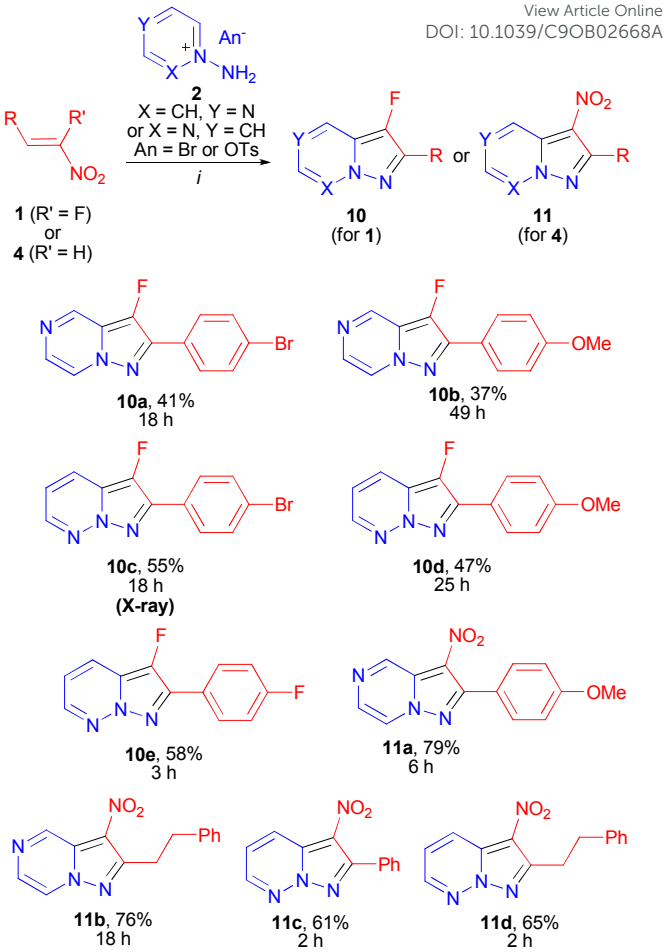
To the best of our knowledge only two reports of pyrazolopyridine synthesis based on nitroalkene/pyridinium imine cycloaddition have been published in the literature. However, under oxidant-free conditions formation of mixture of 3-nitro and 3-unsubstituted heterocycles has been observed.[29] Application of air as oxidant was demonstrated to obtain nitro-substituted heterocycles.[30] Our methodology for the preparation of pyrazolo[1,5-a]pyridines involving $Cu(OAc)_2·H_2O$/2,6-lutidine oxidation system has many advantages. Target products were obtained in high yield using shorter reaction times. Moreover, not only aromatic but aliphatic nitroalkenes can be used for the synthesis.

The observed reactivity patterns allow us to propose a mechanism for the studied transformation. Dependence of the reaction rate on the electronic properties of aryl groups indicates to stepwise, rather than concerted [3+2]-mechanism (Scheme 6). Most probably, Michael addition (formation of the anion **A**) is the rate-determining step of the process that is

significantly slowing down for electron-rich nitroalkenes. Importantly, lower concentration of the anionic species in the solution may be responsible for the slight increase of yields in these cases, because oligomerization of anionic species is suppressed. We can also note that copper salt may promote Michael addition to nitroalkenes.[31] Next, intramolecular cyclization of **A** resulted in formation of unstable adduct **B**. As was already mentioned, regioselectivity of this cyclization depends on electronic properties of the substituents as electron donating ones predominantly led to 4-isomer (**3n,o,5f**) while electron accepting ones led to 6-isomer (**3p, 5g,h**). Oxidation of **B** to form intermediate **D**[32-34] followed by elimination of nitrous acid resulted in formation of aromatic heterocycle **3**. The chemoselective synthesis of nitro derivatives **5** can be explained by tautomerization of **D** (for X = H) to nitroenamine **F**, that precludes elimination of nitrite anion and ultimately lead to oxidation into nitro-derivatives **5**. Here we should also note the possible influence of the substituents on the reaction pathway. Thus, erosion of chemoselectivities observed for *m*-nicotinate derivatives (product mixtures **3p+5g**, **5g,h+6**, see above) may be attributed to conjugation of bridgehead nitrogen atom with EWG-group (structure **G**), that makes formation of **E** (that leads to **3**) and **F** (that leads to **5**) less favorable. Similarly, it should also increase the oxidation potential of **B** and decrease the stability of cation radical **C**. Overall, this increase the opportunities for side-reactions.



Scheme 6 Proposed reaction mechanism.



Scheme 7 Synthesis of pyrazolo[1,5-a]pyrazines and pyrazolo[1,5-a]pyridazines **10,11** *via* oxidative aza-[3+2]-annulation.[26] *i*: $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), 2,6-lutidine (5 equiv.) DCE, MS 4Å, 55°C.

Finally, we decided to demonstrate the possibility of the synthesis of some aza-derivatives of pyrazolopyridines using the present methodology (Scheme 7).[35] Novel fluorinated pyrazolo[1,5-a]pyrazines and pyrazolo[1,5-b]pyridazines **10** were successfully obtained from the corresponding aminodiazinium salts **2** and fluoronitroalkenes **1**. However, more prolonged heating was necessary to achieve complete conversion for these substrates. It was found that the method provided efficient synthesis of the corresponding 3-nitro derivatives **11** as well.

Experimental

General experimental

All reactions were performed in oven-dried (150 °C) glassware. Most of the chemicals were acquired from commercial sources and used as received. Starting fluoronitroalkenes **1** were prepared by radical nitration of corresponding fluorobromostyrenes (see ESI).[14] *N*-aminoazinium bromides **2a,b,e,f,h,i** were prepared by literature procedure,[36] albeit using HBr instead of HI. *N*-aminoazinium tosylates **2c,d,g,j** were prepared by amination of corresponding azines with

$TsONH_2$.[37] TLC were performed on silica coated on aluminium with UV_{254} indicator. Visualization was accomplished with UV. Column chromatography was performed on silica (0.04–0.063 mm, 60 Å). High resolution mass spectra were acquired at TOF spectrometer using electrospray ionization (ESI). Melting points were determined on a Koffler melting point apparatus and are uncorrected. NMR spectra were recorded at the 300 MHz (^{1}H NMR), 75 MHz (^{13}C NMR), and 282 MHz (^{19}F NMR) frequencies at 300 K unless otherwise stated. Chemical shifts are given relative to the (residual) solvent peak.[38] Multiplicities are assigned as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad), app (apparent). Assignment of signals was made basing on 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC) for selected compounds (**3a**, **3i**, **3l, 3m**, **3o**, **3p**, **5d-g, 6a**, **8**, **10a,c,d,e, 11**) and then extended to other products. Note: Signal of C3–NO_2 often could not be unambiguously identified in 1D ^{13}C NMR due to quadrupole broadening/low intensity, although it can be assigned based on HMBC (see products **5d**,**e, 11b,d**).

General procedure for the synthesis of pyrazolo[1,5-a]pyridines and their derivatives.

To the stirred suspension of *N*-aminoazinium salt **2** (0.4 mmol, 2 equiv.) powdered 4Å molecular sieves (100 mg), and 2,6-lutidine (107 mg, 1 mmol, 5 equiv.) in 1,2-dichloroethane (2 ml) copper acetate monohydrate (60 mg, 0.3 mmol, 1.5 equiv.) and nitroalkene **1** or **4** (0.2 mmol, 1.0 equiv.) were added. The mixture was heated at 55°C for 4-28 h, then evaporated under reduced pressure after addition of silica gel. The crude product was purified by column chromatography (PE/EtOAc) to afford pyrazolo[1,5-a]pyridines **3**.

