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Pd/Cu-assisted C–S activation and N–H insertion: highly versatile synthesis of 2-aminopyrimidines from 3,4-dihydropyrimidine-2(1*H*)-thiones

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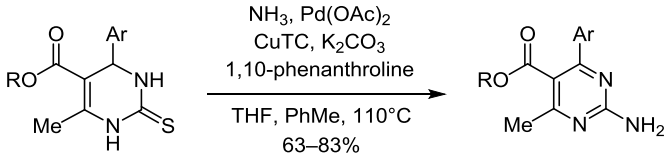


A method for the synthesis of 2-aminopyrimidines from readily available 3,4-dihydropyrimidine-2(1*H*)-thiones *via* a palladium-assisted C–S activation and N–H insertion reaction is developed. The process provides an access to a variety of highly diverse 2-aryl(alkyl)-aminopyrimidine adducts in good yields.

Keywords: 2-aminopyrimidines, Biginelli reaction, C–S activation, N–H insertion.

Recently, metal-mediated cross-coupling reactions of sulfur electrophiles have shown highly effective and practical approaches for the formation of carbon–carbon bonds. Desulfitative cross-coupling reactions of sulfur electrophiles, such as thiols, sulfoxides, thioethers, thioesters, aryl sulfones, and sulfoximines, have number of advances as they are often less expensive and more reactive than corresponding aryl chlorides. Generally, these sulfur electrophiles are involved in Suzuki–Miyaura, Negishi, Stille, Sonogashira–Hagihara, Mizoroki–Heck type of cross-coupling reaction.[1–15]

Buchwald and Hartwig exploited the transition metal-catalyzed direct amination reactions of aryl halides and provides most powerful methods for the synthesis of arylamines. Since then the coupling of ammonia through metal-amido complex for the synthesis of primary arylamines has undergone significant advancement.[16–21] However, to date, amination reactions involving organo-sulfur as electrophile are relatively rare. Therefore, we envisaged that desulfitative cross coupling perhaps can provide a novel and attractive approach for the direct amination of heteroaryl thiols.

2-Aminopyrimidine is a common core motif in variety of natural products and pharmaceuticals and displays a wide range of biological properties. Several natural products and drugs such as variolin B, meridianin A, and annomontine, containing 2-aminopyrimidine scaffolds, and also abacavir, used for the treatment of HIV infections and AIDS,[22–31] (Fig. 1) raised our interest toward the desulfitative synthesis of amino-functionalized heterocycles. Herein we

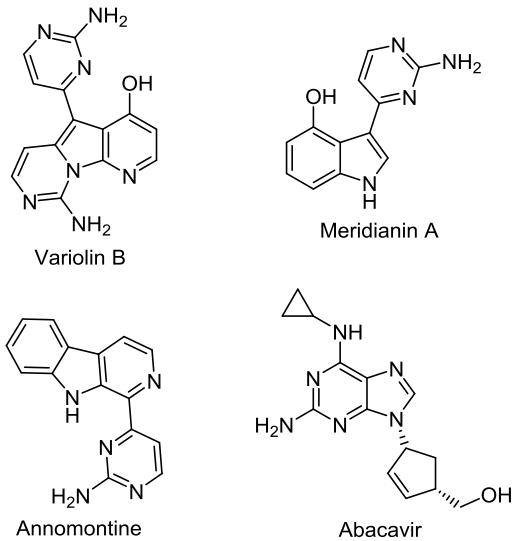
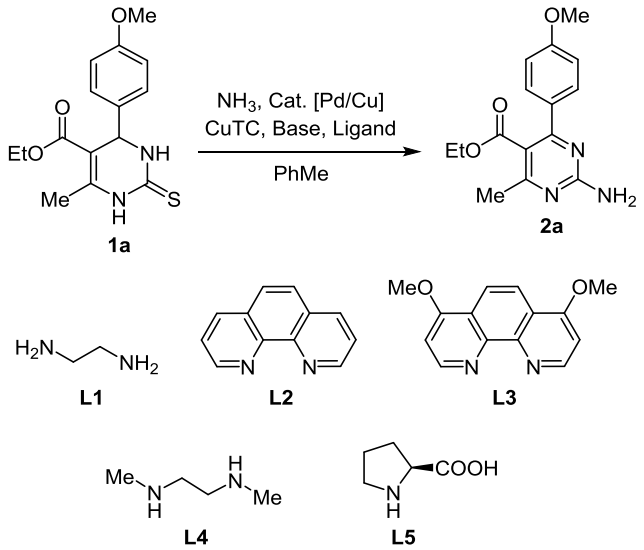


Figure 1. Some biologically important 2-aminopyrimidines.

sought to uncover a palladium-assisted C–S activation of heteroaromatic thiols *via* a direct amination with ammonia, which provide a versatile method for the synthesis of substituted 2-aminopyrimidines and also extends the scope of the metal-mediated desulfitative reactions.

