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An improved amide coupling procedure for the synthesis of *N*-(pyridin-2-yl)amides

Allyn T. Londregan *, Gregory Storer, Ceshea Wooten, Xiaojing Yang, Joseph Warmus

Pfizer Global Research and Development, Groton, CT 06340, United States

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ABSTRACT

Dehydrative amide couplings with 2-pyridylamines suffer from variable yields. A mild and high-yielding synthesis of *N*-(pyridin-2-yl)amides employing 2-aminopyridine-*N*-oxides is presented as a solution.

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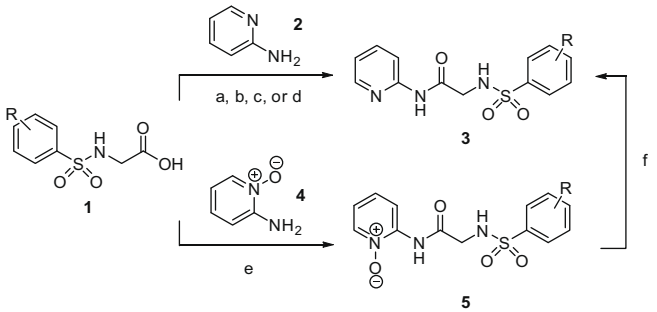
The amide bond is an ubiquitous connection in proteins and peptides and is found in a large number of small-molecule chemotherapeutics.[1] Unsurprisingly, the preparation of amide bonds is among the most common synthetic transformations in organic chemistry. Most methods employ the dehydrative coupling of carboxylic acids with amines. The literature is replete with coupling reagents and additives[2] which facilitate this transformation. When the acylations are attempted with weakly nucleophilic amines, however, they are often met with long reaction times and harsh conditions.[3] During the course of our studies, we required a high-yielding and reproducible procedure for the coupling of carboxylic acid derivative **1** with 2-aminopyridine **2** (Scheme 1). Although there is ample literature precedent for carboxylic acid couplings with 2-aminopyridines, the yields tend to be quite variable and more often than not, require transformation to the acid chloride prior to coupling.[4] In our hands, we obtained very poor yields (<5%) of **3** when using standard coupling protocols (EDCI, BOP, HATU, or acid chloride) with **2**, presumably due to the decreased nucleophilicity of the amine. Neither heating nor the addition of rate enhancers, such as DMAP (used with the acid chloride and EDCI), afforded any additional product. We were able to overcome this intrinsic limitation by replacing **2** with 2-aminopyridine-*N*-oxide **4**. In the case of coupling between **1** and **4**, a nearly quantitative yield of *N*-oxide-(pyridin-2-yl)amide **5** was observed in 1 h. A simple catalytic hydrogenation afforded the desired *N*-(pyridin-2-yl)amide **3** in excellent yield. Upon further investigation, we found this coupling protocol to be readily reproducible and applicable to a variety of different carboxylic acid derivatives.

Comparisons of this new methodology versus a traditional coupling procedure were conducted with a number of carboxylic acids. As indicated in Table 1, the difference between the two methods is extreme. For a standard coupling condition (condition A), we elected to use the BOP reagent. Dehydrative couplings mediated by BOP proceed quickly and are usually high-yielding.[5] These conditions, however, showed at best a 25% conversion (entry 7) at 48 h to the desired *N*-(pyridin-2-yl)amides. In some cases, no reaction was observed when using 2-aminopyridine under condition A. In contrast, all coupling reactions between 2-aminopyridine-*N*-oxide and the carboxylic acids (condition B) were complete in 1 h. Subsequent catalytic hydrogenation of the *N*-oxide proceeded smoothly, typically in 15 h. Yields ranged from 76–97% for the two-step sequence. Amino acid derivatives **6**–**9** worked very well in the reaction, as did aromatic (**10** and **12**) and aliphatic (**11**) acids. As shown in entry 8, substituted 2-aminopyridine-*N*-oxides were also effective partners in the coupling reaction. Although not presented in Table 1, the replacement of BOP with EDCI in entry 5 also afforded the desired *N*-(pyridin-2-yl)amide in excellent yield (86%, two steps). This would suggest that the improved method is compatible with alternative coupling reagents.

The direct reaction of amine and acid chloride is a common procedure for amide bond formation and on first inspection would



Scheme 1. Reagents and conditions: (a) EDCI, DMAP, no rxn; (b) BOP, DIEA, no rxn; (c) HATU, DIEA, no rxn; (d) oxalyl chloride, NEt_3, DMAP <5%; (e) BOP, DIEA or HATU, DIEA 100%; (f) H_2, 30 psi, Pd/C, 76–93%.

* Corresponding author. Tel.: +1 860 715 6150; fax: +1 860 686 0001.
E-mail address: allyn.t.londregan@pfizer.com (A.T. Londregan).