2-(4-Chlorophenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3a

Pyrazolo[1,5-a]pyridine **3a** was obtained from α-fluoronitroalkene **1a** (50.4 mg, 0.25 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 6 h). Column chromatography (eluent: 7:1 PE/EtOAc) afforded **3a** (45 mg, 73%) as slightly yellow solid. R_f = 0.45 (PE/EtOAc, 3:1) (UV), mp = 131-133 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (t, *J* = 6.8 Hz, 1H, H6), 7.07 (dd, *J* = 8.5, 7.0 Hz, 1H, H5), 7.45 (m, 3H), 7.96 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 8.26 (d, *J* = 7.0 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC): δ 112.1 (C6-H), 115.0 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 122.5 (d, $^4J_{CF}$ = 1.8 Hz, C5-H), 128.0 (d, $^4J_{CF}$ = 3.8 Hz, CH_{Ar}), 128.0 (C7-H), 128.8 (d,$^2J_{CF}$ = 27.4 Hz, C3a), 128.9 (CH_{Ar}), 129.3 (d, $^3J_{CF}$ = 3.0 Hz, C_{Ar}), 134.3 (C-Cl), 136.7 (d, $^2J_{CF}$ = 4.6 Hz, C2), 137.8 (d, $^1J_{CF}$ = 247.2 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -180.7 (s). HRMS (ESI): m/z calcd. for $[C_{13}H_8{}^{35}ClFN_2 + H^+]$: 247.0433, found: 247.0440.

2-(4-Bromophenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3b

Pyrazolo[1,5-a]pyridine **3b** was obtained from α-fluoronitroalkene **1b** (49.2 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 6 h). Column chromatography (eluent: 7:1 PE/EtOAc) afforded **3b** (39 mg, 67%) as white solid. For the 3 mmol scale synthesis, **3b** was obtained from **1b** (738 mg, 3 mmol) and **2a** (1.5 equiv.) as white solid (642 mg, 74%, reaction time 20 h). R_f = 0.46 (PE/EtOAc, 3:1) (UV), mp = 142-143 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (t, *J* = 6.6 Hz, 1H, H6), 7.07 (dd, *J* = 8.9, 7.0 Hz, 1H, H5), 7.49 (d, *J* = 8.9 Hz, 1H, H4), 7.59 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.90 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.27 (d, *J* = 7.0 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.2 (C6-H), 115.1 (d, $^3J_{CF}$ = 4.3 Hz, C4-H), 122.5 (d, $^4J_{CF}$ = 2.1 Hz, C5-H), 122.6 (C-Br), 128.1 (C7-H), 128.3 (d, $^4J_{CF}$ = 4.4 Hz, CH_{Ar}), 128.9 (d, $^2J_{CF}$ = 28.0 Hz, C3a), 129.8 (d, $^3J_{CF}$ = 4.2 Hz, C_{Ar}), 131.9 (CH_{Ar}), 136.8 (d, $^2J_{CF}$ = 4.6 Hz, C2), 137.9 (d, $^1J_{CF}$ = 247.1 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -180.6 (s). HRMS (ESI): m/z calcd. for $[C_{13}H_8{}^{79}BrFN_2 + H^+]$: 290.9928, found: 290.9932.

2-(4-Fluorophenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3c

Pyrazolo[1,5-a]pyridine **3c** was obtained from α-fluoronitroalkene **1c** (37 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 6 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3c** (36 mg, 78%) as white solid. R_f = 0.42 (PE/EtOAc, 3:1) (UV), mp = 112-115°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (app t, *J* = 6.9 Hz, 1H, H6), 7.07 (dd, *J* = 8.9, 7.0 Hz, 1H, H5), 7.16 (t, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.48 (d, *J* = 8.9 Hz, 1H, H4), 8.01 (dd, *J* = 8.7, 5.5 Hz, 2H, CH_{Ar}), 8.27 (d, *J* = 7.0 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.0 (C6-H), 115.0 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 115.6 (d, $^2J_{CF}$= 21.6 Hz, CH_{Ar}), 122.5 (d, $^4J_{CF}$ = 2.0 Hz, C5-H), 128.1 (C7-H), 128.6 (dd, J_{CF} = 8.2, 4.4 Hz, CH_{Ar}), 128.8 (d,$^2J_{CF}$ = 27.6 Hz, C3a), 132.9 (app t, J_{CF} = 8.5 Hz, C_{Ar}), 137.0 (d, $^2J_{CF}$ = 4.6 Hz, C2), 137.6 (d, $^1J_{CF}$ = 246.2 Hz, C3-F), 162.9 (d, $^1J_{CF}$ = 248.0 Hz, C_{Ar}-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -112.7 (s, C_{Ar}-F), -181.7 (s, C3-F). HRMS (ESI): m/z calcd. for $[C_{13}H_8F_2N_2 + H^+]$: 231.0728, found: 231.0732.

2-(4-Methylphenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3d

Pyrazolo[1,5-a]pyridine **3d** was obtained from α-fluoronitroalkene **1d** (21.7 mg, 0.12 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 12 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3d** (21.5 mg, 79%) as slightly yellow solid. R_f = 0.48 (PE/EtOAc, 3:1) (UV), mp = 93-95 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, Me), 6.69 (t, *J* = 6.9 Hz, 1H, H6), 7.02-7.09 (m, 1H, H5), 7.29 (d, *J* = 8.0 Hz, 2H, CH_{Ar}), 7.48 (d, *J* = 8.7 Hz, 1H, H4), 7.92 (d, *J* = 8.0 Hz, 2H, CH_{Ar}), 8.29 (d, *J* = 6.9 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (Me), 111.7 (C6-H), 114.9 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 122.3 (d, $^4J_{CF}$ = 2.1 Hz, C5-H), 126.8 (d, $^4J_{CF}$ = 4.2 Hz, CH_{Ar}), 128.0 (d, $^3J_{CF}$ = 4.0 Hz, C_{Ar}), 128.1 (C7-H), 128.8 (d,$^2J_{CF}$ = 28.2 Hz, C3a), 129.5 (CH_{Ar}), 137.8 (d, $^1J_{CF}$ = 246.0 Hz, C3-F), 138.0 (d, $^2J_{CF}$ = 4.6 Hz, C2), 138.5 (C_{Ar}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -181.5 (s). HRMS (ESI): m/z calcd. for $[C_{14}H_{11}FN_2 + H^+]$: 227.0979, found: 227.0978.

2-(4-(Methyloxycarbonyl)phenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3e

Pyrazolo[1,5-a]pyridine **3e** was obtained from α-fluoronitroalkene **1e** (33.8 mg, 0.15 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 9 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3e** (26.5 mg, 65%) as white solid. R_f = 0.41 (PE/EtOAc, 3:1) (UV), mp = 138-140 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H, CO_2Me), 6.76 (td, *J* = 6.8, 0.8 Hz, 1H, H6), 7.09 (dd, *J* = 8.7, 7.0 Hz, 1H, H5), 7.52 (d, *J* = 8.9 Hz, 1H, H4), 8.11 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 8.15 (d, *J* = 8.7

Hz, 2H, CH_{Ar}), 8.30 (d, *J* = 7.0 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2 (Me), 112.5 (C6-H), 115.2 (d, $^3J_{CF}$ = 4.3 Hz, C4-H), 122.6 (d, $^4J_{CF}$ = 2.2 Hz, C5-H), 126.6 (d, $^4J_{CF}$ = 4.5 Hz, CH_{Ar}), 128.1 (C7-H), 128.9 (d,$^2J_{CF}$ = 28.1 Hz, C3a), 129.8 (C_{Ar}), 130.0 (CH_{Ar}), 135.2 (d, $^2J_{CF}$ = 4.2 Hz, C2), 136.7 (C_{Ar}), 138.4 (d, $^1J_{CF}$ = 243.3 Hz, C3-F), 166.8 (**C**O_2Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ -179.5 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_{11}FN_2O_2$ + H^+]: 271.0877, found: 271.0875.

2-(4-Trifluoromethylphenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3f

Pyrazolo[1,5-a]pyridine **3f** was obtained from α-fluoronitroalkene **1f** (59 mg, 0.25 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 3.5 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3f** (48 mg, 68%) as white solid. R_f = 0.52 (PE/EtOAc, 3:1) (UV), mp = 124-125 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (td, *J* = 7.0, 1.2 Hz, 1H, H6), 7.09 (dd, *J* = 8.9, 7.0 Hz, 1H, H5), 7.51 (app d, *J* = 8.9 Hz, 1H, H4), 7.72 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 8.14 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 8.26 (d, *J* = 7.0 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.6 (C6-H), 115.3 (d, $^3J_{CF}$ = 4.3 Hz, C4-H), 122.7 (d, $^4J_{CF}$ = 1.8 Hz, C5-H), 124.1 (q, $^1J_{CF}$= 271.9 Hz, CF_3), 125.6 (q, $^3J_{CF}$ = 3.6 Hz, CH_{Ar}), 126.9 (d, $^4J_{CF}$ = 4.5 Hz, CH_{Ar}), 128.1 (C7-H), 128.9 (d,$^2J_{CF}$ = 28.1 Hz, C3a), 130.2 (q, $^2J_{CF}$ = 32.5 Hz, C-CF_3), 134.3 (d, $^3J_{CF}$ = 4.7 Hz, C_{Ar}), 136.3 (d, $^2J_{CF}$ = 4.4 Hz, C2), 138.2 (d, $^1J_{CF}$ = 247.9 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -62.7 (s, 3F, CF_3), -180.0 (s, 1F, C3-F). HRMS (ESI): m/z calcd. for [$C_{14}H_8F_4N_2$ + H^+]: 281.0696, found: 281.0697.

