A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201706915
Angew. Chem. 10.1002/ange.201706915

Link to VoR: http://dx.doi.org/10.1002/anie.201706915
http://dx.doi.org/10.1002/ange.201706915

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10.1002/anie.201706915

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Copper-Catalyzed Synthesis and Applications of Yndiamides

Steven J. Mansfield, Kirsten E. Christensen, Amber L. Thompson, Kai Ma, Michael W. Jones, Aroonroj Mekareeya and Edward A. Anderson*

Abstract: The first synthetic route to yndiamides, a novel class of double aza-substituted alkyne, has been established *via* copper (I)-catalyzed cross-coupling of 1,1-dibromoenamides with nitrogen nucleophiles. The utility of these compounds is demonstrated in a range of transition metal- and acid-catalyzed transformations, which afford a wide variety of 1,2-diamide functionalized products.

Ynamides (**1**, Figure 1) are extremely versatile building blocks in organic synthesis.[1] Their rich chemistry can in part be attributed to the conjugation and polarization effects afforded by the amide group, which leads to heightened reactivity and regioselectivity in their reactions. In contrast, the synthesis and chemistry of yndiamides (**2**), acetylenes featuring two amido substituents, is unknown.[2] This class of alkyne would be of considerable interest as a synthetic building block – as well as introducing an additional nitrogen substituent, yndiamides could exhibit distinct reactivity compared to ynamides. Here we report the first method for the preparation of yndiamides, and an exploration of their unique reactivity, which reveals them to be valuable components in azacycle synthesis.

Exploration of potential yndiamide precursors revealed the copper-catalyzed coupling of 1,1-dibromoenamide **3a**[3] with sulfonamide **4a** to be most promising (Table 1).[4] While conditions developed for dibromoalkene-amide coupling (CuI, dmeda, Cs_2CO_3)[5] led mainly to decomposition of **3a** (Entry 1), those more usually applied to bromoalkynes ($CuSO_4$•$5H_2O$, 1,10-phenanthroline, K_3PO_4)[6] delivered appreciable amounts of yndiamide **2a**, along with the byproduct bromoketene aminal **5a** (Entries 2, 3). **5a** was formed almost exclusively in the absence of the copper salt (Entry 4), suggesting its origin to be independent of yndiamide formation. While the use of CuI led to similar results (Entry 5),[7] the formation of **5a** could be reduced by using a lower loading of Cs_2CO_3 (Entry 6), with THF being superior to solvents such as toluene, acetonitrile or DMF. The choice of 1,10-phenanthroline as ligand was crucial, with other imine-based ligands proving ineffective (Entries 7, 8). Lowering the reaction temperature to 60 °C dramatically improved the proportion of yndiamide, with **2a** isolated in 83% yield (Entry 9).

A variety of amide nucleophiles **4** were screened using these optimized conditions. Sulfonamides and phosphoramidates[8] underwent smooth coupling with **3a**, giving yndiamides **2b**-**s** in high yields (Figure 2a).[9] A wide range of functionality was tolerated on the amide, including alkenes and alkynes (**2g**-**m**, **2o**), esters (**2p**), acetals (**2p**-**q**), silyl ethers (**2r**) and heterocycles (**2s**). Evaluation of dibromoenamide scope (Figure 2b) showed that sulfonamide-based enamides were required for effective coupling, with amides or carbamates proving unreactive.[9] The

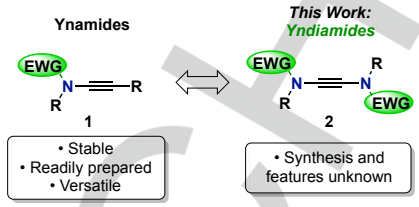
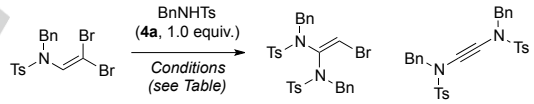


Figure 1. Comparison between ynamides and yndiamides.

sidechain of the sulfonamide was readily varied, leading to a selection of difunctionalized yndiamides (**2j**, **2t**-**bb**). The flexibility of this approach to unsymmetrical yndiamides is emphasized by compounds **2j** and **2x**, which could be made from either of their respective sulfonamide / enamide partners in comparable yields (**2j**: 78 / 79%; **2x**: 72 / 79%). Efficiency was maintained on larger scales, with >3 g of yndiamide **2j** prepared using 10 mmol (5 g) of **3a** (61%). Throughout, the yndiamides were found to be bench stable compounds (see inset) which can be routinely purified *via* silica gel chromatography.

