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The diverse reactivity of homopropargylic amines as the "masked" 1C synthons for the aza-Friedel-Crafts alkylation of indoles

Hao Chen,[a]† Ming Ni,[c]† Xiaofeng Bao,[c] Chan Wang,[a] Lingyan Liu,*[a] Weixing Chang,[a] Jing Li,*[a],[b]

Dedication ((optional))

Abstract: A novel type of "masked" **1C** synthons was developed through the hydroamination cyclization-protonation of homopropargylic amines to act as aza-Friedel-Crafts alkylation reagents to react with indoles. And a variety of 3-(2-pyrrolidinyl)indoles were generated in good to high yields. More significantly, some of these corresponding products display potential bioactivity for the anti-chlamydial infection, which specifically target the mid-stage of the chlamydial life cycle by interfering with RB replication.

Introduction

The development of new synthetic methodologies for the access to the bioactive targets has attracted increasing attention in the field of organic synthetic chemistry.[1] Among them, the cascade reaction for the combination of two or more bioactive fragments is particularly important as its high efficiency and atom economy as well as potential new bioactivity of the corresponding products. For instance, the pyrrolidines and indoles are the dominant structural frames or building blocks in most biologically active molecules and natural products.[2] Combining these two bioactive fragments to a molecule, new bioactivity may be brought about. Currently, little research work dabbles in the synthesis and bioactivity assessment of the 3-(2-pyrrolidinyl)indoles.[3] To the best of our knowledge, only niggard literatures present the pyrrolidinylindoles are potent and selective 5-HT agonists. Of these, Eletriptan (R)-pyrrolidinylindole, which was approved in the United States in 2002, is assigned to the class of triptans drugs. It is a low volume product at present (Figure 1).

On the other hand, 3-substituted Indole derivatives have always received considerable attention due to their significant bioactivities, such as antibacterial, antioxidant and insecticidal properties as well as antibiotics.[4] Of particular note in this regard are Friedel-Crafts alkylation strategies that employ various alkylation reagents, nitrostyrenes, α,β-unsaturated carbonyl compounds (aldehydes, ketones and esters) and imines, including acyclic and cyclic imines.[5] whereas the cyclic imines are sparse. Therefore, developing new cyclic amino-alkylation reagents for the indole derivation are highly desirable from two aspects of both expanding organic synthetic chemistry range and exploring novel bioactive molecules.

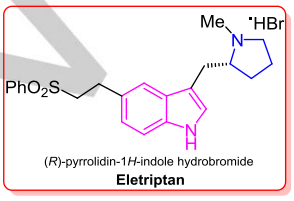
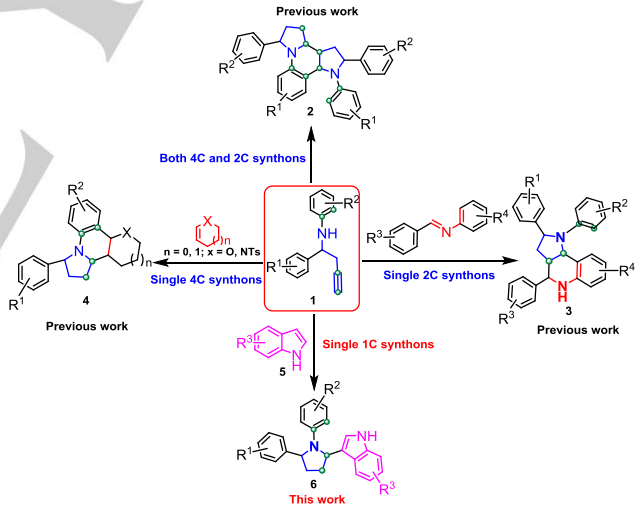


Figure 1. The 3-pyrrolidinylindole drug



Scheme 1. The diverse reactivity of homopropargylic amines

The Gold-catalyzed the intramolecular hydroamination cyclization cascade reactions of homopropargylic amines or amides have been successfully developed.[6] Our research group has reported various cascade reactions of homopropargylic amines **1** in the presence of copper salts and provided simple and facile synthetic routes for the construction of complex fused N-containing heterocycles (Scheme 1).[7] Among these reactions, the key cycloenamine or cycloiminium intermediate was involved to act as **2C** synthon or **4C** synthon, respectively. Thus, we herein envisioned to introduce indole molecule, which may serve as **2C** synthon to react with the

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† Hao Chen and Min Ni are the first *co*-author, H Chen completed the synthetic work and M Ni did the bioactivity assay.

