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A Scalable Approach to Primary Amines *via* the Petasis Reaction

Abstract

The efficient and scalable synthesis of homoallylic amines is a subject of significant interest due to the potential applications of these compounds in medicinal and synthetic chemistry. The three-component Petasis reaction is an excellent approach for obtaining these compounds. Based on previous studies, this work explores the α-aminoallylation of ketones and aldehydes using allylboronic acid pinacol ester. Compared to classical methods, the protocol developed reduces the excess of reagents, increasing the environmental friendliness of the process, while maintaining high yields. A wide range of substrates, including various aliphatic, cyclic, and heterocyclic ketones, was studied to identify factors affecting the reactivity. The method was also successfully applied to aldehydes, producing amine-containing building blocks on a large scale. Various work-up procedures were optimized for efficient isolation of the homoallylamines synthesized without the need for chromatographic purification.

Keywords: Petasis reaction; three-component reaction; primary amines; multigram synthesis

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Масштабований синтез первинних амінів на основі реакції Петасіса

Анотація

Ефективний і масштабований синтез гомоаліламінів викликає значний інтерес через потенційне застосування цих сполук у медичній та синтетичній хімії. Трикомпонентна реакція Петасіса є чудовим підходом для їх одержання. Спираючись на попередні дослідження, у цій роботі розглянули α-аміноалілювання кетонів і альдегідів із використанням пінаколового естеру алілборонової кислоти. Проти класичних методів, розроблений протокол зменшує надлишок реагентів, підвищуючи екологічність процесу і водночас зберігаючи високі виходи. Досліджено широкий діапазон субстратів, зокрема різні аліфатичні, циклічні та гетероциклічні кетони, що дозволило виявити фактори, які впливають на реакційну здатність. Метод також успішно застосовано до альдегідів, що дало змогу отримати відповідні будівельні блоки у великому масштабі. Було оптимізовано різні методи очищення для ефективного виділення синтезованих гомоаліламінів без необхідності використання хроматографії.

Ключові слова: реакція Петасіса; трикомпонентна реакція; первинні аміни; багатограмовий синтез

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Supporting information: Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra.
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Introduction

The amino group is a fundamental structural and functional motif in medicinal chemistry, playing a crucial role in molecular interactions and drug design [1]. Its versatility stems from several key advantages. First, it facilitates strong binding interactions between a drug molecule and its biological target by acting as both a hydrogen bond donor and acceptor. Additionally, the presence of a basic nitrogen center allows for fine-tuning of physicochemical properties, which can significantly enhance the ADMET profile of lead compounds [2]. The nitrogen atom, capable of forming three bonds, serves as one of the essential structural elements for controlling molecular geometry and steric bulk. Furthermore, the synthetic accessibility of the NH_2 group makes it an attractive handle for a wide range of chemical transformations, enabling the construction of diverse organic compounds [3].

Taking into account these advantages, medicinal chemistry relies on a rich synthetic toolbox that provides numerous methodologies for introducing amino functionality into target molecules. Of particular interest are approaches that rapidly expand the chemical space, such as diversity-oriented synthesis (DOS) for building amine libraries relevant to fragment-based drug discovery (FBDD) [4]. One such approach is multicomponent reactions (MCRs), which have gained widespread use as complexity-generating transformations, enabling the rapid synthesis of diverse scaffolds of both synthetic and biological interest [5].

Among these, the Petasis reaction stands out as a particularly powerful and versatile three-component transformation. Originally reported in 1993 by Petasis and colleagues, this reaction involves a secondary amine, paraformaldehyde, and (*E*)-vinylboronic acid, providing a streamlined route to allylamines [6]. Over time, it has evolved into a general MCR incorporating amines, carbonyl compounds, and vinyl- or arylboronic acids, functioning as a modular assembly tool for rapidly constructing structurally complex amines from readily available (either synthetically or commercially) precursors. The reaction widespread adoption is reflected in numerous reviews covering its scope [7], including a 2019 comprehensive review by *Wu et al.*, which discusses substrate expansion, non-classical Petasis variants, asymmetric versions using chiral catalysts, and multistep cascade reactions leading to natural product-like heterocycles. Other recent reviews have explored novel catalytic variants [8], asymmetric approaches, and non-directed transformations [9], with the latest comprehensive review by *Pandit and Kamble* providing an up-to-date perspective on the reaction's utility [10].

Compared to other amine synthesis methods, the Petasis reaction offers a remarkable functional group tolerance, accommodating alcohols, carboxylic acids, and amines under mild conditions. Compatible organoboron species include vinylboronate esters, arylboronate esters, and potassium organotrifluoroborates, and the reaction does not require anhydrous or inert conditions. Notably, it serves as a highly selective method for the synthesis of α-amino acids, making it a valuable tool in combinatorial chemistry and drug discovery. The reaction stereoselectivity is particularly pronounced when chiral amines or aldehydes are used as substrates. Beyond its synthetic flexibility, the biological relevance of its products makes it an essential component in the probe compound development and drug discovery efforts. In fact, the Petasis reaction was originally applied in the synthesis of naftifine (Exoderil®), a widely used antifungal agent.

Further advancements in the Petasis reaction have introduced allylboronic components [11, 12], opening new avenues for the synthesis of homoallylamines – highly versatile intermediates in pharmaceutical chemistry, natural product synthesis, and heterocyclic compound development [13]. Despite several reports on allylboron reagents in the Petasis reaction, a comprehensive study of its scope and limitations remains largely unclear.

