

The Reaction of Nitriles with Phosgene. V¹⁾. Cyclization Reactions of *N*-(α -Chlorobenzylidene)carbamoyl Chloride

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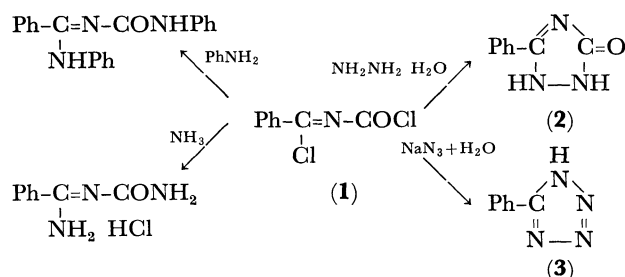
(Received January 20, 1971)

N-(α -Chlorobenzylidene)carbamoyl chloride (**1**) reacts with hydrazine hydrate to give 3-phenyl-1,2,4-triazolone (**2**), with sodium azide in the presence of water to give 5-phenyltetrazole (**3**), and with aliphatic nitriles in the presence of hydrogen chloride to give 6-chloro-2-phenyl-5-substituted-4(3*H*)-pyrimidones (**5**) and 4,6-dichloro-2-phenyl-5-substituted pyrimidines (**6**). However, the reaction of **1** with trichloroacetonitrile or pivalonitrile in the presence of hydrogen chloride did not give the expected triazines.

N-(α -Chlorobenzylidene)carbamoyl chloride (**1**) was prepared first by the reaction of benzoyl isocyanate with phosphorous pentachloride.²⁾ However, in the course of our work on the reaction of nitriles with phosgene, the carbamoyl chloride (**1**) has been found to be easily obtainable by the reaction of benzonitrile with phosgene in the presence of hydrogen chloride.³⁾ The carbamoyl chloride (**1**) has two reactive chlorine atoms in the molecule and thus can be expected to be useful as a precursor for the synthesis of nitrogen heterocycles. The Netherlands patent claims that the carbamoyl chloride (**1**) reacts with amidines to give 2-hydroxy-6-phenyl-4-substituted-*s*-triazines.⁴⁾ In this paper we will report some cyclization reactions of the carbamoyl chloride (**1**) with some nucleophiles.

The reaction of the carbamoyl chloride (**1**) with excess aniline or ammonia gave *N*-phenyl-*N'*-anilinoformyl benzamidine and *N*-carbamoyl benzamidine hydrochloride respectively. On the other hand, the treatment of the carbamoyl chloride (**1**) with hydrazine hydrate gave the compound formulated as C₈H₇N₃O, which was confirmed to be 3-phenyl-1,2,4-triazolone (**2**) on the basis of the IR, NMR, and mass spectra.

When the carbamoyl chloride (**1**) was allowed to react with sodium azide in aqueous acetone, 5-phenyltetrazole (**3**) was obtained, with the evolution of carbon dioxide. However, the reaction did not occur under anhydrous conditions, such as those in anhydrous THF.

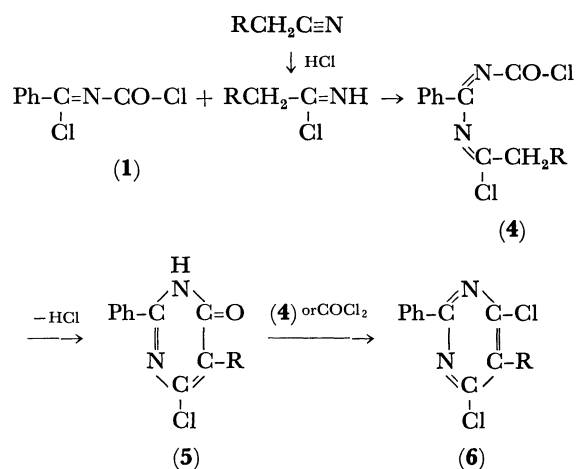


Scheme 1

Recently several reactions concerning the electrophilic attack on the α -methylene of the C=N group

have been reported.⁵⁻⁷⁾ In our previous papers,^{7,8)} we reported the preparation of 6-chloro-2,5-disubstituted-4(3*H*)-pyrimidones (**7**) by the reaction of aliphatic nitriles with phosgene in the presence of hydrogen chloride, in which *N*-(chloroformyl)-*N'*-(α -chloroalkylidene)alkylamidines was proposed as an intermediate. We assumed that the presence of hydrogen chloride promotes the polarization of the C=N bond in the intermediate, thus making the α -methylene more nucleophilic.

