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Scope and Mechanism of "Double-Agent" Halogenation

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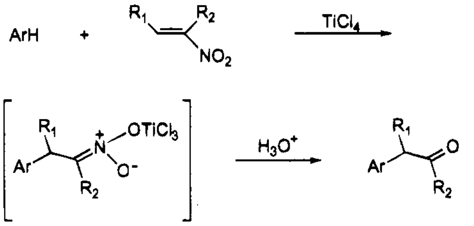
Introduction

This research was initially conceived as a kinetic study of a recently reported[1] acylmethylation reaction, schematically portrayed in eq 1, and was reported to produce good yields (62−94%) of exclusively para product in dry CH_2Cl_2 as the solvent.



(1)

Our preliminary studies suggest this reaction to be *far* different than proposed by Lee and Oh.[1] For example, with 1-nitrocyclohexene, they reported 94% para product with toluene and 90% para product with anisole. With the same nitroalkene, we observed *no* acyl product with toluene and only modest amounts with anisole. Further, our GC/MS data suggest this to be an unusual reaction involving chlorination of the arene and a combination chlorination/Nef[2] reaction of the nitro olefin resulting in an α-chloro ketone product. When toluene is used as the aryl component, the major products are 2-chlorocyclohexanone and monochlorinated toluenes; smaller amounts of 1-chlorocyclohexene and nitrosotoluenes are also produced. Because we apparently are seeing both electrophilic chlorination of arenes and nucleophilic chlorination of the nitro olefin, we call this reaction "double-agent" chlorination. Since this reaction appeared to be a promising method of producing α-halo ketones which are difficult to synthesize regioselectively,[3] we have examined it with a variety of nitro olefins, metal halides, solvents, and arenes. These results are reported along with other mechanistic studies.

Results

Given the scope of double-agent halogenation, we have optimized yields only for 1-nitrocyclohexene (**1**), $TiCl_4$, toluene, and the solvent CH_2Cl_2 (Table 1). GC yields reached 92% for 2-chlorocyclohexanone (based on 1-nitrocyclohexene) and 70% for chlorotoluenes (based on toluene) with minimal side products: the GC area ratio of nitrosotoluene/chlorinated toluenes was 0.03 with 1-chlorocyclohexene/2-chlorocyclohexanone being 0.02. Other conjugated nitro olefins produced reasonable, nonoptimized yields with toluene and $TiCl_4$ (Table 1). Even *trans-β*-nitrostyrene **6** reacted to some extent to produce the analagous α-chloro aldehyde. Interestingly, neither type of chlorination occurred with toluene and an unconjugated nitroalkene **5**. The reaction does have steric limitations; as expected, 1,1-diphenyl-2-nitroethylene (**7**) does not react, even at 56 °C, with $TiCl_3$. Significantly, toluene chlorination did not occur in this system.

In the presence of 1-nitrocyclohexene and $TiCl_4$, a variety of aromatic compounds are chlorinated (Table 2). Reactive arenes such as anisole and mesitylene chlorinate readily; benzene and chlorobenzene chlorinate, but appreciable amounts of side products 1-chlorocyclohexene and 1,1,2-trichlorocyclohexane are produced instead of 2-chlorocyclohexanone. Nitrobenzene did not chlorinate, but again yields of 2-chlorocyclohexanone were low and 1,1,2-trichlorocyclohexane yields were high.

A range of metal halides were also tested for double-agent halogenation effectiveness under normal conditions (room temperature, toluene, solvent CH_2Cl_2, 1-nitrocyclohexene). $SnCl_4$ did not react. However, $AlCl_3$ produced both products (Table 1). With $TiBr_4$, bromination of the nitroalkene occurred, but no bromotoluenes were found. When $TiCl_3$ was used toluene was not attacked, but excellent yields of α-chloro ketones were produced, especially in the solvent CH_3NO_2.

Double-agent halogenation occurs in a number of solvents. Although methylene chloride and nitromethane have given the best product yields, nitrobenzene, THF, and excess toluene are also effective media (Table 1).

