Towards near-infrared light-activated combination chemotherapy

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Simple and efficient method for mono- and di-amination of polypyridine *N*-oxides

Herein we report a simple synthetic route towards both known and novel aminated polypyridyl ligands. The use of tosyl chloride in combination with potassium phthalimide followed by hydrolysis allows for chemoselective ortho-amination of (poly)pyridyl mono- and di-N-oxides with good to excellent yield. The reactions are scalable and reproducible while using inexpensive, commercially available reagents.

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2.1. Introduction

Nitrogen heterocycles form an important class of chemicals used in a wide variety of scientific disciplines such as medicinal chemistry, photochemistry, or catalysis.[1] Polypyridyl derivatives, in particular, are in high demand as they form the core of many functional molecules. Therefore, the development of simple and efficient functionalization methods remains of high interest in chemistry. Among the wide range of preparative reactions available for the functionalization of polypyridine compounds, amination reactions are of particular interest, as amine-functionalized polypyridyl compounds have shown fascinating applications in drug discovery or catalysis. Fier *et al.* discussed the importance of 2-aminopyridines as pharmacophores and gave an excellent overview of their preparation using conventional methods such as the Chichibabin reaction.[2] More recently, Chen and Li demonstrated the application of 2-aminopyridines in the synthesis of various imidazo[1,2-*a*]pyridines as key intermediates in the synthesis of *e.g.* aldehyde dehydrogenase inhibitors.[3,4]

Although great progress has been made towards the direct C-H activation of N-heterocycles, the reported procedures are generally limited by a poor regioselectivity, a narrow functional group tolerance, and/or the use of harsh conditions and special equipment (*e.g.*, for reactions in liquid ammonia).[5] The challenges of selective functionalization mainly arise from the electron deficiency of N-heterocycles and their tendency to coordinate to metal ions. Conversely, pyridines and quinolines can be more easily functionalized *ortho* to the nitrogen atom of the heterocycle from their corresponding *N*-oxides, which have enhanced electrophilic character of the C2 carbon.[6] The conversion of pyridine *N*-oxides into their 2-amino-pyridyl analogues was already reported in the 1960's by Abramovitch.[7] As reported by Yin *et al*, these reactions typically utilize an N-O activator such as acetic anhydride (Ac_2O), tosyl anhydride (Ts_2O) or tosyl chloride (TsCl), to make the *ortho*-C2 more reactive towards an amine-based nucleophile (**Figure 2.1a**).[8]