2-(4-Methoxyphenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3g

Pyrazolo[1,5-a]pyridine **3g** was obtained from α-fluoronitroalkene **1g** (39.4 mg, 0.20 mmol) and *N*-aminopyridinium salt **2a** (2.3 equiv.) following the general procedure (reaction time 26 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3g** (41 mg, 85%) as yellow solid. R_f = 0.38 (PE/EtOAc, 3:1) (UV), mp = 155-156 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, OMe), 6.68 (td, *J* = 6.8, 1.0 Hz, 1H, H6), 7.01 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.04 (dd, *J* = 8.2, 7.1 Hz, 1H, H5), 7.46 (d, *J* = 8.9 Hz, 1H, H4), 7.97 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 8.27 (d, *J* = 7.1 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3 (OMe), 111.5 (C6-H), 114.2 (CH_{Ar}), 114.8 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 122.3 (d, $^4J_{CF}$ = 1.8 Hz, C5-H), 123.4 (d, $^3J_{CF}$ = 4.0 Hz, C_{Ar}), 128.0 (C7-H), 128.2 (d, $^4J_{CF}$ = 4.2 Hz, CH_{Ar}), 128.6 (d,$^2J_{CF}$ = 28.0 Hz, C3a), 137.5 (d, $^1J_{CF}$ = 245.3 Hz, C3-F), 137.9 (d, $^2J_{CF}$ = 4.8 Hz, C2), 159.9 (C-OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -182.1 (s). HRMS (ESI): m/z calcd. for [$C_{14}H_{11}FN_2O$ + H^+]: 243.0928, found: 243.0935.

2-(3,4-Dimethoxyphenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3h

Pyrazolo[1,5-a]pyridine **3h** was obtained from α-fluoronitroalkene **1h** (18 mg, 0.078 mmol) and *N*-aminopyridinium salt **2a** (2.3 equiv.) following the general procedure (reaction time 28 h). Column chromatography (eluent: 4:1 PE/EtOAc) afforded **3h** (17.5 mg, 81%) as slightly yellow amorphous solid. R_f = 0.13 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H, OMe), 4.00 (s, 3H, OMe), 6.69 (td, *J* = 7.1, 1.2 Hz, 1H, H6), 6.98 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.07 (dd, *J* = 8.8, 6.8 Hz, 1H, H5), 7.48 (d, *J* = 8.8 Hz, 1H, H4), 7.62 (m, 2H, CH_{Ar}), 8.28 (d, *J* = 7.1 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): 55.9 (OMe), 56.0 (OMe), 109.7 (d, $^4J_{CF}$ = 4.0 Hz, CH_{Ar}), 111.3 (CH_{Ar}), 111.6 (C6-H), 114.8 (d, $^3J_{CF}$ = 4.0 Hz, C4-H), 119.9 (d, $^4J_{CF}$ = 5.0 Hz, CH_{Ar}), 122.4 (d, $^4J_{CF}$ = 1.9 Hz, C5-H), 123.7 ($^3J_{CF}$ = 4.0 Hz, C_{Ar}), 128.0 (C7-H), 128.8 (d, $^2J_{CF}$ = 28.4 Hz, C3a), 137.6 (d, $^1J_{CF}$ = 245.3 Hz, C3-F), 137.9 (d, $^2J_{CF}$ = 4.5 Hz, C2), 149.2 (C-OMe), 149.5 (C-OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -181.7 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_{13}FN_2O_2$+ H^+]: 273.1034, found: 273.1034.

2-(3-Methoxyphenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3i

Pyrazolo[1,5-a]pyridine **3i** was obtained from α-fluoronitroalkene **1i** (39.4 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 7 h). Column chromatography (eluent: 9:1 to 5:1 PE/EtOAc) afforded **3i** (31 mg, 64%) as slightly yellow solid. R_f = 0.32 (PE/EtOAc, 3:1) (UV), mp = 146-150°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 2.96 (s, 3H, OMe), 6.70 (td, *J* = 6.9, 1.3 Hz, 1H, H6), 6.95 (dd, *J* = 8.5, 2.2 Hz, 1H, CH_{Ar}), 7.05 (dd, *J* = 8.9, 6.9 Hz, 1H, H5), 7.39 (t, *J* = 7.9 Hz, 1H, CH_{Ar}), 7.49 (d, *J* = 8.9 Hz, 1H, H4), 7.60 (d, *J* = 2.2 Hz, 1H, CH_{Ar}), 7.64 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.29 (d, *J* = 6.9 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 55.4 (OMe), 111.8 (d, $^4J_{CF}$ = 3.9 Hz, CH_{Ar}), 112.0 (C6-H), 114.7 (CH_{Ar}), 115.1 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 119.5 (d, $^4J_{CF}$ = 4.7 Hz, CH_{Ar}), 122.4 (d, $^4J_{CF}$ = 1.9 Hz, C5-H), 128.1 (C7-H), 128.8 (d,$^2J_{CF}$ = 28.3 Hz, C3a), 129.8 (CH_{Ar}), 132.1 (d, $^3J_{CF}$ = 3.9 Hz, C_{Ar}), 137.8 (d, $^2J_{CF}$ = 4.8 Hz, C2), 137.9 (d, $^1J_{CF}$ = 246.7 Hz, C3-F), 159.9 (**C**-OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -180.7 (s). HRMS (ESI): m/z calcd. for [$C_{14}H_{11}FN_2O$ + H^+]: 243.0928, found: 243.0934.

2-(2-Chlorophenyl)-3-fluoro-pyrazolo[1,5-a]pyridine 3j

Pyrazolo[1,5-a]pyridine **3j** was obtained from α-fluoronitroalkene **1j** (31 mg, 0.15 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 8 h). Column chromatography (eluent: 19:1 to 7:1 PE/EtOAc) afforded **3j** (30 mg, 80%) as white semisolid. R_f = 0.34 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (dd, *J* = 7.1, 1.1 Hz, 1H, H6), 7.11 (dd, *J* = 8.8, 6.9 Hz, 1H, H5), 7.34-7.41 (m, 2H), 7.50-7.64 (m, 3H), 8.33 (d, *J* = 7.1 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.1 (C6-H), 115.3 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 122.5 (d, $^4J_{CF}$ = 2.1 Hz, C5-H), 126.7 (CH_{Ar}), 128.1 (d, $^2J_{CF}$ = 27.5 Hz, C3a), 128.2 (C7-H), 129.9 (d, $^3J_{CF}$ = 3.5 Hz, C_{Ar}), 130.0 (CH_{Ar}), 130.1 (CH_{Ar}), 132.1 (CH_{Ar}), 133.9 (C-Cl), 137.3 (d, $^2J_{CF}$ = 8.3 Hz, C2), 137.7 (d, $^1J_{CF}$ = 244.6 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -176.8 (s). HRMS (ESI): m/z calcd. for [$C_{13}H_8{}^{35}ClFN_2$ + H^+]: 247.0433, found: 247.0443.