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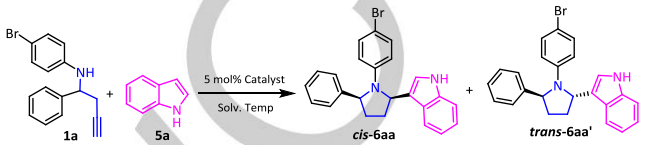
homopropargylic amine **1**. Nevertheless, the unexpected pyrrolidine-substituted indole derivative **6** was obtained in good to high yields via a formal Friedel-Crafts alkylation of indole and pyrrolocycloiminiun. The results indicated that the homopropargylic amines can be considered as a "masked" **1C** synthon besides the **2C** and **4C** synthons previously developed by us. This interesting reaction emerged a new realm about the Friedel-Crafts alkylation reagents—cycloimimium ions formed in situ through a simple intramolecular hydroamination cyclization and protonation of homopropargylic amines. More importantly, the 3-(2-pyrrolidinyl) indoles are first found to possess the potential bioactivity for the anti-chalmydial infection with the ascendant IC_{50} value (<1 uM).[8] The C. trachomatis infection is known to be one of the most prevalent[9,10] mainly through sexually transmitted pathogenic bacterium in the world.[11] Every year, there are about 92 million new cases all over the world according to the World Health Organization.[10] Chlamydial urogenital infections may lead to various inflammation such as cervicitis, urethritis, pelvic inflammatory disease and infertility.[9] In view of this, we further investigated this cascade reaction between the homopropargylic amines and indoles.

Results and Discussion

Initially, we selected 4-bromo-N-(1-phenylbut-3-yn-1-yl)aniline **1a** and indole **5a** as model substrates. Under the optimal reaction conditions previously developed,[7a] the unexpected 3-pyrrolidine substituted indoles **6aa** and **6aa'** were obtained in moderate yields (entry 1, Table 1). Screening the counterion cation of Cu^{2+} salt, such as $Cu(OAc)_2$, $CuCl_2$ and $CuBr_2$, no improved results were obtained (entries 2-4). In the presence of $Cu(OAc)_2$, only small amount of competitive self-dimerization side product of homopropargylic amine **1a** was obtained with the starting material partially recovered. Changing to employ the CuCl, the target compounds were generated in increased yield of 71% (entry 5). The CuBr catalyst displayed slightly inferior to the CuCl (entry 6). Using other protonic solvents, n-PrOH gave the slightly increased yield of target molecules (77%), whereas i-PrOH in decreased yield (59%) (entries 7 and 8). In the hexafluoroisopropanol (HFIP) solvent, the reaction performed a formal hydroamination cyclization dimerization of the homopropargylic amine **1a** with indole **5a** remaining untouched (entry 9). Increasing the reaction temperature from 50 to 80 °C, the reaction resulted in a decreased yield of target product in the presence of CuCl in n-PrOH solvent (entry 10). Adjusting the amount of indole **5a**, we found that 3.0 equivalent indole provided high yields of 3-(2-pyrrolidinyl)indole products (Table 1, entries 11-13) at 50 ℃. To achieve the better transformation of homopropargylic amine **1a** and indole **5a**, other metal salts were then investigated. However, the $Fe(OTf)_3$, $FeCl_3$, $Fe(acac)_3$ and $ZnCl_2$ were all terrible. Even the typical transition metals catalysts for activating alkynes, such as PPh_3AuCl, PtI_2 or PPh_3RhCl also appeared powerless (Table S1). Moreover, the reactions catalyzed by the CuCl were sluggish in other common used organic solvents, PhMe, CH_3CN, THF, DMF and DCE, whether polar or nonpolar solvents. No obvious product spot was observed by TLC but with complicated reaction systems in all these cases (Table S1). These results demonstrated that only protonic alcohol solvent was suitable. Additionally, it should be noted that the corresponding products **6aa** and **6aa'** were obtained with nearly 1:1 diastereoselectivity of cis-**6aa**/trans-**6aa'** in all cases.