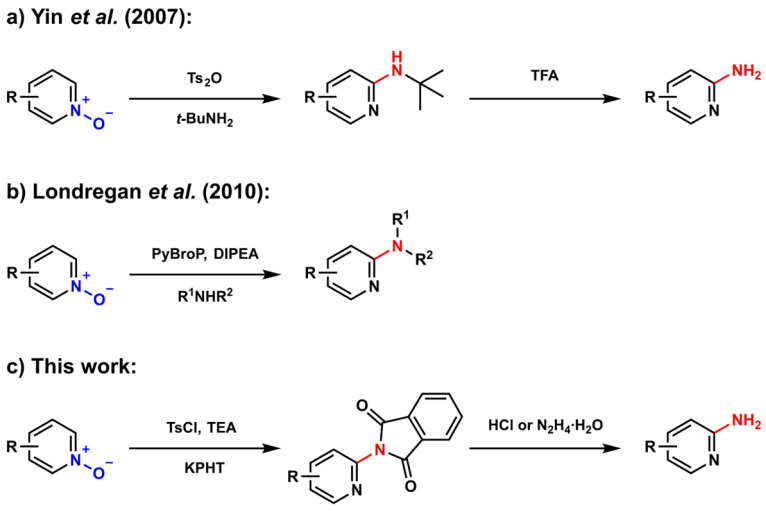


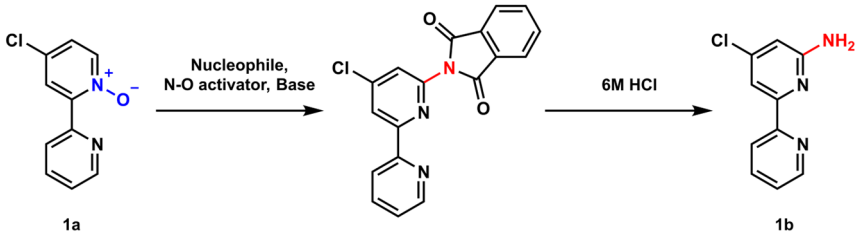
Figure 2.1. Current methods towards 2-aminopyridines.

However, competing side reactions between the two reagents are relatively common, which significantly lowers preparative yields, and complicates both the product isolation and the general applicability of this method notably at multigram scales.[8] One way to minimize the formation of side-products is to use phosphonium salts as activating agent, such as bromotris(1-pyrrolidinyl)phosphonium hexafluorophosphate (PyBroP), which are less reactive towards nucleophilic amines (**Figure 2.1b**).[9] Despite all efforts made to improve the selective amination of pyridines, these methods are still focused on single pyridines.[10,11] For example, the preparation of [2,2'-bipyridine]-6,6'-diamine, which is widely used in synthesis of polypyridine ligands, has only been reported using harsh reaction conditions and/or multistep synthesis routes.[12–14] To our knowledge, amination procedures of polypyridine *N*-oxides using mild conditions and without extensive isolation have not been reported yet (**Figure 2.1c**).

2.2. Results and Discussion

To investigate the synthesis of 4-chloro-2,2'-bipyridine-6-amine **1b** from the corresponding *N*-oxide **1a**, we screened a selection of previously reported reagents (**Figure 2.1**, **Table 2.1**).

Table 2.1. Screening of reaction conditions for the *ortho*-amination of **1a**.



1a 1b

Entry	Nucleophile, eq		N-O activator, eq		Base, eq		C, M	Solvent	Yield,[a] %
1	*t*-BuNH$_2$	6.0	Ts$_2$O	2.5	–	–	0.20	PhCF$_3$	23
2	*t*-BuNH$_2$	6.0	Ts$_2$O	2.5	–	–	0.20	PhCF$_3$	16
3	*t*-BuNH$_2$	1.3	PyBroP	3.0	DIPEA	3.75	0.25	DCM	26
4	*t*-BuNH$_2$	1.8	PyBroP	2.5	DIPEA	3.75	0.25	DCM	5
5	HMDS	4.0	TsCl	1.2	DIPEA	2.0	0.32	DCM	18
6	Saccharin	1.2	TsCl	1.2	DIPEA	2.0	0.32	DCM	40
7	PHT	1.2	TsCl	1.2	DIPEA	2.0	0.32	DCM	94
8	PHT	1.2	TsCl	1.2	DIPEA	2.0	0.32	DCM	82

[a] Yields are given for the isolated product **1b**.

The procedure described by Yin was chosen as a starting point, since it reported good yields for monoaminated products starting from 4-chloro-pyridine-1-oxide and 2,2'-bipyridine-1-oxide (between 71 and 81%) using Ts$_2$O and *tert*-butyl amine (*t*-BuNH$_2$).[8] Unfortunately, application of these conditions on **1a** resulted in a low yield (**Table 2.1**, entry 1), also when the reaction was performed at four times larger scale (entry 2). This is likely

related to a side reaction between Ts_2O and *t*-$BuNH_2$, as we observed significant amounts of the resulting *N*-(*t*-Bu)-tosylamide. The use of PyBroP as a milder activator resulted in less side products but not in increased yields (**Table 2.1**, entry 3-4). Therefore, we investigated the use of other amine sources as nucleophiles. While using bis(trimethylsilyl)amine (HMDS) (**Table 2.1**, entry 5) did not result in an increased yield, Gabriel-type reagents saccharin (**Table 2.1**, entry 6) and phthalimide (PHT) (**Table 2.1**, entry 7) provided a major breakthrough. Although saccharin and phthalimide are chemically relatively similar, the reaction yields dramatically increased from 40% with saccharin to 94% when phthalimide was used as nucleophile. Moreover, the latter reaction conditions allowed for significant upscaling in more than 80 times (**Table 2.1**, entry 8) without major reduction of the yield or formation of side products, illustrating the excellent potential of this methodology. After establishing a working procedure (Method A), we applied it to a variety of polyaryl *N*-oxides (**Figure 2.2**).