In our recent studies, we successfully applied this modification to two in-house projects, focusing on the multigram-scale synthesis of 3D-shaped spirocyclic piperidines and azepanes using the Petasis/Grubbs reaction sequence (**Figure 1**, *A*) [14]. Additionally, we developed a scalable preparation of δ-amino acids, employing the Petasis reaction between ketones, allylboronic acid pinacol ester, and methanolic ammonia, followed by the cross-metathesis (**Figure 1**, *B*) [15].

The later approach is particularly valuable as it yields derivatives with an unprotected NH_2 group, allowing for selective functionalization at a later stage, with the possibility of installing protecting groups or additional substituents. Furthermore, this strategy leverages ammonia – a cost-effective and versatile nitrogen source – instead of pre-functionalized amines, adding to its synthetic practicality. The foundational work on this transformation was laid in two seminal studies

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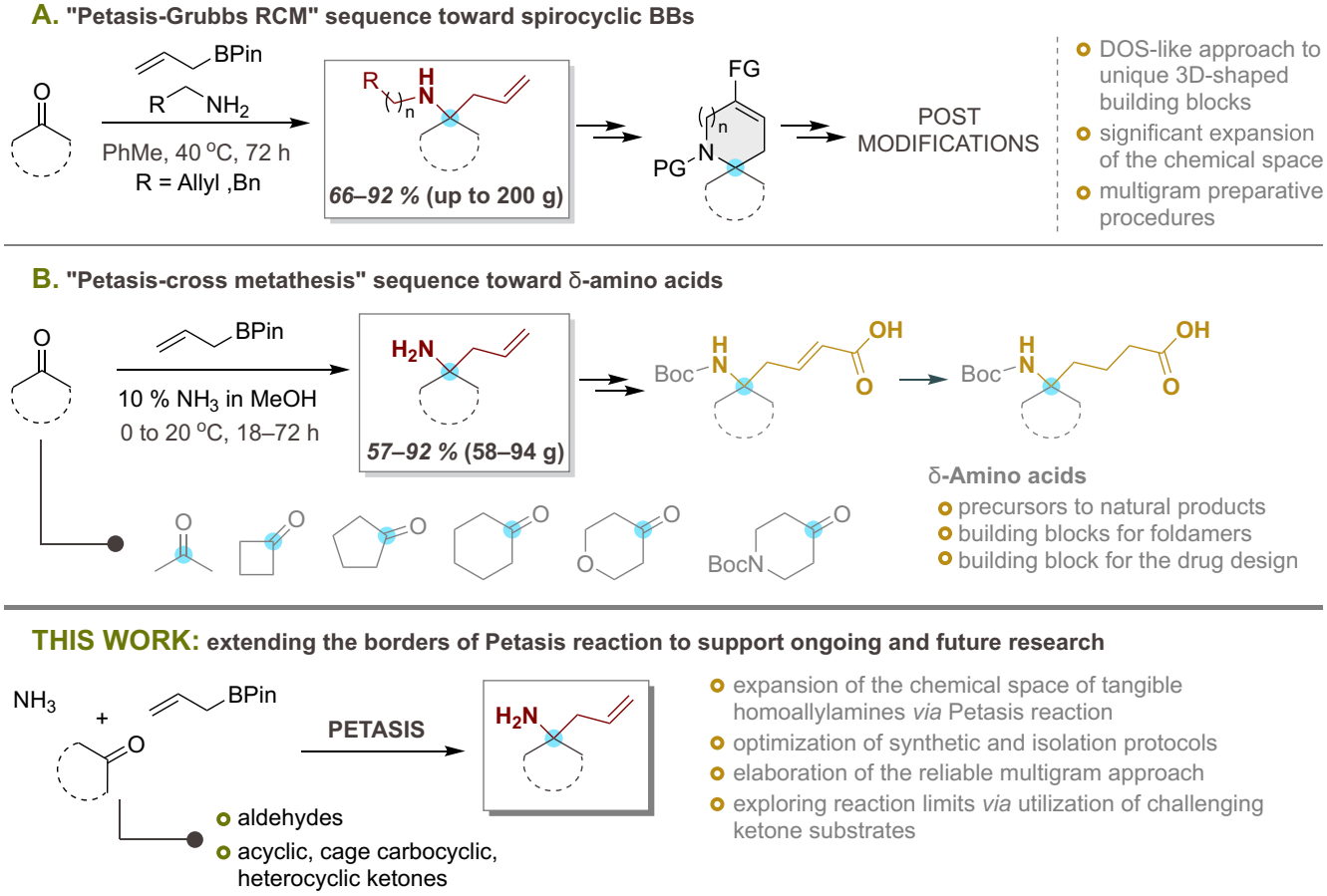

Figure 1. Background and synopsis of the work

by *Kobayashi et al.* [16], which demonstrated its applicability to aldehydes, producing homoallylic primary amines in high yields with excellent chemo- and stereoselectivity. Subsequent studies, such as those by *Dhudshia et al.* [17], extended the reaction to ketones, yet both investigations were conducted at sub-millimolar scales, significantly limiting their commercial potential and practical integration into drug discovery pipelines. Moreover, although this reaction was sometimes used for specific purposes in subsequent years, we have not found any other work exploring its further potential.

