Synthesis and Photophysical Properties of Charge-Transfer-Based Pyrimidine-Derived α-Amino Acids

Sineenard Songsri, Alexander H. Harkiss, and Andrew Sutherland*

ABSTRACT: The four-step synthesis of fluorescent pyrimidine-derived α-amino acids from an l-aspartic acid derivative is described. The key synthetic steps involved preparation of ynone intermediates via the reaction of alkynyl lithium salts with a Weinreb amide, followed by an ytterbium-catalyzed heterocyclization reaction with amidines. Variation of substituents at the C2- and C4-position of the pyrimidine ring allowed tuning of the photoluminescent properties of the α-amino acids. This revealed that a combination of highly conjugated or electron-rich aryl substituents with the π-deficient pyrimidine motif resulted in fluorophores with the highest quantum yields and overall brightness. Further analysis of the most fluorogenic α-amino acid demonstrated solvatochromism and sensitivity to pH.

INTRODUCTION

The importance of α-amino acids as the building blocks of life along with their role in fundamental biological processes continues to drive new discoveries and applications of unnatural analogues. In organic chemistry, nonproteinogenic α-amino acids are widely used in synthesis as the chiral component of ligands and auxiliaries for novel asymmetric methods, while readily available proteinogenic α-amino acids are used as chiral starting materials in total synthesis. In medicinal chemistry and chemical biology, unnatural α-amino acids are used as enzyme inhibitors and as probes to study biological mechanisms, protein–protein interactions, and peptide conformations.

In combination with the continued advances of fluorescence spectroscopy techniques, which allow the study of biological processes and the imaging of cellular processes, there has been significant recent interest in the development of unnatural α-amino acids as fluorescent probes. This is partly due to the limitations of other approaches. The attachment of large extrinsic fluorescent labels to a protein such as green fluorescent protein or commercially available chromophores can alter structure and function. The naturally occurring proteinogenic α-amino acids, phenylalanine, tyrosine, and tryptophan, have poor photoluminescent properties and the presence of these at multiple sites and in different environments within a protein complicates analysis (Figure 1). These limitations have led to the development of unnatural mimics of these α-amino acids, which are more similar in size and can be selectively embedded into peptides without altering structure. For example, 4-biphenyl-α-phenylalanine was incorporated into dihydrofolate reductase to study conformational changes of inhibitor binding using Förster resonance energy-transfer (FRET) measurements. Tyrosine analogues with extended conjugation and improved photoluminescent properties such as bis-styrene have been incorporated into cell-penetrating peptides and used for cell imaging. As tryptophan has the strongest fluorescent properties of the proteinogenic amino acids, many studies have focused on the modification of this α-amino acid. In particular, the reactivity of the C2-position of the indole ring has allowed the preparation of a wide range of analogues with extended conjugation (e.g., 6). Several of these tryptophan mimics have been incorporated into peptides and used to image fungal infections and cancer cells.

We have been interested in developing fluorescent α-amino acids with biaryl side chains as brighter, structural analogues of phenylalanine, tyrosine, and tryptophan. As well as the synthesis of pyrazole- and benzotriazole-derived α-amino acids, we recently reported the synthesis and photoluminescent properties of pyridine-derived α-amino acids (Figure 1). These were prepared using a Lewis-acid-catalyzed hetero-Diels–Alder reaction of enone-derived α-amino acids with ethyl vinyl ether, followed by a Knoevenagel–Stobbe reaction to access the pyridine motif. Analysis of the photoluminescent...
properties of these α-amino acids revealed that a combination of electron-rich aryl substituents with the π-deficient pyridines resulted in charge-transfer-based fluorescence. Although several of the pyridine-derived α-amino acids displayed good quantum yields (0.18–0.46) and brightness, the main absorption bands were found at similar wavelengths to the fluorescent proteinogenic α-amino acids, thus restricting applications of these compounds. To overcome this limitation, we considered various structural changes that may result in fluorescent α-amino acids with red-shifted absorption and emission properties. To avoid increasing the size of the side chain resulting in α-amino acids significantly larger than proteinogenic analogues, we proposed that the incorporation of a more π-deficient heterocycle, such as a pyrimidine would enhance charge-transfer properties of the biaryl system, leading to a bathochromic shift of optical properties. Here, we report the synthesis of pyrimidine-derived α-amino acids (Figure 1) using an ytterbium-catalyzed heterocyclization reaction of ynones with amidines as the key step. By tuning the fluorescent properties of these compounds through variation of the C2- and C4-substituents of the pyrimidine, we also demonstrate the most effective biaryl systems that generate charge-transfer-based fluorescent α-amino acids with red-shifted photoluminescent properties.

■ RESULTS AND DISCUSSION

Our proposed synthesis of pyrimidine-derived α-amino acids involved three key disconnections (Scheme 1). Preparation of the pyrimidine ring and introduction of late-stage diversity would be achieved by heterocyclization of ynones with amidines. The ynones were prepared from commercially available N-Boc L-aspartic acid t-butyl ester 8.

