Synthetic Study on 2,2′-(1,4-Phenylene)bis(3-alkyl-1*H*-inden-1-ones): The First Application of a Sodium Enolate as a 'Protecting Group' in the Grignard Reaction

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Abstract: A new series of 2,2′-(1,4-phenylene)bis(3-substituted-1*H*-inden-1-ones) were prepared and their structures were established by ^{1}H and ^{13}C NMR, IR, and HRMS spectroscopy. One molecular structure was further confirmed by single crystal X-ray crystallography. The synthetic mechanism was studied in detail. The key step involves the reaction of the Grignard reagent with the sodium enolate of 2,2′-(1,4-phenylene)bis[1*H*-indene-1,3(2*H*)-dione]. This is the first example of a sodium enolate being employed as the protecting reagent for a carbonyl group in the Grignard reaction.

Key words: 2,2′-(1,4-phenylene)bis(3-alkyl-1*H*-inden-1-one), enols, Grignard reactions, protecting groups, regioselectivity

Biindenylidenedione derivatives, which are derived from 1*H*,1′*H*-2,2′-biindene-1,1′,3,3′(2*H*,2′*H*)-tetrone (**1**, Figure 1), are a class of unique photochromic compounds. They can simultaneously generate stable radicals and undergo photochromism in the crystalline state.[1–5] This property is particularly promising for their potential use in optoelectronic devices.[6,7]

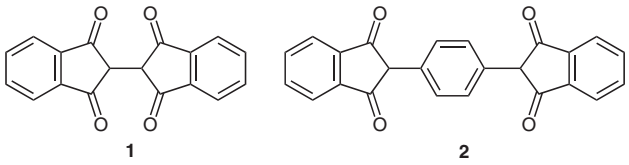
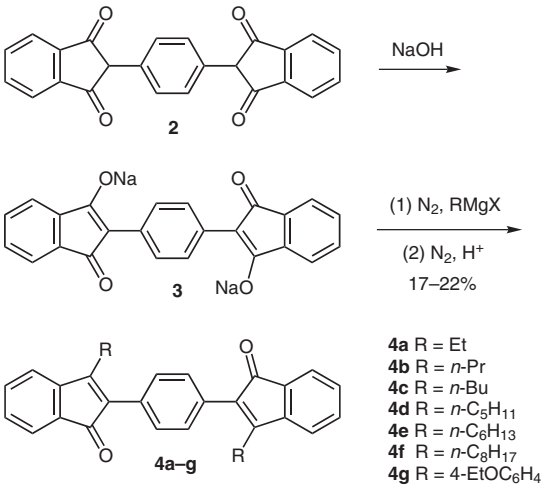


Figure 1

In connection with our previous work and with the aim of expanding the scope of biindenylidenedione derivatives, we extended the conjugated system by embedding a phenylene group in the middle of compound **1** to form 2,2′-(1,4-phenylene)bis[1*H*-indene-1,3(2*H*)-dione] (**2**, Figure 1).[8] In this paper, the reaction between compound **2** and Grignard reagents was studied in detail. A plausible synthetic mechanism was proposed and compared with the reaction mechanism of compound **1** and Grignard reagents. For the first time, we introduced a sodium enolate as the protecting group for a carbonyl group in the Grignard reaction. Through this procedure, a new series of 2,2′-(1,4-phenylene)bis[3-substituted-1*H*-inden-1(2*H*)-ones] **4a**–**g** were synthesized (Scheme 1) and fully characterized by spectroscopy. The structure of one of them, **4a**, was further confirmed by single crystal X-ray crystallography.



