

Cascade and multicomponent synthesis of structurally diverse 2-(pyrazol-3-yl)pyridines and polysubstituted pyrazoles

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The cascade reaction between *N*-tosylhydrazones and 2-alkynylpyridines leads to 2-(pyrazol-3-yl)pyridines, important structural motifs in ligands for transition metals and bioactive molecules. When the reaction is conducted with 2,6-diethynylpyridine the important 2,6-bis(pyrazolyl)pyridines are obtained, featuring the arrangement of tridentate and also pentadentate ligands. A novel three-component version of the reaction has been designed, which involves the use of α -bromo-*N*-tosylhydrazones, alkynylpyridines and NH-azoles. The generality of the multicomponent reaction is further illustrated by the preparation of different polysubstituted pyrazoles employing an array of terminal alkynes. In these multicomponent reactions, complex molecules featuring three different heterocycles are assembled in one single step from commercial materials enabling the fast generation of molecular diversity.

Introduction

The pyrazole heterocycle is a privileged structure of outmost importance in current organic chemistry.¹ The pyrazole structural motif is present in a wide number of molecules with biological activity with medicinal applications,² and are also very useful structural fragments in supramolecular chemistry,³ coordination chemistry,⁴ catalysis⁵ and materials chemistry.⁶ In particular, the 2-(pyrazol-3-yl)pyridine moiety **A** (Figure 1) represents a very common fragment that is present in a large number of metal complexes with catalytic activity.⁷ Moreover, this bidentate substructure has been also employed as key element in the design of coordination complexes with interesting electronic properties,⁸ as well as fundamental building block for supramolecular coordination complexes that feature a variety of applications.⁹ Furthermore, the 2-(pyrazol-3-yl)pyridine moiety is also present in molecules with reported biological activities and therapeutical applications.¹⁰ A particularly important class of compounds are 2,6-bis(pyrazolyl)pyridines (bpp) **B** (Figure 1).¹¹ This family of tris-heterocyclic ligands has attracted enormous attention due to their unique metal binding properties. On one side, they have been shown to produce coordination complexes featuring properties such as spin-crossover¹² or luminescence.¹³ Additionally, 2,6-bis(pyrazolyl)pyridine transition metal complexes are efficient catalysts in a variety of organic transformations.¹⁴

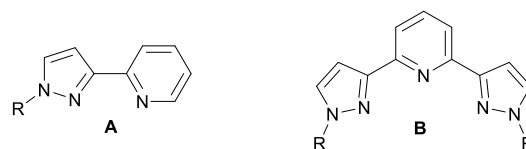


Figure 1. 2-(1*H*-pyrazol-3-yl) pyridine **A** and 2,6-bis-[2-(1*H*-pyrazol-3-yl)]pyridine **B** substructures

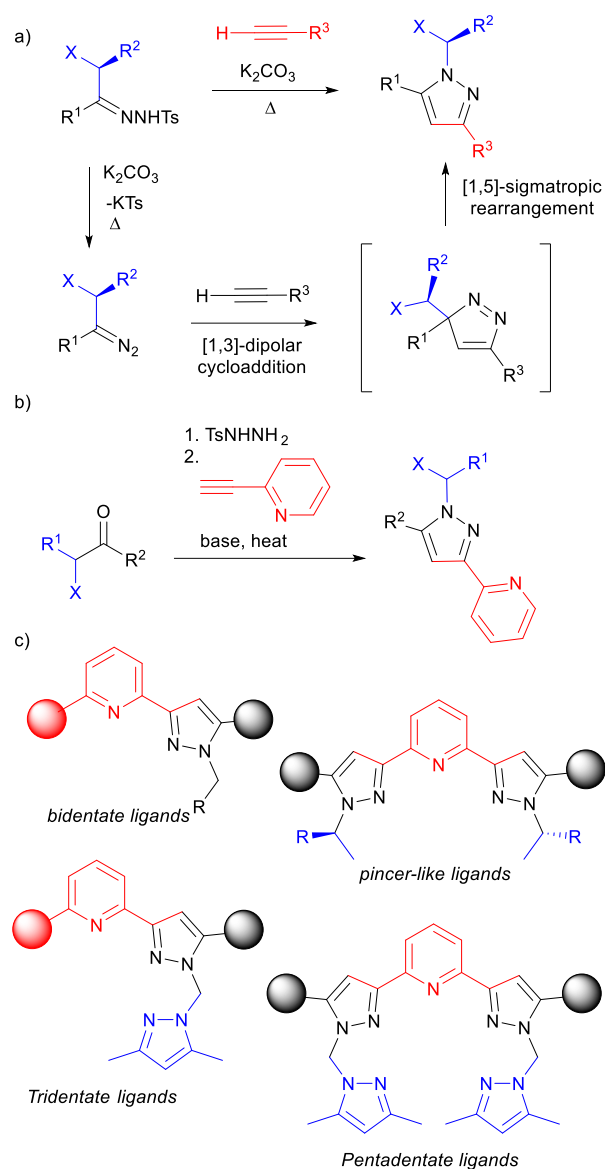
In spite of the wide interest and applications of the 2-(pyrazol-3-yl)pyridine substructure, the methods for the synthesis of polysubstituted systems are quite limited, and usually require stepwise protocols with poor yields, and thus have been applied to a limited number of substituents. Therefore, the ability to synthesize structurally diverse 2-(pyrazol-3-yl)pyridines in an efficient and straightforward manner from easily available materials might be of great interest, as it would enable to study the influence of the substituents in the properties or these important types of molecules both in medicinal chemistry and catalysis.

