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Studies on triacetic acid lactone-annulated heterocycles: synthesis of 3-aryloxyacetyl-6-methyl-2,3-dihydrothieno-[3,2-*c*]pyran-4-ones by tandem cyclization

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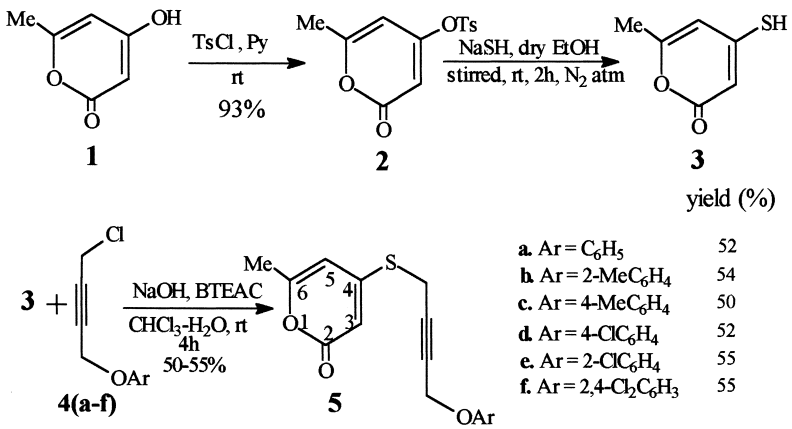
Abstract—The hitherto unreported 3-aryloxyacetyl-6-methyl-2,3-dihydrothieno[3,2-*c*]pyran-4-ones were synthesized in 62–71% yield by the sulfoxide rearrangement of 4-(4′-aryloxybut-2′-ynylthio)-6-methyl-2-pyrone. The substrates were synthesized by phase-transfer-catalysed alkylation of the hitherto unreported 4-mercapto-6-methylpyran-2-one.

1. Introduction

4-Hydroxy-6-methyl-2-pyrone (triacetic acid lactone) **1** is a natural product of polyketide origin.[1] It may also be obtained by deacetylation of dehydroacetic acid.[2] Many natural products containing the basic structures of 4-hydroxy or (methoxy)-6-methyl-2-pyrone have been isolated, some of them carrying biogenetically plausible groups at C3 or C5 or both. Elasnin, isolated from *Streptomyces* sp., for example, is a specific inhibitor of human leucocyte elastase, an enzyme involved in inflammatory processes such as pulmonary emphysema.[3] As a logical extension, many more simple pyrones structurally related to elasnin have been synthesized and evaluated as inhibitors of several elastases.[4] Some 4-hydroxy-2-pyrones have also been tested as anticoagulant agents.[5] In continuation of our work on the synthesis of bioactive heterocycles by the application of [2,3] sigmatropic rearrangements[6–10] we became interested in incorporating the 4-hydroxy-6-methyl-2-pyrone system in the substrates in order to achieve the synthesis of new heterocycles.

2. Results and discussion

The starting materials for this investigation, 4-(4′-aryloxy-but-2′-ynylthio)-6-methylpyran-2-ones **5a–f** were synthesized in 50–55% yields by the treatment of 4-mercapto-6-methylpyran-2-one **3** with 1-aryloxy-4-chlorobut-2-yne **4a–f** at room temperature under phase-transfer catalysis condition using benzyl triethyl ammonium chloride (BTEAC). Compound **3**, in turn, was prepared by the



Scheme 1.

Keywords: [2,3] sigmatropic rearrangement; regioselective synthesis; Claisen rearrangement; phase-transfer catalysis.

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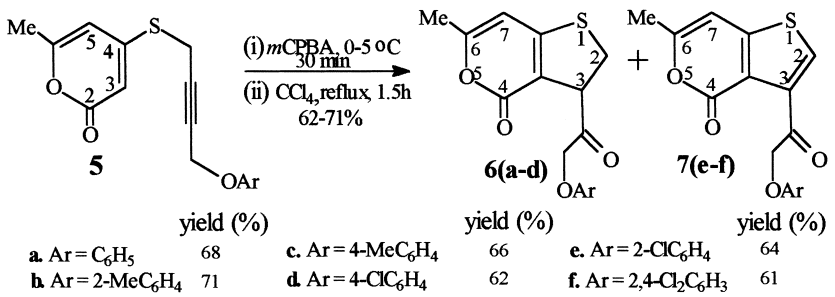


Scheme 2.