To bridge this gap, our recent work has focused on scaling up the Petasis reaction for the δ-amino acid synthesis, using acetone and simple carbo(hetero)cyclic ketones to generate six homoallylamines in moderate-to-high yields at a multigram scale (**Figure 1**, *B*). In this study, we continue expanding the synthetic potential of the Petasis reaction to create a diverse array of primary homoallylamines, with a specific emphasis on optimizing synthetic and isolation protocols, as well as exploring its applicability to structurally distinct ketones (**Figure 1**, *C*). This research is aimed not only at expanding the chemical field available for medicinal chemistry, but also at creating practical and scalable methodologies for integrating the Petasis reaction into modern drug discovery programs.

■ Results and discussion

Kobayashi et al. first demonstrated that the reaction of aldehydes with pinacol allylboronate and a large excess of ammonia (saturated in the solvent) at -10°C efficiently produced homoallylic primary amines with high yields, as well as excellent chemo- and stereoselectivity [16a]. Further optimization of the reaction conditions revealed that α-aminoallylation of aldehydes with allylboronate could also proceed smoothly in aqueous ammonia when surfactants (e.g., dodecylbenzene sulfonic acid) were present [16b]. However, in some cases, significant amounts of the competing alcohol by-product were observed. Expanding on this work, *Dhudshia et al.* explored the use of ketones in α-aminoallylation, identifying allylboronic acid as the most effective boronic reagent, while pinacol allylboronate proved the least efficient among the boronic components tested [17].

Preliminary experiments

At the beginning of our study, we used reaction conditions based on our previous work