Single-crystal X-ray analysis[10] revealed that yndiamides possess highly twisted conformations,[11] with C-N-N-C dihedral angles generally between 60–100° (Figure 3).[9] The amide substituents adopt near trigonal planar arrangements, and alkyne bond lengths were found to range from 1.17–1.19 Å (c.f.

Table 1. Selected optimization of yndiamide formation.



Entry	[Cu]/L (equiv.)	Base (equiv.)	T (°C)	Solvent	**3a**:**4a**:**5a**:**2a**[a]
1	CuI (0.12) dmeda (0.18)	Cs_2CO_3 (4.0)	60 60	dioxane DMF	0:90:10:0 0:78:15:7
2	$CuSO_4$·$5H_2O$ (0.2) 1,10-phen (0.4)	K_3PO_4 (2.5)	110 85	PhMe	11:10:20:59 10:10:10:70
3	$CuSO_4$·$5H_2O$ (0.2) 1,10-phen (0.4)	K_3PO_4 (4.0)	85[b]	THF	13:11:10:66
4	-	Cs_2CO_3 (4.0)	85	THF	0:0:94(**92**):6
5	CuI (0.2) 1,10-phen (0.4)	Cs_2CO_3 (4.0)	85	THF	3:0:33:64
6	CuI (0.2) 1,10-phen (0.4)	Cs_2CO_3 (2.5)	85	THF	2:2:21:75
7	CuI (0.2) bipy (0.4)	Cs_2CO_3 (2.5)	85	THF	9:11:73:7
8	CuI (0.2) terpy (0.4)	Cs_2CO_3 (2.5)	85	THF	6:8:80:6
9	CuI (0.2) 1,10-phen (0.4)	Cs_2CO_3 (2.5)	60	THF	9:0:2:89(**83**)

[a] Ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after 18 h. Isolated yields in parentheses. [b] Sealed tube. Ts = 4-$MeC_6H_4SO_2$; dmeda = *N*,*N*'-dimethylethylenediamine; 1,10-phen = 1,10-phenanthroline; bipy = 2,2'-bipyridine; terpy = 2,2':6',2''-terpyridine.

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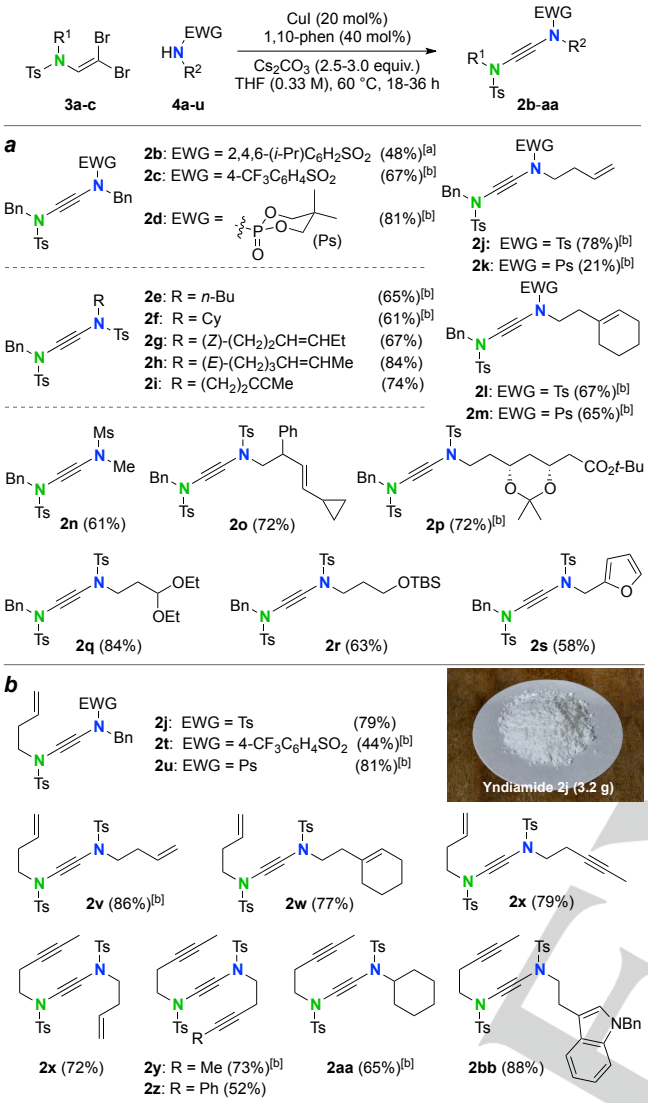