Scheme 1

In previous reports,[1–5] compound **1** was reacted with Grignard reagent directly in moderate to good yield, when a similar procedure was employed in the reaction between **2** and a Grignard reagent, no major product was obtained and the byproducts were complex, showing a long line on TLC (Scheme 2). The failure of this reaction may be attributed to the different existence of the forms of **1** and **2**. In compound **1**, the enolic form is highly preferred as the two carbonyl groups and the two neighboring enol hydroxy groups are strongly tied by forming intramolecular hydrogen bonds. When treated with a Grignard reagent, the active hydroxy hydrogen reacts with R^- firstly to release RH, and then, only two positions (the two remaining carbonyl groups in the 3- and 3′-positions) in intermediate **5** can accept the nucleophilic addition of the Grignard reagent, hence the desired product was obtained successfully (Scheme 3). When a similar procedure was employed with compound **2**, the situation was quite different. The favored structure of compound **2** is the keto form (Scheme 2). This can be clearly seen from the color and appearance of **2** in comparison with that of **1**. For **1**, the dark purple color shows the existence of extended conjugation in the enolic form and the good planar properties

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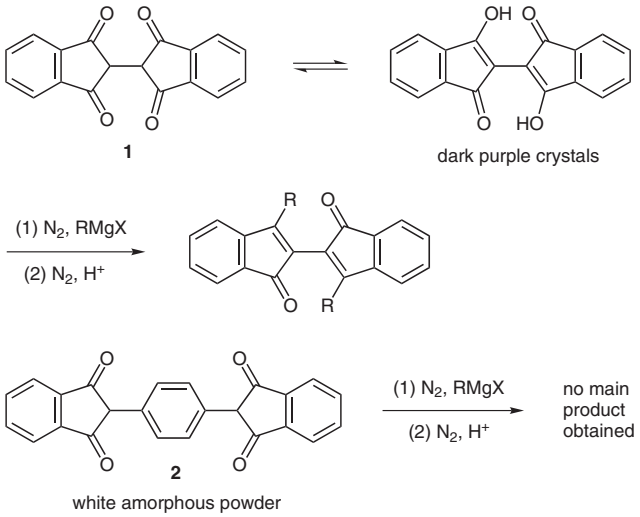
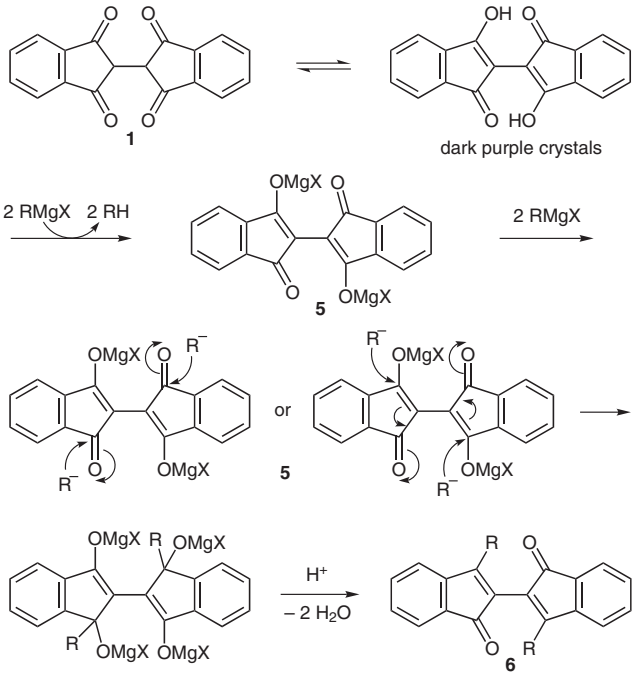
leads to the ease of forming π–π stacking crystals. For **2**, the white color shows that no extended conjugation exists. This can be attributed to a lack of intramolecular hydrogen bonding owing to the embedding of the phenylene group which increases the distance between the enol hydroxy group and the neighboring carbonyl group, thus the enolic form is not sufficiently stable. On the other hand, the existence of two sp^3 carbons in the indanyl ring leads to the torsional structure of **2**, and hence its difficulty in forming crystals. Only amorphous powders can be obtained for **2** despite many attempts at crystallization. When **2** was treated with a Grignard reagent, all four carbonyl groups have the same priority for nucleophilic addition of R^-, thus obviously, the reaction is rather complex and no separable products can be obtained.

