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Intramolecular Azide-Alkene 1,3-Dipolar Cycloaddition/Enamine Addition(s) Cascade Reaction: Synthesis of Nitrogen-Containing Heterocycles

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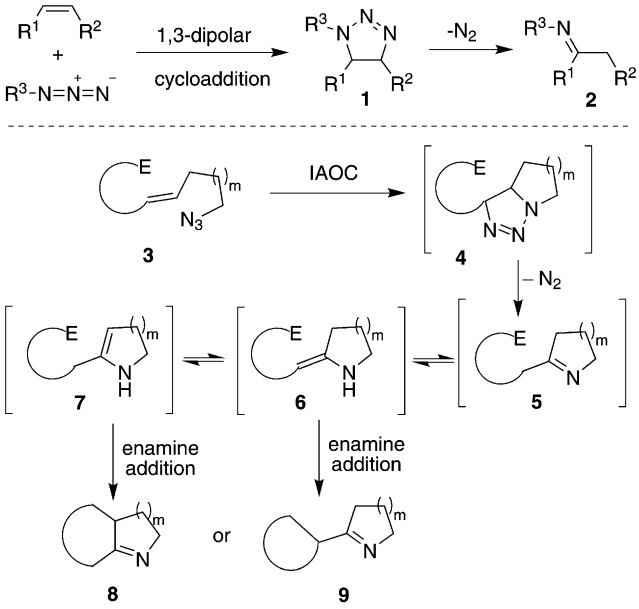
Abstract: A cascade intramolecular azide-alkene 1,3-dipolar cycloaddition/1,2 enamine and/or 1,4 enamine addition reaction sequence has been developed, and provides access to a variety of nitrogen containing heterocycles from readily available ω-azido alkenes.

Keywords: azides; conjugated addition; cycloaddition; enamines; ketimines

The development of new cascade processes is a topic of major interest in organic synthesis.[1] These transformations are generally accompanied by a rapid increase in structural complexity. Furthermore, concepts such as "atom economy",[2] "steps economy"[3] or "redox economy"[4] are inherent to them. In particular, cascade reactions involving the formation of C–C bonds in a stereoselective way are of special importance due to the fundamental role of this transformation in the design of almost any synthetic plan.[5]

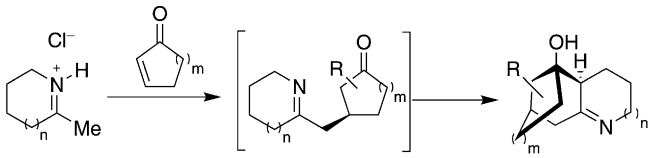
In connection with our interest in the stereoselective synthesis of nitrogen-containing heterocyclic compounds,[6] herein we report our preliminary findings on an efficient cascade reaction that is well-suited for the preparation of complex and diverse pyrrolidine- and piperidine-containing polycyclic heterocycles.[7]

Under thermal conditions, azides react with olefins through a 1,3-dipolar cycloaddition reaction to form 1,2,3-Δ^2-triazolines (**1**)[8] that, unlike their aromatic analogues, 1,2,3-triazoles, are in general not isolable and evolve after nitrogen loss to the corresponding imines (**2**) (Scheme 1). In particular, the ***i***ntramolecular ***a***zide-***o***lefin ***c***ycloaddition reaction (IAOC), has found broad application in the synthesis of complex molecules.[9] We envisioned that cyclic ketimines **5** generated from the IAOC reaction of readily available ω-azidoalkenes **3** (Scheme 1), after decomposition of the resulting triazolines (**4**), could tautomerize to the corresponding exocyclic (**6**) and endocyclic (**7**) enamines and react with a conveniently located electrophilic functionality to afford imines **8** or **9** in one single synthetic operation. Thus, the success of this approach relies on the intrinsic reactivity of the imine functional group, and the correct position of the electrophile group with respect to the enamine location.



Scheme 1. IAOC/enamine addition cascade reaction.