2-(4-Bromophenyl)-3-fluoro-5-methyl-pyrazolo[1,5-a]pyridine 3k

Pyrazolo[1,5-a]pyridine **3k** was obtained from α-fluoronitroalkene **1b** (49.2 mg, 0.2 mmol) and *N*-aminopyridinium salt **2b** (2.0 equiv.) following the general procedure (reaction time 5 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3k** (29.5 mg, 48%) as white solid. R_f = 0.50 (PE/EtOAc, 3:1) (UV), mp = 128-130 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, Me), 6.53 (dd, *J* = 7.2, 1.7 Hz, 1H, H6), 7.22 (br s, 1H, H4), 7.58 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.88 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.14 (d, *J* = 7.2 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (Me), 113.1 (d, $^3J_{CF}$ = 4.2 Hz, C4-H), 115.0 (C6-H), 122.5 (d, $^6J_{CF}$ = 0.7 Hz, C-Br), 127.3 (C7-H), 128.3 (d, $^4J_{CF}$ = 4.4 Hz, CH_{Ar}), 129.0 (d,$^2J_{CF}$ = 28.1 Hz, C3a), 131.9 (CH_{Ar}), 130.0 (d, $^3J_{CF}$ = 4.1 Hz, C_{Ar}), 133.4 (d, $^4J_{CF}$ = 2.1 Hz, C5),

137.0 (d, $^{2}J_{CF}$ = 4.8 Hz, C2), 137.1 (d, $^{1}J_{CF}$ = 245.6 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -181.7 (s). HRMS (ESI): m/z calcd. for $[C_{14}H_{10}{}^{79}BrFN_2 + H^+]$: 305.0084, found: 305.0081.

Ethyl 2-(4-bromophenyl)-3-fluoropyrazolo[1,5-a]pyridine-5-carboxylate 3l

Pyrazolo[1,5-a]pyridine **3l** was obtained from α-fluoronitroalkene **1b** (49 mg, 0.2 mmol) and *N*-aminopyridinium salt **2c** (2.0 equiv.) following the general procedure (reaction time 6 h at r.t.). Column chromatography (eluent: 30:1, then 5:1, PE/EtOAc) afforded **3l** (61 mg, 85%) as slightly yellow solid. R_f = 0.50 (PE/EtOAc, 3:1) (UV), mp = 158-159 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.1 Hz, 3H, CH_3), 4.43 (q, *J* = 7.1 Hz, 2H, CH_2), 7.30 (d, *J* = 7.3 Hz, 1H, H6), 7.60 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.89 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.26 (s, 1H, H4), 8.27 (d, *J* = 7.3 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC): δ 14.3 (Me), 61.7 (CH_2), 111.3 (C6-H), 118.1 (d, $^{3}J_{CF}$ = 4.7 Hz, C4-H), 123.0 (C-Br), 124.9 (d, $^{4}J_{CF}$ = 2.4 Hz, C5), 127.8 (C7-H), 127.9 (d, $^{2}J_{CF}$ = 28.1 Hz, C3a), 128.3 (d, $^{4}J_{CF}$ = 4.4 Hz, CH_{Ar}), 129.2 (d, $^{3}J_{CF}$ = 4.1 Hz, C_{Ar}), 132.0 (CH_{Ar}), 137.7 (d, $^{2}J_{CF}$ = 4.7 Hz, C2), 139.8 (d, $^{1}J_{CF}$ = 252.3 Hz, C3-F), 164.6 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -176.5 (s, 1F). HRMS (ESI): m/z calcd. for $[C_{16}H_{12}{}^{79}BrFN_2O_2 + H^+]$: 363.0139, found: 363.0133.

2-(4-Bromophenyl)-5-(1,3-dioxolan-2-yl)-3-fluoropyrazolo[1,5-a]pyridine 3m

Pyrazolo[1,5-a]pyridine **3m** was obtained from α-fluoronitroalkene **1b** (49 mg, 0.2 mmol) and *N*-aminopyridinium salt **2d** (2.0 equiv.) following the general procedure (reaction time 21 h). Column chromatography (eluent: 9:1, then 3:1, PE/EtOAc) afforded **3m** (48 mg, 68%) as white solid. R_f = 0.23 (PE/EtOAc, 3:1) (UV), mp = 151-153 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06-4.18 (m, 4H, CH_2CH_2), 5.84 (s, 1H, CH–O), 6.84 (dd, *J* = 7.3, 1.7 Hz, 1H, H6), 7.61 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.62 (s, 1H, H4), 7.91 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.28 (d, *J* = 7.3 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 65.5 (CH_2), 102.3 (CH–O), 110.5 (C6-H), 112.9 (d, $^{3}J_{CF}$ = 4.3 Hz, C4-H), 122.7 (C-Br), 128.2 (C7-H), 128.2 (d, $^{2}J_{CF}$ = 27.4 Hz, C3a), 128.3 (d, $^{4}J_{CF}$ = 4.4 Hz, CH_{Ar}), 129.7 (d, $^{3}J_{CF}$ = 4.3 Hz, C_{Ar}), 131.9 (CH_{Ar}), 133.3 (d, $^{4}J_{CF}$ = 2.0 Hz, C5), 137.4 (d, $^{2}J_{CF}$ = 4.9 Hz, C2), 138.5 (d, $^{1}J_{CF}$ = 248.0 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -179.6 (s, 1F). HRMS (ESI): m/z calcd. for $[C_{16}H_{12}{}^{79}BrFN_2O_2 + H^+]$: 363.0139, found: 363.0135.

4-Bromo-2-(4-bromophenyl)-3-fluoropyrazolo[1,5-a]pyridine 3n

Pyrazolo[1,5-a]pyridine **3n** was obtained from α-fluoronitroalkene **1b** (24.6 mg, 0.1 mmol) and *N*-aminopyridinium salt **2e** (2 equiv.) similarly to the general procedure at 65°C (reaction time 36 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3n** (31 mg, 84%, contains ca. 12% of corresponding 6-bromo-isomer) as white solid. R_f = 0.44 (PE/EtOAc, 3:1) (UV), mp = 207-210 °C ($CHCl_3$). Note: compound **3n** has very low solubility at r.t. even in DMSO-d_6. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 3.87 (s, 3H, OMe), 6.60 (t, *J* = 7.1 Hz, 1H, H6), 7.27-7.30 (m, 1H, H5), 7.62 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.91 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.26 (d, *J* = 7.1 Hz, 1H, H7). ^{19}F NMR (282 MHz, $CDCl_3$, 300 K): -174.4 (s). ^{1}H NMR (400 MHz, DMSO-d_6, 363 K): δ 6.84 (t, *J* = 7.1 Hz, 1H, H6), 7.51 (d, *J* = 7.1 Hz, 1H, H5), 7.74 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.88 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.58 (d, *J* = 7.1 Hz, 1H, H7). ^{13}C NMR (100 MHz, DMSO-d_6, 363 K): δ 107.6 (d, $^{3}J_{CF}$ = 5.4 Hz, C4), 113.5 (C6-H), 122.9 (C-Br), 127.3 (d, $^{2}J_{CF}$ = 19.0 Hz, C3a), 127.5 (d, $^{4}J_{CF}$ = 2.1 Hz, C5-H), 128.5 (C7-H), 129.0 (d, $^{4}J_{CF}$ = 4.5 Hz, CH_{Ar}), 129.6 (d, $^{3}J_{CF}$ = 4.4 Hz, C_{Ar}), 132.5 (CH_{Ar}), 137.7 (d, $^{2}J_{CF}$ = 4.9 Hz, C2), 137.8 (d, $^{1}J_{CF}$ = 251.3 Hz, C3-F). ^{19}F NMR (376 MHz, DMSO-d_6, 363 K): -175.6 (s). HRMS (ESI): m/z calcd. for $[C_{13}H_7{}^{79}Br^{81}BrFN_2 + H^+]$: 370.9013, found: 370.9000.

