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RESEARCH ARTICLE

Facile ring opening reaction of oxazolone enables efficient amidation for aminoisobutyric acid

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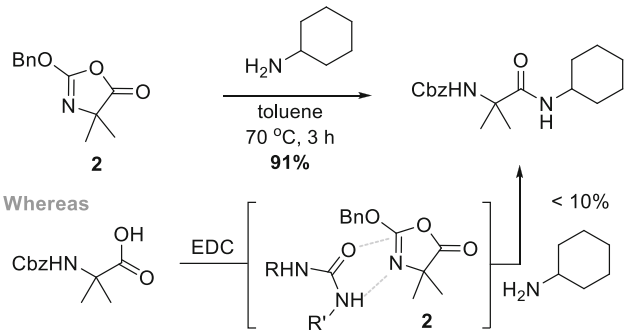
Abstract 4,4-Dimethyloxazolones derived from *N*-protected aminoisobutyric acid (AIB) are particularly known as poor electrophiles due to the steric hindrance around the carbonyl and not employed as useful intermediates for amidation whereas numerous examples have been reported to support the utility of other oxazolones in amidation. AIB is an important and strategical synthon in medicinal chemistry but the peptide bond formation of the *N*-protected urethane derivatives of AIB is known to be often unproductive due to the rapid formation of the stable 4,4-dimethyloxazolone via an intramolecular cyclization. We discovered that the 4,4-dimethyloxazolone of an AIB urethane is in fact an excellent electrophile that enables efficient amidation even with weakly reactive nucleophiles. The 4,4-dimethyloxazolone can be stored in a pure form and used as a reagent offering an efficient and convenient synthetic tool for generating AIB-peptide analogs.

Graphical Abstract



Keywords Aminoisobutyric acid (AIB) · 4,4-Dimethyloxazolone · Amidation · Urea by-product

Introduction

Peptides offer a vast chemical space in drug discovery and a myriad of therapeutic agents were developed based on natural or unnatural peptide structures (Henninot et al. 2018; Wieland and Bodanszky 2012; Pekary 2013). Plasma exposure level and duration time of peptide agents are most affected by their ability resisting hydrolysis engaged by endogenous proteolytic enzymes. Medicinal chemists endeavor to employ unnatural amino acids bearing a bulky substituent or a non-protogenic α-carbon in the peptide design in order to overcome the metabolic hurdle. Aminoisobutyric acid (AIB) is therefore a very useful structural motif in medicinal chemistry and often strategically incorporated in drug molecules to enhance metabolic stability or induce tighter binding to biological target protein (Fig. 1) (Frydman-Marom et al. 2011; Hansen et al. 1986).

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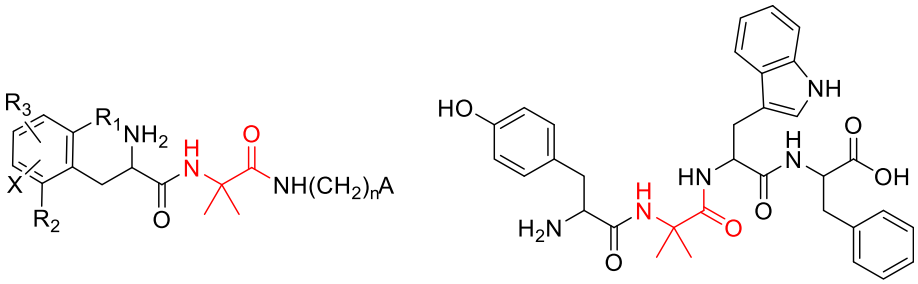
Fig. 1 Examples of pharmaceutical agents bearing AIB



Despite its utility in medicinal chemistry, peptide bond formation with AIB is often found to be unproductive because its carboxyl group is sterically very hindered by the geminal dimethyl groups. Moreover, the reaction intermediate from the commercial *N*-protected urethanes of AIB undergoes an elusive formation of 4,4-dimethyloxazolone as the byproduct and it is highly accelerated owing to Thorpe-Ingold effect (Fig. 2) (Hroch et al. 2012; Kaneti et al. 2004; Humphrey and Chamberlin 1997). In contrary to the common knowledge that oxazolones are also useful tools for peptide bond formation (Plucinska and Liberek 1987; Savage 2015), 4,4-dimethyloxazolones are particularly classified as poor electrophiles for the purpose due to steric hindrance. The troubles with amidating AIB get aggravated when reactivity of the amine coupling partner is sterically or electronically challenged.

The unmet needs associated with AIB chemistry have been recognized by Schafmeister's group with a view to circumvent the formation of the oxazolone byproduct and develop a new amidation protocol for AIB. They found that the acid fluoride derivative of Fluorenylmethyloxycarbonyl-protected AIB is free of the unproductive intramolecular cyclization and reacts with amino acids to afford the desired dipeptides. They hypothesized that the reaction initially proceeds through an amino-anhydride intermediate which rearranges to the desired peptide product (Scheme 1) (Brown and Schafmeister 2008).

