A Facile Synthesis and Chemoselective Reactions of Dihydrothiouracils

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Abstract: A highly efficient procedure was devised for the synthesis of 3-(3-arylthioureido)propanoic/butanoic acid and its cyclization to (3-aryl/3-aryl-6-methyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one derivatives. Carbonyl diimidazole proved to be a very effective coupling reagent for the cyclization. Studies carried out to examine the ambident nature of the thioamide moiety towards substitution reactions demonstrated the preference for alkylation at sulfur, and acylation and 1,4-addition at nitrogen.

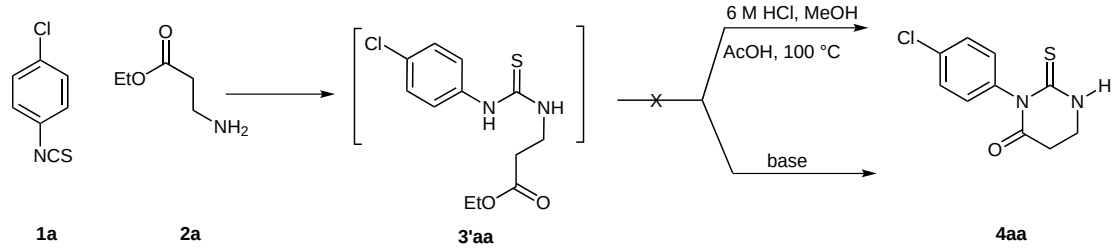
Key words: uracils, amino esters, carbonyl diimidazole, thioamide, ambident nucleophile

The pyrimidinone moiety is an important constituent of the genetic materials RNA and DNA, in the form of nitrogen bases uracil, thymine and cytosine.[1] Many drugs, for example 5-fluorouracil, uramustine, floxuridine, lamivudine, telbivudine, sorivudin, trifluridine, alogliptin and aminometradine, contain pyrimidinones as the pharmacophore.[2,3] Associated with diverse biological properties, various structural modifications have been carried out on the pyrimidinone moiety in the search for more potent derivatives. Their analogues, dihydrothiouracils and their homologues, the thiohydantoins, are well known for their biological properties, pharmaceutical applications and agricultural importance.[4–6] Among the dihydrothiouracils, the 3-aryl derivatives were extensively studied for their usefulness in treating atherosclerotic conditions such as dyslipoproteinemias and coronary heart disease.[5] These scaffolds are also known to possess anticonvulsant, anticancer, antibacterial, insecticidal and herbicidal properties.[5,6] The applications of thioxotetrahyropyrimidin-4(1*H*)-ones is not only limited to the biological field but have also been extended to chemical reactions as organocatalysts.[7] Thus, the extensive biological properties and applications have revealed a need for more efficient syntheses of these molecules and their derivatives.

The reported methods for the formation of 3-(3-arylthioureido)propanoic acid and its subsequent cyclization using $POCl_3$ or acetic/propanoic anhydride[8–12] affords only low yields of 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-ones, while side-products were obtained in considerable amounts. With our interest in developing new synthetic methodologies for heterocyclic compounds,[13] a highly efficient and economic strategy was developed for the synthesis of 2-thioxotetrahydropyrimidin-4(1*H*)-ones, at ambient temperature. The need for purification by chromatography was also eliminated, preventing solvent wastage as well. The course of the reaction involves the one-pot synthesis of 3-(3-arylthioureido)propanoic/butanoic acids and their subsequent cyclization using carbonyl diimidazole (CDI) to afford the products in excellent yields.

The one-pot strategy for the synthesis of dihydrothiouracils by electrophilic activation using lithium perchlorate[13a,b] works well for the cyclocondensation of aryl isothiocyanates with activated β-amino esters such as ethyl 3-(alkylamino)propanoate, but fails in the case of ethyl 3-aminopropanoate, affording instead ethyl 3-(3-arythioureido)propanoate as the sole product. The cyclization of the intermediate ethyl 3-[3-(4-chlorophenyl)thioureido]propanoate **3′aa** was tried (Scheme 1) with different bases in order to enhance the nucleophilicity of the nitrogen N3 attached to the phenyl group, but the results were disappointing. Attempts to cyclize ethyl 3-[3-(4-chlorophenyl)thioureido]propanoate under acidic conditions using 6 M HCl in MeOH and acetic acid at 100 °C afforded only the transesterification product. However, the same reaction conditions led to the formation of the cyclized product for cases in which an *N*-alkylthioureido substituent was present instead of an *N*-aryl substituent.[8]