A control experiment showed that no reaction was observed in the absence of any catalyst and K_2CO_3 as a base (Table 1, entry 1). Our initial studies focused on the survey for optimal catalyses by the use of several catalysts such as $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and CuI.

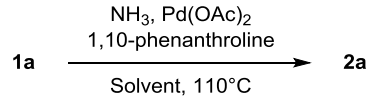
Table 1. Metal/ligand-catalyzed desulfitative amination of compound **1a** by ammonia*



Entry	Catalyst	Ligand	Base	Yield, %
1	–	–	K_2CO_3	0
2	$PdCl_2$	**L1**	K_2CO_3	18
3	$Pd(PPh_3)_4$	**L1**	K_2CO_3	45
4	CuI	**L1**	K_2CO_3	22
5	$PdCl_2(PPh_3)_2$	**L1**	K_2CO_3	53
6	$Pd(OAc)_2$	**L1**	K_2CO_3	61
7	$Pd(OAc)_2$	**L2**	K_2CO_3	77
8	$Pd(OAc)_2$	**L3**	K_2CO_3	71
9	$Pd(OAc)_2$	**L4**	K_2CO_3	32
10	$Pd(OAc)_2$	**L5**	K_2CO_3	27
11	$Pd(OAc)_2$	**L2**	Cs_2CO_3	51
12	$Pd(OAc)_2$	**L2**	K_3PO_4	56
13	$Pd(OAc)_2$	**L2**	NEt_3	49
14**	$Pd(OAc)_2$	**L2**	K_2CO_3	44
15***	$Pd(OAc)_2$	**L2**	K_2CO_3	60
16*[4]	$Pd(OAc)_2$	**L2**	K_2CO_3	Not isolated
17*[5]	$Pd(OAc)_2$	**L2**	K_2CO_3	62

* Reaction conditions: **1a** (0.5 mmol), 0.4 M NH_3 solution in THF (2.5 mmol), Pd catalyst (5 mol %), CuTC (1.1 equiv), ligand (10 mol %), base (1 mmol), toluene (2 ml), temperature 110°C, air atmosphere.
** Temperature was 80°C.
*** Catalyst loading was 2 mol %.
*[4] Aqueous NH_3 (2.5 mmol) was used as ammonia surrogate.
*[5] Ammonium acetate (2.5 mmol) was used as ammonia surrogate.

Table 2. Screening of solvents for desulfitative amination*



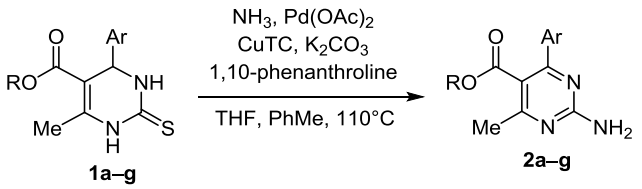
Entry	Solvent	Yield, %
1	DMSO	56
2	Dioxane	63
3	DMF	36
4	NMP	52
5	Toluene	77

* Reaction conditions: compound **1a** (0.5 mmol), 0.4 M NH_3 solution in THF (2.5 mmol), $Pd(OAc)_2$ (5 mol %), CuTC (1.1 equiv), 1,10-phenanthroline (10 mol %), Cs_2CO_3 (1 mmol), solvent (2 ml), air atmosphere.

Among all the tested catalysts, $Pd(OAc)_2$ emerged as the best catalyst along with copper(I) thiophene-2-carboxylate (CuTC) as a cocatalyst (Table 1, entry 7). Concerning the selectivity, no di- or trisubstituted pyrimidines were obtained with the palladium-catalyzed amination reaction. Subsequently, the effect of ligands was further investigated using the optimized catalyst (Table 1, entries 6–10). We were pleased to observe that 1,10-phenanthroline (Table 1, entry 7) was the most efficient ligand to push the reaction forward. In the next step of the screening procedure, different bases were examined for their ability to promote the cross coupling of the model substrates. It is worth noting that the reaction carried out with K_2CO_3 as a base (Table 1, entry 7) gave best results for the desulfitative cross-coupling reaction. Further tuning of the reaction conditions by decreasing the catalyst load to 2 mol % decrease the yield of compound **2a** by 17% (Table 1, entry 15). Temperature effect revealed 110°C as optimum temperature for the model reaction. Interestingly, ammonium acetate as ammonia surrogate gave the desired product in good yield (Table 1, entry 17), however, no product has been isolated in the case of aqueous NH_3 (Table 1, entry 16). Toluene was found to be the optimal solvent for the desulfitative amination catalyzed by $Pd(OAc)_2$ (5 mol %) among various solvents used (yield 77%, Table 2, entry 5).