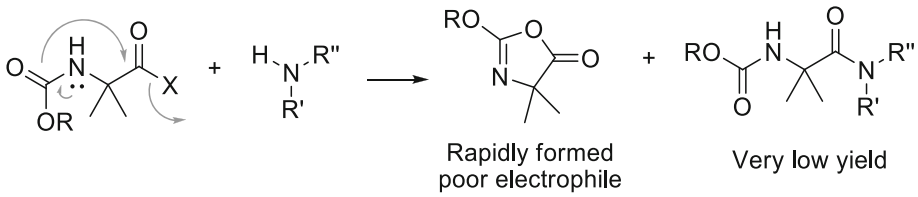
While preparation of AIB-containing dipeptides has been well addressed by the work, the examples of coupling partners therein are limited to amino acids mechanistically and a rather expensive solvent has to be used and the yields were reported based only on HPLC analysis. We were prompted at discovering an alternative protocol that enables a scalable and more general synthesis of AIB-amides by using the AIB-oxazolone formation to our advantage. In extension of our recent work on an efficient amidation of AIB methyl ester (Jo et al. 2018), herein we report a practical method of amidating AIB by rediscovering the 4,4-dimethyloxazolone as a useful coupling reagent.

Results and discussion

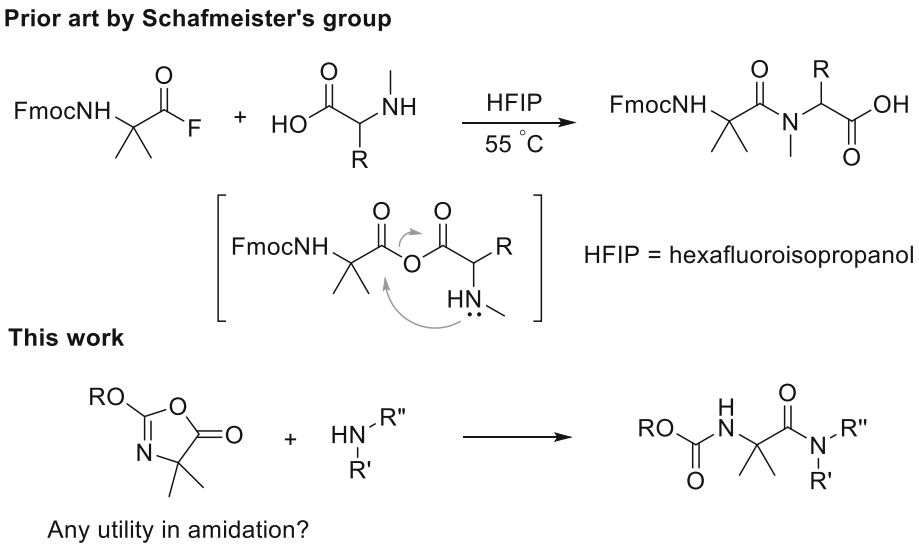
We set out our research by taking a commercial benzyl urethane of AIB (Carboxybenzyl-AIB-OH, Cbz-AIB-OH) in an ethylcarbodiimide(EDC)-mediated coupling condition with a highly reactive cyclohexylamine and monitored the formation of the oxazolone and the amidation product. As reported in literature a high percentage of 2-benzyloxy-4,4-oxazolone (**2**) formation was observed and the desired coupling product **1** was obtained only in less than 10% yield (Scheme 2) even at elevated temperature up to 80 °C in toluene. The similar product ratio was obtained with other coupling reagents such as dicyclohexylcarbodiimide, HATU (hexafluorophosphate azabenzotriazole tetramethyl uronium) and T3P (propylphosphonic anhydride). We witnessed formation of **2** was very rapid indeed even at − 78 °C and did not detect any starting acid by TLC analysis at 2 min of the reaction. By treating Cbz-AIB-OH only with EDC, **2** could be obtained consistently in near quantitative yields and stored at ambient temperature.

With the readily available **2** in hand, we began to question if **2** is an actual cul-de-sac of AIB amidation as generally accepted and became much curious about its reactivity and the potential utility for amidation. Since 2-aminothiazoles frequently serve to be key elements of pharmacophores in medicinal chemistry, we proposed that a coupling reaction with 2-aminothiazole should be a good model study to set a standard for the reactivity of **2**. Therefore, we treated a purely isolated material of **2** with

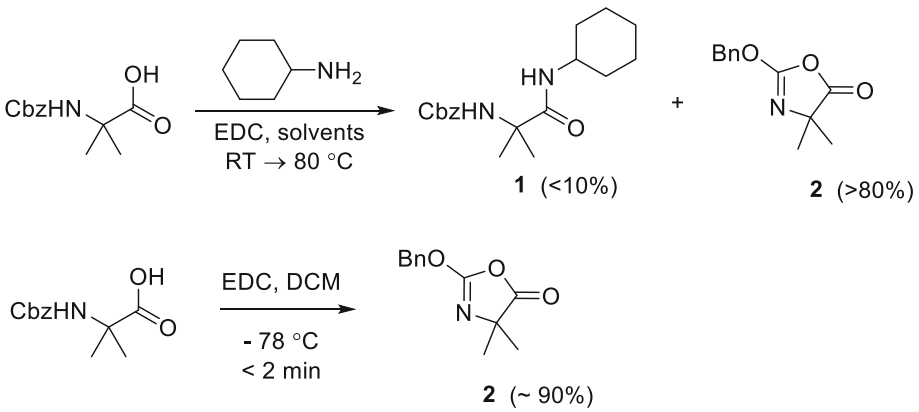
Fig. 2 Formation of 4,4-dimethyloxazolone during amidation of AIB