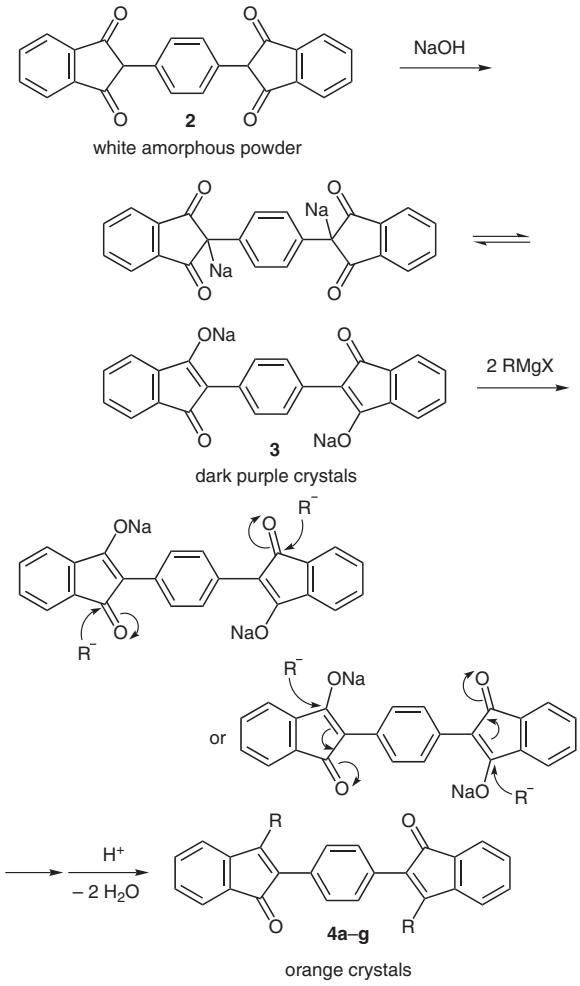


Scheme 2



Scheme 3

The successful regioselective reaction between **1** and a Grignard reagent encouraged us to make a deeper analysis of its reaction mechanism (Scheme 3).[3] We can see that the existence of the enolic form plays an important role in the regioselectively nucleophilic addition. Although compound **2** is difficult to change into its enolic form spontaneously (which is the case for **1**), we can use sodium hydroxide to accomplish the transformation from ketone form **2** to the sodium enolate **3**. The enolate **3** has a very similar structure to intermediate **5**. The reaction of **3** and the Grignard reagent was expected to proceed similarly to that of **5** (Scheme 4). Fortunately, we obtained the desired product **4a** in 22% yield according to our expectations, and its structure was further confirmed by single crystal X-ray crystallography.



Scheme 4

A perspective view of molecule of **4a** with the crystallographic atom numbering is presented in Figure 2. Compound **4a** has central symmetry with two indenone moieties linked by a phenylene group. Two loops of indenone are almost perfectly planar, while the deviation of the planes of the two indenones relative to the plane of the phenylene ring is +47.42° for one ring and –47.42° for the other. This phenomenon may be interpreted by the signif-

icant steric hindrance between the carbonyl or ethyl group in the indanone and the hydrogen atom in phenylene group, and hence only partial conjugation is present in this molecule. This can also be shown by the orange-colored tint of **4a** due to the low extent of the conjugation even though all sp^2 carbon atoms in the indenone and phenylene moieties are linked directly without any interruption.