With this efficient system in hand, we explored the scope of the reaction. Therefore, the Biginelli reaction was chosen for exploration because of its high variability of initial substrates in multicomponent reaction. Substituted Biginelli reaction products **1a**–**g** were prepared by using reported procedure.[32,33] We found that the reaction was equally applicable to a broad range of phenyl-substituted derivatives, and electron-donating and electron-withdrawing groups were equally tolerated (Table 3). However, napthyl-substituted 2-aminopyrimidine **2e** was obtained in relatively lower yield (63%). A plausible mechanism for the synthesis of 2-aminopyrimidine derivatives is proposed in Scheme 1. Substitution of copper cofactor CuTC with compound **1** in the presence of base gives copper thiolate **A**, oxidative addition of palladium to it leads to palladium complex **B**. Treatment of intermediate **B** with ammonia *via* a transmetalation step in the presence of base (K_2CO_3) provides complex **C**, reductive elimination of which

Table 3. Desulfitative amination of pyrimidine-2(1*H*)-thiones **1a–g** obtained *via* Biginelli reaction*



Starting compound	Ar	R	Resulting 2-amino-pyrimidine	Yield, %
1a	4-$MeOC_6H_4$	Et	**2a**	77
1b	4-$BnOC_6H_4$	Et	**2b**	74
1c	4-$O_2NOC_6H_4$	Et	**2c**	71
1d	3,4-$(MeO)_2C_6H_4$	Et	**2d**	72
1e	1-Naphthyl	Et	**2e**	63
1f	4-$BnOC_6H_4$	Me	**2f**	83
1g	3,4-$(MeO)_2C_6H_4$	Me	**2g**	73

* Reaction conditions: pyrimidine-2(1*H*)-thione **1a–g** (0.5 mmol), 0.4 M NH_3 solution in THF (2.5 mmol), $Pd(OAc)_2$ (5 mol %), CuTC (1.1 equiv), 1,10-phenanthroline (10 mol %), K_2CO_3 (1 mmol), toluene (2 ml), air atmosphere.

affords product **D** leaving behind the palladium catalyst. Further air-promoted dehydrogenation in dihydropyrimidine **D** provides the desired target product **2**.

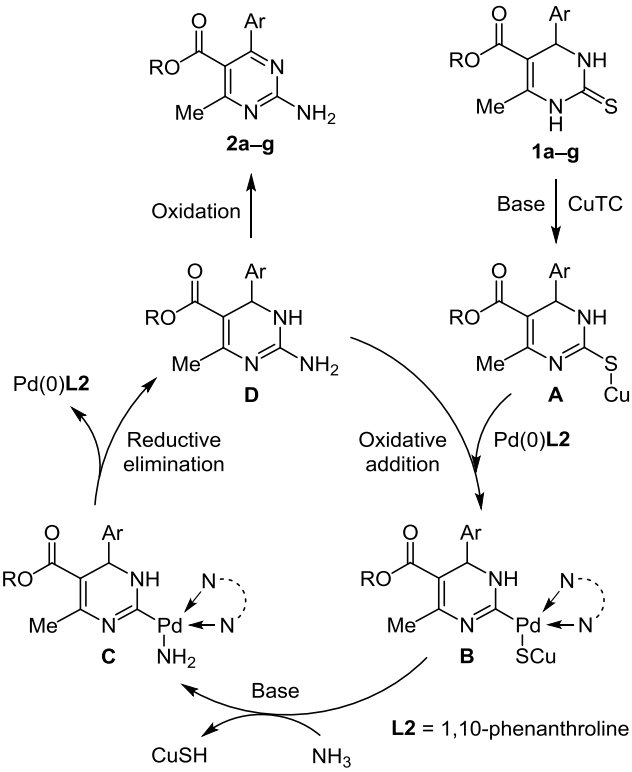
In conclusion, we have discovered a general, highly chemoselective, and efficient method for the synthesis of 2-aminopyrimidines *via* desulfitative amination of sulfur electrophiles and ammonia. We believe that our palladium-mediated desulfitative coupling reaction of ammonia should find widespread application and open new access for metal-mediated cross-coupling reactions of sulfur electrophiles.