Table 1. Optimization studies of the cascade reaction of homopropargylic amine **1a** and indole **5a**[a].

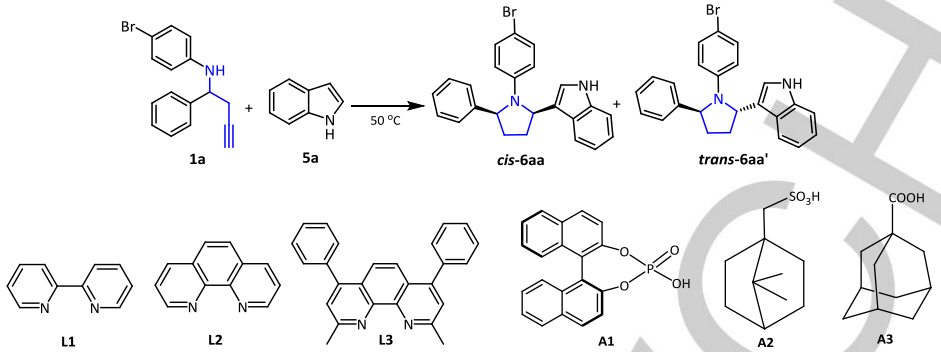


Entry	Catalyst (5 mol%)	Condition	Yield (%)[b]
1	$Cu(OTf)_2$	MeOH, 50 °C	55
2	$Cu(OAc)_2$	MeOH, 50 °C	33[c]
3	$CuCl_2$	MeOH, 50 °C	49
4	$CuBr_2$	MeOH, 50 °C	<10
5	CuCl	MeOH, 50 °C	71
6	CuBr	MeOH, 50 °C	61
7	CuCl	*n*-PrOH, 50 °C	77
8	CuCl	*i*-PrOH, 50 °C	59
9	CuCl	$(CF_3)_2CHOH$, 50 °C	21[c]
10	CuCl	*n*-PrOH, 80 °C	52
11[d]	CuCl	*n*-PrOH, 50 °C	73
12[e]	**CuCl**	***n*-PrOH, 50 °C**	**85**
13[f]	CuCl	*n*-PrOH, 50 °C	50

[a] Standard procedure: Under a nitrogen atmosphere homo- propargylic amine **1a** (30 mg, 0.1 mmol), indole **5a** (17.6 mg, 0.15 mmol, 1.5 equiv.) and 5 mol% catalyst and solvent (1 mL) were sequentially added into the Schlenk tube. The reaction mixture was stirred at given reaction conditions for 12 h. [b] Isolated yield. [c] The product was self-dimerization of homopropargylic amine **4a**. [d] 2.0 equiv. indole **5a**. [e] 3.0 equiv. **5a**. [f] 1.0 equiv. **5a**.

To improve the diastereoselectivity of the product **6aa**, some ligands or additives were introduced (Table 2). Unfortunately, no good results were observed after the great amount of screenings. As shown in Table 2, the introduction of ligands was unfavorable to this reaction with the results that either the expected products could not be obtained or in low yields (entries 2-6 and 10). And the additive rendered no obvious improved diastereoselectivity of corresponding products with decreased yields (Table 2, entries 9-14). Therefore, the optimal reaction conditions were 5 mol% CuCl, 3.0 equiv. indoles, 0.1 M n-PrOH, 50 ℃ for 12 h.

Table 2. The screening of other ligands and Cu salts in the reaction of homopropargylic amine **1a** and indole **5a**[a].



