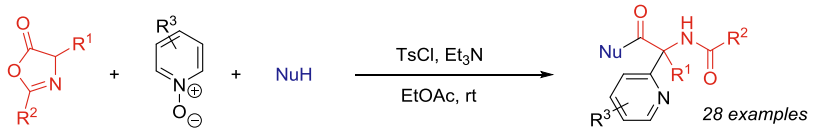
Article:
Johnson, TC and Marsden, SP (2016) Precious-Metal-Free Heteroarylation of Azlactones: Direct Synthesis of α-Pyridyl, α-Substituted Amino Acid Derivatives. Organic Letters, 18 (20). pp. 5364-5367. ISSN 1523-7060

https://doi.org/10.1021/acs.orglett.6b02731

Precious-Metal-Free Heteroarylation of Azlactones: Direct Synthesis of α-Pyridyl,α-Substituted Amino Acid Derivatives

Tarn C. Johnson and Stephen P. Marsden*

School of Chemistry and Institute of Process Research and Development, University of Leeds, Leeds, LS2 9JT, UK

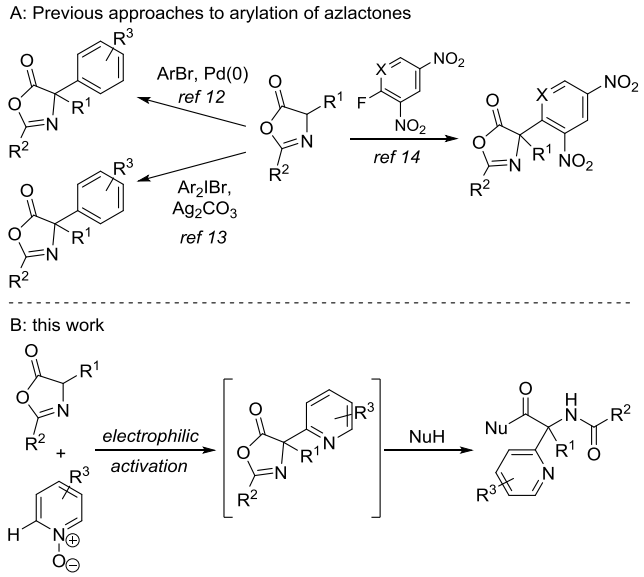


A one-pot, three-component synthesis of α-pyridyl,α-substituted amino acid derivatives is described. The key transformation is a direct, precious-metal-free heteroarylation of readily available, amino acid-derived azlactones with electrophilically-activated pyridine N-oxides. The resulting intermediates can be used directly as efficient acylating agents for a range of nucleophiles, leading to the heteroarylated amino acid derivatives in a single vessel.

α,α-Disubstituted amino acids are found in many biologically active compounds, both naturally occurring and man-made.[1] The incorporation of such motifs into peptides and peptidomimetics confers conformational preferences (frequently inducing β-turns) as well as hydrolytic stability on the resulting peptides.[2] Amongst these structures, α-pyridyl,α-substituted amino acid derivatives have attracted interest as potent and selective inhibitors of proteases such as cathepsin[3] and β-secretase,[4] the latter as potential treatments for Alzheimer's disease. Additionally, the hydrogen-bond accepting capability of the pyridine nitrogen atom promotes well-defined conformational behaviour upon short peptides containing α-2-pyridyl,α-substituted amino acids.[5]

Building on our interest in quaternary amino acids,[6] we wished to develop a direct, convergent approach to α-pyridyl,α-substituted amino acids based upon heteroarylation of readily available α-amino acids. The intermolecular arylation of amino acid enolates or their equivalents is non-trivial. There are only isolated reports of the arylation of non-stabilised amino acid enolates by S_NAr reactions[7] or oxidative coupling to nitroarenes.[8] The arylation of stabilized enolates derived from amino acid aldimines is limited to S_NAr substitution of fluoronitroarenes[9] and (fluoroarene)chromium(0) carbonyl complexes,[10] or to direct coupling with arylbismuth reagents.[11] By contrast, the use of azlactones as relatively acidic amino acid enolate equivalents has been exploited in a broader range of arylation reactions (Scheme 1, panel A), including palladium-catalysed cross-coupling to aryl halides,[12] direct condensation with diaryliodonium salts[13] and S_NAr reactions with nitrohaloarenes,[14] as well as direct Michael addition/aromatization reactions with quinones.[15] Amongst all of these examples, there are only isolated reports of the synthesis of α-pyridyl,α-substituted amino acids.[8c,12b,14]

