# Efficient solvent- and metal-free Sonogashira protocol catalysed by 1,4-diazabicyclo(2.2.2) octane (DABCO)

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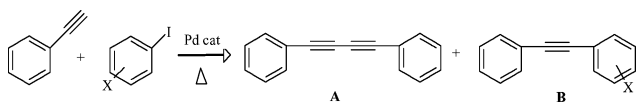
An efficient metal-free Sonogashira coupling protocol catalysed by DABCO is reported, where very good conversions and selectivities to the cross-coupling product were obtained under mild reaction conditions. The reported solvent-, phosphane- and metal-free protocol, that uses a cheap base as catalyst, considerably improves the green credentials of the reaction.



## Introduction

The Sonogashira coupling between alkynes and aryl or alkenyl halides (Scheme 1) is an easy, efficient, and long-established route in organic synthesis. This reaction has been widely reported as an interesting option for the creation of C–C bonds.[1]




**Scheme 1** Product distribution of the Sonogashira coupling.

Many research efforts have been devoted to the development of new catalytic systems due to the wide range of target compounds that can be synthesized, including: natural products,[2] pharmaceuticals[3] and molecular organic materials.[4] The Sonogashira coupling is generally carried out in organic solvents including toluene, dioxane and THF with the requirement of a stoichiometric amount of base and usually a Pd(0)-Cu(I) catalytic system.[1a]

In an attempt to improve and broaden the applications of the catalytic systems to fine and green chemistry, elimination of CuI[5–7] (to avoid homocoupling reactions between terminal alkynes), solventless reactions,[8] microwave enhanced couplings[8–10] and solvent-, copper- and phosphane-free protocols have been considered.[11] However, despite the need for improvements in the green credentials of the reactions in the synthesis of pharmaceuticals,[12] many of the reported protocols still rely on homogeneous catalysis.[1a,13,14] These homogeneous experiments often involve time-demanding purification-isolation procedures to achieve high purity in the product as well as to ensure the removal of traces of undesired metals (*e.g.* Pd, Cu). Compared to their homogeneous counterparts, stable heterogeneous systems may offer high purities in products at relatively comparable reaction rates, combined with high reusabilities that significantly improve the green credentials of the reactions as well as making them more cost-efficient.[15] Alternative systems to the Sonogashira coupling have been reported,[16,17] including a few metal-free coupling protocols.[9,18]

Recent studies of Leadbeater *et al.* showed that only small traces of palladium as impurities in basic salts (*e.g.* $Na_2CO_3$) were able to catalyse C–C bond forming reactions, yielding the cross-coupled product in a free transition metal reaction.[19] Consequently, the choice of the base in the process seems to be a critical step in order to design novel and more efficient catalytic systems able to provide improved yields and selectivities combined with shorter reaction times and milder and more environmentally friendly conditions.

We have previously investigated the use of triethylamine (TEA) as the base, combined with the use of heterogeneous palladium complexes under mild reaction conditions (70 °C).[20] However, the reported protocol required long reaction times, and an unusual inversion in selectivity to the homocoupling product was observed when the coupling of bromoaryls was attempted. Other bases including diethylamine (DEA)[21] and piperidine[5–7] have been widely employed in this coupling.

Compared to these bases, 1,4-diazabicyclo(2.2.2) octane (DABCO) has been regarded as an unhindered and nucleophilic base, and considered one of the best amine catalysts due to its unique properties.[22–26] DABCO was reported as a stronger Lewis base than TEA and DEA when employed in the Baylis–Hillman coupling between arylaldehydes and activated ketones/enones.[22] DABCO seemed to promote the Baylis–Hillman reaction by itself whereas the addition of TEA or DEA as bases required catalytic amounts of L-proline to allow the successful coupling of the starting materials. Furthermore, DABCO has also been employed as a ligand in C–C coupling reactions catalysed by $Pd(OAc)_2$[24] and CuI.[25] Encouraged by these promising results, we were prompted to investigate the effect of DABCO in a solvent-, phosphane- and transition metal-free protocol under mild conditions. To the best of our knowledge, this is the first report of the direct utilisation of DABCO as a catalyst in the Sonogashira reaction.