2-(4-Bromophenyl)-3-fluoro-4-methyl-pyrazolo[1,5-a]pyridine 3o and 2-(4-bromophenyl)-3-fluoro-6-methyl-pyrazolo[1,5-a]pyridine 3o'

Pyrazolo[1,5-a]pyridines **3o/3o'** were obtained from α-fluoronitroalkene **1b** (49.2 mg, 0.2 mmol) and *N*-aminopyridinium salt **2f** (2.0 equiv.) following the general procedure (reaction time 4 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3o/3o' =** 3:1, total yield 67%) as white solid. R_f = 0.49 (PE/EtOAc, 3:1) (UV), mp (for mixture) = 126-127 °C and then 135-136 °C ($CHCl_3$). Major isomer (**3o**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H, Me), 6.60 (t, *J* = 6.8 Hz, 1H, H6), 6.76 (d, *J* = 6.8 Hz, 1H, H5), 7.61 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.91 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.10 (d, *J* = 6.9 Hz, 1H, H7). ^{13}C NMR (75 MHz, CDCl3, ^{1}H-^{13}C HSQC): δ 17.2 (d, $^{4}J_{CF}$ = 2.8 Hz, Me), 112.3 (C6-H), 121.9 (d, $^{4}J_{CF}$ = 1.8 Hz, C5-H), 122.4 (br s, C-Br), 125.7 (C7-H), 127.2 (d, $^{3}J_{CF}$ = 4.2 Hz, C4), 128.2 (d, $^{4}J_{CF}$ = 4.3 Hz, CH_{Ar}), 129.0 (d, $^{2}J_{CF}$ = 23.4 Hz, C3a), 129.9 (d, $^{3}J_{CF}$ = 4.2 Hz, C_{Ar}), 131.8 (CH_{Ar}), 136.6 (d, $^{2}J_{CF}$ = 5.2 Hz, C2), 139.0 (d, $^{1}J_{CF}$ = 247.4 Hz, C3-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -178.7 (s). Minor isomer (**3o'**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, Me), 6.91 (d, *J* = 9.1 Hz, 1H, H5), 7.38 (d, *J* = 9.1 Hz, 1H, H4), 7.60 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.90 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 8.05 (s, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, characteristic signals): δ 18.2 (Me), 114.3 (d, $^{3}J_{CF}$ = 4.3 Hz, C4-H), 125.8 (s, C5-H and C7-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -180.7 (s). HRMS (ESI): m/z calcd. for $[C_{14}H_{10}{}^{79}BrFN_2 + H^+]$: 305.0084, found: 305.0078.

Methyl 2-(4-bromophenyl)-3-fluoropyrazolo[1,5-a]pyridine-6-carboxylate 3p and Methyl 2-(4-bromophenyl)-3-fluoropyrazolo[1,5-a]pyridine-4-carboxylate 3p'

Pyrazolo[1,5-a]pyridines **3p,p'** were obtained from α-fluoronitroalkene **1b** (74 mg, 0.3 mmol) and *N*-aminopyridinium salt **2g** (2.0 equiv.) following the general procedure (reaction time 2.5 h). Column chromatography (eluent: 9:1, then 3:1, PE/EtOAc) afforded two fractions: (1) pure **3p** (33 mg, 32%), R_f = 0.43 (PE/EtOAc, 3:1) (UV), slightly yellow solid (2) mixture of **5g** and **3p'** (35 mg, **5g**:**3p'** = 1.7:1.0, yields: **5g** – 20%, **3p'** – 12%), R_f = 0.30 (PE/EtOAc, 3:1) (UV), slightly yellow amorphous solid. **3p**: mp = 156-157 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H, CO_2Me), 7.49 (d, *J* = 9.4 Hz, 1H, H4), 7.60-7.63 (m, 3H, CH_{Ar} and H5), 7.91 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 9.00 (s, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 52.5 ($CO_2\underline{Me}$), 114.4 (d, $^{3}J_{CF}$ = 4.3 Hz, C4-H), 116.1 (C6), 122.1 (d, $^{4}J_{CF}$ = 2.0 Hz, C5-H), 123.4 (C-Br), 128.5 (d, $^{4}J_{CF}$ = 4.4 Hz, CH_{Ar}), 129.0 (C_{Ar}), 129.3 (d, $^{2}J_{CF}$ = 29.4 Hz, C3a), 132.0 (CH_{Ar}), 132.3 (C7-H), 138.4 (d, $^{1}J_{CF}$ = 249.3 Hz, C3-F), 140.2 (d, $^{2}J_{CF}$ = 5.1 Hz, C2), 165.0 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -178.8 (s). HRMS (ESI): m/z calcd. for

$[C_{15}H_{10}{}^{79}BrFN_2O_2 + H^+]$: 348.9982, found: 348.9982. **3p'**: ^{1}H NMR (300 MHz, $CDCl_3$, COSY): δ 4.03 (s, 3H, CO_2Me), 6.78 (t, *J* = 7.1 Hz, 1H, H6), 7.62 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.85 (d, *J* = 7.1 Hz, 1H, H5), 7.94 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.43 (d, *J* = 7.1 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, characteristic signals): δ 52.6 ($CO_2\underline{Me}$), 110.5 (C6-H), 128.4 (C5-H), 128.6 (d, $^4J_{CF}$ = 4.5 Hz, CH_{Ar}), 132.0 (CH_{Ar}), 132.3 (C7-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -168.5 (s).

2-(4-Chlorophenyl)-3-nitro-pyrazolo[1,5-a]pyridine 5a

Pyrazolo[1,5-a]pyridine **5a** was obtained from α-unsubstituted nitroalkene **4a** (37 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 2 h). Column chromatography (eluent: 3:1 PE/EtOAc) afforded **5a** (48.5 mg, 88%) as yellow solid. R_f = 0.17 (PE/EtOAc, 3:1) (UV), mp = 206-210 °C (dec.) ($CHCl_3$). NMR matches previously reported data.[30]

2-Phenyl-3-nitro-pyrazolo[1,5-a]pyridine 5b

Pyrazolo[1,5-a]pyridine **5b** was obtained from α-unsubstituted nitroalkene **4b** (14.9 mg, 0.1 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 2 h). Column chromatography (eluent: 3:1 PE/EtOAc) afforded **5b** (22.5 mg, 93%) as yellow solid. R_f = 0.17 (PE/EtOAc, 3:1) (UV), mp = 194-195 °C ($CHCl_3$). NMR matches previously reported data.[30]

2-(4-Methoxyphenyl)-3-nitro-pyrazolo[1,5-a]pyridine 5c

1. *via* reaction of *N*-aminopyridinium salt **2a** with α-unsubstituted nitroalkene **4c**: Pyrazolo[1,5-a]pyridine **5c** was obtained from α-unsubstituted nitroalkene **4c** (35.8 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 4 h). Column chromatography (eluent: 9:1 to 1:1 PE/EtOAc) afforded **5c** (47 mg, 86%) as yellow solid.

2. *via* reaction of *N*-aminopyridinium salt **2a** with α-chlorosubstituted nitroalkene **6**: To the stirred suspension of *N*-aminopyridinium bromide **2a** (106 mg, 0.6 mmol, 2 equiv.) powdered 4Å molecular sieves (150 mg), and 2,6-lutidine (160 mg, 1.5 mmol, 5 equiv.) in DCE (2 ml) copper acetate monohydrate (90 mg, 0.45 mmol, 1.5 equiv.) and chloronitroalkene **7** (64 mg, 0.3 mmol, 1.0 equiv.) were added. The mixture was heated at 55°C for 24 h, then evaporated under reduced pressure after addition of silica gel. The crude product was purified by column chromatography (9:1 PE/EtOAc) to afford 3-nitro-pyrazolo[1,5-a]pyridine **5c** (43.5 mg, 54%) as yellow solid and 3-chloro-pyrazolo[1,5-a]pyridine **8** (11 mg, 14%) as white semisolid.

3. *via* reaction of *N*-aminopyridinium salt **2a** with α-bromosubstituted nitroalkene **9**: Application of the above conditions (as for reaction **2a**+**6**) to bromonitroalkene **9** (51.6 mg, 0.2 mmol) afforded 3-nitro-pyrazolo[1,5-a]pyridine as single product according to the NMR of crude mixture. Column chromatography (7:1 PE/EtOAc) afforded **5c** (42 mg, 78%) as yellow solid.

R_f = 0.11 (PE/EtOAc, 3:1) (UV), mp = 147-149 °C ($CHCl_3$). NMR matches previously reported data.[30]

2-(2-Phenylethyl)-3-nitro-pyrazolo[1,5-a]pyridine 5d

Pyrazolo[1,5-a]pyridine **5d** was obtained from α-unsubstituted nitroalkene **4d** (35.8 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure (reaction time 2 h). Column chromatography (eluent: 9:1 to 1:1 PE/EtOAc) afforded **5b** (35 mg, 87%) as a dark yellow oil, which solidifies upon storage in a refrigerator. R_f = 0.24 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 3.13-3.18 (m, 2H, PhC$\underline{H}_2$), 3.49-3.54 (m, 2H, C2-C$\underline{H}_2$), 7.11 (app t, *J* = 6.9 Hz, 1H, H6), 7.18-7.36 (m, 5H, CH_{Ph}), 7.64 (app dd, *J* = 8.2, 7.7 Hz, 1H, H5), 8.35 (d, *J* = 8.9 Hz, 1H, H4), 8.49 (d, *J* = 6.9 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 30.2 (C2-$\underline{C}H_2$), 33.8 (Ph$\underline{C}H_2$), 115.5 (C6-H), 118.6 (C4-H), 122.5 (br s, C-NO_2), 126.1 (CH_{Ph}), 128.4 (CH_{Ph}), 128.5 (CH_{Ph}), 129.3 (C7-H), 130.7 (C5-H), 137.7 (C3a), 141.0 (C_{Ph}), 154.4 (C2). HRMS (ESI): m/z calcd. for $[C_{15}H_{13}N_3O_2 + H^+]$: 268.1081, found: 268.1087.