We have recently reported a novel method for the synthesis of polysubstituted pyrazoles by a 1,3-dipolar cycloaddition/1,5-sigmatropic rearrangement sequence starting from *N*-tosylhydrazones derived from ketones and terminal alkynes (Scheme 1, a).¹⁵ The method is very general and regioselective, and depending on the structure of the *N*-tosylhydrazone allows for the selective synthesis of 3,4,5- or 1,3,5-trisubstituted pyrazoles. Moreover, the employment of *N*-tosylhydrazones derived from ketones featuring a stereogenic center in the α -carbon, leads to chiral pyrazoles with the stereogenic center attached at the nitrogen atom (Scheme 1, a).¹⁶

We envisioned that the employment of a 2-alkynylpyridine in the cascade reaction would lead in a very straightforward manner to 2-(pyrazol-3-yl)pyridines (Scheme 1, b). Considering the modularity and wide scope of the reaction, this general approach might allow to access to an ample variety of

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structures featuring this bidentate ligand moiety, enabling the flexible modification of steric and electronic properties of potential ligands. The implementation of this methodology has allowed us to devise efficient synthetic routes that gain access to a variety of polyheterocyclic systems featuring the 2-(pyrazol-3-yl)pyridine moiety, that might be used as bidentate, tridentate and even pentadentate chelating ligands (Scheme 1, c).



Scheme 1. a) Synthesis of 1,3,5-trisubstituted pyrazoles developed by our group. b) General approach for the synthesis of 2-(pyrazol-3-yl)pyridines explored in this work. c) Structures prepared in this work.

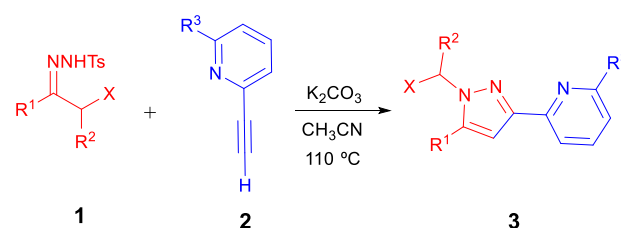
Results and discussion

Synthesis of 2-(pyrazol-3-yl)pyridines by the cascade reaction

We initiated our study by focusing on the reaction between *N*-tosylhydrazones **1** and 2-alkynylpyridines **2** (Scheme 2).⁵ We had previously demonstrated that in order to drive the 1,5-rearrangement to the nitrogen atom, and obtain the desired

1,3,5-trisubstituted pyrazoles, the starting *N*-tosylhydrazone must feature a π -electron-donating substituent (X) at the α -position. Thus, we concentrated our study towards this particular type of *N*-tosylhydrazones.

