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Safe and Efficient Preparative Approach to Chiral α -Chloroketones Based on In-Flow Generated Diazomethane

Abstract

α -Chloroketones are valuable semi-products in the organic synthesis and pharmaceutical industry. In particular, they are used as key building blocks for the production of HIV protease inhibitors, such as atazanavir and darunavir. A well-known approach to their synthesis involves the Arndt-Eistert homologation, which relies on the formation of diazoketones followed by their halogenation. However, this process poses significant safety and implementation challenges due to the use of diazomethane (CH_2N_2). The high toxicity, carcinogenicity, and explosion hazard of CH_2N_2 limit its large-scale application and require design of specialized laboratory setups to reduce the risks.

In this study, we present a new continuous-flow diazomethane generator that integrates the membrane technology with a traditional flow reactor setup for a safe and efficient generation of CH_2N_2 . The flow technology eliminates the need for storage and handling of diazomethane, while facilitating its direct use in multistep synthesis. As a proof-of-concept, we demonstrate its application in the three-step synthesis of chiral α -chloroketones from *N*-protected amino acids. The approach newly developed offers a safer, more efficient, and scalable alternative to conventional diazomethane-based processes, paving the way for broader industrial applications.

Keywords: flow processes; diazomethane; α -chloroketones; diazoketones; halomethylation; chiral compounds

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вул. Академіка Кухаря, 5, м. Київ, 02094, Україна² ТОВ НВП «Єнамін», вул. Вінстона Черчилля, 78, м. Київ, 02094, Україна**Безпечний та ефективний препаративний підхід до хіральних α -хлорокетонів на основі діазометану, що синтезується в проточному режимі**

Анотація

α -Хлорокетони є цінними напівпродуктами в органічному синтезі та у фармацевтичній промисловості. Зокрема, їх використовують як ключові будівельні блоки для отримання інгібіторів ВІЛ протеази, як-от атазанавір і дарунавір. Широко відомий підхід до їх синтезу передбачає гомологізацію Арндта-Айстерта, яка базується на утворенні діазокетонів із подальшим галогенуванням. Однак цей процес створює значні проблеми з безпекою та впровадженням через використання діазометану (CH_2N_2). Висока токсичність, канцерогенність і вибухонебезпечність CH_2N_2 обмежують його широкомасштабне застосування та вимагають створення спеціального лабораторного устаткування для зниження ризиків.

У цьому дослідженні ми репрезентуємо новий проточний генератор діазометану, який об'єднує мембранні технології з класичним реактором проточного синтезу. Ця система забезпечує безпечне та ефективне генерування CH_2N_2 , усуваючи потребу у його зберіганні та транспортуванні й одночасно полегшуючи його пряме використання в багаторічному синтезі. Як доказ концепції ми демонструємо застосування реактора в тристадійному синтезі хіральних α -хлорокетонів із *N*-захисених амінокислот. Нещодавно розроблений підхід пропонує безпечнішу, ефективнішу та придатну до масштабування альтернативу звичайним процесам на основі діазометану, прокладаючи шлях до його більш широкого промислового застосування.

Ключові слова: потокові процеси; діазометан; α -хлорокетони; діазокетони; галогенування; хіральні сполуки

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

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■ Introduction

Over the past two decades, a series of highly potent, orally bioavailable HIV protease inhibitors have been developed and approved for clinical use [1, 2]. These inhibitors, including atazanavir and darunavir, play a crucial role in highly active antiretroviral therapy (HAART) and are listed by the World Health Organization as essential medicines [3]. Structurally, they belong to the class of peptidomimetics, mimicking natural substrates by incorporating non-hydrolyzable hydroxyethylene or hydroxyethylamine moieties at the protease cleavage site (**Figure 1**). Notably, most FDA-approved HIV protease inhibitors contain a chiral amino alcohol core, which is typically introduced through a nucleophilic ring-opening of the corresponding *N*-protected aminoepoxide [4].

A well-established route for preparing these chiral semi-products involves the transformation

of *N*-protected amino acids into α -haloketones, followed by a selective reduction to produce chiral amino epoxides or amino alcohols. Among various methods available for the α -haloketone formation, one of the most straightforward and cost-effective strategies relies on the halomethylation using diazomethane (CH_2N_2) (**Scheme 1**) [5]. This method, involving the condensation of an activated amino acid with CH_2N_2 followed by the α,α -substitution with a hydrogen halide, is known due to its efficiency and diastereoselectivity [6]. However, diazomethane, an extremely versatile reagent in organic synthesis, is also highly toxic, volatile, carcinogenic, and prone to explosive decomposition, which pose significant limitations on its large-scale implementation. Its sensitivity to heat, light, and mechanical shock necessitates careful handling, and even the use of specialized equipment does not guarantee the avoidance of accidents [7]. Therefore, the industrial-scale production of CH_2N_2 could be provided using batch

