One-pot three-component access to pyranocyclopentendiones

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An efficient synthesis of dialkyl 2-(alkylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[*b*]pyran-3,4-dicarboxylates from one-pot three-component reaction of the zwitterions generated from dialkyl acetylenedicarboxylates and alkyl isocyanides with 3,5-diphenylcyclopentane-1,2,4-trione is described.

Keywords: acetylenic ester, CH-acid, Huisgen zwitterions, isocyanide, multicomponent reaction

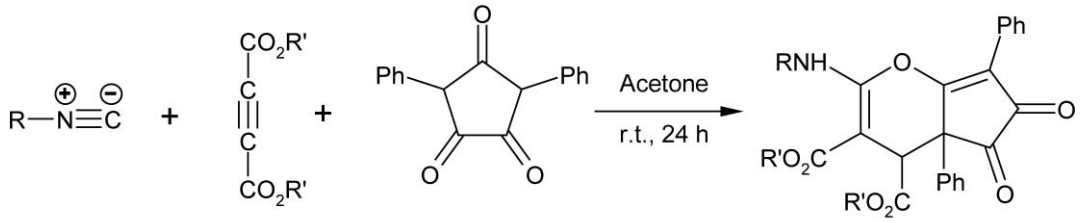
Multicomponent reactions (MCRs) constitute excellent manifolds to generate molecular complexity and have received considerable attention due to their high efficiency in the synthesis of organic building blocks from the easily available starting materials.[1–4] Unlike the usual stepwise formation of individual bonds in the target molecule, the most attractive attribute of MCRs is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding further reagents.

The reaction of nucleophiles with activated acetylenes for C–C bond formation is of great significance in organic synthesis.[5] The electron-deficient alkynes are often used as Michael acceptors for the formation of carbon-carbon bonds and recent studies on the chemistry of heterocycles via conjugate addition of C-, N- and P-nucleophiles have uncovered a number of interesting reactions.[6–8] Extensive work has been done by many groups on the reactivities of Huisgen zwitterions derived from activated acetylenic compounds and isocyanides.[9] Recently, these highly reactive 1,4-dipolar intermediates have been captured by suitable CH-,[10–12] NH-,[13–15] and OH-acid[16–18] substrates. These studies have led to a number of interesting carbon–carbon bond forming reactions and heterocyclic constructions.

In connection with our recent interest aimed at the efficient preparation of biologically active heterocycles *via* isocyanide-based multicomponent reactions involving acidic substrates,[18,19] we now report the facile synthesis of some new pyranocyclopentendione heterocycles. 3,5-Diphenylcyclopentane-1,2,4-trione is a very interesting carbocyclic compound, which has two rather acidic protons. This was used advantageously in the formation of polyfunctional pyranocyclopentendione derivatives incorporating the 4,4a-dihydrocyclopenta[*b*] pyran-5,6-dione substructure via a three-component condensation reaction of isocyanides.

The one-pot, three-component condensation reactions of alkyl isocyanides **1** with dialkyl acetylenedicarboxylates **2** in the presence of 3,5-diphenylcyclopentane-1,2,4-trione **3** proceeded at room temperature in dry acetone and were complete after 24 hours to afford corresponding dialkyl 2-(alkylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[*b*]pyr an-3,4-dicarboxylates **4** in 59–83% yields and the full results are summarized in Scheme 1. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of fused pyranocyclopentendione **4**. Any other products could not be detected by NMR spectroscopy.

The structures of the products **4a–h** were deduced from their elemental analyses and IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4a** exhibited four single sharp lines readily recognised as arising from *tert*-butyl (δ_H 1.35 ppm), two methoxy protons (δ_H 3.63 and 3.68 ppm), and allylic methine (δ_H 4.76 ppm) along with multiplets for the 10 aromatic protons (δ_H 7.29–7.80). A fairly broad singlet



1 **2** **3** **4**

	R	R'
1a	*tert*-Butyl	**2a** Methyl
1b	Cyclohexyl	**2b** Ethyl
1c	*tert*-Octyl	
1d	Benzyl	