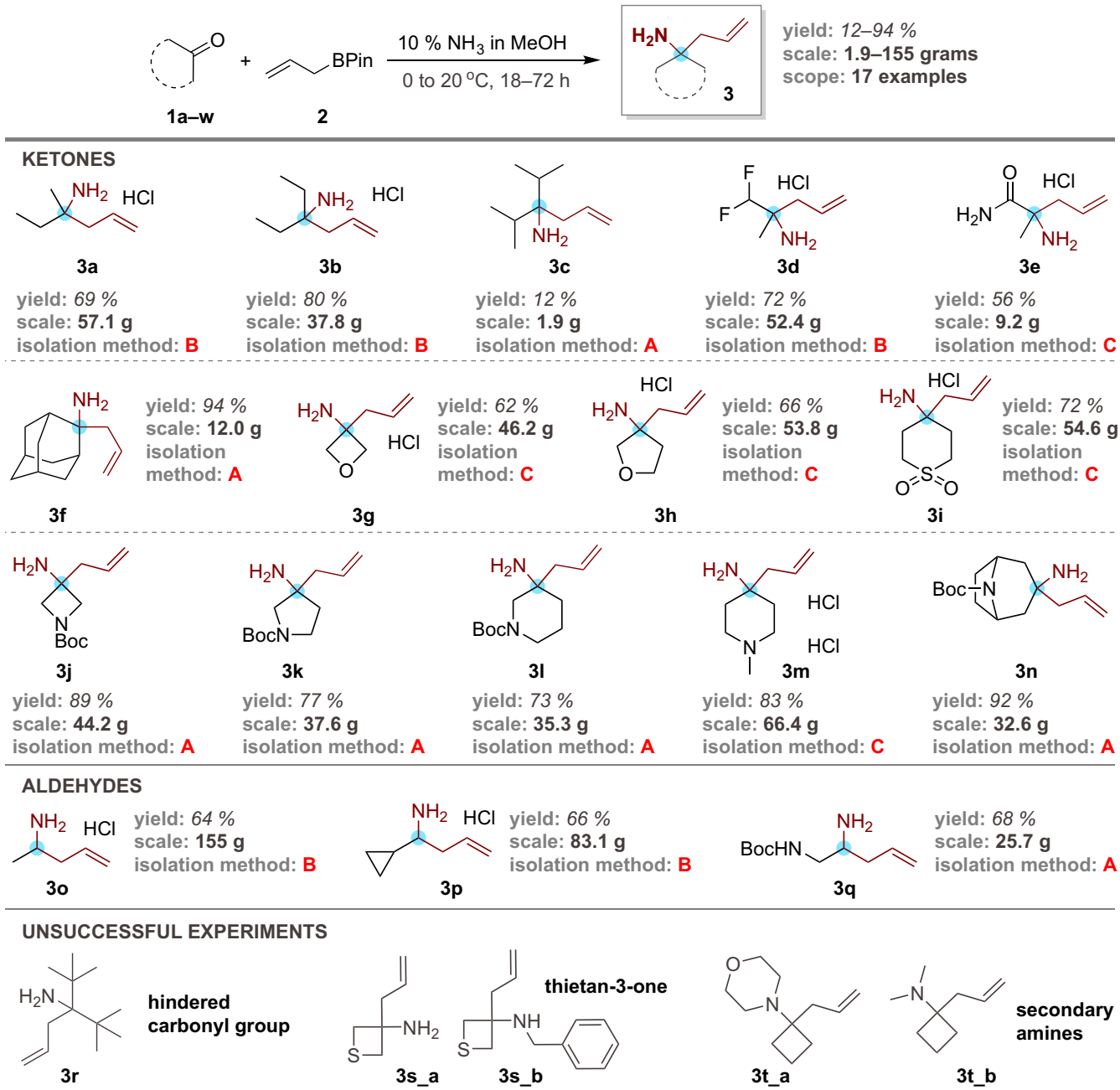

Figure 2. The scope, yields, and scales of achievable homoallylamines **3**

on δ-amino acids [15]. Since allylboronic acid is commercially unavailable, we opted for its readily accessible pinacol ester. The initial reaction was conducted using butanone (**1a**, 1.0 equiv) and allylboronic acid pinacol ester (**2**, 1.1 equiv) in a 10% ammonia solution in methanol (~5.8 equiv) at 0–20°C. Complete consumption of the ketone, monitored by GCMS, was observed in 18 hours. A straightforward acid-base extraction made it possible to obtain homoallylamine **3a** with a yield of 72% (on a 0.01 mol scale). Scaling up the reaction to 0.5 mol of butanone resulted in a comparable efficiency, yielding **3a** in 69% as its hydrochloride salt (for products **3** isolation *see below*). One critical detail observed during scale-up was the mode of addition of the pinacol ester. Adding it gradually from a dropping funnel led to the formation of a solid complex between ammonia and the boronic ester, producing a bulky precipitate that hindered further addition and complicated the process overall. To avoid this issue, the ester should be added in one portion. Notably, in contrast to the protocol used by *Dhudshia et al.*, we successfully reduced the excess of ammonia (from 10 equiv. to 5.8 equiv.) and the boronic ester (from 1.6 equiv. to 1.1 equiv.). Increasing the amounts of these reagents did not enhance the reaction efficiency. These optimizations rendered our method more sustainable and practical for the multigram-scale preparation of homoallylamines.

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Substrate scope investigation

To evaluate the scope of the protocol, we tested a range of alicyclic and cyclic ketones, as well as aldehydes. Special attention was given to structurally diverse ketones as a recent study highlighted the challenges associated with ketimines in the homoallylic amine synthesis due to their low electrophilicity – contrasting with the well-established allylation of aldimines [18]. However, our successful results with butanone called this assumption into question, prompting a systematic study of the ketone reactivity.

We examined various aliphatic ketones, including functionalized derivatives (**1b–e,r**), cage-shaped adamantanone (**1f**), and heterocyclic ketones containing oxygen (**1g,h**), sulfur (**1i,s**), or nitrogen (**1j–n**).

Experiments proved that linear aliphatic ketones (**1b,d,e**) performed well, yielding homoallylamines in good to high yields on a large scale. However, steric hindrance around the carbonyl significantly impacted the reaction efficiency. For example, introducing two methyl groups in positions α and α' of pentan-2-one (diisopropyl ketone, **1c**) drastically reduced the yield of **3c** to just 12% under prolonged reaction conditions (60°C, 72 h, closed vial). In the case of *di*(*tert*-butyl) ketone (**1r**), no detectable (by ^{1}H NMR) homoallylamine was formed. Interestingly, adamantanone (**1f**), being structurally similar to diisopropyl ketone but conformationally locked, exhibited the highest efficiency among the ketones tested, providing **3f** in the yield of 94%. Apparently, the enhanced reactivity of adamantanone can be attributed to its conformational rigidity, which minimizes conformational penalties and locks the molecule into an optimal conformation for attack by the boronic ester.

Heterocyclic ketones generally gave the expected homoallylamines **3** in good to high yields, regardless of the ring size or heteroatom identity, with all frameworks tested (including *N*-Boc-protected ketones) proving stable under the reaction conditions. The only exception was thietane-3-one, which proved to be a particularly challenging substrate. Literature suggests it behaves as a typical ketone [19], yet the imine formation has not been extensively reported, aside from Ti(O*i*Pr)$_4$-catalyzed reactions with *tert*-butylsulfinamide [20]. Using up to a 20-fold excess of ammonia (standard protocol) or 1.0 equiv. of benzylamine in methanol or toluene at 60°C led to complex mixtures (according to ^{1}H NMR) unsuitable for further purification. A stepwise approach involving the preliminary formation of benzylimine also failed.

We also tested our protocol on secondary amines, using cyclobutanone – a previously successful substrate in our earlier work [15]. However, neither morpholine nor dimethylamine yielded the expected homoallylamines (**3u** and **3w**).

These results suggest that the standard protocol is well-suited for most ketones without requiring activation to enhance electrophilicity as claimed previously.

Application to aldehydes

Compared to ketones, the Petasis reaction involving aldehydes is relatively well-studied. However, despite its practicality and versatility, it is rarely employed to construct amine-containing building blocks with a NH_2 group attached to a secondary carbon atom. For example, 2-aminopent-4-ene, which can be directly synthesized from bulk acetaldehyde, is typically prepared *via* indirect routes, such as the Gabriel synthesis [21] or azide-based strategy [22] exploiting the corresponding commercially available but expensive OH precursor. Recognizing this gap, we sought to demonstrate the general applicability of our method to aldehydes.

We selected acetaldehyde (**1o**), cyclopropanecarboxaldehyde (**1p**), and 2-*N*-Boc-aminoacetaldehyde (**1q**) as representative aldehydes. The latter was synthesized following the procedure of *Dilek et al.* [23] and used immediately without further purification due to its low stability. All three aldehydes performed similarly, yielding amines in the yield of 64–68% and up to 155 g scale.

Although previous Petasis reaction studies examined the competitive formation of alcohol by-products, our primary goal was to develop a robust preparative protocol rather than investigate mechanistic nuances. Nevertheless, analytical results confirmed that the isolated amines **3** contained negligible amounts of the alcohol side product, which was efficiently removed during work-up.