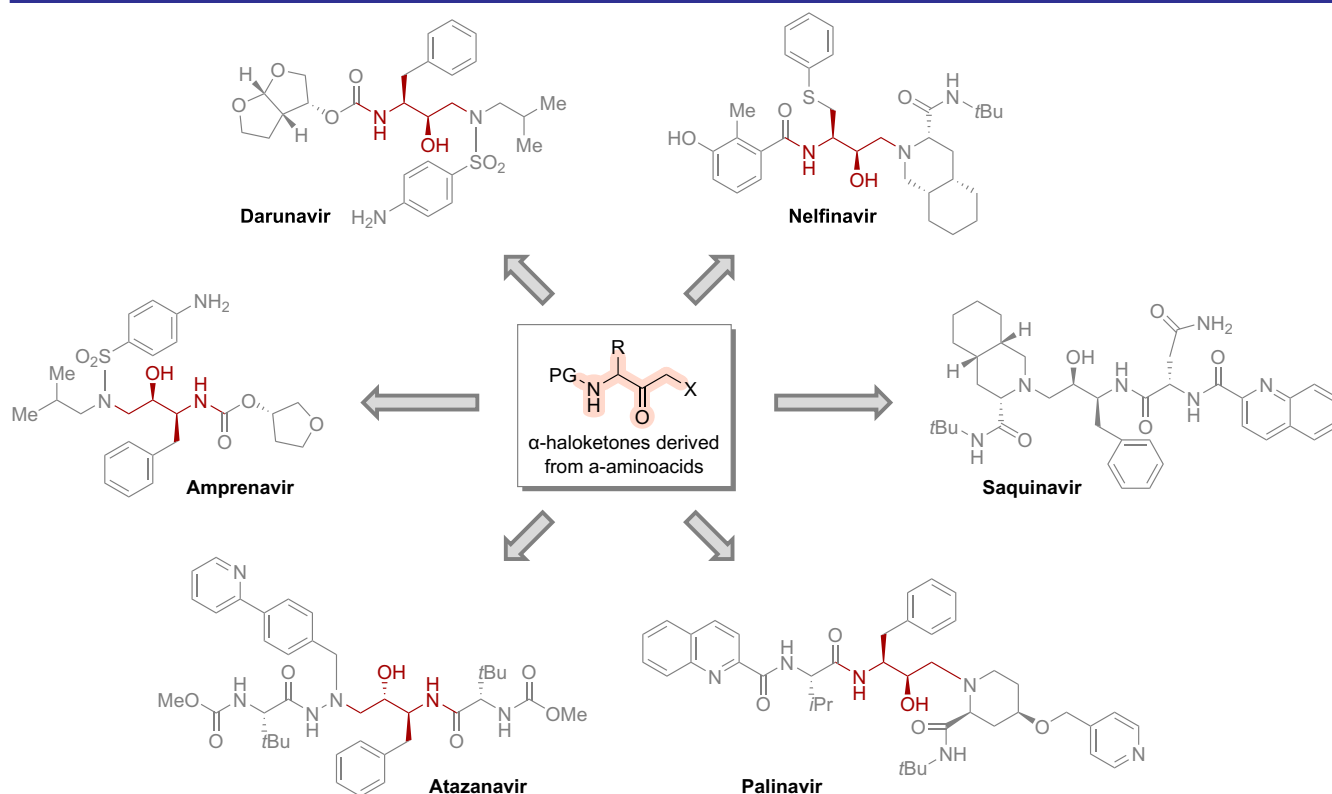
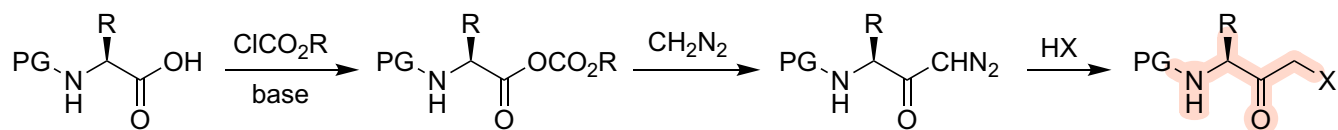


Figure 1. HIV protease inhibitors derived from α -haloketones



Scheme 1. The diazomethane-based synthesis of α -haloketones from *N*-protected chiral amino acids

and continuous flow processes, with notable examples including the Aerojet process and other industrial setups utilizing the phase-transfer catalysis or continuous nitrogen stream transport [8]. Despite these advancements, the large-scale application of diazomethane remains restricted due to the challenges of safe storage, transport, and handling. To overcome these limitations, recent developments in flow chemistry have introduced safer, on-demand CH_2N_2 generation methods, integrating the membrane separation technology to minimize the risks associated with its accumulation [9, 10]. Continuous flow systems have long been employed for the large-scale chemical production and are being increasingly adapted for fine chemical and pharmaceutical syntheses [11]. These systems enable controlled multistep transformations, while ensuring greater safety, reproducibility, and efficiency.