	R	R'	Yield (%)
4a	*tert*-Butyl	Methyl	75
4b	Cyclohexyl	Methyl	83
4c	*tert*-Octyl	Methyl	78
4d	Benzyl	Methyl	70
4e	*tert*-Butyl	Ethyl	72
4f	Cyclohexyl	Ethyl	77
4g	*tert*-Octyl	Ethyl	66
4h	Benzyl	Ethyl	59

Scheme 1

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(δ_H 8.90 ppm) was observed for the NH group. The presence of an amine proton was confirmed by exchange with D_2O. The chemical shift of the NH group indicates that this moiety must have participated in a six-membered intramolecular hydrogen bond formation with the vicinal carbonyl group.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 22 distinct resonances, which confirmed the proposed structure. The characteristic signal due to the allylic methine carbon was discernible at δ_C 73.8 ppm and four carbonyl groups were resonated at δ_C 192.9, 185.6, 172.3 and 172.1 ppm. Partial assignment of these resonances is given in the Experimental section.

The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compound **4a** was supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorptions at 1774, 1723, 1668 and 1629 cm^{-1} due to the carbonyls and the amino group at 3168 cm^{-1} as a weak broad band.

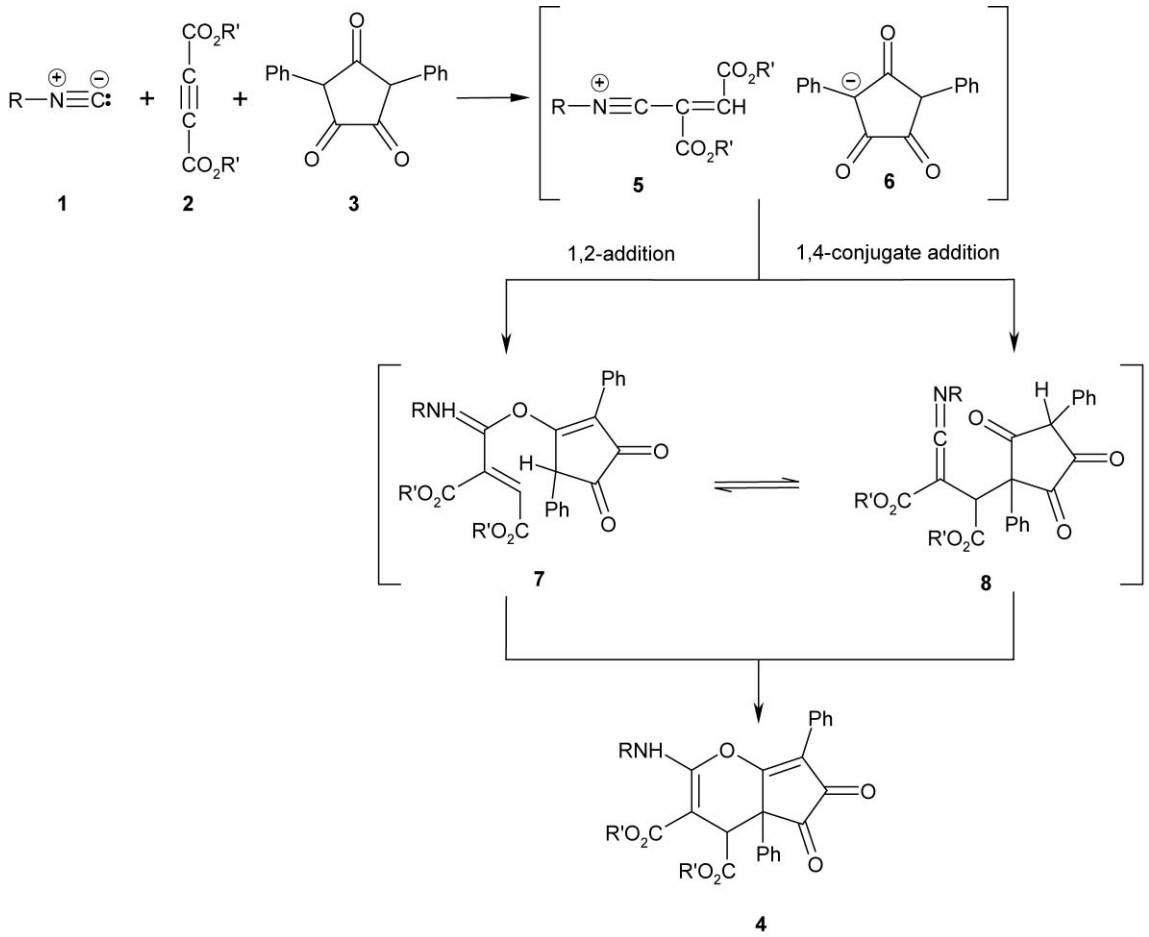
The scope and limitations of this three-component reaction were explored by using three dialkyl acetylenedicarboxylates and four alkyl isocyanides. The results show that the three-component reaction is quite general with dialkyl acetylenedicarboxylates affording the expected pyranocyclopentendione **4** in good yields. Note that even moderate yields are synthetically useful because these reactions form complex structures and a number of bonds are formed. Also, we examined the scope of reactive isocyanides in the three-component reaction. As shown in Scheme 1, a variety of structurally diverse alkyl isocyanides are used in this protocol with good results.

