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Mateus da Silva Roza

Estudo mecanístico da reação multicomponente do ceteno

Governador Valadares
2026

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Trabalho de Conclusão de Curso (TCC) apresentado ao curso de Farmácia da Universidade Federal de Juiz de Fora, campus Governador Valadares, como requisito parcial para a conclusão do curso de Bacharel em Farmácia.

Orientador: Pedro Pôssa de Castro

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RESUMO

A reação de três componentes do ceteno (K-3CR) e a reação de três componentes do ceteno sililativo (SK-3CR) são transformações multicomponentes valiosas para a síntese eficiente de α-aciloxiacrilamidas e α-sililoxiacrilamidas, estruturas frequentemente encontradas em compostos bioativos e intermediários sintéticos estrategicamente importantes. Neste estudo, uma investigação combinada de cálculos computacionais empregando a teoria do funcional de densidade (DFT) e experimentos de monitoramento por espectrometria de massas forneceu uma descrição detalhada e consistente dos prováveis caminhos de reações envolvidos em ambas as transformações. Os resultados permitiram a compreensão das principais etapas elementares, intermediários e pontos de divergência entre a K-3CR e a SK-3CR, oferecendo uma estrutura mecanística unificada que alinha e racionaliza as observações experimentais relatadas na literatura.

Palavras-chave: Reação multicomponente. Mecanismo. Ceteno. Rearranjo. DFT

ABSTRACT

Ketene three-component reaction (K-3CR) and silylative ketene three-component reaction (SK-3CR) are valuable multicomponent transformations for the efficient synthesis of α-acyloxy- and α-silyloxyacrylamides, structural motifs frequently found in bioactive compounds and strategically important synthetic intermediates. In this study, a combined investigation employing density functional theory (DFT) calculations and mass spectrometry monitoring experiments provides a detailed and consistent description of the full reaction pathways involved in both transformations. The results elucidate the principal elementary steps, intermediates, and divergence points between the K-3CR and SK-3CR, offering a unified mechanistic framework that aligns and rationalizes experimental observations reported in the literature.

Keywords: Multicomponent reaction. Mechanism. Ketene. Rearrangement. DFT

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On the mechanism of ketene three-component reaction☆

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ABSTRACT

Ketene three-component reaction (K-3CR) and silylative ketene three-component reaction (SK-3CR) are valuable multicomponent transformations for the efficient synthesis of α-acyloxy- and α-silyloxyacrylamides, structural motifs frequently found in bioactive compounds and strategically important synthetic intermediates. In this study, a combined investigation employing density functional theory (DFT) calculations and mass spectrometry monitoring experiments provides a detailed and consistent description of the full reaction pathways involved in both transformations. The results elucidate the principal elementary steps, intermediates, and divergence points between the K-3CR and SK-3CR, offering a unified mechanistic framework that aligns and rationalizes experimental observations reported in the literature.

Introduction

Multicomponent reactions (MCRs) are synthetic transformations in which at least three reagents participate in a single operational process to form a product that incorporates most, if not all, of the atoms from the starting materials, typically with the elimination of small molecules such as water [1–3]. Owing to this high level of atom efficiency, MCRs have long attracted the attention of synthetic organic chemists, as they enable the rapid assembly of structurally complex molecules from readily available building blocks while minimizing the number of synthetic steps and purification procedures. These features translate into reduced solvent consumption and waste generation, placing MCRs in close alignment with several principles of green and sustainable chemistry [4–6]. Beyond their synthetic efficiency, MCRs are also mechanistically intriguing, as they often proceed through non-intuitive pathways involving transient or unconventional intermediates that play a decisive role in product formation [7–9].

Among the broad family of MCRs, transformations based on isocyanide chemistry occupy a particularly prominent position, exemplified by classical reactions such as the Ugi, Passerini, and Groebke–Blackburn–Bienaymé reactions [10–12]. Due to the importance of isocyanide-based MCRs, several variations of these classical approaches have been reported in the scientific literature [13]. In this context, for instance, Basso and co-workers reported an isocyanide-based three-component reaction promoted by UV irradiation, involving α-diazoketones, carboxylic acids, and isocyanides, to access α-acyloxyacrylamides (Scheme 1) [14]. This transformation, named ketene three-component reaction (K-3CR), relies on the UV light mediated photochemical in situ generation of a highly reactive ketene intermediate from the corresponding Wolff rearrangement of diazo compounds [14,15]. Subsequent studies demonstrated that irradiation with visible light is sufficient to efficiently promote the reaction. Additionally, extension of the methodology revealed that replacement of the carboxylic acid component with a silanol enables access to α-silyloxyacrylamides via a silylative ketene three-component reaction (SK-3CR) [16,17]. Despite the synthetic utility and conceptual elegance of these transformations, a comprehensive understanding of the full mechanistic governing both K-3CR and SK-3CR processes remains scarce in the literature, limiting their broader adoption, rational optimization, and further methodological development.