In view of these speculations, the carbamoyl chloride (**1**) can be expected to react with aliphatic nitriles in the presence of hydrogen chloride to afford 6-chloro-2-phenyl-5-substituted-4(3*H*)-pyrimidones (**5**) through *N*-(chloroformyl)-*N'*-(α -chloroalkylidene)-benzamidine (**4**), as is shown in Scheme 2. As ex-



Scheme 2

pected, we have found the cyclization reaction of the carbamoyl chloride (**1**) with aliphatic nitriles in the presence of hydrogen chloride.

When the carbamoyl chloride (**1**) was allowed to react with acetonitrile in the presence of hydrogen chloride (molar ratio 1 : 2 : 2) in a sealed glass tube at 60°C and the products were subjected to chromatographic separation, 6-chloro-2-phenyl-4(3*H*)-pyrimi-

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TABLE 1. THE REACTION OF THE CARBAMOYL CHLORIDE (1) WITH ALIPHATIC NITRILES

Run No.	R	Molar ratio 1 : RCN : HCl	Reaction time (hr)		Yield (%)		
			30—35°C	60—65°C	5	6	7
1	H	1 : 2 : 1.6	0	180	3.9	5.4	12
2	H	1 : 2 : 1.8	190	0	7.6	3.6	0
3	CH ₃	1 : 2 : 1.7	0	220	8.2	trace	5.3
4	CH ₃	1 : 2 : 2.0	170	290	1.8	23	trace
5	C ₂ H ₅	1 : 2 : 2.0	170	240	15	9.4	0
6	C ₃ H ₇	1 : 2 : 2.3	310 ^{a)}	300	19	9.4	trace
7	C ₃ H ₇	1 : 2 : 2.3	190	0	13	trace	0
8	C ₄ H ₉	1 : 2 : 2.2	160	260	24	5.0	trace

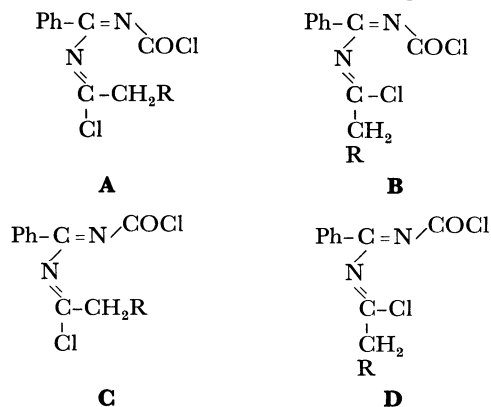
a) At room temperature.

done (5a), 4,6-dichloro-2-phenylpyrimidine (6a), 6-chloro-2-methyl-4(3*H*)-pyrimidone (7a), benzonitrile, and a tarry product were isolated. They were confirmed on the basis of the IR, NMR, and mass spectra, and by elemental analysis. It is known that the carbamoyl chloride (1) decomposes to benzonitrile and phosgene by heating.³⁾ Thus, the formation of 7a is apparently due to the reaction of acetonitrile with the phosgene thus formed and hydrogen chloride.

The reaction of 1 with aliphatic nitriles was extended to propionitrile, butyronitrile, valeronitrile, and capronitrile, giving the corresponding pyrimidine derivatives, 5b-e, 6b-e, and 7b-e. (Table 1)

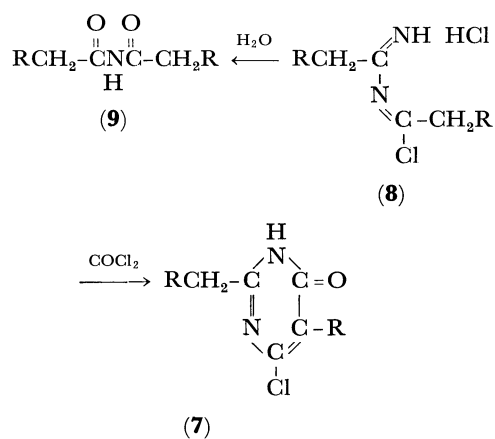
The treatment of 1 with 3-chloropropionitrile under comparable conditions, however, resulted in the isolation of a polymeric product which was similar in both appearance and quality to that obtained by the reaction of 3-chloropropionitrile with phosgene in the presence of hydrogen chloride.⁷⁾