Discussion

Our understanding of the reaction mechanism(s) of this unusual reaction continues to evolve. It appears that the *aci*-nitro intermediate may be produced through an internal delivery[4] of nucleophilic chlorine (Scheme 1). The resultant nitronate species **9** may electrophilicly chlorinate arenes, may be converted to an α-chloro ketone via the Nef reaction or can be converted to side products, possibly by the reactions depicted in Scheme 2. We have GC/MS evidence for 1,1,2-trichlorocyclohexane (**11**) and 1-chlorocyclohexene (**10**) and note that **11** appears only when less active arenes such as benzene, chlorobenzene, and nitrobenzene are used.

There are other published examples of nucleophilic attacks at the 2-carbon position of conjugated nitroalkenes. Pecunioso and Menicagli[5] proposed a similar regiospecific transfer of an alkyl group from trialkylaluminum compounds complexed via Al to nitro oxygen.

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(1) Lee, K.; Oh, D. Y. *Tetrahedron Lett.* **1988**, *29*, 2977.

(2) For a review, see: Pinnick, H. W. *Org. React.* **1990**, *38*, 655.

(3) (a) Glaser, J.; Toth, I. *J. Chem. Soc., Chem. Commun.* **1986**, 1336 and references therein. (b) See also: Hiegel, G. A.; Peyton, K. B. *Synth. Commun.* **1985**, *15*, 385.

(4) The question of whether the chlorine is delivered intra- or intermolecularly is unresolved. In a somewhat analogous reaction, Reetz et al. found complexed CH_3TiCl_3 delivered the methyl group to a carbonyl carbon through an intramolecular process when the substrate was a chiral α-alkoxy aldehyde (Reetz, M. T.; Raguse, B.; Seitz, T. *Tetrahedron* **1993**, *49*, 8561) but with the corresponding ketone the addition more closely followed second-order kinetics (Reetz, M. T.; Hullmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477). A review of the complexities of this mechanism is available: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(5) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 45.

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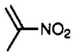
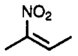
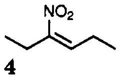
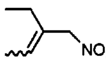
Table 1. Preparation of α-Chloro Ketones and Chlorotoluenes with Metal Chlorides and Nitro Olefins

olefin	metal chloride	arene, other reagent(s)	solvent	% yield[a] α-chloro ketone	% yield[a] chlorotoluenes
1	$TiCl_4$	toluene	CH_2Cl_2	92[b]	70[b]
1	$TiCl_4$		CH_3NO_2	56[b]	N/A
1	$TiCl_4$	toluene	$ArNO_2$	34[b]	70[b]
1	$TiCl_3$		CH_3NO_2	90[b]	N/A
1	$TiCl_3$		CH_2Cl_2:THF (2:1)	81[b]	N/A
	$TiCl_3$	toluene	CH_3NO_2	0	0
1	$AlCl_3$	toluene, 2-propanol	CH_2Cl_2	95[b]	18[b]
1	$TiBr_4$		CH_2Cl_2	36[b] (α-Br)	N/A
1	$TiCl_4$	1-methylcyclohexene	CH_2Cl_2	33[b]	21 (1,2 dichloride)
 (2)	$TiCl_4$		CH_2Cl_2	10[b]	N/A
2	$TiCl_3$		CH_3NO_2	33[b]	N/A
 (3)	$TiCl_4$	toluene	CH_2Cl_2	39[b]	17[b]
3	$TiCl_3$		CH_3NO_2	100[b]	N/A
 (4)	$TiCl_4$	toluene	CH_2Cl_2	69	71[b]
4	$TiCl_3$		CH_3NO_2	72	N/A
 (5)	$TiCl_4$	toluene	CH_2Cl_2	0	0
5	$TiCl_3$		CH_3NO_2	0	N/A
6	$TiCl_4$	toluene	CH_2Cl_2	17	70[b]
6	$TiCl_4$		CH_3NO_2	34	N/A
7	$TiCl_3$	toluene	CH_3NO_2	0	0
8	$TiCl_4$	2-propanol	CH_2Cl_2	56 (β-Cl)[c]	N/A
8	$TiCl_3$		CH_3NO_2	33 (β-Cl)[c]	N/A
8	$TiBr_4$		CH_2Cl_2	43[b] (β-Br)[c]	N/A