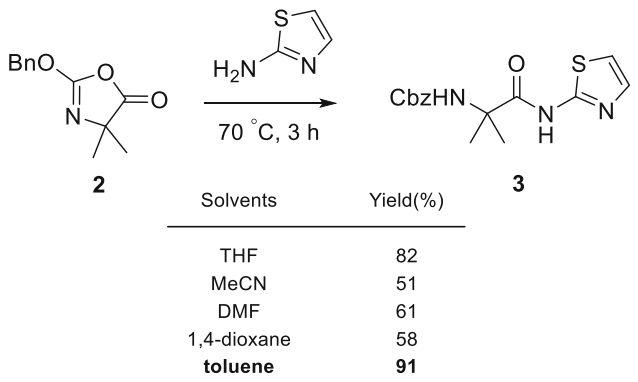


Scheme 1 Precedent synthetic methods in literature



Scheme 2 Rapid formation of 4,4-dimethyloxazolone under a conventional amidation condition





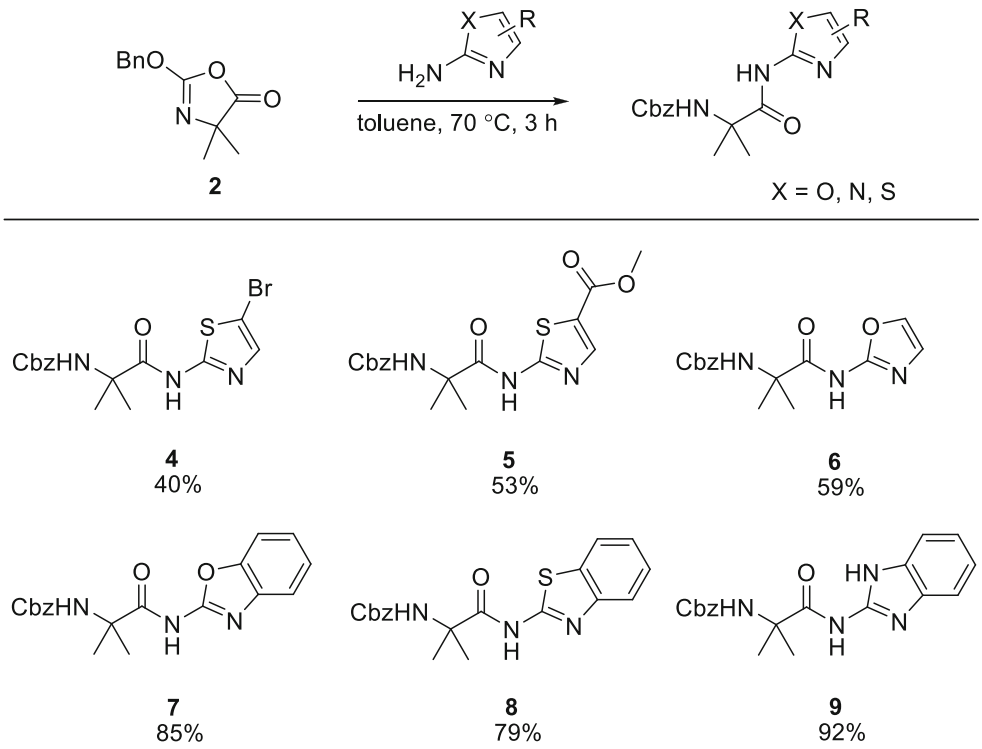
Solvents	Yield(%)
THF	82
MeCN	51
DMF	61
1,4-dioxane	58
toluene	**91**

Scheme 3 A model study: reaction of 4,4-dimethyloxazolone with 2-aminothiazole using no other additive

the commercial 2-aminothiazole in different solvents using no other additive. We were pleasantly surprised to observe by TLC that the desired coupling product **3** started to form even at room temperature. Mild heating was necessary to completely consume **2** which, upon elevating temperature, began to slowly decompose to unidentified multiple products more significantly in solvents more polar than toluene. In the optimized condition, **2** was transformed in toluene to the coupling product **3** after 3 h at 70 °C in a 91% isolated yield (Scheme 3).

With this evidence suggesting that **2** is rather a potentially useful and reactive species for amidation, our attention was then attracted toward investigating other amine nucleophiles. As a starting platform, we selected the 2-aminoazoles that are frequently employed in peptidomimetic design hoping to validate the utility of **2** for pharmaceutically valuable scaffolds. Under the same reaction condition various 2-aminoazoles were tested and the results are summarized in the Scheme 4. **2** responded to the amine nucleophile's electronic character in a very straightforward manner. As demonstrated by the examples **4** and **5**, substitution on the 2-aminothiazole ring by electron withdrawing groups negatively impacted the efficiency of the reaction. By the same token, the reaction with 2-aminooxazole was less productive compared with 2-aminothiazole. Bicyclic 2-aminobenzoazoles, however, were excellent nucleophiles and produced the