![Scheme 1. Proposed Synthesis of Pyrimidine-Derived α-Amino Acids](image)

![Scheme 2. Two-Step Synthesis of Ynone-Derived α-Amino Acids 10a–d](image)

would be prepared by the chemoselective reaction of alkynyl lithium salts with Weinreb amide 9, which would also allow the incorporation of various side chains. Weinreb amide 9 would be prepared under standard conditions from commercially available N-Boc L-aspartic acid t-butyl ester 8.

The first stage of the synthetic program focused on the scalable synthesis of ynone-derived α-amino acids. Renault and co-workers previously reported an efficient route to these compounds and thus, with some modifications, this was used for the preparation of ynones 10a–10d (Scheme 2).

![Figure 1. Fluorescent, proteinogenic α-amino acids and selected unnatural mimics.](image)
acid and L-glutamic acid derivatives.\textsuperscript{18} The majority of these procedures involved reaction of the ynone with an amidine by heating under reflux in the presence of sodium carbonate. Our initial studies investigated the reaction of phenyl-substituted ynone 10a with benzamidine hydrochloride under similar conditions (Table 1, entry 1). Although this gave pyrimidine 11a cleanly, the compound was isolated in only 23% yield. Attempts were then made to modify this approach. In addition, we wanted to avoid the combination of basic conditions and high temperatures (80 °C) and so a reaction at 50 °C and with a longer reaction time (24 h) was investigated (entry 2). This gave pyrimidine 11a in an improved 42% yield. To avoid the use of water as a cosolvent, DMF was then investigated under the same conditions, but this gave no reaction (entry 3). In their work, Baldwin and co-workers highlighted that reaction of ynones with formamidine under these conditions gave low yields of the corresponding pyrimidine. This was a concern as we believed that pyrimidine-derived \(\alpha\)-amino acids with no C2-substituent were likely to produce the most effective fluorophores. For this reason and the modest yields already observed for base-mediated heterocyclizations, we considered a different approach for the preparation of the pyrimidines. Bagley and co-workers showed that ynones could be activated with ytterbium salts for reaction with enamines and the subsequent synthesis of pyridine derivatives.\textsuperscript{19} Based on this, the use of ytterbium triflate as a Lewis acid catalyst for pyrimidine synthesis was investigated. An initial attempt involved the reaction of phenyl-substituted ynone 10a with benzamidine hydrochloride in the presence of ytterbium triflate (10 mol %) (entry 4). Using THF as the solvent and potassium carbonate to neutralize the benzamidine salt, this generated pyrimidine 11a cleanly and with an isolated yield of 69%.

The scope of the ytterbium triflate catalyzed heterocyclization reaction of ynone-derived \(\alpha\)-amino acids 10a−10d with benzamidine, acetamidine, and formamidine was then explored (Scheme 3). The reaction of ynones 10a−10d with benzamidine and acetamidine under the Lewis-acid-catalyzed conditions was found to be highly effective and gave the pyrimidine products in 61−89% yields.\textsuperscript{20} For the more challenging heterocyclization reaction with formamidine, the optimized conditions gave low yields. For example, reaction of \(p\)-methoxyphenyl-substituted ynone 10c with formamidine hydrochloride and using ytterbium triflate (10 mol %) gave the corresponding pyrimidine 11k in 19% yield. However, it was found that the use of higher catalyst loading (20 mol %) resulted in an improved 50% yield. This modification was also effective with the other ynones, allowing the synthesis of pyrimidines 11i−11l in 50−64% yields. Having successfully synthesized a small library of pyrimidine-derived \(\alpha\)-amino acids, the protecting groups were removed in the presence of 1 M hydrochloric acid under mild conditions, which gave parent amino acids 12a−12l in excellent yields.

### Table 1. Optimization Studies for Pyrimidine Formation from Ynone 10a\textsuperscript{4}

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>base</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na\textsubscript{2}CO\textsubscript{3}</td>
<td>MeCN/H\textsubscript{2}O</td>
<td>4</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Na\textsubscript{2}CO\textsubscript{3}</td>
<td>MeCN/H\textsubscript{2}O</td>
<td>24</td>
<td>42</td>
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<tr>
<td>3</td>
<td>Na\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10 K\textsubscript{2}CO\textsubscript{3}</td>
<td>THF</td>
<td>48</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yields are shown. \textsuperscript{b}Reaction done at 80 °C.

\textsuperscript{4}Isolated yields are shown.
Table 2. Photophysical Data of Pyrimidine-Derived α-Amino Acids