The mechanism of this reaction has not been established experimentally, a likely mechanism for the formation of these heterocycles **4** is shown in Scheme 2. In a first step, nucleophilic attack of the isocyanide on to the acetylenic ester and subsequent protonation of the highly reactive 1:1 zwitterionic intermediate by CH-acid (3,5-diphenylcyclopentane-1,2,4-trione) affords the vinylisonitrilium cation **5**. Then, vinylisonitrilium cation **5** could undergo addition reactions with the conjugate base of the CH-acid **6** at the two possible electrophilic sites (1,2-addition and 1,4-conjugate addition) to produce two possible intermediates **7** and **8** in equilibrium with each other. These intermediates can then cyclise under the reaction conditions employed to produce the dialkyl 2-(alkylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[*b*]pyran-3,4-dicarboxylates **4**.

In summary, the three-component reactions of alkyl isocyanides, dialkyl acetylenedicarboxylates and 3,5-diphenylcyclopentane-1,2,4-trione were achieved under mild conditions, providing a convenient method for the synthesis of dialkyl 2-(alkylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[*b*]pyran-3,4-dicarboxylates. Using this method, a series of fused pyranocyclopentendione were synthesized from commercially easily available starting materials.

Experimental

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an elementar vario EL *III* instrument. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 400.13 and 100.77 MHz, respectively, with $CDCl_3$ as solvents and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in parts per million relative to TMS as internal reference. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualised with UV light. All chemical reagents were



Scheme 2

obtained from Aldrich, Merck or Acros and were used without further purification.

Preparation of **4a***; typical procedure*

To a magnetically stirred solution of 3,5-diphenylcyclopentane-1,2,4-trione (0.264 g, 1.0 mmol) and *tert*-butyl isocyanide (0.084 g, 1.0 mmol) in dry acetone (20 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.142 g, 1.0 mmol) in acetone (2 ml) at room temperature over 10 min *via* a syringe. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the solid residue was washed with diethyl ether and crystallised from CH_2Cl_2: *n–h*exane (1:5) to give **4a** as a yellow powder (0.368 g, 75%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

Dimethyl 2-(tert-bytylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4a**): M.p. 166–168 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3168 (N–H), 1774, 1723, 1668 and 1629 (C=O), 1493 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 1.35 (9 H, s, $C(CH_3)_3$), 3.63 and 3.68 (6 H, 2 s, 2 OCH_3), 4.76 (1 H, s, NCH), 7.29–7.80 (10 H, m, 2 C_6H_5), 8.90 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): δ_C 192.9, 185.6, 172.3, 172.1, 169.1, 159,3, 134.1, 129.7, 129.4, 129.0, 128.9, 128.6, 127.5, 127.2, 126.3, 77.3, 73.8, 53.2, 52.8, 51.6, 42.8, 30.4. Anal. Calcd for $C_{28}H_{27}NO_7$ (489.51): C, 68.70; H, 5.56; N, 2.86. Found: C, 68.47; H, 5.60; N, 2.88%.

The synthesis of **4b–h** was performed under similar conditions as for **4a**.