Movassaghi and Chen recently reported an intermolecular formal [3+3]cycloaddition of cyclic enamines and cyclic enones that provides tricyclic imino alcohols in a stereoselective way (Scheme 2).[10] This methodology was successfully applied to the elegant synthesis of galbulimima alkaloids GB-13[11] and himandrine.[12] In order to test our working hypotheses, we chose some members of that kind of tricyclic imino alcohols as model targets.

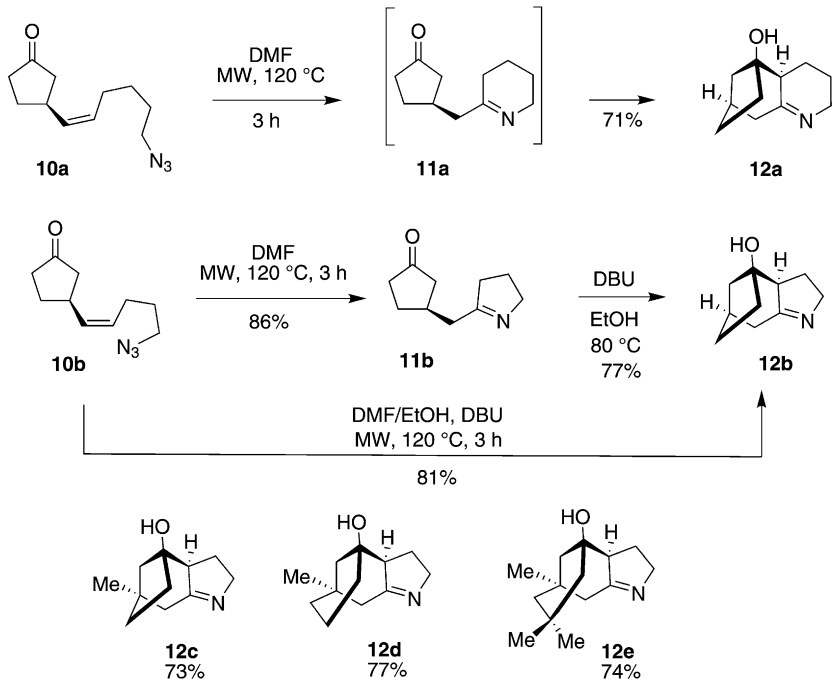


Scheme 2. Movassaghi's intermolecular [3+3]cycloaddition.

