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Solvent-free synthesis of functionalized pyridine derivatives using Wells-Dawson heteropolyacid as catalyst

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ABSTRACT

Wells-Dawson heteropolyacids ($H_6P_2W_{18}O_{62}\cdot 24H_2O$) were used as catalysts in the Hantzsch-like multicomponent condensation reaction with 3-formylchromones as aldehyde component, a β-ketoester and ammonium acetate, under solvent-free conditions at 80 °C. Although the desired products were obtained, functionalized pyridines were the main reaction product and became the alternative route to dihydropyridine ring formation. Based on the proposed mechanisms for the formation of each of the obtained products, the multicomponent reaction was modified to afford only the functionalized pyridines (60–99%). Our procedure represents a clean alternative for the synthesis of several highly functionalized pyridines.

3-Formylchromones **1** have been used to prepare a variety of heterocyclic compounds, their reactivity towards nucleophiles (e.g. hydrazine, phenylhydrazine, amidines and aminopyrazoles) being extensively investigated.[1–4] In addition, a variety of bioactive heterocyclic compounds can be obtained via the Hantzsch condensation reaction of an aldehyde, a β-dicarbonyl compound and an ammonia source.[5–7] When a 3-formylchromone is incorporated, the Hantzsch reaction affords dihydropyridines **2** functionalized in the 4-position with the 3-chromonyl substituent (Scheme 1).[8–11]

Recently, we demonstrated the usefulness of Wells-Dawson heteropolyacids as recyclable catalysts in the synthesis of dihydropyridines via the Hantzsch reaction. Our reported green method affords these heterocycles under solvent-free conditions for short periods, in excellent yields.[12]

Continuing with our studies on the green synthesis of heterocyclic compounds using heteropolyacids as recyclable catalysts, we now present our findings about the course of the reaction when 3-formylchromones are subjected to Hantzsch reaction conditions. The use of 3-formylchromones would give a new perspective to this reaction, mainly for two reasons. First, 3-formylchromones represent a very reactive system owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3 and, above all, a very reactive electrophilic center at C-2.[13] Second, derivatives of chromones are important natural products possessing a wide range of valuable physiological activities.[14] In addition, 3-formylchromones represent useful synthetic building blocks in organic and medicinal chemistry.[15]

Initially, we conducted blank experiments without the presence of Wells-Dawson acid (HPA). Mixtures of several uncharacterized products were detected by thin layer chromatography. Then, 3-formylchromone, methyl acetoacetate and ammonium acetate were selected as representative substrates in order to optimize the reaction conditions for the synthesis of 1,4-dihydropyridines in a faster and more efficient way. After some experiments, we found a set of conditions that allows the isolation of 1,4-dihydropyridines **2**, but show the co-existence of a second reaction route through the appearance of an important amount of a 2,3,5-substituted pyridine **3** (Scheme 1).

In contrast to our first report, where we used simple aldehydes, 3-formylchromones showed an alternative direction of the Hantzsch condensation reaction. The functionalized pyridine in the 2-, 3-, and 5-positions was formed by opening the γ-pyrone ring after nucleophilic attack and subsequent cyclodehydration. Yields depend on the reaction conditions and range from very good to almost quantitative. The tendency to the opening of the pyrone ring