Scheme 4 Reaction of the benzyloxyoxazolone **2** with 2-aminoazoles

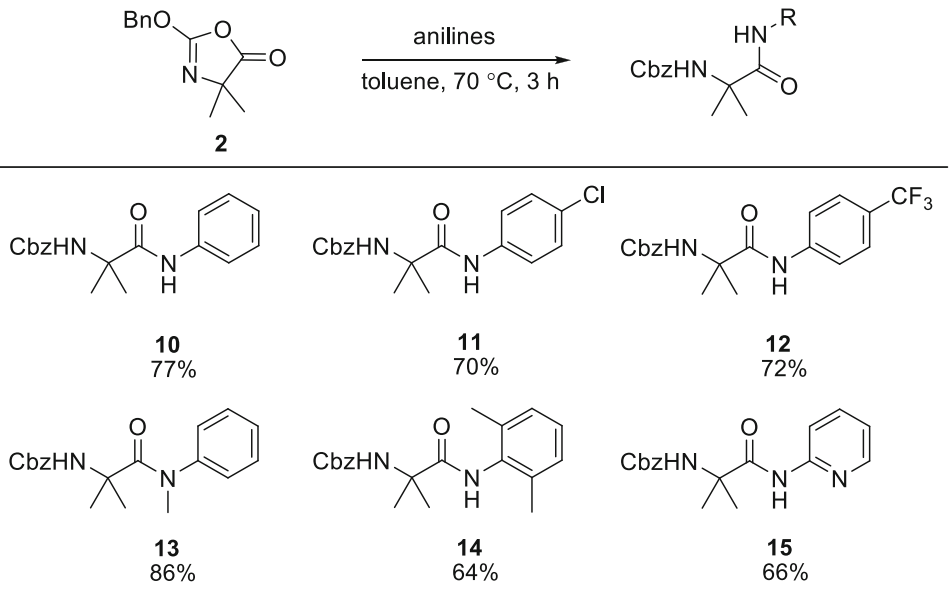


corresponding coupling products **7**–**9** in very good yields. Overall, the efficiency of the coupling reaction using **2** was highly acceptable or rather very satisfactory for the class of only moderately reactive nucleophiles.

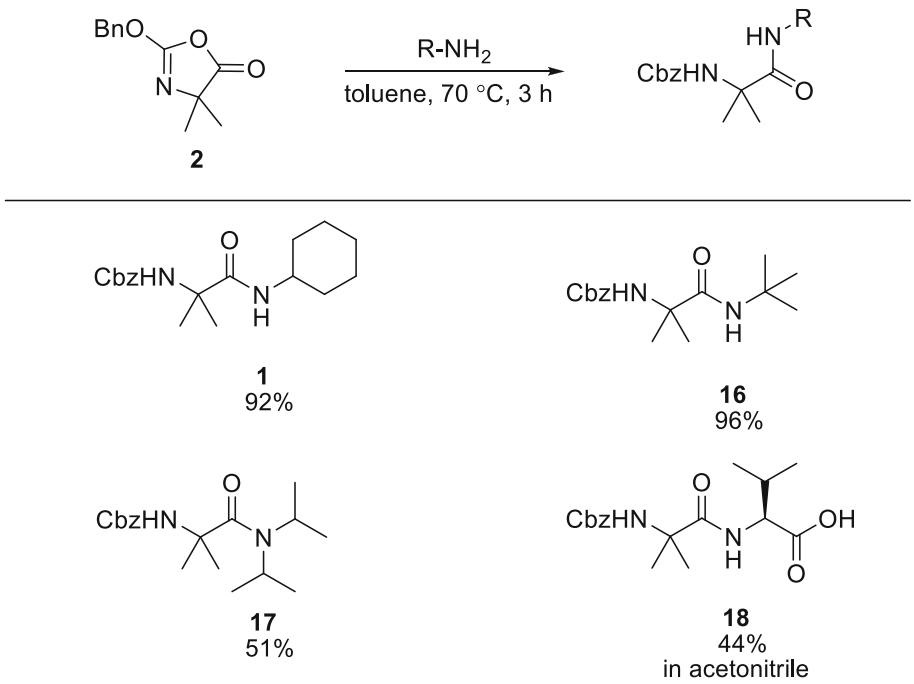
In the case of anilines, the electron withdrawing substituents did not significantly influence the productivity and the coupling reaction afforded the desired amides in good to excellent yields (Scheme 5). Even when we challenged the reaction with various levels of steric hindrance, ring-opening of **2** occurred efficiently to give **13** and **14** in good yields. 2-Aminopyridine also reacted with **2** faithfully and produced **15** in 66% yield that is comparable or superior to the reported yields reported for amidating 2-aminopyridine using conventional methods (Xu et al. 2011; Priepke 2007).

Aliphatic amines were also tested using this protocol as depicted in Scheme 6. The oxazolone **2** reacted almost quantitatively with the cyclohexylamine that previously failed to react with Cbz-AIB under the EDC-mediated coupling condition.

Scheme 5 Reaction of the bezyloxyoxazolone **2** with anilines



Scheme 6 Reaction of the benzyloxyoxazolone **2** with aliphatic amines



Other aliphatic amines carrying a large steric bulk such as *t*-butylamine and diisopropylamine also successfully produced the corresponding coupling adducts in 96 and 51% yields respectively. Amino acids were not sufficiently soluble in toluene. In acetonitrile L-valine reacted with **2** and **18** was isolated in 44% yield. However, a reaction with *N*-methyl-L-valine was not successful and it can be ascribed to the extreme steric interaction between the two reactants.