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Diverse studies employing computational methods to investigate the mechanistic details of MCRs demonstrate how their integration with experimental data can significantly enhance mechanistic interpretation and rationalization [18–20]. Our group has extensively studied plausible mechanisms for various transformations [21–24], including neglected aspects in MCRs, such as solvent effects and reagents concentration, and how these factors may influence the reaction pathway [25,26]. Therefore, we herein present a combined theoretical and mass spectrometry investigation of the K-3CR and SK-3CR, focusing on the identification of key reaction intermediates and the establishment of a general reaction pathway for these transformations, along with an analysis of the relative energies associated with each elementary step.

Results and discussion

To gain mechanistic insight into the K-3CR and SK-3CR reactions, density functional theory (DFT) calculations were carried out to map the full reaction profiles and characterize key intermediates and transition states. For the mechanistic analysis, 2-diazo-1-phenylethan-1-one, *tert*-butyl isocyanide, and benzoic acid (for K-3CR) or triphenylsilanol (for SK-3CR) were employed as representative model substrates. Geometry optimizations and vibrational frequency calculations were performed at the gas phase using the M06-2X functional in combination with the 6-31G(d,p) basis set (employing a grid=ultrafine). All thermochemical corrections were computed at 298 K and 1 atm. This level of theory was selected due to its well-established performance in describing reaction energetics involving main-group elements, noncovalent interactions, and rearrangement processes relevant to multicomponent transformations [26].

Solvent effects were included through single-point energy calculations using the SMD implicit solvation model, performed on gas-phase optimized geometries at the same level of theory (M06-2X functional and 6-31G(d,p) basis set). Dichloromethane and toluene were evaluated as solvents, as both media have been employed in reported experimental protocols for K-3CR and SK-3CR [14,17,27]. Assessing both solvents allowed a direct comparison of their respective energetic profiles, providing an evaluation of the influence of solvent polarity on the elementary steps governing each transformation.

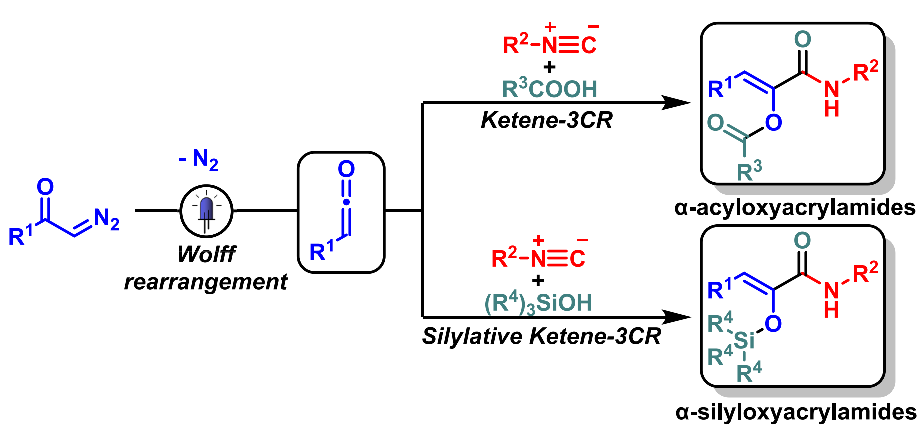
Gibbs free energies (ΔG) were obtained by combining the electronic energy and solvation free energy derived from single-point calculations with thermal corrections to enthalpy and entropy extracted from gas-phase frequency calculations. Specifically, ΔG values were calculated as the sum of the single-point electronic energy, the SMD solvation contribution, and the thermal corrections (ΔH and $-T\Delta S$) computed at the M06-2X/6-31G(d,p) level in the gas phase.

Based on the literature data, the most plausible mechanistic proposal for the K-3CR transformation begins with the photochemical generation of the ketene intermediate via a Wolff rearrangement of the α-diazoketone (Scheme 2). This step is well established and constitutes the entry point to the multicomponent transformation [28]. Once formed, the highly electrophilic ketene undergoes nucleophilic addition of the isocyanide. Importantly, this step also determines the configuration of the C=C double bond in the final product, leading preferentially to the *Z*-isomer under low-energy light irradiation [16], whereas the use of UV light may promote post-formation photoisomerization to the *E*-isomer [29]. The presence of the carboxylic acid, however, deserves special attention, as it is expected to play a dual role: in addition to acting as a reaction component, its protonation state facilitates isocyanide addition by increasing the electrophilicity of the ketene through hydrogen-bonding or partial proton-transfer interactions.