In this study, we present the development of a procedure based on a continuous-flow generated diazomethane, applied to the three-step synthesis of α -chloroketones from *N*-protected amino acids. This approach eliminates the need for diazomethane storage and handling while enabling a scalable and efficient synthesis of some key chiral building blocks without racemization. The full continuous process demonstrates high yields and safety improvements, making it a viable alternative to traditional batch methods for producing α -haloketones in pharmaceutical applications.

■ Results and discussion

Generation of Anhydrous Diazomethane

Access to anhydrous diazomethane (CH_2N_2) is essential for the modified Arndt-Eistert reaction, which serves as a key step in the synthesis of chiral amino alcohols – crucial semi-products in the production of HIV protease inhibitors. Ensuring the complete removal of water from CH_2N_2 is critical as even trace moisture can affect the reaction efficiency and selectivity.

Previous studies have employed the reaction between CH_2N_2 and activated organic acids as an indirect method to verify anhydrous conditions [12]. However, our investigations revealed that this technique lacks the required sensitivity.

When benzoyl chloride was exposed to CH_2N_2 under controlled conditions, the expected formation of benzoic acid (a marker for water presence) was only detectable by GC-FID when at least 50 vol% of water was added.

To obtain more accurate moisture measurements, we turned to the Karl-Fischer titration, a highly sensitive technique for water quantification [12]. In our setup, a 0.1 M CH_2N_2 solution in the $\text{THF}:\text{CH}_2\text{Cl}_2$ mixture was generated and subsequently quenched with benzoic acid. A reference Karl-Fischer titration was performed on a pure benzoic acid solution, and this baseline value was subtracted from the reading obtained for the quenched CH_2N_2 solution. The final titration results confirmed that our system successfully produces anhydrous CH_2N_2 , with a measured water content of 347 ± 7 ppm, demonstrating that the membrane-based diazomethane generation effectively prevents the moisture contamination.

By ensuring a continuous supply of high-purity CH_2N_2 , our method provides a safe, efficient, and scalable alternative to conventional batch approaches, further enhancing its applicability in multistep synthetic processes.

Synthesis of α -Chloroketones

The synthesis of α -chloroketones was carried out *via* a well-established three-step pathway comprising the activation of the *N*-protected amino acid, the formation of the diazoketone semi-product, and the selective halogenation to yield the final product. This methodology, originally optimized for the α -bromoketone synthesis in the previous study [10], was successfully adapted for the α -chloroketone formation by substituting hydrogen bromide (HBr) with hydrogen chloride (HCl) as a halogenating agent.

Step 1: The Activation of N-Protected Amino Acids

In the first step, *N*-protected amino acids **1** were converted into reactive mixed anhydrides **1-act** by the treatment with ethyl chloroformate in the presence of a base, such as triethylamine or *N*-methylmorpholine, in an anhydrous solvent (**Figure 2, A**). The procedure was performed under mild reaction conditions that avoided excessive heating or drastic pH changes (*see Experimental section*), and it was compatible with