## Results and discussion

### Preliminary experiments

We initially performed a range of experiments in order to optimise the different reaction parameters using a DABCO promoted

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Sonogashira coupling between phenylacetylene and an electron-deficient reagent (*e.g.* 3-iodobenzotrifluoride) as a model reaction, using a palladium system and reaction conditions similar to those previously reported.[20] The results obtained for the coupling reaction at different temperatures (ranging from 70 °C to 100 °C) showed an increase in the conversion values, with an increase in the temperature, reaching a maximum at 100 °C. Almost quantitative conversion (>95%) of starting material was achieved at 100 °C in less than 1 h, preserving a complete selectivity to the cross-coupled product regardless of the temperature increase. These preliminary results were a remarkable improvement on those previously reported by our group.[20]

Heterogeneous activity tests were carried out in order to ascertain the truly heterogeneous nature of the materials under the reaction conditions. For this purpose, both ICP analysis of the filtrate after the reaction and a hot filtration test were carried out.

The reaction mixture was filtered off and extracted in order to quantify any leached palladium in solution. No palladium was detected by ICP, implying that the concentration of Pd in solution (if any) was below the detection limit (<0.5 ppm).

A hot filtration test was also performed. Small liquid aliquots were poured out from reactions, typically at the halfway point (around 20–30 min), rapidly filtered off and added to another mixture with fresh starting materials (SM). In general, no significant increase in the conversion of the SM was observed after 6 h in the liquid aliquot taken from the first reaction. In contrast, the conversion remarkably increased in the unfiltered fraction containing the solid catalyst, thus indicating that the solid catalyst remained active.

Samples from the poured liquid mixture containing DABCO, taken after 12 h, displayed a substantial increase in catalytic activity compared to that initially observed. Further experiments without catalysts were then needed to fully understand this unusual increase in catalytic activity.

## Metal-free Sonogashira couplings

Firstly, a comprehensive study of a range of basic molecules employed in the reaction, including: TEA (1), diisopropylethylamine (DIEA, 2), 1,1,3,3-tetramethylguanidine (TMG, 3), 1,3 -dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 4), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5) and DABCO (6) was performed. The results are summarised in Fig. 1.

Interestingly, no significant increase in conversion was found in the Sonogashira coupling with the exception of DABCO for which a 35% conversion was found after 12 h at 100 °C (Fig. 1, entry 6). These promising results pointed to a conversion increase in the systems directly related to the addition of DABCO that may act as a catalyst in the Sonogashira coupling.

DABCO was consequently employed as the catalyst in the Sonogashira coupling. Results have been included in Table 1.

Blank runs (without DABCO) gave virtually no coupling activity. Only poor conversions (ranging from 15 to 40%) were found for the DABCO catalysed Sonogashira cross-coupling reaction using electron-deficient reagents under similar conditions to those employed with the palladium systems. When substituted arenes with electron-donating groups were used, virtually no conversion was obtained (Table 1, entries 6 and 7). These reactions seemed to

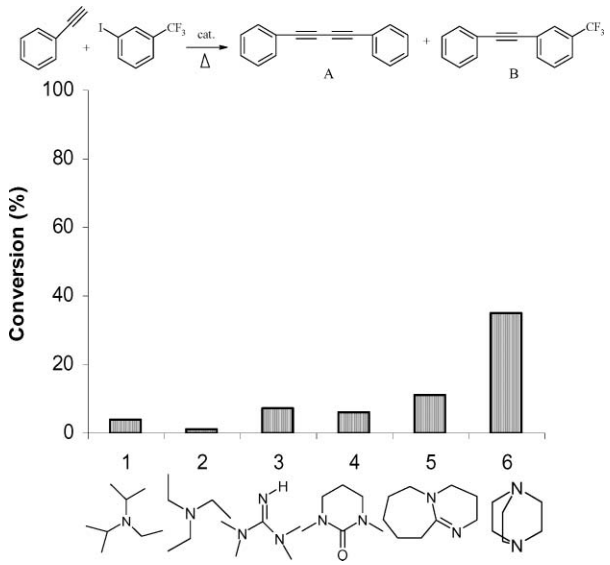



**Fig. 1** Metal-free Sonogashira coupling of iodobenzotrifluoride and phenylacetylene using different basic molecules as catalysts. Phenylacetylene : iodobenzotrifluoride : base ratio = 1 : 1 : 2, 100 °C, 12 h.

be promoted by a previous substrate activation through stirring the starting material with DABCO under mild heating (50–70 °C).