entry	Catal (mol%)	Ligand (mol%)	Additive (mol%)	Solv.	Yield(%)[b]	*dr* (*cis*:*trans*)[c]
1	CuCl (5)	--	--	n-PrOH	85	50:50
2	CuCl (5)	**L1** (10)	--	n-PrOH	24	67:33
3[d]	CuCl (5)	**L2** (10)	--	n-PrOH	--	--
4[d]	CuCl (5)	**L3** (10)	--	n-PrOH	--	--
5[d]	$CuCl_2$ (5)	**L1** (10)	--	n-PrOH	--	--
6[d]	$CuCl_2$ (5)	**L1** (10)	--	toluene	--	--
7	$CuCl_2$ (5)	**--**	--	toluene	36	57:43
8	$CuCl_2$ (5)	**--**	--	n-PrOH	54	54:46
9	$CuCl_2$ (5)	**--**	Al_2O_3	n-PrOH	61	65:35
10[d]	$CuCl_2$ (5)	**L2** (10)	Al_2O_3	n-PrOH	--	--
11	$Cu_2(OH)_2CO_3$ (10)	--	**A1**	toluene	32	64:36
12	$Cu_2(OH)_2CO_3$ (10)	**--**	**A2**	toluene	37	56:44
13	$Cu_2(OH)_2CO_3$ (10)	**--**	**A2** + 4Å MS	toluene	65	66:34
14	$Cu_2(OH)_2CO_3$ (10)	**--**	**A3**	toluene	N. R.	--

[a] Standard procedure: Under a nitrogen atmosphere, homopropargylic amine **1a** (60 mg, 0.2 mmol) and indole **5a** (70 mg, 0.6 mmol, 3.0 equiv.), 5 mol% catalyst, 10 mol% ligand, additive (20 mol%) and solvent (2 mL) were sequentially added into the Schlenk tube. The reaction mixture was stirred at given reaction conditions for 12 h. [b] Isolated yield. [c] The result was determined by the ^{1}H NMR of reaction system. [d] The small amount of compound **8** (SI, Figure S1) was obtained via head-to-head dimerization of terminal alkyne with the starting material remaining surpluses after reacting for 20 h.

With the optimized reaction conditions in hand, we next examined various homopropargylic amines **1** and indoles **5**. As shown in Table 3, all reactions could smoothly proceed and afford the corresponding 3-(2-pyrrolidinyl)indoles in good to high yields. Moreover, the homopropargylic amines with electron-withdrawing substituted aryls on *N* atom or *C* atom generally rendered better yields of corresponding products than that of electron-donating substituted aryls compounds. Especially for the nitro-substituted aryl substrate **1g**, the reaction resulted in the **6ga** and **6ga'** with up to 89% total yields. In two cases of homopropargylic amines with heteroatomic thiophenyl and steric hindrance naphthyl groups, the corresponding 3-pyrrolidinylindoles (**6pa**, **6pa'** and **6qa**, **6qa'**) were produced in good total yields (63% and 84%). Nevertheless, the reaction gave 30% 3-(2-pyrrolidinyl) indole addition product (**6ra** and **6ra'**) with part of *self*-dimerization **7r** (35%) when using the cinnamyl homopropargylic amine, and the cyclohexyl homopropargylic amine delivered only *self*-dimerization side product **7s** in moderate yield (50%). When R^2 was H atom, the reaction afforded the target molecule in low yield (**6ta**, 18%) but with *self*-dimerization side product (**7t**) in 50% yield under the standard reaction conditions. Interestingly, while employing AgOAc/ phosphoric acid derived from binaphthol system in CH_2Cl_2, the **6ta** could be generated in 56% yield. Using *Ts*–protected homopropargylic amine **1u**, no reaction was occurred. Additionally, various indoles with different substituents (Me, MeO, Br) on different positions (2-, 4-, 5-, 7-) were also competent in this reaction (**6ab'**-**6af'**). To our delight, in the cases of the 2-methylindole **5b,** the diastereoselectivities of the corresponding products were generally higher than that of indole **5a**. Especially, the diastereoselectivities of **6ab** and **6ab'**, **6mb** and **6mb'** were high up to 8:92 and 7:93, respectively. However, replacement of the N-H of indole with Me or Boc lead to the complicated system in the reaction of homopropargylic amine **1a** under the optimized reaction conditions (**6ag**, **6ag'** and **6ah**, **6ah'**). Notably, the *trans*-configurational structure was unambiguously confirmed by the *X*-ray single crystal diffraction for the product *trans*-**6ab'** (Figure 2).[12]