3-Nitro-pyrazolo[1,5-a]pyridine 5e

Pyrazolo[1,5-a]pyridine **5e** was obtained from α-unsubstituted nitroalkene **4e** (25.8 mg, 0.2 mmol) and *N*-aminopyridinium salt **2a** (2.0 equiv.) following the general procedure with heating at 60 °C for 11 h. Column chromatography (eluent: 3:1 to 1:1 PE/EtOAc) afforded **5e** (28 mg, 85%) as a yellow solid. R_f = 0.17 (PE/EtOAc, 3:1) (UV), mp = 181-182 °C ($CHCl_3$). (Lit.: 182 °C,[39] 186 °C ($CHCl_3$)[40]). ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 7.18 (t, *J* = 7.0 Hz, 1H, H6), 7.70 (dd, *J* = 8.7, 7.0 Hz, 1H, H5), 8.38 (d, *J* = 8.7 Hz, 1H, H4), 8.60 (d, *J* = 7.0 Hz, 1H, H7), 8.64 (s, 1H, H2). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 115.7 (C6-H), 118.5 (C4-H), 125.0 (C3), 130.0 (C7-H), 130.9 (C5-H), 136.2 (C3a), 140.5 (C2-H). HRMS (ESI): m/z calcd. for $[C_7H_5N_3O_2 + H^+]$: 164.0455, found: 164.0457.

2-Phenyl-3-nitro-4-methyl-pyrazolo[1,5-a]pyridine 5f and 2-phenyl-3-nitro-6-methyl-pyrazolo[1,5-a]pyridine 5f'

Pyrazolo[1,5-a]pyridines **5f/5f'** were obtained from α-unsubstituted nitroalkene **4b** (29.8 mg, 0.2 mmol) and *N*-aminopyridinium salt **2f** (2.0 equiv.) following the general procedure (reaction time 2 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **5f/5f'** (42 mg, **5f:5f' =** 4:1, total yield 84%) as yellow amorphous solid. R_f = 0.24 (PE/EtOAc, 3:1) (UV). Major isomer (**5f**): ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 2.71 (s, 3H, Me), 7.01 (t, *J* = 7.1 Hz, 1H, H6), 7.33 (d, *J* = 7.1 Hz, 1H, H5), 7.46-7.54 (m, 3H, *m*-Ph and *p*-Ph), 7.72-7.76 (m, 2H, *o*-Ph), 8.42 (d, *J* = 7.1 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 20.4 (Me), 114.9 (C6-H), 127.3 (C7-H), 128.3 (CH_{Ph}), 129.2 (C4), 129.3 (CH_{Ph}), 129.6 (CH_{Ph}), 130.3 (C_{Ph}), 130.4 (C5-H), 136.5 (C3a), 151.4 (C2). Minor isomer (**5f'**), characteristic signals: ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 2.46 (s, 3H, Me), 7.46-7.54 (m, 3H, *m*-Ph and *p*-Ph), 7.53-7.56 (m, 1H, H5), 7.81-7.84 (m, 2H, *o*-Ph), 8.33 (d, *J* = 9.0 Hz, 1H, H4), 8.36 (s, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 18.1 (Me), 118.4 (C4-H), 126.4 (C6), 127.6 (C7-H), 128.2 (CH_{Ph}), 129.9 (CH_{Ph}), 133.6 (C5-H). HRMS (ESI): m/z calcd. for $[C_{14}H_{11}N_3O_2 + H^+]$: 254.0924, found: 254.0917.

Methyl 2-(4-bromophenyl)-3-nitropyrazolo[1,5-a]pyridine-6-carboxylate 5g and Methyl 2-(4-bromophenyl)pyrazolo[1,5-a]pyridine-6-carboxylate 6a

Pyrazolo[1,5-a]pyridines **5g** and **6a** were obtained from nitroalkene **4f** (45 mg, 0.2 mmol) and *N*-aminopyridinium salt

2g (2.0 equiv.) following the general procedure (reaction time 2.5 h). Column chromatography (eluent: 9:1, then 3:1, PE/EtOAc) afforded **6a** (11 mg, 17%) as white solid and **5g** (45 mg, 60%) as slightly yellow amorphous solid. **5g**: R_f = 0.30 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 4.05 (s, 3H, CO_2Me), 7.65-7.74 (m, 4H, CH_{Ar}), 8.23 (d, *J* = 9.3 Hz, 1H, H5), 8.47 (d, *J* = 9.3 Hz, 1H, H4), 9.26 (s, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 53.1 ($CO_2\underline{Me}$), 118.7 (C4-H), 120.0 (C6), 125.0 (C-Br), 128.5 (C_{Ar}), 129.6 (CH_{Ar}), 130.3 (C5-H), 131.5 (CH_{Ar}), 131.6 (CH_{Ar}), 132.6 (C7-H), 139.4 (C3a), 152.7 (C2), 163.8 (C=O). HRMS (ESI): m/z calcd. for [$C_{15}H_{10}{}^{79}BrN_3O_4$ + H^+]: 375.9927, found: 375.9935. **6a**: R_f = 0.42 (PE/EtOAc, 3:1) (UV), mp = 167-171 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H, CO_2Me), 6.84 (s, 1H, H3), 7.53 (d, *J* = 9.3 Hz, 1H, H4), 7.61 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.67 (d, *J* = 9.3 Hz, 1H, H5), 7.86 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 9.20 (s, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 52.4 ($CO_2\underline{Me}$), 94.9 (C3-H), 115.9 (C6), 117.2 (C4-H), 123.2 (C5-H and C-Br), 128.2 (CH_{Ar}), 129.6 (C_{Ar}), 132.0 (CH_{Ar}), 132.5 (C7-H), 142.7 (C3a), 155.2 (C2), 165.4 (C=O). HRMS (ESI): m/z calcd. for [$C_{15}H_{11}{}^{79}BrN_2O_2$ + H^+]: 331.0077, found: 331.0072.

Methyl 3-nitro-2-phenylpyrazolo[1,5-a]pyridine-6-carboxylate 5h and Methyl 2-phenylpyrazolo[1,5-a]pyridine-6-carboxylate 6b

Pyrazolo[1,5-a]pyridines **5h** and **6b** were obtained from nitroalkene **4b** (44.5 mg, 0.3 mmol) and *N*-aminopyridinium salt **2g** (2.0 equiv.) following the general procedure (reaction time 1 h). Column chromatography (eluent: 9:1, then 3:1, PE/EtOAc) afforded **6b** (14 mg, 19%) as white solid and **5h** (47 mg, 53 %) as slightly yellow solid. **5h**: R_f = 0.26 (PE/EtOAc, 3:1) (UV), mp = 148-150 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.02 (s, 3H, CO_2Me), 7.40-7.53 (m, 3H, CH_{Ph}), 7.79-7.82 (m, 2H, CH_{Ph}), 8.19 (dd, *J* = 9.3, 1.1 Hz, 1H, H5), 8.43 (d, *J* = 9.3 Hz, 1H, H4), 9.23 (br s, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.9 ($CO_2\underline{Me}$), 118.6 (C4-H), 119.8 (C6), 123.0 (C3–NO_2), 128.2 (CH_{Ph}), 129.6 (C_{Ph}), 129.9 (CH_{Ph}), 130.0 (C5-H), 130.2 (CH_{Ph}), 132.6 (C7-H), 139.3 (C3a), 153.8 (C2), 163.8 (C=O). HRMS (ESI): m/z calcd. for [$C_{15}H_{11}N_3O_4$ + H^+]: 298.0822, found: 298.0819. **6b**: R_f = 0.36 (PE/EtOAc, 3:1) (UV), mp = 152-154 °C ($CHCl_3$) (Lit.: 136-138 °C[24b]). NMR matches previously reported data.[24b]