In order to improve these promising results, several parameters were investigated including the temperature and time of reaction, the quantity of DABCO and the use of microwave irradiation instead of conventional heating.

### Effect of the reaction time

Setting the temperature of the systems at 130 °C, the conversion increased in systems with longer reaction times as expected. Almost quantitative conversion of starting material was found after 48 h (Table 2, entries 1 and 3), with a remarkable increase in conversion for electron-donating susbtituted arenes (Table 2, entries 8 and 9).

### Effect of the reaction temperature

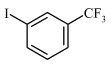
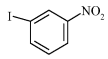
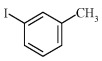
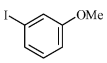
The results in Fig. 2 show that an increase in temperature up to 130 °C considerably increased the conversions of starting materials in the systems, reaching around 60–80% after 12 h for a range of selected electron-poor reagents. In contrast, poor conversions were achieved in arenes with electron-donating substituents (*e.g.* 28% conversion for *m*-iodoanisole). Temperatures above 130 °C did not offer significantly higher yields of cross-coupling products (Fig. 2).

### Effect of the quantity of DABCO

A 1 : 1 : 2 ratio of phenylacetylene : arene : DABCO was initially employed in the coupling reaction. Smaller quantities of DABCO considerably decreased the conversion in the systems (*e.g.* a 1 : 1 : 1 ratio provided a 78% conversion in the coupling of phenylacetylene and 3-iodobenzotrifluoride compared to a 93% for a 1 : 1 : 2 ratio, Table 2, entry 1). Interestingly, an increase in the quantity of DABCO (*e.g.* 1 : 1 : 3 or 1 : 1 : 4) did not seem to have a remarkable effect on the reaction in terms of conversion and selectivity to cross-coupling products, regardless of the arene and

**Table 1** Metal-free Sonogashira cross-coupling reaction experiments between phenylacetylene and different electron-deficient aryl halides using DABCO as catalyst[a]

| Entry | Starting material (SM) | Conversion (%)[b] | B : A ratio[c] | Time/h |
|---|---|---|---|---|
| 1 |  3-Iodobenzotrifluoride | 35 | 90 : 10 | 12 |
| 2 |  1-Fluoro-3-iodobenzene | 15 | 99 : 1 | 12 |
| 3 |  1-Iodopentafluorobenzene | 40 | 99 : 1 | 12 |
| 4 |  1-Fluoro-4-iodobenzene | 27 | 70 : 30 | 12 |
| 5 |  1-Iodo 3-nitrobenzene | 15 | 99 : 1 | 12 |
| 6 |  3-iodotoluene | <10 | 99 : 1 | 12 |
| 7 |  3-iodoanisole | <5 | 99 : 1 | 12 |

[a] *Reaction conditions*: phenylacetylene : SM : DABCO ratio = 1 : 1 : 2, 100 °C. [b] Based on the conversion in moles of starting material. Determined by GC-analysis with dodecane as the internal standard. [c] Determined by GC-analysis of the crude product.

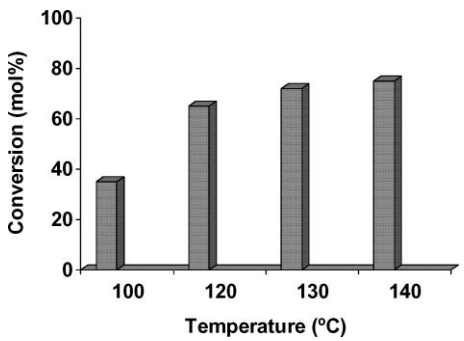


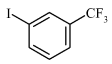
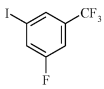
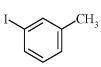
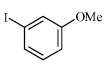
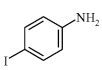
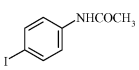

**Fig. 2** Metal-free Sonogashira coupling of iodobenzotrifluoride and phenylacetylene at different temperatures using DABCO as catalyst. Phenylacetylene : iodobenzotrifluoride : DABCO ratio = 1 : 1 : 2, 12 h.

the substituent(s). Therefore, a 1 : 1 : 2 ratio was selected as optimum for the coupling reaction.