Dimethyl 2-(cyclohexylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4b**): Yellow powder (0.428 g, 83%); m.p. 181–183 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3256 (N–H), 1769, 1719 and 1676 (C=O), 1495 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 1.99–2.01 (10 H, m, 5 CH_2), 3.62 and 3.84 (6 H, 2 s, 2 OCH_3), 3.74 (NHC*H*), 4.70 (1 H, s, NCH), 7.25–7.97 (10 H, m, 2 C_6H_5), 8.60 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): 192.7, 185.4, 172.4, 172.3, 168.9, 157.8, 134.4, 129.5, 129.3, 128.9, 128.6, 128.3, 127.7, 126.4, 126.3, 77.2, 72.8, 52.8, 51.5, 51.1, 50.9, 42.8, 34.0, 33.4, 25.3, 24.7. Anal. Calcd for $C_{30}H_{29}NO_7$ (515.55): C, 69.89; H, 5.67; N, 2.72. Found: C, 70.24; H, 5.64; N, 2.70%.

Dimethyl 2-[(1,1,3,3-tetramethylbutyl)amino]-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4c**): Yellow powder (0.426 g, 78%); m.p. 196–198 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3437 (N–H), 1763, 1726 and 1673 (C=O), 1495 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 0.82 (9 H, s, $C(CH_3)_3$), 1.36 and 1.37 (6 H, 2 s, $C(CH_3)_2$), 1.48 and 1.78 (2 H, AB system, $^2J_{HH}$ = 15.0 Hz, CH_2), 3.63 and 3.69 (6 H, 2 s, 2 OCH_3), 4.77 (1 H, s, NCH), 7.31–7.74 (10 H, m, 2 C_6H_5), 8.95 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): δ_C 192.9, 185.6, 172.3, 172.2, 169.1, 159.0, 134.1, 129.5, 129.3, 128.9, 128.6, 127.9, 127.2, 126.4, 77.4, 73.5, 56.9, 53.0, 52.8, 51.6, 50.9, 42.4, 31.5, 31.1, 30.9. Anal. Calcd for $C_{32}H_{35}NO_7$ (545.62): C, 70.44; H, 6.47; N, 2.57. Found: C, 70.21; H, 6.51; N, 2.55%.

Dimethyl 2-(benzylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4d**): Yellow powder (0.367 g, 70%); m.p. 160–162 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3155 (N–H), 1770, 1727 and 1666 (C=O), 1500 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 3.66 and 3.71 (6 H, 2 s, 2 OCH_3), 4.36 and 4.40 (2 H, AB system, $^2J_{HH}$ = 14.8 Hz, $NHCH_2Ph$), 4.80 (1 H, s, NCH), 7.20–8.07 (10 H, m, 3 C_6H_5), 8.96 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): δ_C 190.1, 185.3, 173.1, 172.5, 169.8, 159.7, 138.6, 134.5, 129.5, 129.2, 129.0, 128.9, 128.7, 128.5, 127.9, 127.8, 127.1, 126.8, 126.5, 77.5, 74.3, 53.1, 52.8, 48.5, 43.2. Anal. Calcd for $C_{31}H_{25}NO_7$ (523.53): C, 71.12; H, 4.81; N, 2.68. Found: C, 70.91; H, 4.78; N, 2.70%.

Diethyl2-(tert-butylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4e**): Yellow powder (0.373 g, 72%); m.p. 178–180 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3210 (N–H), 1769, 1721 and 1670 (C=O), 1498 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 1.19 and 1.22 (6 H, 2 t, $^3J_{HH}$ = 7.0 Hz, 2 -CH_2CH_3), 1.33 (9 H, s, $C(CH_3)_3$), 4.08–4.19 (4 H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 4.81 (1 H, s, NCH), 7.30–8.02 (10 H, m, 2 C_6H_5), 8.86 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): δ_C 192.1, 184.7, 172.2, 172.0, 169.6, 159,1, 134.2, 129.5, 129.2, 129.1, 128.7, 128.3, 127.8, 127.1, 125.9, 77.3, 74.1, 62.0, 60.7, 52.2, 42.7, 30.6, 14.1, 13.9. Anal. Calcd for $C_{30}H_{31}NO_7$ (517.56): C, 69.62; H, 6.04; N, 2.71. Found: C, 69.91; H, 6.10; N, 2.68%.

