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Iodine-catalyzed green and efficient synthesis of secondary and *tert*-esters of *N*-acetyl-protected amino acids

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Esterification of amino acids is a critical transformation in synthetic and peptide chemistry. In this study, a green and effective I_2-catalyzed method was developed for the esterification of *N*-acetyl protected amino esters and their hydrolysis. It is an environmentally friendly protocol that uses a less amount of catalyst, and does not require strong mineral acid or metal-based reagents, making it especially appealing as a synthesis protocol in synthetic and peptide chemistry. Primary and secondary esters were synthesized effectively in excellent yield, while *tert*-butyl esters were obtained in up to 80% yield using 4 mol% I_2 and 0.02 mg (0.55×10^{-3} mol%) of DMAP as a co-catalyst. In addition to ester formation, the system enables selective de-esterification of *tert*-butyl esters using a minimum amount of I_2 (0.03 mg) with 100% conversion to corresponding *N*-acetylated amino acids. This dual catalytic approach of I_2 in both the introduction and deprotection sequences introduces a practical and sustainable alternative to conventional acid-mediated processes. This strategy highlights the versatility of I_2 as an inexpensive, metal-free, and environmentally benign catalyst, and may inspire further exploration of Lewis acid-based catalysis in green amino acid and peptide chemistry.

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1 Introduction

The *tert*-butyl group is widely recognized as a strategically valuable functional group in organic synthesis and peptide chemistry[1,2] due to its pronounced steric hindrance and significant influence on reactions.[3] The large spatial demand of the *tert*-butyl moiety imparts kinetic stability and reduces susceptibility toward nucleophilic attack, as well as its convenient hydrolysis using a mild acidic environment, making *tert*-butyl an effective protecting group for carboxylic acids in organic synthesis and peptide chemistry.[4] This combination of steric hindrance and controlled reactivity has enabled their extensive application in multistep synthesis, especially in the preparation of peptide molecules.[5,6] Notably, *tert*-butyl-based protecting strategies have been employed in the synthesis of therapeutically relevant compounds, including hepatitis C virus NS3 protease inhibitors[7] and γ-aminobutyric acid aminotransferase (GABA-T) inhibitors.[8] In these cases, selective protection and deprotection are crucial for achieving both synthetic efficiency and structural precision. The synthesis of *tert*-butyl esters has a long-standing significance in the fields of organic synthesis and peptide chemistry. Numerous effective and reliable esterification methods for amino acids have been documented in the literature.[9–13] These synthetic approaches including *tert*-butylating coupling reagents,[14,15] a variety of different catalysts, such as hydrochloric acid, sulfuric acid, ionic liquids, zeolites, microwaves and metal oxides.[16,17] One of the earliest methods for their preparation is Fischer–Speier esterification, which was developed in 1895. This classical approach involves acid-catalyzed condensation of a carboxylic acid with a *tert*-butyl alcohol.[18]

The method provides a basis for *tert*-butyl esterification reactions and remains a classic method in organic chemistry. In 1997 Stephen *et al.* synthesized *tert*-butyl ester using an excess amount of *tert*-butanol and sulfuric acid in the presence of anhydrous magnesium sulfate (Scheme 1a).[19] This improvement increased reaction efficiency and broadened substrates compatibility, providing a versatile alternative to the classical Fischer Speier method for *tert*-butyl ester synthesis. Isobutylene gas with concentrated H_2SO_4 in ether was also used to protect carboxylic acids with a *tert*-butyl group.[20] However, these methods have limitations for the esterification of substrates containing acid-sensitive functional groups (Scheme 1b).

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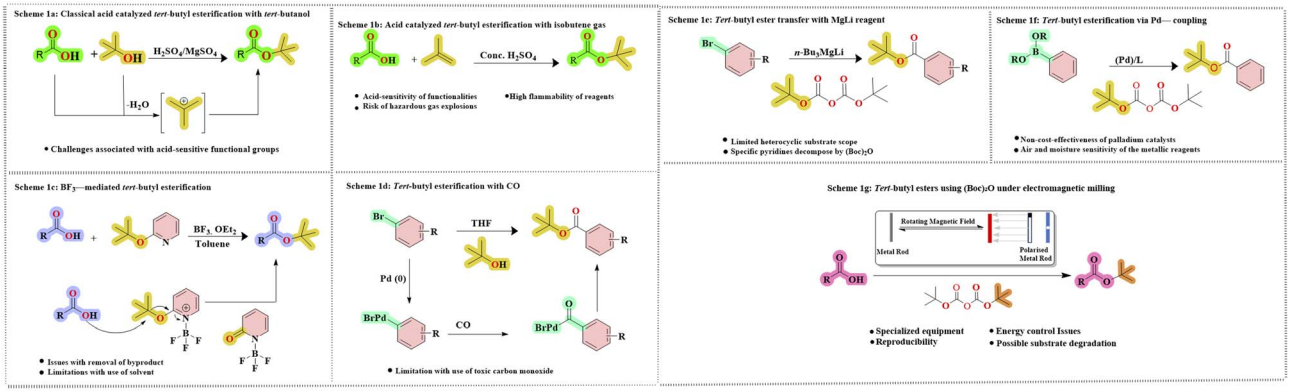


Scheme 1 A summary of research strategies (**1a–g**) on the synthesis of *tert*-butyl esters using different reagents.

Meanwhile La *et al.* developed a more efficient esterification method for the synthesis of *tert*-butyl esters using 2-*tert*-butoxypyridine as a source of the *tert*-butyl group in the presence of $BF_3 \cdot OEt_2$ and toluene as the solvent.[21] This approach overcomes the limitation of using strong acids. However, certain limitations persist, particularly the use of high-boiling solvents which complicate solvent recovery and product isolation, as well as removal of the generated byproducts (Scheme 1c).

In 2012 Xin *et al.* reported a palladium-catalyzed *tert*-butyloxy carbonylation of aryl bromides using carbon monoxide, providing a more direct route toward the synthesis of *tert*-butyl esters (Scheme 1d).[22] Despite the efficiency of this method, the use of toxic carbon monoxide presents a notable limitation. These safety concerns emphasize the need for alternatives to milder synthetic strategies.

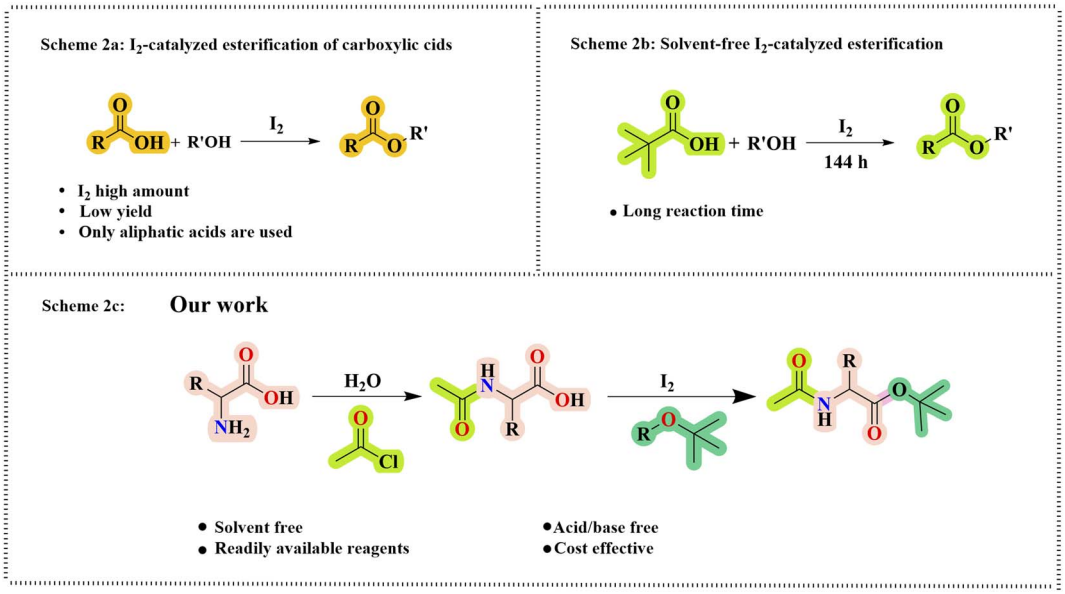
To overcome the use of these hazardous reagents (carbon monoxide), di-*tert*-butyl dicarbonate $(Boc)_2O$, a safer, more cost-effective, and efficient amino acid protecting group, has been extensively used in protein and peptide synthesis, biochemical food production, and cosmetics.[23] Owing to the broad applicability of $(Boc)_2O$, Bal *et al.* synthesize *tert*-butyl esters by reacting aryl bromides with MgLi and $(Boc)_2O$, at low temperatures (Scheme 1e).[24] Despite its efficiency, this method is constrained by a limited heterocyclic substrate, as specific pyridines completely decompose upon the addition of $(Boc)_2O$. Additionally, in 2014, Li *et al.* reported a palladium (Pd)-catalyzed synthetic approach for *tert*-butyl esters using $(Boc)_2O$ and boric acid or boronic acid esters (Scheme 1f).[25] Although these methods offer mild and efficient routes that minimize racemization and neutralization issues.[26–28] However, their use is limited by the non-cost-effectiveness of Pd-catalysts, air, and moisture sensitivity of the metallic reagents.[29–31]

In addition, the use of $(Boc)_2O$ in amino acid esterification is associated with several challenges, like competing *N*-Boc protection which compromises the selectivity toward carboxyl ester formation. The reagent is also susceptible to moisture and produces *tert*-butanol and carbon dioxide as byproducts, which can affect reaction efficiency.[15,32] In 2025, Liu and coworkers synthesized *tert*-butyl esters by using $(Boc)_2O$ under solvent and base-free electromagnetic milling conditions (Scheme 1g). These electromagnetic milling conditions have been reported as an efficient and green approach, but its practical application is limited by the requirement for specialized equipment, challenges in controlling energy input and localized heating, scale-up difficulties, and potential reproducibility issues.