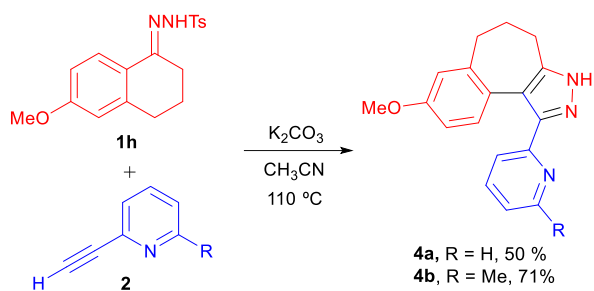
We took as starting point the reaction conditions that had been previously developed for the synthesis of 1,3,5-trisubstituted pyrazoles:^{15a} treatment of an equimolar mixture of tosylhydrazone **1** and terminal alkyne **2** in 1,4-dioxane at 110 °C, and in the presence of an excess of K_2CO_3 (Scheme 2). After some experimentation it was discovered that in these cases acetonitrile was the best solvent to achieve the transformations. Additionally, in some instances it was recommended slow syringe pump addition of a solution of the *N*-tosylhydrazone to the reaction mixture. These conditions were applied to a variety of *N*-tosylhydrazones **1** and 2-alkynylpyridines **2** to provide a set of structurally diverse 2-(pyrazol-3-yl)pyridines **3** (Scheme 2, Table 1). Noteworthy, the structural variety of pyrazolopyridines **3** that can be accessed is remarkable. Variations in the structure of the *N*-tosylhydrazone **1** enable to introduce different substitution in the pyrazole ring. On one side, aryl and alkyl groups can be placed at position 5 of the pyrazole. Moreover, it is particularly interesting the substitution at N1 in the pyrazole. Benzyl (**3a**, **3b**) and methoxymethyl (**3c**) can be introduced by employing the *N*-tosylhydrazones **1a** and **1b** respectively. Additionally, the use of the *N*-tosylhydrazone **1c** derived from α -methoxycyclohexanone provides the interesting condensed systems **3d-3f**, with expansion of the saturated ring. The use of *N*-tosylhydrazones **1d** and **1e** derived from α -(*N*-azole)-substituted ketones provided new pyrazolopyridines which feature an additional heterocycle. Thus, derivatives having three different heterocycles are assembled in a very simple manner. Particularly appealing are the derivatives of *N*-tosylhydrazone **1d**, that carries another pyrazole ring, as the adducts obtained (**3g**, **3h**) are a new class of potential N,N,N-tridentate ligands.



Scheme 2. Synthesis of 2-(pyrazol-3-yl)pyridines **3**.

In our previous work, we had demonstrated that when *N*-tosylhydrazones featuring a stereogenic center at the α -position are used, the 1,3-dipolar cycloaddition/1,5-sigmatropic rearrangement sequence takes place with retention of configuration on the migrating group,¹⁶ therefore, enantiomerically pure pyrazoles featuring a stereogenic group attached at N1 are obtained. This reaction was applied for the preparation of chiral enantiomerically pure pyrazolopyridines featuring a stereogenic center on the nitrogen of the pyrazole. To this purpose, the tosylhydrazones **1f**, derived from *L*-proline,

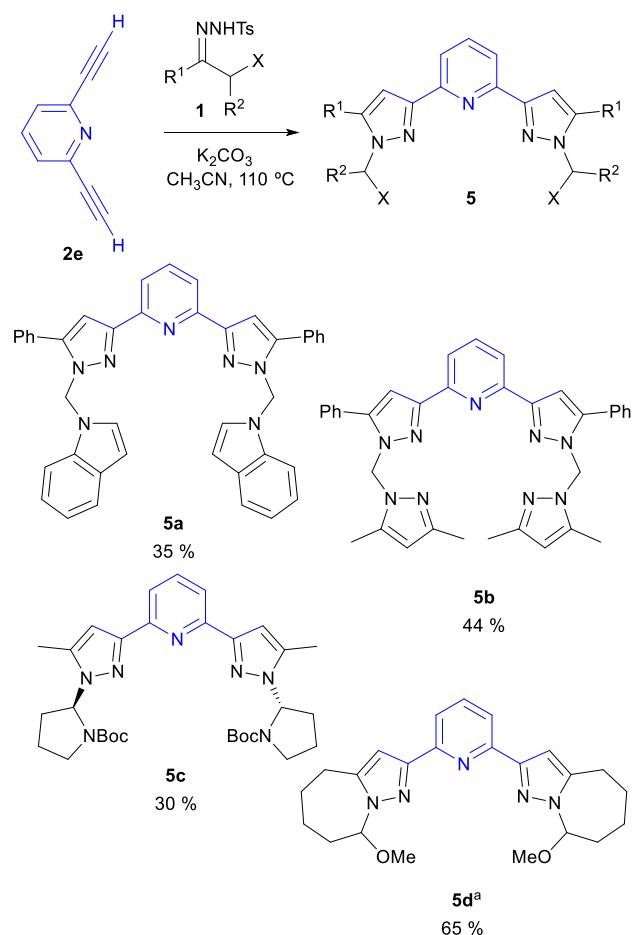
structures for coordination chemistry and catalysis,¹⁷ and additionally could be easily derivatized at the NH position to increase the molecular complexity.