<table>
<thead>
<tr>
<th>amino acid</th>
<th>(\lambda_{\text{Abs}}) (nm)</th>
<th>(\varepsilon) (cm(^{-1}) M(^{-1}))</th>
<th>(\lambda_{\text{Em}}) (nm)</th>
<th>Stokes shift (cm(^{-1}))</th>
<th>(\Phi_F) (^{b})</th>
<th>brightness (cm(^{-1}) M(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>12b</td>
<td>311</td>
<td>24,000</td>
<td>497</td>
<td>12,033</td>
<td>0.12</td>
<td>2880</td>
</tr>
<tr>
<td>12c</td>
<td>305</td>
<td>12,700</td>
<td>314</td>
<td>940</td>
<td>0.003</td>
<td>38</td>
</tr>
<tr>
<td>12f</td>
<td>305</td>
<td>12,800</td>
<td>490</td>
<td>12,379</td>
<td>0.11</td>
<td>1408</td>
</tr>
<tr>
<td>12g</td>
<td>299</td>
<td>16,400</td>
<td>314, 381</td>
<td>1598, 7198</td>
<td>0.016</td>
<td>262</td>
</tr>
<tr>
<td>12j</td>
<td>310</td>
<td>10,400</td>
<td>421</td>
<td>8505</td>
<td>0.30</td>
<td>3120</td>
</tr>
<tr>
<td>12k</td>
<td>306</td>
<td>13,600</td>
<td>384</td>
<td>6638</td>
<td>0.27</td>
<td>3672</td>
</tr>
</tbody>
</table>

\(^{a}\)Spectra were recorded at 2 \(\mu\)M in methanol. \(^{b}\)Quantum yields (\(\Phi_F\)) were determined in methanol using anthracene and \(\alpha\)-tryptophan as standards.

On synthesis of the pyrimidine-derived \(\alpha\)-amino acids, the photoluminescent properties were measured for each compound. The ultraviolet–visible (UV–vis) absorption and photoluminescence spectra of the \(\alpha\)-amino acids were recorded in methanol at a concentration of 2 \(\mu\)M. As expected, pyrimidines with weakly donating (Ph) or electron-withdrawing (4-NCPh) C4-substituents displayed weak fluorescence and low brightness (see the Supporting Information). The most interesting properties were found for pyrimidines with highly conjugated (naphthyl) and strongly electron-donating (4-MeOPh) C4-substituents (Table 2). These \(\alpha\)-amino acids exhibited red-shifted absorption bands in comparison to proteinogenic \(\alpha\)-amino acids 1–3 and the previously reported pyridine analogues,\(^{13}\) with fluorescence in the visible region. For the C4-naphthyl compounds (12b, 12f, and 12j), all three compounds showed absorption bands between 305 and 311 nm, possessed megaStokes shifts, and good quantum yields, resulting in the brightest series of \(\alpha\)-amino acids (Table 2 and Figure 2). The main difference in this series was observed in the fluorescence spectra, in which \(\alpha\)-amino acids 12b and 12f showed emission maxima between 490 and 500 nm, while a hypsochromic shift in emission to 421 nm was observed for C2-unsubstituted analogue 12j (Figure 2b). For 12j, we believe that the lack of a C2-substituent allows emission from a more planar locally excited state, while \(\alpha\)-amino acids 12b and 12f, which have more distorted conformations due to C2-substituents, emit from twisted intramolecular charge-transfer excited states. For the p-methoxyphenyl series, the trend of emission maxima was found to be reversed. The C2-substituted compounds 12c and 12g displayed weak emission maxima at 314 nm, while 12k with no C2-substituent showed a bathochromic shift in emission to 384 nm (Figure 3b). In this series, the C2-substituent obviously has a strong influence on the interaction between the C4-aryl group and the pyrimidine ring. While the C2-phenyl and methyl groups disrupt this interaction, no substituent at C2 allows strong interplay between the electron-rich p-methoxyphenyl ring and the \(\alpha\)-deficient pyrimidine heterocycle, resulting in strong intramolecular charge-transfer emission. As well as strong fluorescence, \(\alpha\)-amino acid 12k displayed red-shifted absorption compared to the corresponding pyridine (283 nm),\(^{13}\) a large Stokes shift, as well as a good quantum yield (0.27) and brightness. Overall, these results provide insight into the relationship between the structure and photoluminescence properties of these \(\alpha\)-amino acids and, in particular, the use of substituents to control biaryl conformation, leading to emission from either locally excited or twisted/planar intramolecular charge-transfer excited states.

Although the naphthyl series of \(\alpha\)-amino acids gave strong, red-shifted emission and good quantum yields, the p-methoxyphenyl pyrimidine-derived \(\alpha\)-amino acid 12k was found to be the brightest. For this reason, the properties of 12k were further explored via solvatochromic and pH studies. Analysis of \(\alpha\)-amino acid 12k in a range of solvents produced similar absorption spectra, indicating that in the ground state, the absorbance is independent of solvent polarity (see the Supporting Information). In contrast, a bathochromic shift in emission maxima was observed with increasing solvent polarity (Figure 4a). For example, the emission maximum was found at 352 nm in ethyl acetate, while this shifted to 384 nm in water. The solvatochromism displayed by \(\alpha\)-amino acid 12k confirms the intramolecular charge-transfer character of the excited state, which is stabilized in more polar solvents. To determine the effect of pyrimidine ring protonation on the photophysical properties of \(\alpha\)-amino acid 12k, pH studies were conducted. A change of pH from 7 to 1, resulted in stronger absorbance around 300 nm and the formation of a second minor band at longer wavelength (≈360 nm) (see the Supporting Information). A significant change was also observed for the emission properties of \(\alpha\)-amino acid 12k (Figure 4b). While the position
of the emission band is unchanged, the fluorescence is "turned off" following acidification. Protonation of substituted pyrimidines typically leads to a change in conformation, resulting in either a hypsochromic or bathochromic shift of emission bands. For α-amino acid 12k, formation of a positively charged pyrimidine ring results in effective fluorescence quenching. These results suggest that α-amino acid 12k may have potential as a fluorescent probe for biological applications, which involve a change of polarity or pH conditions.