Diethyl 2-(cyclohexylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4f**): Yellow powder (0.419 g, 77%); m.p. 201–203 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3193 (N–H), 1770, 1726 and 1668 (C=O), 1500 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 1.20 and 1.24 (6 H, 2 t, $^3J_{HH}$ = 7.0 Hz, 2 –CH_2CH_3), 2.01–2.11 (10 H, m, 5 CH_2), 3.72 (NHC*H*), 4.06–4.14 (4 H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 4.76 (1 H, s, NCH), 7.14–7.88 (10 H, m, 2 C_6H_5), 8.84 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): 192.9, 184.8, 172.5, 172.3, 169.0, 157.5, 134.6, 129.4, 129.3, 129.0, 128.7, 128.1, 127.7, 126.4, 126.2, 77.4, 72.5, 62.1, 61.7, 51.6, 50.6, 42.8, 34.2, 33.5, 25.3, 24.9, 14.6, 14.1. Anal. Calcd for $C_{32}H_{33}NO_7$ (543.60): C, 70.70; H, 6.12; N, 2.58. Found: C, 70.58; H, 6.08; N, 2.55%.

Diethyl 2-[(1,1,3,3-tetramethylbutyl)amino]-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4g**): Yellow powder (0.379 g, 66%); m.p. 209–211 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3367 (N–H), 1759, 1723 and 1680 (C=O), 1492 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 0.84 (9 H, s, $C(CH_3)_3$), 1.19 and 1.26 (6 H, 2 t, $^3J_{HH}$ = 7.0 Hz, 2 -CH_2CH_3), 1.39 and 1.40 (6 H, 2 s, $C(CH_3)_2$), 1.46 and 1.75 (2 H, AB system, $^2J_{HH}$=14.9 Hz, CH_2), 4.10–4.15 (4 H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 4.85 (1 H, s, NCH), 7.26–7.72 (10 H, m, 2 C_6H_5), 8.90 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): δ_C 192.5, 185.5, 172.4, 172.1, 168.8, 159.2, 134.0, 129.7, 129.3, 129.0, 128.7, 127.6, 127.1, 126.7, 77.3, 74.0, 62.3, 61.6, 57.2, 53.1, 52.1, 42.6, 31.9, 31.1, 30.9, 14.3, 14.0. Anal. Calcd for $C_{34}H_{39}NO_7$ (573.67): C, 71.18; H, 6.85; N, 2.44. Found: C, 70.97; H, 6.78; N, 2.41%.

Diethyl 2-(benzylamino)-5,6-dioxo-4a,7-diphenyl-4,4a,5,6-tetrahydrocyclopenta[b]pyran-3,4-dicarboxylate (**4h**): Yellow powder (0.326 g, 59%); m.p. 202–204 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3230 (N–H), 1766, 1721 and 1670 (C=O), 1493 (C=C); ^{1}H NMR ($CDCl_3$): δ_H 1.21 and 1.24 (6 H, 2 t, $^3J_{HH}$ = 7.0 Hz, 2 -CH_2CH_3), 4.09–4.15 (4 H, m, 2 ABX_3 overlapping systems, 2 OCH_2CH_3), 4.33 and 4.38 (2 H, AB system, $^2J_{HH}$ = 15.0 Hz, $NHCH_2Ph$), 4.72 (1 H, s, NCH), 7.23–8.10 (10 H, m, 3 C_6H_5), 9.01 (1 H, br s, NH…O=C); ^{13}C NMR ($CDCl_3$): δ_C 190.2, 186.0, 172.9, 172.5, 169.9, 159.9, 137.7, 134.3, 129.5, 129.2, 129.1, 128.9, 128.6, 128.5, 128.0, 127.4, 127.0, 126.6, 126.5, 77.4, 73.6, 62.3, 62.0, 48.5, 43.2, 14.3, 13.9. Anal. Calcd for $C_{33}H_{29}NO_7$ (551.58): C, 71.86; H, 5.30; N, 2.54. Found: C, 71.57; H, 5.27; N, 2.56%.

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