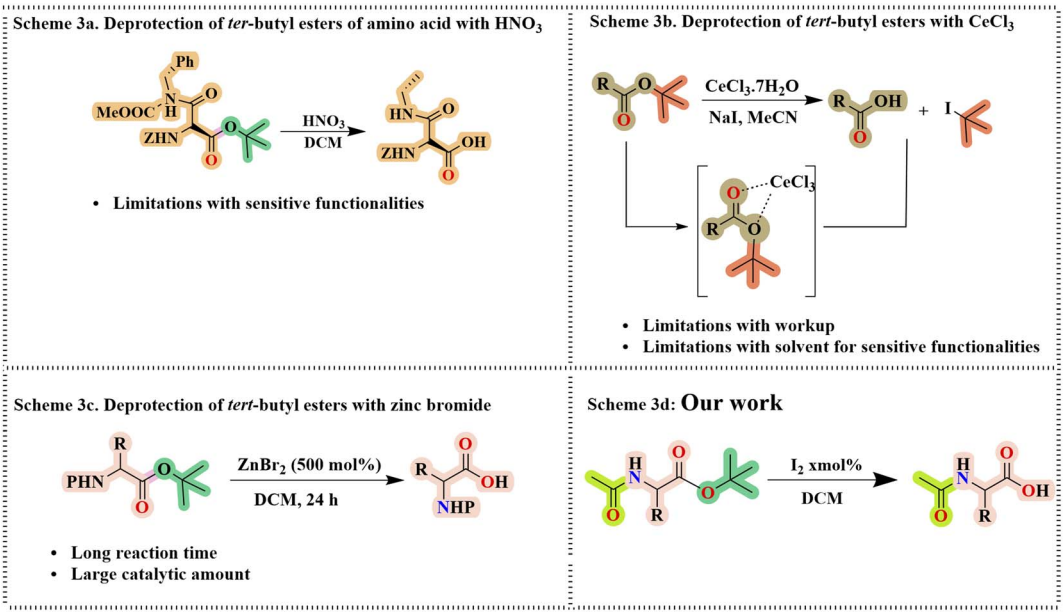
Therefore, the quest for an easy and convenient method for the synthesis of *tert*-butyl esters continues. In this regard, I_2 has emerged as an effective Lewis acid for the preparation of a variety of organic compounds and for the protection and deprotection of many functional groups.[33,34] I_2 has several advantages over transition-metal catalysis, including its solubility in many organic solvents such as acetonitrile, chloroform, acetone, and alcohols. Molecular I_2 is a highly reactive, nonmetallic, cheaper, environmentally friendly[35,36] and compatible with a broader range of substrates,[37,38] as catalyst in organic synthesis.[39] I_2 acts as a mild Lewis acid catalyst, activating the carboxyl group without strong acids under solvent-free conditions,[40,41] which is advantageous for many protecting groups, such as Boc, Fmoc, Cbz, and acetyl.[42–44] In previous studies, the esterification of aliphatic long-chain acids, aromatic acids, and in some cases, the methyl ester of amino acids, was achieved using I_2 (Scheme 2).[45,46]

Ramalinga *et al.* reported the esterification of *tert*-alcohols as well as sterically hindered primary and secondary alcohols with various aliphatic and unsaturated aliphatic carboxylic acids using molecular I_2 (100 mg) as a catalyst with moderate yields up to 56% for *tert*-esters (Scheme 2a).[47] Jereb *et al.* (2009) documented the I_2-catalyzed esterification of sterically hindered acids. In the case of *tert*-butyl substituted acids, the yield was 15% after 20 hours. However, extending the reaction time significantly enhanced the yield, achieving 72% after 144 hours[40] (Scheme 2b). Although the I_2-catalyzed synthesis of *tert*-butyl esters of aliphatic and aromatic carboxylic acids has been reported. However, the application of I_2-catalysis toward the synthesis of *tert*-butyl esters of *N*-acetyl-protected amino acids remains limited and underexplored. In this study, molecular I_2 was employed as a catalyst to develop an efficient method for preparing *tert*-butyl esters of *N*-protected amino acids (Scheme 2c).

The hydrolysis of *tert*-butyl esters of amino acids is also a crucial step in peptide synthesis. In 2000, Paolo and coworkers deprotected *tert*-butyl esters of amino acids using HNO_3 and



Scheme 2 Comparative research approaches (**2a–c**) on I_2-catalyzed ester synthesis of *tert*-butyl esters.

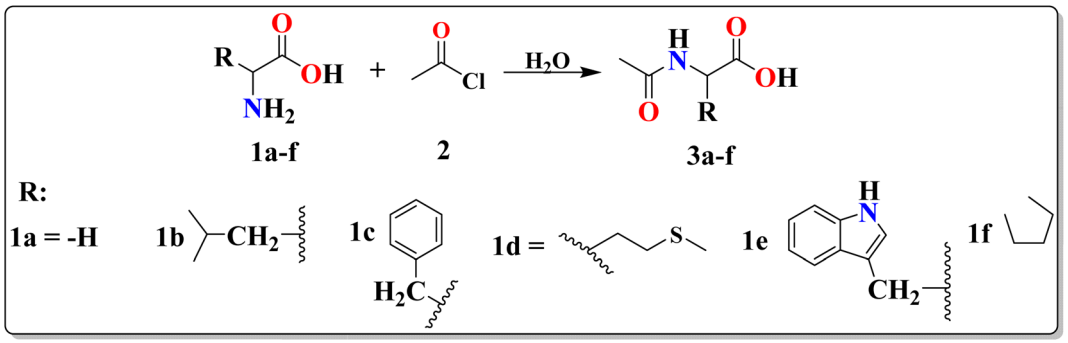


Scheme 3 Hydrolytic cleavage of *tert*-butyl esters of amino acids under different reaction conditions.

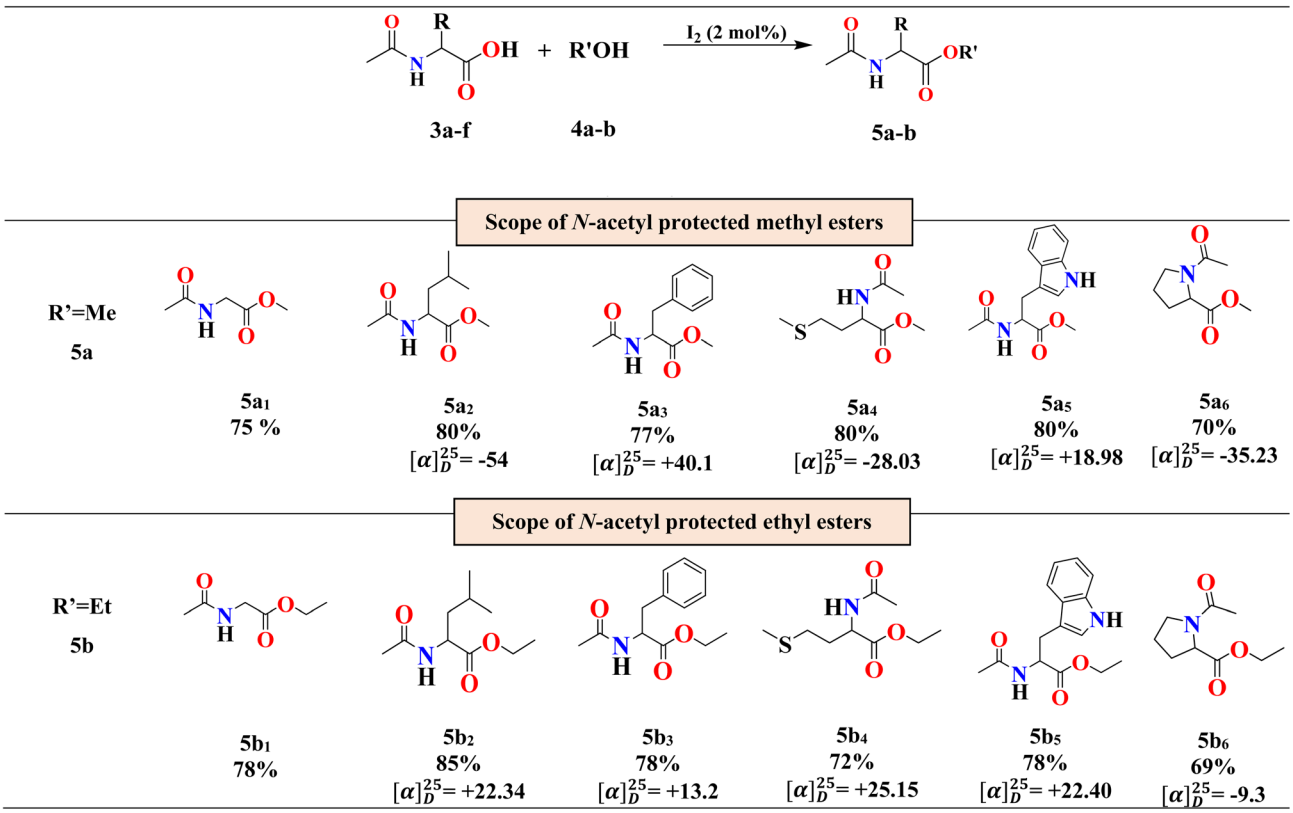
DCM. This hydrolysis was limited by sensitive residues (Scheme 3a).[48] To avoid these limitations, Marcantoni and colleagues deprotected *tert*-butyl ester amino acids using $CeCl_3$, $7H_2O$/NaI in acetonitrile (Scheme 3b).[49] In 2004, Kaul *et al.* selectively deprotected the *tert*-butyl group in the presence of an acid-labile Boc using $ZnBr_2$ in DCM (Scheme 3c).[32]

Although $CeCl_3$ and $ZnBr_2$ enable the selective removal of the *tert*-butyl group, their application is limited by their sensitivity toward Lewis acid-labile functional groups, the need for controlled reaction conditions, and challenges associated with metal residue removal and scalability. Therefore, we develop a method to deprotect *N*-acetyl protected amino acid esters using I_2 (Scheme 3d).