### Microwave irradiation *vs.* conventional heating

Microwaves have been proved to be a very useful tool in organic synthesis, allowing fast and homogeneous heating that can considerably improve yields and even selectivities in catalysed reactions,[27]

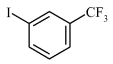
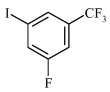
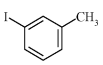
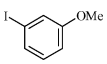
**Table 2** DABCO catalysed Sonogashira cross-coupling reaction between phenylacetylene and various substituted aryl iodides under optimised conditions[a]

| Entry | Starting material (SM) | Conversion (%)[b] | B : A ratio[c] |
|---|---|---|---|
| 1 |  3-Iodobenzotrifluoride | >90 (86) | 85 : 15 |
| 2 |  1-Fluoro-3-iodobenzene | 73 | 95 : 5 |
| 3 |  1-Iodopentafluorobenzene | 90 (84) | 99 : 1 |
| 4 |  3-Fluoro 5-iodobenzotrifluoride | 84 (77) | 95 : 5 |
| 5 |  1-Fluoro-4-iodobenzene | 82 (76) | 80 : 20 |
| 6 |  5-iodouracil | <20 | 99 : 1 |
| 7 |  2-iodophenol | 77 (72)[d] | 90 : 10 |
| 8 |  3-iodotoluene | 61 | 99 : 1 |
| 9 |  3-iodoanisole | 55 | 99 : 1 |
| 10 |  4-iodoaniline | 49 | 99 : 1 |
| 11 |  4-iodoacetanilide | <40 | 95 : 5 |

[a] *Reaction conditions*: phenylacetylene : SM : DABCO ratio = 1 : 1 : 2, 130 °C, 48 h. [b] Based on the conversion in moles of starting material. Determined by GC-analysis using dodecane as internal standard. Isolated yields (where appropriate) are given in brackets. [c] Determined by GC-analysis of the crude product. [d] 60 h reaction time.

with already proven reports in palladium heterogeneously catalysed Sonogashira protocols.[15a,28] The efficiency of the microwave metal-free DABCO catalysed Sonogashira coupling is clearly demonstrated in Table 3. Under the optimised conditions (1 mmol phenylacetylene, 1 mmol arene, 4 mmol DABCO, 200 W, 120 °C, 1 h), quantitative conversion of starting material was achieved in most cases, except for electron-donating substituted arenes that

**Table 3** DABCO catalysed Sonogashira cross-coupling reaction under microwave irradiation[a]

| Entry | Starting material (SM) | Time/h | Conversion (%)[b] | B : A ratio[c] |
|---|---|---|---|---|
| 1 |  3-Iodobenzotrifluoride | 1 | 87 (80) | 95 : 5 |
| 2 |  1-Fluoro-3-iodobenzene | 1.5 | 75 | 99 : 1 |
| 3 |  1-Iodopentafluorobenzene | 1 | 83 | 99 : 1 |
| 4 |  3-Fluoro 5-trifluoroiodobenzene | 1 | 77 | 99 : 1 |
| 5 |  1-Fluoro-4-iodobenzene | 1 | 80 | 95 : 5 |
| 6 |  3-iodotoluene | 2 | 66 | 99 : 1 |
| 7 |  3-iodoanisole | 2 | 49 | 99 : 1 |

[a] *Reaction conditions*: phenylacetylene : SM : DABCO ratio = 1 : 1 : 2, 200 W, 140 °C (maximum temperature reached). [b] Based on the conversion in moles of starting material. Determined by GC-analysis using dodecane as internal standard. Isolated yields (where appropriate) are given in brackets. [c] Determined by GC-analysis of the crude product.

required longer irradiation times to achieve comparable results (Table 3, entries 6 and 7).