Figure 2. Yndiamide synthesis. **a:** amide scope (**4**). **b:** dibromoenamide scope (**3**). Isolated yields are given. [a] Bromoketene aminal **5b** (see SI) was also produced in this reaction (28% yield); [b] X-ray crystallographic data has been obtained for this compound.[9-10] Cy = cyclohexyl; Ms = $MeSO_2$; Ps = $Me_2C(CH_2O)_2PO$; TBS = *t*-$BuMe_2Si$.

'typical' alkyne = ~1.20 Å). This behaviour was also manifested in solution, with ^{1}H NMR spectra of **2o** and **2p** showing the diastereotopic nature of the benzylic protons, despite being rather remote from the stereocenter(s), thus implying restricted rotation of the axially chiral yndiamide. This conformational effect was found to derive from stereoelectronic factors: DFT calculations (B3LYP/6-31G)[9] showed partial conjugation of the lone pairs of both nitrogen atoms with each of the alkyne π systems (to different extents, according to the dihedral angles between the N lone pair and the C p-orbitals). This results in two near-degenerate alkyne-centered HOMOs for the yndiamide, compared to HOMOs of rather different energy for an ynamide. Interestingly, the LUMO of the yndiamide also extends across the whole N-C-C-N structure, encompassing both N-S σ* orbitals, and is thus lowered in energy compared to that of an ynamide.

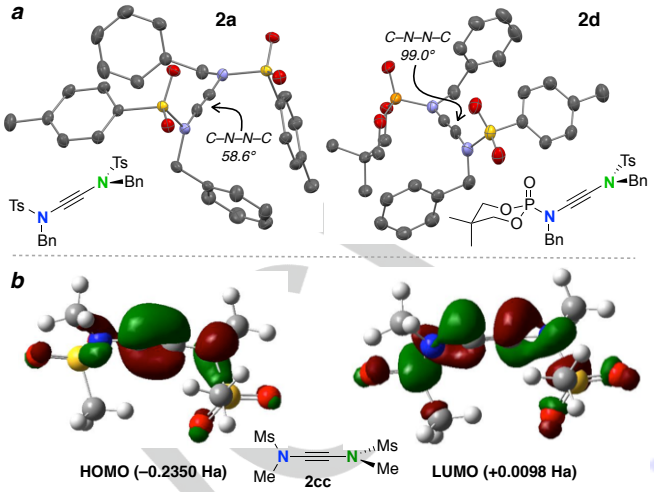

Figure 3. a) Solid state structures[10] of **2a** and **2d**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms are omitted for clarity. **b)** HOMO and LUMO shapes for yndiamide **2cc** (B3LYP/6-31G).[9]

Yndiamides proved excellent substrates for a variety of transformations. Palladium-catalyzed cycloisomerizations using $Pd(OAc)_2$ / bbeda (Table 2, Entries 1-6)[12] proceeded at reduced rates compared to equivalent ynamides,[12a, b] but afforded 1,3-diene **6a** and various 1,4-dienes, including spirocycle **6d**, in good yields (72-79%, Entries 1-4).[13] High levels of substrate stereocontrol were observed in the reaction of vinylcyclopropane **2o**, which gave triene **6e** as a single diastereomer at the newly-formed stereocenter (66%, Entry 6). In contrast to ynamides, bbeda was an essential component in these cyclizations; in its absence, the reaction of **2j** resulted in the surprising formation of imine **6f** (63%, Entry 6) following initial rapid formation of diene **6a**. It is possible that bbeda suppresses further reaction of **6a** by promoting decomplexation of palladium from the product.

