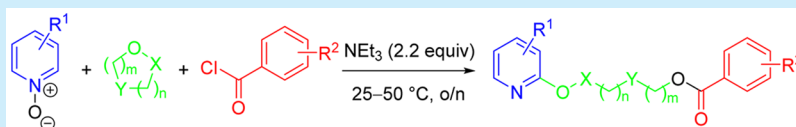


Regioselective Three-Component Reaction of Pyridine *N*-Oxides, Acyl Chlorides, and Cyclic EthersD. Heulyn Jones, Steven T. Kay, Jayde A. McLellan, Alan R. Kennedy,^{ID} and Nicholas C. O. Tomkinson^{*ID}

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S Supporting Information



ABSTRACT: A novel three-component reaction of pyridine *N*-oxides, acyl chlorides, and cyclic ethers is described. Treatment of an electron-deficient pyridine *N*-oxide with an acyl chloride in the presence of a cyclic ether at 25–50 °C leads to a substituted pyridine as a single regioisomer in up to 58% isolated yield. Isotopic-labeling experiments and substrate scope support the reaction proceeding through a carbene intermediate.

The pyridine ring is a fundamental heterocycle¹ that is present in over 100 marketed drugs including the block busters esomeprazole and etoricoxib (Figure 1). The prevalence

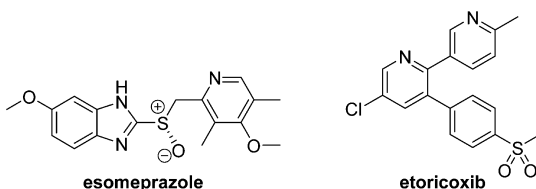
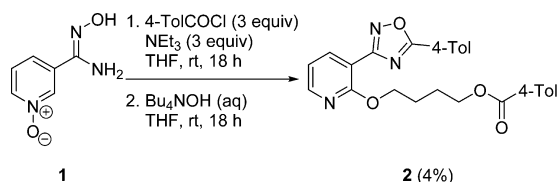


Figure 1. Drug molecules containing a pyridine group.

of the pyridine core in both pharmaceuticals and agrochemicals² means that new methods for the synthesis and functionalization of this privileged structure are of great interest and represents an exciting area of contemporary research.³

During the course of our investigations to realize new chemical probes for discovery research,⁴ a curious product was isolated from an acylation/heterocyclization sequence (Scheme 1).

Scheme 1. Unusual Three-Component Reaction of Pyridine *N*-Oxide, Acyl Chloride, and THF

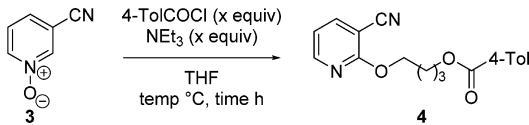
Treatment of the pyridine *N*-oxide derivative 1 with 3 equiv of both 4-toluoyl chloride and triethylamine at room temperature overnight followed by stirring the crude reaction mixture with tetra-*n*-butyl ammonium hydroxide in THF gave the unexpected product 2 in 4% isolated yield. It appeared that two separate

transformations were occurring within this process: first, the expected heterocyclization procedure resulting in an oxadiazole heterocycle,⁵ and second, and more interestingly, a reaction between a pyridine *N*-oxide, an acyl chloride, and a molecule of THF. This represented a novel multicomponent reaction (MCR) and presented an intriguing method for the functionalization of a pyridine ring.

MCRs are important processes in which three or more starting materials react to form a single product.⁶ These reactions are of particular relevance to discovery research by enabling diverse structures to be generated rapidly through a single process.⁷ MCRs that generate pyridine and its saturated derivatives are established and include the Hantzsch dihydropyridine synthesis⁸ and the Bagley–Bohlmann–Rahtz pyridine synthesis⁹ along with more recent transition-metal-catalyzed processes.¹⁰ MCRs that functionalize a pre-existing pyridine ring are less developed yet represent an intriguing alternative strategy by which to prepare diverse structures of this important heterocycle. Curious about the overall process highlighted in Scheme 1 and the potential to develop a novel MCR, we set about investigating the procedure further. Within this paper, we describe the optimization of the reaction, explore the scope and limitations of each component, and present a series of experiments to aid understanding of the reaction mechanism.