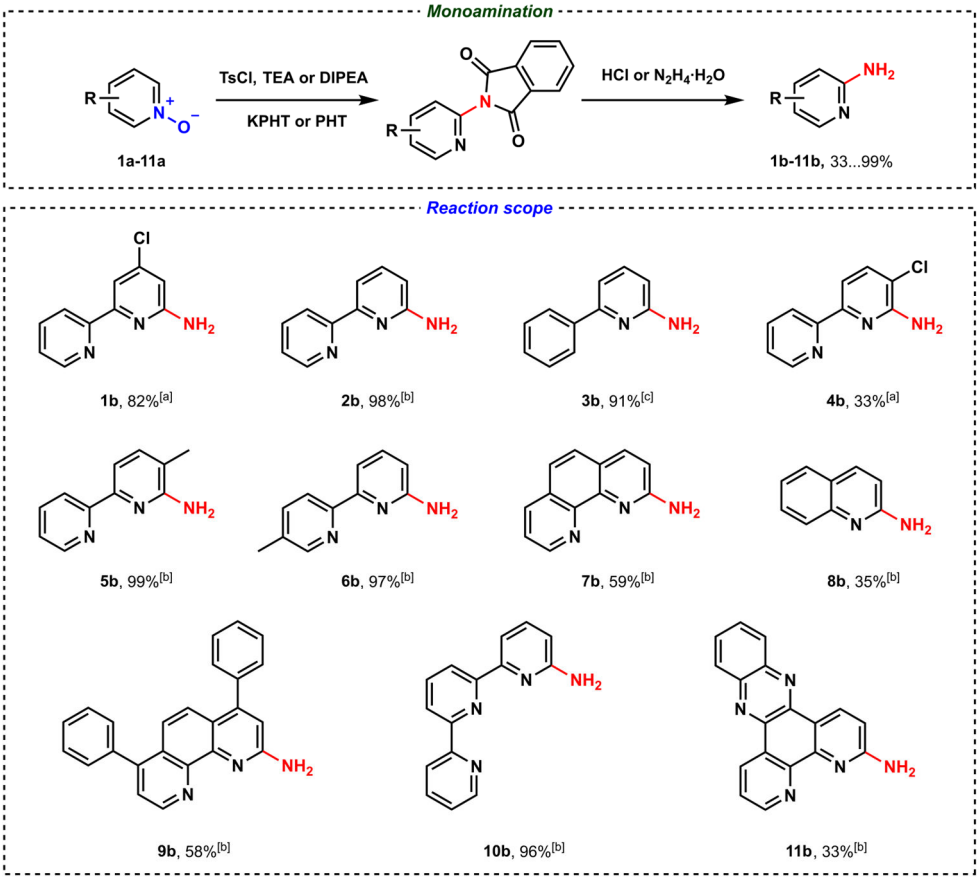
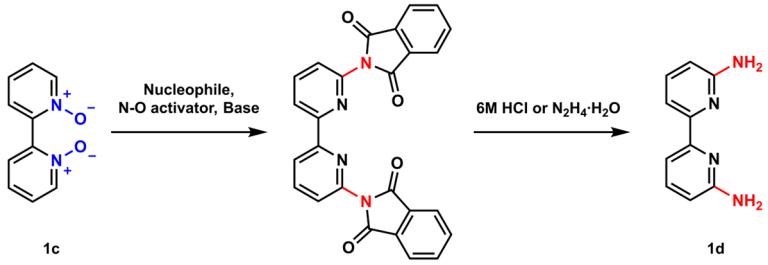