This prompted us to reinvestigate the reaction by cyclization of the 3-(3-arylthioureido)propanoic acid instead of



1a **2a** **3'aa** **4aa**

Scheme 1 Formation of 3-(4-chlorophenyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one

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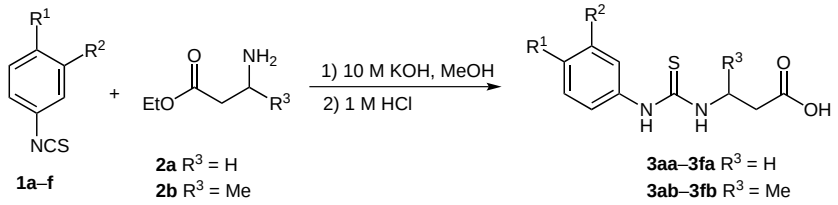


Scheme 2 One-pot synthesis of 3-(3-arylthioureido)propanoic/butanoic acids

the ester. Reported methods for the synthesis of 3-(3-arylthioureido)propanoic acid involves the direct condensation of aryl isothiocyanate with 3-aminopropanoic acid in aqueous NaOH for 24 h at 20 °C, but suffer from major disadvantages such as poor yield, short reaction time, and difficulty in purification.[5d] Therefore, we attempted an alternate procedure for the synthesis of thioureido acid by condensation of aryl isothiocyanate with ethyl 3-aminopropanoate and subsequent hydrolysis. Interestingly, a solution of ethyl 3-aminopropionate and 4-chlorophenyl isothiocyanate in *N*,*N*-dimethylformamide (DMF), when reacted with aqueous NaOH, underwent condensation followed by hydrolysis in eight hours, affording a good yield of 3-[3-(4-chlorophenyl)thioureido]propanoic acid **3aa** in a one-pot process. The reaction was then optimized by using different solvents and varying concentrations of the base, and the best result was obtained in two hours by using 10 M KOH in methanol. The reaction conditions were then applied to different β-amino esters and aryl isothiocyanates (Scheme 2), which afforded the potassium salts of the 3-(3-arylthioureido)propanoic/butanoic acids. Acidification of the carboxylate salt by 1 M HCl led to precipitation of the free acid (Table 1), which was subjected to cyclization without further purification. The cyclization of 3-(3-arylthioureido)propanoic/butanoic acid to the corresponding 2-thioxotetrahydropyrimidin-4(1*H*)-one was explored under different reaction conditions. It was anticipated that activation of the carboxylic acid by incorporating a good leaving group on the acyl carbon would facilitate attack by the nitrogen N3 on the carbonyl carbon to afford the cyclized product.

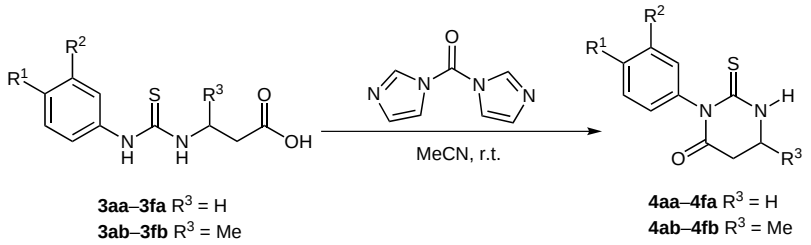
Table 1 Syntheses of 3-(3-Arylthioureido)propanoic/butanoic Acids

Entry	R^1	R^2	R^3	Time (h)	Yield (%)	Product
1	Cl	H	H	1.6	85	**3aa**
2	F	Cl	H	2.0	88	**3ba**
3	CN	Cl	H	1.8	87	**3ca**
4	Cl	CF_3	H	2.2	91	**3da**
5	CN	CF_3	H	2.4	93	**3ea**
6	NO_2	CF_3	H	2.5	84	**3fa**
7	Cl	H	Me	1.5	90	**3ab**
8	F	Cl	Me	1.8	84	**3bb**
9	CN	Cl	Me	2.1	84	**3cb**
10	Cl	CF_3	Me	2.3	87	**3db**
11	CN	CF_3	Me	2.2	91	**3eb**
12	NO_2	CF_3	Me	2.5	83	**3fb**