Scheme 3. Synthesis of NH-free 2-(pyrazol-3-yl)pyridines 4.

Then, we decided to explore the cascade process with 2,6-diethynylpyridine **2e** oriented to the synthesis of pincer NNN-tridentate ligands upon a double cycloaddition/rearrangement sequence. The reactions were conducted under the same conditions but employing an excess of the *N*-tosylhydrazone. Delightfully, the adducts **5**, featuring the 2,6-bis(pyrazolyl)pyridine moiety were obtained (Scheme 4).

The 2,6-bis(pyrazolyl)pyridines **5** are obtained with only moderate yields. Nevertheless, it must be taken into account that the same cascade reaction must take place twice on the same adduct. Moreover, it is remarkable the high complexity that is achieved under very simple experimental conditions and from readily available precursors. Therefore, it is indeed a synthetically useful transformation. It should be highlighted in particular compound **5b** that features the arrangement of five nitrogen atoms in a proper position to behave as a NNNNN-pentadentate ligand. The compound **5c**, that has been prepared from *L*-proline, is also noteworthy, as it is an example of a novel C2 symmetric enantiomerically pure tridentate ligand.

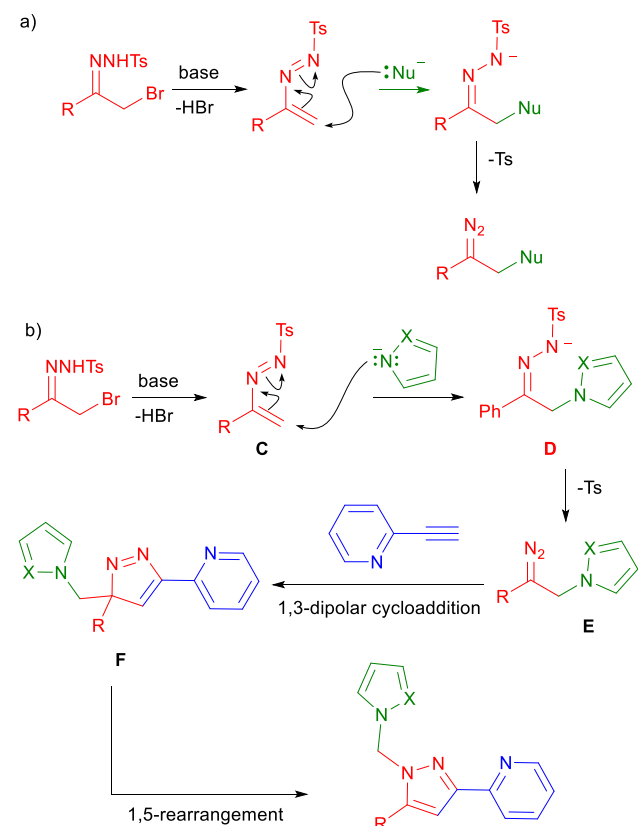


Scheme 4. Synthesis of 2,6-bis(pyrazolyl)pyridines **5** by reaction of **2e** with *N*-tosylhydrazones **1**. a) Slow addition of the *N*-tosylhydrazones **1**.

