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General and Scalable Amide Bond Formation with Epimerization-Prone Substrates Using T3P and Pyridine

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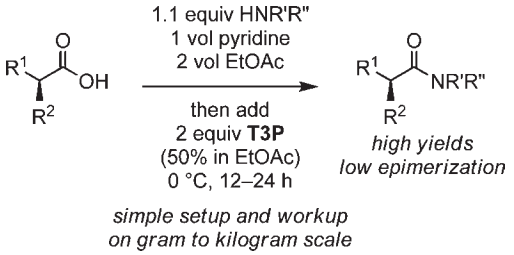
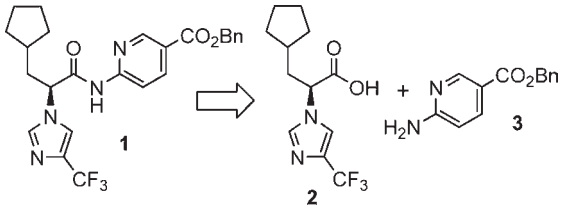
ABSTRACT



The mild combination of T3P (*n*-propanephosphonic acid anhydride) and pyridine has been developed for low-epimerization amide bond formation and implemented for the synthesis of a key intermediate to a glucokinase activator. This robust method is general for the coupling of various racemization-prone acid substrates and amines, including relatively non-nucleophilic anilines, and provides amides in high yields with very low epimerization. With easy reaction setup and product isolation, this protocol offers several practical and experimental benefits.

Amides are widespread in compounds of biological and pharmaceutical importance; in fact, a survey found these structures present in 25% of known pharmaceuticals.[1] Not surprisingly, amide bond formations via the coupling of amines and carboxylic acid derivatives are the most common transformations for the synthesis of drug candidates.[2] Despite continuing advances in methods to prepare amide bonds,[3] a recurring challenge involves avoiding epimerization of activated carboxylic acid substrates at stereogenic centers adjacent to the carbonyl. This epimerization typically occurs via deprotonation of the α-carbon, and substrates which can better stabilize the resulting carbanion through resonance are more susceptible to racemization. Herein, we describe the development of high-yielding amide coupling conditions that suppress the epimerization of acid substrates which are particularly sensitive to racemization. These conditions have been applied successfully to various acids and amines, including relatively non-nucleophilic anilines.

Our work in this area stems from development efforts to manufacture clinical API supplies of a glucokinase activator. Glucokinase is an enzyme in the liver and pancreas which regulates glucose metabolism,[4] and compounds which activate this enzyme are promising therapies for type II diabetes.[5] We needed to develop a robust process for the multikilogram synthesis of amide **1**, a key



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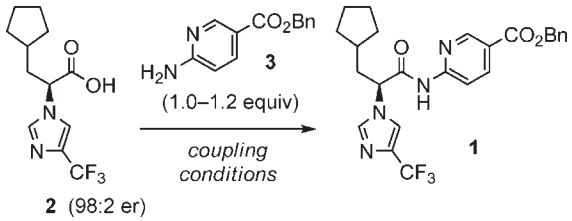
intermediate to the API (active pharmaceutical ingredient). The medicinal chemistry preparation of **1** coupled acid **2** and amine **3** in a two-step procedure via the acid chloride derivative of **2**. This approach proved effective for the synthesis of amide **1** on gram scale, but several issues had to be addressed to enable the preparation of **1** on kilogram scale. First, we strongly preferred coupling **2** and **3** in a one-pot procedure with minimal handling of a sensitive activated acid intermediate. In addition, other factors besides yield and chiral purity of **1** influenced our optimization of this reaction for scaleup. These included the ease of reaction workup and product purification, as well as reagent costs and health safety issues (e.g., toxicity, sensitization).

Our investigation of reagents for the one-pot condensation of acid **2** and amine **3** quickly revealed an obstacle to our synthesis of **1**: activated coupling intermediates derived from acid **2** are highly susceptible to epimerization.[6] Among the conditions outlined in Table 1, reactions with DCC[7] provided the amide with the greatest enantiopurity (entries 2−3); however, this reagent (and its dicyclohexylurea byproduct) can be difficult to purge without chromatography and poses significant handling concerns due to toxicity and sensitization risks. Related carbodiimide EDC[8] has an amino side chain that allows for its easy extraction from reaction mixtures via acidic workup, but couplings of **2** and **3** with this reagent either proceeded with epimerization or too sluggishly to be useful (entries 4−6). Only slight racemization was observed from our best HATU[9] conditions (entry 10), but this uronium compound is expensive and, much like DCC, degrades to byproducts via coupling that are difficult to remove without chromatography. Initial efforts to couple **2** and **3** via CDI,[10] CDMT,[11] or DEPBT[12] also proceeded with racemization (entries 11−14) and were abandoned.