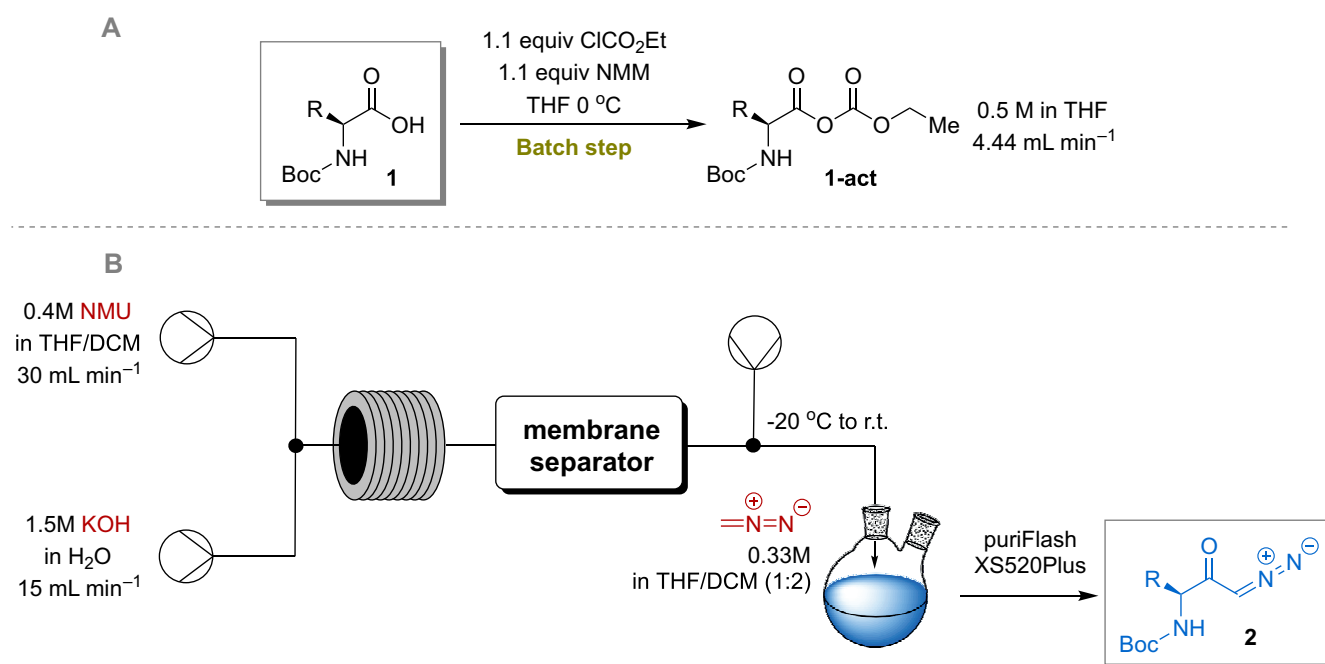


Figure 2. The intermediate synthesis (A) and reactor setup (B)

a broad range of amino acid protecting groups, thereby offering flexibility in the precursor selection. Moreover, the reaction proceeded with a high conversion efficiency, which minimized side reactions and the by-product formation.

Step 2: The Formation of the α -Diazoketone

Once the mixed anhydride was generated, it reacted with anhydrous diazomethane (CH_2N_2) under carefully controlled conditions. By employing a continuous-flow CH_2N_2 generator (**Figure 2, B**), a high-purity stream of diazomethane was directed into the reaction mixture, ensuring a rapid and efficient conversion of the mixed anhydride to the corresponding α -diazoketone. The continuous-flow approach enhanced safety by eliminating the need for accumulation and storage of a large amount of diazomethane, provided a high reproducibility through the consistent conversion efficiency across various substrates, and improved the reaction kinetics by facilitating a rapid formation of the diazoketone. The formation of the diazoketone intermediates was confirmed *via* ^1H and ^{13}C NMR spectroscopy, with characteristic peaks in agreement with literature reports for similar compounds [9, 10].

Step 3: The Halogenation to α -Chloroketones

In the final step, α -diazoketone semi-products were selectively converted into the corresponding α -chloroketones using aqueous HCl. Chlorination, unlike bromination where rapid elimination side reactions can occur, benefited from the lower nucleophilicity of chloride ions, which enhanced selectivity. Initial attempts focused on developing a fully continuous α -chloroketone synthesis

using a flow reactor. However, challenges emerged since the high surface tension of the aqueous HCl phase impeded a reliable flow control, which in turn led to uncontrolled increases in solvent levels. Drawing on insights from previous work, the process was modified by transitioning to a conventional batch synthesis approach. In this modified protocol, a pure isolated diazoketone obtained *via* the continuous-flow process in *Step 2* was used as the starting material for the halogenation. The isolated diazoketone reacted with 3 equiv. of the conc. HCl at room temperature. The complete conversion was achieved within 10 minutes of stirring. It is important to note that increasing the HCl quantity beyond 3 equiv. resulted in the unwanted deprotection of α -chloroketone, underscoring the necessity for the precise reagent control. The final α -chloroketones were isolated with purities exceeding 98%, as confirmed by the HPLC analysis.

The chloroketones prepared by this protocol are shown in **Figure 3 (B)**. The protocol was easily scaled up to 100 g of chloroketone in a single synthetic run. We developed individual protocols for the optical purity control based on the chiral HPLC for all chiral representatives. As a result, we found that the optical purity of the starting amino acids was retained for all chloroketones. It also proves the preservation of the absolute configuration for the intermediate diazoketones.

Comparison with Alternative Methods

The performance of the elaborated method was evaluated against other reported approaches based on the diazoketone formation and