Three-component reactions

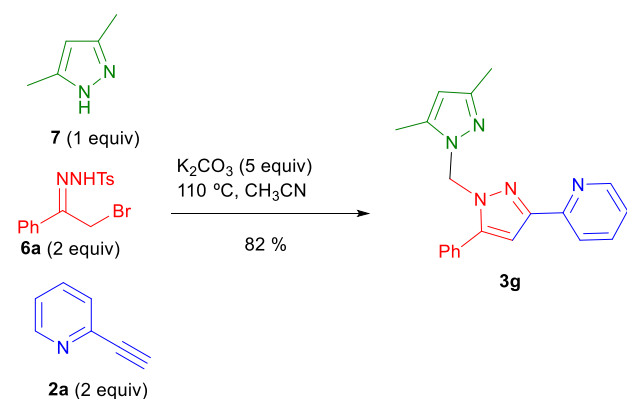
α -Halo-*N*-tosylhydrazones are valuable intermediates for multicomponent reactions. Upon treatment with a base they undergo dehydrohalogenation to give α,β -unsaturated azoalkenes, that may suffer conjugate addition of a proper nucleophile to give a substituted *N*-tosylhydrazone salt,¹⁸ that in turn might experiment thermal decomposition to generate a diazo compound. Recently Wang et al took advantage of this strategy to develop novel three-component cross-couplings using α -bromo-*N*-tosylhydrazones and C-nucleophiles (Scheme 5, a).¹⁹ We envisioned that the base promoted generation of the azoalkene **C** in the presence of a NH-azole might lead to tosylhydrazone salt **D** upon nucleophilic attack of the azole anion to the azoalkene, which is an ideal substrate for our pyrazole synthesis. Therefore, we set out to develop a new three-component pyrazole synthesis combining the formation of a functionalized diazo compound with the 1,3-dipolar cycloaddition/1,5-rearrangement process. Thus, the formation of the pyrazole through the three-component reaction should involve: 1) formation of azoalkene **C** by base promoted elimination on the α -bromo-*N*-tosylhydrazone; 2) nucleophilic attack of the azolyl anion to produce the *N*-tosylhydrazone salt **D**; iii) generation of diazo compound **E** by thermal

decomposition of **D**; iv) 1,3-dipolar cycloaddition to give 3H-pyrazole **F**; v) 1,5-sigmatropic rearrangement to produce the final adduct (Scheme 5, b).



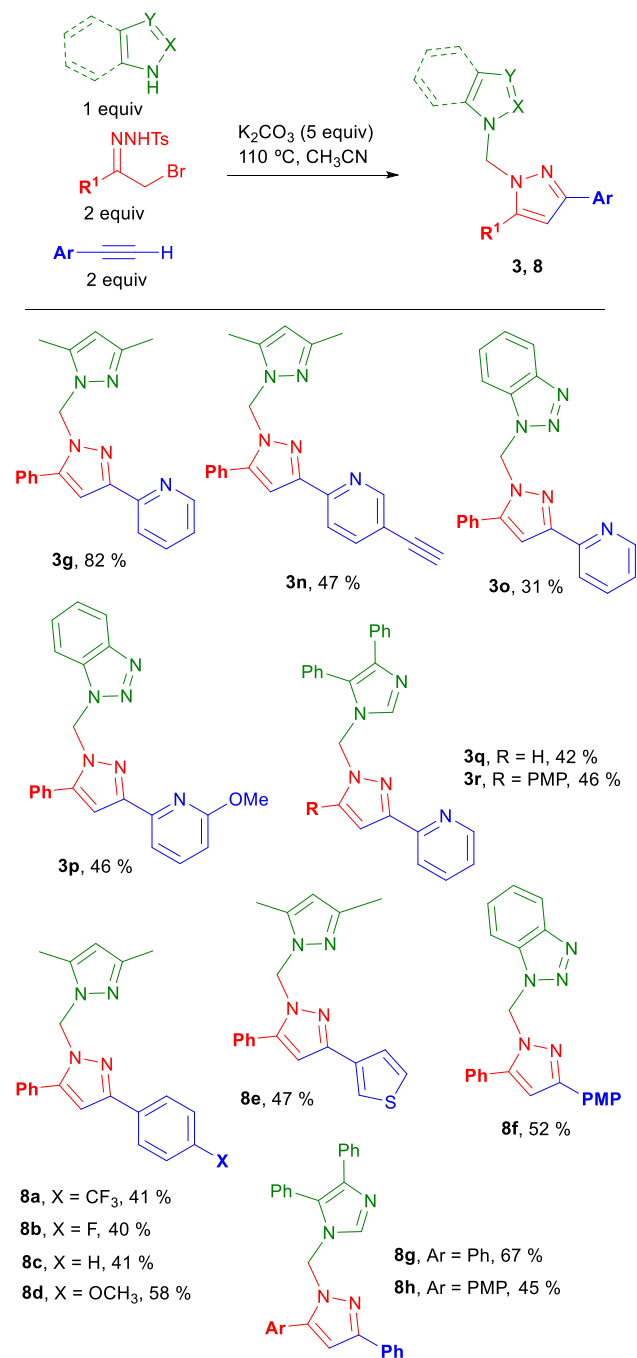
Scheme 5. a) Generation of substituted diazo compounds from α -bromo-*N*-tosylhydrazones. b) Our proposal for a three-component synthesis of pyrazolopyridines.