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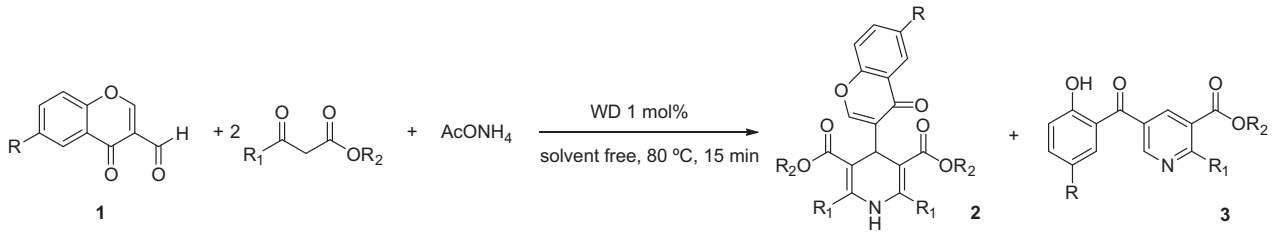
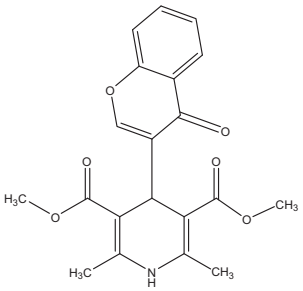
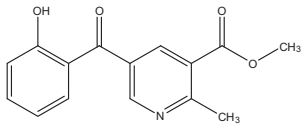
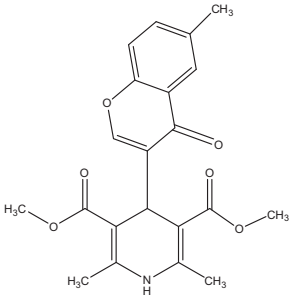
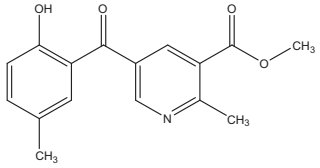
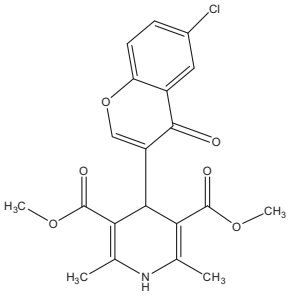
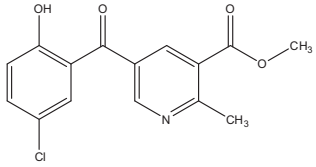
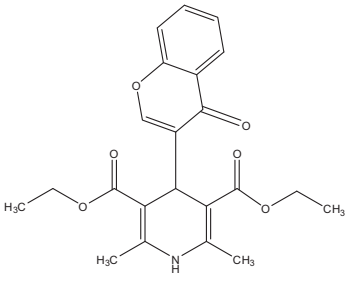
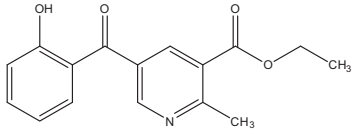
is well known[16] and was also observed in 3-formylchromones and in substituted 3-formylchromones when amines or C-nucleophilic anilines were used as nucleophiles.[17–19] Ammonium and primary amines also act as nucleophiles on other closely related activated chromones. 2-Methylchromones[20] and 2-trifluoromethylchromones[21,22] afford aminoenones by attack at the C-2 position.

Afterwards, the catalytic activity of the bulk Wells-Dawson acid was tested. The molar ratio of the reactants 3-formylchromone,



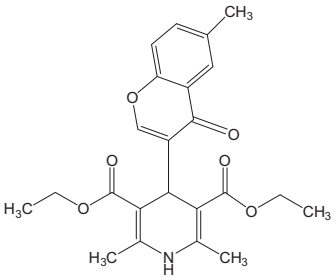
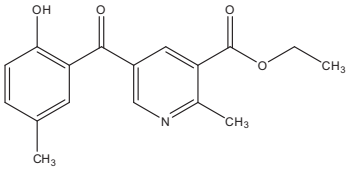
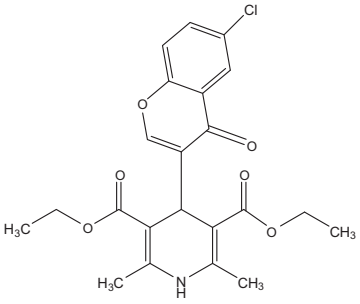
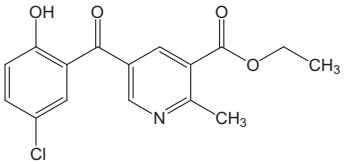
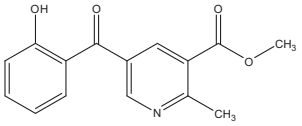
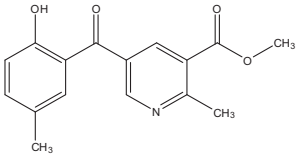
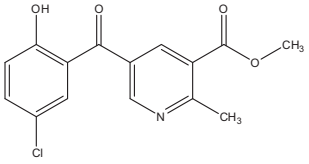
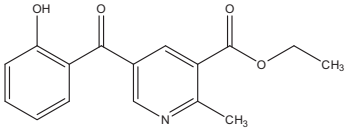
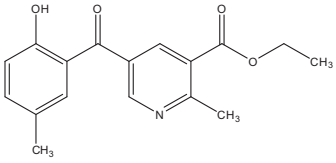
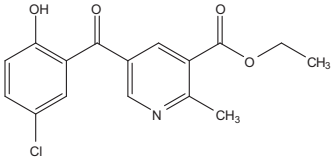
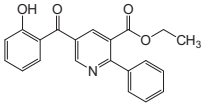
Scheme 1. General outcome of a solvent-free Hantzsch-like condensation reaction with 3-formylchromone.