Isolation of homoallylamines

Finally, we would like to discuss protocols for the isolation of the homoallylamines synthesized. While all products could be purified *via* the acid-base extraction, we found that different approaches were optimal depending on the compound volatility and lipophilicity. Volatile amines (**3a,b, d,o,p**) were best isolated as hydrochloride salts (*Work-up Procedure B*). This protocol secures the removal of starting volatiles and possible

alcohol by-products. Another aspect for this group of amines concerns the amount of ammonia equivalents used in the reaction. The experiments indicated that the amount can be reduced twice (from ~5.8 to ~2.9 equiv.) without the loss of the reaction efficiency. This also conveniently reduces the quantity of the acid used for the neutralization of excessive ammonia, which is especially valuable for the large reagent loads. At the same time, amines with a high lipophilicity and a high boiling point (over 100 °C) can be isolated as free bases (*Work-up procedure A*) provided that all ketone is consumed in the reaction (TLC control). Although *Procedure B* is also applicable, this method stands as more convenient due to fewer operations, which again is crucial for the large-scale experiments. This way of isolation is proper for N-Boc ketones (**1j–l,n,q**) and ketones with a large hydrocarbon portion (**1c,f**). Notably, this method seems handier than reported previously for amine **3l** *via* the consecutive treatment of the reaction mixture with citric acid and NaOH [24]. The last group of amines **3** covers polar non-volatile compounds. Their polarity enabled them to be isolated as hydrochlorides from the dioxane solution (*Work-up procedure C*). Importantly, all the methods do not require a chromatography step. These approaches eliminate the need for chromatographic purification, streamlining the large-scale synthesis.

■ Conclusion

A highly efficient and scalable approach for the synthesis of homoallylic amines *via* α-aminoallylation of ketones, using an optimized protocol with allylboronic acid pinacol ester has been found. Key improvements include the reduction of excess reagents, enhanced reaction efficiency, and broad substrate compatibility. Additionally, the methodology extends to aldehydes, providing a streamlined and practical route to amine-containing building blocks. The optimized isolation procedures ensure easy purification without chromatography, providing suitability for the large-scale synthesis. Most of the compounds synthesized were previously unreported or had only been obtained through impractical methods on a mmol scale. Findings of this work contribute to advancing sustainable and practical synthetic strategies in amine chemistry, offering a valuable tool for future applications in pharmaceutical and material sciences.

■ Experimental part

This section contains protocols for the preparation of the compounds described in the paper. All starting compounds were obtained from commercial sources and used without additional purification unless otherwise stated. All solvents were purified according to the standard procedures. All compounds known from the literature are given appropriate references; experimental data comply with the referenced papers.

^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 AVANCE 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 (100 MHz), a Bruker 170 AVANCE 500 (126 MHz), or an Agilent ProPulse 600 (151 MHz) spectrometer. The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$, and 2.48 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6. LCMS and GCMS analyses were performed using an Agilent LC/MSD SL 1100 instrument [atmospheric pressure electrospray ionization (ES-API)] or an Agilent 5890 Series II 5972 GCMS instrument [electron impact (EI) ionization (70 eV)], respectively. The results for the elemental analysis were obtained at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. The composition of hydrochloride salts was determined by the acid-base titration method. Melting points were determined on an MPA100 OptiMelt automated melting point system.

The general procedure for the preparation of homoallylamines

The starting ketone (0.50 mol, 1.0 equiv) was dissolved in a 10% ammonia in methanol solution (500 mL) at 0°C, and the resulting mixture was stirred for 10 min at this temperature (for substrates isolated *via* the *Work-up procedure B* the amount of the ammonia solution can be reduced to 250 mL without a loss of efficiency). Allylboronic acid pinacol ester (92.4 g, 0.55 mol, 1.1 equiv) was added to the reaction mixture in one portion at 0°C. The resulting mixture was warmed to 20°C and stirred at this temperature for 18-72 hours (until full consumption of all the starting ketone was shown by TLC or GCMS).

Work-up procedure A

The volatiles were removed *in vacuo*, and the residue was dissolved in a mixture of hexanes (900 mL) and MTBE (300 mL). The resulting solution was washed with 5% aqueous NaOH (500 mL)

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and then with water (4×500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the desired product.

Work-up procedure B

Aqueous HCl solution (12 M, 150 mL) was added to the reaction mixture. The volatiles were removed *in vacuo*, and the residue was dissolved in 10% aqueous NaOH solution (1.0 L). The resulting solution was extracted with the hexanes-MTBE mixture (1:1, 3×500 mL). Combined organic layers were stirred over anhydrous Na_2SO_4, and Na_2SO_4 was filtered off. 4 M HCl solution in dioxane was added to the resulting mixture until the amine solution turns acidic. The precipitate formed was collected *via* filtration, washed with an additional 300 mL of MTBE and dried in vacuum to obtain the desired product as a hydrochloric salt.

Work-up procedure C

The volatiles were removed *in vacuo*, and the residue was treated with 800 mL of MTBE. Solids were removed *via* filtration, and HCl solution in dioxane (4 M, 130 mL) was added to the resulting mixture. The precipitate was collected *via* filtration, washed with an additional 300 mL of MTBE and dried in vacuum, giving the product as a hydrochloric salt.

3-Methylhex-5-en-3-amine hydrochloride (3a) [25]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from butan-2-one (**1a**) (40 g, 0.555 mol).

A white solid. Yield – 69% (57.1 g, 0.383 mol). M. p. 217–220ºC. Anal. Calcd for $C_7H_{16}ClN$, %: C 56.18, H 10.78, N 9.36. Found, %: C 56.32, H 10.70, N 9.53. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 0.86 (3H, t, J = 7.5 Hz), 1.16 (3H, s), 1.54 (2H, q, J = 7.7 Hz), 2.25–2.36 (2H, m), 5.12–5.20 (2H, m), 5.75–5.87 (1H, m), 8.09 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 132.00, 119.60, 55.69, 41.30, 30.01, 22.56, 7.37. LCMS (ES-API), m/z: 114.2 $[M-Cl]^+$.