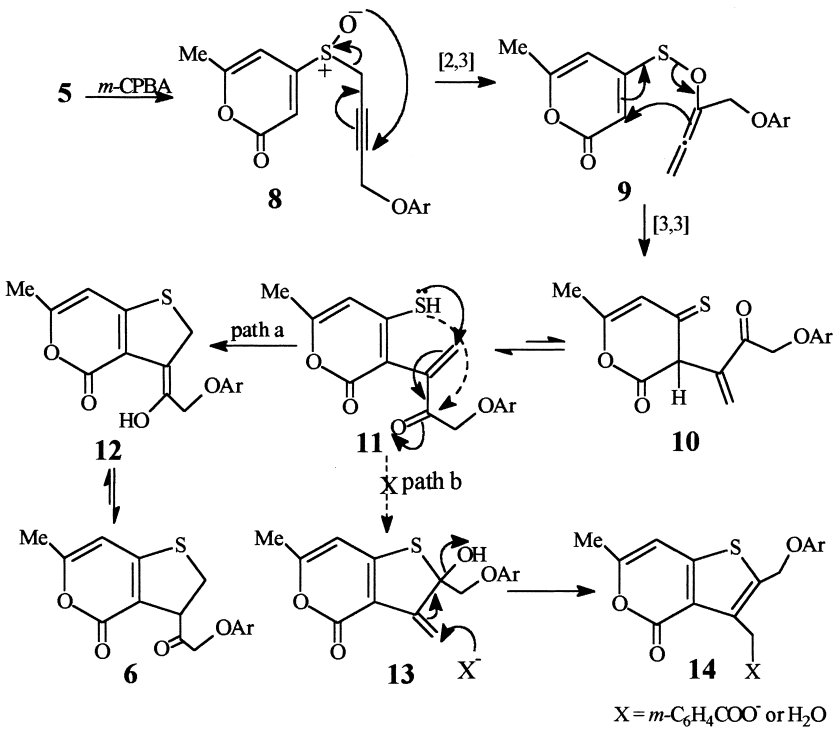
reaction of 6-methyl-4-tosyloxypyran-2-one[11] **2** with NaSH in dry ethanol at room temperature under a nitrogen atmosphere (Scheme 1).

Substrates **5a–f** contain a suitably placed alkynyl segment so as to allow the occurrence of a [2,3] sigmatropic rearrangement in the corresponding sulfoxides. With this end in view, compound **5a** was treated with *m*-chloroperoxybenzoic (*m*-CPBA) acid at 0–5°C in chloroform solution. A spot corresponding to a highly polar compound appeared on TLC as soon as the addition of *m*-CPBA to compound **5a** was started. Compound **5a** was completely converted to this newly developed spot in 0.5 h. During hydrolytic work up, another new spot appeared on TLC but the conversion was only partial. The solvent was removed from this mixture of compounds and the reaction was refluxed in dry carbon tetrachloride. Complete conversion required 1.5 h (Scheme 2).

A compound corresponding to this new spot was isolated and shown to be **6a** from its elemental analysis and spectral data. The ^{1}H NMR spectrum of compound **6a** displayed two one-proton doublet of doublets at δ 3.55 (J=9, 12 Hz) and δ 3.70 (J=6, 12 Hz) indicating the presence of two C_2–*H*. The C_3–*H* appeared as another one-proton double doublet at δ 4.59 (J=6, 9 Hz). Two one-proton doublets at δ 4.87 (J=17 Hz) and 4.91 (J=17 Hz) showed the presence of the aryloxymethylene protons adjacent to ketonic carbonyl group at C_3.