As a starting point to understanding the reaction, we performed the transformation on the commercially available 3-cyanopyridine *N*-oxide 3 (Table 1). Confirmation that the coupling procedure was independent of the *N*-hydroxyimide functionality present in substrate 1 or the Bu₄NOH came from treatment of 3 with 4-toluoyl chloride (2.2 equiv) and NEt₃ (2.2 equiv), which led to the three-component product 4 in 35% conversion by ¹H NMR spectroscopic analysis (entry 1). Performing the

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Table 1. Reaction Optimization^a


entry	4-TolCOCl (equiv)	NEt ₃ (equiv)	temp (°C)	time (h)	conv ^b (%)
1	2.2	2.2	25	18	35
2	2.2	2.2	−78 to +25	8	33
3	2.2	2.2	50	18	33 (25) ^c
4	2.2	3.0	50	18	34
5	2.2	1.0	50	18	0
6	1.0	2.2	50	18	29
7 ^d	2.2	2.2	50	18	31
8 ^e	2.2	2.2	50	18	32

^aReactions carried out at 0.2 M concentration unless otherwise stated. ^bDetermined by ¹H NMR analysis. ^cIsolated yield. ^dReaction carried out at 0.1 M concentration. ^eReaction performed in the presence of 4 Å molecular sieves.

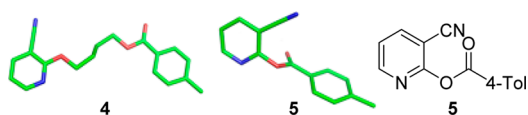
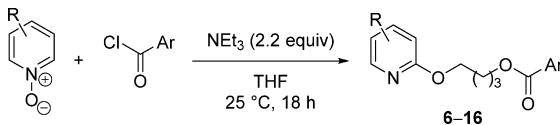


Figure 2. Single-crystal X-ray structure of 4 and the coproduct 5.

mixing of reagents at low temperature followed by warming (entry 2) or carrying out the reaction at 50 °C (entry 3) made no difference to the overall outcome. Reducing the amount of NEt₃ to 1 equiv caused the reaction to shut down (entry 5), suggesting the base had an important role beyond the acylation process whereas reducing the amount of acyl chloride had little impact (entry 6). Reduction of reaction concentration (entry 7) or performing the reaction under strictly anhydrous conditions and in the presence of molecular sieves also made no impact on the transformation (entry 8). Overall, the reaction appeared to be robust and could deliver the three-component reaction product 4 in a reliable manner.

Confirmation of the structure of the product 4 came through single-crystal X-ray analysis (Figure 2). This clearly showed substitution of the pyridine ring at the 2-position and confirmed the regioselectivity of the procedure alongside the introduction of a four-carbon unit from the THF group linking the pyridine to the 4-toluoyl benzoate. In addition to the three-component product observed within the process, the ester 5 was also isolated from the optimized reaction (2.2 equiv of 4-TolCOCl, 2.2 equiv of NEt₃, THF, 50 °C, 18 h) and whose structure was also confirmed through X-ray analysis. Selectivity for substitution at the 2-position suggested that 4 and 5 could arise through a common intermediate and prompted further investigation of the reaction mechanism.