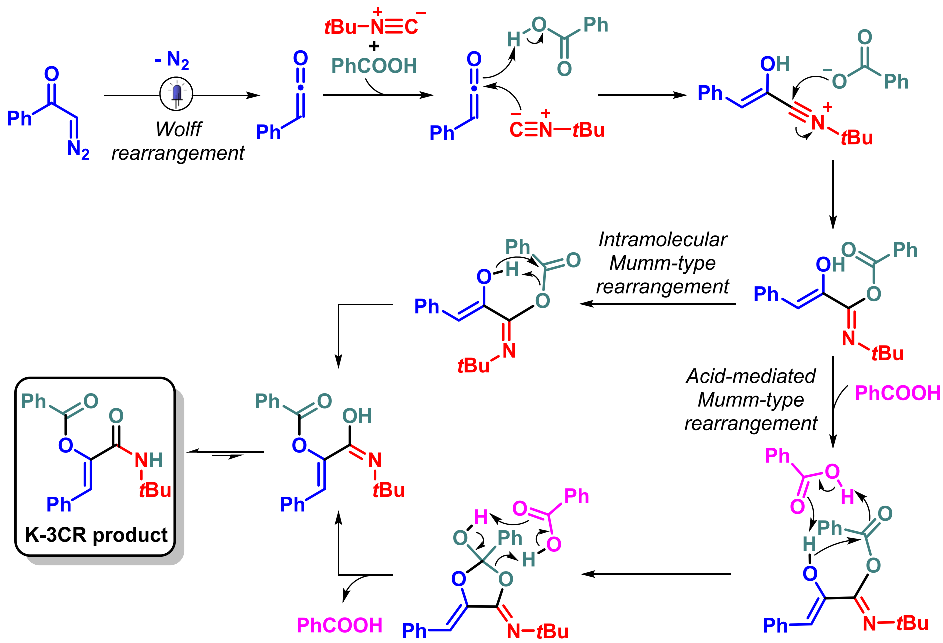
The addition of the isocyanide to the ketene leads to the formation of a nitrilium intermediate, closely analogous to those invoked in classical Passerini and Ugi reactions [19]. From this point, the carboxylate anion generated in the previous step acts as a nucleophile, attacking the nitrilium carbon to form an *O*-acyl imidate species. Subsequent rearrangement of this intermediate furnishes the observed α-acyloxyacrylamide product. This final step is formally analogous to a Mumm-type rearrangement, which is a well-established feature in isocyanide-based MCRs.

Importantly, two mechanistic possibilities can be envisioned for the rearrangement step: the first involves a direct intramolecular acyl transfer, leading straightforwardly to product formation; alternatively, proton transfer may be assisted by an additional molecule of the carboxylic acid, lowering the energetic demand of the rearrangement, as previously described for the Passerini and Ugi reactions [20,26]. In this context, the additional acid molecule acts as a proton shuttle and is regenerated along the reaction pathway, consistent with a catalytic role and not requiring an excess under the experimental conditions. In this latter scenario, the K-3CR can be more accurately described as a pseudo-four-component reaction rather than a strictly three-component process. Both possibilities were considered in the calculations, providing a consistent framework to rationalize experimental observations. Finally, a tautomerism of the formed intermediate would lead to the desired product.

The computed energy profiles provide strong support for the mechanistic proposal outlined above and allow a clear differentiation between viable and nonviable pathways in the K-3CR. The acid-mediated addition of the isocyanide to the ketene emerges as a kinetically accessible step, displaying low activation barriers of 6.92 and 6.60 kcal mol^{-1} in dichloromethane and toluene, respectively. This step is also thermodynamically favorable, with reaction free energies of −6.62 kcal mol^{-1} (dichloromethane) and −5.27 kcal mol^{-1} (toluene), highlighting the crucial role of the carboxylic acid in activating the ketene toward nucleophilic attack. These results rationalize the experimentally observed efficiency of the isocyanide addition and underscore the cooperative nature of this step. In addition, this transformation is



Scheme 1. Ketene and silylative ketene multicomponent reactions (MCRs).



Scheme 2. Investigated reaction pathways for the ketene MCR (namely K-3CR).

responsible for establishing the configuration of the C═C double bond, with the pathway leading to the *Z*-isomer being strongly kinetically favored over the *E*-isomer, as evidenced by the significantly lower activation barriers ($\Delta G^{\ddagger} = 6.92$ vs 12.54 kcal mol^{-1} in dichloromethane and 6.60 vs 12.40 kcal mol^{-1} in toluene). These results are fully consistent with the preferential formation of *Z*-configured products observed experimentally [16].

Following nitrilium formation, the addition of the carboxylate anion proceeds with an exceptionally low kinetic demand, with barriers of only 1.87 kcal mol^{-1} in dichloromethane and 1.29 kcal mol^{-1} in toluene, and is accompanied by a pronounced thermodynamic driving force ($\Delta G = -31.08$ and -32.98 kcal mol^{-1}, respectively). This step is therefore effectively irreversible under the reaction conditions and rapidly funnels the system toward the imidate intermediate.

In contrast, the calculations clearly indicate that a direct intramolecular Mumm rearrangement from this intermediate is kinetically unfeasible, as evidenced by prohibitively high activation barriers of 48.32 kcal mol^{-1} in dichloromethane and 48.21 kcal mol^{-1} in toluene. These values effectively rule out this pathway, despite its formal simplicity, and suggest that additional assistance is required to enable acyl migration. When a second molecule of carboxylic acid is explicitly included, however, a markedly different picture emerges. The acid-mediated Mumm rearrangement proceeds through a two-step sequence with substantially reduced barriers. The first proton-transfer-assisted step displays activation free energies of 10.09 kcal mol^{-1} (dichloromethane) and 9.86 kcal mol^{-1} (toluene) and is only mildly exergonic ($\Delta G = -3.57$ and -3.64 kcal mol^{-1}, respectively), while the subsequent rearrangement step presents similarly accessible barriers of 11.50 and 11.22 kcal mol^{-1}. These values are fully compatible with the experimental conditions and strongly support the involvement of an additional acid molecule in facilitating the rearrangement.