The formation of **6** from **5** may be mechanistically interpreted as depicted in Scheme 3. [2,3] Sigmatropic rearrangement in the sulfoxide **8** may give the allenyl derivative **9**. Occurrence of [3,3] sigmatropic rearrangement in **9** may generate the intermediate **10** which may undergo tautomerization to **11**. Intermediate **11** has a nucleophilic –SH functionality favourably juxtaposed to an α,β-enone moiety so as to allow a Michael-type addition to produce compound **6**. (pathway a, Scheme 3).

Another mode of cyclization[9,12,13] (pathway b) may also be operative in the intermediate **11**. Thus, –SH can deliver its nucleophilic attack to the carbonyl carbon of the enone moiety leading to the allylic alcohol **13**. S_N2' attack of



Scheme 3.

water[12] or *m*-chlorobenzoate[9,13] ion on **13** may give rise to compound **14**. However, we did not obtain compound **14** in any case.

Substrates **5a–d** gave compounds **6a–d**. Surprisingly the corresponding oxidized compounds **7e** and **f** were achieved from substrates **5e** and **f**. These were also characterized from their elemental analysis and spectral data. The ^{1}H NMR spectrum of compound **7e** revealed two one-proton singlets at δ 7.73 and δ 6.54 assignable to C_2–*H* and C_7–*H*, respectively, a two-proton singlet at δ 5.32 due to aryloxymethylene protons, a three-proton singlet at δ 2.35 owing to C_6–*Me* and a four-proton complex multiplet at δ 6.86–7.31 assignable to four aromatic protons. However, the reason for the tendency of compounds **6e** and **f** to get oxidized is not clear.

The reaction displayed appreciable generality and regioselectivity. This can be treated as a mild and direct method for synthesizing fused thienopyrone polyheterocycles.

3. Experimental

Melting points were measured on a sulphuric acid bath and are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200-20 Spectrophotometer. IR spectra were run on KBr disks on a Perkin–Elmer 1330 apparatus. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard on a Bruker DPX-300 (300 MHz) instrument. Elemental analyses and recording of mass spectra were carried out by RSIC(CDRI) Lucknow on a [JEOL D-300 (El)] instrument. Silica gel (60–120 mesh), Spechrochem, India, was used for chromatographic separation. Petroleum ether refers to the fraction boiling between 60 and 80°C.

3.1. Synthesis of 4-mercapto-6-methylpyran-2-one 3

To a magnetically stirred solution of NaSH (2.30 g, 40 mmol) in dry ethanol (50 mL), a solution of 6-methyl-4-tosyloxypyran-2-one[11] **2** (2.8 g, 10 mmol) in dry ethanol was added dropwise at room temperature under nitrogen atmosphere over a period of 30 min. Stirring was continued for additional 2 h after the completion of addition. Ethanol was removed in vacuo at room temperature. The residue was acidified with conc. HCl (20 mL). This was extracted with chloroform (4×25 mL). The chloroform solution was washed with water (2×20 mL) and dried (Na_2SO_4). Attempt to evaporate chloroform led to considerable decomposition of compound **3**. So this chloroform solution was directly used for the subsequent phase-transfer-catalysed alkylations.

3.2. General procedure for the synthesis of compounds 5a–f

To a mixture of 4-mercapto-6-methylpyran-2-one (**3**) (obtained from 2.8 g, 10 mmol of compound **2**) and 1-aryloxy-4-chlorobut-2-yne (10 mmol) (**4a–f**) in chloroform (100 mL) was added a solution of benzyl triethyl ammonium chloride (BTEAC, 0.5 g, 1.8 mmol) in 1% aqueous NaOH (100 mL) and the mixture was magnetically stirred at room temperature for 4 h. The reaction mixture was then diluted with water (50 mL). Chloroform layer was separated and washed with 2N HCl (20 mL), brine (20 mL), water (20 mL) and dried (Na_2SO_4). Evaporation of chloroform left a gummy residue which was subjected to column chromatography. Elution of the column with benzene–ethyl acetate (9:1) afforded compounds **5a–f**. All the compounds **5a–f** were recrystallised from chloroform–petroleum ether. The yields were calculated with respect to the quantity of compound **2** used for the preparation of compound **3**.