Rh-catalyzed [5+2] cycloisomerization of vinylcyclopropane yndiamide (–)-**2o** yielded a single diastereomer of the 5,7-fused bicycle **7** (Entry 7),[14] again requiring more forcing conditions compared to equivalent ynamides. However, cyclization of triynes **2y** and **2z** using Wilkinson's catalyst[15] proceeded more rapidly than related ynamides, giving pyrroloindolines **8a** and **8b** in excellent yields (91-96%, Entries 8, 9).[16] Pauson-Khand reaction of **2j** afforded the amidocyclopentenone **9** (88%, Entry 10), while Au-catalyzed cyclization led to cyclobutenamide **10** (Entry 11), an outcome that is again distinct from equivalent ynamide chemistry, which affords ring-opened products.[17]

Yndiamide activation could also be achieved using Brønsted acids. Treatment of **2a** with triflic acid gave dihydroisoquinoline **11** (78%, Entry 12), while use of trifluoroacetic acid led to amide **12** (*via* the enol trifluoroacetate, Entry 13). These reactions reveal the potent reactivity of yndiamides towards Brønsted acids, and in the former case represent the first test of 5- vs 6-membered ring formation in keteniminium ion cyclizations.[18] Finally, reaction of **2q** with HCl resulted in smooth conversion to enone **13** (Entry 14), presumably *via* a 1,5-hydride transfer onto an intermediate keteniminium ion.[1l, 19]

Further transformations of dienamide **6a** underline the utility of yndiamides. Diels-Alder reactions with *N*-phenylmaleimide,

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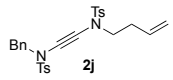
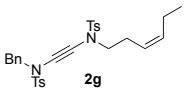
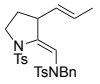
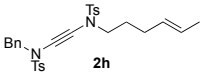
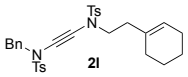
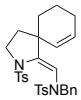
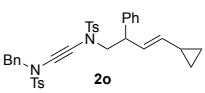
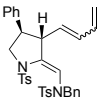
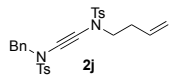
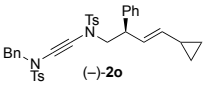
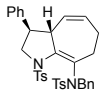
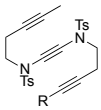
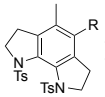
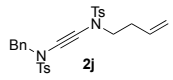
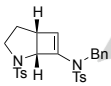
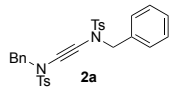
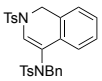
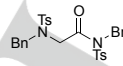
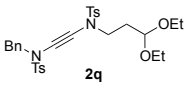
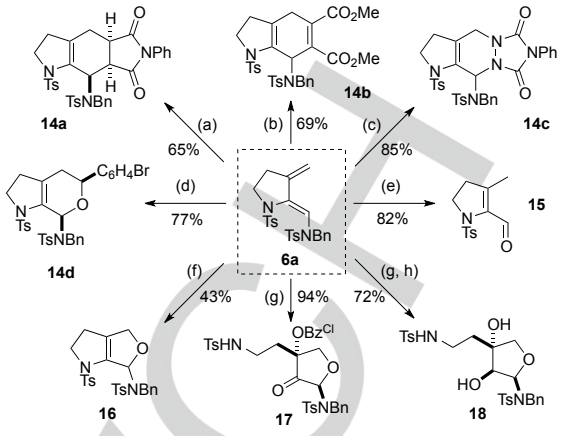
Table 2. Transition metal- and acid-catalyzed reactions of enyndiamides.