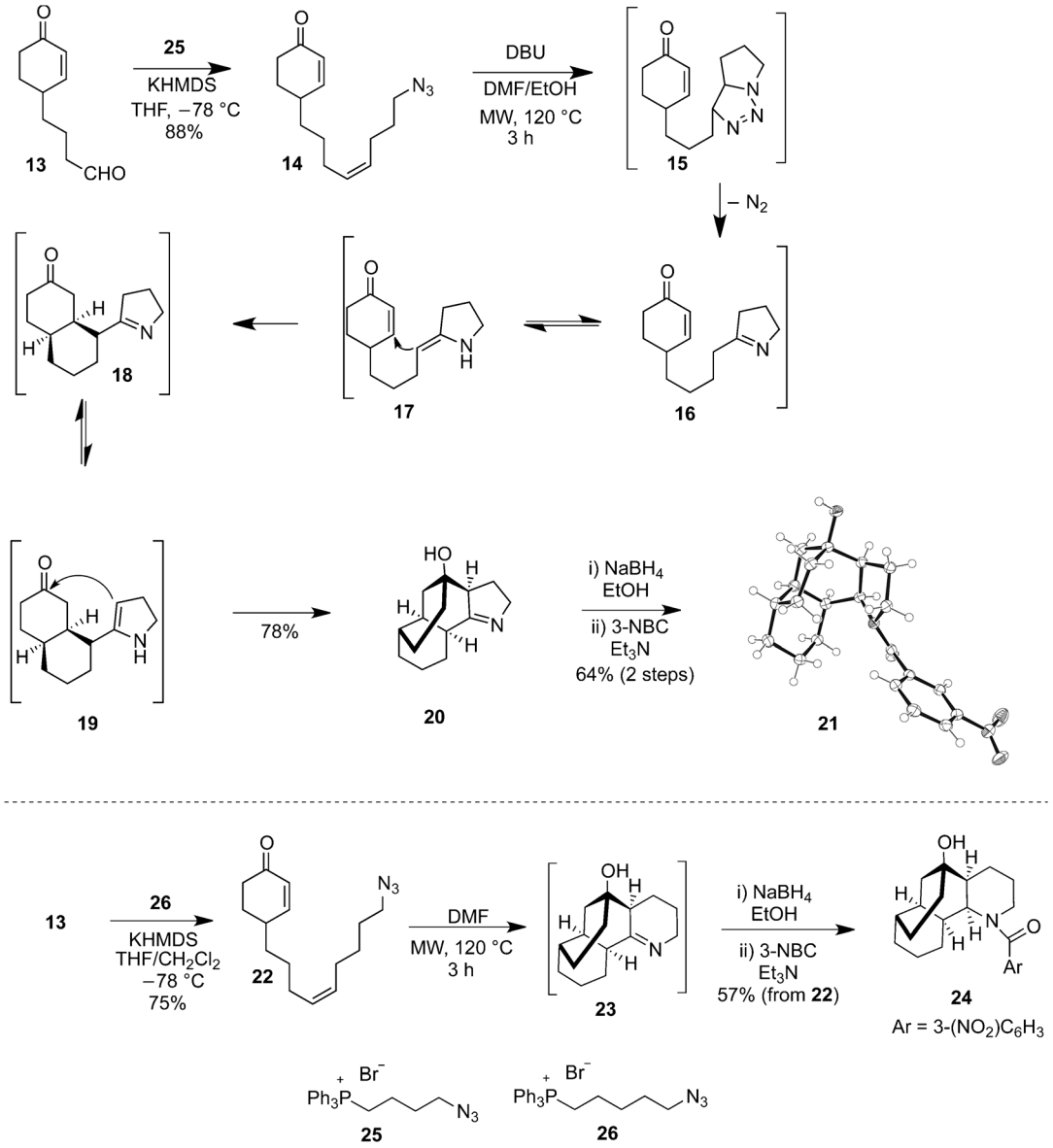
Initial studies were performed with ω-azido alkenes **10a** and **b** (Scheme 3), synthesized in three steps from cyclopenten-2-one.[13] After screening different reaction conditions it was found that the employment of anhydrous dimethylformamide (DMF) as solvent was critical for optimal results. We were pleased to find that heating a solution of ω-azidoalkene **10a** in DMF in a sealed tube at 120 °C for 14 h afforded tricyclic amino alcohol **12a** as a single diastereomer in 64% yield. Gratifyingly, when the reaction was performed under similar conditions but under microwave irradiation, compound **12a** was obtained in 71% yield in only 3 h. On the other hand, when ω-azidoalkene **10b** was subjected to the same protocol, only cyclic imino ketone **11b** was isolated in 86% yield. Treatment of **11b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing ethanol, as previously reported,[10] afforded imino alcohol **12b** in 77% yield as a single diastereomer. Interestingly, we observed that just treating **10b** with DBU in a DMF/ethanol mixture under microwave irradiation provided compound **12b** in a single synthetic operation in an excellent 81% yield, avoiding the necessity of isolating the intermediate imino ketone **11b** (Scheme 3).

Applying the optimized conditions for this cascade reaction, we also prepared imino alcohols **12c–e**, starting from the correspondent ω-azidoalkenes.[13] Formation of the corresponding aziridines resulting of decomposition of the unstable triazoline intermediates was not detected in any case. While related with the methodology described by Movassaghi, our approach is fundamentally different in the way that the enamine group is introduced in the molecule and, since it is not only limited to the use of cyclic enones (*vide infra*), it allows an access to compounds of wide structural diversity.