Finally, the tautomerization of the rearranged intermediate to the amide product is associated with a substantial thermodynamic stabilization, with free energy changes of -18.09 kcal mol^{-1} in dichloromethane and -18.07 kcal mol^{-1} in toluene, providing a strong driving force toward product formation. Collectively, these results demonstrate that the K-3CR proceeds through a highly cooperative, acid-assisted mechanism, in which proton shuttling is essential to overcome otherwise prohibitive barriers. This analysis not only explains the efficiency of the reaction but also substantiates its classification as a pseudo-four-component process, in close mechanistic analogy to the Passerini reaction. The reaction energy profile corresponding to the most favorable mechanistic pathway in dichloromethane and toluene is depicted in Fig. 1.

To complement the computational study and provide experimental support for the proposed mechanism, the K-3CR was reproduced under controlled conditions and monitored by high-resolution mass spectrometry (HR-MS), and ketene formation was additionally probed by EPR (electron paramagnetic resonance). It should be noted that ion detection by HR-MS does not unambiguously establish molecular structure; therefore, the assignments are supported by accurate mass measurements and interpreted in conjunction with the proposed mechanistic framework. The HR-MS monitoring, the reaction was carried out using 2-diazo-1-(4-methoxyphenyl)ethan-1-one (0,25 mmol, 1 equiv.), benzoic acid (0,25 mmol, 1 equiv.), and *tert*-butyl isocyanide (0,25 mmol, 1 equiv.). The mixture was kept at 20 °C and irradiated with blue LEDs (40 W) in dichloromethane (2,5 mL). Aliquots were withdrawn at defined time intervals (0, 5, 10, 15, 45, 60, 120, 180, 240, 300 min, and 24 h), diluted in acetonitrile, and directly injected into a mass spectrometer operating in positive ion mode. The crude reaction mixture after 5 min, 240 min, and 24 h are displayed at Fig. 2a, b, and c, respectively.

Upon irradiation, rapid formation of the ketene intermediate was observed. The protonated ketene ion $[M+H]^+$ was readily detected at the very early stages of the reaction, with an experimental *m/z* of 149.0598, in excellent agreement with the calculated value (*m/z* 149.0598). The relative intensity of this signal decreases progressively as the reaction proceeds, becoming nearly undetectable after 24 h, which is consistent with the consumption of the ketene intermediate along the reaction pathway.

In addition, the nitrilium intermediate could be detected at *m/z* 232.1346 (calculated *m/z* 232.1332 $[M]^+$), albeit with very low intensity, reflecting its transient nature and rapid conversion into other intermediates (Fig. 2d). Following this stage, the imidate intermediate, as well as all intermediates involved in the subsequent Mumm rearrangement and final tautomerization share the same nominal mass (Fig. 2c), corresponding to the product framework (calculated *m/z* 354.1700). As expected, the signal at this *m/z* increases steadily over time, becoming detectable after 5 min of reaction and progressively growing in intensity. This ion becomes the base peak after 300 min and