**CONCLUSIONS**

In conclusion, a small library of α-amino acids with pyrimidine side chains were prepared using a novel ytterbium-catalyzed heterocyclization reaction of ynone-derived α-amino acids with amidines as the key step. The pyrimidine heterocycle was selected as a strong π-deficient motif, which with conjugated or electron-rich aryl substituents would result in strong fluorescence. Analysis of the optical properties of these compounds proved this to be the case. Pyrimidines with no C2-substituent and with highly conjugating (12j) or electron-donating C4-substituents (12k) displayed red-shifted absorption bands (compared to the corresponding pyridine analogue), strong fluorescence emission in the visible region, large Stokes shifts, and good quantum yields (0.27−0.30). (a) Absorption spectra of 12c, 12g, and 12k, recorded at 2 µM in methanol. (b) Emission spectra of 12c, 12g, and 12k, recorded at 2 µM in methanol.

sensitive to pH, with protonation of the pyrimidine ring resulting in fluorescence quenching. This study has generated further insight into the relationship between structure, conformation, and photoluminescent properties of biaryl-derived α-amino acids such as 12k that have the potential to act as fluorescent probes. Current work is investigating this potential for biological applications.

**EXPERIMENTAL SECTION**

All reagents and starting materials were obtained from commercial sources and used as received. Reactions were performed open to air unless otherwise mentioned. All reactions performed at elevated temperatures were heated using an oil bath. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was performed using silica gel 60 (40−63 μm). Aluminum-backed plates precoated with silica gel 60F254 were used for thin-layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate, vanillin, or ninhydrin. 1H NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer and data are reported as follows: chemical shift in ppm relative to the solvent as an internal standard (CHCl3, δ 7.26 ppm; CD3OH, δ 3.31 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, integration). The abbreviation br s refers to broad singlet. 13C NMR spectra were recorded on an NMR spectrometer at 101 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as an internal standard (CDCl3, δ 77.2 ppm; CD3OD, δ 49.0 ppm). Infrared spectra were recorded using a Shimadzu IR Prestige-21 spectrometer; wavenumbers are indicated in cm−1. Mass spectra were recorded using electrospray techniques. HRMS spectra were recorded using Bruker micrOTOF-Q or Agilent 6546 LC/Q-TOF mass spectrometers. Melting points are uncorrected. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. [α]D values are given in...
units 10⁻¹ deg cm⁻¹ g⁻¹. UV–vis spectra were recorded on a PerkinElmer Lambda 25 instrument. Fluorescence spectra were recorded on a Shimadzu RF-5301PC spectrofluorophotometer. Absorbance spectra were recorded with an integration time of 0.05 s and a band pass of 5 nm. Fluorescence spectra were recorded with excitation and emission band pass of 10 nm, an integration time of 0.1 or 2 s, and with detector accumulations set to 1. Quantum yield data were measured using anthracene and L-tryptophan as standard references.

**tert-Butyl (2S)-[tert-Butyloxycarbonyl]amino)-4-oxo-6-(4-cyanophenyl)hex-5-ynoate (10a).** A solution of n-butyllithium (2.5 M in hexane, 0.40 mL, 1.0 mmol), and tert-butyl (2S)-(tert-butyloxycarbonyl)amino)-4-oxo-6-phenylhex-5-ynoate (10b) as a white solid (0.42 g, 1.3 mmol), n-butyllithium (2.5 M in hexane, 0.40 mL, 1.0 mmol), and tert-butyl (2S)-(tert-butyloxycarbonyl)amino)-4-oxo-6-(4′-methoxyphenyl)hex-5-ynoate (10c) as a white solid (0.32 g, 74%). mp 118–120 °C; IR (neat) 3376, 2978, 2361, 2193, 1710, 1655, 1509, 1367, 1253, 1153, 1086, 739 cm⁻¹; [alpha]D = +16.4 (c = 0.1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 7.57–7.51 (m, 2H), 6.92–6.87 (m, 2H), 5.43 (d, J = 8.5 Hz, 1H), 4.50 (dt, J = 8.5, 4.5 Hz, 1H), 3.85 (s, 3H), 3.31 (dd, J = 17.5, 4.5 Hz, 1H), 3.16 (dd, J = 17.5, 4.5 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H); ¹³C(CH₃) NMR (CDCl₃, 101 MHz): δ 184.6, 169.9, 161.9, 155.5, 135.3, 114.4, 111.3, 98.7, 82.4, 79.5, 52.4, 47.2, 28.3, 27.9; MS (ESI) m/z 426 (M + Na)⁺ Calcd for C₂₆H₂₄NO₄Na: 426.8187; found 426.1727.