In an initial experiment we mixed the *N*-tosylhydrazone **6a**, derived from 2'-bromoacetophenone, 2-ethynylpyridine **2a** and 3,5-dimethylpyrazole **7** in the presence of an excess of K_2CO_3 . The adduct **3g** was isolated although in low yield. After some optimization work, it was determined that best results were obtained by employing a 2: 2: 1, hydrazone **6a**: alkyne **2a**: pyrazole **7** molar ratio, in the presence of 5 equiv of K_2CO_3 , leading to compound **3g** in high yield (Scheme 6).



Scheme 6. Three-component synthesis of pyrazolopyridine **3g**. Preliminary results.

To illustrate the versatility of this new three-component methodology a collection of pyrazolopyridines **3** was prepared (Scheme 7).



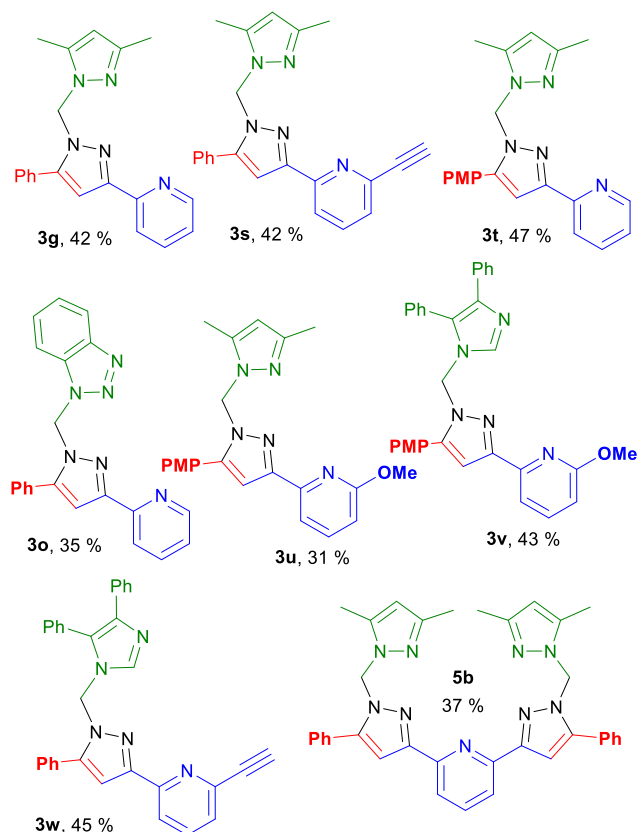
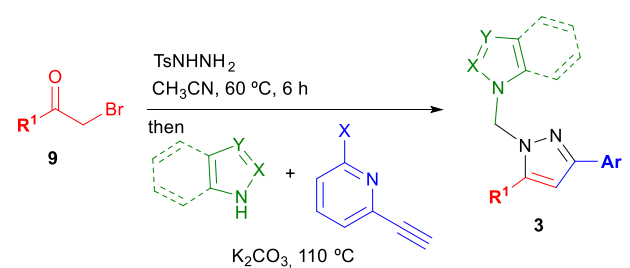
Scheme 7. Three-component synthesis of structurally diverse trisubstituted pyrazoles **3** and **8**.