Keeping in view the importance of Green Chemistry nowadays, we planned to synthesize the *N*-acetyl protected amino acid esters using a "Green catalyst". We tried to achieve both the esterification and de-esterification using I_2 as a catalyst. For the synthesis of amino acid esters, including *tert*-butyl esters, first protection of amino acids (**1a–f**) was done using acetyl chloride as a protecting group to yield *N*-acetyl protected amino acid (**3a–f**) (Scheme 4). Then their esterification was done using a catalytic amount of I_2 (**5a–d**) (Schemes 5 and 6). Further, de-



Scheme 4 A representative method for the acetylation of amino acids.



Scheme 5 I_2 -catalyzed synthesis of amino acid esters.

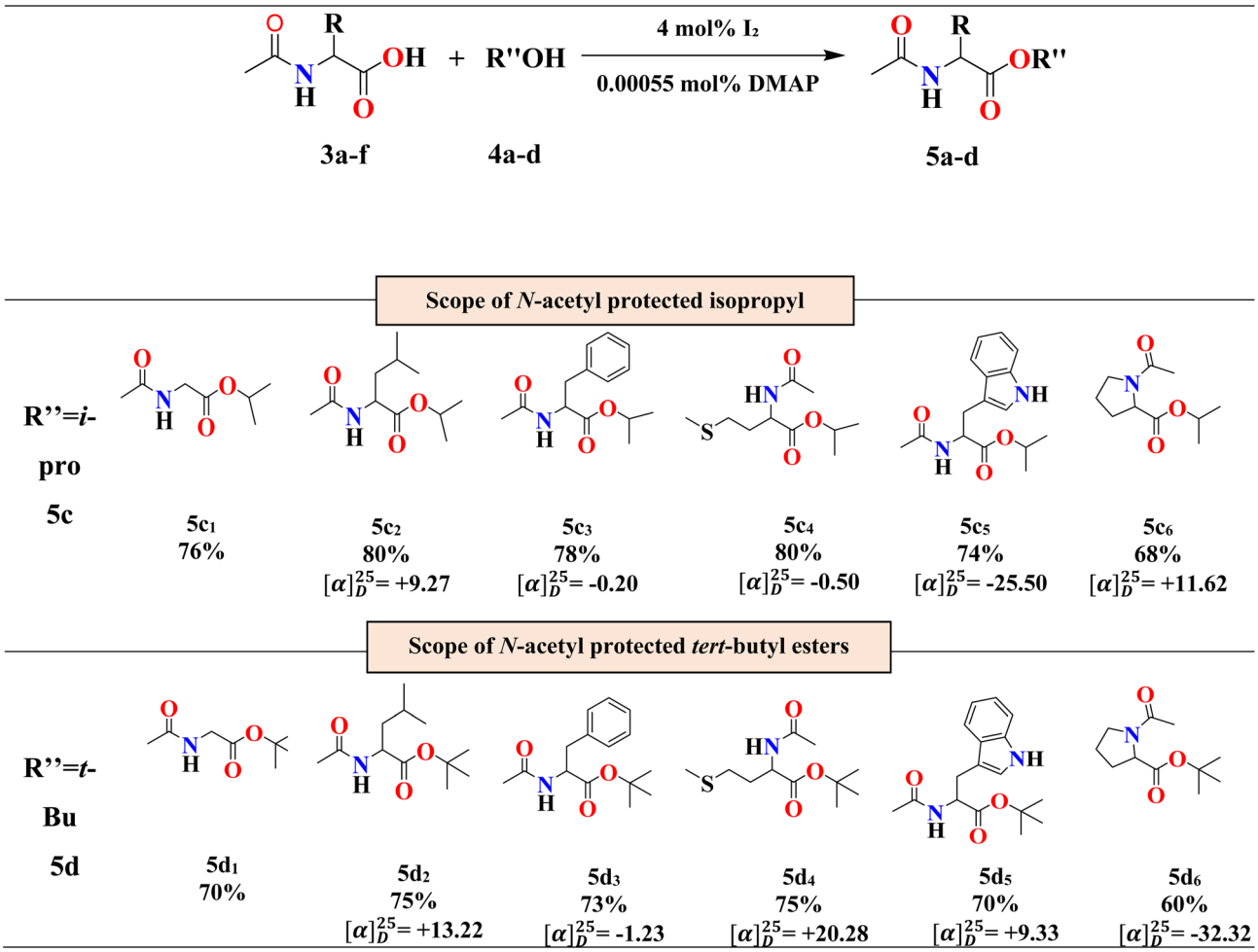
esterification of esters was conducted using I_2 ($\mathbf{5d_{1-6}}$) (Scheme 7).

2 Results and discussion

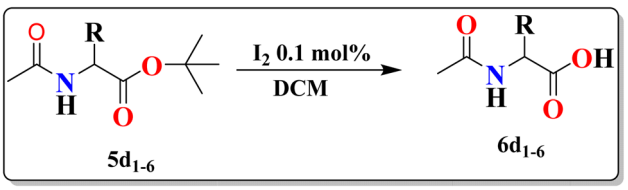
2.1 Synthesis of *N*-acetyl protected amino acids (3a–f)

N-acetyl protected amino acid (**3a–f**) was successfully achieved by reacting selected amino acid **1a–f** (1eq, 6.36 mmol) and acetyl chloride **2** (1eq, 6.36 mmol) in water (8 mL) as the solvent. Acetyl chloride (**2**) was incrementally introduced over a duration of 20 minutes, sustained for 2–3 hours at 70 °C. The completion of the reaction was monitored initially by thin-layer chromatography (TLC) and subsequently confirmed using the ninhydrin test. Following the synthesis of compounds **3a–f**, the solvent water was removed under reduced pressure using rotary evaporator, and the crude product was dissolved in methanol to eliminate any unreacted acid. Subsequently, methanol was removed through vacuum distillation until dryness, resulting in pure precipitates of *N*-acetyl amino acids (**3a–f**) with yields ranging from 96% to 99%. The physical data of all *N*-acetylated amino acids is summarized in Table 1.

First, the reaction conditions for esterification were optimized. All selected amino acids were *N*-acetylated and obtained in good to excellent yield and subsequently subjected to esterification. *N*-acetyl glycine (**3a**) was used as the standard substrate and reacted with methyl alcohol at room temperature.



Scheme 6 I_2 catalyzed synthesis of amino acid esters.



Scheme 7 Iodine-mediated cleavage of *tert*-butyl ester protecting groups.

At room temperature, the isolated yield was only 50% after 48 hours using 8 mol% I_2 in DCM (Table 2, entry 1). Therefore, the reaction was shifted to elevated temperature, and the *N*-acetyl glycine methyl ester (**5a**) was synthesized with a 20% yield utilizing a catalytic amount of 8 mol% I_2, employing DCM as the solvent at a temperature of 70 °C for a duration of 24 hours (Table 2, entry 2). Various solvents, including THF and acetonitrile, were employed to enhance the yield. Nevertheless, only a modest improvement was achieved, with the yield reaching a maximum of 35% at 70 °C after 24 hours (Table 2, entry 3 and 4). This limited enhancement can be attributed to the poor solubility of *N*-acetyl amino acids in these solvents. Subsequently, the reaction was conducted under solvent-free conditions utilizing 8 mol% I_2 as the catalyst, resulting in an increased yield of 45% for primary esters (Table 2, entry 5). Further optimization of the catalyst loading demonstrated that reducing the I_2 concentration to 5 mol% enhanced the yield to 60% (Table 2, entry 6). Further increase in temperature up to 75 °C has no significant effect on yield (Table 2, entry 7).

Notably, a further reduction in I_2 loading to 2 mol% led to a significant improvement, yielding the desired product up to 85% at 75 °C after 6 hours (Table 2, entry 8). Low I_2 concentration promotes carbonyl activation and ester formation, whereas higher amounts of I_2 decreased the yield. This reduction in yield is attributed to competing side reactions, such as hydrolysis and the generation of acidic species during the reaction, which compromise substrate stability.[50,51]

Following the establishment of optimal reaction conditions, the investigation proceeded to examine the range of different *N*-acetyl protected amino acids. A scalable experiment was conducted utilizing 0.5 g (2.88 mmol) of compounds **3a–f** (*N*-acetyl protected amino acids) in alcohol (**4a–b**, 20 mL) under reflux conditions (Scheme 5). The yield of the target primary esters was 85%, except for the proline ester, which exhibited a yield of

Table 1 Acetylation of amino acids (**3a–f**)

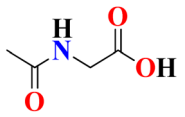
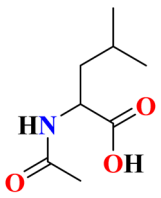
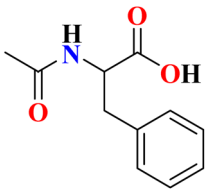
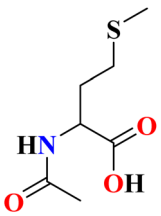
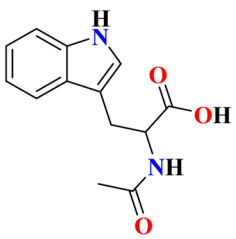
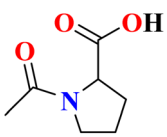
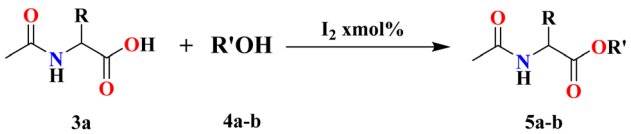
Compound	Yield %	Melting points (°C)	$[\alpha]_D^{20}$ (C = 0.5g. 50 mL methanol)
 **3a**	97	208–210	—
 **3b**	94	190–195	−24.32
 **3c**	96	176–178	+39.47
 **3d**	93	103–105	−8.2
 **3e**	96	182–188	+27.46
 **3f**	91	117–120	−86

Table 2 Optimization of I_2 for esterification[a]

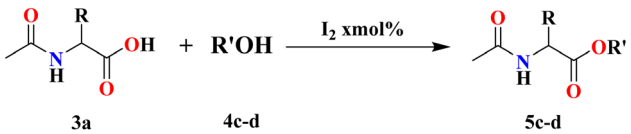


a = Me, b = Et

Entry	Compound	Solvent	I_2 mol%	Time h	Temperature °C	Yield %
1	**5a**	DCM	8	48	Room temp	50
2	**5a**	DCM	8	24	70°	20
3	**5a**	THF	8	24	70°	35
4	**5a**	CH_3CN	8	24	70°	35
5	**5a**	—	8	24	70°	45
6	**5a**	—	5	24	70°	60
7	**5a**	—	5	24	75°	62
8	**5a**	—	2	6	75°	85

[a] Reaction conditions: **3a** (2.88 mmol), **4a–b** (20 mL), and I_2 (mol%). Isolated yield.