**tert-Butyl (2S)-[tert-Butyloxycarbonyl]amino)-4-oxo-6-phenylpyrimidin-6-ylpyranoate (11a).** tert-butyl (2S)-(tert-butyloxycarbonyl)amino)-4-oxo-6-phenylpyrimidin-6-ylpyranoate (10a) (0.046 g, 0.11 mmol) was dissolved in tetrahydrofuran (2 mL), followed by sequential addition of benzamidine hydrochloride (0.026 g, 0.17 mmol), potassium carbonate (0.018 g, 0.13 mmol), and ytterbium triflate (0.0070 g, 0.011 mmol). The mixture was heated to 50 °C for 48 h and then concentrated in vacuo. The residue was redissolved in dichloromethane (10 mL) and washed with a saturated solution of sodium hydrogen carbonate (5 mL) and then brine (5 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography eluting with 30% diethyl ether in petroleum gave tert-butyl (2S)-(tert-butyloxycarbonyl)amino)-4-oxo-6-phenylpyrimidin-6-ylpyranoate (11a) (0.039 g, 69%) as a yellow solid. Mp 95–100 °C; IR (neat) 3426, 2977, 1706, 1583, 1501, 1364, 1250, 1149, 1031, 837, 712 cm⁻¹; [alpha]D = +26.0 (c = 0.1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 8.61–8.57 (m, 2H), 8.23–8.19 (m, 2H), 7.53–7.49 (m, 6H), 7.47 (s, 1H), 5.94 (d, J = 8.6 Hz, 1H), 4.73 (dt, J = 8.6, 5.1 Hz, 1H), 3.49 (d, J = 15.7, 5.1 Hz, 1H), 3.36 (dd, J = 15.7, 5.1 Hz, 1H), 1.44 (s, 9H), 1.34 (s, 9H); ¹³C(CH₃) NMR (CDCl₃, 101 MHz): δ 170.7, 166.9, 160.3, 163.9, 157.6, 137.7, 137.0, 130.9, 130.7, 128.9, 128.5, 128.46, 127.2, 114.2, 81.9, 79.7, 52.5, 39.3, 28.4, 28.0; MS (ESI) m/z 498 (M + Na⁺, 100); HRMS (ESI) m/z: [M + Na⁺] Calcd for C₃₂H₂₄N₄O₄Na: 498.2363; found 498.2355.

**tert-Butyl (2S)-[tert-Butyloxycarbonyl]amino)-3′-[(2′-naphthyl)-2′-phenoxyphenylidin-6′-yl]pyranoate (11b).** tert-butyl (2S)-(tert-butyloxycarbonyl)amino)-3′-[(2′-naphthyl)-2′-phenoxyphenylidin-6′-yl]pyranoate (11b) was synthesized as described for...
11a using tert-butyl (2S)-(tert-butyloxycarbonylamo)-4-oxo-6-(2'-naphthyl)hex-5-yne-3-carboxylic acid (10b) (0.076 g, 0.18 mmol), benzamidine hydrochloride (0.042 g, 0.27 mmol), potassium carbonate (0.030 g, 0.22 mmol), and ytterbium triflate (0.014 g, 0.025 mmol). Purification by flash column chromatography eluting with 30% ethyl acetate in petroleum ether gave tert-butyl (2S)-(tert-butyloxycarbonylamo)-3-[4'-(2'-naphthyl)-2'-phenylpyrimidin-6-yl]-propanoate (11a) (0.067 g, 71%) as a white solid. Mp 130–133 °C; IR (neat) 3366, 2978, 1713, 1537, 1495, 1367, 1153, 1058, 760, 698 cm⁻¹; [α]D25 +10.0 (c 0.1, CHCl₃); [H] NMR (CDCl₃, 400 MHz): δ 8.72 (br s, 1H), 8.66–8.62 (m, 2H), 8.33 (dd, J = 8.6, 1.7 Hz, 1H), 8.03–8.01 (m, 3H), 7.63 (s, 1H), 7.58–7.50 (m, 5H), 5.95 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 5.2 (s, 2H), 1H), 3.40 (dd, J = 15.7, 5.2 Hz, 1H), 1.44 (s, 9H), 1.35 (s, 9H); 13C[H] NMR (CDCl₃, 101 MHz): δ 170.7, 166.5, 163.9, 163.0, 156.5, 135.6, 135.0, 128.0, 129.4, 128.8, 128.5, 128.4, 114.3, 113.3, 81.9, 79.6, 55.4, 52.5, 39.2, 28.4, 28.0; MS (EI) m/z 506 (M + H⁺) Calcd for C₄₃H₄₆N₄O₂H 506.2649; found 506.2647.