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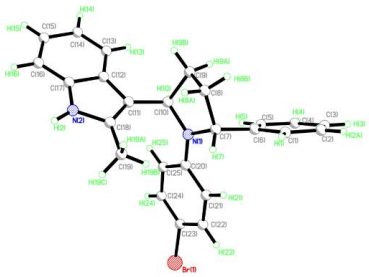
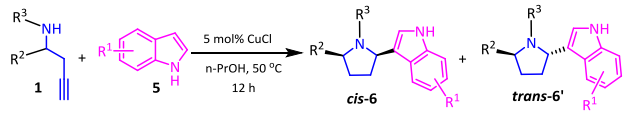
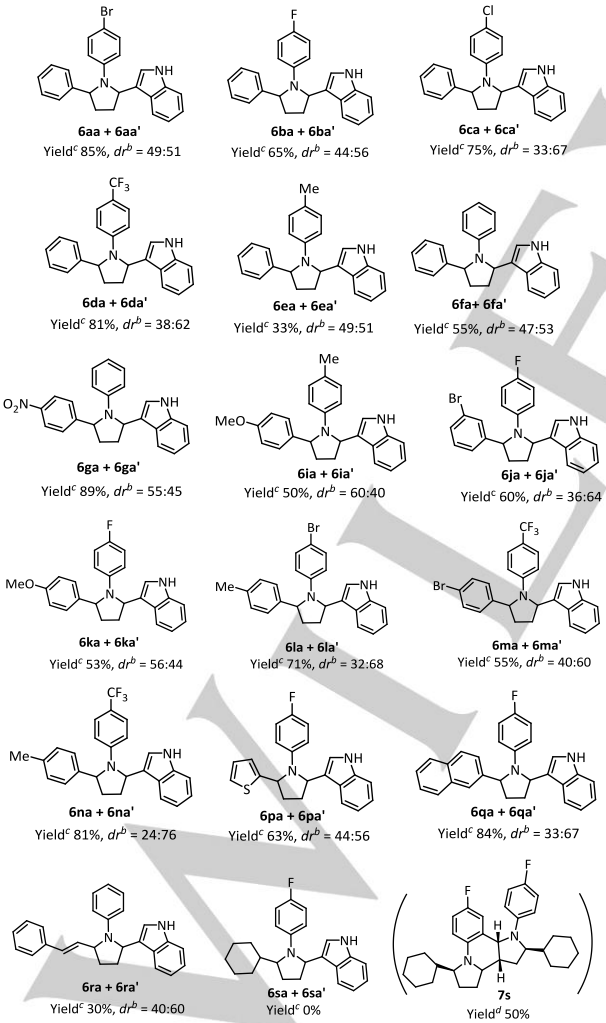


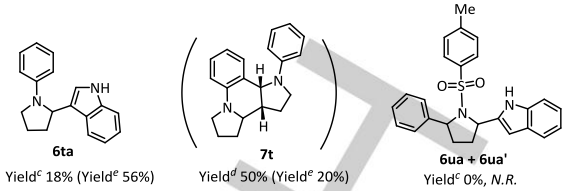
Figure 2. The ORTEP drawing (30% thermal ellipsoids) of *trans*-**6ab'**

Table 3. The hydroamination cyclization-protonation/Friedel-Crafts alkylation of various indoles and homopropargylic amines[a].