Table 3 Optimization of I_2 loading for *sec* and *tert*-esters[a]



c = *i*-Pro, d = *t*-Bu

Entry	Compound	I_2 mol%	Time h	Temperature °C	DMAP mol%	Yield %
1	**5c**	2	6	75°	—	40
2	**5c**	1	6	75°	—	—
3	**5c**	3	6	75°	—	60
4	**5c**	4	24	75°	—	70
5	**5c**	5	24	80°	—	50
6	**5c**	6	24	80°	—	48
7	**5c**	7	36–40	80°	—	Mess
8	**5c**	4	6–7	80°	0.00055	90
9	**5d**	6	12	80°	—	45
10	**5d**	7	72–80	80°	—	Mess
11	**5d**	4	12	80°	0.00055	85

[a] Reaction conditions: **3a** (2.88 mmol), **4c–d** (20 mL), and I_2 (mol%). Isolated yield. The reaction was refluxed.

70%. This discrepancy can be attributed to the presence of a cyclic secondary amine group, known as the pyrrolidine ring, in proline. This ring structure induces steric hindrance and conformational constraints, thereby reducing the accessibility of alcohol to the carboxyl group.[52] Under the optimized conditions, a series of *N*-acetyl protected primary amino esters (**5a**$_{1-6}$ and **5b**$_{1-6}$) were synthesized in good to excellent yields (Scheme 5).

In contrast, when secondary and *tert*-alcohols were employed under these optimized conditions (2 mol% I_2), a noticeable decline in yield was observed, with product formation reduced to approximately 40% (Table 3, entry 1). Further decrease in concentration resulted in no ester formation. Therefore, we performed a series of reactions to optimize the I_2 concentration for the secondary and *tert*-ester. The I_2 concentration was gradually increased from 2 mol% to 6 mol%. It was observed that by increasing the I_2 amount to 4 mol%, the yield increased to 70% for secondary esters after 24 hours (Table 3, entry 4). In the case of *tert*-esters, the yield was still 45% using 6 mol% of I_2 (Table 3, entry 9). However, beyond these concentrations, further increase in I_2 leads to a decrease in yield and significantly prolonged reaction time (36–40 h) (Table 3, entry 7) for

secondary and (72–80 h) (Table 3, entry 10) for *tert*-esters. To minimize the reaction time and improve the yield, we added DMAP as a co-catalyst along with I_2, which allowed the use of I_2 at a lower concentration of 4 mol%. The use of DMAP not only reduced the reaction time but also improved the overall yield up to 85–90% for both secondary and *tert*-esters.

Therefore, optimized conditions were developed for the synthesis of secondary and *tert*-butyl esters. For the esterification of secondary alcohol, 4 mol% of I_2 and 0.00055 mol% DMAP were added and refluxed for approximately 6–7 h (Table 3, entry 8). All secondary esters were obtained in good yield except for $\mathbf{5c_5}$ (74%), bearing an indole ring moiety, and $\mathbf{5c_6}$ (68%), containing a pyrrolidine ring. For *tert*-esters 4 mol% of I_2 and 0.00055 mol% DMAP were added at reflux for approximately 12 h (Table 3, entry 11). In contrast, the synthesis of *tert*-esters required the same catalyst amount (4 mol% I_2 and 0.00055 mol% DMAP), however, the reaction time was extended to approximately 12 h under reflux to achieve satisfactory conversion. Again, the yields were low in the case of $\mathbf{5d_5}$ (70%), containing indole ring, and $\mathbf{5d_6}$ (60%), bearing a proline cyclic secondary amine group (pyrrolidine ring). This reduction in efficiency was due to the increased nucleophilicity and acid sensitivity of the indole and pyrrolidine rings (Scheme 6). The reaction progress was monitored by thin layer chromatography (TLC).

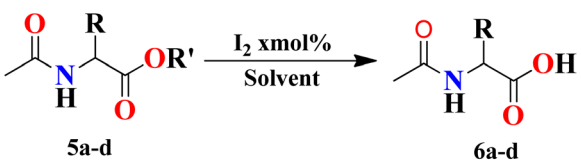
After the completion of reaction, excess alcohol was removed under vacuum, and the residue was extracted with diethyl ether or DCM. The organic layer was washed with a solution of sodium thiosulfate and sodium bicarbonate and dried over anhydrous $Na_2SO_4/MgSO_4$ to obtain the pure products **5a–d** (0.86 g, 70–85%).

Following the esterification process, all synthesized esters underwent de-esterification. The de-esterification, facilitated by the presence of I_2, proceeded at a significantly faster rate than the esterification. This process was initially conducted using a catalytic amount of I_2 in a biphasic system comprising methanol/DCM or DCM/H_2O, and subsequently in a single solvent DCM (*N*-acetylated amino acids are insoluble in DCM can be easily precipitated out). To optimize the de-esterification process, the concentration of I_2 was systematically varied. It was observed that primary esters achieved deprotection with up to 85% efficiency when utilizing 1.6 mol% I_2. Notably, lower concentrations of I_2 resulted in higher reaction yields (entry 11), attributed to the minimization of side reactions.[53]

The reaction conditions were systematically optimized by varying the I_2 amount, reaction time, and temperature, and the results are summarized in Table 4. Initial experiments were performed with a higher I_2 concentration (3.29 mol%) at 40 °C resulting in complex reaction mixtures (mess) for substrates **5a–d** (Table 4, entries 1, 3, 5, and 8), indicating that excessive catalyst amount promotes undesired side reactions. After decreasing the I_2 concentration to 1.66 mol%, reaction yields improved for the primary esters (entries 2 and 4), with isolated yields of 85% and 82%, respectively.

Further optimization of **5c**, revealed that lowering the catalyst loading and temperature had a pronounced effect on reaction efficiency. At 1 mol% I_2 and 25 °C (**5c**, entry 7), the reaction proceeded rapidly, affording an improved yield of 80% within only 30 min. Further decreasing the I_2 concentration to 0.1 mol% provided corresponding secondary esters **5c** up to 90% yield (Table 4, entry 8). In contrast, *tert*-esters **5d** showed relatively lower reactivity under similar conditions, giving

Table 4 Screening and optimization of I_2 -mediated conditions for the de-esterification of esters[a]



5a-d 6a-d

a = Me, b = Et, c = *i*-Pro, d = *t*-Bu

Entry	Compound	Solvent	I_2 mol%	Time min	Temperature °C	Yield %
1	**5a**	DCM	3.29	120	40	Mess
2	**5a**	DCM	1.66	60	40	85
3	**5b**	DCM	3.29	120	40	Mess
4	**5b**	DCM	1.66	80	40	82
5	**5c**	DCM	3.29	120	40	Mess
6	**5c**	DCM	1.66	90	40	60
7	**5c**	DCM	1	30	25	80
8	**5c**	DCM	0.1	25	25	90
9	**5d**	DCM	3.29	120	40	Mess
10	**5d**	DCM	1.66	80	40	45
11	**5d**	DCM	1	30–40	50	75
12	**5d**	DCM	0.1	15	25	100

[a] Reaction conditions: **1a** (1.155 mmol), DCM (10 mL), and I_2 (mol%). Isolated yield.

moderate yields with 1.66 mol% I_2 (45%, entry 10), at higher temperature (75%, entry 11), due to side reactions.

Surprisingly, a considerable improvement was achieved when the I_2 concentration was further reduced to 0.1 mol% at 25 °C (entry 12), allowing quantitative conversion (100% yield) within 15 minutes. These results demonstrate that lower catalyst loadings not only suppress side reactions but also significantly improve reaction efficiency, suggesting that controlled I_2 activation is critical for achieving optimal yield. In contrast, secondary and *tert*-esters were completely deprotected at lower I_2 concentration (entries 8 and 12, Table 4). The enhanced efficiency of deprotection for secondary and *tert*-esters at lower I_2 concentrations can be attributed to the formation of more stable alcohols upon deprotection (Scheme 7). The physical data of all *N*-acetylated amino acids (**6d$_1$–d$_6$**) were gathered and summarized in Table 5.

The synthesis of *tert*-butyl esters of *N*-acetyl protected amino acids has not been extensively investigated in the existing literature. In this study, we present the development of an environmentally friendly and efficient methodology for their preparation under mild conditions. Additionally, we have established a complementary protocol for the selective de-esterification of *tert*-butyl esters, offering a practical and sustainable approach for both protection and deprotection strategies in peptide chemistry.