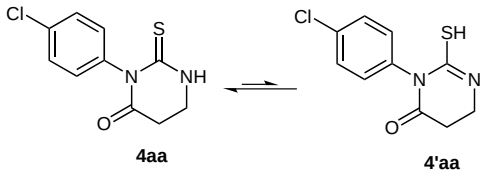
To our dismay, neither the acid chloride nor the anhydride afforded quantitative yields of the product. Carbodiimides are known to afford different heterocycles by carbonyl insertion and acyl activation reactions.[14] We decided, therefore, to employ coupling reagents, and *N*,*N*-dicyclohexylcarbodiimide (DCC) afforded the desired product in moderate yield. However, removal of the dicyclohexyl urea formed during the course of reaction from the product was difficult. Alternatively, the coupling reagent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) did not show any significant improvement in yield from that obtained with DCC, in addition to the fact that employing stoichiometric quantities of the reagent was also not economical. Quite surprisingly, when the cyclization was attempted using carbonyl diimidazole (CDI), the product was afforded in a few minutes with excellent yields[15] (Scheme 3). Evaporation of the solvent under reduced pressure followed by addition of water led to precipitation of the desired product. The pure product was isolated simply by filtration and no further purification was required. Based on the success of this reaction, the conditions were then applied to various thioureido acids and excellent yields of products were obtained in all cases (Table 2).

Our interests then focused on the substitution reactions of 3-aryl-2-thioxtetrahydropyrimidin-4(1*H*)-ones. It was expected that these compounds can tautomerize to the corresponding 3-aryl-2-mercapto-5,6-dihydropyrimidin-4(3*H*)-ones (Scheme 4). An energy comparison of the tautomers **4aa** and **4′aa** by ab initio calculations, performed using Gaussian B3 LYP with basis set 6-31G* (d,p), showed that the thioxo form **4aa** was more stable than the corresponding imine form **4′aa**.[16] This was substantiated by ^{13}C NMR spectra, which showed a peak at δ = 180.1 ppm corresponding to the thione carbon.

The molecular electrostatic potential map for **4aa** showed a high electron density on the sulfur atom.[17] Therefore, it is expected that the substitution reactions of these derivatives should proceed through sulfur instead of nitrogen. Consequently, a reaction of 3-(4-chlorophenyl)-2-thioxtetrahydropyrimidin-4(1*H*)-one, when tried with benzyl



Scheme 3 Cyclization of 3-(3-arylthioureido)propanoic/butanoic acids using CDI



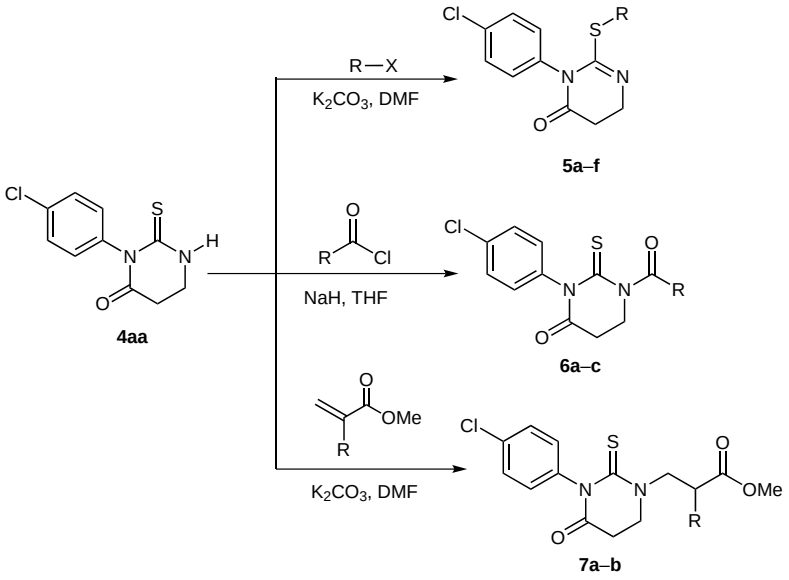
Scheme 4 Tautomeric forms of 3-(4-chlorophenyl) dihydrothiouracil

bromide in CH_2Cl_2 using triethylamine at room temperature, afforded the *S*-benzyl derivative (Scheme 5).

For optimization, the reaction was conducted with a range of bases, solvents, and electrophiles, as shown in Table 3. The best result was obtained with potassium carbonate as base and DMF as solvent[18] (Table 3, entries 1–10). The reaction proceeded well with activated and sterically less demanding electrophiles, whereas the bulky *tert*-butyl bromide did not afford the product. Hence, it is evident that the ambident nucleophile reacts with alkyl halides by an S_N2 reaction mechanism through the sulfur atom. In all these cases, a characteristic signal near δ = 150 ppm was observed in the ^{13}C NMR spectra, indicative of the C=N bond. Interestingly, when the reaction of 3-(4-chlorophenyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one was conducted with acyl chloride the reaction occurred on the nitrogen atom and not on the sulfur. Reactions were carried out with a range of acid chlorides under the optimized conditions with NaH as base and THF as solvent[19] (Table 3, entries 12–14). The ^{13}C NMR spectra revealed a peak at