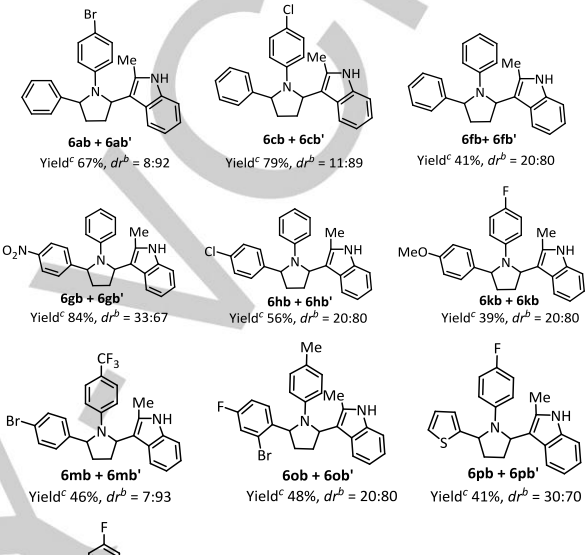


Various homopropargylic amines and indole 5a

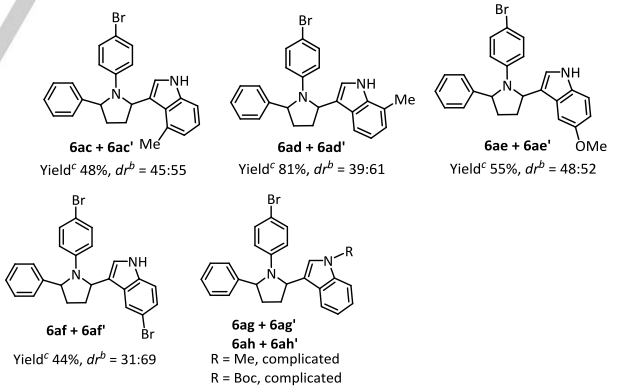




Various homopropargylic amines and indole 5b



homopropargylic amine 1a and various indoles 5c-5h



[a] Standard procedure: Under a nitrogen atmosphere, homo- propargylic amines 1 (0.2 mmol) and indoles 5 (0.6 mmol, 3.0 equiv.) and, 5 mol% CuCl (1 mg, 0.01 mmol) and n-PrOH (2 mL) were sequentially added into the Schlenk tube. The reaction mixture was stirred at 50 °C for 12 h. [b] The diastereoisomers ratios were determined by the ^{1}H NMR. [c] Isolated yield. [d] The product was *self*-dimerization of homopropargylic amine and the yield was determined by the ^{1}H NMR of crude product based on our previous work. [e] The reaction condition was CuCl (5 mol%), AgOAc (10 mol%), phosphoric acid (10 mol%), CH_2Cl_2 (2 mL), 50 °C.

Bioactivity assay (Inhibition of *C. trachomatis* growth by 3-(2-pyrrolidinyl)indoles)

The *anti*-chlamydial effect of the above pyrrolidinylindoles obtained was determined by a reinfection assay that quantified the production of infectious progeny EBs following compounds treatment. Briefly, HeLa cells infected with *C. trachomatis L2* were treated with various concentrations of individual compound as previous and incubated for 36 h, lysed, and the released progeny EBs were used to reinfect fresh HeLa cells. The percent inhibition data of compound-treated samples relative to untreated DMSO control was quantified by counting the recoverable IFUs, corresponding to the number of infectious progeny EBs. The inhibition level was finally evaluated by IC_{50} values that were calculated by non-linear regression using Graphpad Prism 5 software. Cytotoxicity was also assessed on HeLa cells by WST-1 cell proliferation and cytotoxicity kit at 16 *μM* of individual compound, the highest tested concentration, to ensure that any observed inhibitory effects were ascribed to the direct action of the compound on Chlamydial rather than an indirect cytotoxic effect on the host cells. The IC_{50} values and cell viability data of all compounds were presented in Table 4.

Table 4. The IC_{50} values and cell viability data of 3-(2-pyrrolidinyl)indoles.

Entry	Compounds	IC_{50} (*μM*) Mean (Confidence interval)	Cell viability (16 *μM*)
1	**6aa** + **6aa'**	1.54 (1.21 ~ 1.98)	88.56
2	**6ba** + **6ba'**	1.61 (1.26 ~ 2.06)	71.75
3	**6ca** + **6ca'**	1.98 (1.43 ~ 2.73)	52.47
4	**6da** + **6da'**	0.86 (0.77 ~ 0.97)	69.25
5	**6ea** + **6ea'**	**1.28 (0.71 ~ 2.31)**	**99.67**
6	**6fa** + **6fa'**	1.67 (1.34 ~ 2.07)	39.09
7	**6ga** + **6ga'**	**0.63 (0.41 ~ 0.97)**	**100**
8	**6ia**+ **6ia'**	0.62 (0.45 ~ 0.87)	55.70
9	**6ja** + **6ja'**	1.46 (1.36 ~ 1.58)	69.87
10	**6ka** + **6ka'**	**1.09 (0.92 ~ 1.29)**	**100**
11	**6la** + **6la'**	**0.34 (0.25 ~ 0.47)**	66.99
12	**6ma** + **6ma'**	0.59 (0.50 ~ 0.70)	53.10
13	**6na** + **6na'**	1.08 (0.98 ~ 1.19)	45.61
14	**6qa** + **6qa'**	**1.37 (0.91 ~ 2.05)**	**100**
15	**6ab** + **6ab'**	1.83 (1.62 ~ 2.07)	91.12
16	**6ac**+ **6ac'**	1.05 (0.73 ~ 1.50)	64.89
17	**6ad** + **6ad'**	**0.30 (0.23 ~ 0.38)**	80.76
18	**6ae + 6ae'**	**1.86 (0.89 ~ 3.86)**	**100**
19	**6af + 6af'**	**1.58 (1.45 ~ 1.72)**	**98.31**