3.2.1. 4-(4-Phenoxybut-2-ynylthio)-6-methyl-2-pyrone (5a). 1.48 g, 52%. Pale brown solid, mp 78–80°C. [Found: C, 67.32; H, 4.98. $C_{16}H_{14}O_3S$ requires C, 67.13; H, 4.89%]; R_f (10% ethyl acetate/benzene) 0.39; λ_{max} 220, 269, 302 nm; ν_{max} (KBr) 1700, 1610, 1475, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H, C_6–C*H*$_3$), 3.67 (s, 2H, –SC*H*$_2$), 4.69 (s, 2H, –OC*H*$_2$), 5.82 (s, 1H, C_3–*H*), 5.94 (s, 1H, C_5–*H*), 6.91–7.31 (m, 5H, Ar*H*); *m*/*z* 286 (M^+).

3.2.2. 4-[4-(2′-Methylphenoxybut-2-ynylthio)]-6-methyl-2-pyrone (5b). 1.62 g, 54%. Pale brown solid, mp 77–79°C. [Found: C, 68.25; H, 5.51. $C_{17}H_{16}O_3S$ requires C, 68.00; H, 5.33%]; R_f (10% ethyl acetate/benzene) 0.38; λ_{max} 221, 270, 302 nm; ν_{max} (KBr) 1700, 1620, 1470, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H, –C*H*$_3$), 2.22 (s, 3H, –C*H*$_3$), 3.67 (s, 2H, –SC*H*$_2$), 4.71 (s, 2H, –OC*H*$_2$), 5.82 (s, 1H, C_3–*H*), 5.94 (s, 1H,C_5–*H*), 6.86–7.16 (m, 4H, Ar*H*); *m*/*z* 300 (M^+).

3.2.3. 4-[4-(4′-Methylphenoxybut-2-ynylthio)]-6-methyl-2-pyrone (5c). 1.50 g, 50%. Pale brown solid, mp 71–72°C. [Found: C, 68.21; H, 5.48. $C_{17}H_{16}O_3S$ requires C, 68.00; H, 5.33%]; R_f (10% ethyl acetate/benzene) 0.39; λ_{max} 222, 270, 302 nm; ν_{max} (KBr) 1700, 1620, 1485, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H, –C*H*$_3$), 2.28 (s, 3H, –C*H*$_3$), 3.66 (s, 2H, –SC*H*$_2$), 4.66 (s, 2H, –OC*H*$_2$), 5.82 (s, 1H, C_3–*H*), 5.93 (s, 1H,C_5–*H*), 6.81 (d, *J*=9 Hz, 2H, Ar*H*), 7.06 (d, *J*=9 Hz, 2H, Ar*H*); *m*/*z* 300 (M^+).

3.2.4. 4-[4-(4′-Chlorophenoxybut-2-ynylthio)]-6-methyl-2-pyrone (5d). 1.65 g, 52%. Pale brown solid, mp 76–78°C. [Found: C, 60.12; H, 4.26. $C_{16}H_{13}ClO_3S$ requires C, 59.90; H, 4.05%]; R_f (10% ethyl acetate/benzene) 0.39; λ_{max} 224, 271, 303 nm; ν_{max} (KBr) 1700, 1620, 1480, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.20 (s, 3H, C_6–C*H*$_3$), 3.66 (s, 2H, –SC*H*$_2$), 4.67 (s, 2H, –OC*H*$_2$), 5.81 (s, 1H, C_3–*H*), 5.91 (s, 1H,C_5–*H*), 6.84 (d, *J*=9 Hz, 2H, Ar*H*), 7.21 (d, *J*=9 Hz, 2H, Ar*H*); *m*/*z* 320, 322 (M^+).