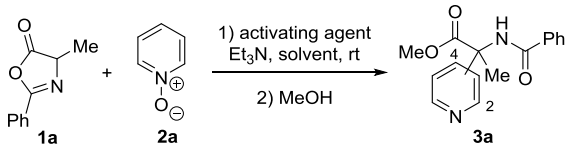
Scheme 1. Arylation of azlactones



Londregan and colleagues at Pfizer have recently demonstrated the in situ activation/substitution of pyridine N-oxides using PyBroP with a range of nucleophiles,[16-18] including carbon-based nucleophiles such as β-dicarbonyls (malonates, ketoesters, diketones and cyanoacetate)[17] and silyl ketene acetals.[18] Given the similar pKa of azlactones (ca. 9-10)[19] and the carbon acids (and other nucleophiles such as phenols) examined by Londregan, we anticipated that they might act as competent nucleophiles for the activated pyridine N-oxide, facilitating the direct, precious-metal-free synthesis of α-pyridyl,α-substituted amino acid derivatives (Scheme 1, Panel B).[20] Moreover, the azlactones can be regarded as activated acylating agents, nucleophilic ring opening of which would lead directly to diverse α-pyridyl,α-substituted amino acid derivatives. This strategy is particularly significant and advantageous given the documented issues with facile decarboxylation of α-pyridyl amino acids,[21] compounding the known poor electrophilicity of activated α,α-disubstituted amino acids. We report herein the successful demonstration of this strategy, exemplified in the one-pot, three-component synthesis of a wide range of α-pyridyl quaternary amino acid derivatives.[22]

We commenced our study with a screen of electrophilic activating agents for the direct coupling of 4-methyl-2-phenyloxazolin-5-one **1a** with pyridine N-oxide **2a**; for ease of analysis, after a standard reaction time of 16h the presumed intermediate azlactones were subjected to methanolysis to generate the α-methyl,α−pyridyl amino acid ester **3a** as a mixture of C2- and C4-regioisomers.

Table 1. Screening of electrophilic activating agents[a]



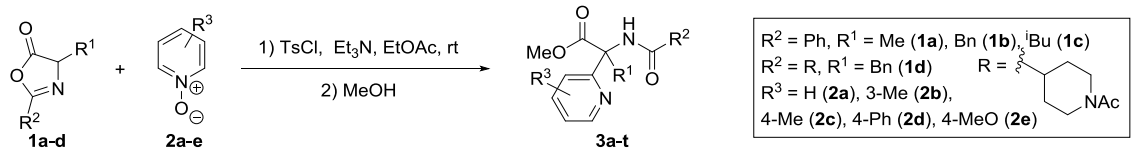
entry	reagent	solvent	ratio C2:C4	isolated yield %
1	PyBroP	THF	1:0.7	53
2	TsCl	THF	1:2.2	68
3	4-NsCl	THF	1:1.7	11
4	MsCl	THF	1:3.8	16
5	Ac_2O	THF	n/a	0
6	AcCl	THF	n/a	0
7	TsCl	2-MeTHF	1:1.6	51
8	TsCl	EtOAc	1:1.5	68 (67[b])
9	TsCl	PhMe	1:1.6	67
10	TsCl	PhOMe	1:1.4	57
11	TsCl	TBME	1:1.4	47
12	TsCl	MeCN	1:1.7	42

[a]Conditions: Azlactone (0.29 mmol), pyridine N-oxide (0.32 mmol), activating agent (0.32 mmol), NEt_3 (0.86 mmol) and solvent (1.4 mL) at rt for 16 h followed by addition of MeOH (1 mL) and stirring for a further 3 h. [b] 0.61 mmol NEt_3

A screen of potential activating agents in THF (Table 1, Entries 1-6) revealed that both PyBroP and TsCl were competent reaction partners, with the former showing modest C2 selectivity and the latter a higher level of selectivity in favour of the C4 isomer. Mindful that THF is regarded as problematic in industrially-led analyses of solvents,[23] we screened a variety of more favourable solvents in conjunction with TsCl (Entries 7-12). Pleasingly, a comparable yield to that achieved in THF was obtained using ethyl acetate (a 'recommended' solvent[23]), albeit with a slightly reduced regioselectivity (Entry 8). Additionally, the charge of triethylamine base could also be reduced to two equivalents versus the N-oxide/activating agent without detriment. Other bases (KOAc, K_3PO_4, K_2CO_3) were unsuccessful in the reaction.