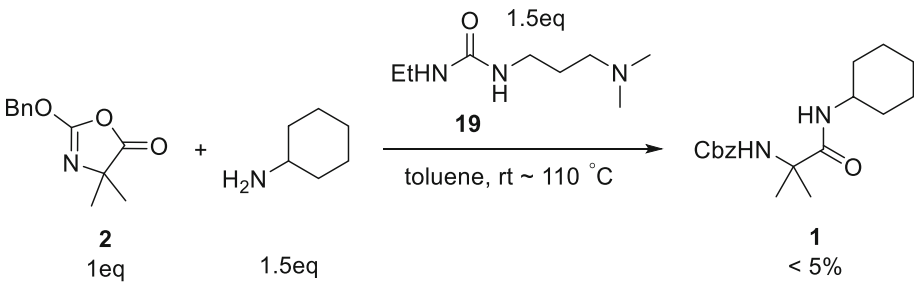
Finally, we questioned why the conventional carbodiimide-mediated amidation has been unproductive and we designed an experiment adding the urea **19** to the same reaction that previously led **2** to form **1** in 92% yield (Scheme 7). It turned out the presence of **19** suppressed the reaction to almost none and the identical pattern was observed with all the amine nucleophiles we tested with **2**. It suggested that carbodiimide-based amidations are deterred unavoidably by its urea byproduct (Chen and Turecek 2005). In order to elucidate the mechanism of this unproductive event with **19**, we followed ^{1}H-NMR spectra of **19** in deuterated toluene altering **2**'s concentration. We obtained a spectroscopic evidence of a bimolecular interaction between **19** and **2** as shown in Fig. 3. A proton of **19**'s urea region notably reacted along with dose escalation of **2** indicating an intermolecular hydrogen bond building between the two molecules. We propose that the oxazolone **2** is stabilized through a 6-membered ring formation as depicted below, which should account for the reduced reactivity of **2** observed in Scheme 7.

Materials and methods

General

All reactants or reagents were purchased from Sigma Aldrich Co. or Tokyo Chemical Industry and used without purification. Silica gel column chromatography was performed with Silica Gel of Kieselgel 60 F254 plate(Merck). All ^{1}H NMR and ^{13}C NMR spectra of organic products

Scheme 7 Observation of the urea **19** deterring **2**'s amidation



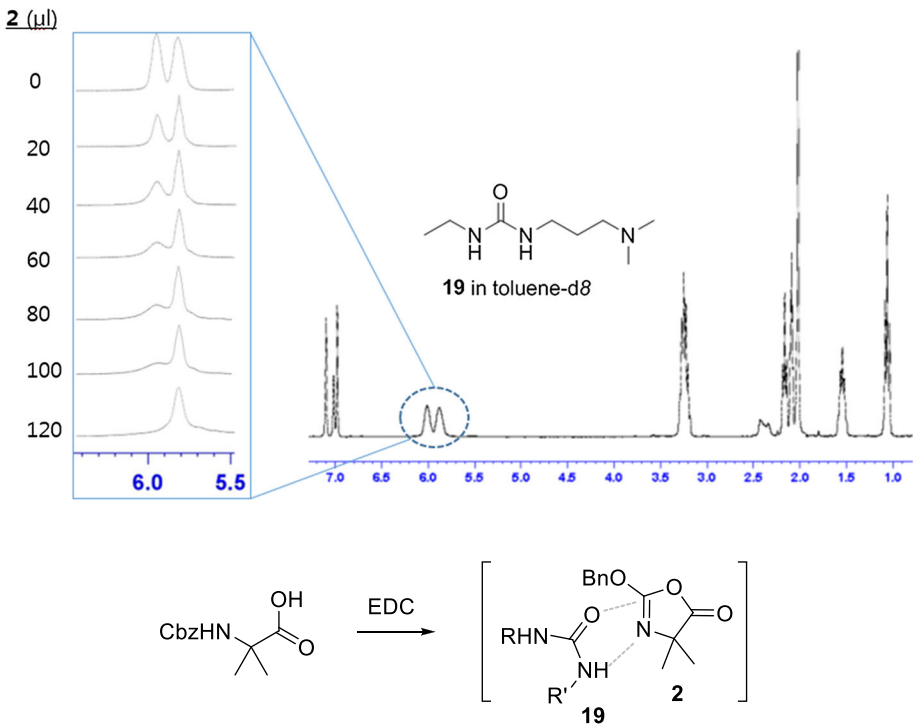


Fig. 3 Evidence of an interaction between **2** and **19** by ^{1}H-NMR experiments and a proposal for the bimolecular adduct

were recorded on Bruker DPX 300 MHz or 600 MHz Spectrometer. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), and integration. High-resolution mass spectra (HRMS) were recorded on the Agilent 6530 Q-TOF mass spectrometer.

General procedure for transamidation

Oxazolone (**2**; 0.251 mmol, 1 eq) and amine nucleophile (0.326 mmol, 1.3 eq) was dissolved in toluene (1 mL) to a concentration of 0.251 M. The reaction mixture was stirred at 70 °C for 3 h, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-heptane/EtOAc as the eluents to afford compound.