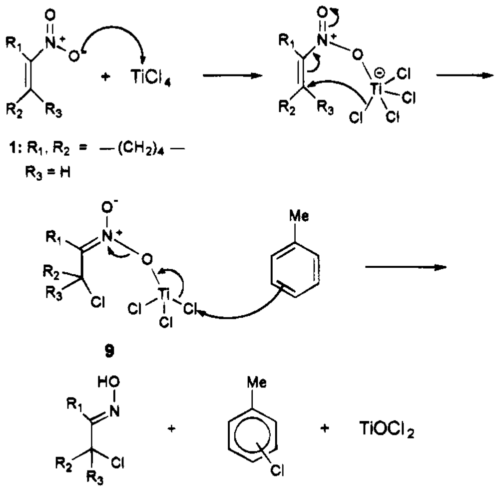
[a] GC yields. [b] GC and GC/MS characterization agreed with that of authentic compounds. [c] Stereochemistry unknown.

Table 2. Double-Agent Chlorination of Arenes[a]

arene	time (h)	chlorinated arenes % yield[b]	% ortho	% meta	% para	α-chloro ketone % yield[b]
nitrobenzene	18	0				12[c]
chlorobenzene	18	18	30		70	26[c]
benzene	2.5	23				67
toluene	0.5	70	68	1	31	92
toluene[d]	2	37	60	~1	39	N/A
m-xylene	0.5	56	32		68	51
anisole	0.5	34	28		72	22

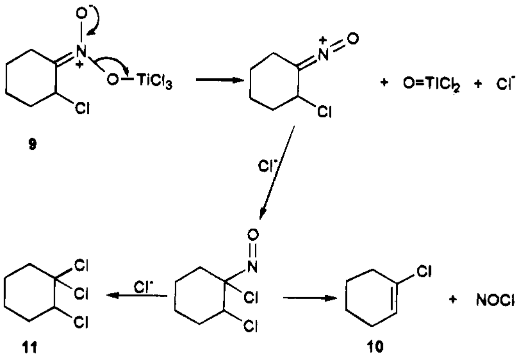
[a] 1:1:1 ratio of 1-nitrocyclohexene:arene:$TiCl_4$ in CH_2Cl_2 at 25 °C. [b] GC yields. [c] High yields of side products 1-chlorocyclohexene and 1,1,2-trichlorocyclohexane. [d] From 2-nitropropane, Et_3N, toluene, and $TiCl_4$ in CH_2Cl_2 at 25 °C.

Scheme 1



Shudo and co-workers[6] were able to add arenes to the β-carbon of O,O-diprotonated nitroalkenes.

Scheme 2



The generality of internal halide delivery to a positive carbon center is seen in the production of 2-chloro-1-acetylcyclohexane (**12**) from 1-acetyl-1-cyclohexene (**8**) in 56% yield (Scheme 3). It is advantageous[7] to use a 2:1 excess of 2-propanol:$TiCl_4$; presumably the alcohol affects the chloride ion transfer from Ti to carbon by increasing the electron density at Ti, probably through additional complexation with the ketone–$TiCl_4$ complex (Scheme 3). With this system we saw no evidence of chlorotoluene formation. It may be of some mechanistic significance that, in our one try, we produced a reasonable yield of 2-bromo-1-acetylcyclohexane from $TiBr_4$ without the addition of 2-propanol. This suggests that the lower electronegativity of the remaining ligands (compared to Cl) facilitates the nucleophilic transfer of Br^- to the β-carbon.