We next turned our attention to the application of this methodology to more complex substrates. Due to the presence of two non-equivalent nucleophilic positions (Cα and Cα′) in the transient cyclic ketoimines generated after triazoline decomposition, we postulated that sequential 1,4-addition/1,2-addition of these ketoimines to a conveniently located enone functionality would afford the corresponding tetracyclic imino alcohols in a single synthetic operation. As shown in Scheme 4, Wittig reaction of readily available aldehyde **13**[13] with known azidophosphonium salt **25**[14] employing KHMDS as base, gave (*Z*)-ω-azidoalkene **14** in good yield. When compound **14** was subjected to our optimized conditions described above, tetracyclic imino alcohol **20** was obtained as a single diastereomer in 78% yield. Hypothetically, formation of **20** probably proceeds by an initial IAOC followed by triazoline decomposition that would afford the cyclic imine **16**. Tautomerization of **16** to the corresponding exocyclic enamine **17** and subsequent conjugate addi-



Scheme 3. One-pot synthesis of compounds **12a–e**.

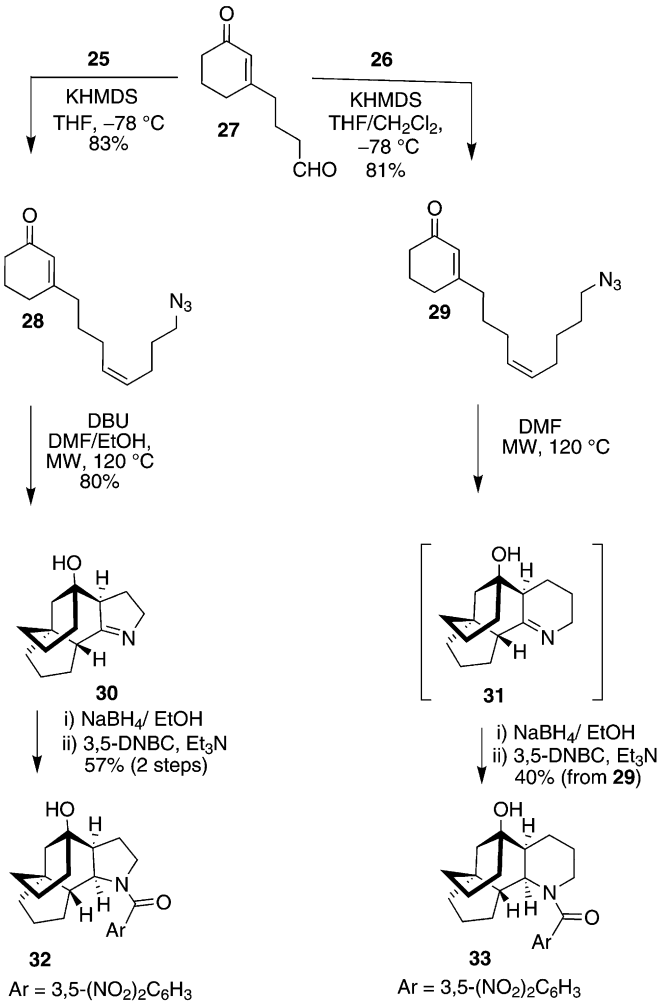


Scheme 4. Synthesis of tetracyclic imino alcohols **20** and **23**.

tion to the enone functionality would afford imino ketone **18**, which might undergo a second tautomerization to the endocyclic enamine **19** and final addition to the carbonyl group to give **20**. Four stereogenic centers and three new rings are formed during this 1,3 dipolar cycloaddition/1,4 addition/1,2 addition cascade process. Finally, **20** was converted into 3-nitrobenzoyl derivative **21** and the relative stereochemistry of the six contiguous stereocenters present in this molecule was confirmed by X-ray diffraction analysis.[15] Formally, *this transformation corresponds to the intramolecular version of the Movassaghi formal [3+3] cycloaddition reaction*.

