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A Mild Method for the Formation and in Situ Reaction of Imidoyl Chlorides: Conversion of Pyridine-1-oxides to 2-Aminopyridine Amides

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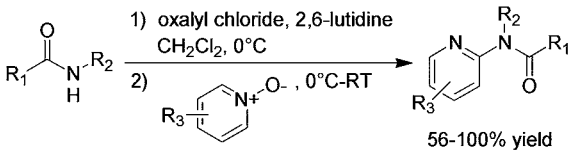
ABSTRACT



A mild, practical, one-pot method for the generation of imidoyl chlorides and their subsequent in situ reaction with pyridine-1-oxides is described. The imidoyl chlorides were formed from the reaction of secondary amides with a stoichiometric amount of oxalyl chloride and 2,6-lutidine in CH_2Cl_2 at 0 °C. Upon warming of the reaction mixture to room temperature in the presence of pyridine-1-oxides, a rapid conversion to 2-aminopyridine amides was observed in moderate to excellent isolated yields.

Substituted 2-aminopyridines are commonly occurring structural motifs found in many pharmaceuticals. One of the more efficient approaches to making such substituted 2-aminopyridines would be their direct formation from readily available pyridine-1-oxides. The literature contains only a few isolated examples of this transformation. Among these is a series of papers by Abramovitch and co-workers that describes a displacement and rearrangement reaction of pyridine-1-oxides with isolated imidoyl chlorides at elevated temperatures to provide 2-aminopyridine amides.[1] Our goal was to couple this basic transformation with a mild method for generating activated amides to provide a mild and practical method for the formation of 2-aminopyridine amides. Herein we report a new mild formation of imidoyl chlorides using a stoichiometric amount of oxalyl chloride and the in situ reaction of the generated imidoyl chlorides with pyridine-1-oxides at low temperatures to provide 2-aminopyridine amides in good yields.

Historically, the dehydration of secondary amides to give imidoyl chlorides has been accomplished by heating them with reagents such as $SOCl_2$, PCl_5, or $POCl_3$ in excess or by treating them with Ph_3P/CCl_4 at room temperature.[2] A downfall in using most of these methods is that the excess dehydrating agent and reagent-derived byproducts must be removed. The isolation of pure imidoyl chlorides often involves a fractional distillation or a precipitation method under anhydrous conditions. Due to the inconvenience of these procedures and their lack of generality, our hope was to develop a method to generate imidoyl chlorides from a variety of amides and use them in situ in subsequent transformations.

We have found that secondary amides can be converted to imidoyl chlorides by using 1 equiv of oxalyl chloride in the presence of an excess of 2,6-lutidine at 0 °C.[3] These products can be converted in situ with pyridine-1-oxides to afford 2-aminopyridine amides. In contrast to the reactions reported by Abramovitch, which require the generation and isolation of imidoyl chlorides followed by reaction with

(1) Abramovitch, R. A.; Singer, G. M. *J. Am. Chem. Soc.* **1969**, *91*, 5672. Abramovitch, R. A.; Singer, G. M. *J. Org. Chem.* **1974**, *39*, 1795. Abramovitch, R. A.; Rogers, R. B. *J. Org. Chem.* **1974**, *39*, 1802. Abramovitch, R. A.; Pilski, J.; Konitz, A.; Tomasik, P. *J. Org. Chem.* **1983**, *48*, 4391.

(2) Kantlehner, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991, Vol. 6, p 485.

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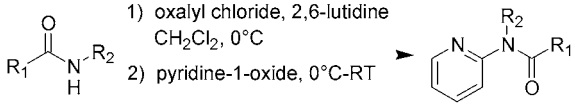
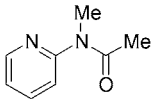
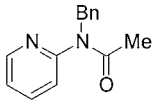
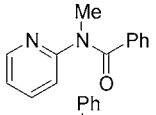
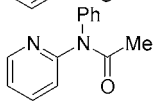
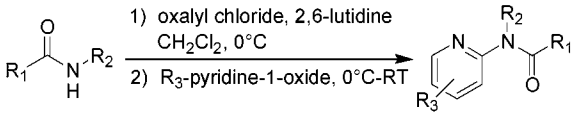
Table 1. Amide Substitution Effects