3.2.5. 4-[4-(2′-Chlorophenoxybut-2-ynylthio)]-6-methyl-2-pyrone (5e). 1.75 g, 55%. Pale brown solid, mp 112–113°C. [Found: C, 60.14; H, 4.21. $C_{16}H_{13}ClO_3S$ requires C, 59.90; H, 4.05%]; R_f (10% ethyl acetate/benzene) 0.38; λ_{max} 221, 271, 302 nm; ν_{max} (KBr) 1700, 1630, 1475, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H, C_6–C*H*$_3$), 3.66 (s, 2H, –SC*H*$_2$), 4.78 (s, 2H, –OC*H*$_2$), 5.82 (s, 1H, C_3–*H*), 5.92 (s, 1H,C_5–*H*), 6.91–7.38 (m, 4H, Ar*H*); *m*/*z* 320, 322 (M^+).

3.2.6. 4-[4-(2′,4′-Dichlorophenoxybut-2-ynylthio)]-6-methyl-2-pyrone (5f). 1.95 g, 55%. Pale brown solid, mp 140–141°C. [Found: C, 54.32; H, 3.54. $C_{16}H_{12}Cl_2O_3S$

requires C, 54.08; H, 3.38%]; R_f (10% ethyl acetate/benzene) 0.39; λ_{max} 222, 270, 301 nm; ν_{max} (KBr) 1700, 1620, 1470, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.21 (s, 3H, C_6-CH_3), 3.66 (s, 2H, $-SCH_2$), 4.77 (s, 2H, $-OCH_2$), 5.81 (s, 1H, C_3-H), 5.90 (s, 1H,C_5-H), 6.92 (d, J=9 Hz, 1H, Ar*H*), 7.16 (dd, J=9, 3 Hz, 1H, Ar*H*), 7.36 (d, J=3 Hz, 1H, Ar*H*); *m/z* 354, 356, 358 (M^+).

3.3. General procedure for the preparation of compounds 6a–d and 7e and f

m-Chloroperoxybenzoic acid (50%, 210 mg, 1.22 mmol) in chloroform (20 mL) was slowly added to a well-stirred solution of the sulfides **5a–f** (0.6 mmol) in chloroform (25 mL) at 0–5°C over a period of 30 min. The reaction mixture was stirred for additional 30 min. Then the chloroform solution was washed with saturated sodium carbonate solution (3×20 mL) to remove the organic acid followed by brine (3×20 mL), H_2O (3×20 mL) and dried (Na_2SO_4). At this time, the solution assumed a pale yellow colour. The solvent was removed and the residue was refluxed in carbon tetrachloride (25 mL) for 1.5 h. Then carbon tetrachloride was distilled off and a viscous liquid was obtained. It was then chromatographed over silica gel using benzene as eluent to give compounds **6a–d** as viscous oil and **7e** and **f** as white solid.

3.3.1. Compound 6a. 120 mg, 68%. Viscous oil. [Found: C, 63.41; H, 4.50. $C_{16}H_{14}O_4S$ requires C, 63.57; H, 4.63%]; R_f (benzene) 0.39; λ_{max} 220, 309 nm; ν_{max} (neat) 1260, 1490, 1600, 1710, 2920 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.25 (s, 3H, C_6-CH_3), 3.55 (dd, J=9, 12 Hz, 1H, C_2-H), 3.70 (dd, J=6, 12 Hz, 1H, C_2-H), 4.59 (dd, J=6, 9 Hz, 1H, C_3-H), 4.87 (d, J=17 Hz, 1H, $-OCH_2$), 4.91 (d, J=17 Hz, 1H, $-OCH_2$), 6.09 (s, 1H, C_7-H), 6.87–7.31 (m, 5H, Ar*H*); *m/z* 302 (M^+).

3.3.2. Compound 6b. 135 mg, 71%. Viscous oil. [Found: C, 64.32; H, 4.89. $C_{17}H_{16}O_4S$ requires C, 64.55; H, 5.06%]; R_f (benzene) 0.38; λ_{max} 221, 316 nm; ν_{max} (neat) 1250, 1485, 1610, 1710, 2920 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.25 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$), 3.56 (dd, J=9, 12 Hz, 1H, C_2-H), 3.68 (dd, J=6, 12 Hz, 1H, C_2-H), 4.65 (dd, J=6, 9 Hz, 1H, C_3-H), 4.86 (d, J=17 Hz, 1H, $-OCH_2$), 4.92 (d, J=17 Hz, 1H, OCH_2), 6.08 (s, 1H, C_7-H), 6.87–7.18 (m, 4H, Ar*H*); *m/z* 316 (M^+).