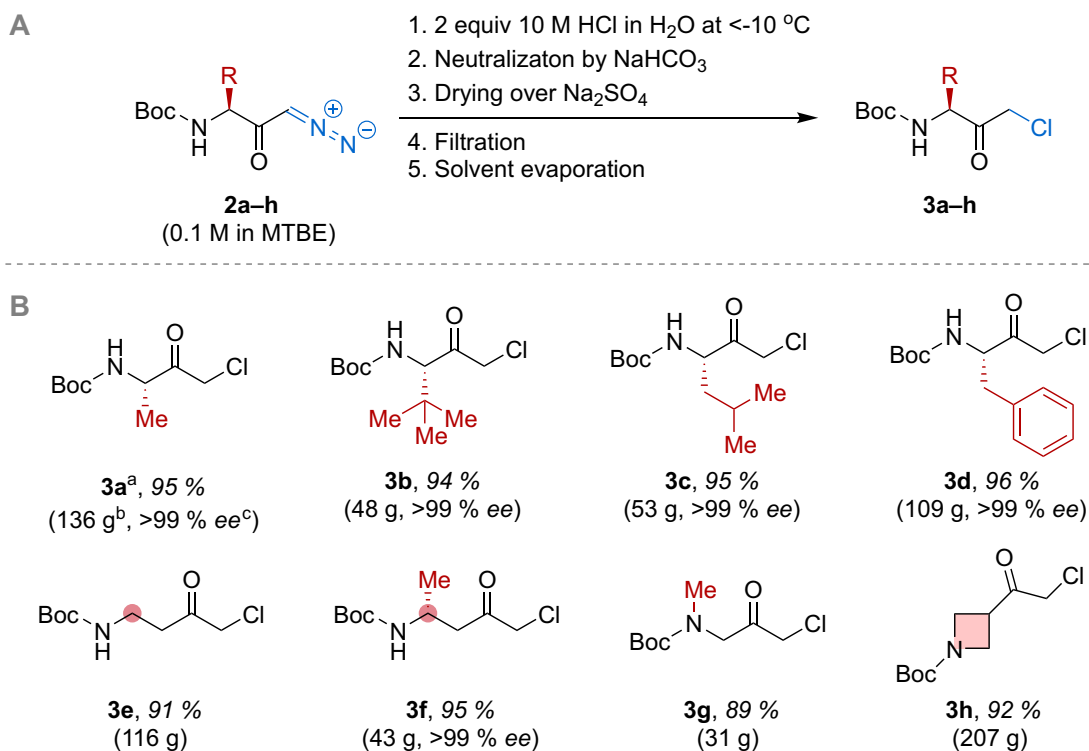


Figure 3. The general scheme for the preparation of chloroketones from diazoketones (A); the scope of chloroketones **3a-h** (B) prepared. ^a For all chiral products, both enantiomers were independently synthesized (see **Experimental section**). ^b The amount of the compound obtained. ^c Measured using chiral HPLC.

halogenation time, yield, purity, and overall safety profile. The classic batch method, which employs pre-made CH₂N₂, typically requires 2–3 hours for the halogenation, with yields of products in the range of 65–75%, the purity between 90–95% and is associated with a high safety risk. The tube-in-tube method described by *Pinho et al.* [13] uses a continuous diazoketone formation and achieves the halogenation in 1–2 hours, with yields of 75–85% and the purity of 95–98%, presenting a moderate safety profile. In contrast, our method, which combines a continuous CH₂N₂ generation in *Step 2* with the batch halogenation in *Step 3*, achieves the diazoketone formation within 30–60 minutes and the halogenation in 10 minutes, resulting in yields of 85–92% and the purity higher than 98% while offering a high safety profile.

Conclusion

By adapting our bromoketone synthesis method previously reported for the chloroketone preparation, we have developed a preparative process that combines the continuous-flow generation of α -diazoketones with the subsequent batch halogenation step. This hybrid approach enhances scalability and reproducibility while maintaining a high safety profile by eliminating the need for the hazardous diazomethane accumulation,

storage and handling. Taking into account the significant role of α -haloketones in pharmaceutical applications, our methodology represents a noteworthy advance in flow chemistry and a new synthetic employment of easily available diazo compounds.

Experimental section

General

The solvents were purified according to standard procedures. All starting materials were obtained from Enamine Ltd. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500 MHz for ¹H and 126 MHz for ¹³C nuclei) and a Varian Unity Plus 400 spectrometer (400 MHz for ¹H and 101 MHz for ¹³C nuclei). Tetramethylsilane was used as an internal standard. Melting points were measured on the MPA100 OptiMelt automated melting point system. HPLC analyses were performed on an Agilent 1200 chromatograph. A preparative chromatograph puriFlash XS520Plus with a column containing 800 g of silica gel was used for diazoketones purification.

General Methods for the Synthesis of Compounds

The NMU precursor was prepared by nitrosation of methylurea using the standard protocol [14].

The Synthesis of Mixed Anhydrides

In a three-necked flask equipped with a thermometer, a magnetic stirrer, a dropping funnel, and a water seal, 1 equiv. of methylmorpholine was added. The reaction mixture was cooled below $-10\text{ }^{\circ}\text{C}$ and then 1 equiv. of ethyl chloroformate was slowly added, keeping the temperature in the flask below $0\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at this temperature for 30 min. The precipitate formed was filtered off, and the solution of the mixed anhydride was used in the further transformations without isolation.

The Synthesis of Diazoketones

The procedure of diazomethane generation

Solutions of NMU (0.37 M, $\text{CH}_2\text{Cl}_2/\text{THF} = 2:1$) and KOH (1.5 M, H_2O) were injected into the reaction unit through two channels of the reactor pump unit in a molar ratio of 1:2 (30 and 15 mL min^{-1}). The combined stream passed through the reaction column and then through the membrane separator. The aqueous waste stream leaving the outer tube of the separator was directed into a flask containing acetic acid to decompose any residue of diazomethane in the aqueous solution. The resulting organic solution of diazomethane was transferred from the inner tube to a reactor containing a substrate. The flux of diazomethane (0.45 mol h^{-1}) was directed into a three-necked flask equipped with a magnetic stirrer and an electronic thermometer. The substrate flow kept in a molar ratio of 1:2 in relation to diazomethane was fed into the reactor with a delay of 1 min. After the entire amount of the substrate was added, the reactor was switched to wash the mode, and the reaction mixture was stirred for an additional 2 h. The system was able to operate continuously for 5–6 h (stationary conditions) generating and consuming up to 1.8 mol of diazomethane. After evaporation of solvents under vacuum, diazoketone was purified using a preparative chromatograph puriFlash XS520Plus and hexane with a gradient addition of ethyl acetate up to 30% as an eluent. The total amount of diazoketone after the isolation and purification exceeded 1 mol.