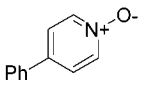
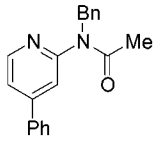
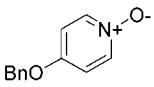
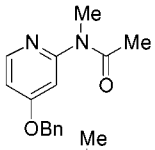
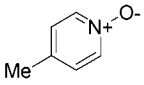
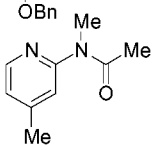
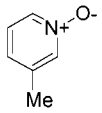
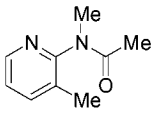
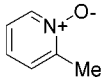
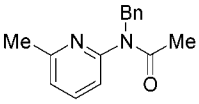
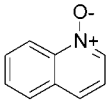
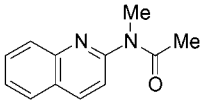
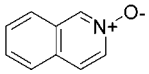
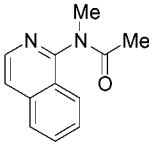


entry	R_1	R_2	product	yield (%)[a]
1	Me	Me		73
2	Me	Bn		79
3	Ph	Me		100
4[b]	Me	Ph		56

[a] Isolated yields of compounds, which were characterized by ^{1}H and ^{13}C NMR and HRMS. [b] Phosgene was used in place of oxalyl chloride.

Table 2. *N*-Oxide Substituent Effects



entry	N-oxide	amide[a]	product	yield (%)[b]
1		2		85
2		1		66
3		1		61
4		1	 + isomer	64[c]
5		2		73
6		1		73
7		1		90

[a] *N*-Methyl acetamide (**1**) or *N*-benzyl acetamide (**2**). [b] Isolated yields of compounds, which were characterized by ^{1}H and ^{13}C NMR and HRMS. [c] Combined yield, 3:2 mixture with 5-methyl isomer.

pyridine-1-oxides at elevated temperatures, we have found that the reactions of our in situ-generated imidoyl chlorides proceed quickly and cleanly between 0 °C and ambient temperature. We have also found that these mild conditions do not produce the byproducts observed in the previous cases, which proceeded at elevated temperatures.

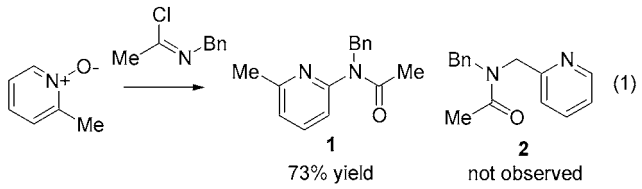
A typical experiment involved treatment of a solution of *N*-acetylbenzylamine in CH_2Cl_2 (0.2 M) with an excess of 2,6-lutidine and an equimolar amount of oxalyl chloride dropwise at 0 °C resulting in the evolution of gas. After the mixture was stirred for 15 min, pyridine-1-oxide was added all at once and the mixture was warmed to room temperature. In these experiments we typically have used 1.5 equiv of the imidoyl chloride relative to pyridine-1-oxide due to the hygroscopic nature of most pyridine-1-oxides. After aqueous workup and purification, *N*-benzyl-*N*-pyridin-2-ylacetamide was isolated in 79% yield on the basis of pyridine-1-oxide (Table 1, entry 1). With this result in hand, we chose to further examine the scope and limitations of this mild one-pot transformation.

Table 1 describes the reactivity of several different amides. All were uneventful except the reaction of acetanilide (entry 4), where it was observed that our standard conditions failed to give any of the desired 2-aminopyridine amide. Upon the addition of oxalyl chloride, very little gas evolution was observed compared to that encountered with the other examples. Quenching experiments also indicated that the desired imidoyl chloride had not formed. The use of phosgene (as a solution in toluene) in place of oxalyl chloride in this case was found to provide the imidoyl chloride, which readily reacted with pyridine-1-oxide to afford the desired 2-aminopyridine amide (Table 1, entry 4).[3] It was also observed that this particular substrate formed the imidoyl chloride relatively slowly even at room temperature.