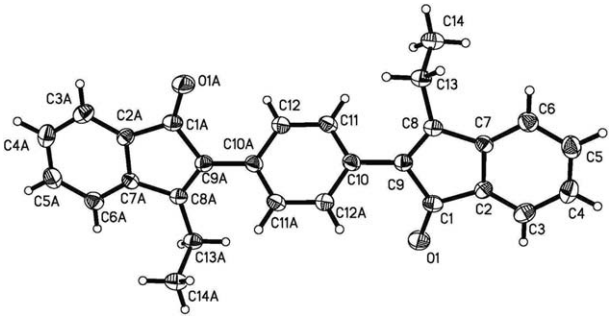


Figure 2

Though the yield is lower, this reaction has fascinated us because this is the first report of a sodium enolate acting as a carbonyl 'protecting group' in the Grignard reaction. We have, therefore, used various alkylmagnesium bromides and 4-methoxyphenylmagnesium bromide to react with **3**, and obtained a new series of the desired 2,2′-(1,4-phenylene)bis[3-substituted-1*H*-inden-1(2*H*)-ones] **4a–g** in reasonable yields (17–22%). After acidification with hydrochloric acid, the unreacted sodium enolate **3** can be reclaimed almost quantitatively to give the keto form **2**, and reclaimed **2** can be reused without any loss of reactivity.

In summary, a new series of 2,2′-(1,4-phenylene)bis[3-substituted-1*H*-inden-1(2*H*)-ones)] were synthesized, and the structure of one of them was further confirmed by single crystal X-ray crystallography. The synthetic mechanism was studied in detail. The results show that the enolic form plays an important role in the reaction between the tetrone and a Grignard reagent. For the first time, a sodium enolate was introduced as a selective carbonyl 'protecting group' in the Grignard reaction. The potential application and derivation from this series of compounds are currently under investigation.

All chemicals were purchased from commercial sources, and solvents were dried by refluxing under N_2 over an appropriate drying agent and distilled prior to use. Compound **2** was synthesized according to the literature.[8] Melting points were determined with a Yanagimoto MP-35 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-P300 and Oxford 400 respectively. MS were recorded on Thermo Finnigan LCQ Advantage spectrometer in ESI mode-I with spray voltage 4.8 kV. HRMS spectra were performed on an Ionspec. 7.0T. FTMS apparatus. IR were recorded on a Nicolet-380-FT-IR spectrophotometer. X-ray data collection was performed on a Bruker SMART 1000 diffractometer with MoKα radiation.

Disodium 2,2′-(1,4-Phenylene)bis(3-oxo-3*H*-inden-1-olate) (3)
Compound **2** (1.83 g, 5 mmol) was added in one portion to a soln of NaOH (0.4 g, 10 mol) in H_2O (10 mL); the mixture was allowed to stir for 5 min. The solvent was removed under reduced pressure. Sodium enolate **3** was obtained almost quantitatively as a dark purple powder and can be used for the next step without further purification.

2,2′-(1,4-Phenylene)bis(3-substituted-1*H*-inden-1-ones) 4a–g; General Procedure
To a soln of alkyl- or arylmagnesium bromide [prepared from bromoalkane (50 mmol) and Mg (40 mmol) in anhyd THF (50 mL)], **3** (5 mmol) suspended in anhyd THF (120 mL) was added portionwise over a period of 10 min. The dark green mixture was refluxed for an additional 6 h under N_2 at which point the mixture turned yellow. The reaction was quenched by the addition of sat. aq NH_4Cl soln (30 mL) and the organic fraction was separated and dried ($MgSO_4$). Filtration and removal of the solvent under reduced pressure afforded crude products **4a–g**, which were purified by column chromatography (silica gel, petroleum–EtOAc, 8:1). Compound **4a** was further crystallized (CH_2Cl_2) to give crystals suitable for X-ray analysis.

2,2′-(1,4-Phenylene)bis(3-ethyl-1*H*-inden-1-one) (4a)
Orange needle-shaped crystals; yield: 22%; mp 207–208 °C.

IR (KBr): 3063, 2965, 2868 (C–H), 1708 (C=O), 1595, 1457, 1339, 1178, 1080, 1054 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.41–7.53 (m, 8 H, ArH), 7.21–7.30 (m, 4 H, ArH), 2.75–2.83 (q, 4 H, 2 CH_2), 1.37 (t, *J* = 7.5 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 13.1, 20.3, 120.1, 122.6, 129.0, 129.5, 130.9, 131.0, 132.6, 133.8, 145.1, 160.4, 197.0.