Entry	Substrate	Condns (t)[a]	Product	Yield (%)[b]
1	 **2j**	**A** (40 min)	 **6a**	73
2	 **2g**	**A** (25 min)	 (*E*)-**6b**	79[c]
3	 **2h**	**A** (90 min)	 **6c**	72[d]
4	 **2l**	**A** (30 min)	 **6d**	73[e]
5	 **2o**	**A** (60 min)	 **6e**	66[f]
6	 **2j**	**B** (35 min)	 **6f**	63[g]
7	 (–)-**2o**	**C** (16 h)	 **7**	58
8	 **2y**: R = Me **2z**: R = Ph	**D** (2 h)	 **8a**: R = Me **8b**: R = Ph	96
9		**D** (8 h)		91
10	 **2j**	**E** (5 h)	 **9**	88
11		**F** (8 h)	 **10**	51
12	 **2a**	**G** (10 min)	 **11**	78
13		**H** (10 min)	 **12**	86
14	 **2q**	**I** (24 h)	 **13**	63

[a] Conditions **A**: $Pd(OAc)_2$ / *N*,*N*′-bis(benzylidene)ethylene diamine (bbeda) (10 mol%), PhMe, 60 °C; **B**: $Pd(OAc)_2$ (10 mol%), PhMe, 60 °C; **C**: $[(C_{10}H_8)Rh(cod)]SbF_6$ (5 mol%), 1,2-dichloroethane, 80 °C; **D**: $RhCl(PPh_3)_3$ (10 mol%), PhMe, 50 °C; **E**: $Co_2(CO)_8$ (1.1 equiv.), PhMe, 110 °C; **F**: $AuCl(PPh_3)$ / $AgSbF_6$ (30 mol%), CH_2Cl_2; **G**: TfOH (2.0 equiv.), CH_2Cl_2, –60 °C; **H**: CF_3CO_2H (2.0 equiv.), silica gel, CH_2Cl_2, 0 °C; **I**: HCl (1.8 equiv.), dioxane, $CHCl_3$; [b] Isolated yields; [c] 81:15:4 (*E*)-**6c**:(*Z*)-**6c**:1,5-diene; [d] 85:15 **6d**:1,3-diene; [e] 85:15 **6e**:1,5-diene; [f] 57:43 (*Z*)-**6f**:(*E*)-**6f**; [g] NMR yield; cod = cycloocta-1,5-diene, Tf = CF_3SO_2.

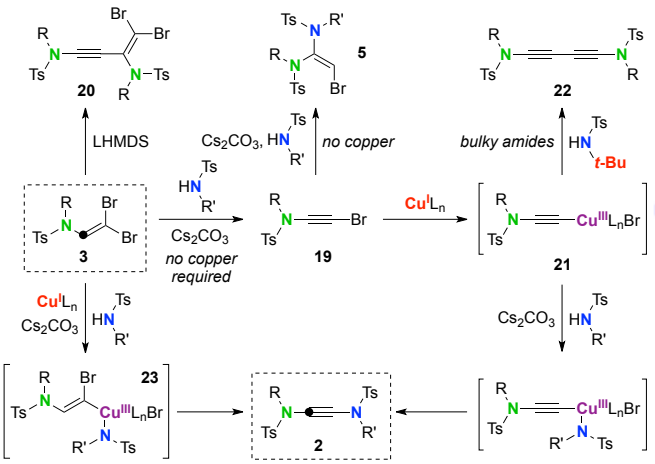
dimethylacetylene dicarboxylate, and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) afforded cycloadducts **14a-c**, all in high yields (65-85%). Dihydropyran **14d** was formed as a single regio- and diastereoisomer through Lewis acid-catalyzed reaction of **6a** with 4-bromobenzaldehyde, a result which shows the powerful electron-donating effect of the exocyclic enamide compared to