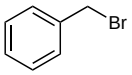
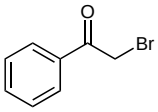
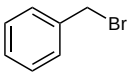
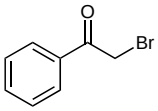
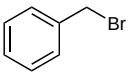
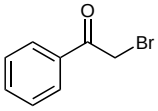
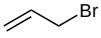
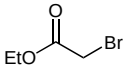
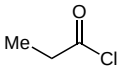
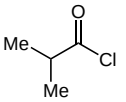
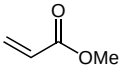
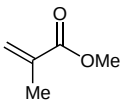
Table 2 Syntheses of 3-Aryl-2-thioxotetrahydropyrimidin-4(1*H*)-ones

Entry	R^1	R^2	R^3	Time (min)	Yield (%)	Product
1	Cl	H	H	10	90	**4aa**
2	F	Cl	H	15	84	**4ba**
3	CN	Cl	H	15	89	**4ca**
4	Cl	CF_3	H	20	82	**4da**
5	CN	CF_3	H	20	84	**4ea**
6	NO_2	CF_3	H	20	85	**4fa**
7	Cl	H	CH_3	15	93	**4ab**
8	F	Cl	CH_3	10	86	**4bb**
9	CN	Cl	CH_3	15	84	**4cb**
10	Cl	CF_3	CH_3	20	81	**4db**
11	CN	CF_3	CH_3	20	82	**4eb**
12	NO_2	CF	CH_3	20	86	**4fb**



Scheme 5 Chemoselective reactions of 3-(4-chlorophenyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one

Table 3 Reactions of 3-(4-Chlorophenyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one with Electrophiles

Entry	Base	Solvent	Electrophile	Time (h)	Yield (%)	Product
1	Et_3N	CH_2Cl_2		2.0	68	**5a**
2	Et_3N	CH_2Cl_2		2.0	65	**5b**
3	NaH	THF		2.0	70	**5a**
4	NaH	THF		1.8	72	**5b**
5	K_2CO_3	DMF		1.0	88	**5a**
6	K_2CO_3	DMF		1.5	85	**5b**
7	K_2CO_3	DMF		6.0	82	**5c**
8	K_2CO_3	DMF		8.0	76	**5d**
9	K_2CO_3	DMF		1.5	88	**5e**
10	K_2CO_3	DMF		2.0	80	**5f**
11	Et_3N	CH_2Cl_2		2.0	–	–
12	NaH	THF		2.0	70	**6a**
13	NaH	THF		12.0	78	**6b**
14	NaH	THF		12.0	75	**6c**
15	K_2CO_3	DMF		5.0	70	**7a**
16	K_2CO_3	DMF		5.0	55	**7b**

δ = 185 ppm corresponding to the C=S carbon. Similarly, reactions with Michael acceptors such as methyl acrylate and methyl methacrylate afforded the N-substituted products only[20] (Table 3, entries 15 and 16). From the results it can be inferred that the course of the reaction depends on the nature of electrophile. The formation of the products can be explained on the basis of the HSAB principle. The alkyl halides are soft in nature and hence attack by the softer atom of the ambident nucleophile led to the S-alkylated product. The S-alkylations are also preferred on steric grounds and because of the higher partial charge and better polarizability of the 3p orbital. On the other hand, the acid chlorides, being hard in nature, undergo acylation reactions on the nitrogen. With α,β-unsaturated esters, reactions of 2-thioxotetrahydropyrimidin-4(1*H*)-one proceed at the harder nitrogen atom. The conjugation of the C=C bond with the ester group increases the electrophilic character at the β-carbon of the Michael acceptor, leading to a partial positive charge and hence a much harder site than the alkyl halides. Thus, the reaction can be expected to occur on the harder atom of the ambident nucleophile through strong coulombic interactions, affording the N-substituted product.[21]

To conclude, an economic and efficient method has been developed for the synthesis of 3-aryl-2-thioxtetrahydropyrimidin-4(1*H*)-ones. The chemoselectivity of the thioamide moiety was investigated as an ambident nucleophile in S-alkylation, and N-acylation and 1,4-addition.