Preparation of 2-benzyloxy-4,4-dimethyloxazolone and spectral data of all compounds

*2-(Benzyloxy)-4,4-dimethyloxazol-5(4H)-one (**2**) (Nakajima et al. 2016)*

Cbz-Aib-OH (2.107 mmol, 1 eq) and EDC (2.53 mmol, 1.2 eq) was dissolved in DCM (8 mL) to a concentration of 0.263 M. The reaction mixture was stirred at RT for 5 h, and washed with water. The aqueous layer was extracted with DCM (3 times) and the combined organic extracts were washed with brine and dried over $MgSO_4$. It was then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-heptane/EtOAc as the eluents to afford compound (yield: 70 ∼ 80%).

^{1}H NMR (300 MHz, ($CDCl_3$): δ 7.45–7.35 (m, 5H), 5.322 (s, 2H), 1.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8, 156.9, 134.1, 128.9, 128.6, 128.3, 71.5, 66.7, 25.2.

*Benzyl (1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)carbamate (**1**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.38–7.31 (m, 5H), 6.84 (s, 1H), 6.55 (s, 1H), 5.05 (s, 2H), 3.65–3.62 (m, 1H), 1.794–1.66 (m, 4H), 1.47 (s, 6H), 1.38–1.08 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.2, 155.1, 136.4, 128.6, 128.2, 128.1, 66.6, 56.8, 48.2, 32.8, 25.5, 24.7; HRMS (ESI): m/z calcd for $C_{18}H_{26}N_2NaO_3$: 341.1841 $[M + Na]^+$; found: 341.1850.

*Benzyl (2-methyl-1-oxo-1-(thiazol-2-ylamino)propan-2-yl)carbamate (**3**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 10.92 (s, 1H) 7.43 (d, J = 3.6 Hz, 6H), 7.34 (s, 1H), 7.12 (d, J = 3.6 Hz, 1H), 6.85 (s, 1H), 5.06 (s, 2H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 172.9, 158.6, 155.2, 137.6, 137.0, 128.3, 128.1, 127.8, 113.1, 65.9, 56.7, 24.5; HRMS (ESI): m/z calcd for $C_{15}H_{17}N_3NaO_3S$: 342.0888 $[M + Na]^+$; found: 342.0893.

*Benzyl (1-((5-bromothiazol-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (**4**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 11.02 (s, 1H), 7.29 (s, 1H), 7.20 (s, 5H), 6.74 (s, 1H), 4.91 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): 173.6, 159.0, 155.2, 138.6, 136.9, 128.3, 128.1, 127.8, 101.9, 66.0, 56.6, 24.41; HRMS (ESI): m/z calcd for $C_{15}H_{16}BrN_3NaO_3S$: 419.9993 $[M + Na]^+$; found: 420.0010.

*Methyl 2-(2-(((benzyloxy)carbonyl)amino)-2-methylpropanamido)thiazole-5-carboxylate (**5**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 11.39 (s, 1H), 8.06 (s, 1H), 7.35 (s, 5H), 6.96 (s, 1H), 5.05 (s, 2H), 3.85 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 173.7, 162.9, 162.0, 155.2, 144.8, 136.9, 128.3, 127.8, 127.6, 121.9, 66.0, 56.7, 51.4, 24.3; HRMS (ESI): m/z calcd for $C_{17}H_{19}N_3NaO_5S$: 400.0943 $[M + Na]^+$; found: 400.0947.

*Benzyl (2-methyl-1-(oxazol-2-ylamino)-1-oxopropan-2-yl)carbamate (**6**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.44 (s, 1H), 7.35 (s, 5H) 6.99 (s, 1H), 5.12 (br s, 3H), 1.599 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 173.2, 155.3, 153.9, 137.3, 136.8, 128.7, 128.2, 128.1, 127.1, 65.7, 56.9, 25.2; HRMS (ESI): m/z calcd for $C_{15}H_{17}N_3NaO_4$: 326.1117 $[M + Na]^+$; found: 326.1112.

*Benzyl (1-(benzo[d]oxazol-2-ylamino)-2-methyl-1-oxopropan-2-yl)carbamate (**7**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.353 (s, 2H), 7.20 (br s, 7H), 6.81 (s, 1H), 4.90 (s, 2H), 2.83 (s, 1H), 1.45 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 172.9, 156.1, 155.4, 148.2, 141.2, 137.4, 128.7, 128.2, 128.1, 124.9, 124.0, 118.6, 110.4, 65.8, 57.3, 25.1; HRMS (ESI): m/z calcd for $C_{19}H_{19}N_3NaO_4$: 376.1273 $[M + Na]^+$; found: 376.1279.

*Benzyl (1-(benzo[d]thiazol-2-ylamino)-2-methyl-1-oxopropan-2-yl)carbamate (**8**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.95 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.46–7.29 (m, 7H), 6.94 (s, 1H), 5.07 (s, 2H), 1.65 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 158.2, 155.5, 148.3, 135.5, 132.2, 128.6, 128.4, 128.4, 126.2, 123.9, 121.4, 120.9, 67.6, 57.4, 25.3; HRMS (ESI): m/z calcd for $C_{19}H_{19}N_3NaO_3S$: 392.1045 $[M + Na]^+$; found: 392.1055.