3 Material and method

Acetyl chloride, glycine, leucine, phenylalanine, methionine, tryptophan, and proline were purchased from Sigma-Aldrich, Merck, and Fluka. All commercial solvents were distilled and dried prior to use. Thin-layer chromatography (TLC) with silica gel-coated plates (0.5 mm thick, Merck) was used to monitor the reaction progress, and spots were visualized under a UV lamp and ninhydrin solution. The synthesized compounds were recrystallized using ethyl acetate and ethanol. Physical properties such as the melting point were determined using a Gallen Kamp melting point apparatus. An FT-IR 6300 SHIMADZU spectrophotometer was used to record the IR spectra of the synthesized compounds. A Bruker Advance nuclear magnetic resonance spectrometer resonating at 400 MHz was used for the structural elucidation of the target compounds in $CDCl_3$ as the solvent and TMS as the internal standard.

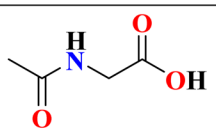
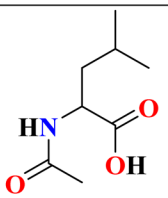
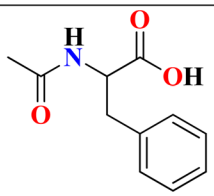
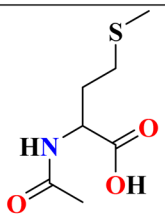
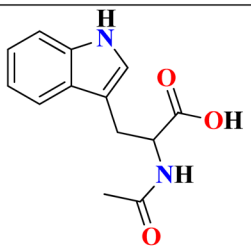
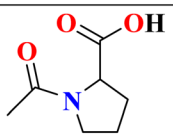
3.1 Synthesis of *N*-acetylated amino acids (3a–f)

L-amino acids (**1a–f**, 5–7 mmol) were dissolved in water, and an equimolar amount of acetyl chloride (**2**) was added; the mixture was then refluxed for 2 h at 70 °C. *N*-acetyl amino acid (**3a–f**) formation was monitored by TLC and then ninhydrin test, and the solvent was evaporated using a rotary evaporator. The crude product was dissolved in methanol and filtered to remove any unreacted amino acid. Methanol was removed under vacuum to dryness to obtain the pure precipitates of *N*-acetyl protected amino acids.

3.1.1 Acetamidoacetic acid (3a). Mol. formula: $C_4H_7NO_3$,-mol. wt: 117.10g mol^{-1}, appearance: white crystalline solid, M.P: 207–208 °C, R_f: 0.68 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform. (FT-IR cm^{-1}) ν_{max}: O–H (acidic) 3630–2500, (N–H) 3251, Csp^3–H (stretching) 2989–2842, C=O (acid) 1710, C=O (amide) 1645.

3.1.2 (*S*)-2-Acetamido-4-methylpentanoic acid (3b). Mol. formula: $C_8H_{15}NO_3$, mol. wt: 173.21g mol^{-1}, appearance: white solid, M.P: 190–195 °C, $[\alpha]_D^{25} = -24.32°$ (c = 0.01g/100 mL MeOH), R_f: 0.68 ($CHCl_3$, MeOH), yield: 80%, solubility:

Table 5 Substrate scope for the hydrolysis of structurally diverse *tert*-butyl esters (6d$_1$–d$_6$)

 **6d$_1$** **100%**	 **6d$_2$** **100%**	 **6d$_3$** **100%**
 **6d$_4$** **100%**	 **6d$_5$** **95%**	 **6d$_6$** **100%**

chloroform, DMSO. (FT-IR, cm^{-1}) ν_{max}: O–H (acidic) 3530–2500, N–H 3236, Csp^3–H (stretching) 2987–2550, C=O (acid) 1703, C=O (amide) 1679.

3.1.3 (*S*)-1-Acetylpyrrolidine-2-carboxylic acid (3c). Mol. formula: $C_7H_{11}NO_3$, mol. wt: 157.17g mol^{-1}, appearance: off-white solid, M.P: 117–120 °C, $[\alpha]_D^{25} = -86°$ (c = 0.01g/100 mL MeOH), R_f: 0.68 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: O–H (acidic) 3550–2500, Csp^3–H (stretching) 2980–2850, C=O (acid) 1718, C=O (amide) 1656.

3.1.4 (*S*)-2-Acetamido-3-phenylpropanoic acid (3d). Mol. formula: $C_{11}H_{13}NO_3$, mol. wt: 207.23g mol^{-1}, appearance: off white crystalline solid, M.P: 176–178 °C,$[\alpha]_D$25 = +39.47° (c = 0.01g/100 mL MeOH), R_f: 0.68 ($CHCl_3$, MeOH), yield: 98%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: O–H (acidic) 3660–2500, 3373 (N–H), 2976–2617 (Csp^3–H stretching), C=O (acid) 1731, C=O (amide) 1679, C=C (aromatic) 1603–1481.

3.1.5 (*S*)-2-Acetamido-3-(1*H*-indol-3-yl)propanoic acid (3e). Mol. formula: $C_{13}H_{14}N_2O_3$, mol. wt: 246.26g mol^{-1}, appearance: crystalline solid, M.P: 182–188 °C, $[\alpha]_D^{25} = +27.46°$ (c = 0.01g/100 mL MeOH), R_f: 0.68 ($CHCl_3$, MeOH), yield: 97%, solubility: chloroform. (FT-IR cm^{-1}) ν_{max}: O–H (acidic) 3660–2500, N–H 3238, Csp^3–H (stretching) 2987–2550, C=O (acid) 1703, C=O (amide) 1679, C=C (aromatic) 1502–1595.

3.1.6 (*S*)-2-Acetamido-4-(methylthio) butanoic acid (3f). Mol. formula: $C_7H_{13}NO_3S$, mol. wt: 191.25g mol^{-1}, appearance: white crystalline solid, M.P: 103–105 °C, $[\alpha]_D^{25} = -8.2°$ (c = 0.01g/100 mL MeOH), R_f: 0.68 ($CHCl_3$, MeOH), yield: 98%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: O–H (acidic) 3450–2500, (N–H) 3256, Csp^3–H (stretching) 3050–2853, C=O (acid) 1719, C=O (amide) 1632.

The synthesis of *N*-acetyl amino acids was confirmed by IR spectroscopy, which showed a band of carbonyl stretching in the range of 1696–1704 cm^{-1}, a characteristic of amide, an NH band in the range of 3200–3400 and a broad cup-shaped band of acidic O–H stretching in the range of 2500–3650 cm^{-1}.

3.2 Synthesis of *N*-acetyl protected amino esters

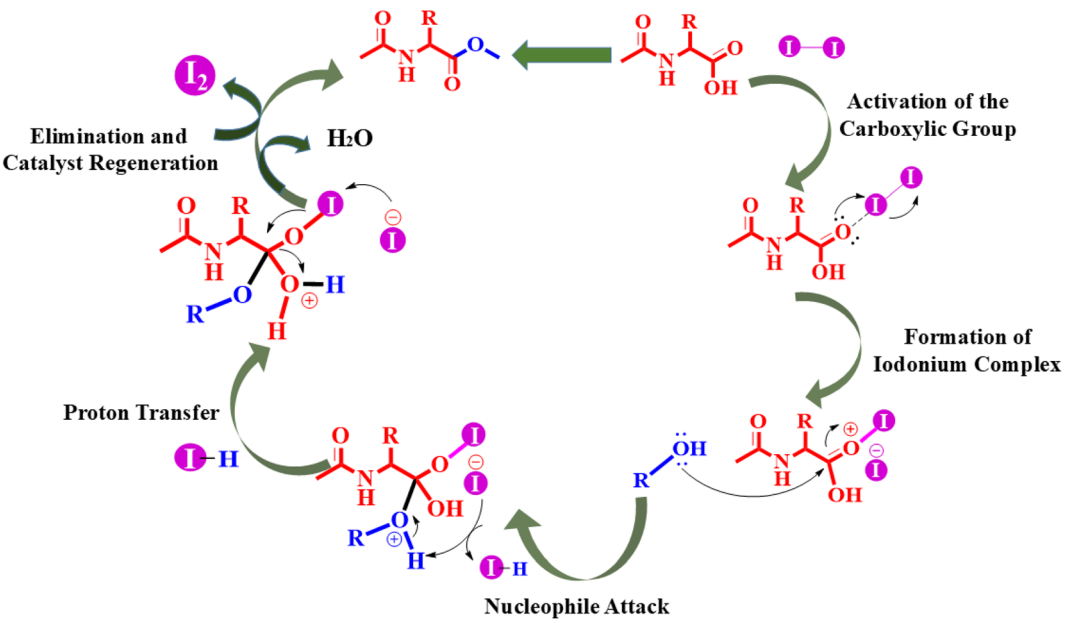
N-Protected amino acids (0.5 g, 2.88 mmol) were dissolved in 20 mL alcohol, followed by the addition of I_2 (25 mg, 0.01 equiv; doubled for *tert*-butyl esters) under stirring. The reaction mixture was refluxed for 6–8 hours, monitored by TLC. After completion, excess alcohol was removed under reduced pressure. The residue was extracted with diethyl ether or DCM, and the organic layer was washed successively with sodium thiosulfate, sodium bicarbonate, and water. It was then dried over anhydrous Na_2SO_4 or $MgSO_4$ and concentrated under vacuum. This general procedure was applied to all the substrates for esterification.

3.2.1 Synthesis of methyl esters ($5a_{1-6}$) of *N*-acetylated amono acids

*3.2.1.1 Methyl 2-acetamidoacetate (**5a$_1$**).* Mol. formula: $C_5H_9NO_3$, mol. wt: 131.13g mol^{-1}, appearance: white solid, M.P: 58–60 °C, R_f: 0.8 ($CHCl_3$, MeOH), yield: 80%, solubility: alcohol, DMSO. (FT-IR, cm^{-1}) ν_{max}: 3392 (N–H), Csp^3–H (stretching) 2976–2617, C=O (ester) 1746, 1632 (C=O amide).