A similar argument may explain the enhanced α-chloro ketone yields (Table 1) with $TiCl_3$, i.e., one less Cl ligand should also help Cl^- transfer. Noteworthy is the absence

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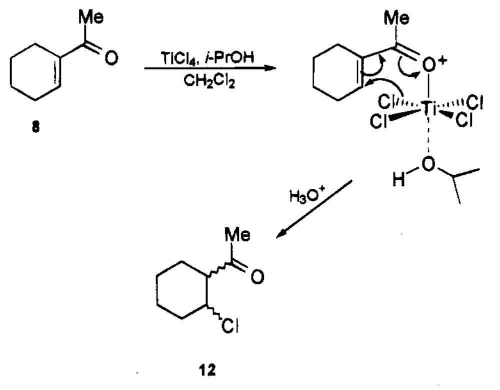
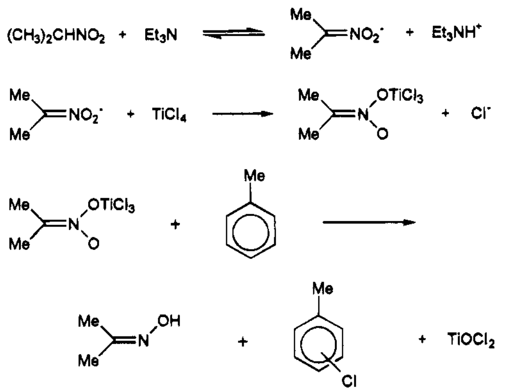
(6) Okabe, K.; Ohwada, T.; Ohta, T.; Shudo, K. *J. Org. Chem.* **1989**, *54*, 733.

(7) Kishikawa, K.; Furusawa, A.; Kohmoto, S.; Yamamoto, M.; Yamada, K. *J. Org. Chem.* **1993**, *58*, 7296.

Scheme 3



Scheme 4



of electrophilic arene halogenation with either $TiBr_4$ or $TiCl_3$. This was also the case in the acetyl-1-cyclohexene–$TiCl_4$ system, which suggests this reaction can be "fine tuned" by an appropriate choice of a metal halide and a substrate. For example, it appeared that electrophilic aromatic chlorination alone might occur if an intermediate analagous to **9** was produced in the presence of toluene. Chlorination did indeed occur (37% yield) when triethylamine was added to an excess of 2-nitropropane in the presence of a limiting amount of toluene in solvent CH_2Cl_2. Arene chlorination occurred when $TiCl_4$ was added to the solution (Scheme 4). Thus, with a proper choice of a nitro reactant and a metal halide, one can attain nucleophilic chlorination (to form an α-chloro ketone) or electrophilic chlorination of arenes, or both.

Our suggested mechanism of double-agent halogenation is supported by the following additional studies. First, the system has electrophilic chlorinating ability in a general sense. This is evident from the range of aromatic compounds which undergo chlorination but also from the fact that under anhydrous conditions 1,2-dichloro-1-methylcyclohexane is produced along with the expected α-chloro ketone when 1-methyl-1-cyclohexene is substituted for toluene (Table 1). Second, the ortho, meta, and para product isomer percentages (Table 2) are typical for electrophilic chlorination of toluene,[8] chlorobenzene,[8] anisole,[8] and *m*-xylene.[9] Third, a competitively determined k_t/k_b ratio of 142 (±9 standard deviation, five samples) and the competitively determined toluene product isomer percentages, ortho 69.9 ± 0.1, meta 0.87 ± 0.02, and para 29.2 ± 0.1, yield a calculated Brown selectivity relationship[8] slope $b = 1.31$, an excellent fit to Brown and Stock's least-squares slope of $b = 1.31 \pm 0.10$.[8] Fourth, in the absence of water an oxime is the expected precursor to the α-chloro ketone (Scheme 1). The oxime hydrogen typically produces a broad NMR peak in the 8–10.5 ppm range. For all other reactants and expected products, the most downfield peak occurs at 7.5 ppm. When a typical double-agent chlorination reaction with 1-nitrocyclohexene, $TiCl_4$, and toluene was carried out in CD_2Cl_2 in an NMR tube under anhydrous conditions, all spectra showed a broad peak at 9.8 ppm, strongly suggestive of the presence of 2-chlorocyclohexanone oxime.