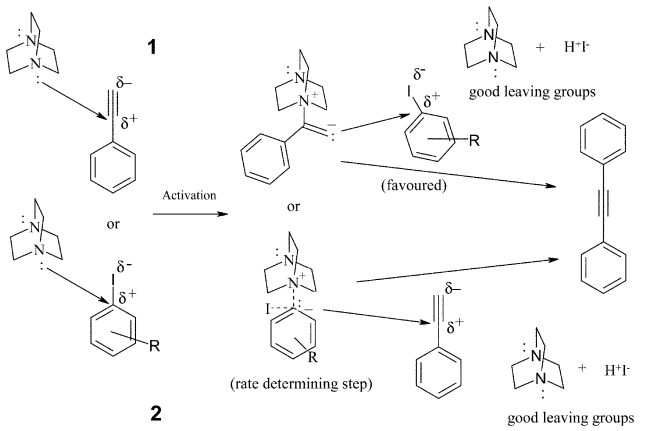
Most importantly, the selectivities to the cross-coupling products were improved under microwave conditions, being >95% in all cases (Table 3).

## Discussion of results and proposed reaction mechanism

Following studies by Leadbeater *et al.*[19] in which they report that the metal impurities (*e.g.* Pd) in basic salts were able to catalyse C–C bond forming reactions, a sample of the reaction mixture was further checked for Pd traces in solution. ICP and AAS gave no Pd content in solution, implying that the Pd concentration (if any) was below the detection limit of the techniques (<0.5 ppm).

We tried to rationalise these interesting findings by proposing a plausible mechanism for the DABCO catalysed Sonogashira coupling in the absence of metal catalysts (Scheme 2). These mechanisms may be supported by the fact that the coupling does not work very well with electron-donating substituents in the aromatic ring as they may partially stabilise the positive charge generated in the C–I bond through an inductive effect.

Thus, in the proposed reaction mechanism, DABCO acts as a nucleophile attacking the electrophilic carbon from the triple




**Scheme 2** Plausible reaction pathways for the metal-free DABCO-catalysed Sonogashira coupling.

bond in the alkyne (route 1). The intermediate formed, relatively stabilised through conjugation with the aromatic ring, may then attack the aryl halide to yield the cross-coupling product through elimination of HI.

An alternative pathway (route 2) may involve nucleophilic substitution of the aryl halide through the iodine and then attack of the newly generated nucleophilic carbon in the aromatic ring (after DABCO leaving) to another molecule of alkyne, to give the substituted diphenylacetylene.

We believe that the reaction progresses mainly through route 1 as the rate determining step is likely to be the nucleophilic attack, by the intermediate formed after the initial DABCO attack, of another molecule (either the aryl iodide or the alkyne, rate determining step, Scheme 2). This rate determining step will be expected to be slower in route 2 compared to that of route 1 due to nucleophilic substitution in the aryl halide being favoured (the iodine has a big electronic cloud that facilitates the nucleophilic attack leaving as HI), as well as the stability of the route 2 intermediate formed after nucleophilic substitution (DABCO-aryl halide, rate determining step, Scheme 2). Electron-withdrawing substituents in the aromatic ring may help to reduce electron density in the aromatic ring, thus destabilising the positive charge generated in the C–I bond and facilitating the attack of the nucleophile.

Then, why did the other basic molecules, including DBU and TMG, not work in the coupling? In general, the nucleophilicity and steric constraints of a base are critical parameters to consider in order to employ it as a catalyst or a promoter in a catalysed reaction.[23] Aliphatic amines including TEA, DIEA and TMG are good nucleophiles but, comparatively, pyrrolidines and piperidines are generally accepted as more nucleophilic and stable. DBU is a non-nucleophilic base.[29] Strictly speaking DMPU cannot be considered as a base but it has been reported to have Lewis basicity when employed as a catalyst in some reported reactions.[30] Furthermore, compared to the other bases where steric effects may be present, DABCO has two sterically unhindered N groups due to its particular conformation that are readily available to act as nucleophilic centres in a range of reactions (*e.g.* etherifications).[31] In particular, the presence of a second N withdraws electronic density from the neighbouring N atom through an inductive effect, making it less nucleophilic and basic and consequently a better

leaving group in the reaction.[29] These properties may also explain the fact that the transition metal-free reaction takes place with DABCO but not with the other investigated bases.

The rates of the reaction are, in any case, slower than those obtained in the Sonogashira coupling catalysed by transition metal (supported) catalysts.