We also explored T3P (**4**; *n*-propanephosphonic acid anhydride[13]) for the one-pot condensation of acid **2** and amine **3**. Although this reagent was developed over

Table 1. Survey of Coupling Reagents and Conditions



entry	conditions[a]	er (amide **1**)
1	DCC, HOAt, DMF	93:7
2	DCC, HOAt, CH_2Cl_2	98:2
3	DCC, CH_2Cl_2	98:2
4	EDC, CH_2Cl_2	sluggish
5	EDC•HCl, CH_2Cl_2	94:6
6	EDC•HCl, HOAt, DMF	60:40
7	HATU, EtN(*i*-Pr)$_2$, DMF	86:14
8	HATU, EtN(*i*-Pr)$_2$, CH_2Cl_2	96:4
9	HATU, 2,6-lutidine, CH_2Cl_2	87:13
10	HATU, pyridine, CH_2Cl_2	97:3
11	CDI, THF	50:50
12	CDMT, NMM, MeCN	70:30
13	CDMT, 2,6-lutidine, MeCN	sluggish
14	DEPBT, EtN(*i*-Pr)$_2$, THF	50:50

[a] All reactions at room temperature. DCC = *N*,*N*′-dicyclohexylcarbodiimide; HOAt = 1-hydroxy-7-azabenzotriazole; EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; CDI = carbonyldiimidazole; HATU = *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate; CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine; NMM = *N*-methylmorpholine; DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one.

30 years ago,[14,15] we found only two examples[16] outside the patent literature using T3P to prepare amide bonds from nonamino acid substrates containing an epimerizable α-stereocenter.[17] Of these two examples, one employs racemic acid[16a] and the other was not reported with an

(6) In control experiments, amide **1** did not epimerize when exposed to coupling conditions. Furthermore, acid **2** did not epimerize under the same conditions excluding coupling reagent.

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(13) T3P is a registered trademark of Archimica Gmbh.

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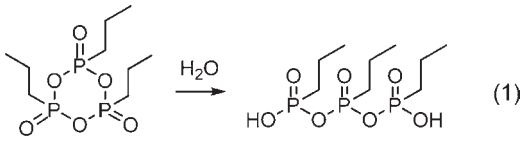
(17) Despite the prevalence of peptide couplings, we also found relatively few examples in which T3P mediates the coupling of an amino acid containing an α-stereocenter: (a) Morales-Avila, E.; Ferro-Flores, G.; Ocampo-García, B. E.; De León-Rodríguez, L. M.; Santos-Cuevas, C. L.; García-Becerra, R.; Medina, L. A.; Gómez-Oliván, L. *Bioconjugate Chem.* **2011**, *22*, 913. (b) Petit, S.; Fruit, C.; Bischoff, L. *Org. Lett.* **2010**, *12*, 4928. (c) Thoss, M.; Seidel, R. W.; Feigel, M. *Tetrahedron* **2010**, *66*, 8503. (d) Vasantha, B.; Hemantha, H. P.; Sureshbabu, V. V. *Synthesis* **2010**, 2990. (e) Patterson, D. E.; Powers, J. D.; LeBlanc, M.; Sharkey, T.; Boehler, E.; Irdam, E.; Osterhout, M. H. *Org. Process Res. Dev.* **2009**, *13*, 900. (f) Wehner, M.; Janssen, D.; Schäfer, G.; Schrader, T. *Eur. J. Org. Chem.* **2006**, 138. (g) Lange, U. E. W.; Baucke, D.; Hornberger, W.; Mack, H.; Seitz, W.; Höffken, H. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2648. (h) Mack, H.; Baucke, D.; Hornberger, W.; Lange, U. E. W.; Seitz, W.; Höffken, H. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2641. (i) Bernard, H.; Bülow, G.; Lange, U. E. W.; Mack, H.; Pfeiffer, T.; Schäfer, B.; Seitz, W.; Zierke, T. *Synthesis* **2004**, 2367. (j) Dai, X.; Su, Z.; Liu, J. O. *Tetrahedron Lett.* **2000**, *41*, 6295. (k) Klose, J.; Bienert, M.; Mollenkopf, C.; Wehle, D.; Zhang, C.-w.; Carpino, L. A.; Henklein, P. *Chem. Commun.* **1999**, 1847. (l) Hiebl, J.; Alberts, D. P.; Banyard, A. F.; Baresch, K.; Baumgartner, H.; Bernwieser, I.; Bhatnagar, P. K.; Blanka, M.; Bodenteich, M.; Chen, T.; Esch, P. M.; Kollmann, H.; Lantos, I.; Leitner, K.; Mayrhofer, G.; Patel, R.; Rio, A.; Rovenszky, F.; Stevenson, D.; Tubman, K. D.; Undheim, K.; Weihtrager, H.; Welz, W.; Winkler, K. *J. Peptide Res.* **1999**, *54*, 54. (m) Escher, R.; Bünning, P. *Angew Chem., Int. Ed.* **1986**, *25*, 277. (n) Kessler, H.; Kühn, M.; Löschner, T. *Liebigs Ann. Chem.* **1986**, 1. (o) Wenger, R. M. *Helv. Chim. Acta* **1984**, *67*, 502.