Table 3. Halogenation Mechanisms of Nitronate-Metal Halide Complexes

$=\overset{+}{N}(O^-)O{:}MX_n$	halogenation mechanism	
	electrophilic	nucleophilic
$TiCl_4$		√
$Ti^{IV}Cl_3$	√	
$Ti^{III}Cl_3$		√
$Ti^{IV}Cl_2$, $Ti^{III}Cl_2$	neither	
$AlCl_3$		√
$AlCl_2$	√	
$TiBr_4$		√
$SnCl_4$	neither	

In conclusion, we have discovered a simple regioselective route to α-halo ketones[10] which will become more attractive as a greater variety of conjugated nitro olefins become commercially available. This reaction also provides a way to produce chlorinated aromatic molecules concomitantly or separately (Table 3), appears to be faster than and as versatile an arene halogenation reaction as that of $TiCl_4$:peroxytrifluoracetic acid,[11] and has the added advantage of not requiring the synthesis of one of the reagents (CF_3CO_3H). We have also shown that the list of metal halides capable of serving as aromatic halogenating agents may be far broader than we thought.[11]

Experimental Section

Materials. Metal halides were purchased in neat form or as 1 M solutions in CH_2Cl_2 or CH_2Cl_2:THF and were used without further purification. Nitro olefins **1** and **6** were commercially available; literature methods were used to synthesize **2**,[12] **3**,[12] **4**,[12] **5**,[13] and **7**[14] (propionaldehyde and 3-pentanone were distilled before use). With the exception of nitromethane (*vide infra*), solvents were used without further purification. Internal standard nonane, all arenes, and 1-acetyl-1-cyclohexene were also used without further purification. The GC and GC/MS retention times and mass spectra of the products 2-chlorocyclohexanone, chloroacetone, and 3-chloro-2-butanone matched those of authentic samples. The retention times and mass spectrum of the product 2-bromocyclohexanone also matched those of a known sample synthesized by a literature procedure.[15]

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[8] Stock, L. M.; Brown, H. C. In *Advances in Physical Organic Chemistry*, Gold, V., Ed.; Academic Press: New York, 1963; Vol. 1, p 57.

[9] Brown, H. C.; Stock, L. M. *J. Amer. Chem. Soc.* **1957**, *79*, 5175.

[10] For other recent methods of producing α-monohalogenated ketones see ref. 3 and Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44. Also of interest is the very recent report of β-carbon chlorination of β-nitrostyrenes with $TiCl_4$ and Et_3SiH: Kumarin, K.; Kulkarni, G. H. *Tetrahedron Lett.* **1994**, *35*, 9099. Given that Et_3SiH, in the presence of Lewis acids, is a hydride donor, it would appear that electrophilic chlorination followed H^- donation and, on the basis of our results, probably involved a nitronate–$Ti^{IV}Cl_3$ complex.

[11] Chip, G. K.; Grossert, J. S. *Can. J. Chem.* **1972**, *50*, 1233.

[12] Ballini, R.; Castagnani, R.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 2160.

[13] Tamura, R.; Sata, M.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4368.

[14] Govindachari, T. R.; Pai, B. R.; Rao, U. R. *Proc. Indian Acad. Sci. Sect. A*, **1958**, *48A*, 111.

[15] George, B. K.; Pillai, V. N. R. *Polymer* **1989**, *30*, 178.