Figure 2.2. Scope of monoamination of polyaryl *N*-oxides. [**a**] PHT (1.2 eq), TsCl (1.2 eq) DIPEA (2.0 eq) in DCM (0.4 M) at r.t. for 24 h; hydrolysis with HCl (6.0 M) at 80 °C for 6 h (Method A). [**b**] KPHT (2.0 eq), TsCl (2.0 eq), TEA (2.0 eq) in DCM (0.2 M) at r.t. for 24 h; hydrolysis with hydrazine hydrate (5.0 eq) at 80 °C for 6 h (Method B). [**c**] KPHT (2.5 eq), TsCl (2.5 eq), TEA (2.5 eq) in ACN (0.05 M); hydrolysis with hydrazine hydrate (5.0 eq) at 80 °C for 24 h (Method C). Yields are given for the isolated product.

Interestingly, changing the position of the chloro-substituent from *para* to *meta* relative to the *N*-oxide (**1b** and **4b**), resulted in a lower yield of 33%. Since complete consumption of the corresponding starting *N*-oxide towards **4b** was observed, we hypothesize that the lower yield might be due to isolation challenges. To circumvent the need of acid neutralization after hydrolysis of the phthalimide intermediate, hydrazine hydrate was used instead of hydrochloric acid. Additionally, the use of potassium phthalimide (KPHT) omits the need for deprotonation of the nucleophile, reducing the amount of base needed in the reaction (Method B). This leads to an overall higher concentration of the reaction mixture and facilitates unambiguous product isolation. With these conditions we were able to obtain various aminated products in good to excellent yields, including derivatives of methyl-2,2'-bipyridine (**5b**, **6b**), phenanthroline (**7b**, **9b**, **11b**), terpyridine (**10b**) and quinoline (**8b**). Changing the solvent to acetonitrile to ensure solubilization of the reagents when more equivalents were used (Method C), enabled the synthesis of **2b** and **3b** in excellent yield, on a notably large scale for **2b** (>11 g). For this reaction, most polar aprotic solvents could be used as long as *i)* there was no reactivity towards the reagents (*e.g.*, DMF and DMSO did not work well), and *ii)* the solubility of the substrate and reagent were sufficient.

Table 2.2. Optimization of reaction conditions towards the synthesis of **1d**.



Entry	Nucleophile, eq		N-O activator, eq		Base, eq		C, M	Solvent	Yield,[a] %
1	PHT	2.5	TsCl	2.5	DIPEA	5.0	0.1	ACN	34
2	PHT	2.5	TsCl	2.5	DBU	5.0	0.1	ACN	0
3	PHT	2.5	TsCl	2.5	Pyridine	5.0	0.1	ACN	0
4	PHT	2.5	TsCl	2.5	DIPEA	5.0	0.1	PhCN	14
5	PHT	2.5	TsCl	2.5	DIPEA	5.0	0.1	Acetone	20
6	PHT	3.0	TsCl	3.0	DIPEA	6.0	0.1	ACN	38
7	PHT	3.0	TsCl	3.0	TEA	6.0	0.1	ACN	39
8	PHT	3.0	TsCl	3.0	K_2CO_3	6.0	0.1	ACN	44
9[b]	PHT	3.0	TsCl	3.0	DIPEA	6.0	0.1	ACN	35
10	PHT	5.0	TsCl	5.0	DIPEA	10.0	0.1	ACN	47
11	KPHT	5.0	TsCl	5.0	TEA	5.0	0.05	ACN	51
12[c]	KPHT	5.0	TsCl	5.0	K_2CO_3	2.5	0.05	ACN	75
13[c]	KPHT	5.0	TsCl	5.0	TEA	5.0	0.05	ACN	>99

[a] Yields of **1d** are quantified by ^{1}H qNMR using 1,3,5-trimethoxybenzene as internal standard.[15]
[b] The first reaction step was performed at 50 °C instead of r.t.
[c] Hydrazine hydrate was used for the hydrolysis instead of 6M HCl.