*Benzyl (1-((1H-benzo[d]imidazol-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (**9**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.45 (m, 2H), 7.34 (s, 4H), 7.26–7.219 (m, 2H), 5.09 (s, 2H), 1.63 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.8, 175.6, 154.7, 147.9, 135.9, 128.4, 128.2, 128.1, 122.3, 113.9, 67.1, 57.3, 25.1; HRMS (ESI): m/z calcd for $C_{19}H_{20}N_4NaO_3$: 375.1433 $[M + Na]^+$; found: 375.1439.

*Benzyl (2-methyl-1-oxo-1-(phenylamino)propan-2-yl)carbamate (**10**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 9.11 (s, 1H), 7.65 (d, J = 0.9 Hz, 2H), 7.36–7.26 (m, 7H), 7.05 (t, J = 7.5 Hz, 1H), 6.70 (s, 1H), 5.07 (s, 2H), 1.57 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.1, 155.7, 137.9, 135.9, 128.9, 128.6, 128.4, 128.3, 124.2, 119.9, 67.2, 57.9, 25.6; HRMS (ESI): m/z calcd for $C_{18}H_{20}N_2NaO_3$: 335.1372 $[M + Na]^+$; found: 335.1378.

*Benzyl (1-((4-chlorophenyl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (**11**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 9.28 (s, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.36–7.30 (m, 7H), 6.74 (s, 1H), 5.06 (s, 2H), 1.55 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.2, 155.8, 136.5, 135.8, 129.1, 128.9, 128.6, 128.5, 128.3, 121.2, 67.3, 57.9, 25.6; HRMS (ESI): m/z calcd for $C_{18}H_{19}ClN_2NaO_3$: 369.0982 $[M + Na]^+$ found: 369.0977.

*Benzyl (2-methyl-1-oxo-1-((4-(trifluoromethyl)phenyl)amino)propan-2-yl)carbamate (**12**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 9.53 (s, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.36 (s, 5H), 6.80 (s, 1H), 5.06 (s, 2H), 1.56 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 173.4, 155.1, 143.0, 137.1, 128.3, 127.8, 125.8, 125.7, 125.7, 125.6, 119.5, 65.8, 57.3, 24.6; HRMS (ESI): m/z calcd for $C_{19}H_{19}F_3N_2NaO_3$: 403.1245 $[M + Na]^+$ found: 403.1243.

*Benzyl (2-methyl-1-(methyl(phenyl)amino)-1-oxopropan-2-yl)carbamate (**13**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.34–7.23 (m, 10H), 6.04 (s, 1H), 4.99 (s, 2H), 3.18 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.2, 154.0, 144.5, 136.4, 129.3, 128.5, 128.4, 128.2, 127.8, 127.6, 66.3, 57.8, 41.3, 27.2; HRMS (ESI): m/z calcd for $C_{19}H_{22}N_2NaO_3$: 349.1528 $[M + Na]^+$ found: 349.1538.

*Benzyl (1-((2,6-dimethylphenyl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (**14**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 8.57 (s, 1H), 7.39–7.33 (m, 5H), 7.04 (s, 3H), 6.75 (s, 1H), 5.09 (s, 2H), 2.19 (s, 6H), 1.64 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 172.5, 155.0, 137.2, 136.0, 135.1, 128.3, 127.8, 127.7, 127.6, 126.5, 65.7, 56.9, 25.0, 17.7; HRMS (ESI): m/z calcd for $C_{20}H_{24}N_2NaO_3$: 363.1685 $[M + Na]^+$ found: 363.1690.

*Benzyl (2-methyl-1-oxo-1-(pyridin-2-ylamino)propan-2-yl)carbamate (**15**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 9.11 (s, 1H), 8.29 (d, J = 3.9 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.73 (t, J = 8.1 Hz, 1H), 7.35 (br s, 5H), 7.11–7.07 (m, 1H), 6.91 (s, 1H), 5.08 (s, 2H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $(CDCl_3)$: δ 172.8, 155.1, 151.4, 147.7, 138.3, 135.9, 128.5, 128.2, 128.2, 119.8, 113.9, 67.2, 57.7, 25.5; HRMS (ESI): m/z calcd for $C_{17}H_{19}N_3NaO_3$: 336.1324 $[M + Na]^+$; found: 336.1327.

*Benzyl (1-(tert-butylamino)-2-methyl-1-oxopropan-2-yl)carbamate (**16**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.38-7.34 (m, 5H), 6.56 (s, 2H), 5.07 (s, 2H), 1.45 (s, 6H), 1.28 (s, 9H)); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.4, 155.0, 136.4, 128.5, 128.2, 128.1, 66.5, 57.2, 50.9, 28.5, 25.5; HRMS (ESI): m/z calcd for $C_{16}H_{24}N_2NaO_3$: 315.1685 $[M + Na]^+$; found: 315.1689.