Table 1
Hantzsch and functionalized pyridine synthesis[a]

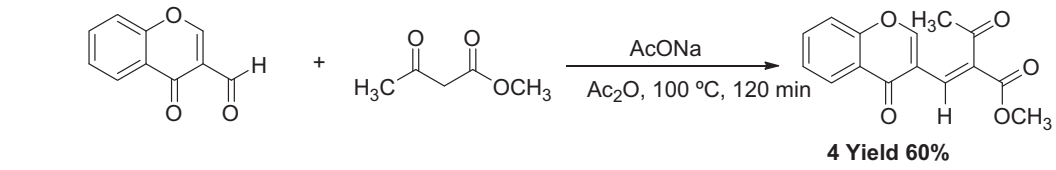
Entry	R	R_1	R_2	Molar ratio[b]	Product 2[c]	Product 3[c]	Time (min)	Selectivity 2[d] (%)	Selectivity 3[d] (%)
1	–H	$-CH_3$	$-CH_3$	1:2:1			15	30	65
2	$-CH_3$	$-CH_3$	$-CH_3$	1:2:1			15	25	70
3	–Cl	$-CH_3$	$-CH_3$	1:2:1			15	31	65
4	–H	$-CH_3$	$-CH_2CH_3$	1:2:1			15	19	49

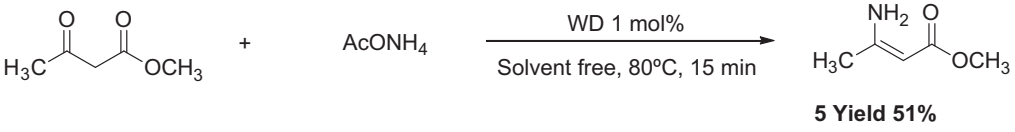
(*continued on next page*)

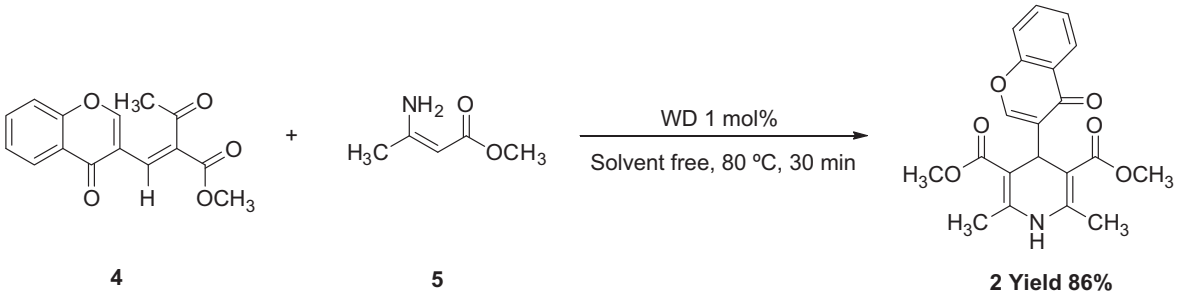
Table 1 (*continued*)