3-Chloro-2-(4-methoxyphenyl)-pyrazolo[1,5-a]pyridine 8

Obtained as a side-product in the synthesis of product **5c** *via* reaction of *N*-aminopyridinium salt **2a** with α-chlorosubstituted nitroalkene **7** (see above). R_f = 0.34 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 3.87 (s, 3H, OMe), 6.78 (td, *J* = 7.0, 1.2 Hz, 1H, H6), 7.02 (d, *J* = 8.9 Hz, 2H, CH_{Ar}), 7.17 (dd, *J* = 8.6, 7.2 Hz, 1H, H5), 7.52 (app d, *J* = 8.6 Hz, 1H, H4), 8.02 (d, *J* = 8.9 Hz, 2H, CH_{Ar}), 8.40 (app d, *J* = 7.0 Hz, 1H, H7). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 55.3 (OMe), 112.2 (C6-H), 114.0 (CH_{Ar}), 116.0 (C4-H), 123.8 (C5-H), 124.1 (C_{Ar}), 128.5 (C7-H), 129.3 (CH_{Ar}), 138.4 (C3a), 148.6 (C2), 160.0 (C-OMe). HRMS (ESI): m/z calcd. for [$C_{14}H_{11}{}^{35}ClN_2O$ + H^+]: 259.0633, found: 259.0632.

2-(4-Bromophenyl)-3-fluoro-pyrazolo[1,5-a]pyrazine 10a

Pyrazolo[1,5-a]pyrazine **10a** was obtained from α-fluoronitroalkene **1b** (49.2 mg, 0.2 mmol) and *N*-aminopyrazinium salt **2h** (2.0 equiv.) following the general procedure (reaction time 18 h). Column chromatography (eluent: 4:1 PE/EtOAc) afforded **10a** (24 mg, 41%) as white solid. R_f = 0.14 (PE/EtOAc, 3:1) (UV), mp = 168-170 °C (PE/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 7.84 (d, *J* = 4.5 Hz, 1H, H6), 7.91 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 8.19 (d, *J* = 4.5 Hz, 1H, H7), 9.05 (s, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC): δ 121.0 (C7-H), 123.4 (d, $^6J_{CF}$ = 0.6 Hz, C-Br), 124.9 (d,$^2J_{CF}$ = 28.8 Hz, C3a), 128.5 (d, $^4J_{CF}$ = 4.4 Hz, CH_{Ar}), 128.8 (d, $^3J_{CF}$ = 4.3 Hz, C_{Ar}), 129.6 (C6-H), 132.1 (CH_{Ar}), 137.2 (d, $^2J_{CF}$ = 5.3 Hz, C2), 138.2 (d, $^1J_{CF}$ = 254.2 Hz, C3-F), 142.1 (d, $^3J_{CF}$ = 5.0 Hz, C4-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -175.6 (s). HRMS (ESI): m/z calcd. for [$C_{12}H_7{}^{79}BrFN_3$+ H^+]: 291.9880, found: 291.9881.

3-Fluoro-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrazine 10b

Pyrazolo[1,5-a]pyrazine **10b** was obtained from α-fluoronitroalkene **1g** (19.7 mg, 0.1 mmol) and *N*-aminopyrazinium salt **2h** (2.0 equiv.) following the general procedure (reaction time 49 h). Column chromatography (eluent: 4:1, then 1:1, PE/EtOAc) afforded **10b** (9.0 mg, 37%) as white solid. R_f = 0.13 (PE/EtOAc, 3:1) (UV), mp = 144-146 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, OMe), 7.05 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.81 (d, *J* = 4.9 Hz, 1H, H6), 8.00 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 8.21 (d, *J* = 4.5 Hz, 1H, H7), 9.04 (s, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3 (OMe), 114.4 (CH_{Ar}), 121.0 (C7-H), 122.4 (d, $^3J_{CF}$ = 4.5 Hz, C_{Ar}), 124.8 (d, $^2J_{CF}$ = 26.4 Hz, C3a), 128.5 (d, $^4J_{CF}$ = 4.4 Hz, CH_{Ar}), 128.8 (d, $^3J_{CF}$ = 4.3 Hz, C_{Ar}), 128.4 (d, $^4J_{CF}$ = 4.2 Hz, CH_{Ar}), 129.0 (C6-H), 137.8 (d, $^1J_{CF}$ = 252.6 Hz, C3-F), 138.4 (d, $^2J_{CF}$ = 5.9 Hz, C2), 141.7 (d, $^3J_{CF}$ = 5.0 Hz, C4-H), 160.4 ($\underline{C}_{Ar}$–OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -177.4 (s). HRMS (ESI): m/z calcd. for [$C_{13}H_{10}FN_3O$+ H^+]: 244.0881, found: 244.0884.

2-(4-Bromophenyl)-3-fluoro-pyrazolo[1,5-b]pyridazine 10c

Pyrazolo[1,5-b]pyridazine **10c** was obtained from α-fluoronitroalkene **1b** (49.2 mg, 0.2 mmol) and *N*-aminopyridazinium salt **2i** (2.0 equiv.) following the general procedure (reaction time 18 h). Column chromatography (eluent: 7:1 PE/EtOAc) afforded **10c** (30 mg, 55%) as white solid. R_f = 0.21 (PE/EtOAc, 3:1) (UV), mp = 163-165 °C (PE/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 9.0, 4.4 Hz, 1H, H5), 7.61 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.96 (dd, *J* = 9.1, 1.8 Hz, 1H, H4), 8.00 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.26 (dd, *J* = 4.4, 1.8 Hz, 1H, H6). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC): δ 115.1 (d, $^4J_{CF}$ = 3.4 Hz, C5-H), 122.6 (d,$^2J_{CF}$ = 27.2 Hz, C3a), 123.1 (br s, C-Br), 124.1 (d, $^3J_{CF}$ = 4.5 Hz, C4-H), 128.6 (d, $^4J_{CF}$ = 4.4 Hz, CH_{Ar}), 129.1 (d, $^3J_{CF}$ = 4.2 Hz, C_{Ar}), 132.0 (CH_{Ar}), 135.0 (d, $^2J_{CF}$ = 4.5 Hz, C2), 136.9 (d, $^1J_{CF}$ = 253.7 Hz, C3-F), 142.4 (C6-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -177.3 (s). HRMS (ESI): m/z calcd. for [$C_{12}H_7{}^{79}BrFN_3$ + H^+]: 291.9880, found: 291.9882.

3-Fluoro-2-(4-methoxyphenyl)pyrazolo[1,5-b]pyridazine 10d

Pyrazolo[1,5-b]pyridazine **10d** was obtained from α-fluoronitroalkene **1g** (38.5 mg, 0.2 mmol) and *N*-aminopyridazinium salt **2j** (2.0 equiv.) following the general procedure (reaction time 25 h). Column chromatography (eluent: 5:1, then 3:1, PE/EtOAc) afforded **10d** (22.5 mg, 47%) as white solid. R_f = 0.17 (PE/EtOAc, 3:1) (UV), mp = 123-125 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, OMe), 6.94 (dd, *J* = 9.1, 4.4 Hz, 1H, H5), 7.04 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.91 (dd, *J* = 9.1, 1.9 Hz, 1H, H4), 8.06 (dd, *J* = 8.6 Hz, 2H, CH_{Ar}), 8.20

(dd, *J* = 4.4, 1.9 Hz, 1H, H6). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 55.3 (OMe), 114.3 (CH_{Ar}), 114.8 (d, $^4J_{CF}$ = 3.2 Hz, C5-H), 122.5 (d, overlapped, $^2J_{CF}$ ≈ 27 Hz, C3a), 122.7 (d, overlapped, $^3J_{CF}$ = 3.9 Hz, C_{Ar}), 123.8 (d, $^3J_{CF}$ = 4.5 Hz, C4-H), 128.5 (d, $^4J_{CF}$ = 4.3 Hz, CH_{Ar}), 136.0 (d, $^2J_{CF}$ = 4.2 Hz, C2), 136.5 (d, $^1J_{CF}$ = 252.2 Hz, C3-F), 141.7 (C6-H), 160.2 ($\underline{C}_{Ar}$–OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -179.0 (s). HRMS (ESI): m/z calcd. for $[C_{13}H_{10}FN_3O + H^+]$: 244.0881, found: 244.0889.