MS (ESI): *m*/*z* = 413.54 [M + Na]$^+$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{22}NaO_2$: 413.1512; found: 413.1504.

X-ray Crystal Structure of **4a**:[9] Compound **4a** with formula $C_{28}H_{22}O_2$ crystallizes in the triclinic system, space group $P\bar{1}$, with unit cell parameters *a* = 7.801(3), *b* = 8.438(4), *c* = 8.844(4) Å, α = 96.408(7)°, β = 100.485(8)°, γ = 115.993(7)°, *V* = 502.3(4) Å^3, *Z* = 1. A total of 1773 independent reflections [*R*(int) = 0.0321] were collected on a sample (size 0.24 × 0.20 × 0.18 mm) using MoKα radiation (λ = 0.71073 Å) on a Bruker SMART 1000 diffractometer and the q scan mode at r.t. The structure solution and refinement were carried out using the programs SHELXS97[10] and SHELXL97.[11] Final *R* indices for $I > 2\sigma(I)$ were equal *R*1 = 0.0479, *wR*2 = 0.0910, and *R*1 = 0.1094, *wR*2 = 0.1111 for all data. The extinction coefficient was refined and converged to 0.080. The final difference Fourier map of electron density was featureless with the largest peak and hole at 0.132 and –0.173 eA^{-3}, respectively.

2,2′-(1,4-Phenylene)bis(3-propyl-1*H*-inden-1-one) (4b)
Orange needle-shaped crystals; yield: 22%; mp 194–196 °C.

IR (KBr): 3063, 2957, 2863 (C–H), 1704 (C=O), 1602, 1462, 1337, 1181, 1087, 1060 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.40–7.53 (m, 8 H, ArH), 7.29–7.19 (m, 4 H, ArH), 2.71–2.77 (t, *J* = 8.1 Hz, 4 H, 2 CH_2), 1.73–1.80 (m, 4 H, 2 CH_2), 1.05–1.10 (t, *J* = 7.2 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.8, 22.0, 29.1, 120.3, 122.6, 129.1, 129.6, 131.0, 131.9, 133.9, 145.7, 159.2, 197.0.

MS (ESI): *m*/*z* = 441.39 [M + Na]$^+$.

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{26}NaO_2$: 441.1825; found: 441.1825.

2,2′-(1,4-Phenylene)bis(3-butyl-1*H*-inden-1-one) (4c)
Orange crystals; yield: 20%; mp 148–151 °C.

IR (KBr): 3064, 2950, 2930, 2863 (C–H), 1710 (C=O), 1594, 1511, 1457, 1370, 1337, 1175, 1063 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.40–7.52 (m, 8 H, ArH), 7.19–7.29 (m, 4 H, ArH), 2.73–2.78 (t, *J* = 8.1 Hz, 4 H, 2 CH_2), 1.66–1.76 (m, 4 H, 2 CH_2), 1.45–1.52 (m, 4 H, 2 CH_2), 0.94–0.98 (t, *J* = 7.2 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 13.8, 23.1, 26.7, 30.4, 120.0, 122.4, 128.8, 129.3, 130.8, 132.9, 133.6, 145.3, 159.2, 196.7.

MS (ESI): *m*/*z* = 915.20 $[2 M + Na]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{30}NaO_2$: 469.2138; found: 469.2140.

2,2′-(1,4-Phenylene)bis(3-pentyl-1*H*-inden-1-one) (4d)
Orange powder; yield: 17%; mp 122–125 °C.