To further study the scope of this reaction, we decided to investigate the possibility of conducting two aminations in the same molecule. For this study 2,2′-bipyridine-1,1′-dioxide **1c** was chosen as a substrate, with the aim to synthesize the corresponding diamino product **1d** (**Table 2.2**, **Figure 2.3**). Since double amination of a substrate comes with new challenges, related to reactivity and solubility, an additional optimization study was performed.

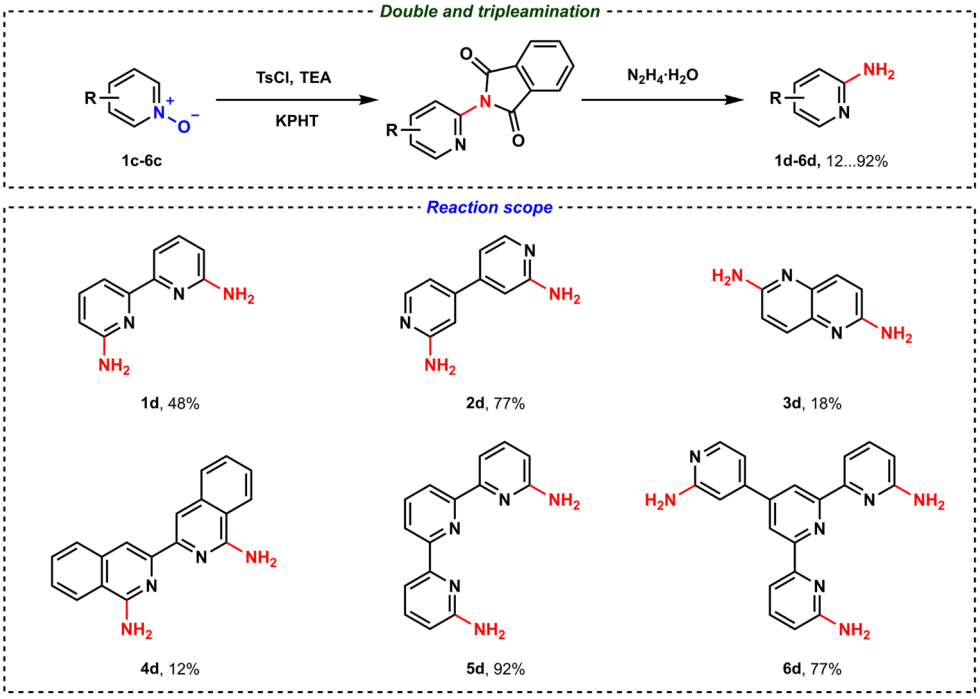


Figure 2.3. Scope of double and tripleamination of polypyridyl *N*-oxides with isolated yields. All reactions were performed at r.t. with KPHT (2.5 eq per N-O group), TsCl (2.5 eq per N-O group), TEA (2.5 eq per N-O group) in ACN (0.05 M); hydrolysis with hydrazine hydrate (2.5 eq per N-O group) at 80 °C for 24 h (Method C). Yields are given for the isolated product.

The main problem to be solved for the di-amination reactions is the poor solubility of di-*N*-oxides in the organic aprotic solvents that were used for the monoamination reactions. Polar solvents like DMF and DMSO were found to be unsuitable for this transformation, due to their reactivity towards TsCl.[16,17] Of the solvents investigated, acetonitrile seemed to be most suitable (entry 1, 4, 5). When other bases than TEA and DIPEA were used such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entry 2) or pyridine (entry 3), no product formation was observed. However, the use of K_2CO_3 (entry 8, 12) resulted in a decent yield. Performing the reaction under mild heating (50 °C) during the first step, did not lead to an increase in yield (entry 9). A moderate increase of product formation was observed when an excess of reagents was used (entry 1 *versus* 6 and 10), this however led us to use a higher dilution to avoid stirring disruption. Subsequently, changing nucleophile from PHT to KPHT and hydrolysis agent from HCl to hydrazine hydrate (entry 10-13) increased the yield to