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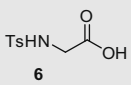
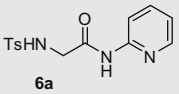
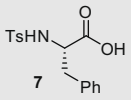
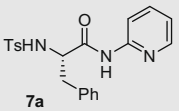
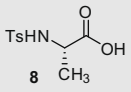
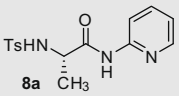
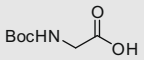
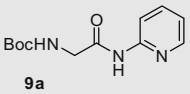
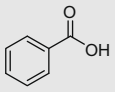
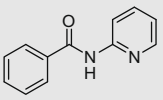
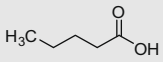
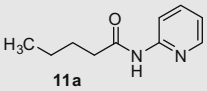
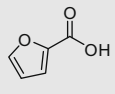
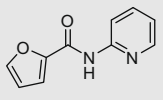
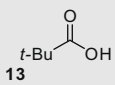
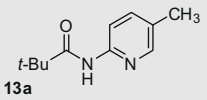
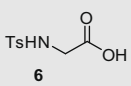
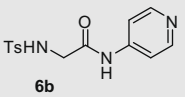
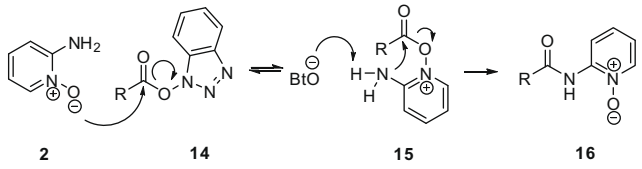
Table 1
Comparison of coupling procedures for the synthesis of *N*-(pyridin-2-yl)amides

Entry	Substrate	Product	Conditions	Conversion[d](%)	Yield[e] (%)
1	 **6**	 **6a**	A[a] B[b]	0 >95	n/d[f] 93
2	 **7**	 **7a**	A B	14 >95	n/d 90
3	 **8**	 **8a**	A B	4 >95	n/d 81
4	 **9**	 **9a**	A B	10 >95	n/d 93
5	 **10**	 **10a**	A B C[c]	15 >95 60	n/d 97 55
6	 **11**	 **11a**	A B	20 >95	5 94
7	 **12**	 **12a**	A B	25 >95	n/d 76
8	 **13**	 **13a**	A[g] B[g]	0 >95	n/d 84
9	 **6**	 **6b**	A[h] B[h]	0 0	n/d n/d

[a] Substrate (1.0 equiv), 2-aminopyridine **2** (1.1 equiv), BOP (1.2 equiv), DIEA (2.5 equiv), DMF, 48 h, rt.
[b] (a) Substrate (1.0 equiv), 2-aminopyridine-*N*-oxide **4** (1.1 equiv), BOP (1.2 equiv), DIEA (2.5 equiv), DMF, 1 h. (b) H_2, 10% Pd/C, MeOH, 30 psi, 15 h.
[c] 2-Aminopyridine **2** (1.0 equiv), benzoyl chloride (1.0 equiv), NEt_3 (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 24 h, 40 °C.
[d] HPLC measured at reaction completion. Measured over two steps for condition B.
[e] Isolated yield after purification. Yield over two steps for condition B.
[f] Not determined.
[g] 2-Amino-5-methylpyridine and 2-amino-5-methylpyridine-*N*-oxide used in place of **2** and **4**, respectively.
[h] 4-Aminopyrdine and 4-aminopyridine-*N*-oxide used in place of **2** and **4**, respectively.

seem to be a viable approach to **6a**–**13a**. As we observed in Scheme 1 (vide supra), the reaction of tosyl-protected amino acid chlorides with 2-aminopyridine was unsuccessful. In fact, the instability of tosyl-protected amino acid chlorides has been previously reported[6] and limits their use in amide syntheses. Our new methodology provides a clear advantage when using such systems. The corresponding acid chlorides of entries 5–8, however, do not suffer from the aforementioned instability. For a comparison, we examined the synthesis of **10a** using benzoyl chloride and 2-aminopyridine (condition C). Despite the use of DMAP in the reaction, we observed only a 60% conversion to the desired product after 24 h at 40 °C. It is noteworthy that under these conditions, the use of a highly reactive acid chloride was less effective than our new method (55% vs 97%).

A possible mechanism for this new transformation is shown in Scheme 2. Activation of a carboxylic acid derivative with BOP results in ester **14**, which undergoes nucleophilic attack by the oxide in **2** to form intermediate **15**. A subsequent intramolecular attack of the pendant amine on the newly formed ester results in the formation of **16**. The fast rate of this reaction can partly be attributed to its intramolecular nature. As would be expected for



Scheme 2. Proposed mechanism for the coupling reaction of acid derivatives with 2-aminopyridine-*N*-oxide and BOP.

this proposed mechanism, the independent synthesis of ester **14**, followed by treatment with **2**, produces **16** in analogous fashion. When the reaction is attempted with 4-aminopyridine-*N*-oxide in place of **2**, no reaction is noted (see entry 9 in Table 1). This observation lends further support to an intramolecular 5-*exo* mechanism, which is not possible in the case of other aminopyridine isomers.

In summary, a high-yielding and mild synthesis of *N*-(pyridin-2-yl)amides from 2-aminopyridine-*N*-oxides has been presented. The reaction most likely proceeds via a novel intramolecular aminolysis. The methodology is applicable to a number of different carboxylic acids.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.071.

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