It was found that the **6la (6la')** and **6ad (6ad')** exhibited the lowest IC_{50} as ~ 0.3 *μM* but owning strong cytotoxicity, the **6ea (6ea'), 6ga (6ga')**, **6ka (6ka')**, **6qa (6qa')**, **6ae (6ae')** and **6af (6af')** revealed the IC_{50} values ~ 1 *μM*, consistent with most of the compounds, while they have no obvious cytotoxicity. Therefore, these six compounds were chosen for further assay to explore the *anti*-chlamydial action mode. Firstly, *C. trachomatis L2 EBs* were pretreated with 16 *μM* of individual compound or 0.5% DMSO for 1 h at 4 °C, and their titers were then quantified on HeLa cell monolayers after washing off the compound. As a result, no detectable decrease of inclusion counts was observed after pretreatment of these six compounds (Fig. 3), demonstrating that the direct EBs inactivation was excluded about the *anti*-chlamydial effect of pyrrolidinylindoles. Next, we added individual compound to the infected cultures at different times postinoculation (Fig. 4A), and then quantified the formation of infectious progenies. As shown in Figure 4B, addition of compound at 2 and 12 h postinoculation resulted in about 100% inhibition, same as the data of compound added simultaneously with chlamydial inoculation (Fig. 4B). Nevertheless, when the compound was added at 24 h postinfection, the inhibition efficacy was significantly dropped for all six compounds. As we known, the EBs differentiated into RBs around 6 h after entry host cell, and the RBs replicate exponentially before they asynchronously reorganize into EBs.[13] The time impact data indicated that trisubstituted pyrroles specifically targeted the *mid*-stage of the chlamydial life cycle by interfering with RB replication. Future studies would focus on the detailed inhibition mechanism.

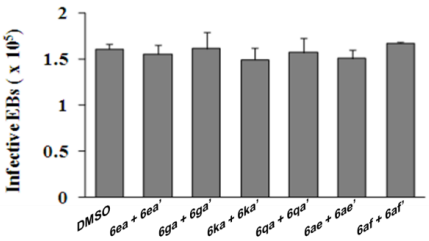


Figure 3. Lack of direct inactivation effect of compounds on chlamydial EBs. C. trachomatis L2 EBs were incubated with 16 *μM* individual compound or 0.5% DMSO at 4 °C for 1 h. The residual chemical was removed by twice washes with SPG. Infective EBs counts were determined by measuring inclusion counts using immunofluorescence staining after inoculation of HeLa cells for 36 h.

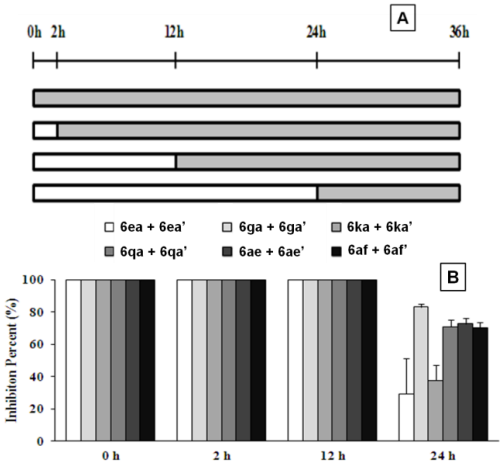


Figure 4. Impact of exposure times on anti-chlamydial effect of compounds. (A) HeLa cells infected with C. trachomatis L2 EBs at MOI of 0.2 were treated with 16 μM of individual compound at different time points as described. (B) The inhibition effect of compounds on the formation of infectious progeny EBs at different time points was determined by counting recoverable IFUs in compound treated samples relative to untreated negative control at 36 h.