3-Ethylhex-5-en-3-amine hydrochloride (3b) [26]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from pentan-3-one (**1b**) (25 g, 0.260 mol).

A white solid. Yield – 80% (37.8 g, 0.232 mol). M. p. >300ºC. Anal. Calcd for $C_8H_{18}ClN$, %: C 58.70, H 11.08, N 8.56. Found, %: C 58.78, H 11.12, N 8.41. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 0.85 (6H, td, J = 7.5, 2.1 Hz), 1.49–1.57 (4H, m), 2.29 (2H, d, J = 7.3 Hz), 5.12–5.22 (2H, m), 5.82 (1H, dddd, J = 17.3, 14.5, 7.3, 2.0 Hz), 8.02 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 7.56, 28.22, 39.76, 58.62, 120.04, 132.37. LCMS (ES-API), m/z: 128.2 $[M-Cl]^+$.

3-Isopropyl-2-methylhex-5-en-3-amine (3c)

Synthesized according to the **General procedure** (The reaction mixture was stirred at 60 ºC for 72h in a closed vial) followed by **Work-up procedure A** starting from 2,4-dimethylpentan-3-one (**1c**) (11.4 g, 0.100 mol).

A colorless oil. Yield – 12% (1.9 g, 12.2 mmol). Anal. Calcd for $C_{10}H_{21}N$, %: C 77.35, H 13.63, N 9.02. Found, %: C 77.27, H 13.57, N 9.13. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.65–0.86 (2H, br. s), 0.9 (12H, t, J = 6.6 Hz), 1.72–1.87 (2H, m), 2.15 (2H, dd, J = 7.4, 1 Hz), 4.89–5.07 (2H, m), 5.79–5.92 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 17.35, 17.65, 34.10, 39.83, 57.04, 116.57, 136.07. LCMS (ES-API), m/z: 156.2 $[M+H]^+$.

1,1-Difluoro-2-methylpent-4-en-2-amine hydrochloride (3d)

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from 1,1-difluoropropan-2-one (**1d**) (40 g, 0.425 mol).

A white solid. Yield – 72% (52.4 g, 0.306 mol). M. p. 223–226 ºC. Anal. Calcd for $C_6H_{12}ClF_2N$, %: C 41.99, H 7.05, N 8.16. Found, %: C 42.08, H 7.10, N 8.29. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.26 (3H, s), 2.46 (2H, d, J = 3.1 Hz), 5.19–5.26 (2H, m), 5.77–5.89 (1H, m), 6.19 (1H, t, J = 54.2 Hz), 8.80 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 16.92, 37.13, 56.35 (t, $^2J_{CF}$ = 21 Hz), 115.45 (t, $^1J_{CF}$ = 247 Hz), 120.85, 130.00. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -131.70 (d, J = 281.3 Hz), -130.73 (d, J = 281.5 Hz). LCMS (ES-API), m/z: 241.2 $[M-Cl]^+$.

2-Amino-2-methylpent-4-enamide hydrochloride (3e)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from ethyl 2-oxopropanoate (**1e**) (11.6 g, 0.100 mol).

A white solid. Yield – 56% (9.2 g, 55.9 mmol). M. p. 106–110ºC. Anal. Calcd for $C_6H_{13}ClN_2O$, %: C 43.77, H 7.96, N 17.02. Found, %: C 43.84, H 7.89, N 17.14. ^{1}H NMR (400 MHz, DMSO), δ, ppm: 1.47 (3H, s), 2.54–2.72 (2H, m), 5.03–5.25 (2H, m), 5.86–5.60 (1H, m), 7.53 (1H, br. s), 7.90 (1H, br. s), 8.31 (3H, br. s). ^{13}C NMR (101 MHz, DMSO), δ, ppm: 22.33, 41.31, 59.68, 120.92, 131.30, 172.57. LCMS (ES-API), m/z: 129.2 $[M+H]^+$.

(1*r*,3*r*,5*r*,7*r*)-2-Allyladamantan-2-amine (3f)

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from (1*r*,3*r*,5*r*,7*r*)-adamantan-2-one (**1f**) (10.0 g, 66.7 mmol).

A colorless oil. Yield – 94% (12.0 g, 62.6 mmol). Anal. Calcd for $C_{13}H_{21}N$, %: C 81.61, H 11.06, N 7.32. Found, %: C 81.79, H 11.12, N 7.19. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 1.34 (2H, s), 1.51–1.62 (4H, m), 1.62–1.71 (4H, m), 1.82 (2H, q, *J* = 3.6 Hz), 1.96–2.04 (2H, m), 2.04–2.12 (2H, m), 2.36 (2H, d, *J* = 7.5 Hz), 5.07 – 5.15 (2H, m), 5.79–5.97 (1H, m). ^{13}C NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 134.24, 117.96, 54.55, 43.11, 38.96, 37.37, 33.90, 33.00, 27.58, 27.32. LCMS (ES-API), m/z: 192.2 $[M+H]^+$.

3-(Prop-2-en-1-yl)oxetan-3-amine hydrochloride (3g)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from oxetan-3-one (**1g**) (36.0 g, 0.50 mol).