Experimental

IR spectra were registered on a PerkinElmer RX-1 spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were registered on a Bruker DRX 300 FT NMR spectrometer (300 and 75 MHz, respectively). ^1H NMR spectra were recorded in $CDCl_3$–DMSO-d_6, 10:1, mixture. ^{13}C NMR spectra were recorded in $CDCl_3$ with complete proton decoupling. TMS was used as internal standard for all NMR spectra. Electrospray ionization mass spectra were recorded on a Micromass Quattro II triple quadruple mass spectrometer. Elemental analyses were performed on a Carlo Erba EA-1108 micro analyzer. All compounds were analyzed for C, H, N and the results obtained were within ±0.4% of least count error of the instrument. Melting points were detected on a Buchi-530 melting point apparatus and are uncorrected.

All reactions were carried out in oven- or flame-dried glassware unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using precoated silica gel glass plates (0.25 mm) with a F254 indicator. Visualization was accomplished by UV light (254 nm). Flash column chromatography was performed using silica gel (100–200 mesh). Yields refer to pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification.

Scheme 1. Plausible mechanism for the desulfitative amination



Pyrimidine-2(1*H*)-thiones **1a–g** were obtained using literature procedure.[32,33]

Synthesis of 2-aminopyrimidines 2a–g *via* Pd-assisted desulfitative amination (General method). An oven-dried vial containing a stir bar was charged with pyrimidine-2(1*H*)-thione **1a–g** (0.50 mmol), $Pd(OAc)_2$ (6 mg, 25 μmol, 5 mol %), CuTC (105 mg, 0.55 mmol, 1.1 equiv), 1,10-phenanthroline (9 mg, 0.05 mmol, 10 mol %), and K_2CO_3 (138 mg, 1.00 mmol). Then PhMe (2 ml) and 0.4 M solution of NH_3 in THF (6.25 ml, 2.50 mmol) were sequentially added *via* syringe. The reaction mixture was stirred at 110°C under air atmosphere. The completion of reaction was monitored by TLC. The reaction mixture was cooled to room temperature and then extracted with water (3 × 20 ml) and EtOAc (3 × 20 ml). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by column chromatography on silica gel.

Ethyl 2-amino-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (2a). White solid. Mp 100–102°C. R_f 0.59 (EtOAc–hexane, 3:7). IR spectrum, ν, cm^{-1}: 3425, 3317, 1715, 1552, 1255. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.06 (3H, t, *J* = 6.0, $OCH_2C\underline{H}_3$); 2.48 (3H, s, 6-CH_3); 3.86 (3H, s, $ArCH_3$); 4.11 (2H, q, *J* = 9.0, $OC\underline{H}_2CH_3$); 5.25 (2H, s, NH_2); 6.94 (2H, d, *J* = 9.0, H Ar); 7.53 (2H, d, *J* = 9.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.9; 22.9; 55.5; 61.4; 114.0; 116.4; 129.7; 131.1; 161.1; 162.1; 165.8; 167.4; 169.1. Mass spectrum, *m*/*z*: 287 $[M]^+$. Found, %: C 62.20; H 5.81; N 13.96. $C_{15}H_{17}N_3O_3$. Calculated, %: C 62.71; H 5.96; N 14.62.

Ethyl 2-amino-4-(4-benzyloxyphenyl)-6-methylpyrimidine-5-carboxylate (2b). White solid. Mp 93–95°C. R_f 0.63 (EtOAc–hexane, 2:8). IR spectrum, ν, cm^{-1}: 3319,

3196, 1713, 1559, 1252. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.01 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.47 (3H, s, 6-CH_3); 4.08 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.13 (2H, s, $OC\underline{H}_2Ph$); 5.90 (2H, s, NH_2); 7.00 (2H, d, *J* = 8.7, H Ar); 7.28–7.46 (5H, m, H Ph); 7.50 (2H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.9; 21.2; 22.0; 61.5; 70.1; 114.9; 116.1; 127.6; 128.2; 128.8; 129.7; 130.2; 130.9; 136.7; 160.3; 161.9; 166.3; 167.6; 168.7; 176.1. Mass spectrum, *m*/*z*: 364 $[M+H]^+$. Found, %: C 69.20; H 5.69; N 11.02. $C_{21}H_{21}N_3O_3$. Calculated, %: C 69.41; H 5.82; N 11.56.