In order to avoid the side reactions and to increase the yield of 5, the reaction was carried out at 30—35°C and finally the reaction temperature was raised to 60—65°C, as is shown in Runs 4, 5, 6, and 8 in Table 1. The formation of 7 was indeed diminished, as expected, but the dichloropyrimidines (6) were still formed in considerable amounts. In all the experiments the total yields of 5 and 6 were independent of the chain length of nitriles, but did not exceed 30%. It is assumed that the low yields are partly due to the configurations of the intermediate *N*-chloroformyl-*N'*-(α -chloroalkylidene)benzamidines (4) and/or the protonated one (4'). The intermediates 4 and/or 4', may have the following four configurations:



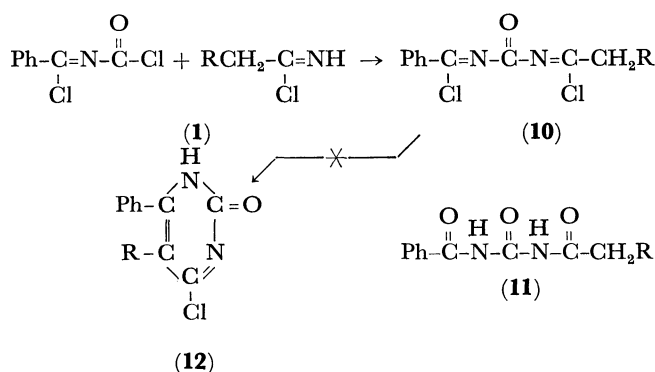
The protonation of **A**, **B**, **C**, and **D** would occur on a nitrogen bearing chloroalkylidene group.⁷⁾ It seems that **A** and protonated **A** are favorable configurations for the cyclization giving the 5 pyrimidones. However, judging from the facts that 6 did not produce under mild reaction conditions as is shown in Run 7 and that the pyrimidone 7 was formed only in traces in Runs 4, 6, and 8, non-cyclized intermediates which may exist in the **B**, **C**, and **D** and protonated **B**, **C**, and **D** forms may have a chlorinating ability and thus chlorinate 5 to give 6, especially when the reaction temperature is raised. The chlorination by phosgene can not be neglected, either.

The treatment of the tarry residue obtained after column chromatographic separation with water gave a considerable amount of diacylamines (9) and a small amount of *N,N'*-diacylurea (11). The formation of 9 indicates the presence of *N*-(α -chloroalkylidene)-alkylamidines hydrochloride (8). As has been reported previously,⁷⁾ the pyrimidones 7 are formed by the reaction of 8 with phosgene. The isolation of 8 is now under investigation (Scheme 3).



Scheme 3

The isolation of 11 suggests the formation of *N*-(α -chlorobenzylidene)-*N'*-(α -chloroalkylidene)urea (10), which appears to be formed by the attack of the carbonyl carbon of 1 on the nitrogen atom of the imidoyl chloride (Scheme 4). The pyrimidone 12, which may be formed by the intramolecular cyclization of 10, was not isolated.



Scheme 4

In our preceding paper³⁾ we reported that the carbamoyl chloride **(1)** reacts with *p*-tolunitrile or benzonitrile in the presence of hydrogen chloride to give 2-chloro-4-phenyl-6-(*p*-tolyl)-*s*-triazine and 2-chloro-4,6-diphenyl-*s*-triazine respectively. Accordingly, it can be expected that **1** will react with aliphatic nitriles which have no α -hydrogen to give the corresponding triazines. However, the reaction of **1** with trichloroacetonitrile or pivalonitrile in the presence of hydrogen chloride gave only a small amount of 2-chloro-4,6-diphenyl-*s*-triazine, and the expected triazines were not obtained.

Experimental

All the melting points were determined on a Yanagimoto micromelting point apparatus and were corrected. The IR spectra were measured on a JASCO IR-E apparatus, the NMR spectra on a JEOL J.M. M-G-60 apparatus, and the mass spectra on a Hitachi RMU-6E apparatus.