Several different azoles can be introduced as nucleophiles (green color) by means of this strategy, including pyrazoles, benzotriazole and imidazole. Importantly, the reaction is not restricted to the employment of 2-ethynylpyridines. Indeed, other terminal alkynes were examined in the multi-components process successfully, leading to new trisubstituted pyrazoles **8** featuring an additional aryl or heteroaryl substituent. This

three-component reaction is remarkable, as it yields the important pyrazole heterocycles, with three points of diversity and from readily available reactants.²⁰ Moreover, these are also the first examples of the in situ generation and further reaction of α -(*N*-azole)-*N*-tosylhydrazones, versatile reagents in the synthesis of polyheterocycles.^{21,22}

One-pot/four-component reaction

It is well known that many of the reactions that involve *N*-tosylhydrazones can be carried out in a one pot fashion, starting from the corresponding ketone and tosylhydrazide, by generating the *N*-tosylhydrazone in situ.²³ To push the applicability of the multicomponent reaction even further, we decided to examine this strategy, and combine the one pot generation of the α -bromo-*N*-tosylhydrazone **6** with the three-component cascade synthesis of pyrazoles.

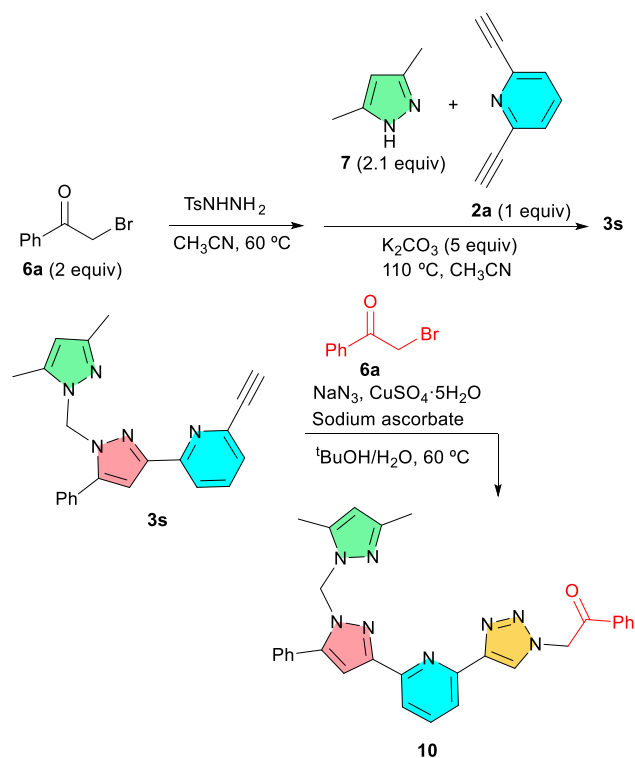


Scheme 8. One pot/four-component synthesis of 2-(pyrazol-3-yl)pyridines **3** directly from α -bromoketones **9**.

The one pot/four-component sequence could be accomplished by treating the α -bromoketone **9** with tosylhydrazide in CH_3CN

at 60 °C for 6h, followed by the addition of the alkyne, the NH-azole and K_2CO_3 . Using this procedure, the 2-(pyrazol-3-yl)pyridines **3** were obtained with moderate yields (Scheme 8). Nevertheless, it must be noted that the highly complex trisubstituted pyrazoles are assembled in one single operational step directly from commercially available materials. Remarkably, the one pot/four-component strategy was also appropriate for the 2,6-bis(pyrazolyl)pyridine **5b**.

Finally, we have shown that under the proper experimental conditions, the reactions with 2,6-diethynylpyridine can be controlled to give the 2-(pyrazol-3-yl)pyridines **3** leaving one of the triple bonds untouched (**3l**, **3s**, **3w**), and susceptible of a further derivatization. To illustrate the usefulness of the selective transformation, compound **3s** was subjected to a Cu catalyzed azide-alkyne cycloaddition (Scheme 9).²⁴ In this manner, the reaction of **3s** with sodium azide and bromoketone **6a** led to the new adduct **10**, featuring four different heterocycles, and interestingly, with the proper arrangement of a tetradentate NNNN ligand (Scheme 9). This example shows the potential of this approach for the generation of molecular diversity around the 2-(pyrazol-3-yl)pyridine moiety, as compound **10** has been synthesized in only two steps from commercially available starting materials.



Scheme 9. Two steps synthesis of polyheterocyclic system **10** by the cascade pyrazole formation/CuAAC sequence.