*3.2.1.2 (R)-Methyl 2-acetamido-4-methylpentanoate (**5a$_2$**).* Mol. formula: $C_9H_{17}NO_3$, mol. wt: 187.24g mol^{-1}, appearance: white solid, M.P: 47–50 °C, $[\alpha]_D^{25} = -54°$ (c = 0.01g/100 mL MeOH), R_f: 0.78 ($CHCl_3$, MeOH), yield: 80%, solubility: alcohol, DMSO. (FT-IR, cm^{-1}) ν_{max}: 3325 (N–H), Csp^3–H (stretching) 3000–2850, 1743 (C=O, ester), 1660 (C=O, amide).

*3.2.1.3 Methyl 2-acetamido-3-phenylpropanoate (**5a$_3$**).* Mol. formula: $C_{12}H_{15}NO_3$, mol. wt: 221.25g mol^{-1}, appearance: white solid, M.P: 68–70 °C, $[\alpha]_D^{25} = +40.1°$ (c = 0.01g/100 mL MeOH) R_f: 0.8 ($CHCl_3$, MeOH), yield: 77%, solubility: chloroform. (FT-



Scheme 8 Proposed catalytic cycle of I_2.

IR, cm^{-1}) ν_{max}: 3310 (N–H), 2960–2775 (Sp^3C–H), 1746 (ester C=O), 1676 (C=O, amide), 1620–1515 (aromatic), 1348 (C–N).

*3.2.1.4 Methyl 2-acetamido-4-(methylthio)butanoate) (**5a$_4$**).* Mol. formula: $C_8H_{15}NO_3S$, mol. wt: 205.27g mol^{-1}, appearance: white solid, M.P: 80–82 °C, $[\alpha]_D^{25} = -28.03°$ (c = 0.01g/100 mL MeOH), R_f: 0.69 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3310 (N–H), 2960 –2775, (Csp^3–H), 1740 (C=O ester), 1676 (C=O amide), 1348 (C–N).

*3.2.1.5 Methyl 2-acetamido-3-(1H-indol-3-yl)propanoate) (**5a$_5$**).* Mol. formula: $C_{14}H_{16}N_2O_3$, mol. wt: 260.29g mol^{-1}, appearance: white solid, M.P: 100–103 °C, $[\alpha]_D^{25} = +18.98°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3477 (N–H, indol ring), 3427 (N–H), 2993–2837 (C–H), 1730 (C=O ester), 1660 (C=O, amide), 1602 (C=C), 1348 (C–N).

*3.2.1.6 Methyl 1-acetylpyrrolidine-2-carboxylate (**5a$_6$**).* Mol. formula: $C_5H_9NO_3$, mol. wt: 131.13g mol^{-1}, appearance: white solid, M.P: 72–73 °C, $[\alpha]_D^{25} = -35.23°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 70%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 2920–2850 (Sp^3C–H), 1728 (C=O, ester), 1628 (C=O, amide), 1348 (C–N) cm^{-1}.

IR spectroscopy indicated the formation of methyl esters by the disappearance of the O–H stretching of carboxylic acid at 2500–3600 cm^{-1} and the appearance of the ester carbonyl (C=O) band at 1725–1750 cm^{-1}.

3.2.2 Synthesis of ethyl esters (5b$_{1-6}$) of *N*-acetylated amono acids

3.2.2.1 Ethyl 2-acetamidoacetate (5b$_1$). Mol. formula: $C_6H_{11}NO_3$, mol. wt: 145.16g mol^{-1}, appearance: white solid, M.P: 47–50 °C, R_f: 0.68 ($CHCl_3$, MeOH), yield: 78%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3400 (N–H), 3000–2920 (Csp^3–H), 1639 (C=O), 1728 (C=O), 1228 (C–N), 1348 (C–O).

*3.2.2.2 Ethyl 2-acetamido-4-methylpentanoate (**5b$_2$**).* Mol. formula: $C_{10}H_{19}NO_3$, mol. wt: 201.26g mol^{-1}, appearance: white solid, M.P: 60–63 °C, $[\alpha]_D^{25} = +22.34°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 85%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3220 (N–H), 2954–2850 (weak, C–H stretching), 1658 (C=O amide), 1743 (strong, C=O stretching), 1460 (C–O), 1063 (ester O–C stretching), 1150–1250 (C–N).

*3.2.2.3 Ethyl 2-acetamido-3-phenylpropanoate (**5b$_3$**).* Mol. formula: $C_{13}H_{17}NO_3$, mol. wt: 235.28g mol^{-1}, appearance: white solid, M.P: 85–90 °C, $[\alpha]_D^{25} = +13.2°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 78%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3340 (N–H), 3101–2760 (C–H), 1747 (C=O), 1639 (C=O), 1610–1420 (aromatic C=C)1348 (C–N).

*3.2.2.4 Ethyl 2-acetamido-4-(methylthio)butanoate (**5b$_4$**).* Mol. formula: $C_5H_9NO_3S$, mol. wt: 131.13g mol^{-1}, appearance: white solid, M.P: 79–80 °C, $[\alpha]_D^{25} = +25.15°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 72%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 3411 (N–H), 2997–2840 (Csp^3–H), 1728 (C=O), 1606 (C=O), 1348 (C–N).

*3.2.2.5 Ethyl 2-acetamido-3-(1H-indol-3-yl)propanoate (**5b$_5$**).* Mol. formula: $C_{15}H_{18}N_2O_3$, mol. wt: 274.32g mol^{-1}, appearance: white solid, M.P: 109–111 °C, $[\alpha]_D^{25} = +22.40°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 78%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 3475–3424 (N–H), 3110 (C_{SP}^2 C–H), 2600 (Csp^3 C–H), 1751 (C=O), 1681 (C=O), 1343 (C–N).

*3.2.2.6 Ethyl 1-acetylpyrrolidine-2-carboxylate (**5b$_6$**).* Mol. formula: $C_9H_{15}NO_3$, mol. wt: 185.22g mol^{-1}, appearance: white solid, M.P: 64–65 °C, $[\alpha]_D^{25} = -9.3°$ (c = 0.01g/100 mL MeOH) R_f: 0.8 ($CHCl_3$, MeOH), yield: 69%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 2930–2860 (Csp^3–H), 1749 (C=O), 1635 (C=O), 1328 (C–N).

3.2.3 Synthesis isopropyl esters (5c$_{1-6}$) of *N*-acetylated amono acids

*3.2.3.1 Isopropyl 2-acetamidoacetate (**5c$_1$**).* Mol. formula: $C_7H_{13}NO_3$, mol. wt: 159.18g mol^{-1}, appearance: oily liquid, R_f: 0.69 ($CHCl_3$, MeOH), yield: 76%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 3310 (N–H), 2960–2775 (C–H), 1710 (C=O), 1676 (C=O), 1348 (C–N). ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 6.15 (s, 1H, NH), 5.1 (m, 1H, C<u>H</u>–$(CH_3)_2$), 3.95 (s, 2H, C<u>H</u>–NH), 2.01 (s, 3H, acetyl), 0.92 (d, J = 6.32 Hz, 6H, $C(CH_3)_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.26 (C=O ester), 169.59 (C=O amide), 69.35 (C–O), 41.64 (CH_2–NH), 22.90 (CH_3, acetyl), 21.70 $(CH_3)_2$.

*3.2.3.2 Isopropyl 2-acetamido-4-methylpentanoate (**5c$_2$**).* Mol. formula: $C_{11}H_{21}NO_3$, mol. wt: 215.29g mol^{-1}, appearance: semi solid liquid, $[\alpha]_D^{25} = +9.27°$ (c = 0.01g/100 mL MeOH) R_f: 0.7 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3165 (N–H), 2956–2854, (Csp^3–H), 1732 (C=O), 1673 (C=O amide). ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.21 (1H, NH), 5.05 (m, 1H, COC<u>H</u>), 4.2 (t, J = 7Hz, NH–C<u>H</u>), 2.6 (t, J = 7.1 Hz, CH–C<u>H_2</u>), 2.03 (s, 3H, acetyl CH_3), 1.26 (d, 6H, J = 6.5 Hz, $(CH_3)_2$), 0.95 (d, 6H, J = 6.3Hz, CO–CH(C<u>H_3</u>)$_2$. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.32 (C=O ester), 168.20 (C=O acetyl), 69.29 $(CH_3)_2$C), 68.13 (CHNH), 41.83 (CH_2), 29.66, ($(CH_3)_2$), 24.39 (CH), 22.95 (CH_3 acetyl), 21.64 $(CH_3)_2$ ppm.

*3.2.3.3 Isopropyl 2-acetamido-3-phenylpropanoate (**5c$_3$**).* Mol. formula: $C_{14}H_{19}NO_3$, mol. wt: 249.31g mol^{-1}, appearance: white solid, M.P: 62–64 °C, $[\alpha]_D^{25} = -0.2°$ (c = 0.01g/100 mL MeOH) R_f: 0.82 ($CHCl_3$, MeOH), yield: 78%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 1730 (C=O ester), 1676 (C=O amide), 3300 (N–H), 3100–2860 (Sp^3C–H), 1585–1465 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 7.3–7.6 (m, 5H, aromatic), 7.33 (s 1H, NH), 4.3 (t, 1H, J = 7.2, C<u>H</u>NH), 3.3 (dd, 1H, 13.1, C<u>H_2</u>), 3.45 (dd, 1H, J = 13.2, CH_2), 1.98 (s, 3H, acetyl), (sept, 6H, C<u>H</u>$(CH_3)_2$, 1.32 (d, 6H, CH(C<u>H_3</u>)$_2$. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 178.36 (C=O ester), 170.85 (C=O amid), 135.45–128.22 (C_6H_5), 77.26 ($C(CH_3)_3$), 64.28 (CHNH), 34.77 (CH_2), 22.96 ($(CH_3)_3$), 21.65 (CH_3, acetyl) ppm.