Entry	R	R_1	R_2	Molar ratio[b]	Product 2[c]	Product 3[c]	Time (min)	Selectivity 2[d] (%)	Selectivity 3[d] (%)
5	$-CH_3$	$-CH_3$	$-CH_2CH_3$	1:2:1			15	16	64
6	–Cl	$-CH_3$	$-CH_2CH_3$	1:2:1			15	12	80
7	–H	$-CH_3$	$-CH_3$	1:1:1	—		15	0	99 (99,98)[e] (89)[f]
8	$-CH_3$	$-CH_3$	$-CH_3$	1:1:1	—		15	0	93
9	–Cl	$-CH_3$	$-CH_3$	1:1:1	—		15	0	99
10	–H	$-CH_3$	$-CH_2CH_3$	1:1:1	—		30	0	99
11	$-CH_3$	$-CH_3$	$-CH_2CH_3$	1:1:1	—		30	0	98
12	–Cl	$-CH_3$	$-CH_2CH_3$	1:1:1	—		30	0	94
13	–H	–Ph	$-CH_2CH_3$	1:1:1	—		15	0	60

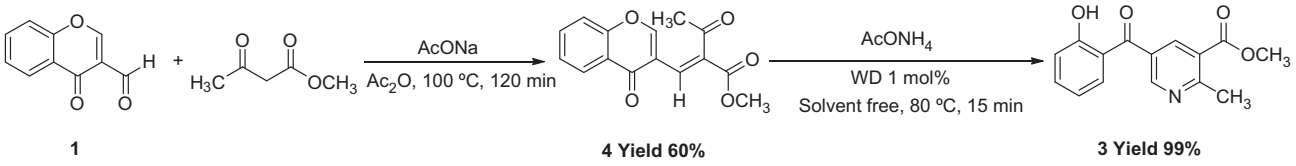
[a] Reactions and condition: catalyst 1% mmol; temperature 80 °C; solvent free-condition. For all cases the conversion was 100% (TLC).
[b] Molar ratio: aldehyde: β-ketoester: ammonium acetate.
[c] All the products were characterized by NMR (^1H and ^{13}C) and melting points. In all cases these physical constants match those previously reported.
[d] Yields (%) determined after recrystallization.
[e] Catalyst reuse: first and second cycles. Yields (%) of recrystallized products.
[f] The reaction was performed using acetonitrile as reaction solvent. Yields (%) of recrystallized products.







Scheme 2. Multistep solvent-free Hantzsch synthesis.



Scheme 3. Solvent-free synthesis of substituted pyridines in two steps.

methyl acetoacetate and ammonium acetate was 1:2:1, respectively. The obtained results are shown in Table 1.[23]

The experiments were carried out under solvent-free conditions, in the presence of 1% mmol catalyst. Temperature and molar ratio between the HPA and substrates were checked to optimize the reaction. The use of just 1 mmol of HPA is enough to push the reaction forward; higher amounts of the catalyst did not improve the results. The reactions were completed within 15 min at 80 °C, and the crude products were obtained by simple filtration of the catalyst and evaporation of the hot hexane or toluene solution of the product. The experiments were run until consumption of the substrates (TLC). In all cases, products **2** and **3** were both obtained with high selectivity, almost free of other secondary products (Table 1, entries 1–6).[23]