N-(α -chlorobenzylidene)carbamoyl chloride was prepared from benzonitrile, phosgene, and hydrogen chloride according to our method.³⁾ The fraction with a bp of 85–90°C/1 mmHg was used.

Reaction of Aniline with 1. A solution of carbamoyl chloride **1** (1.0 g, 5 mmol) in 10 ml of benzene was added, drop by drop, to a solution of aniline (1.9 g, 20 mmol) in 15 ml of benzene under cooling in an ice-water bath. The precipitate thus formed was filtered and washed with cold water. After drying, they were recrystallized from aqueous acetone. The yield was almost quantitative (1.6 g, 100%), but the melting point was broad even after several recrystallizations. It began to melt around 159°C and melted completely below 172°C (lit.⁹⁾ 179–180°C). It was identified as *N*-phenyl-*N'*-anilinoformylbenzamidinium on the basis of the following analytical results: IR(mull), 3200, 3070, 1695 and 1647 cm⁻¹; NMR(DMSO)(τ), 0.32(s, 1H), 0.55(s, 1H), 2.2–3.2(m, 15H); Mass(M⁺) 315. Found: C, 76.30; H, 5.37; N, 13.42%. Calcd for C₂₀H₁₇N₃O, C, 76.17; H, 5.43; N, 13.33%.

Reaction of Ammonia with 1. The carbamoyl chloride **1** (1.8 g, 9.1 mmol) was stirred into an ethanol solution of ammonia under cooling. The precipitate thus formed was filtered, washed, dried, and recrystallized from a mixed solvent of methanol and isopropanol. The yield was 49%. The melting point was also broad even after several recrystallizations. It began to melt around 167°C and melted completely below 185°C (Lit.¹⁰⁾ 192–194°C). However,

it was analyzed and identified as *N*-carbamoylbenzamidinium hydrochloride on the basis of the following data: IR(mull), 3280, 3210, 1743 and 1671 cm⁻¹; Mass(M⁺–HCl), 163. Found: C, 47.83; H, 5.05; N, 21.05; Cl, 18.09%. Calcd for C₈H₁₀N₃OCl: C, 48.13; H, 5.05; N, 21.05; Cl, 18.09%.

Reaction of 1 with Hydrazine Hydrate. An acetone solution of hydrazine hydrate (0.25 g, 5 mmol) was mixed with the carbamoyl chloride **1** (0.5 g, 2.4 mmol) under cooling in an ice-water bath. The precipitate thus formed was treated as usual and recrystallized from acetone (58% yield). It was identified as 3-phenyl-1,2,4-triazolone (**2**) on the basis of the following data; mp 316.0–318.0°C (lit.¹¹⁾ 321–322°C). Mass(M⁺) 161, IR(KBr) ca. 3000, 1740 cm⁻¹, NMR (DMSO) (τ) ca. 2.25(m, 3H, *o*-H), –1.60(s, 1H, NH), –1.95(s, 1H, NH). Found: C, 59.50; H, 4.49; N, 26.29%. Calcd for C₈H₇N₃O: C, 59.62; H, 4.37; N, 26.07%.

Reaction of 1 with Sodium Azide. To a solution of sodium azide (0.16 g) in 1 ml of water we added a solution of the carbamoyl chloride **1** (0.5 g, 2.5 mmol) in 0.75 ml of acetone. The mixture was shaken in a water bath at 30°C. The precipitate thus formed was filtered, washed with acetone, and dried *in vacuo*. It was recrystallized from aqueous ethanol and identified as 5-phenyltetrazole (**3**) on the basis of the following analytical results: mp 217.0–219°C(dec)(lit.¹²⁾ 215°C(dec). Mass(M⁺) 146, IR(KBr) ca. 3000, 1560 cm⁻¹. Found: C, 58.00; H, 3.91; N, 38.53%. Calcd for C₇H₆N₄: C, 57.53; H, 4.14; N, 38.33%. Yield, 53%.