*3.2.3.4 Isopropyl 2-acetamido-4-(methylthio)butanoate (**5c$_4$**).* Mol. formula: $C_{10}H_{19}NO_3$, mol. wt: 233.33g mol^{-1}, appearance: oily liquid, $[\alpha]_D^{25} = -0.05°$ (c = 0.01g/100 mL MeOH) R_f: 0.75 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3346 (N–H), 2965–2870 (Csp^3–H), 1735 (C=O ester), 1677 (C=O amide), 1348 (C–N). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H, NH), 5.02 (t, J = 6.1 Hz, 1H, C<u>H</u>NH), 4.2 (m, OC<u>H</u>$(CH_3)_3$), 2.48 (m, 1H, CH_2), 2.15 (m, 2H, C<u>H_2</u>S), 2.07 (s, 3H, SC<u>H_3</u>), 2.06 (s, 3H, C<u>H_3</u> acetyl), 1.23 (d, 11.9 Hz, 6H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (C=O ester), 167.73 (C=O amide), 68.11 ($C(CH_3)_3$), 52.01 (CHNH), 38.68 (CH_2S), 30.31 (CH_2CH), 28.88.0 (CH_3 of acetyl), 22.94 ($(CH_3)_3$), 14.01 (SCH_3) ppm.

*3.2.3.5 Isopropyl 2-acetamido-3-(1H-indol-3-yl)propanoate (**5c$_5$**).* Mol. formula: $C_{16}H_{20}N_2O_3$, mol. wt: 288.34g mol^{-1}, appearance: white solid, M.P: 150–152 °C, $[\alpha]_D^{25} = -25.5°$ (c = 0.01g/100 mL MeOH) R_f: 0.72 ($CHCl_3$, MeOH), yield: 74%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3409 (N–H), 2962–2854 (Csp^3–H), 1734 (C=O ester), 1665 (C=O amide). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.4 (s, NH), 7.46 (s, NH), 7.60–7.08 (m, 5H, indole), 4.99 (m, 1H, $CH(CH_3)_3$), 3.83 (t, 6.8 Hz, 1H, CHNH 1H) 3.28 (dd, 1H, J = 14.6, 5.2, Hz, 1H CH_2), 3.04 (dd, 1H, J = 14.5, 8.0 Hz, CH_2), 2.25 (s, 3H, CH_3 acetyl), 1.25 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O ester), 169.12 (C=O amide), 135.2, 111.28 (indole), 77.20 (OCH_3), 68.87 (CHNH), 29.67 (CH_2), 21.7 ($(CH_3)_3$), 21.66 (CH_3 acetyl) ppm.

*3.2.3.6 Isopropyl 1-acetylpyrrolidine-2-carboxylate (**5c$_6$**).* Mol. formula: $C_{10}H_{17}NO_3$, mol. wt: 199.25g mol^{-1}, appearance: oily liquid, $[\alpha]_D^{25} = +11.62°$ (c = 0.01g/100 mL MeOH) R_f: 0.8 ($CHCl_3$, MeOH), yield: 68%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 2971–2882 (Csp^3–H), 1740 (C=O ester), 1654 (C=O amide), 1354 (C–N). ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 5.0 (m, C<u>H</u>$(CH_3)_2$) 4.14 (t, J = 8.1 Hz, 1H, NCH) 3.6 (dd, dd, J = 8.7, 5.5 Hz, 1H, HC<u>H</u>NH), 3.5 (dd, J = 8.7, 5.5 Hz, 1H, <u>H</u>CHNH), 2.28–2.14 (m, 2H, $CH_2C\underline{H}_2CH$), 2.04 (s, 3H), 1.90 (m, 2H, C<u>H</u>$_2$-CH_2CH), 1.23 (d, J = 6.2 Hz, 6H, $(CH_3)_2$).·^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.85 (C=O ester), 166.36 (C=O amide), 68.46 (<u>C</u>H$(CH_3)_2$), 60.50 (CHNH), 45.16 (CH_2N), 29.36 (CH_2–CHN), 27.64 (–CH_2–), 23.30 ($(CH_3)_2$), 21.64 (CH_3) ppm.

3.2.4 Synthesis of *tert*-butyl esters (5d$_{1–6}$) of *N*-acetylated amono acids

*3.2.4.1 Tert-butyl 2-acetamidoacetate (**5d$_1$**).* Mol. formula: $C_8H_{15}NO_3$, mol. wt: 173.21g mol^{-1}, appearance oily liquid, R_f: 0.8 ($CHCl_3$, MeOH), yield: 70%, solubility: chloroform. (FT-IR, cm^{-1}) ν_{max}: 3274 (NH), 2954 (Csp^3–H), 1733 (C=O, ester), 1648 (C=O amide). ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 7.72 (1H, NH), 4.22 (s, 2H, C<u>H</u>–NH), 1.72 (s, 3H, acetyl), 0.92 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.3 (C=O ester), 172.3 (C=O amide), 68.14 (C–O), 38.70 (CH_2), 30.33 $(CH_3)_3$, 23.71 CH_3ppm.

*3.2.4.2 Tert-butyl 2-acetamido-4-methylpentanoate (**5d$_2$**).* Mol. formula: $C_{12}H_{23}NO_3$, mol. wt: 229.32g mol^{-1}, appearance: oily liquid, yield: 75% $[\alpha]_D^{25} = +13.22°$ (c = 0.01g/100 mL MeOH), R_f: 0.75 ($CHCl_3$, MeOH), yield: 75%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 3330 (NH), 2962–2868 (Csp^3–H), 1734 (C=O, ester), 1671 (C=O amide). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.2 (s. 1H, NH), 4.54–4.49 (t, J = 11.2 Hz, 1H, C<u>H</u>–NH), 2.3 (s, 3H, CH_3 acetyl), 1.77–1.4 (d, J = 6.5, Hz,2H, CH_2), 1.51 (m 1H, C<u>H</u>-$(CH_3)_2$), 1.45 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.25 (s, 9H, $C(CH_3)_3$), 0.94 (d, J = 6.8 Hz, 2Hd, 6H, $(CH_3)_2$),. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.85 (C=O ester), 166.36 (C=O acetyl), 68.46. $(CH_3)_3C$), 58.77 (CHNH), 45.16 (CH_2), 27.64, ($(CH_3)_3$), 24.67 (CH), 23.68 (CH_3 acetyl), 23.30 $(CH_3)_2$ ppm.

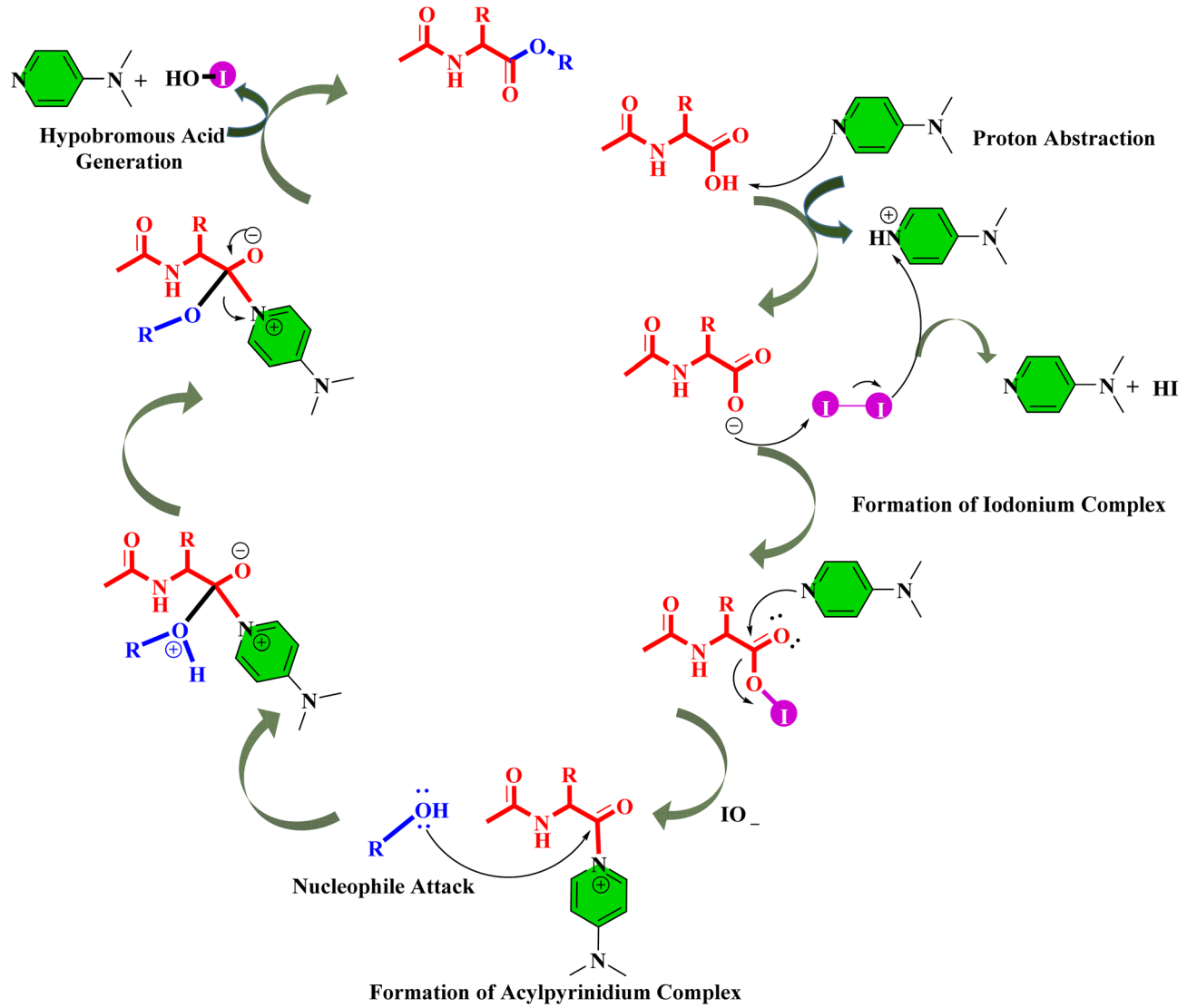
*3.2.4.3 Tert-butyl 2-acetamido-3-phenylpropanoate (**5d$_3$**).* Mol. formula: $C_{15}H_{21}NO_3$, mol. wt: 263.33g mol^{-1}, appearance: oily liquid, $[\alpha]_D^{25} = -123°$ (c = 0.01g/100 mL MeOH) R_f: 0.73 ($CHCl_3$, MeOH), yield: 80%, solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 3207 (NH), 2917–2870 (Csp^3–H), 1750 (C=O, ester), 1633 (C=O amide), 1600–1460 (C=C aromatic) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, NH), 7.50–7.15 (m, 5H, aromatic), 4.30 (m, 1H, CHNH), 4.19 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 1.98 (s, 3H, acetyl), 0.92 (s, 9H, $C(CH_3)_3$ ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.36 (C=O ester), 164.26 (C=O amid), 129–127 (C_6H_5), 77.19 ($C(CH_3)_3$), 68.14 (CHNH), 38.70 (CH_2), 28.90 ($(CH_3)_3$), 14.03 (CH_3, acetyl) ppm.