Experimental section

Details of experimental conditions, characterization data and copies of ^1H and ^{13}C NMR spectra for all isolated compounds are included in the Supplementary Information.

General procedure for the synthesis of 2-(pyrazol-3-yl)pyridines from *N*-tosylhydrazones 1 and 2-alkynylpyridines 2.

A reaction tube was charged with *N*-tosylhydrazone 1 (0.24 mmol), 2-ethynylpyridine 2 (0.2 mmol) and K₂CO₃ (0.4 mmol, 55 mg) and 2 ml of CH₃CN and the mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH₂Cl₂ and 10 mL of NaHCO₃ saturated aqueous solution. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2x5 mL). The organic layers were combined, washed with brine (5 mL), dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The resulting oily residue was purified by flash chromatography in silica gel to afford the 2-(pyrazol-3-yl)pyridine.

General Procedure with slow addition of the *N*-Tosylhydrazone.

A reaction tube was charged with 2-ethynylpyridine 2 (0.2 mmol) and K₂CO₃ (0.4 mmol, 55 mg) and 1 ml of CH₃CN under nitrogen atmosphere and the solution was heated to 100 °C. Then, a solution of the *N*-tosylhydrazone 1 (0.3 mmol) in 1 ml of CH₃CN was slowly added with a syringe pump over a period of 2h. The mixture was stirred for 16 h at 100 °C. Then, the workup of the reaction is identical to that described above.

General procedure for the synthesis of 2,6-bis(pyrazolyl)pyridines 5 by reaction of *N*-tosylhydrazones 1 with 2,6-ethynylpyridine

The procedure is identical to that described above for 2-(pyrazol-3-yl)pyridines but employing 0.2 mmol of 2,6-diethynylpyridine 2e, 0.8 mmol of *N*-tosylhydrazone and 0.8 mmol (110 mg) of K₂CO₃.

General procedure for the three-component synthesis of 2-(pyrazol-3-yl)pyridines from α -bromo-*N*-tosylhydrazones 6, 2-alkynylpyridines 2 and NH-azoles.

A reaction tube was charged with the α -bromo-*N*-tosylhydrazone 6 (0.2 mmol), 2-ethynylpyridine 2 (0.2 mmol), the NH-azole (0.1 mmol), K₂CO₃ (0.5 mmol, 70 mg) and 3 ml of CH₃CN, and the mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. Then, the workup of the reaction is identical to that described above.

General procedure for the one pot/four-component synthesis of 2-(pyrazol-3-yl)pyridines from α -bromoketones, *N*-tosylhydrazide, 2-alkynylpyridines and NH-azoles.

A reaction tube was charged with the α -bromoketone (0.2 mmol), the *N*-tosylhydrazide (0.22 mmol) and CH₃CN (1.5 ml) were. After 2 – 12 h at 60 °C, the 2-ethynylpyridine (0.2 mmol), the NH-azole (0.1 mmol), K₂CO₃ (0.5 mmol, 70 mg) and 2.5 ml of CH₃CN were added to the mixture and it was stirred at 110 °C for 16 h under nitrogen atmosphere. Then, the workup of the reaction is identical to that described above.

Conclusion

As summary, in this work we have reported the application of the synthesis of pyrazoles by cascade reaction between *N*-

tosylhydrazones and alkynes to the preparation of structurally diverse 2-(pyrazol-3-yl)pyridines, interesting structures for their potential applications as NN bidentate ligands as well as their possible biological activity. Moreover, the application of the methodology to 2,6-diethynylpyridine led to the obtention of new 2,6-bis(pyrazolyl)pyridines. This method led to the preparation of new potential NNN-tridentate ligands and also unprecedented NNNNN-pentadentate ligands.

We have also developed new three-component and four-component procedures for the synthesis of trisubstituted pyrazoles from α -bromo-*N*-tosylhydrazones or α -bromoketones, NH-azoles and terminal alkynes. These methods allow for the assembly of various heterocyclic systems along with the construction of the trisubstituted pyrazoles. The variety of structures synthesized, (40 different adducts) clearly proves the versatility and usefulness of this multicomponent approach for the generation of molecular diversity.

Conflicts of interest

“There are no conflicts to declare”.

Acknowledgements

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Notes and references

§ See supporting information for synthetic details.

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