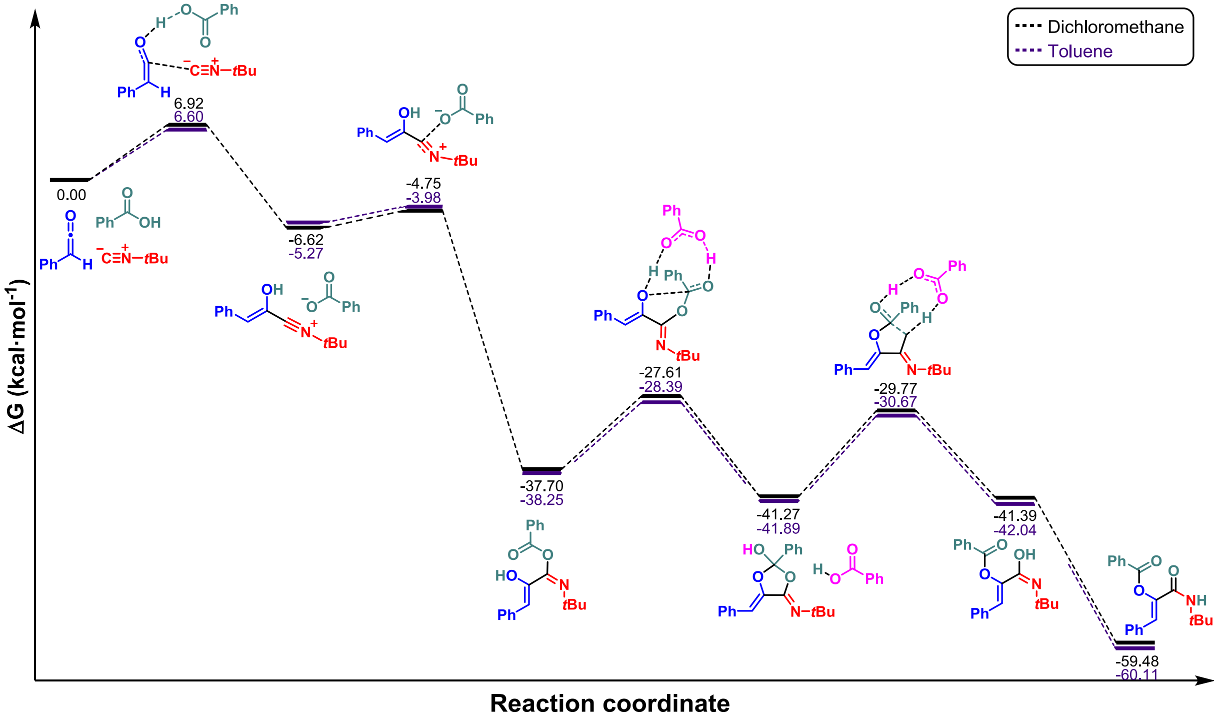


Fig. 1. Energy profile of the most plausible mechanism for the ketene three-component reaction (K-3CR) in dichloromethane and toluene.

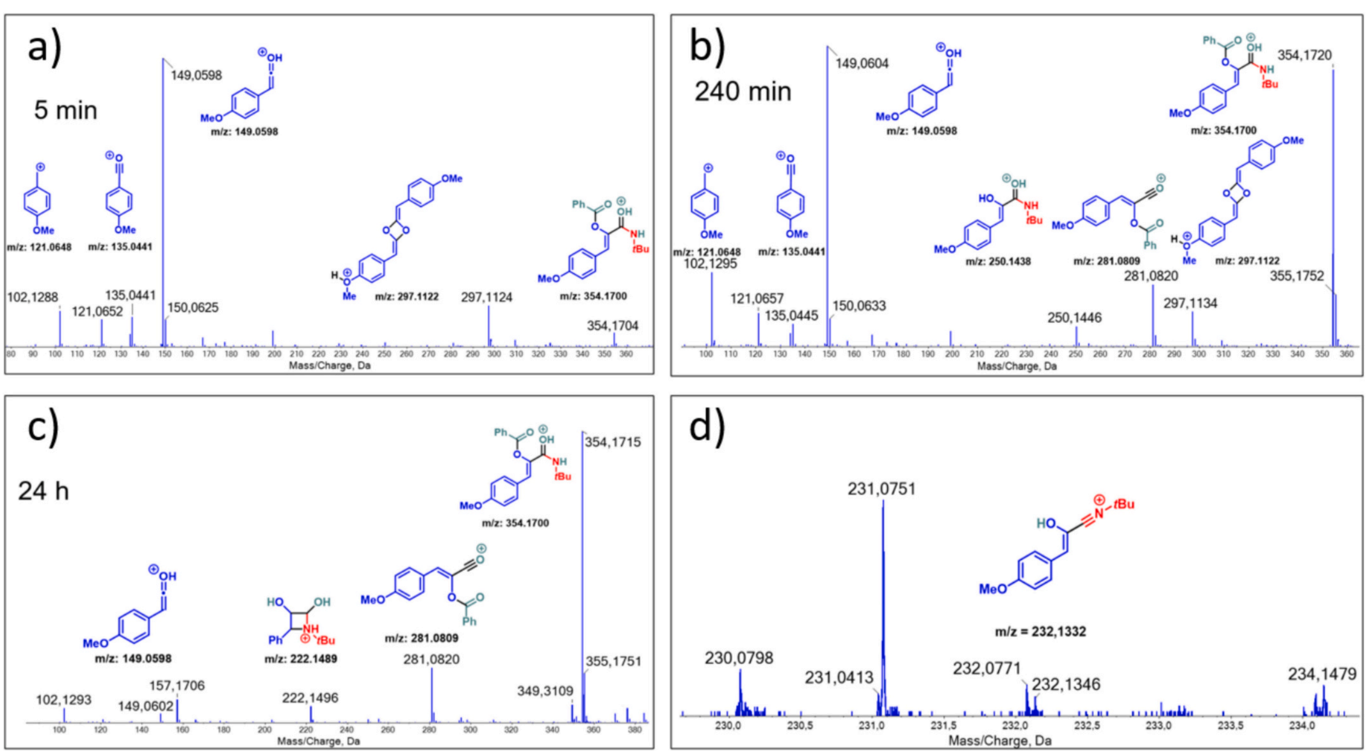


Fig. 2. High-resolution mass spectrometry (HR-MS) monitoring of the K-3CR reaction under blue LED irradiation. (a) Mass spectrum recorded after 5 min of reaction, showing the early formation of reaction intermediates. (b) Mass spectrum recorded after 240 min of reaction, showing product framework formed during the Mumm rearrangement and subsequent tautomerization (*m/z* 354). (c) Mass spectrum recorded after 24 h, highlighting the predominance of the final α-acyloxyacrylamide product. (d) Expanded view of the ion at *m/z* 232 recorded after 240 min, attributed to the transient nitrilium intermediate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is by far the most intense signal after 24 h, in full agreement with the formation and accumulation of the final α-acyloxyacrylamide product.