experimental procedure.[16b] Furthermore, only recently has this relatively underappreciated reagent been reported for any amide bond formation on kilogram scale,[17e,i,18] which is surprising as this phosphonic acid anhydride offers several practical and experimental benefits. First, its byproducts (e.g., **5**) from coupling are water-soluble and easily separated from reaction mixtures, which greatly simplifies the purification of amide product without chromatography and minimizes the environmental impact of this coupling reagent. In addition, commercially available T3P solutions (50% in various solvents) are easily handled, are moderately priced, and have long shelf-life stability. Furthermore,

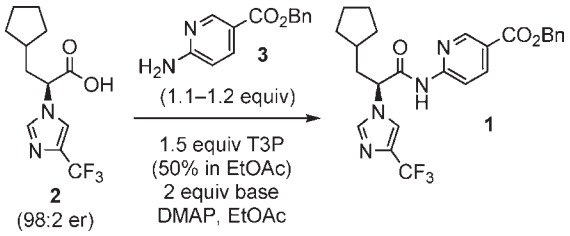


4 (T3P) **5** (1)

this reagent lacks the toxicity and shock sensitivity associated with other coupling reagents and additives.

Table 2 shows our optimization of the T3P-catalyzed coupling of **2** and **3** with respect to epimerization. Negligible product was obtained in the absence of added base (entry 1). As racemization involves deprotonation at the stereogenic center of the T3P-activated intermediate, we hypothesized that weaker and bulkier bases would minimize the loss of chiral purity in converting acid **2** to amide **1**.[6,19] Indeed, replacing Et_3N with hindered TMP for this T3P-catalyzed amide coupling suppressed epimerization considerably (entries 2–4). Additional improvements were realized using weaker morpholine and lutidine bases (entries 5–10), with *N*-methylmorpholine (NMM) inducing more racemization than the bulkier *N*-ethylmorpholine (NEM). Switching from 2,6-lutidine to pyridine, a weaker base, further reduced epimerization (entries 12–14). Interestingly, we observed enhanced racemization using DMAP as an additive; the resulting acylpyridinium appears more susceptible to epimerization than its T3P-activated precursor, and sufficient reaction rates were observed without this nucleophilic catalyst. In the end, we achieved the best results with pyridine at 0 °C, providing **1** with near-complete preservation of enantiopurity (entry 14). This combination of T3P and pyridine is particularly well-suited for amide bond formation from epimerization-prone substrates (vide infra),