tert-Butyl (2S)-(tert-Butoxy carbonylamino)-3-[4'-(2'-methoxyphenyl)-2'-phenylpyrimidin-6-yl]-propanoate (11d). tert-Butyl (2S)-(tert-butyloxycarbonylamo)-3-[4'-(2'-methoxyphenyl)-2'-phenylpyrimidin-6-yl]-propanoate (11d) was synthesized as described for 11a using tert-butyl (2S)-(tert-butyloxycarbonylamo)-4-oxo-6-(2'-methoxyphenyl)hex-5-yne-3-carboxylic acid (10c) (0.44 g, 1.2 mmol), benzamidine hydrochloride (0.29 g, 1.8 mmol), potassium carbonate (0.30 g, 2.2 mmol), and ytterbium triflate (0.056 g, 0.91 mmol) was dissolved in tetrahydrofuran (30 mL), followed by sequential addition of acetamide hydrochloride (0.13 g, 1.4 mmol), potassium carbonate (0.30 g, 2.2 mmol), and ytterbium triflate (0.056 g, 0.91 mmol). The mixture was heated to 50 °C for 48 h and was concentrated in vacuo. The residue was redissolved in dichloromethane (30 mL), washed with a saturated solution of sodium hydrogen carbonate (20 mL), brine (20 mL), dried (MgSO₄), and concentrated in vacuo. Purification by flash column chromatography eluting with 30% ethyl acetate in petroleum ether gave tert-butyl (2S)-(tert-butyloxycarbonylamino)-3-[2'-methyl-4'-(phenylpyrimidin-6-yl)]propanoate (11e) (0.27 g, 71%) as a white solid. Mp 98–103 °C; IR (neat) 3665, 2979, 1705, 1580, 1541, 1366, 1149, 1055, 752, 693 cm⁻¹; [α]D18 +16.4 (c 0.1, CHCl₃); [H] NMR (CDCl₃, 400 MHz): δ 8.07–8.03 (m, 2H), 7.51–7.47 (m, 3H), 7.41 (s, 1H), 5.65 (d, J = 8.1 Hz, 1H), 4.67–4.62 (m, 1H, 3.33 (dd, J = 15.1, 5.7 Hz, 1H), 3.27 (dd, J = 15.1, 5.2 Hz, 1H), 2.76 (s, 3H), 1.42 (s, 9H), 1.40 (s, 9H); 13C[H] NMR (CDCl₃, 101 MHz): δ 170.4, 167.7, 166.4, 163.4, 155.4, 136.9, 128.9, 127.2, 113.8, 82.0, 79.7, 52.8, 39.4, 28.3, 27.9, 26.0; MS (ESI) m/z 436 (M + Na⁺, 100); HRMS (ESI) m/z: [M + Na⁺]⁺ Calcd for C₃₂H₄₂N₄O₄Na 436.2207; found 436.2208.
tert-Butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(4″-cya
nophenyl)-2′-methylpyrimidin-6′-yl]propanoate (11h). tert-
Butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(4″-cyanophenyl)-2′-
methylpyrimidin-6′-yl]propanoate (11h) was synthesized as de-
scribed for 11e using tert-butyl (2S)-(tert-butyloxycarbonyl)-4-
oxo-6-4′-cyanophenyl]hex-5-ynoate (10d) (0.084 g, 0.21 mmol), ace-
acetamide hydrochloride (0.030 g, 0.32 mmol), potassium car-
bonate (0.070 g, 0.50 mmol), and ytterbium triflate (0.013 g, 0.021 mmol). Purification by flash column chromatography eluting with 30% ethyl acetate in petroleum ether gave tert-butyl (2S)-(tert-
butyloxycarbonyl)amino]-3-[4′-(4″-cyanophenyl)-2′-
methylpyrimidin-6′-yl]propanoate (11k) (0.054 g, 50%) as a colorless oil. IR (neat) 3368, 2979, 1714, 1592, 1529, 1565, 1254, 1105, 1025 cm−1; [α]D20 +19.0 (c 0.1, CHCl3); 1H NMR (CDCl3, 400 MHz): δ 9.08 (s, 1H), 8.07–8.03 (m, 2H), 7.53 (s, 1H), 7.03–7.00 (m, 2H), 5.71 (d, J = 8.2 Hz, 1H), 4.65 (dt, J = 8.2, 5.6 Hz, 1H), 3.88 (s, 3H), 3.33 (dd, J = 15.1, 5.6 Hz, 1H), 3.25 (d, J = 15.1, 5.6 Hz, 1H), 1.42 (d, J = 14.1, 3.8 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 170.5, 166.1, 165.2, 162.1, 158.4, 155.5, 128.9, 128.7, 115.8, 114.4, 82.1, 79.8, 55.4, 52.8, 39.6, 28.3, 27.9; MS (ESI) m/z 430 (M + H+, 100); HRMS (ESI) m/z: [M + H+] Calculc for C28H25N3O4H 430.2386; found 430.2389.