Employing azidophosphonium salt **26**, (*Z*)-ω-azidoalkene **22** was prepared from aldehyde **13** in a similar fashion. In this case, we observed that the presence of dichloromethane as cosolvent (THF/CH_2Cl_2, 9:1) was critical for optimal results in the Wittig reaction. When compound **22** was subjected to the cyclization conditions, the stereoselective formation of tetracyclic imino alcohol **23** was observed. Due to the low stability of compound **23** towards air oxidation during isolation,[16] it was converted into the 3-nitrobenzoyl derivative **24** for ease of isolation and characterization (Scheme 4).

We also tested this IAOC/double enamine addition process in compounds **28** and **29** (Scheme 5). Since **28** and **29** are 3-substituted enones, a stereogenic quaternary carbon center could be built after enamine conjugate addition. Aldehyde **27** (prepared in two steps from commercially available 3-ethoxy-2-cyclohexenone)[13] was converted into ω-azidoalkenes **28** and **29**



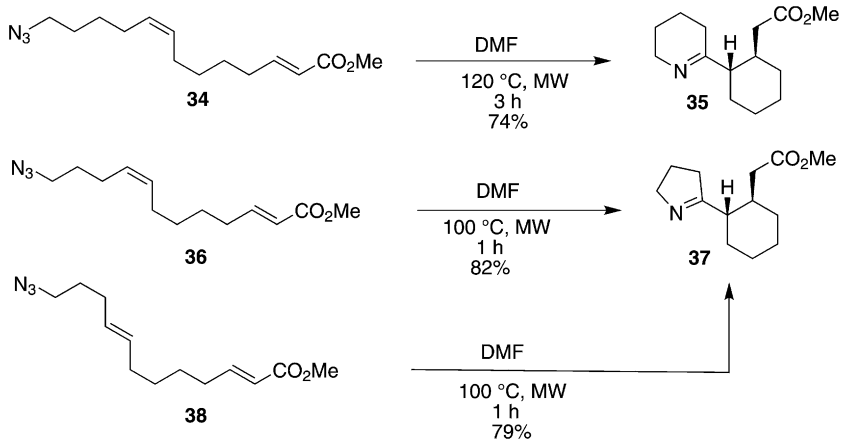
Scheme 5. Synthesis of tetracyclic imino alcohols **30** and **31**.

using a Wittig reaction. Subsequent heating of these compounds under optimized conditions afforded tetracyclic imino alcohols **30** and **31** respectively, which were separately converted into amido alcohols **32** and **33**. The relative sterochemistry of imino alcohol **30** was confirmed by X-ray crystallographic analysis of the corresponding amido alcohol **32**.[15]

There are interesting aspects to this cascade process: as in compounds **20** and **23**, (Scheme 4) four stereogenic centers (two of them quaternary) and three new cycles are created in a single synthetic operation, but while in **20** and **23** the final stereochemistry is dictated by the configuration of the stereogenic center already present in the ω-azidoalkenes **14** and **22**, in the case of imino alcohols **30** and **31** the cyclization precursors (**28** and **29**) are achiral. This fact implies the possibility of applying asymmetric synthesis methodologies based on enone activation in order to access to enantiomerically pure derivatives.[17]

Finally, the possibility of carrying out the IAOC/enamine addition sequence with acyclic substrates was examined (Scheme 6). When a DMF solution of linear *ω*-azidoalkene **34**[13] was heated at 120 °C for three hours under microwave irradiation, the bicyclic imino ester **35** was obtained in 74% yield as a single diastereomer. Imino ester **37** was prepared from ω-azidoalkene **36** in a similar way in 82% yield, but in this case lower temperature (100 °C) and shorter reaction time (1 h) were required. In order to examine the influence of the alkene geometry on the reaction outcome, compound **38** was prepared and subjected to our cyclization conditions. Treating a solution of *(E,E)*-azidoalkene **38** in DMF under the same conditions employed for its isomer **36**, also furnished bicylic imino ester **37** in a similar yield. This result indicates that neither the efficiency nor the stereochemical outcome of the process is affected by the geometry of the employed starting *ω*-azidoalkene.