Reaction of 1 with Aliphatic Nitriles in the Presence of Hydrogen Chlorides. General Procedure. In a 20-ml glass tube we placed the carbamoyl chloride **1** (9.9 mmol), aliphatic nitrile (20 mmol), and chlorobenzene (2 g). Dry hydrogen chloride (16–17 mmol) was bubbled into the mixture under cooling. The tube was then stoppered, cooled in a dry ice-acetone mixture, sealed carefully, and allowed to stand at 30–35°C or heated to 60–65°C, as is shown in Table 1. After the end of the reaction, the reaction tube was chilled in dry ice-acetone mixture, and opened. The reaction mixture was concentrated under reduced pressure. In some cases, the removal of the hydrogen chloride gave the precipitate of the pyrimidone **5**. After the filtration of the precipitate, the mixture was concentrated as has been mentioned above. The resulting residue was chromatographed on silica gel. The dichloropyrimidines **6** were eluted with petroleum ether, the pyrimidones **5** with chloroform, and the pyrimidones **7** with a mixture of chloroform and ethanol. The pyrimidones **5** were purified by recrystallization from ethanol. The dichloropyrimidines **6** were purified by sublimation or recrystallization from aqueous ethanol. The analytical data are summarized in Tables 2 and 3.

The pyrimidones **7** were identified by comparison with authentic samples.

Isolation of Diacylamines (9) and N-Benzoyl-*N'*-acylureas (11). Oily products eluted with a mixture of chloroform and ethanol on the above-mentioned column chromatography were treated with aqueous acetone. The reaction mixture was then allowed to stand overnight. The resulting precipitates were filtered and sublimated under reduced pressure. Diacylamines **9** sublimed at 90°C under reduced pressure and *N*-benzoyl-*N'*-acylureas **11** at 140°C under the same conditions.

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TABLE 2. ANALYSES OF 6-CHLORO-5-ALKYL-2-PHENYL-4(3*H*)-PYRIMIDONES (5)

Pyrimidones (5)	mp (°C)	IR (KBr) (cm ⁻¹)	NMR (in CF ₃ COOH) (τ)	Mass (70 eV) (M ⁺)	Elemental analysis ^{a)}		
					C%	H%	N%
5a	228.0—231.0	1680, 1550 ^{b)} 1535	1.9—2.6 (m, 5H, ring) 3.13 (s, 1H, CH)	206	58.11 (58.13)	3.30 (3.41)	13.53 (13.56)
5b	272.0—274.0	1642, 1565 1541	1.8—2.4 (m, 5H, ring) 7.58 (s, 3H, CH ₃)	220	59.97 (59.87)	3.93 (4.11)	12.81 (12.70)
5c	219.0—220.0	1640, 1573 1540	1.8—2.5 (m, 5H, ring) 7.17 (q, 2H, CH ₂) 8.68 (t, 3H, CH ₃)	234	61.70 (61.41)	5.00 (4.73)	11.85 (11.94)
5d	195.0—197.0	1648, 1548	1.78 (m, 2H, <i>o</i> -ring) ^{c)} 2.53 (m, 3H, <i>m</i> , <i>p</i> -ring) 7.35 (t, 2H, CH ₂) 8.35 (m, 2H, CH ₂) 8.94 (t, 3H, CH ₃)	248	62.87 (62.78)	5.18 (5.27)	11.22 (11.26)
5e	194.0—196.0	1650, 1546	1.9—2.5 (m, 5H, ring) 7.18 (c, 2H, CH ₂) 8.33 (c, 4H, CH ₂ CH ₂) 8.98 (c, 3H, CH ₃)	262	63.87 (64.00)	5.84 (5.76)	10.67 (10.66)

a) Values in parenthesis are calculated ones. b) Nujol. c) In CDCl₃.

TABLE 3. ANALYSES OF 4,6-DICHLORO-5-ALKYL-2-PHENYLPYRIMIDINES (6)