We next applied these optimized conditions to a substrate scoping study, utilizing a matrix combination of azlactones **1a-d** and pyridine N-oxides **2a-e**, again with methanolytic ring-opening of the presumed intermediate azlactone. The results are shown in Scheme 2. Variation of the azlactone C4-substituent (which becomes the α-alkyl group of the amino acid products **3**) was well tolerated, with little variation in average yield across five pyridine N-oxide substrates for R^1= methyl (56%), benzyl (64%) or iso-butyl (52%) Changing the azlactone C2-substituent from aromatic (R^2 = Ph) to aliphatic (R^2 = N-acetyl-4-piperidinyl), was less well tolerated: although each of the reactions was still successful, the average yield dropped from 64% to 31% (with R^1 = Bn). Regarding the pyridine N-oxide, the reactions of the parent reagent **2a** all gave similar regioselectivities in favour of the C4 isomer (1.6:1 to 1.9:1). Reaction of 3-methylpyridine N-oxide **2b** gave rise to a mixture of 2,3-, 3,4- and 2,5-disubstituted products, but with the 3,4-disubstitution product dominating in all cases. The reaction of 4-substituted pyridine N-oxides **2c-e** gives rise to good yields of the 2,4-disubstituted products as expected. Alkyl or aryl substituents were well tolerated, though the presence of an electron-donating 4-methoxy group in **2e** leads to systematically lower yields. Overall, though, the reaction shows excellent robustness, with the full matrix of 20 substrate pairings giving products in an average yield for the three-component coupling of >50%.

Scheme 2. Substrate scope in the one-pot, three-component synthesis of α-pyridyl,α-substituted amino acid methyl esters[a]

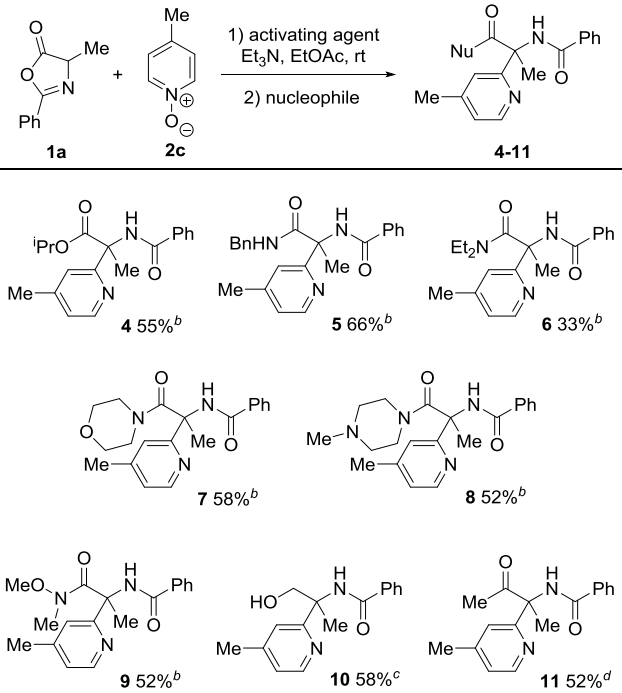


	2a:	2b:	2c:	2d:	2e:
1a:	**3a** 59% 1:1.7 C2/C4	**3b** 62% 1:2.6:1 C2/C4/C6	**3c** 72%	**3d** 55%	**3e** 33%
1b:	**3f** 59% 1:1.9 C2/C4	**3g** 72% 1:3.4:1 C2/C4/C6	**3h** 81%	**3i** 74%	**3j** 35%
1c:	**3k** 56% 1:1.6 C2/C4	**3l** 52% 1:2.7:1 C2/C4/C6	**3m** 60%	**3n** 61%	**3o** 29%
1d:	**3p** 31% 1:1.9 C2/C4	**3q** 40% 1:2.2:1 C2/C4/C6	**3r** 24%	**3s** 34%	**2t** 25%

[a]Conditions: azlactone (0.50 mmol), N-oxide (0.55 mmol), TsCl (0.55 mmol), NEt_3 (1.05 mmol) and EtOAc (2.5 mL) at rt for 16 h followed by NaOMe (1.10 mmol) and MeOH (1 mL) and stirring for a further 3 h.

We next turned our attention to the range of nucleophiles that could be used to open the intermediate arylated azlactones. The formation of peptides and peptidomimetics from α,α-disubstituted amino acids is not straightforward,[24] with N-functionalisation limited by the poor nucleophilicity of the hindered amine and C-functionalisation slowed by the difficulty of forming adjacent quaternary centres in the tetrahedral intermediate for acyl substitution. An additional complication in attempting C-functionalisation of α-pyridyl,α-substituted amino acids is that the free acids undergo facile decarboxylation, accelerated by the potential for charge delocalization into the pyridyl ring;[21] we have already exploited this in a direct two-component synthesis of 2-(1-amidoalkyl)pyridines by arylation/decarboxylative ring-opening of azlactones.[22] Direct access to a range of C-functionalised α-pyridyl,α-substituted amino acids by nucleophilic opening of the azlactones would therefore be synthetically valuable. The results are shown in Scheme 3.