tert-Butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(4″-
cyanophenyl)-2′-methylpyrimidin-6′-yl]propanoate (11l). tert-Butyl (2S)-(tert-butyloxycarbonyl)-4-
oxo-6-4′-cyanophenyl]hex-5-ynoate (10d) (0.085 g, 0.22 mmol) was dissolved in tert-butyl-
difluoride (15 mL) followed by sequential addition of formamide hydrochloride (0.18 g, 2.20 mmol), potassium carbonate (0.61 g, 4.40 mmol), and ytterbium triflate (0.027 g, 0.044 mmol). The mixture was heated to 50 °C for 48 h and was concentrated in vacuo. The residue was redissolved in dichloromethane (20 mL), washed with a saturated solution of sodium hydrogen carbonate (20 mL), brine (20 mL), dried (MgSO4), and concentrated in vacuo. Purification by flash column chromatography eluting with 30% ethyl acetate in petroleum ether gave tert-butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(4″-cyanophenyl)-2′-
methylpyrimidin-6′-yl]propanoate (11l) (0.053 g, 64%) as a colorless oil. IR (neat) 3668, 2977, 2977, 1713, 1587, 1512, 1368, 1254, 1156, 1024, 840, 747 cm−1; [α]D20 +40.0 (c 0.1, CHCl3); 1H NMR (CDCl3, 400 MHz): δ 9.15 (s, 1H), 8.09–8.05 (m, 2H), 7.60 (s, 1H), 7.53–7.49 (m, 3H), 5.69 (d, J = 8.5 Hz, 1H), 4.65–4.64 (m, 1H), 3.36 (dd, J = 15.2, 5.7 Hz, 1H), 3.29 (dd, J = 15.2, 5.0 Hz, 1H), 1.42 (s, 9H), 1.39 (s, 9H); 13C NMR (CDCl3, 101 MHz): δ 170.0, 166.8, 163.9, 158.5, 155.4, 136.6, 131.0, 129.0, 127.1, 116.8, 82.9, 79.8, 52.9, 39.7, 28.3, 27.9; MS (ESI) m/z 400 (M + H+, 100); HRMS (ESI) m/z: [M + H+] Calcd for C28H25N3O4H 400.2221; found 400.2229.

tert-Butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(2-
aphthyl)pyrimidin-6′-yl]propanoate (11j). tert-Butyl (2S)-2-
[(tert-Butyloxycarbonyl)amino]-3-[4′-(2-naphthyl)pyrimidin-6′-
yl]propanoate (11j) was synthesized as described for 11i using tert-butyl (2S)-(tert-butyloxycarbonyl)-4-
oxo-6-[2-naphthyl]hex-5-ynoate (10b) (0.080 g, 0.12 mmol), formamide hydrochloride (0.097 g, 1.20 mmol), potassium carbonate (0.33 g, 2.40 mmol), and ytterbium triflate (0.015 g, 0.024 mmol). Purification by flash column chromatography eluting with 30% ethyl acetate in petroleum ether gave tert-butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(2-
naphthyl)pyrimidin-6′-yl]propanoate (11j) (0.028 g, 52%) as a white solid. Mp 162–165 °C; IR (neat) 3436, 2979, 2273, 1715, 1497, 1366, 1152, 752, 694 cm−1; [α]D20 +340.0 (c 0.1, CHCl3); 1H NMR (CDCl3, 400 MHz): δ 9.20 (s, 1H), 8.61 (brs, s, 1H), 8.15 (dd, J = 8.6, 1.5 Hz, 1H), 7.99–7.95 (m, 2H), 7.92–7.87 (m, 1H), 7.75 (s, 1H), 7.59–7.53 (m, 2H), 5.72 (d, J = 8.2 Hz, 1H), 4.72–4.67 (m, 1H), 3.40 (d, J = 15.1, 5.9 Hz, 1H), 3.33 (dd, J = 15.1, 5.1 Hz, 1H), 1.43 (s, 9H), 1.40 (s, 9H); 13C NMR (CDCl3, 101 MHz): δ 170.5, 166.9, 163.8, 158.5, 155.5, 134.6, 133.7, 133.3, 129.0, 128.84, 128.75, 127.5, 126.7, 123.8, 116.9, 82.2, 79.9, 52.8, 39.7, 28.3, 27.9; MS (ESI) m/z 448 [M + H+]100; HRMS (ESI) m/z: [M + H+] Calcd for C25H22N3O4 448.2242; found 448.2230.

tert-Butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(4-
methoxyphenyl)-2′-methylpyrimidin-6′-yl]propanoate (11k). tert-Butyl (2S)-2-[(tert-Butyloxycarbonyl)amino]-3-[4′-(4″-methoxyphenyl)-2′-
methylpyrimidin-6′-yl]propanoate (11k) was synthesized as described for 11i using tert-butyl (2S)-(tert-butyloxycarbonyl)-4-
oxo-6-(4-
(2S)-2-Amino-3-[(4′-methoxyphenyl)-2′-phenylpyrimidin-6-′]yl)propanoic Acid Hydrochloride (12c). (2S)-2-Amino-3-[(4′-methoxyphenyl)-2′-phenylpyrimidin-6-′]yl)propanoic acid hydrochloride (12c) was prepared as described for 12a using tert-butyl (2S)-2-(tert-butoxycarbonylamo)ino-3-[(4′-methoxyphenyl)-2′-phenylpyrimidin-6′]ylpropanoate (11c) (0.124 g, 0.28 mmol). This gave (2S)-2-amino-3-[(4′-methoxyphenyl)-2′-phenylpyrimidin-6′]yl)propanoic acid hydrochloride (12c) as a white solid (0.073 g, 95%). Mp 167–168 °C; IR (neat) 3354, 2922, 1641, 1592, 1526, 1501, 1490, 1362, 1011 cm−1; [α]32 +130 (c 0.1, MeOH); 1H NMR (CD3OD, 400 MHz): δ 8.38−8.33 (m, 2H), 7.70 (s, 1H), 7.64−7.57 (m, 2H), 4.67 (t, J = 4.7 Hz, 2H), 3.69 (d, J = 4.6 Hz, 2H); 13C[3]H NMR (CD3OD, 101 MHz): δ 169.1, 165.7, 164.4, 162.6, 140.8, 137.0, 132.6, 130.9, 128.3, 128.2, 127.9, 117.9, 115.0, 114.2, 50.6, 36.0; MS (ESI) m/z 345 (M + H, 100); HRMS (ESI) m/z: [M + H]+ Calcd for C21H19NO2H 345.3416; found 345.3419.