quantitative. As we observed poor solubility of phthalimide intermediate in both organic solvents and water, it could be simply isolated before hydrolysis by filtration. Additionally, lowering the amount of hydrolysis reagent we managed to generate conditions in which the target product precipitated from the final reaction mixture, enabling its isolation and purification by simple filtration.

Altogether, the optimized procedure is very simple to perform and was applied on a series of polypyridyl substrates (**Figure 2.3**). While it was optimized towards **1d**, this methodology also allowed for the preparation of its *para* isomer **2d** with a good yield. Additionally, this procedure also allowed for the synthesis of biisoquinoline **4d** and naphthyridine **3d** albeit with a lower yield. Strikingly, the reaction conditions allow for the synthesis towards terpyridine derivative **5d** with an excellent yield at a 20 mmol scale. This is particularly interesting since the synthesis of this compound has only been reported using liquid ammonia under high pressure.[18] As demonstrated by the preparation of compound **6d**, the procedure allows for multiple amination reactions within a substrate.

The mechanism of the reaction is assumed to be similar to that discussed in previous reports (**Figure 2.4**).[8] In short, a nucleophilic attack of starting *N*-oxide towards TsCl results in the formation of pyridinium tosylate. The *N*-tosylate withdraws electron density from the pyridine and allows for a nucleophilic substitution by a phthalate anion on the C2 position of the pyridyl ring while between the activator and the nucleophile. This advantage is due to the use of TsCl as activator and KPHT as nucleophile, which releases tosylic acid. The formed phthalate intermediate is then hydrolyzed to produce the target amine product. The phthalate intermediate towards product **2b** has been isolated and characterized (see **Appendix II**). The main difference of our conditions compared to previous work is the prevention of a side-reaction taking place, as side product can only form at elevated temperatures.[19]

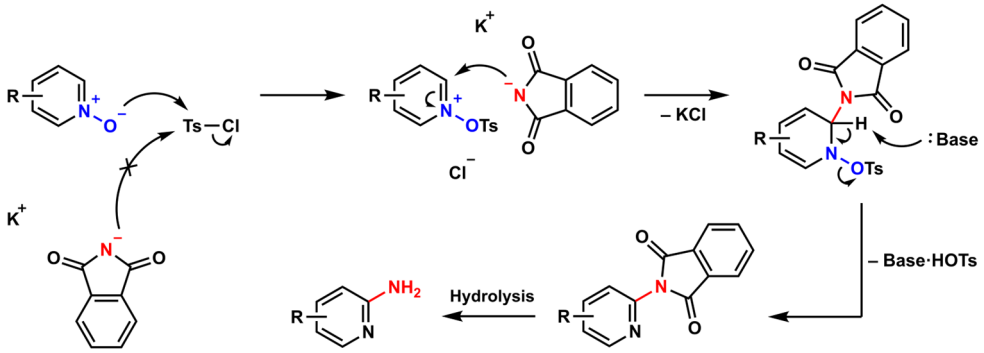


Figure 2.4. Proposed reaction mechanism.

2.3. Conclusions

In summary, we have developed an efficient and facile procedure for mono- and di-amination of (poly)pyridine *N*-oxides in an operationally simple manner with high selectivity and good to excellent yields. While the substrate examples reported here are primarily focused on the preparation of polyaminopyridyl building blocks for ligands to be used in coordination complexes, the scope might be extended to pharmaceutical compounds.

Especially the possibility to prepare diaminopolypyridyl compounds with ease in a two-step procedure makes this a useful methodology. Further exploration of the substrate scope is currently ongoing.

2.4. References

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