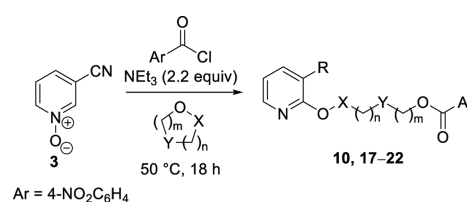
Having established optimal conditions for the reaction of 3-cyanopyridine *N*-oxide, 4-toluoyl chloride, and THF, we went on to examine alternative acyl chloride and pyridine *N*-oxide substrates (Table 2). The presence of electron-withdrawing groups on the acyl chloride greatly enhanced the efficiency of the process (entries 1–6). For example, reaction of 4-methoxybenzoyl chloride with 3-cyanopyridine *N*-oxide gave the three-component product 6 in 17% yield (entry 1), whereas the use of 4-nitrobenzoyl chloride delivered the product 10 in a much improved 48% isolated yield (entry 6). On the basis of these observations, 4-nitrobenzoyl chloride was used in subsequent

Table 2. Scope of Acyl Chloride and Pyridine *N*-Oxide^a


entry	Ar	R	product	yield ^b (%)
1	4-OMeC ₆ H ₄	3-CN	6	17
2	4-MeC ₆ H ₄	3-CN	4	25
3	C ₆ H ₅	3-CN	7	33
4	C ₆ F ₅	3-CN	8	34
5	4-CF ₃ C ₆ H ₄	3-CN	9	40
6	4-NO ₂ C ₆ H ₄	3-CN	10	48
7	4-NO ₂ C ₆ H ₄	4-CN	11	40
8	4-NO ₂ C ₆ H ₄	2-CN	12	22
9	4-NO ₂ C ₆ H ₄	3-Cl	13	46
10	4-NO ₂ C ₆ H ₄	4-Cl	14	38
11	4-NO ₂ C ₆ H ₄	3-NO ₂	15	33
12	4-NO ₂ C ₆ H ₄	H	16	0

^aReactions carried out at 0.2 M concentration with 2.2 equiv of aryl chloride. ^bIsolated yield.

Table 3. Scope of Cyclic Ether



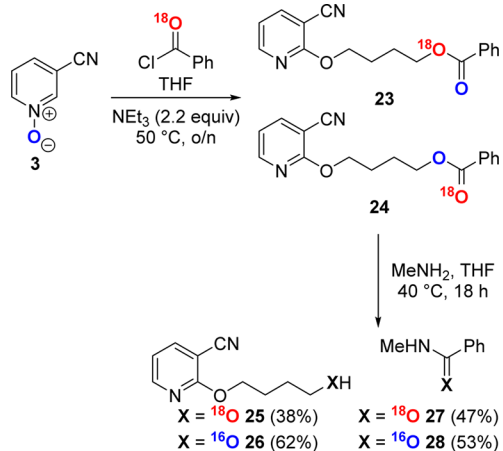
entry	X	Y	n	m	compound	yield (%)
1	CH(CH ₂) ₄ CH		0	0	17	— ^a
2	CH ₂	CH ₂	1	0	18	— ^a
3	CH ₂	CH ₂	1	1	10	48
4	CH ₂	CH ₂	2	1	19	31
5	CH ₂	CH ₂	2	2	20	38
6	CHMe	CH ₂	1	1	21	36 ^b
7	CH ₂	O	1	2	22	58

^aComplex mixture of products observed by ¹H NMR spectroscopy. ^bProduct isolated as an inseparable 1:1 mixture of regioisomers.

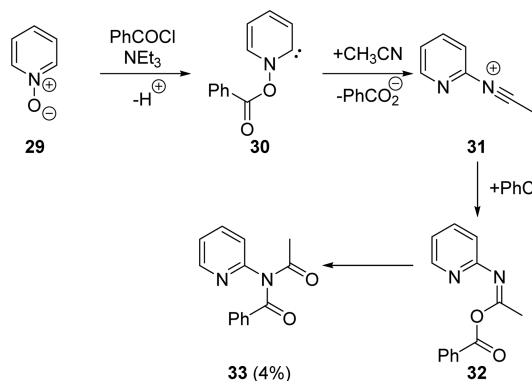
transformations (entries 7–12). The reaction proceeded effectively with 3- (entry 6; 48%) and 4-substituted (entry 7; 40%) pyridine *N*-oxide substrates. Although less efficient, 2-substituted substrates also delivered the expected three-component product (entry 8; 22%). Alternative electron-withdrawing groups were also tolerated on the pyridine *N*-oxide ring including chloro (entries 9 and 10) and nitro substituents (entry 11; 33%). An electron-withdrawing group on the pyridine *N*-oxide substrate was essential to bring about the transformation with the unsubstituted pyridine *N*-oxide failing to deliver the three-component product 16 (entry 12; 0%).