Ethyl 2-amino-6-methyl-4-(4-nitrophenyl)pyrimidine-5-carboxylate (2c). White solid. Mp 158–160°C. R_f 0.57 (EtOAc–hexane, 3:7). IR spectrum, ν, cm^{-1}: 3415, 3312, 1703, 1556, 1270. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.00 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.54 (3H, s, 6-CH_3); 4.07 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.38 (2H, s, NH_2); 7.69 (2H, d, *J* = 8.7, H Ar); 8.28 (2H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.9; 23.3; 61.7; 116.5; 123.7; 129.2; 145.2; 148.5; 162.0; 164.6; 167.8; 168.8. Mass spectrum, *m*/*z*: 303 $[M+H]^+$. Found, %: C 54.20; H 4.24; N 18.12. $C_{14}H_{14}N_4O_4$. Calculated, %: C 55.63; H 4.67; N 18.53.

Ethyl 2-amino-4-(3,4-dimethoxyphenyl)-6-methylpyrimidine-5-carboxylate (2d). White solid. Mp 93–95°C. R_f 0.60 (EtOAc–hexane, 3:7). IR spectrum, ν, cm^{-1}: 3374, 3268, 1710, 1560, 1269. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.46 (3H, s, 6-CH_3); 3.93 (6H, s, $2OCH_3$); 4.10 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.94 (2H, s, NH_2); 6.89 (2H, d, *J* = 8.2, H Ar); 7.28 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.9; 21.2; 22.0; 56.0; 61.6; 110.8; 111.2; 116.2; 121.2; 130.7; 149.0; 161.9; 166.1; 168.7; 176.0. Mass spectrum, *m*/*z*: 318 $[M+H]^+$. Found, %: C 60.20; H 5.79; N 13.02. $C_{16}H_{19}N_3O_4$. Calculated, %: C 60.56; H 6.03; N 13.24.

Ethyl 2-amino-6-methyl-4-[4-(1-naphthyl)phenyl]-pyrimidine-5-carboxylate (2e). White solid. Mp 106–108°C. R_f 0.55 (EtOAc–hexane, 3:7). IR spectrum, ν, cm^{-1}: 3388, 3268, 1701, 1541, 1254. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.42 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.59 (3H, s, 6-CH_3); 3.65 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.50 (2H, s, NH_2); 7.38–7.52 (4H, m, H Ar); 7.72–7.75 (2H, m, H Ar); 7.86–7.91 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.9; 22.7; 61.2; 112.4; 123.2; 126.4; 128.6; 129.7; 130.2; 132.4; 136.2; 138.7; 142.2; 143.9; 162.5; 163.7; 164.7; 169.8. Mass spectrum, *m*/*z*: 309 $[M+2H]^+$. Found, %: C 70.16; H 5.19; N 13.17. $C_{18}H_{17}N_3O_2$. Calculated, %: C 70.34; H 5.58; N 13.67.

Methyl 2-amino-4-(4-benzyloxyphenyl)-6-methyl-pyrimidine-5-carboxylate (2f). White solid. Mp 130–132°C. R_f 0.61 (EtOAc–hexane, 2:8). IR spectrum, ν, cm^{-1}: 3474, 3306, 1716, 1550, 1248. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (3H, s, 6-CH_3); 3.65 (3H, s, OCH_3); 5.13 (2H, s, $OC\underline{H}_2Ph$); 5.33 (2H, s, NH_2); 7.01 (2H, d, *J* = 8.7, H Ar); 7.28–7.46 (5H, m, H Ph); 7.52 (2H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.6; 29.7; 52.1; 114.8; 115.7; 127.5; 127.7; 128.0; 128.2; 128.6; 129.5; 130.0; 131.0; 136.2; 136.6; 160.0; 162.0; 165.5; 167.2; 169.4. Mass spectrum, *m*/*z*: 350 $[M+H]^+$. Found, %: C 68.02; H 5.19; N 11.92. $C_{20}H_{19}N_3O_3$. Calculated, %: C 68.75; H 5.48; N 12.03.

Methyl 2-amino-4-(3,4-dimethoxyphenyl)-6-methyl-pyrimidine-5-carboxylate (2g). White solid. Mp 103–105°C. R_f 0.60 (EtOAc–hexane, 2:8). IR spectrum, ν, cm^{-1}: 3422, 3368, 1717, 1554, 1268. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (3H, s, 6-CH_3); 3.67 (3H, s, $COOCH_3$); 3.93 (6H, s, $Ar(OCH_3)_2$); 5.40 (2H, s, NH_2); 7.13 (2H, d, *J* = 8.3, H Ar); 7.28 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.4; 40.9; 52.2; 55.9; 110.7; 111.0; 115.9; 120.9; 130.8; 148.9; 150.5; 161.9; 165.4; 167.1; 169.5. Mass spectrum, *m*/*z*: 304 $[M+H]^+$. Found, %: C 59.20; H 5.19; N 13.22. $C_{15}H_{17}N_3O_4$. Calculated, %: C 59.40; H 5.65; N 13.85.

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