A beige solid. Yield – 62% (46.2 g, 0.31 mol). M. p. 153–155ºC. Anal. Calcd for $C_6H_{12}ClNO$, %: C 48.17, H 8.08, N 9.36. Found, %: C 48.03, H 8.14, N 9.46. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm: 2.61 (2H, d, *J* = 7.2 Hz), 4.41 (2H, d, *J* = 7.1 Hz), 4.62 (2H, d, *J* = 7.1 Hz), 5.21–5.31 (2H, m), 5.94 (1H, ddt, *J* = 17.4, 10.3, 7.2 Hz), 8.85 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6), *δ*, ppm: 38.73, 55.21, 76.91, 121.06, 131.54. LCMS (ES-API), m/z: 114.0 $[M-Cl]^+$.

3-(Prop-2-en-1-yl)oxolan-3-amine hydrochloride (3h) [27]

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from dihydrofuran-3(2*H*)-one (**1h**) (43.0 g, 0.50 mol).

A beige solid. Yield – 66% (53.8 g, 0.33 mol). M. p. 159–162ºC. Anal. Calcd for $C_7H_{14}ClNO$, %: C 51.38, H 8.62, N 8.56. Found, %: C 51.49, H 8.58, N 8.45. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 2.01 (2H, t, *J* = 7.2 Hz), 2.52–2.57 (2H, m), 3.57 (1H, d, *J* = 9.8 Hz), 3.70–3.80 (2H, m), 3.93 (1H, q, *J* = 7.8 Hz), 5.15–5.26 (2H, m), 5.87 (1H, ddt, *J* = 17.2, 10.0, 7.2 Hz), 8.48 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 131.85, 120.11, 73.76, 66.57, 61.86, 34.86. LCMS (ES-API), m/z: 128.2 $[M-Cl]^+$.

4-Allyl-4-aminotetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (3i)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from tetrahydro-4*H*-thiopyran-4-one 1,1-dioxide (**1i**) (50.0 g, 0.337 mol).

A white solid. Yield – 72% (54.6 g, 0.243 mol). M. p. 220–223ºC. Anal. Calcd for $C_8H_{16}ClNO_2S$, %: C 42.57, H 7.14, N 6.21. Found, %: C 42.70, H 7.04, N 6.26. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 2.05–2.26 (4H, m), 2.53–2.59 (2H, m), 3.19 (2H, ddd, *J* = 14.0, 8.4, 3.6 Hz), 5.24 (1H, dd, *J* = 10.1, 2.2 Hz), 5.29 (1H, dd, *J* = 17.0, 2.2 Hz), 5.81–5.96 (1H, m), 8.56 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 31.36, 45.52, 52.90, 121.02, 130.89. LCMS (ES-API), m/z: 190.2 $[M-Cl]^+$.

***tert*-Butyl 3-allyl-3-aminoazetidine-1-carboxylate (3j)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxoazetidine-1-carboxylate (**1j**) (40 g, 0.234 mol).

A yellow oil. Yield – 89% (44.2 g, 0.208 mol). Anal. Calcd for $C_{11}H_{20}N_2O_2$, %: C 62.24, H 9.50, N 13.20. Found, %: C 62.08, H 9.61, N 13.34. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 1.45 (9H, d, *J* = 1.2 Hz), 1.73 (2H, s), 2.39–2.46 (2H, m), 3.64 (2H, d, *J* = 8.6 Hz), 3.82–3.89 (2H, m), 5.16–5.26 (2H, m), 5.74–5.89 (1H, m). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 27.86, 43.49, 50.42, 61.80, 78.94, 118.90, 131.96, 155.96. LCMS (ES-API), m/z: 157.2 $[M-C_4H_8+H]^+$.

***tert*-Butyl 3-allyl-3-aminopyrrolidine-1-carboxylate (3k)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxopyrrolidine-1-carboxylate (**1k**) (40 g, 0.216 mol).

A yellow oil. Yield – 77% (37.6 g, 0.166 mol). Anal. Calcd for $C_{12}H_{22}N_2O_2$, %: C 63.69, H 9.80, N 12.38. Found, %: C 63.81, H 9.75, N 12.47. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm 1.45 (11H, s), 1.64–1.72 (1H, m), 1.84 (1H, dt, *J* = 12.2, 8.7 Hz), 2.27 (2H, d, *J* = 7.4 Hz), 3.08–3.31 (2H, m), 3.46 (2H, ddd, *J* = 20.9, 10.6, 4.4 Hz), 5.16 (2H, dd, *J* = 13.6, 9.1 Hz), 5.82 (1H, dd, *J* = 16.2, 8.8 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 27.99, 37.37, 37.89, 43.73, 44.01, 44.19, 44.33, 57.46, 57.84, 58.62, 78.67, 118.58, 132.97, 154.18. LCMS (ES-API), m/z: 171.2 $[M-C_4H_8+H]^+$.

***tert*-Butyl 3-allyl-3-aminopiperidine-1-carboxylate (3l)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxopiperidine-1-carboxylate (**1l**) (40 g, 0.201 mol).

A yellow oil. Yield – 73% (35.3 g, 0.147 mol). Anal. Calcd for $C_{13}H_{24}N_2O_2$, %: C 64.97, H 10.07, N 11.66. Found, %: C 65.15, H 10.12, N 11.51. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm:

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1.22–1.29 (1H, m), 1.45 (10H, s), 1.49–1.69 (4H, m), 2.11 (1H, dd, J = 13.7, 8.0 Hz), 2.17 (1H, dd, J = 13.8, 7.0 Hz), 3.01–3.63 (4H, m), 5.09–5.18 (2H, m), 5.80–5.92 (1H, m). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 21.56, 24.60, 28.42, 36.79, 43.57, 50.27, 55.10, 79.54, 119.00, 133.13, 155.16. LCMS (ES-API), m/z: 241.2 $[M+H]^+$.