We then went on to examine the reactivity of alternative cyclic ethers (Table 3). The reaction of cyclohexene oxide (entry 1) and oxetane (entry 2) under the optimized conditions led to a complex mixture of products with no clear indication of the three-component product in the ¹H NMR spectrum of the crude reaction mixture. This suggests the process is not viable for highly strained cyclic ethers. Increasing the ether ring size led to significantly greater success for the transformation (entries 3–7).

Scheme 2. Isotopic-Labeling Experiments



Scheme 3. Reaction of Pyridine N-Oxide and Benzoyl Chloride in Acetonitrile



Reaction of 5- (entry 3; 48%), 6- (entry 4; 31%), and 7-membered cyclic ethers (entry 5; 38%) led to the expected pyridine derivatives **10**, **19**, and **20**. Substituted ethers were also tolerated within the reaction (entries 6 and 7). Reaction of 2-methyl THF gave the substituted pyridine **21** in 36% isolated yield as an inseparable 1:1 mixture of isomers, showing no regioselectivity in the opening of the THF ring. 1,4-Dioxane proved to be an outstanding substrate leading to the three-component reaction product **22** in an excellent 58% isolated yield.

Isotopically labeled benzoyl chloride was prepared from α,α,α -trichlorotoluene and ^{18}O -labeled water via a two-step literature

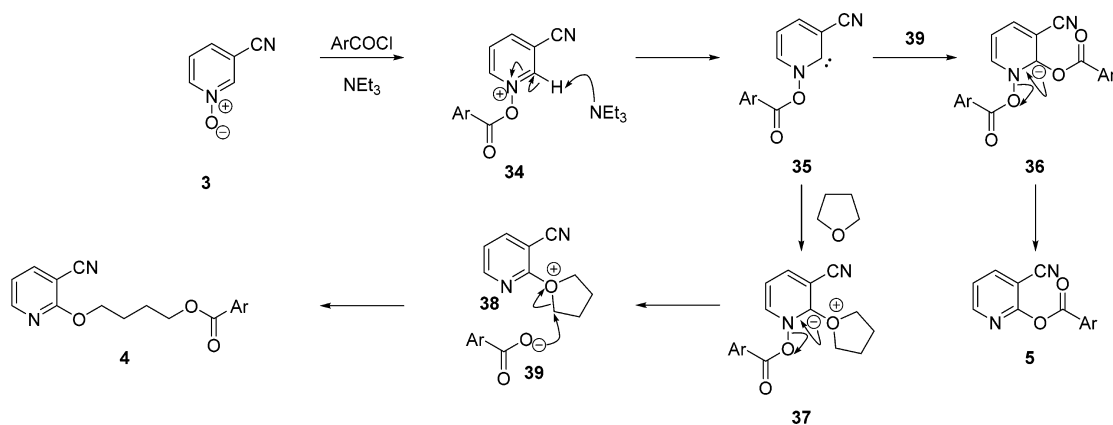
procedure.¹¹ Reaction of this acid chloride with 3-cyanopyridine N-oxide **3** in the presence of THF led to the products **23** and **24** which showed an 88% incorporation of the ^{18}O label by mass spectrometry. Treatment of the mixture of **23** and **24** with methylamine showed 47% incorporation of the ^{18}O label in the N-methylbenzamide product **27** and a 38% ^{18}O incorporation in the pyridyl product **25**, indicating scrambling of the isotopic label (Scheme 2).