EPR was also employed to investigate ketene formation. For this purpose, a dichloromethane solution containing the ketene precursor – (2-diazo-1-(4-methoxyphenyl)ethan-1-one (0.25 mmol, 1 equiv.) – was frozen in liquid nitrogen, and the temperature was stabilized at 100 K

(−173.15 °C). After that, the frozen solution was irradiated for 10 min using blue LED light (Fig. 3). A low-intensity signal was observed, indicating promotion of the reagent to its triplet state. Irradiation of this excited and frozen intermediate using a more energetic light source (254 nm) for an additional 10 min showed the appearance of a new and significantly more intense signal (Fig. 3), indicating not only excitation to the triplet state but also nitrogen elimination, affording the key ketene intermediate.

The EPR results shown in Fig. 3 align well with the previous study by Tomioka and co-workers [30]. In their study, light irradiation promoted excitation of the reagent to the S_1 state, followed by decay to the T_1 state ($S_1 \rightarrow T_1$). According to the mechanistic investigation reported in that work, nitrogen extrusion in the photolysis of α-diazo carbonyl compounds occurs primarily from the singlet excited state under direct irradiation conditions. Upon photoexcitation, the diazo compound is promoted to its excited singlet state, which can undergo the Wolff rearrangement. Sensitization experiments using benzophenone demonstrated a distinct pathway: excitation via energy transfer populates the triplet state (EPR active), which subsequently expels N_2 to form a triplet carbene. This triplet carbene may react as such or undergo intersystem crossing to the singlet carbene (EPR silent) prior to further reaction. Thus, under direct photolysis, nitrogen loss is predominantly a singlet-state process, whereas under sensitized conditions, nitrogen extrusion proceeds from the triplet manifold, with possible secondary conversion to the singlet carbene. By EPR, however, we were able to observe the triplet state, supporting the proposed mechanism. Our experiment was conducted at very low temperature under frozen conditions; therefore, some differences are noteworthy. First, we were able to observe the proposed T_1 formation (Fig. 3, blue). However, because the sample was frozen at very low temperature, more energetic irradiation was required to observe the ketene formed after nitrogen loss (Fig. 3, red). Taken together, these results are fully consistent with the expected mechanism of the Wolff rearrangement [31]. In contrast to the K-3CR, replacement of the carboxylic acid by a silanol in the SK-3CR has profound mechanistic consequences. Although, at first glance, both transformations appear analogous, the substantially higher pK_a of silanols, their pronounced steric bulk (particularly in the case of triphenylsilanol), and the absence of a well-defined hydrogen-bonding arrangement capable of efficiently mediating proton transfer processes (such as those intrinsic to carboxylic acids) lead to a markedly different reaction pathway. To the best of our knowledge, the mechanistic features governing the SK-3CR have not been previously proposed or examined in the literature. These intrinsic differences are consistent with experimental observations, as the SK-3CR typically requires longer reaction times and affords lower yields compared to the corresponding K-3CR [16].

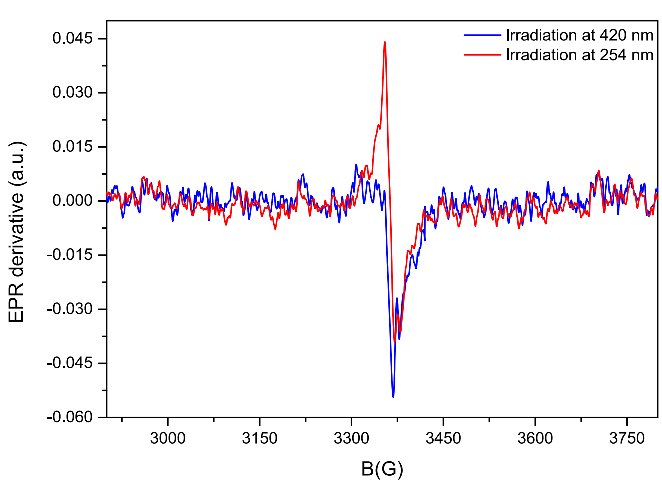


Fig. 3. EPR experiments (at 100 K) irradiating the frozen dichloromethane solution of the ketene precursor 2-diazo-1-(4-methoxyphenyl)ethan-1-one for 10 min using blue LED light (blue), followed by irradiation with more energetic light (254 nm) for an additional 10 min (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Following photochemical ketene formation via the Wolff rearrangement, nucleophilic addition of the isocyanide remains feasible and is likely facilitated by hydrogen bonding between the ketene and the silanol (Scheme 3). However, in contrast to the K-3CR, this interaction does not promote proton transfer upon isocyanide addition. As a result, formation of a nitrilium species occurs without simultaneous proton relocation, fundamentally altering the downstream reactivity. At this stage, one plausible pathway involves nucleophilic addition of the silanol to the nitrilium carbon, concomitant with proton transfer to the anionic oxygen, leading to an intermediate bearing a free alcohol functionality.