A mechanism for 1,4-dihydropyridine formation was suggested by Shen et al.[24] To confirm the step sequence that originates the dihydropyridines via the Hantzsch reaction, we separately synthesized 2-acetyl-3-(3-chromonyl)acrylic acid ethyl ester **4** as the α,β-unsaturated carbonyl compound and methyl 3-aminocrotonate **5** as enamine. 2-Acetyl-3-(3-chromonyl) acrylic acid ethyl ester **4** (Yield 60%) was prepared according to Haas et al.[25] and methyl 3-aminocrotonate (Yield 51%) was obtained from a mixture of methyl acetoacetate (1 mmol) and ammonium acetate (1 mmol), using HPA as catalyst. Then, the solid catalyst (1% mmol) was added to a mixture of the pure α,β-unsaturated carbonyl compound **4** (1 mmol) and the pure enamine **5** (1 mmol). The mixture was stirred at 80 °C for 30 min and the course of the reaction monitored by TLC, yielding the corresponding 1,4-dihydropyridine 86% (Scheme 2). These separate experiments prove that the dihydropyridines formed in the multicomponent Hantzsch reaction follow the proposed mechanism.

But when 2-acetyl-3-(3-chromonyl) acrylic acid ethyl ester **4** (1 mmol) and ammonium acetate (1 mmol) were stirred under the same conditions (80 °C;15 min) in the presence of the solid catalyst (1% mmol), the corresponding pyridine derivate was obtained (99% yield, Scheme 3).

These two results show that in the reaction medium the enamine **5** must be formed to attack then, as N-nucleophile, the carbonyl carbon of the methyl ketone residue of **4.** But if the enamine concentration is low and/or the nucleophilic attack is hindered (e.g. steric effect), the ammonia produced in the acid catalyst medium acts as a better nucleophile at the C-2 position of the pyrone ring. Consequently, cleavages and subsequent dehydrocyclation occur. The route to dihydropyridines is sterically disfavored or leads to 3-bulkily substituted chromones. Moreover, pyridine formation leads to a thermodynamically stable aromatic ring. Besides, these experiments reveal that if enamine formation is inhibited, the dihydropyridine should also be reduced.

Then, we performed a second series of experiments under similar reaction conditions but using a molar ratio of the reactants

of 1:1:1, respectively. The solvent-free reactions were completed within 15–30 min at 80 °C. In all cases, only products with structure **3** were obtained with excellent yields (60–99%) and selectivity, and also free of secondary products (Table 1, entries 7–13).[23]

Recycling of the catalyst (Table 1, entry 7b)[23] was checked in two consecutive batches after the first one; the catalysts showed almost constant activity, 99%, 98% and 98%, respectively. On the other hand, the experiments performed using acetonitrile as reaction solvent showed a decrease of the reaction yields (Table 1, entry 7c, 89%).[23] All the 6-substituted-3-formylchromones studied showed no stereoelectronic effects on the reaction yields.

In summary, we have described the synthesis of polysubstituted pyridines from commercial starting materials and under green reaction conditions.[29] This procedure makes the current method feasible and an attractive protocol for the generation of novel heterocycles. The use of HPA catalysts provides very good yields, also leading to an easy separation and recovery of the catalysts for further use. We continue to study the procedure to synthesize Hantzsch products from 3-formylchromones as aldehydes. We expect to report the results of these investigations in due course.