Pyrimidines (6)	mp (°C)	IR (KBr) (cm ⁻¹)	NMR (in CCl ₄) (τ)	Mass (70 eV) (M ⁺)	Elemental analysis ^{a)}		
					C%	H%	N%
6a	97.0 ^{b)} 98.0	1545, 1514 ^{c)}	1.60 (m, 2H, <i>o</i> -ring) 2.56 (m, 3H, <i>m</i> , <i>p</i> -ring) 2.82 (s, 1H, CH)	224	53.58 (53.36)	2.57 (2.69)	12.36 (12.45)
6b	111.0— ^{d)} 113.0	1550, 1501, 1405	1.68 (m, 2H, <i>o</i> -ring) 2.62 (m, 3H, <i>m</i> , <i>p</i> -ring) 7.56 (s, 3H, CH ₃)	238	55.43 (55.25)	3.29 (3.37)	11.55 (11.72)
6c	74.0— 75.0	1556, 1500, 1406	1.72 (m, 2H, <i>o</i> -ring) 2.65 (m, 3H, <i>m</i> , <i>p</i> -ring) 7.17 (q, 2H, CH ₂) 8.76 (t, 3H, CH ₃)	252	57.17 (56.94)	3.94 (3.98)	11.20 (11.07)
6d	67.0— 70.0	1551, 1505 1405	1.65 (m, 2H, <i>o</i> -ring) 2.61 (m, 3H, <i>m</i> , <i>p</i> -ring) 7.17 (t, 2H, CH ₂) 8.33 (m, 2H, CH ₂) 8.92 (t, 3H, CH ₃)	266	58.73 (58.44)	4.56 (4.53)	10.47 (10.49)
6e	62.0— 63.0	1556, 1507 1400	1.68 (m, 2H, <i>o</i> -ring) 2.62 (m, 3H, <i>m</i> , <i>p</i> -ring) 7.16 (c, 2H, CH ₂) 8.48 (c, 4H, CH ₂ CH ₂) 9.00 (c, 3H, CH ₃)	280	59.73 (59.80)	4.97 (5.02)	10.00 (9.96)

a) Values in parenthesis are calculated ones. b) Lit.¹³⁾ 96°C. c) Nujol. d) Lit.¹⁴⁾ 110°C

N-Benzoyl-*N'*-acetylurea (**11a**) was confirmed by the following analytical results and by comparing its IR spectrum with that of the authentic sample prepared by the reaction of benzamide with acetyl isocyanate: mp 210—212°C (lit.¹⁵⁾ 187°C); IR(KBr disk) 3360, 3230, 1745 and 1690 cm⁻¹. NMR(CF₃COOH)(τ) 2.07(m, 2H), 2.37(m, 3H), 7.49(s, 3H). Mass(70 eV) *m/e* (rel. intensity) 147(40)- (C₆H₅CONCO⁺), 105(100)(C₆H₅CO⁺), 59(62)(CH₂=C(OH)NH₂⁺). Found: C, 58.43; H, 4.85; N, 13.61%. Calcd for C₁₀H₁₀N₂O₃: C, 58.24; H, 4.89; N, 13.59%.

The other ureas (**11**) and diacylamines (**9**) were confirmed on the basis of the IR and mass spectra as follows:

N-benzoyl-*N'*-valerylurea (**11b**): IR(mull) 3320, 3170, 1733, 1683, 1268, and 1190 cm⁻¹. Mass(70 eV) *m/e* (rel. intensity) 248(M⁺), 147(30)(C₆H₅CONCO⁺), 105(85)- (C₆H₅CO⁺), 59(100)(CH₂=C(OH)NH₂⁺).

N-Benzoyl-*N'*-caproylurea (**11c**): IR(mull) 3320, 3170, 1735, 1683, 1268, and 1187 cm⁻¹. Mass(70 eV) *m/e* (rel. intensity) 262(M⁺), 147(7.5)(C₆H₅CONCO⁺), 105(100)- (C₆H₅CO⁺), 59(25)(CH₂=C(OH)NH₂⁺).

Divalerylamine (**9b**): mp 96.0—99.0°C (lit.¹⁶⁾ 100°C). IR(mull) 3285, 3195, 1740, 1538, and 1506 cm⁻¹. Mass(70 eV) *m/e* 185(M⁺).

Dicaproylamine (**9c**): mp 91.0—93.0°C (lit.¹⁷⁾ 92.5°C). IR(mull) 3280, 3200, 1740, 1538, 1505, and 1170 cm⁻¹. Mass (70 eV) *m/e* 213(M⁺).

This work has been supported in part by a grant-in-aid from Kokusan Gijutsu Shinkokai. We wish to express our thanks to the founder, the late Mr. Chikara Kurata.

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