The synthesis of chloroketones

Diazoketone was dissolved in MTBE in a three-necked flask equipped with a thermometer, a magnetic stirrer, a dropping funnel and a water seal. The solution was cooled with ice to a temperature below $10\text{ }^{\circ}\text{C}$. Two (2) equiv. of the concentrated HCl was slowly added, keeping the temperature in the flask below $10\text{ }^{\circ}\text{C}$. The reaction mixture

was stirred at this temperature for 45 min. The resulting solution was neutralized with aq. NaHCO_3 to $\text{pH} = 7\text{--}8$, washed with water, dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The purity of the chloroketones prepared was $>95\%$, no further purification was necessary.

(S)-tert-Butyl (4-Chloro-3-oxobutan-2-yl)-carbamate (3a)

A white powder. Yield – 136 g (95%). M. p. = $59\text{--}60\text{ }^{\circ}\text{C}$. Anal. Calcd for $\text{C}_9\text{H}_{16}\text{ClNO}_3$, %: C 46.85, H 6.94, N 5.26, Cl 15.40. Found, %: C 46.63, H 6.93, N 5.12, Cl 15.07. $^1\text{H NMR}$ (400 MHz, CDCl_3), δ , ppm: 1.41 (d, $J = 7.2\text{ Hz}$, 3H), 1.46 (s, 9H), 4.08 (d, $J = 4.0\text{ Hz}$, 2H), 4.50–4.67 (m, 1H), 5.10 (s, 1H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3), δ , ppm: 17.77, 28.28, 31.61, 53.22, 80.30, 155.16, 201.53. $[\alpha]_{\text{D}}(25^{\circ}\text{C}) = -54.2$ ($c = 0.5$, CH_3OH).

(R)-tert-Butyl (4-Chloro-3-oxobutan-2-yl)-carbamate (3a')

A white powder. Yield – 37 g (94%). M. p. = $59\text{--}60\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}} = +54.2$ ($c = 0.5$, CH_3OH).

(S)-tert-Butyl (1-Chloro-4,4-dimethyl-2-oxopentan-3-yl)-carbamate (3b)

A white crystalline powder. Yield – 48 g (94%). M. p. = $82\text{ }^{\circ}\text{C}$. Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{ClNO}_3$, %: C 52.84, H 8.07, N 5.14, Cl 13.03. Found, %: C 52.51, H 7.88, N 4.92, Cl 13.13. $^1\text{H NMR}$ (400 MHz, CDCl_3), δ , ppm: 0.98 (s, 9H), 1.41 (s, 9H), 4.05–4.23 (m, 2H), 4.30 (d, $J = 9.0\text{ Hz}$, 1H), 5.07 (d, $J = 9.1\text{ Hz}$, 1H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3), δ , ppm: 26.5, 28.3, 34.6, 36.2, 64.0, 80.3, 155.5, 201.5. $[\alpha]_{\text{D}}(25^{\circ}\text{C}) = -47.0$ ($c = 0.5$, CH_3OH).

(R)-tert-Butyl (1-Chloro-4,4-dimethyl-2-oxopentan-3-yl)-carbamate (3b')

A white powder. Yield – 25 g (94%). M. p. = $82\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}}(25\text{ }^{\circ}\text{C}) = +48.1$ ($c = 0.5$, CH_3OH).

(R)-tert-Butyl (1-Chloro-5-methyl-2-oxohexan-3-yl)-carbamate (3c)

A white powder. Yield – 53 g (95%). M. p. = $76\text{ }^{\circ}\text{C}$. Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{ClNO}_3$, %: C 52.84, H 8.07, N 5.14, Cl 13.03. Found, %: C 52.53, H 7.89, N 4.95, Cl 13.17. $^1\text{H NMR}$ (400 MHz, CDCl_3), δ , ppm: 0.98 (t, $J = 6.7\text{ Hz}$, 6H), 1.46 (s, 10H), 1.56–1.66 (m, 1H), 1.68–1.84 (m, 1H), 3.98–4.24 (m, 2H), 4.55 (s, 1H), 4.92 (d, $J = 8.0\text{ Hz}$, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3), δ , ppm: 21.1, 22.7, 24.5, 27.8, 31.8, 40.2, 55.6, 79.9, 155.0, 201.3. $[\alpha]_{\text{D}}(25^{\circ}\text{C}) = -45.4$ ($c = 1.0$, CH_3OH).

(R)-tert-Butyl (1-Chloro-5-methyl-2-oxohexan-3-yl)-carbamate (3c')

A white powder. Yield – 23 g (95%). $[\alpha]_{\text{D}}(25^{\circ}\text{C}) = +44.5$ ($c = 1.0$, CH_3OH).