Scheme 1. Conditions: (a) *N*-phenylmaleimide (1.0 equiv.), PhMe, 60 °C; (b) $MeO_2CC{\equiv}CCO_2Me$ (1.0 equiv.), PhMe, 60 °C; (c) PTAD (1.0 equiv.), PhMe, rt; (d) 4-BrC_6H_4CHO (1.1 equiv.), $BF_3{\bullet}OEt_2$ (0.5 equiv.), CH_2Cl_2, –78 °C; (e) CF_3CO_2H (2.0 equiv.), CH_2Cl_2, –60 °C; (f) *m*-CPBA (1.5 equiv.), CH_2Cl_2, –78 °C; (g) *m*-CPBA (5.0 equiv.), CH_2Cl_2, –78 °C; (h) $NaBH_4$ (5.0 equiv.), $MeOH/CH_2Cl_2$, rt, then 15% NaOH (aq), rt. Bz^{Cl} = 3-ClC_6H_4CO.

the pyrrolidine nitrogen atom.[20] Similarly, acidic hydrolysis afforded enal **15** exclusively. Oxidation of **6a** with 1.5 equivalents of *m*-CPBA gave dihydrofuran **16**, which underwent further oxidation using excess *m*-CPBA to give keto-ester **17** (94%). Reduction / hydrolysis of **17** led to a single diastereomer of the unusual, highly functionalized aminosugar **18** (72%).

In considering possible mechanisms for yndiamide formation bromoynamide **19** (Scheme 2) is an attractive intermediate. This is also the likely source of bromoketene aminal **5** (the near exclusive product in the absence of copper catalyst), and could arise from elimination of HBr by the amide anion, albeit efforts to prepare **19** using LiHMDS led only to isolation of the formal bromoynamide dimer **20**.[9] Attempted conversion of the ketene aminal **5** to the yndiamide failed under a variety of conditions, which likely rules out a vinylidene carbene rearrangement pathway (also supported by a ^{13}C labelling experiment as shown in Scheme 2, where a single labelled yndiamide was formed).[9] If the bromoynamide is indeed a reaction intermediate, formation of a copper acetylide such as **21** could offer a feasible route for



Scheme 2. Possible mechanisms for yndiamide formation.

C–N bond formation. Circumstantial evidence for the formation of **21** was found in the isolation of byproduct diyndiamide **22** in reactions with hindered amide coupling partners. Alternative routes, such as amido-cupration of **19** followed by β-elimination of bromide, or direct amination of the dibromoenamide (**23**) followed by elimination of HBr, cannot be ruled out at this stage.

In conclusion, we report the first route to yndiamides – novel, bench-stable alkyne derivativ es that are readily prepared from simple precursors. Yndiamides are highly versatile, and provide access to a range of nitrogen-substituted frameworks using transition metal- or acid-catalyzed processes. Their unique reactivity profile, which both mirrors and contrasts with that of ynamides, suggests significant potential for future applications.

Acknowledgements

SJM is supported by the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1). EAA thanks the EPSRC (EP/M019195/1). AM thanks the Royal Thai Government and the DPST project for a studentship. We thank Diamond Light Source for beamtime on I19-1 (MT13639), and Niels Marien for assistance with DFT calculations.

Keywords: copper catalysis • cycloisomerization • heterocycles • yndiamide • ynamide

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10.1002/anie.201706915

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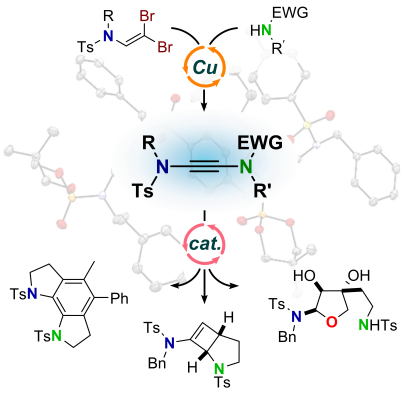
Die, amide! The first synthetic route to yndiamides, a novel class of double aza-substituted alkyne, has been established *via* copper (I)-catalyzed cross-coupling of 1,1-dibromoenamides with nitrogen nucleophiles. The utility of these compounds is demonstrated in a range of transition metal- and acid-catalyzed transformations, which afford a wide variety of 1,2-diamide functionalized products.



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