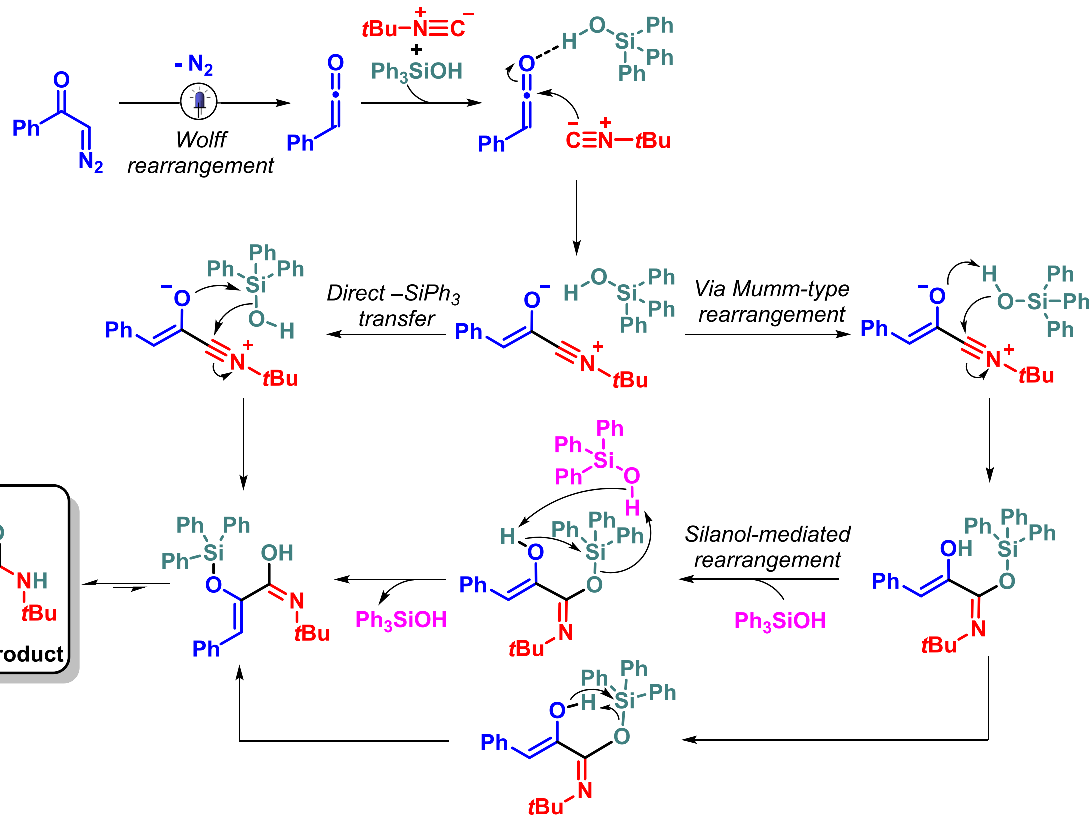
From this intermediate, migration of the proton and the –$SiPh_3$ groups becomes a necessary step for product formation. This transfer may proceed either intramolecularly or be assisted by a second silanol molecule, which could facilitate O—H bond reorganization. Subsequent tautomerization of the resulting intermediate then furnishes the α-silyloxyacrylamide product. Alternatively, a distinct pathway can be envisioned in which direct transfer of the —$SiPh_3$ group to the anionic oxygen occurs during the silanol addition step itself, accompanied by cleavage of the Si—O bond. In this scenario, the resulting intermediate would likewise evolve to the final product through tautomerization. Both mechanistic possibilities are consistent with the absence of efficient proton-shuttling and rationalize the increased energetic demand and reduced efficiency observed experimentally for the SK-3CR relative to the K-3CR.

The computed energy profiles provide clear support for a mechanistic scenario in which direct transfer of the –$SiPh_3$ group to the anionic oxygen is favored over pathways involving proton migration (for full details, see the Supplementary Information). From both kinetic and thermodynamic perspectives, silyl migration is significantly more viable than hydrogen transfer. In both dichloromethane and toluene, the free energy barrier associated with —$SiPh_3$ migration is considerably lower than that for H migration ($\Delta G^{\ddagger} = 6.00$ kcal mol^{-1} against 8.66 kcal mol^{-1} in dichloromethane, and 5.68 kcal mol^{-1} vs 7.98 kcal mol^{-1} in toluene), and this preference is further reinforced by the reaction free energies ($\Delta G = -32.29$ kcal mol^{-1} against -15.25 kcal mol^{-1} in dichloromethane, and -34.07 kcal mol^{-1} against -16.83 kcal mol^{-1} in toluene), underscoring the intrinsic thermodynamic driving force associated with Si—O bond formation.

In contrast, pathways involving rearrangement of the initially formed alcohol intermediate, either via an intramolecular silyl shift or mediated by an additional silanol molecule, were found to be highly unfavorable. These processes display prohibitively high activation barriers, with $\Delta G^{\ddagger}$ values of 43.10 and 27.65 kcal mol^{-1} in dichloromethane, and 42.51 and 27.65 kcal mol^{-1} in toluene for the intramolecular and silanol-assisted routes, respectively. Such energetic penalties effectively rule out these rearrangement mechanisms under experimentally relevant conditions, strongly favoring the alternative proposal involving direct Si—O bond cleavage and simultaneous silyl transfer during silanol addition. The full reaction pathway for this proposal in dichloromethane and toluene is shown in Fig. 4.