Conclusions

In conclusion, the "masked" **1C** synthon role was developed via intramolecular hydroamination cyclization-isomerization of simple homopropargylic amines to act as an aza-Friedel-Crafts alkylation reagent for the indoles. A variety of 3-(2-pyrrolidinyl)indoles were obtained with good to high yields in one pot. This cascade reaction between homopropargylic amines and indoles has the advantages of mild reaction conditions, inexpensive CuCl metal catalyst and the readily available starting materials as well as atom economy with no any wasted small molecules generated. And this reaction actually involved an intramolecular N-H insertion cyclization of alkynes to form dihydropyrrole intermediates, which were followed by the isomerization to give cycloiminium ions, and subsequently performed the aza-Friedel-Crafts alkylation with indoles. More excitedly, this corresponding 3-(2-pyrrolidinyl)- indoles showed excellent anti-chlamydial infection bioactivity. This is the first example about the anti-chlamydial infection bioassay of the pyrrolidinylindoles and will possibly become a potential leading compounds in the antibiotics aspect. Future plans include establishing chiral pyrrolidinylindoles that may be achieved through this methodology with additional chiral ligands, and pursuing other possible bioactivities.

Experimental Section

General Information. The ^{1}H NMR and ^{13}C NMR spectra were recorded at Bruker AV 400 MHz or 600 MHz. ^{1}H and ^{13}C NMR Chemical shifts were calibrated to tetramethylsilane as an internal reference. Chemical shifts are given in (ppm) and coupling constants (J) in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet; High resolution mass spectrometric (HRMS) analyses spectrum was determined on the Varian 7.0T FTMS instrument.

General procedure for synthesis of compound 6. The CuCl (1.0 mg, 5 mol %) was added to a solution of homopropargylic amines **1** (0.2 mmol) and indoles **5** (0.6 mmol) in 2 mL n-PrOH with the atmosphere of N_2, and the mixture was stirred at 50 ℃ until the complete disappearance of the starting material (monitored by TLC). The mixture was passed through a short kieselguhr column by using CH_2Cl_2, the filtration was concentrated in vacuo and purified by column chromatography with gradient elution (Silica gel, petroleum ether : EtOAc, gradient from 200 : 1 to 20 : 1) to give the final product **6**.

Acknowledgements

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Keywords: homopropargylic amines • hydroamination cyclization • Friedel-Crafts alkylation • pyrrolidinylindoles • bioactivity

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[12] Crystal data for the compound ***trans*-6ab'**: C25H23BrN2, MW) 431.36, Orthorhombic, Pna2(1). Final R indices [I>2ó(I)], R1) 0.0220, wR2) 0.0437, R indices (all data) R1) 0.0275, wR2) 0.0442, a) 8.3401 (18) Å, b) 22.365 (5) Å, c) 10.597 (2) Å, V) 1976.5 (8) $Å^3$, T) 113 (2) K, Z) 4. Reflections collected/unique: 24069/4525 (Rint) 0.0241), number of observations [>2ó(I)] 4525, parameters) 258, Goodness-of-fit on F^2) 0.997. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 1515090.

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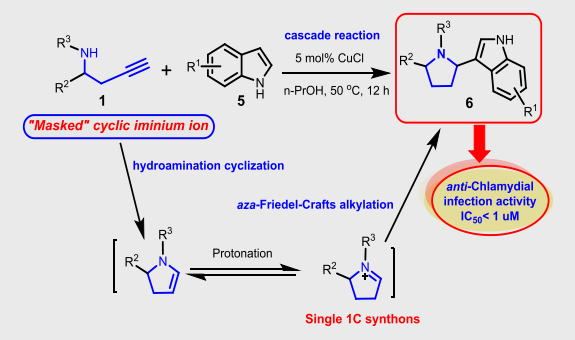

"Masked" Cycloiminium ions*

Hao Chen, Min Ni, Xiaofeng Bao, Chan Wang, Lingyan Liu, Weixing Chang, Jing Li**

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The diverse reactivity of homopropargylic amines as the "masked" 1C synthons for the aza-Friedel-Crafts alkylation of indoles

A novel type of "masked" **1C** synthons was developed through the hydroamination cyclization-protonation of homopropargylic amines to act as aza-Friedel-Crafts alkylation reagents to react with indoles. And a variety of 3-(2-pyrrolidinyl)indoles were generated in good to high yields.

cycloiminium ions formed *in situ*