*Benzyl (1-(diisopropylamino)-2-methyl-1-oxopropan-2-yl)carbamate (**17**)*

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.42–7.30 (m, 5H), 5.47 (s, 1H), 5.07 (s, 2H), 3.79 (m, J = 6.9 Hz, 2H), 1.47 (s, 6H), 1.21 (d, J = 6.9 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 156.3, 136.1, 128.4, 128.0, 128.0, 66.8, 56.5, 44.8, 25.8, 21.3; HRMS (ESI): m/z calcd for $C_{18}H_{28}N_2NaO_3$: 343.1998 $[M + Na]^+$ found: 343.2003.

*(2-(((Benzyloxy)carbonyl)amino)-2-methylpropanoyl)-L-valine (**18**)*

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.33 (s, 5H) 6.91 (s, 1H), 5.41 (s, 1H), 5.11–5.06 (m, 2H), 4.51 (s, 1H), 2.21 (s, 1H), 1.56–1.51 (m, 6H), 0.93-0.86 (m, 6H); ^{13}C NMR (150 MHz, $(CD_3)_2CO$): 174.2, 172.3, 155.0, 128.3, 127.8, 127.7, 127.6, 65.7, 57.0, 56.7, 30.9, 18.6, 17.1; HRMS (ESI): m/z calcd for $C_{17}H_{23}N_2O_5$: 335.1612 $[M-H]^-$ found: 335.1611.

Conclusion

In summary, we believe that it is necessary to reconsider the 4,4-dimethyloxazolone **2** as rather a highly available, storable and synthetically very useful substrate for amidating AIB. We demonstrated that a wide range of nucleophilicity and steric bulk in amine nucleophiles was compatible with **2** attesting to its synthetic utility in AIB chemistry. It's worth to note that, by the nature of the reaction, only minimal purification is needed for this protocol and the procedure is in many aspects advantageous and convenient particularly for medicinal chemists who routinely generate many analogs at a time. We envision that the findings described in this work would serve to position **2** as a new reaction partner for amidating AIB.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Brown ZZ, Schafmeister CE (2008) Exploiting an inherent neighboring group effect of α-amino acids to synthesize extremely hindered dipeptides. J Am Chem Soc 130:14382–14383

Chen X, Turecek F (2005) Simple *b* ions have cyclic oxazolone structures. A neutralization–reionization Mass spectrometric and computational study of oxazolone radicals. J Am Soc Mass Spectrom 16:1941–1956

Frydman-Marom A, Convertino M, Pellarin R, Lampel A, Shaltiel-Karyo R, Segal D, Caflisch A, Shalev DE, Gazit E (2011) Structural basis for inhibiting β-amyloid oligomerization by a non-coded β-breaker-substituted endomorphin analogue. ACS Chem Biol 6:1265–1276

Hansen JDW, Mazur RH, Pilipauskas DR (1986) Substituted tyrosyl alanine dipeptide amides. US 4599325

Henninot A, Collins JC, Nuss JM (2018) The current state of peptide drug discovery: back to the future? J Med Chem 61:1382–1414

Hroch L, Hrušková M, Schmitz J, Schnakenburg G, Gütschow M (2012) 3,5,5-trisubstituted hydantoins from activated (Benzyloxycarbonylamino)malonic acids. Synthesis 44:1907–1914

Humphrey JM, Chamberlin AR (1997) Chemical synthesis of natural product peptides: coupling methods for the incorporation of noncoded amino acids into peptides. Chem Rev 97:2243–2266

Jo M, Won SW, Lee DG, Jung JK, Kim S, Kwak YS (2018) An efficient synthetic protocol for amide derivatives of Boc-2-aminoisobutyrate. Arch Pharmacal Res 41:259–264

Kaneti J, Kirby AJ, Koedjikov AH, Pojarlieff IG (2004) Thorpe-Ingold effects in cyclizations to five-membered and six-membered rings containing planar segments. The rearrangement of N (1)-alkyl-substituted dihydroorotic acids to hydantoinacetic acids in base. Org Biomol Chem 2:1098–1110

Nakajima K, April M, Brewer JT, Daniels T, Forster CJ, Gilmore TA, Jain M, Kanter A, Kwak Y, Li J (2016) Discovery of diamide compounds as diacylglycerol acyltransferase 1 (DGAT1) inhibitors. Bioorg Med Chem Lett 26:1245–1248

Pekary AE (2013) Handbook of biologically active peptides, 2nd edn. Elsevier, New York, pp 951–956

Plucińska K, Liberek B (1987) Synthesis of diazoketones derived from α-amino acids; problem of side reactions. Tetrahedron 43:3509–3517

Priepke HD, Georg, Gerlach K, Pfau R, Wienen W, Schuler-Metz A, Handschuh S, Nar H (2007) Neue substituierte Glycinamide, deren Herstellung und deren Berwendung als Arzneimittel. PCT WO 2007/003536 A1

Savage SAD, Nathan R, Mack B, Vemishetti P, Qiu Y, Fenster M, Hallow DM, Ferreira G, Rogers A, Lou S, Hobson L (2015) Hepatitis C virus inhibitors cross-referenece to related applications. PCT WO 2015200305

Wieland T, Bodanszky M (2012) The world of peptides: a brief history of peptide chemistry. Springer, Berlin

Xu Z, Liu L, Wheeler K, Wang H (2011) Asymmetric inverse-electron-demand hetero-Diels–Alder reaction of six-membered cyclic ketones: an enamine/metal Lewis acid bifunctional approach. Angew Chem 123:3546–3550