Within this preferred mechanistic framework, the addition of the isocyanide to the ketene emerges as the rate-determining step of the SK-3CR. The calculated activation free energies for this transformation ($\Delta G^{\ddagger} = 8.90$ kcal mol^{-1} in dichloromethane and 9.25 kcal mol^{-1} in toluene) are slightly higher than those computed for the analogous step in the K-3CR. This difference is consistent with the absence of efficient proton assistance in the SK-3CR and provides a rational explanation for the experimentally observed longer reaction times and diminished yields associated with silylative variants.

Finally, the terminal tautomerization step leading to the α-silyloxyacrylamide product is strongly thermodynamically favored, delivering



Scheme 3. Investigated reaction pathways for the silylative ketene three-component reaction (SK-3CR).

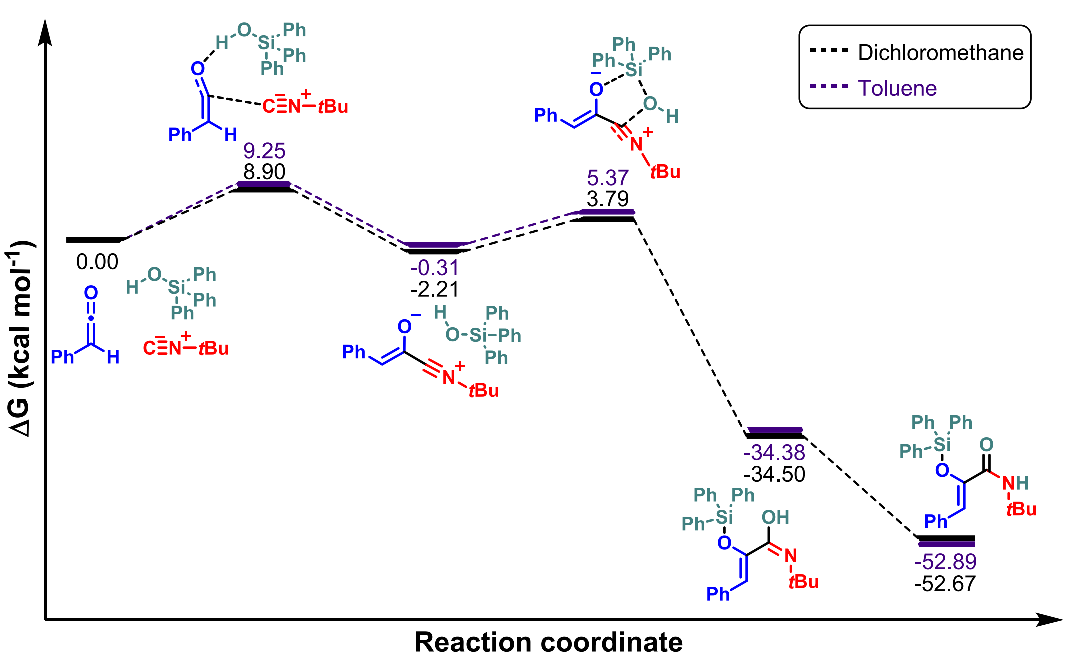


Fig. 4. Energy profile of the most plausible mechanism for the silylative ketene three-component reaction (SK-3CR) in dichloromethane and toluene.

substantial stabilization to the system ($\Delta G = -18.17$ kcal mol^{-1} in dichloromethane and -18.51 kcal mol^{-1} in toluene). This pronounced exergonicity ensures the irreversibility of the final stages of the reaction and reinforces the overall feasibility of the proposed pathway.

In summary, this work provides a comprehensive mechanistic description of both the ketene three-component reaction (K-3CR) and the silylative ketene three-component reaction (SK-3CR) by combining DFT calculations with mass spectrometry monitoring experiments. While the K-3CR follows a mechanistic pathway closely related to classical Passerini-type chemistry, benefiting from efficient proton-transfer events mediated by the carboxylic acid, the SK-3CR proceeds through a fundamentally distinct pathway dictated by the physicochemical properties of silanols. The absence of effective proton shuttling, together with steric and electronic effects, shifts the reaction toward direct —$SiPh_3$ transfer processes, with isocyanide addition emerging as the rate-determining step. Although experimental validation of this pathway (e.g., through labeling or substrate variation studies) is beyond the scope of the present work, such approaches represent valuable directions for future investigation and could provide further support for the mechanistic proposal. The computed energy profiles rationalize the experimentally observed differences in reaction efficiency, timescale, and yields between both transformations and, to the best of our knowledge, constitute the first detailed mechanistic proposal for the SK-3CR. Overall, these insights deepen the understanding of ketene-based multicomponent reactions and provide a solid foundation for future methodological development, optimization, and expansion of this chemistry.

CRediT authorship contribution statement

Marcelo H.R. Carvalho: Writing – original draft, Investigation, Data curation. **Mateus S. Roza:** Writing – original draft, Investigation, Data curation. **Brenno A.D. Neto:** Writing – review & editing, Investigation. **Paulo E.N. De Souza:** Investigation, Data curation. **Hélio F. Dos Santos:** Writing – review & editing. **Pedro P. De Castro:** Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Giovanni W. Amarante:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2026.156041.

Data availability

Data will be made available on request.

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