3.3.3. Compound 6c. 125 mg, 66%. Viscous oil. [Found: C, 64.38; H, 5.06. $C_{17}H_{16}O_4S$ requires C, 64.55; H, 5.06%]; R_f (benzene) 0.38; λ_{max} 224, 310 nm; ν_{max} (neat) 1250, 1500, 1610, 1710, 2920 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.25 (s, 3H, $-CH_3$), 2.27 (s, 3H, $-CH_3$), 3.53 (dd, J=9, 12 Hz, 1H, C_2-H), 3.68 (dd, J=6, 12 Hz, 1H, C_2-H), 4.58 (dd, J=6, 9 Hz, 1H, C_3-H), 4.83 (d, J=17 Hz, 1H, $-OCH_2$), 4.90 (d, J=17 Hz, 1H, $-OCH_2$), 6.07 (s, 1H, C_7-H), 6.80 (d, J=9 Hz, 2H, Ar*H*), 7.06 (d, J=9 Hz, 2H, Ar*H*); *m/z* 316 (M^+).

3.3.4. Compound 6d. 125 mg, 62%. Viscous oil. [Found: C, 57.22; H, 3.98. $C_{16}H_{13}ClO_4S$ requires C, 57.05; H, 3.86%]; R_f (benzene) 0.38; λ_{max} 220, 312 nm; ν_{max} (neat) 1250, 1490, 1620, 1710, 2920 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.26 (s, 3H, C_6-CH_3), 3.55 (dd, J=9, 12 Hz, 1H, C_2-H), 3.73 (dd, J=6, 12 Hz, 1H, C_2-H), 4.53 (dd, J=6, 9 Hz, 1H, C_3-H), 4.85 (d, J=17 Hz, 1H, $-OCH_2$), 4.98 (d, J=17 Hz, 1H, $-OCH_2$), 6.09 (s, 1H, C_7-H), 6.84 (dd, J=3, 9 Hz, 2H, Ar*H*), 7.21 (dd, J=3, 9 Hz, 2H, Ar*H*); *m/z* 336, 338 (M^+).

3.3.5. Compound 7e. 128 mg, 64%. White solid, mp 104–105°C. [Found: C, 57.19; H, 3.15. $C_{16}H_{11}ClO_4S$ requires C, 57.39; H, 3.28%]; R_f (benzene) 0.42; λ_{max} 220, 307 nm; ν_{max} (KBr) 1260, 1485, 1610, 1710, 2910 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.35 (s, 3H, C_6-CH_3), 5.32 (s, 2H, $-OCH_2$), 6.54 (s, 1H, C_7-H), 6.86–7.31 (m, 4H, Ar*H*), 7.73 (s, 1H, C_2-H), *m/z* 334, 336 (M^+).

3.3.6. Compound 7f. 135 mg, 61%. White solid, mp122–123°C. [Found: C, 52.21; H, 2.93 $C_{16}H_{10}Cl_2O_4S$ requires C, 52.03; H, 2.71%]; R_f (benzene) 0.43; λ_{max} 221, 307 nm; ν_{max} (KBr) 1260, 1490, 1610, 1710, 2920 cm^{-1}; δ_H(300 MHz, $CDCl_3$) 2.35 (s, 3H, C_6-CH_3), 5.33 (s, 2H, $-OCH_2$), 6.55 (s, 1H, C_7-H), 6.92 (d, J=9 Hz, 1H, Ar*H*), 7.14 (dd, J=3, 9 Hz, 1H, Ar*H*), 7.31 (d, J=3 Hz, 1H, Ar*H*), 7.73 (s, 1H, C_2-H), *m/z* 368, 370, 372 (M^+).

Acknowledgements

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