Acknowledgements

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23. *General Procedures.* All the yields were calculated from crystallized products. All the products were identified by comparison of analytical data, melting point (mp), thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) data with those reported. The starting materials are commercial products. 2-Acethyl-3(-chromonyl)-acylic acid methyl ester **4** was prepared using a literature procedure[25], and 3-amino-2-butenoic acid methyl ester **5** by warming a 1:5 mixture of methyl acetoacetate and ammonium acetate at 80 °C for 120 min. Melting points of the compounds were determined in open capillary tubes and are uncorrected. ^{13}C NMR and ^{1}H NMR spectra were recorded at room temperature on Bruker AC 400 using tetramethylsilane (TMS) as internal standard.
Catalyst Preparation. The Dawson acid ($H_6P_2W_{18}O_{62}\cdot 24H_2O$) was prepared by the Drechsel method from an α/β $K_6P_2W_{18}O_{62}\cdot 10H_2O$ isomer mixture.[26] This Dawson-type salt was prepared according to the technique reported by Lyon et al.[27,28] *General Procedures for the preparation of substituted pyridines.* The solid catalyst (1 mmol %) was added to a mixture of 3-formylchromones (1 mmol), alkyl or aryl acetylacetates (1 mmol) and ammonium acetate (1 mmol). The mixture was stirred at 80 °C for the indicated time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, hot toluene was added (2 × 2.5 mL) and the catalyst was filtered. The extracts were combined; their solvents were evaporated and then concentrated in vacuum. All the solid crude products were recrystallized.
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28. *Recycling of catalyst.* After reaction, the catalyst was washed with toluene (2 × 2 mL), dried under vacuum, and reused in the next catalytic cycle.
29. *Representative compounds synthesized.* Compound entry 1, Product 2. Yield 30%, mp: 250–252 °C (ethanol) (lit mp: 258 °C[30]), ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 33.6, 51.1, 98.2, 118.7, 124.6, 125.5, 125.6, 126.5, 134.1, 147.2, 154.7, 155.8, 167.8, 176.8.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 6H), 3.55 (s, 6H), 4.85 (s, 1H), 7.44 (t, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 8 Hz, 1H), 8.97 (s, 1H).
Compound entry 2, Product 2. Yield 25%, mp: 258–260 °C (ethanol) (lit. mp: 260 °C[30]), ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 20.9, 33.4, 51.0, 98.5, 118.4, 124.2, 124.8, 126.6, 135.0, 135.1, 147.1, 154.1, 154.5, 167.9, 175.7.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 6H), 2.39 (s, 3H), 3.55 (s, 6H), 4.86 (s, 1H), 7.46 (d, J = 8 Hz, 1H), 7.55 (dd, J = 8 and 2 Hz, 1H), 7.79 (d, J = 2 Hz, 1H), 7.89 (s, 1H), 8.95 (s, 1H).
Compound entry 8. Yield 93%, mp: 109–111 °C (hexanes) (lit. no data), ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 24.8, 52.8, 118.5, 118.7, 125.4, 128.5, 131.4, 132.3, 138.4, 139.5, 150.8, 161.1, 163.0, 165.8, 198.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.00 (s, 3H), 3.98 (s, 3H), 7.03 (d, J = 8 Hz, 1H), 7.28–7.30 (m, 1H), 7.40 (dd, J = 8 and 2 Hz, 1H), 8.58 (d, J = 2 Hz, 1H), 8.92 (d, J = 2 Hz, 1H), 11.65 (s, 1H). Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91; O, 22.43. Found: C, 67.40; H, 5.31; N, 4.90.
Compound entry 9. Yield 98%, mp: 87–89 °C (hexanes) (lit. no data), ^{13}C NMR (100 MHz,$CDCl_3$) δ 52.4, 119.4, 120.5, 124.1, 125.7, 130.8, 131.5, 137.1, 139.5, 150.7, 24,8 161.7, 163.6, 165.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.98 (s, 3H), 7.10 (d, J = 9 Hz, 1H), 7.48–7.56 (m, 2H), 8.58 (d, J = 2 Hz, 1H),8.93 (d, J = 2 Hz, 1H), 11.65 (s, 1H). Anal. Calcd. for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; Cl, 11.60; N, 4.58; O, 20.93. Found: C, 58.90; H, 3.99; N, 4.90.
Compound entry 13. Yield 60%, mp: 88–90 °C (hexanes) (lit no data), ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.89, 62.20, 119.02,119.1, 119.50, 127.4, 128.55, 128.95, 129.72, 131.57, 133.12, 137.47, 138.78, 139.31, 151.02, 161.44, 163.39, 167.53, 198.34. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, J = 7 Hz, 3H), 4.20 (q, J = 7 Hz, 2H), 6.94 (dt, J = 8 and 2 Hz, 1H), 7.11(d, J = 8 Hz, 1H), 7.43–7.53 (m, 3H), 7.54–7.67 (m, 4H), 8.41 (d, J = 2 Hz, 1H), 9.04 (d, J = 2 Hz, 1H), 11.81 (s, 1H).
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