IR (KBr): 3064, 2955, 2922, 2851 (C–H), 1702 (C=O), 1615, 1590, 1512, 1458, 1366, 1333, 1171, 1076 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.40–7.52 (m, 8 H, ArH), 7.19–7.29 (m, 4 H, ArH), 2.72–2.77 (t, *J* = 7.8 Hz, 4 H, 2 CH_2), 1.68–1.77 (m, 4 H, 2 CH_2), 1.19–1.49 (m, 8 H, 2 CH_2CH_2), 0.89–0.93 (t, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 13.9, 22.4, 26.8, 28.0, 32.1, 120.0, 122.4, 128.8, 129.3, 130.8, 130.9, 133.6, 145.3, 159.2, 196.7.

MS (ESI): *m*/*z* = 497.49 $[M + Na]^+$.

HRMS (QFT-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{35}O_2$: 475.2632; found: 475.2628.

2,2′-(1,4-Phenylene)bis(3-hexyl-1*H*-inden-1-one) (4e)
Orange powder; yield: 17%; mp 129–130 °C.

IR (KBr): 3058, 2960, 2926, 2851 (C–H), 1711 (C=O), 1615, 1590, 1466, 1445, 1379, 1337 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.40–7.52 (m, 8 H, ArH), 7.19–7.29 (m, 4 H, ArH), 2.72–2.77 (t, *J* = 8.1 Hz, 4 H, 2 CH_2), 1.70–1.77 (m, 4 H, 2 CH_2), 1.15–1.48 [m, 12 H, 2 $(CH_2)_3$], 0.87–1.91 (t, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.0, 22.6, 26.9, 28.2, 29.6, 31.9, 120.0, 122.3, 128.8, 129.3, 130.8, 132.8, 133.6, 145.3, 159.1, 196.7.

MS (ESI): *m*/*z* = 525.47 $[M + Na]^+$.

HRMS (QFT-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{39}O_2$: 503.2945; found: 503.2939.

2,2′-(1,4-Phenylene)bis(3-octyl-1*H*-inden-1-one) (4f)
Orange powder; yield: 20%; mp 97–99 °C.

IR (KBr): 3070, 2951, 2913, 2843 (C–H), 1706 (C=O), 1615, 1586, 1466, 1449, 1366, 1292, 1180, 1084 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.40–7.52 (m, 8 H, ArH), 7.19–7.29 (m, 4 H, ArH), 2.72–2.77 (t, *J* = 7.8 Hz, 4 H, 2 CH_2), 1.67–1.77 (m, 4 H, 2 CH_2), 1.47–1.52 (m, 4 H, 2 CH_2), 1.27–1.46 [m, 16 H, 2 $(CH_2)_4$], 0.85–0.90 (t, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.1, 22.6, 27.0, 28.3, 29.2, 29.3, 30.0, 31.8, 120.0, 122.4, 128.8, 129.3, 130.8, 130.9, 132.8, 133.6, 145.3, 159.2, 196.7.

MS (ESI): *m*/*z* = 1139.06 $[2 M + Na]^+$.

HRMS (QFT-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{40}H_{47}O_2$: 559.3570; found: 559.3568.

2,2′-(1,4-Phenylene)bis-[3(4-ethoxyphenyl)-1*H*-inden-1-one] (4g)
Red crystals; yield: 20%; mp 292–294 °C.

IR (KBr): 3064, 2988, 2930 (C–H), 1702 (C=O), 1599, 1503, 1474, 1453, 1387, 1337, 1283, 1254, 1171, 1109, 1043 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.28–7.58 (m, 12 H, ArH), 6.88–7.21 (m, 8 H, ArH), 4.03–4.10 (q, 4 H, 2 CH_2), 1.42–1.46 (t, *J* = 7.2 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.8, 63.5, 114.7, 121.2, 122.8, 124.7, 128.9, 129.0, 129.6, 130.2, 130.3, 130.4, 133.2, 145.7, 155.4, 185.6.

MS (ESI): *m*/*z* = 575.37 $[M + H]^+$.

HRMS (MALDI) *m*/*z* $[M + Na]^+$ calcd for $C_{40}H_{30}NaO_4$: 597.2036; found: 597.2039.

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