1-Methyl-4-(prop-2-en-1-yl)piperidin-4-amine dihydrochloride (3m)

Synthesized according to the **General procedure** followed by **Work-up procedure C** starting from 1-methylpiperidin-4-one (**1m**) (40.0 g, 0.354 mol).

A yellow solid. Yield – 83% (66.4 g, 0.294 mol). M. p. 192–195°C. Anal. Calcd for $C_9H_{20}Cl_2N_2$, %: C 47.58, H 8.87, N 12.33. Found, %: C 47.44, H 8.92, N 12.26. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.92–2.13 (4H, m), 2.72 (5H, s), 3.10 (2H, s), 3.61 (2H, s), 5.24 (2H, t, J = 12.3 Hz), 5.80–5.95 (1H, m), 8.64 (3H, s), 11.02 (1H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 30.16, 40.52, 42.26, 48.06, 52.08, 121.27, 131.28. LCMS (ES-API), m/z: 155.4 $[M-Cl]^+$.

***tert*-Butyl 3-allyl-3-amino-8-azabicyclo-[3.2.1]octane-8-carboxylate (3n)**

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**1n**) (30 g, 0.133 mol).

A white solid. Yield – 92% (32.6 g, 0.123 mol). M. p. 53–55°C. Anal. Calcd for $C_{15}H_{26}N_2O_2$, %: C 67.63, H 9.84, N 10.52. Found, %: C 67.48, H 10.01, N 10.39. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.00 (2H, s), 1.33 (2H, d, J = 14.0 Hz), 1.44 (9H, s), 1.82 (3H, d, J = 30.8 Hz), 1.93 (3H, d, J = 7.6 Hz), 2.13 (2H, d, J = 6.3 Hz), 4.10 (1H, s), 4.20 (1H, s), 4.97–5.07 (1H, m), 5.11 (1H, dd, J = 10.3, 2.3 Hz), 5.72 (1H, ddt, J = 17.4, 10.2, 7.4 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 24.33, 27.09, 27.76, 28.00, 41.42, 42.29, 49.59, 52.30, 53.09, 54.33, 78.40, 118.54, 132.93, 153.02. GCMS (EI, 70 eV), m/z: 267.2 $[M]^{+\cdot}$.

Pent-4-en-2-amine hydrochloride (3o) [21]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from acetaldehyde (**1o**) (88.1 g, 2.00 mol).

A white solid. Yield – 64% (155 g, 1.28 mol). M. p. 86–88°C. Anal. Calcd for $C_5H_{12}ClN$, %: C 49.38, H 9.95, N 11.52. Found, %: C 49.53, H 10.08, N 11.36. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.16 (3H, d, J = 6.5 Hz), 2.21 (1H, dt, J = 14.7, 7.8 Hz), 2.41 (1H, ddd, J = 13.9, 6.7, 5.2 Hz), 3.20 (1H, p, J = 6.0 Hz), 5.09–5.20 (2H, m), 5.78 (1H, ddt, J = 17.2, 10.2, 7.1 Hz), 8.10 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 18.11, 38.77, 46.65, 119.06, 133.82. LCMS (ES-API), m/z: 86.2 $[M-Cl]^+$.

1-Cyclopropylbut-3-en-1-amine hydrochloride (3p) [28]

Synthesized according to the **General procedure** followed by **Work-up procedure B** starting from cyclopropanecarboxaldehyde (**1p**) (60.0 g, 0.856 mol).

A white solid. Yield – 66% (83.1 g, 0.565 mol). M. p. 174–177°C. Anal. Calcd for $C_7H_{14}ClN$, %: C 56.94, H 9.56, N 9.49. Found, %: C 57.11, H 9.49, N 9.58. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.30 (1H, dq, J = 9.8, 4.8 Hz), 0.35–0.61 (3H, m), 0.90 (1H, qt, J = 8.8, 4.8 Hz), 2.43 (3H, tt, J = 10.5, 6.7 Hz), 5.07–5.22 (2H, m), 5.86 (1H, ddt, J = 17.1, 10.0, 6.8 Hz), 8.18 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 3.28, 4.11, 13.32, 37.48, 55.48, 118.22, 133.36. LCMS (ES-API), m/z: 112.2 $[M-Cl]^+$.

***tert*-Butyl (2-aminopent-4-en-1-yl)carbamate (3q)** [29]

Synthesized according to the **General procedure** followed by **Work-up procedure A** starting from *tert*-butyl (2-oxoethyl)carbamate (**1q**) (30 g, 0.188 mol).

A colorless oil. Yield – 68% (25.7 g, 0.128 mol). Anal. Calcd for $C_{10}H_{20}N_2O_2$, %: C 59.97, H 10.07, N 13.99. Found, %: C 60.11, H 10.18, N 13.88. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.36 (2H, s), 1.43 (9H, s), 2.00 (1H, dt, J = 14.4, 7.4 Hz), 2.18–2.27 (1H, m), 2.90 (2H, pd, J = 7.9, 3.9 Hz), 3.23 (1H, dd, J = 16.8, 8.1 Hz), 4.96 (1H, s), 5.07–5.14 (2H, m), 5.71–5.83 (1H, m). ^{13}C NMR (151 MHz, Chloroform-*d*), δ, ppm: 28.38, 40.27, 46.65, 50.58, 79.19, 117.84, 134.88, 156.18. GCMS (EI, 70 eV), m/z: 127.0 $[M-C_4H_9O]^+$.

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