(S)-tert-Butyl (4-Chloro-3-oxo-1-phenylbutan-2-yl)-carbamate (3d)

A white powder. Yield – 109 g (96%). M. p. = 101 °C. Anal. Calcd for $C_{15}H_{20}ClNO_3$, %: C 58.73, H 6.52, N 4.57, Cl 11.58. Found, %: C 58.63, H 6.50, N 4.55, Cl 11.38. 1H NMR (400 MHz, $CDCl_3$), δ , ppm: 1.42 (s, 9H), 3.08 (tt, $J = 20.7, 10.0$ Hz, 2H), 3.79–4.13 (m, 2H), 4.73 (q, $J = 6.5, 6.1$ Hz, 1H), 5.04 (s, 1H), 7.13–7.23 (m, 2H), 7.27 (s, 1H), 7.33 (q, $J = 9.0, 7.9$ Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$), δ , ppm: 28.2, 33.2, 37.9, 58.5, 80.5, 127.3, 128.9, 129.1, 135.8, 155.2, 200.8. $[\alpha]_D(25^\circ C) = -43.7$ (c = 0.5, CH_3OH).

(R)-tert-Butyl (4-Chloro-3-oxo-1-phenylbutan-2-yl)-carbamate (3d')

A white powder. Yield – 29 g (97%). $[\alpha]_D(25^\circ C) = +55.4$ (c = 0.5, CH_3OH).

tert-Butyl (4-Chloro-3-oxobutyl)carbamate (3e)

A colorless liquid. Yield – 116 g (91%). Anal. Calcd for $C_9H_{16}ClNO_3$, %: C 46.85, H 6.94, N 6.07, Cl 15.40. Found, %: C 46.71, H 6.90, N 6.17, Cl 15.37. 1H NMR (400 MHz, $CDCl_3$), δ , ppm: 1.44 (s, 9H), 2.91 (t, $J = 5.8$ Hz, 2H), 3.37–3.51 (m, 2H), 3.91 (s, 2H), 4.96 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), δ , ppm: 27.9, 33.6, 34.9, 39.6, 79.0, 155.4, 201.0.

(S)-tert-Butyl (5-Chloro-4-oxopentan-2-yl)carbamate (3f)

A yellow powder. Yield – 43 g (95%). M. p. = 73 °C. Anal. Calcd for $C_{10}H_{18}ClNO_3$, %: C 49.08, H 7.36, N 5.73, Cl 14.52. Found, %: C 49.18,

H 7.27, N 5.77, Cl 14.12. 1H NMR (400 MHz, $CDCl_3$), δ , ppm: 1.23 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 2.86 (d, $J = 5.8$ Hz, 2H), 3.92 (q, $J = 12.6$ Hz, 2H), 4.02–4.15 (m, 1H), 4.78 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), δ , ppm: 20.1, 27.9, 34.0, 43.0, 45.7, 79.1, 154.6, 200.1. $[\alpha]_D(25^\circ C) = -16.8$ (c = 0.5, CH_3OH).

(R)-tert-Butyl (5-Chloro-4-oxopentan-2-yl)carbamate (3f')

A yellow powder. Yield – 200 g (95%). M. p. = 73 °C. $[\alpha]_D(25^\circ C) = +16.1$ (c = 0.5, CH_3OH).

tert-Butyl (3-Chloro-2-oxopropyl)(methyl)carbamate (3g)

An orange oil. Yield – 31 g (89%). Anal. Calcd for $C_9H_{16}ClNO_3$, %: C 46.85, H 6.94, N 6.07, Cl 15.40. Found, %: C 46.74, H 7.02, N 6.17, Cl 15.37. 1H NMR (400 MHz, $CDCl_3$), δ , ppm: 1.46 (d, $J = 18.8$ Hz, 9H), 2.94 (d, $J = 7.7$ Hz, 3H), 3.91 (d, $J = 16.9$ Hz, 2H), 4.22 (d, $J = 18.2$ Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$), δ , ppm: 24.1*, 27.0, 28.2*, 28.3, 30.7*, 31.5, 35.9*, 36.4, 55.9*, 56.3, 80.5*, 80.7, 156.1, 198.4 (rotamers).

tert-Butyl 3-(2-Chloroacetyl)azetidine-1-carboxylate (3h)

A white crystalline powder. Yield – 207 g (92%). M. p. = 73 °C. Anal. Calcd for $C_{10}H_{16}ClNO_3$, %: C 49.48, H 6.60, N 5.77, Cl 14.64. Found, %: C 49.45, H 6.50, N 5.72, Cl 14.63. 1H NMR (400 MHz, $CDCl_3$), δ , ppm: 1.44 (s, 9H), 3.82 (pd, $J = 7.5, 1.2$ Hz, 1H), 3.91 (s, 2H), 4.08 (s, 2H), 4.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$), δ , ppm: 28.3, 32.5, 36.6, 51.1, 80.0, 156.0, 200.2.