Scheme 3. Scope of nucleophilic ring-opening[a]



[a]Conditions: azlactone (0.50 mmol), N-oxide (0.55 mmol), TsCl (0.55 mmol), NEt_3 (1.05 mmol) and EtOAc (2.5 mL) at rt for 7 h followed by [b]nucleophile and stirring for 16-24 h; [c]$NaBH_4$ (0.50 mmol) and 5:1 THF/MeOH (6 mL) at 0 °C for 1 h; [d]3 M MeMgBr in Et_2O (0.51 mmol) and THF 5 mL at -40 °C for 3 h.

While methanol had already been used for azlactone opening (Scheme 2), we were pleased to see that a more hindered secondary alcohol (iso-propanol) was also a competent nucleophile. The use of amines was examined: primary and cyclic secondary aliphatic amines gave good yields of the diamide products. The use of more hindered, less nucleophilic acyclic secondary amines gave a lower yield, as might be expected, though the Weinreb amide **9** was obtained in reasonable yield. Treatment with sodium borohydride in methanol/THF led to reductive ring-opening, giving the amino alcohol derivative **10**, while the use of a Grignard reagent was also successful, leading to ketone **11**. A broad range of nucleophiles is therefore compatible with the one-pot, three-component coupling.

In summary, we have described a new synthetic approach to α-pyridyl,α-substituted amino acid derivatives by direct pyridylation of azlactones with readily-available pyridine N-oxides, followed by ring-opening with diverse nucleophiles. The reaction shows good robustness (average yield 51%, range 25-81% across 28 examples), while the one-pot, three-component nature of the reaction should be readily applicable to array synthesis.

AUTHOR INFORMATION

*****Email: s.p.marsden@leeds.ac.uk

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data and crystallographic information for all compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENTS

The research for this work has received funding from the Innovative Medicines Institute joint undertaking project CHEM21 under grant agreement no. 115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

REFERENCES

[1] For recent reviews of synthetic approaches to □,□-disubstituted amino acids, see: (a) Metz, A. E.; Kozlowksi, M. C. J. Org. Chem. **2015**, 80, 1-7. (b) Vogt, H.; Brase, S. Org. Biomol. Chem. **2007**, 5, 406-430. (c) Cataviela, C.; Diaz-de-Villegas, M. D. Tetrahedron Asymm. **2007**, 18, 569-623.

[2] Venkataraman, J.; Shankaramma, S. C.; Balaram, P. Chem. Rev. **2001**, 101, 3131-3152.

[3] Anselm, L.; Banner, D.; Haap, W.; Kuhn, B.; Luebbers, T.; Peters, J.-U.; Spinnler, B. PCT Int. Appl. 2013, WO 2013117512.

[4] (a) Malamas, M. S.; Barnes, K.; Johnson, M.; Hui, Y.; Zhou, P.; Turner, J.; Hu, Y.; Wagner, E.; Fan, K.; Chopra, R.; Olland, A.; Bard, J.; Pangalos, M.; Reinhart, P.; Robichaud, A. J. Bioorg. Med. Chem. **2010**, 18, 630-639. (b) Zhou, P.; Li, Y.; Fan, Y.; Wang, Z.; Chopra, R.; Olland, A.; Hu, Y.; Magolda, R. L.; Pangalos, M.; Reinhart, P. H.; Turner, M. J.; Bard, J.; Malamas, M. S.; Robichaud, A. J. Bioorg. Med. Chem. Lett. **2010**, 20, 2326-2329.

[5] Hanyu, M.; Ninomiya, D.; Yanagihara, R.; Murashima, T.; Miyazawa, T.; Yamada, T. J. Peptide Sci. **2005**, 11, 491-498. (b) Yamada, T.; Ichino, T.; Hanyu, M.; Ninomiya, D.; Yanagahira, R.; Miyazawa, T.; Murashima, T. Org. Biomol. Chem. **2004**, 16, 2335-2339. (c) Hanyu, M.; Murashima, T.; Miyazawa, T.; Yamada, T. Tetrahedron Lett. **2004**, 45, 8871-8874.