Table 2. Optimization of T3P-Catalyzed Amide Coupling

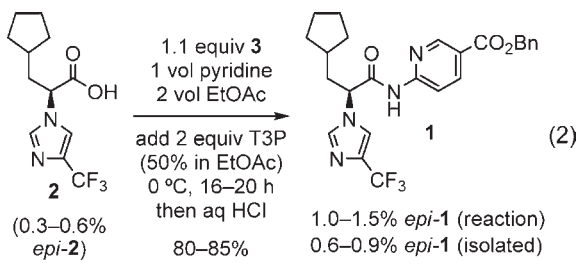


entry	base,[a] additive,[b] temperature	er (amide **1**)
1	no base, no DMAP, rt	NR
2	Et_3N, DMAP, rt	54:46
3	TMP, DMAP, rt	80:20
4	TMP, no DMAP, rt	90:10
5	NMM, DMAP, rt	80:20
6	NMM, no DMAP, rt	92:8
7	NEM, no DMAP, rt	94:6
8	2,6-lutidine, DMAP, rt	93:7
9	2,6-lutidine, DMAP, 0 °C	95:5
10	2,6-lutidine, no DMAP, rt	95:5
11	2,6-*t*-Bu-4-Me-pyridine, DMAP, rt	96:4
12	pyridine, DMAP, rt	96:4
13	pyridine, no DMAP, rt	97:3
14	**pyridine, no DMAP, 0 °C**	**98:2**

[a] DMAP = 4-(dimethylamino)pyridine; TMP = 2,2,6,6-tetramethylpiperidine; NMM = *N*-methylmorpholine; NEM = *N*-ethylmorpholine. [b] Either no DMAP or 0.2 equiv of DMAP.

and although pyridine has greater toxicity than other bases, it is easily purged via acidic workup.[20,21]

These conditions were incorporated into an operationally simple procedure for the synthesis of **1** on gram to kilogram scale (eq 2). T3P (50% in EtOAc) is added to a mixture of **2** and **3** in pyridine and EtOAc, and the resulting homogeneous solution is held at 0 °C as amide is formed with low epimerization (1.0–1.5% *epi*-**1** from 0.3–0.6% *epi*-**2**).[22] Cooling minimizes racemization and mitigates a mild exotherm from T3P addition. Using only a slight excess of **3** is cost-effective and simplifies the purification of amide product. Alternatively, T3P is inexpensive relative to **2** and **3**, and although the coupling proceeds well with only 1.2 equiv of T3P on laboratory scale, a larger excess on kilogram scale ensures robustness and reproducibility. In fact, the reaction does not require anhydrous-grade



(2)

(18) (a) Campeau, L.-C.; Dolman, S. J.; Gauvreau, D.; Corley, E.; Liu, J.; Guidry, E. N.; Ouellet, S. G.; Steinhuebel, D.; Weisel, M.; O'Shea, P. D. *Org. Process Res. Dev.* **2011**, ASAP (DOI: 10.1021/op2001063). (b) Guercio, G.; Castoldi, D.; Giubellina, N.; Lamonica, A.; Ribecai, A.; Stabile, P.; Westerduin, P.; Dams, R.; Nicoletti, A.; Rossi, S.; Bismara, C.; Provera, S.; Turco, L. *Org. Process Res. Dev.* **2010**, *14*, 1153. (c) Boggs, S. D.; Cobb, J. D.; Gudmundsson, K. S.; Jones, L. A.; Matsuoka, R. T.; Millar, A.; Patterson, D. E.; Samano, V.; Trone, M. D.; Xie, S.; Zhou, X.-m. *Org. Process Res. Dev.* **2007**, *11*, 539.

(19) It is possible that epimerization occurs via deprotonation and ketene formation, although trapping studies failed to capture evidence for ketene as an intermediate.

(20) The ICH limit for pyridine in drug substances is 200 ppm.

(21) After optimizing this chemistry, we found a single report in which T3P and pyridine were applied to the synthesis of amide polymers via condensations of achiral acids and dianilines in NMP at 80 °C: Ueda, M.; Honma, T. *Polym. J.* **1988**, *20*, 477.

(22) Supporting Information contains full experimental details on gram and kilogram scale. Volume (vol) is a unit for mL/g or L/kg. In this case, 1 mL of pyridine and 2 mL of EtOAc per gram of **2** (limiting reagent).

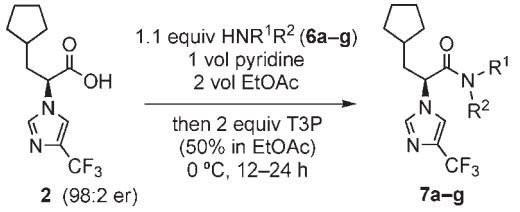
solvents with 2 equiv of the water-scavenging T3P, and on gram scale this coupling is typically performed without inert atmosphere.