References

- Witte, J. M.; Ayim, E.; Sams, C. J.; Service, J. B.; Kant, C. C.; Bambalas, L.; Wright, D.; Carter, A.; Moran, K.; Rohrig, I. G.; Ferrence, G. M.; Hitchcock, S. R. Diastereoselective Synthesis of the HIV Protease Inhibitor Darunavir and Related Derivatives via a Titanium Tetrachloride-Mediated Asymmetric Glycolate Aldol Addition Reaction. *J. Org. Chem.* **2024**, *89* (13), 9569–9585. <https://doi.org/10.1021/acs.joc.4c01057>.
- Singh, G.; Malik, P.; Thakur, Y.; Khurana, S.; Sharma, S.; Sushma; Ritika; Kumar, T. J. D.; Singh, K. N. Development of a Triazole-Linked Bis-Organosilane Compound as Dual-Function Agent: Sensing of Al^{3+} Ion in Aqueous Environments and Inhibition of HIV-1 Protease. *Journal of Molecular Structure* **2025**, *1319*, 139572. <https://doi.org/10.1016/j.molstruc.2024.139572>.
- Banik, B. K.; Das, A. Monocyclic Beta-Lactams: Stereocontrolled Synthesis by Diverse Methods. *Chemistry and Biology of Beta-Lactams*; CRC Press: Boca Raton, 2024. <https://doi.org/10.1201/9780367816339>.
- Ahmad, R.; Choudhary, M. Design and Synthesis of Copper(II) and Nickel(II) Complexes as Potential Inhibitors against SARS-CoV-2 Viral RNA Binding Protein and Omicron RBD Protein. *New J. Chem.* **2024**, *48* (34), 15053–15076. <https://doi.org/10.1039/D4NJ02753A>.
- Laporte, A. A. H.; Masson, T. M.; Zondag, S. D. A.; Noël, T. Multiphasic Continuous-Flow Reactors for Handling Gaseous Reagents in Organic Synthesis: Enhancing Efficiency and Safety in Chemical Processes. *Angew. Chem.* **2024**, *136* (11), e202316108. <https://doi.org/10.1002/ange.202316108>.
- Dallinger, D.; Gutmann, B.; Kappe, C. O. The Concept of Chemical Generators: On-Site On-Demand Production of Hazardous Reagents in Continuous Flow. *Acc. Chem. Res.* **2020**, *53* (7), 1330–1341. <https://doi.org/10.1021/acs.accounts.0c00199>.
- Hone, C. A.; Kappe, C. O. Membrane Microreactors for the On-Demand Generation, Separation, and Reaction of Gases. *Chem. – Eur. J.* **2020**, *26* (58), 13108–13117. <https://doi.org/10.1002/chem.202001942>.
- Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45* (18), 4892–4928. <https://doi.org/10.1039/C5CS00902B>.
- Mastronardi, F.; Gutmann, B.; Kappe, C. O. Continuous Flow Generation and Reactions of Anhydrous Diazomethane Using a Teflon AF-2400 Tube-in-Tube Reactor. *Org. Lett.* **2013**, *15* (21), 5590–5593. <https://doi.org/10.1021/ol4027914>.
- Pendiukh, V. V.; Yakovleva, H. V.; Stadniy, I. A.; Pashenko, A. E.; Rusanov, E. B.; Grabovaya, N. V.; Kolotilov, S. V.; Rozhenko, A. B.; Ryabukhin, S. V.; Volochnyuk, D. M. Practical Synthetic Method for Amino Acid-Derived Diazoketones Shelf-Stable Reagents for Organic Synthesis. *Org. Process Res. Dev.* **2024**, *28* (1), 165–176. <https://doi.org/10.1021/acs.oprd.3c00230>.

11. Chen, Y.; Monbaliu, J. M. Continuous-Flow Multistep Synthesis of Active Pharmaceutical Ingredients. In *Methods and Principles in Medicinal Chemistry*; Alza, E., Ed.; Wiley, 2022; pp 233–268. <https://doi.org/10.1002/9783527824595.ch7>.
12. Wernik, M.; Poehlauer, P.; Schmoelzer, C.; Dallinger, D.; Kappe, C. O. Design and Optimization of a Continuous Stirred Tank Reactor Cascade for Membrane-Based Diazomethane Production: Synthesis of α -Chloroketones. *Org. Process Res. Dev.* **2019**, *23* (7), 1359–1368. <https://doi.org/10.1021/acs.oprd.9b00115>.
13. Pinho, V. D.; Gutmann, B.; Miranda, L. S. M.; de Souza, R. O. M. A.; Kappe, C. O. Continuous Flow Synthesis of α -Halo Ketones: Essential Building Blocks of Antiretroviral Agents. *J. Org. Chem.* **2014**, *79* (4), 1555–1562. <https://doi.org/10.1021/jo402849z>.
14. DIAZOMETHANE. *Org. Synth.* **1935**, *15*, 3. <https://doi.org/10.15227/orgsyn.015.0003>.

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