Hamana has shown that reaction of pyridine N-oxide **29** with benzoyl chloride in acetonitrile under basic conditions leads to the acetamide **33** in 4% isolated yield (Scheme 3).¹² It was proposed that this reaction proceeded through O-acylation followed by deprotonation to give the carbene **30**. Addition of acetonitrile followed by elimination of benzoate led to **31** which on readdition of benzoate and $\text{O} \rightarrow \text{N}$ acyl migration gave the product **33**. Within this report it was also disclosed that solvent participation was not apparent when the reaction was carried out in THF. This is consistent with our results in Table 2 where the pyridine N-oxide substrate needs to be electron deficient in order for the transformation to occur successfully.¹³

Based upon the labeling studies (Scheme 2), together with the report of Hamana,¹² a potential mechanism for the transformation is outlined in Scheme 4. O-Acylation of pyridine N-oxide **3** under the basic reaction conditions leads to the intermediate **34**. Subsequent deprotonation of **34** with triethylamine provides the carbene **35**. Direct reaction of **35** with benzoate **39** followed by restoration of aromaticity gives the ester **5**. Reaction of the carbene **35** with THF followed by elimination of benzoate would lead to the oxonium ion **38**. Finally, ring opening of this oxonium ion with benzoate **39** leads to the observed reaction product **4**. The results from the isotopic-labeling experiments are consistent with this mechanistic proposal and suggest the loss of benzoate **39** and its subsequent readdition occurs in a stepwise rather than a concerted manner.

The complete regioselectivity observed represents a powerful aspect of the transformation. To probe this further, we examined two nonsymmetrical 3,5-disubstituted pyridine N-oxide substrates **40** and **41** (Scheme 5). Reaction of 3-cyano-5-methylpyridine N-oxide **40** under the standard reaction conditions gave the 2-substituted pyridine product **42** exclusively in an excellent

Scheme 4. Potential Mechanism for the Formation of Three-Component Product 4



Scheme 5. Selectivity Using Nonsymmetrical Substrates

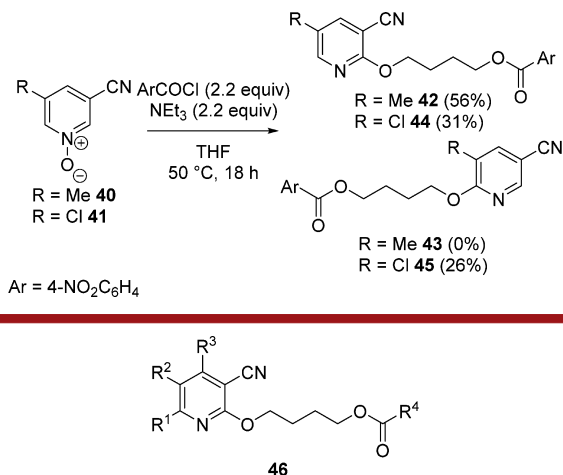


Figure 3. Core pyridine structure which has shown antibacterial and antifungal activity.

56% isolated yield with none of the alternative regioisomer **43** being detected in the crude reaction mixture. This is consistent with the electron-withdrawing nitrile group directing the deprotonation step of the mechanism. Reaction of 3-chloro-5-cyanopyridine *N*-oxide gave the two possible products **44** and **45** as a 1.2:1 mixture of regioisomers. Therefore, with 3,5-disubstituted substrates the relative electron-withdrawing nature of the substituents must be accounted for when considering the regiochemical outcome of the transformation.

In summary, we have described a novel three-component reaction of pyridine *N*-oxides, acyl chlorides, and cyclic ethers, which leads regioselectively to the disubstituted pyridine product. The architecture generated through this three-component procedure has been prepared previously through a multistep reaction sequence providing structures **46** that showed promising antibacterial and antifungal activity (Figure 3).¹⁴ The inherent ability to introduce this functionality directly from readily accessible building blocks suggests this transformation could find application in discovery research. We are currently investigating the reactivity of alternative heterocycles to extend this process further and will report on our findings in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01481.

Analytical data, experimental procedures, and NMR spectra for all compounds (PDF)

X-ray data for compounds **4** and **5** (CIF)

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Notes

The authors declare no competing financial interest.

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