Table 2 describes the reactivity of a number of different *N*-oxides. Either *N*-methyl acetamide or *N*-benzyl acetamide was used in the reaction of each *N*-oxide. Entries 3 and 5 (and eq 1) demonstrate the regioselectivity of this mild transformation. In these cases, only rearrangement to the aromatic ring was observed. Equation 1 shows the two possible reaction products of entry 5 in Table 2. Only product **1** is observed in the reaction. Product **2**, the product of functionalization of the methyl substituent, was not detected. This is in contrast to the results previously reported by Abramovitch.[4] In those experiments, 2- and 4-methylpyridine-1-oxide reacted with *N*-phenylbenzenecarboximidoyl chloride at elevated temperatures to give a mixture of products. Among these products were the rearrangement to both the aromatic ring and the methyl group. Abramovitch

(3) A procedure employing 1.5 equiv of phosgene in the presence of pyridine has previously been described: Fujimoto, K.; Watanabe, T.; Abe, J.; Okawa, K. *Chem. Ind.* **1971**, 175.

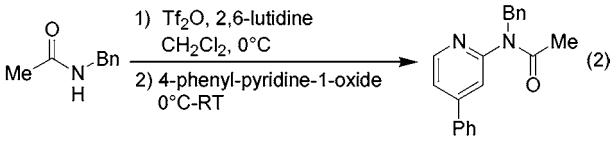
also reported that the addition of a strong base, such as Et_3N or DBU, resulted in a change in the distribution of products to favor rearrangement to the methyl group.



The use of 3-methylpyridine-1-oxide (Table 2, entry 4) resulted in a 3:2 mixture of *N*-methyl-*N*-(3-methylpyridin-2-yl)acetamide and *N*-methyl-*N*-(5-methylpyridin-2-yl)acetamide in 64% combined yield. This result is in agreement with the regioselectivity observed by Abramovitch. Quinolines and isoquinolines have also been shown to participate in this transformation, giving high yields of the single isomers shown (Table 2, entries 6 and 7).[5]

While the use of other carbonyl-containing functionalities that would provide a more readily removable protecting group would be desirable, to date, this has not been accomplished. Substitution of the alkyl or aryl amide with trifluoroacetyl, trichloroacetyl, or carbamates failed to produce significant quantities of iminochlorides or 2-aminopyridine amides (data not shown).

During our search for suitable replacements for phosgene, we also discovered that Tf_2O could be used as an activating agent.[6] In the absence of base or in the presence of Et_3N or Hunig's base, imidotriflate formation was not observed. It was found that pyridine could be used as a suitable base in this reaction at low temperatures (between −45 and −78 °C); however, hindered pyridine derivatives, such as 2,6-lutidine, seem to work best. An unoptimized experiment involved treatment of a solution of *N*-acetylbenzylamine (1.1 equiv) in CH_2Cl_2 (0.2 M) with 2.2 equiv of 2,6-lutidine and 1.1 equiv of Tf_2O dropwise at 0 °C. After the mixture was stirred for 30 min, 1.0 equiv of 4-phenyl-pyridine-1-oxide was added all at once and the mixture was warmed to room temperature. After aqueous workup and purification, *N*-benzyl-*N*-(4-phenylpyridin-2-yl)acetamide was isolated in 46% yield (Equation 2).



In summary, we have described a significant operational improvement in the generation of imidoyl chlorides from secondary amides and their in situ reaction with pyridine-1-oxides to give 2-aminopyridine amides. The reaction conditions have not been completely optimized in terms of reagent equivalents partially due to the hydroscopic nature of pyridine-1-oxides.

Acknowledgment. The authors thank Professor David A. Evans (Harvard University) for helpful advice.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Abramovitch, R. A.; Bailey, T. D. *J. Heterocycl. Chem.* **1975**, *12*, 1079. Abramovitch, R. A.; Abramovitch, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, *21*, 956.

(5) Abramovitch, R. A.; Rogers, R. B. *Tetrahedron Lett.* **1971**, *22*, 1951. Abramovitch, R. A.; Rogers, R. B.; Singer, G. M. *J. Org. Chem.* **1975**, *40*, 41.

(6) For the formation of imino triflates and addition of nucleophiles, see: Thomas, E. W. *Synthesis* **1993**, 767. Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908. Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677. Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.