The reaction workup is equally straightforward. Quenching with 0.5 M aqueous HCl (3 vol) precipitates **1** as the freebase with *>99% achiral purity and >99:1 er* while purging pyridine and excess **3**. The filtered amide is typically isolated in 80−85% yield with traces of **5**, a T3P byproduct which inhibits downstream chemistry. On gram scale, **5** is easily removed by simple water rinses of the filter cake; however, on kilogram scale, it proved more efficient to reslurry the filtered amide in water to remove **5** (without loss of yield). Ultimately, we scaled this process to manufacture over 20 kg of amide **1** per batch in our cGMP facility.

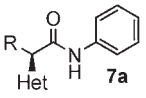
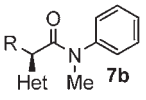
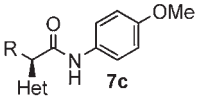
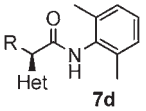
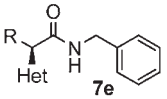
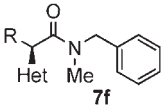
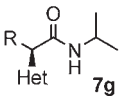
We next explored the generality of these low-epimerization conditions for the condensation of acid **2** with other amines on gram scale. As shown in Table 3, the T3P-catalyzed coupling of **2** with various aryl and alkylamines provided amides in very high yields and enantiopurities. These conditions accommodate both primary and secondary amines, even bulky substrates (e.g., **6d**). As a trend, epimerization increases with the basicity of the amine coupling partner, which is consistent with observations from reaction optimization (Table 2). However, even isopropylamine, the most basic coupling partner in this study, provided amide **7g** with 94:6 er.

These conditions also effect amide formation from other acids whose activated derivatives might be sensitive to racemization. Condensations of 2-phenylpropanoic acid, *N*-Cbz-alanine, and *N*-Cbz-phenylglycine (all >99:1 er) with $PhNH_2$ or $BnNH_2$ provided amides **8**−**10** in high yield and *without detection of epimerization*. Not surprisingly, the application of T3P/pyridine to *N*-Ac-alanine and $PhNH_2$ provided azlactone byproducts.[3]

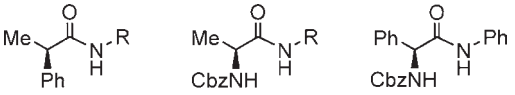
Table 3. Scope of Amines in T3P-Catalyzed Couplings of **2**



6a R^1 = Ph; R^2 = H
6b R^1 = Ph; R^2 = Me
6c R^1 = 4-OMe-Ph; R^2 = H
6d R^1 = 2,6-Me-Ph; R^2 = H
6e R^1 = Bn; R^2 = H
6f R^1 = Bn; R^2 = Me
6g R^1 = *i*-Pr; R^2 = H

entry	amine	amide[a]	er[b]	yield[c]
1	**6a**	 **7a**	98:2	95%
2	**6b**	 **7b**	97:3	89%
3	**6c**	 **7c**	96:4	98%
4	**6d**	 **7d**	97:3	99%
5	**6e**	 **7e**	96:4	98%
6	**6f**	 **7f**	97:3	98%
7	**6g**	 **7g**	94:6	82%

[a] R = cyclopentylmethyl; Het = 4-CF_3-imidazolyl. [b] Enantiomeric ratios unchanged by workup. [c] Isolated yields.



8a (R = Ph)
81% yield
>99:1 er

8b (R = Bn)
82% yield
>99:1 er

9a (R = Ph)
91% yield
>99:1 er

9b (R = Bn)
91% yield
>99:1 er

10
94% yield
>99:1 er

In conclusion, we have developed mild and general conditions for amide bond formation on gram to kilogram scale using T3P and pyridine. This method provides amides in high yields with very low epimerization and is particularly well-suited for the coupling of racemization-prone acids and amines, including relatively non-nucleophilic anilines. With easy reaction setup and product isolation, this protocol offers several practical and experimental benefits to the synthetic chemist.

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Supporting Information Available. Experimental procedures and characterization data for all amides. This material is available free of charge via the Internet at http://pubs.acs.org.