3-Fluoro-2-(4-fluorophenyl)pyrazolo[1,5-b]pyridazine 10e

Pyrazolo[1,5-b]pyridazine **10e** was obtained from α-fluoronitroalkene **1c** (37 mg, 0.2 mmol) and *N*-aminopyridazinium salt **2j** (2.0 equiv.) following the general procedure (reaction time 3 h). Column chromatography (eluent: 3:1, then 2:1, PE/EtOAc) afforded **10e** (27 mg, 58%) as white solid. R_f = 0.23 (PE/EtOAc, 3:1) (UV), mp = 132-137 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (dd, *J* = 9.1, 4.4 Hz, 1H, H5), 7.20 (t, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.94 (dd, *J* = 9.1, 1.9 Hz, 1H, H4), 8.10 (dd, *J* = 8.7, 5.5 Hz, 2H, CH_{Ar}), 8.24 (dd, *J* = 4.4, 1.9 Hz, 1H, H6). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 115.0 (d, $^4J_{CF}$ = 3.2 Hz, C5-H), 115.9 (d, $^2J_{CF}$ = 21.7 Hz, CH_{Ar}), 122.6 (d, $^2J_{CF}$ = 27.3 Hz, C3a), 124.1 (d, $^3J_{CF}$ = 4.5 Hz, C4-H), 126.3 (br s, C_{Ar}), 129.0 (dd, J_{CF} = 8.3, 4.4 Hz, CH_{Ar}), 135.2 (d, $^2J_{CF}$ = 4.8 Hz, C2), 136.6 (d, $^1J_{CF}$ = 252.6 Hz, C3-F), 142.2 (C6-H), 163.1 (d, $^1J_{CF}$ = 249.2 Hz, C_{Ar}-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -112.2 (s, 1F), -178.5 (s, 1F). HRMS (ESI): m/z calcd. for $[C_{12}H_7F_2N_3 + H^+]$: 232.0681, found: 232.0676.

2-(4-Methoxyphenyl)-3-nitro-pyrazolo[1,5-a]pyrazine 11a

Pyrazolo[1,5-a]pyrazine **11a** was obtained from α-unsubstituted nitroalkene **4c** (35.8 mg, 0.2 mmol) and *N*-aminopyrazinium salt **2h** (2.0 equiv.) following the general procedure (reaction time 6 h). Column chromatography (eluent: 7:1 PE/EtOAc) afforded **11a** (38.2 mg, 79%) as yellow solid. R_f = 0.37 (PE/EtOAc, 3:1) (UV), mp = 186-188°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 3.89 (s, 3H, OMe), 7.03 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.83 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 8.29 (d, *J* = 4.2 Hz, 1H, H6), 8.46 (d, *J* = 4.2 Hz, 1H, H7), 9.80 (s, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 55.4 (OMe), 113.9 (CH_{Ar}), 121.1 (C_{Ar}), 121.4 (C7-H), 131.7 (CH_{Ar}), 132.6 (C3a), 133.6 (C6-H), 145.0 (C4-H), 151.5 (C2), 161.5 (C-OMe). HRMS (ESI): m/z calcd. for $[C_{13}H_{10}N_4O_3 + H^+]$: 271.0826, found: 271.0829.

3-Nitro-2-(2-phenylethyl)pyrazolo[1,5-a]pyrazine 11b

Pyrazolo[1,5-a]pyrazine **11b** was obtained from nitroalkene **4d** (17.7 mg, 0.1 mmol) and *N*-aminopyrazinium salt **2h** (2.0 equiv.) following the general procedure (reaction time 18 h). Column chromatography (eluent: 3:1, PE/EtOAc) afforded **9** (20.5 mg, 76%) as slightly yellow. R_f = 0.17 (PE/EtOAc, 3:1) (UV), mp = 138-139 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14-3.19 (m, 2H, Ph$\underline{C}H_2$), 3.54-3.59 (m, 2H, C2-$\underline{C}H_2$), 7.21-7.36 (m, 5H, Ph), 8.29 (d, *J* = 4.5 Hz, 1H, H6), 8.43 (dd, *J* = 4.5, 1.1 Hz, 2H, H7), 9.77 (d, *J* = 1.1 Hz, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 29.8 (C2-$\underline{C}H_2$), 33.8 (Ph$\underline{C}H_2$), 121.5 (C7-H), 123.6 (C3-NO_2), 126.4 (CH_{Ph}), 128.5 (CH_{Ph}), 128.6 (CH_{Ph}), 131.8 (C3a), 133.4 (C6-H), 140.5 (C_{Ph}), 144.4 (C4-H), 154.3 (C2). HRMS (ESI): m/z calcd. for $[C_{14}H_{12}N_4O_2 + H^+]$: 269.1033, found: 269.1028.

3-Nitro-2-phenylpyrazolo[1,5-b]pyridazine 11c

Pyrazolo[1,5-b]pyridazine **11c** was obtained from nitroalkene **4b** (22.3 mg, 0.15 mmol) and *N*-aminopyridazinium salt **2j** (2.0 equiv.) following the general procedure (reaction time 2 h). Column chromatography (eluent: 5:1, then 1:1, PE/EtOAc) afforded **11c** (22 mg, 61%) as slightly yellow solid. R_f = 0.32 (PE/EtOAc, 1:1) (UV), mp = 112-115 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.56 (m, 4H, 3×CH_{Ph} and H5), 7.88-7.92 (m, 2H, $CH_{o\text{-}Ph}$), 8.60 (dd, *J* = 4.5, 1.9 Hz, 1H, H6), 8.80 (dd, *J* = 9.1, 1.9 Hz, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC): δ 122.0 (C5-H), 128.1 (C4-H), 128.3 (CH_{Ph}), 129.2 (C3a), 130.1 (CH_{Ph}), 130.3 (CH_{Ph}), 133.0 (C_{Ph}), 144.6 (C6-H), 149.7 (C2). HRMS (ESI): m/z calcd. for $[C_{12}H_8N_4O_2 + H^+]$: 241.0720, found: 241.0723.

3-Nitro-2-phenethylpyrazolo[1,5-b]pyridazine 11d

Pyrazolo[1,5-b]pyridazine **11d** was obtained from nitroalkene **4d** (26.6 mg, 0.15 mmol) and *N*-aminopyridazinium salt **2j** (2.0 equiv.) following the general procedure (reaction time 2 h). Column chromatography (eluent: 5:1, then 1:1, PE/EtOAc) afforded **11d** (26.5 mg, 65%) as slightly yellow oil. R_f = 0.13 (PE/EtOAc, 1:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.18-3.23 (m, 2H, PhC$\underline{H}_2$), 3.57-3.62 (m, 2H, C2-C$\underline{H}_2$), 7.21-7.37 (m, 5H, Ph), 7.50 (dd, *J* = 9.0, 4.5 Hz, 1H, H5), 8.56 (dd, *J* = 4.5, 1.9 Hz, 1H, H6), 8.73 (dd, *J* = 9.0, 1.9 Hz, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC): δ 29.9 (C2-$\underline{C}H_2$), 33.9 (Ph$\underline{C}H_2$), 121.9 (C5-H and C3–NO_2), 126.3 (CH_{Ph}), 127.5 (C4-H), 128.5 (2×CH_{Ph}), 132.4 (C3a), 140.8 (C_{Ph}), 144.1 (C6-H), 152.2 (C2). HRMS (ESI): m/z calcd. for $[C_{14}H_{12}N_4O_2 + H^+]$: 269.1033, found: 269.1024.

Conclusions

In conclusion, a new highly efficient method for the synthesis of 3-fluoro- and 3-nitro-pyrazolo[1,5-a]pyridines was developed. Application of $Cu(OAc)_2 \cdot H_2O$/2,6-lutidine oxidative system provided an access to the pharmaceutically attractive fluorinated pyrazolopyridines. Moreover, corresponding nitro-substituted heterocycles were also prepared by the present method in excellent yields. In addition, novel fluorinated pyrazolo[1,5-a]pyridazines and pyrazolo[1,5-b]pyrazines were prepared for the first time using the present methodology.

Conflicts of interest

There are no conflicts to declare.

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