Gas Chromatographic Analysis. Typical GC conditions: column, 25 m cross-linked methyl silicone; oven temperature program, 95 °C; injection port, 300 °C; detector, 250 °C; He carrier flow rate, 22 cm/s. Typical retention times (min) are as follows: CH_2CH_2, 2.5; chloroacetone, 2.9; benzene, 3.0; toluene, 3.6; chlorobenzene, 4.6; 2-nitropropene, 5.1; 1-chlorocyclohexene, 5.4; nonane, 5.6; anisole, 5.8; chlorotoluenes, 6.8−7.0; 2-nitrosotoluene, 8.6; 2-chlorocyclohexanone, 9.7; nitrobenzene, 11.8; chloroanisoles, (meta) 12.9, (para) 13.6, (ortho) 14.4; 1-acetyl-1-cyclohexene, 13.8; 2-chloro-1-acetylcyclohexane, 28.7; 2-bromo-1-acetylcyclohexane, 32.5. With temperature programming (T_i 95 °C/19 min, ramp 30 °C/min, T_f 160 °C) retention times are as follows: 2-chloro-2-phenylacetaldehyde, 20.6; *trans*-β-nitrostyrene, 26.4. With 50 m cross-linked FFAP and temperature programming (T_i 95 °C/17.5 min, ramp 30 °C/min, T_f 200 °C; He flow rate 22 cm/s), retention times (min) are as follows: nonane, 7.0; CH_2Cl_2, 7.3; toluene, 9.5; 3-chloro-2-butanone, 12.4; *m*-xylene, 12.5; CH_3NO_2, 12.8; chlorobenzene, 16.1; 4-chloro-3-hexanone, 18.0; chlorotoluenes; (ortho) 20.1, (meta, para) 20.5; 2-nitro-2-butene, 22.1; 2-chloro-*m*-xylene, 23.2; 4-chloro-*m*-xylene, 23.4; 3-nitro-3-hexene, 24.1; *p*-dichlorobenzene, 24.3; *o*-dichlorobenzene, 25.5; 2-ethyl-1-nitro-2-butene, 25.5; 2-chlorocyclohexanone, 28.8; nitrobenzene, 31.2; 1-nitrocyclohexene, 31.4. Chlorotoluenes were separated with this column at a 90 °C isothermal oven temperature, and the retention times were as follows: (ortho) 23.6, (meta) 24.7, (para) 25.0.

General Method of Chlorination of Nitro Olefins and Toluene with $TiCl_4$. An oven-dried 25 mL reaction flask containing a stir bar is sealed with a rubber septum. In a glovebox, 0.6 mL of 1 M $TiCl_4$ (0.6 mmol) in CH_2Cl_2 is injected by a syringe into the flask. In a drybox, an additional 5.0 mL of CH_2Cl_2, 50 μL of internal standard nonane, and 0.6 mmol of toluene were added to the flask. The solution is equilibrated/stirred in a 25 °C constant temperature bath after which 0.6 mmol of the nitro olefin is injected. After 30 min an aliquot is removed via syringe, and the reaction is quenched for 20 min in pH O water. The organic layer is separated and analyzed via GC and GC/MS, and the analyses are compared to similar analyses of authentic compounds.

General Method of Chlorination of Nitro Olefins with $TiCl_3$. In a glovebox, approximately 0.3 g (2 mmol) of $TiCl_3$ is weighed into a dried, tared 25 mL flask, which is then sealed with a septum. In a drybox, 9.7 mL of nitromethane and 20 μL of nonane are added with syringes. The solution is stirred until the color changes from purple to orange−brown or dark brown at which point 1 mmol of nitro olefin is injected. A sample is removed, and the reaction is quenched as above. NOTE: the solution color change marking the formation of a $TiCl_3-CH_3NO_2$ complex is essential and is inhibited by H_2O in the CH_3NO_2. With <0.03% H_2O, complexation usually takes <1 h but may take up to 4 h with nitromethane containing >0.05% H_2O.

General Method of Chlorination of α,β-Unsaturated Ketones. In a glovebox, 2 mL of 1 M $TiCl_4$ (2 mmol) in CH_2Cl_2 is added through a rubber septum into an oven-dried 25 mL flask containing a spin bar. After the solution is equilibrated at 25 °C, 50 μL of nonane and 0.26 mL of 1-acetyl-1-cyclohexene (2 mmol) are added. Twenty minutes later 0.3 mL of 2-propanol (4 mmol) is injected.[7] After 1 h at 25 °C, the reaction is quenched with H_2O, and the oily layer is analyzed by GC and GC/MS.

General Method of Arene Chlorination via a Nitronate Complex (Scheme 4). To a typical flask are added 6 mL of CH_2Cl_2, 50 μL of nonane, 0.54 mL of 2-nitropropane (6 mmol), 0.60 mL of distilled triethylamine (4 mmol), and 0.1 mL of toluene (1 mmol). After stirring at 25 °C for 1 h, 0.60 mL of $TiCl_4$ (5 mmol) is injected into the flask in a glovebox. The solution reequilibrates at 25 °C for 2 h, and then the reaction is quenched with H_2O and analyzed (Table 2).

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