*3.2.4.4 Tert-butyl 2-acetamido-4-(methylthio) butanoate (**5d$_4$**).* Mol. formula: $C_{11}H_{21}NO_3S$, mol. wt: 247.31g mol^{-1}, appearance: oily liquid, yield: 80%, $[\alpha]_D^{25} = -20.28°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 75%, solubility: chloroform, DMSO, (FT-IR, cm^{-1}) ν_{max}: 3403 (NH), (3000–2900) (Csp^3–H), 1735 (C=O, ester), 1642 (C=O amide) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 1H, NH), 4.20 (t, J = 5.9 Hz, 1H, CHNH), 3.2 (s, 3H, SCH_3), 2.6 (m, 1H, CH_2), 2.3 (q, J = 6.4 Hz, 2H, CH_2S), 2.1 (s, 3H, CH_3 acetyl), 1.48 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.34 (C=O ester), 167.38 (C=O amide), 83.79 ($C(CH_3)_3$), 52.12 (CHNH), 39.40 (CH_2S), 28.76 (CH_2CH), 28.37 ($(CH_3)_3$), 27.0 (CH_3 of acetyl), 14.37 (SCH_3) ppm.

*3.2.4.5 Tert-butyl 2-acetamido-3-(1H-indol-3-yl) propanoate (**5d$_5$**).* Mol. formula: $C_{17}H_{22}N_2O_3$, mol. wt: 302.37g mol^{-1}, appearance oily liquid,$[\alpha]_D^{25} = +9.33°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), yield: 70%, solubility: chloroform, yield: 79%, (FT-IR, cm^{-1}) ν_{max}:3250 (NH), 3056–2929 (Csp^3–H, Csp^2–H), 1750 (C=O, ester), 1669 (C=O amide), 1450–1600 (C=C aromatic) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.4 (s, NH indole), 7.46 (s, NH), 7.60–7.08 (m, 5H, indole), 4.9 (m, 1H, CHNH), 3.81 (dd, 1H, J = 13.6, 5.9 Hz, CH_2), 3.28 (dd, 1H, J = 14.6, 5.2 Hz, CH_2), 2.25 (s, 3H, CH_3 acetyl), 1.25 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 178.09 (C=O ester), 172.52 (C=O amide), 141.78, 111.28 (indole), 77.20 (OCH_3), 68.87 (CHNH), 29.67 (CH_2), 21.7 ($(CH_3)_3$), 21.6 (CH_3 acetyl) ppm.

*3.2.4.6 Tert-butyl 1-acetylpyrrolidine-2-carboxylate (**5d$_6$**).* Mol. formula: $C_{11}H_{19}NO_3$, mol. wt: 213.27g mol^{-1}, appearance: oily liquid, yield: 77%, $[\alpha]_D^{25} = -32.23°$ (c = 0.01g/100 mL MeOH) R_f: 0.68 ($CHCl_3$, MeOH), solubility: chloroform, (FT-IR, cm^{-1}) ν_{max}: 2971–2882 (Csp^3-H), 1740 (C=O, ester), 1654 (C=O amide) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.97 (t, J, 7.4 Hz 1H, C<u>H</u>NH), 3.61 (m, 1H, C<u>H</u>$_2$N), 3.45 (tt, J, 7.2, 4.2 Hz 1H, CH_2N), (m, 4H, CH_2CH_2), 2.12 (s, 3H, CH_3 of acetyl), 1.65–1.43 (m, 4H, CH_2CH_2 proline ring), 0.89 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.85 (C=O ester), 166.36 (C=O amide), 77.24 ($C(CH_3)_3$), 69.20 (CHNH), 60.50 (CH_2NH), 29.36 (CH_2–CCO), 27.64 $(CH_3)_3$), 23.3 (CH_2), 22.2 (CH_3 of acetyl) ppm.

FT-IR spectroscopy indicated the formation of *tert*-butyl esters by the disappearance of O–H stretching of carboxylic acid at 2500–3600 cm^{-1} and the appearance of the ester carbonyl (C=O) at 1725–1750 cm^{-1}. The formation of *tert*-butyl esters was confirmed by ^{1}H NMR spectroscopy, which showed a characteristic singlet corresponding to the *tert*-butyl group at δ = 1.50–0.7 ppm (9H), along with the disappearance of the carboxylic acid proton signal, indicating successful esterification. The ^{13}C NMR spectra further supported the ester formation by the appearance of a quaternary *tert*-butyl carbon signal at δ = 80–85 ppm and methyl carbon signals at approximately δ = 27–30 ppm, together with the ester carbonyl resonance observed at δ = 170–175 ppm.



Scheme 9 Possible mechanism in the presence of *N*,*N*-dimethylpyridine and I_2.

4 Possible mechanism of I_2 catalyzation

Based on control experiments and reported literature, a plausible mechanism for the I_2-catalyzed esterification is represented in Scheme 8. I_2 activates carboxylic acid *via* coordination with the carbonyl oxygen, thereby increasing the electrophilicity of the carbonyl carbon. Nucleophilic attack by the alcohol generates a tetrahedral intermediate, which upon proton transfer, affords ester formation and regeneration of the I_2 catalyst.[40,47,54]

5 Possible mechanism in the presence of *N*,*N*-dimethylpyridine

Tert-alcohols and butanol are hindered by saturation; therefore, DMAP is used to activate carboxylic acids. I_2 first coordinates with the carboxylic acid, and DMAP, being a strong nucleophile, attacks the carbonyl carbon, forming a highly reactive acyl pyridinium complex with the release of hypoiodous acid. In the next step, the alcohol attacks the carbonyl carbon of the acyl pyridinium complex, forming a tetrahedral intermediate, followed by the removal of DMAP and HOI[55–57](Scheme 9).

6 Conclusion

In this study, a practical, effective, and green method for the esterification of *tert*-butyl esters of *N*-acetyl-protected amino acids was developed using molecular I_2 as a catalyst. This green protocol successfully afforded methyl, ethyl, isopropyl, and most importantly, *tert*-butyl esters in excellent yields ranging from 70–85%. To synthesize more sterically hindered *tert*-butyl esters, the addition of a small amount of DMAP (0.02 mg, 0.55×10^{-3}) as a co-catalyst, along with I_2 (25–50 mg up to 4 mol%), proved essential to drive the reaction forward. The de-

esterification of esters (especially *tert*-esters) was also achieved under mild reaction conditions using I_2 (0.03 mg). This method overcomes many of the limitations associated with conventional esterification techniques, such as the use of expensive reagents, harsh reaction conditions, and low yields. Notably, this approach is operationally simple, scalable, and compatible with all four classes of amino acids. These results demonstrate the potential of I_2-based catalysis as a sustainable and cost-effective strategy for peptide and amino acid derivative synthesis.

Ethical statement

All procedures performed in studies involving no human participants.

Author contributions

Conceptualization, M. A., G. R. A., and M. L.; methodology, G. R. A., and A. R.; software, G. R. A., and M. F. E.; validation of study, A. R., M. A., I. S., and G. R. A.; formal analysis, M. F. E., G. R. A., M. L., M. A., and A. R.; investigation, G. R. A., and M. F. E.; resources, M. A., I. S., and M. L.; data curation, G. R. A., A. R., and I. S.; writing-original draft preparation, G. R. A., I. S., and M. A.; writing-review and editing, G. R. A., M. F. E., M. A., I. S., A. R., and M. L.; visualization, A. R., M. F. E., M. A., and M. L.; supervision, M. A., and M. L.; project administration, M. A., and I. S.; funding acquisition, M. A., and I. S. All authors have read and agreed to the published version of the manuscript. Ghazala Razaq Abbasi (G. R. A.), Muhammad Arfan (M. A.), Muhammad Fahad Ehsan (M. F. E.), Aamal Rehman (A. R.), Imran Shakir (I. S.), and Muhammad Latif (M. L.).

Conflicts of interest

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Data availability

Research data supporting this publication are available within the article and its supplementary information (SI) file. Supplementary information: experimental details, compounds characterization data, and ^{1}H-NMR, ^{13}C-NMR, and FT-IR spectra for all synthesized compounds. See DOI: https://doi.org/10.1039/d6ra03408j.

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