[6] (a) Watson, E. L.; Marsden, S. P.; Raw, S. A. Tetrahedron Lett. **2009**, 50, 3318-3320. (b) Marsden, S. P.; Watson, E. L.; Raw, S. A. Org. Lett. **2008**, 10, 2905−2908; (c) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. Chem. Commun. **2008**, 4040−4042; (d) Jones, M. C.;Marsden, S. P. Org. Lett. **2008,** 10, 4125–4128; (e) Jones, M. C.; Marsden, S. P.; Muñoz-Subtil, D. M. Org. Lett. **2006,** 8, 5509.

[7] (a) Knight, B. J.; Stache, E. E.; Ferreira, E. M. Org. Lett. 2014, 16, 432-435. (b) Knight, B. J.; Stache, E. E.; Ferreira, E. M. Tetrahedron 2015, 71, 5814-5823.

[8] (a) Makosza, M.; Surowiec, M.; Szczepanska, A.; Sulikowski, D.; Maltsev, O. Synlett **2007**, 470-474. (b) Makosza, M.; Sulikowski, D.; Maltsev, O. Synlett **2008**, 1711-1713. (c) Sulikowski, D.; Makosza, M. Eur. J. Org. Chem. **2010**, 4218-4226.

[9] (a) O'Connor, S. J.; Liu, Z. Synlett **2003**, 2135-2138. (b) Shirakawa, S.; Yamamoto, K.; Tokuda, T.; Maruoka, K. Asian J. Org. Chem. **2014**, 3, 433.

[10] (a) Rose-Munch, F.; Aniss, K.; Rose, E. J. Organomet. Chem. **1990**, 385, C1-C3 (b) Chaari, M.; Jenhi, A.; Lavergne, J.-P.; Viallefont, P. J. Organomet. Chem. **1991**, 401, C10-C13. (c) Chaari, M.; Lavergne, J.-P. Viallefont, P. Synth. Commun. **2006**, 1211-1216. (d) Shirawaka, S.; Yamamoto, K.; Maruoka, K. Angew. Chem. Int. Ed. **2015**, 54, 838-840.

[11] O'Donnell, M. J.; Bennett, W. D.; Jacobsen, W. N.; Ma, Y.-a. Tetrahedron Lett. **1989**, 30, 3913-3914.

[12] (a) Liu, X.; Hartwig, J. F. Org. Lett. 2003, 5, 1915−1918. (b) Arylation of hydantoins leading to □-aryl,□-amino acids derivatives: Fernandez-Nieto, F.; Mas Rosello, J.; Lenoir, S.; Hardy, S.; Clayden, J. Org. Lett. **2015**, 17, 3838-3841.
[13] Chai, Z.; Wang, B.; Chen, J.-N.; Yang, G. Adv. Synth. Cat. **2014**, 356, 2714-2718.
[14] D'Anello, M.; Erba, E.; Gelmi, M. L.; Pocar, D. Chem. Ber., **1988**, 121, 67.
[15] Li, G.; Sun, W.; Li, J.; Jia, F.; Hong, L.; Wang, R. Chem. Commun. **2015**, 51, 11280-11282.
[16] (a) Londregan, A. T.; Jennings, S.; Wei, L. Org. Lett. **2010**, 12, 5254-5257. (b) Lian, Y.; Coffey, S. B.; Li, Q.; Londregan, A. T. Org. Lett. **2016**, 18, 1362-1365.
[17] Londregan, A. T.; Jennings, S.; Wei, L. Org. Lett. **2011**, 13, 1840-1843.
[18] Londregan, A. T.; Burford, K.; Conn, E. L.; Hesp, K. D. Org. Lett. **2014**, 16, 3336-3339.
[19] De Jersey, J.; Zerner, B. Biochemistry **1969**, 8, 1967-1974.
[20] For the activation/substitution of quinoline N-oxide by nitropropionate using acetic anhydride, see: Caldwell, R. D.; Guckian, K. M.; Kumaravel, G.; Lee, W.-C.; Lin, E. Y.-S.; Llu, X.; Ma, B.; Scott, D. M.; Shl, Z.; Thomas, J.; Taveras, A. G.; Zheng, G. Z. U.S. Pat. Appl. Publ., 20140100195, 2014.
[21] Edgar, M. T.; Pettit, G. R.; Krupa, T. S. J. Org. Chem. **1979**, 44, 396-400.
[22] Johnson, T. C.; Marsden, S. P. Beilstein J. Org. Chem. **2016**, 12, 1-4.
[23] Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. Green Chem. **2016**, 18, 288-296.
[24] Schaefer, G.; Bode, J. W. Org. Lett. **2014**, 16, 1526-1529.