In summary, an efficient stereoselective intramolecular azide-olefin cycloaddition/enamine addition(s) reaction cascade of *ω*-azidoalkenes for the preparation of diverse complex polycyclic nitrogen-containing structures has been developed. Further developments of this methodology, including mechanistic insights



Scheme 6. IAOC/enamine addition cascade reaction with linear substrates.

and an enantioselective version as well as its application to the total synthesis of different alkaloids are currently in progress and will be reported in due course.

Experimental Section

Caution: All organic azides should be treated as potential explosion hazards.

rac-(1*S*,4*S*,8*S*,13*S*,15*R*)-10-Azatetracyclo-[6.5.2.0^{4,15}.0^{9,13}]pentadec-9-en-1-ol (20)

DBU (0.18 mL, 1.20 mmol) was added to a solution of compound **14** (100 mg, 0.40 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120 °C for 3 h. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from DCM to 97:3 DCM:MeOH) to afford the desired imino alcohol **19** as a pale yellow viscous oil; yield; 68 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (m, 1H), 3.57 (m, 1H), 2.73 (app t, J = 9.6 Hz, 1H), 2.41 (m, 2H), 2.16 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H), 1.82 (m, 2H), 1.76–1.71 (m, 2H), 1.52–1.42 (m, 4H), 1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9, 71.2, 59.1, 58.7, 44.8, 38.7, 38.5, 35.0, 34.7, 30.7, 26.5, 24.3, 23.2, 15.7; FT-IR (neat): ν_{max} = 3330, 2950, 2860, 1649, 1460 cm^{-1}; HR-MS-ESI: m/z = 220.1695, calcd. for $C_{14}H_{22}NO$ $[M+H]^+$: 220.1696.

rac-(3-Nitrophenyl){(1*S*,4*S*,8*S*,9*S*,13*S*,15*R*)-1-hydroxy-10-azatetracyclo[6.5.2.0^{4,15}.0^{9,13}]pentadecan-10-yl}-methanone (21)

Sodium borohydride (13 mg, 0.36 mmol) was added to a solution of compound **20** (40 mg, 0.18 mmol) in absolute ethanol (5 mL) at 0 °C. After 45 min the reaction mixture was quenched with saturated NH_4Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Et_3N (50 μL, 0.36 mmol) and 3-nitrobenzoyl chloride (50 mg, 0.27 mmol) were sequentially added. After stirring at room temperature for 8 h the reaction mixture was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated under vacuum. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes:EtOAc) to afford compound **21** as a white solid; yield: 43 mg (64%); mp 187–189 °C. The relative stereochemistry of **21** was confirmed by X-ray crystallographic analysis (see the Supporting Information). ^{1}H NMR (400 MHz, CDCl3): δ = 8.46 (m, 1H), 8.31 (m, 1H), 7.95 (m, 1H), 7.62 (m, 1H), 4.86 (t, J = 8.6 Hz, 1H), 3.63 (m, 1H), 3.44 (m, 1H), 2.55 (m, 1H), 2.48 (t, J = 8.4 Hz, 1H), 2.38 (m, 1H), 2.10 (dd, J = 13.7, 6.1 Hz, 1H), 1.97 (m, 1H), 1. 91 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.58–1.51 (m, 5H), 1.36 (m, 1H), 1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 148.4, 139.2, 134.4, 129.8, 125.7, 123.6, 70.4, 59.9, 54.3, 49.9, 45.3, 39.7, 37.1, 35.4, 33.9, 30.8, 28.4, 27.0, 25.3, 18.1; FT-IR (neat): ν_{max} = 3435, 2950, 1625, 1533, 1350 cm^{-1}; HR-MS-ESI: m/z = 371.1964, calcd. for $C_{21}H_{27}N_2O_4$ $[M+H]^+$: 371.1968.

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