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(15) **General procedure for the preparation of 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-ones:** Aryl isothiocyanate (3.0 mmol) was dissolved in methanol (20 mL) and β-amino ester (3.0 mmol) was added, followed by 10 M KOH (2 mL). The reaction mixture was stirred at 20 °C for 2 h. After completion of the reaction, the solution was concentrated under reduced pressure and then neutralized by 1 M HCl until precipitation occurred. The product obtained was filtered and dried to give the desired acid. The acid was dissolved in acetonitrile (15 mL) and CDI (4.0 mmol) was added. The reaction mixture was stirred for 20 min (progress was monitored by TLC). Upon completion, the reaction mixture was concentrated and the product was precipitated in water, filtered, dried and recrystallized in methanol.
3-(4-Chlorophenyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one (4aa): Yield: 90%; white solid; mp 201–203 °C; MS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_9ClN_2OS$: 241.02; found: 241.13. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.81–2.85 (m, 2 H), 3.47–3.51 (m, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 10.01 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.96, 37.89, 128.80, 132.05, 132.63, 138.71, 167.76, 181.48.
3-(4-Chlorophenyl)-6-methyl-2-thioxotetrahydropyrimidin-4(1*H*)-one (4ab): Yield: 93%; white solid; mp 249–251 °C. MS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}ClN_2OS$: 255.03; found: 255.13. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.26 (d, *J* = 6.4 Hz, 3 H), 2.66–2.73 (m, 1 H), 2.84–2.89 (m, 1 H), 3.86–3.87 (m, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 10.06 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.75, 38.10, 45.41, 128.85, 132.03, 132.68, 138.63, 167.57, 180.87.

(16) Energy calculations were performed using the Gaussian 03 program.

(17) The MESP surfaces were obtained by using the software SPARTAN.

(18) **General procedure for alkylation reaction:** To a solution of 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-one (1.0 mmol) in DMF (5 mL) was added K_2CO_3 (1.6 mmol) followed by alkyl halide (1.1 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, the solution was concentrated under reduced pressure and the crude product was precipitated from water. The product was purified by column chromatography on silica gel (60–120 mesh; hexane–EtOAc, 85:15).
2-(Benzylthio)-3-(4-chlorophenyl)-5,6-dihydropyrimidin-4(3*H*)-one (5a): Yield: 88%; white solid; mp 180–182 °C. MS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}ClN_2OS$: 331.07; found: 331.12. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.69 (t, *J* = 7.3 Hz, 2 H), 3.86 (t, *J* = 7.3 Hz, 2 H), 4.12 (s, 2 H), 7.11–7.15 (m, 2 H), 7.20–7.27 (m, 5 H), 7.35–7.40 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.96, 36.83, 44.56, 124.47, 128.54, 129.20, 129.43, 131.02, 133.93, 135.43, 136.04, 154.77, 168.87.

(19) **General procedure for acylation reaction:** A solution of NaH (1.2 mmol) in THF (10 mL) was cooled to 0 °C and 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-one (1.0 mmol) was added. The reaction mixture was stirred for 30 min, then acyl chloride (1.1 mmol) was added. The reaction was monitored by TLC and, after completion, quenched with water and extracted into ethyl acetate. The organic layer was dried and concentrated to provide a gummy compound, which, upon purification by column chromatography on silica gel (60–120 mesh; hexane–EtOAc, 85:15), afforded the pure product.
1-Acetyl-3-(4-chlorophenyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one (6a): Yield: 70%; light-yellow solid; mp 192–194 °C; MS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}ClN_2O_2S$: 283.03; found: 282.88. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.70 (s, 3 H), 2.99 (t, *J* = 6.6 Hz, 2 H), 4.23 (t, *J* = 6.6 Hz, 2 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.60, 33.19, 40.82, 129.69, 130.38, 134.78, 137.08, 166.90, 174.03, 182.58.

(20) **General procedure for 1,4-addition reaction:** A procedure similar to the preparation of 3-aryl-2-(alkylthio)-5,6-dihydropyrimidin-4(3*H*)-ones was adopted for the aza-Michael reactions.
Methyl 3-[3-(4-chlorophenyl)-4-oxo-2-thioxotetrahydropyrimidin-1(2*H*)-yl]propanoate (7a): Yield: 70%; light-brown liquid. MS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}ClN_2O_3S$: 327.06; found: 327.03. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.82–2.84 (m, 4 H), 3.64 (s, 3 H),

3.84 (t, J = 6.5 Hz, 2 H), 4.10 (t, J = 6.5 Hz, 2 H), 6.96–6.99 (m, 2 H), 7.30–7.33 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.58, 31.90, 46.88, 51.80, 52.04, 129.26, 130.74, 134.23, 137.77, 166.60, 172.53, 181.04.

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