Further experiments are currently underway to ascertain whether the reaction follows proposed route 1 or 2.

## Conclusions

1,4-Diazabicyclo(2.2.2) octane (DABCO) was found to act as a catalyst in a novel metal-free Sonogashira coupling using a range of substituted aryl iodides in a solvent- and phosphane-free protocol. Very good to excellent conversions and selectivities were obtained to the cross-coupling products after 24 h+ reaction under conventional heating and the optimised conditions. Microwave irradiation provided comparative yields with improved selectivities with much reduced reaction times (typically 1–2 h). We envisage our novel and exciting results may lead to the development of future metal-free protocols with the use of alternative bases as catalysts in coupling processes.

## Experimental

In a typical metal-free DABCO catalysed Sonogashira coupling, a two-necked flask equipped with a condenser (or alternatively a microwave tube) was charged with the alkyne (phenylacetylene, 1 mmol), DABCO (2 mmol, 224 mg), dodecane (1 mmol, 140 μL) and the desired substituted iodoarene (1 mmol). The reaction mixture was heated/microwaved at 100–130 °C for the required period of time (up to 48 h and 2 h for reactions run under conventional heating and microwave irradiation, respectively) and the colour of the solution gradually turned to deep red-brown. Samples were taken periodically from the reaction mixture and the reaction stopped after 72 h. After cooling down, the extracted sample was filtered off, extracted with dichloromethane (DCM) and analysed by GC/GC-MS. The use of an internal standard technique allows the reaction yields to be determined. All the Sonogashira and dimerisation products were characterised by GC-MS analysis using an Agilent 6890 N GC model equipped with a 7683B series autosampler, fitted with a DB-5 capillary column and an FID detector, and compared with reported analytical data.[5,20,32]

In addition, selected examples (normally those with higher conversions) were isolated and purified by flash chromatography using a cyclohexane (c-Hex) rich/diethylether ($Et_2O$) mixture. In all cases the obtained isolated yields correlated well with the GC yields.

### 4-Fluorodiphenylethyne

Product from entry 5, Table 2: white solid, yield 76%. Mp 108–111 °C. Flash chromatography: c-Hex–$Et_2O$ 98 : 2. GC-MS: 51 (15), 98 (10), 144 (7), 169 (11), 196 (100). $^1$H NMR (300 MHz, $CDCl_3$): 7.52–7.60 (m, 4H), 7.34–7.38 (m, 3H), 7.12–7.15 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): 162.8 (d, $J = 249.8$ Hz), 133.7, 131.6, 128.0, 123.1, 119.5, 115.5, 89.1, 88.7.

### 2-Hydroxydiphenylethyne

Product from entry 7, Table 2: white solid, yield 72%. Mp 45–48 °C. Flash chromatography: c-Hex–$Et_2O$ 90 : 10. GC-MS: 82 (10), 165 (50), 194 (100). $^1$H NMR (300 MHz, $CDCl_3$): 7.22–7.55 (m, 5H), 6.88–7.15 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): 156.2, 131.5, 131.4, 130.0, 128.6, 128.1, 122.3, 120.1, 114.9, 109.7, 96.7, 83.1.

Blank experiments in the absence of DABCO gave no significant coupling yields (<10%) after 48 h. Chemicals were obtained from Aldrich, Merck and Lancaster and used as received. The reactions were highly reproducible and provided very similar results under identical conditions when run several times.

Every single reaction was run with new glassware and stirrer bars to avoid cross-contamination and/or potential contribution of traces of metals in the solution. All reagents were also tested for traces of Pd and other transition metals by means of AAS (Hitachi) and ICP (Perkin-Elmer 40 instrument) and showed no detectable traces of metals (<0.5 ppm).

Microwave experiments were conducted on a CEM-Discover model with PC control and monitored by sampling aliquots of the reaction mixture that were subsequently analysed by GC/GC-MS. Experiments were conducted in a closed vessel (pressure controlled) with continuous stirring. The microwave method was generally power controlled where the samples were irradiated with the required power output (200 W) and temperatures ranged between 120–140 °C depending on the reaction.

Chemicals were bought from Aldrich, Lancaster and Acros Organics and used as purchased.

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