(2S)-2-Amino-3-[(2′-methyl-4′-phenylpyrimidin-6′-yl)propanoic Acid Hydrochloride (12e). (2S)-2-Amino-3-[(2′-methyl-4′-phenylpyrimidin-6′-yl)propanoic acid hydrochloride (12e) was prepared as described for 12a using tert-butyl (2S)-2-(tert-butoxycarbonylamo)ino-3-[(2′-methyl-4′-phenylpyrimidin-6′-yl)propanoate (11e) (0.12 g, 0.53 mmol). This gave (2S)-2-amino-3-[(2′-methyl-4′-phenylpyrimidin-6′-yl)propanoic acid hydrochloride (12e) as a white solid (0.073 g, 95%). Mp 168−169 °C; IR (neat) 3354, 2922, 1641, 1592, 1526, 1490, 1362, 1250, 1173, 770 cm−1; [α]32 +150 (c 0.1, MeOH); 1H NMR (CD3OD, 400 MHz): δ 8.88−8.84 (m, 2H), 8.49 (d, J = 7.9 Hz, 2H), 7.96 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.55−7.50 (m, 3H), 4.69 (t, J = 4.6 Hz, 2H), 3.69 (d, J = 4.6 Hz, 2H); 13C[3]H NMR (CD3OD, 101 MHz): δ 169.1, 165.7, 164.4, 162.6, 140.8, 137.0, 132.6, 130.9, 128.3, 128.2, 127.9, 117.9, 115.0, 114.2, 50.6, 36.0; MS (ESI) m/z 345 (M + H, 100); HRMS (ESI) m/z: [M + H]+ Calcd for C21H19NO2H 345.3416; found 345.3419.

(2S)-2-Amino-3-[(2′-methyl-4′-naphthoyl)pyrimidin-6′-yl]propanoic Acid Hydrochloride (12i). (2S)-2-Amino-3-[(2′-methyl-4′-naphthoyl)pyrimidin-6′-yl]propanoic acid hydrochloride (12i) was prepared as described for 12a using tert-butyl (2S)-2-(tert-butoxycarbonylamo)ino-3-[(2′-methyl-4′-naphthoyl)pyrimidin-6′-yl]propanoate (11i) (0.088 g, 0.18 mmol). Following completion, the reaction mixture was concentrated in vacuo. This gave (2S)-2-amino-3-[(2′-methyl-4′-naphthoyl)pyrimidin-6′-yl]propanoic acid hydrochloride (12i) as a yellow oil (0.057 g, 92%). IR (neat) 3354, 2936, 1712, 1646, 1588, 1516, 1366, 1251, 1173, 770 cm−1; [α]32 +150 (c 0.1, MeOH); 1H NMR (CD3OD, 400 MHz): δ 8.88−8.84 (m, 2H), 8.49 (d, J = 7.9 Hz, 2H), 7.96 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.55−7.50 (m, 3H), 4.69 (t, J = 4.6 Hz, 2H), 3.69 (d, J = 4.6 Hz, 2H); 13C[3]H NMR (CD3OD, 101 MHz): δ 169.8, 165.7, 164.4, 162.6, 140.8, 137.0, 132.6, 130.9, 128.3, 128.2, 127.9, 117.9, 115.0, 114.2, 50.6, 36.0; MS (ESI) m/z 345 (M + H, 100); HRMS (ESI) m/z: [M + H]+ Calcd for C21H19NO2H 345.3416; found 345.3419.
methoxyphenyl)pyrimidin-6-yl]propanoic acid hydrochloride (12k) was prepared as described for 12a using tert-butyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[(4′-methoxyphenyl)pyrimidin-6-yl]propanoate (11k) (0.73 g, 1.7 mmol). Following completion, the reaction mixture was concentrated in vacuo. This gave (2S)-2-amino-3-[(4′-methoxyphenyl)pyrimidin-6-yl]propanoic acid hydrochloride (12k) as a yellow oil (0.44 g, 95%); IR ( neat) 3401, 2844, 1749, 128.2, 118.2, 117.8, 114.7, 50.8, 35.5; MS (ESI) m/z 269.1033; found 269.1037.

The data underlying this study are available in the published Supporting Information is available free of charge at The Journal of Organic Chemistry.

The authors declare no competing financial interest.

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