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Highly regioselective photodimerization of 1,4-dihydropyridines: An efficient synthesis of novel 3,6-diazatetraasteranes

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ABSTRACT

Conventional photocycloaddition of 1,4-dihydropyridines does not afford novel *head-to-head* 3,6-diazatetraasteranes. Herein, we describe a highly regioselective method to synthesize 3,6-diazatetraasteranes via an intramolecular photodimerization of 1,4-dihydropyridines. First, the 1,4-dihydropyridines were tethered by phthaloyl to direct a proximate parallel arrangement in *head-to-head* orientation by the rotation of C–C single bonds in solution. An intramolecular [2 + 2] photocycloaddition proceeded subsequently to give desired 3,6-diazatetraasteranes in high yield (92–97%) and excellent regioselectivity. Furthermore, two different 1,4-dihydropyridines can also be regiocontrolled by this strategy and produce polysubstituted 3,6-diazatetraasteranes via a cross-photodimerization in a concise and efficient way. In addition, this approach can provide direct access to other polysubstituted polyhedron scaffolds from 1,4-dihydropyridine analogues.

1. Introduction

The photodimerization of 1,4-dihydropyridines (DHPs) has attracted considerable interest in recent years.[1] This [2 + 2] photocycloaddition reaction provides access to photodimeric cage compounds, an important structural motif showing significant pharmacological effects as HIV-1 Protease Inhibitors and multidrug resistance (MDR) modulators.[2] Normally, in solid or solution state, the conventional photodimerization of DHPs only yields *head-to-tail* photodimeric cage compounds (3,9-diazatetraasteranes), because of its optimum molecular structure in geometric chemistry.[3] Despite as the important regioisomers, *head-to-head* photodimers of DHPs (3,6-diazatetraasterane derivatives) have not yet been reported before (Scheme 1). Consequently, the regioselective photodimerization of DHPs remains challenging: an available synthetic approach to 3,6-diazatetraasteranes core structures is still awaited.

To construct the novel 3,6-diazatetraasteranes, a regioselective strategy must be adopted to direct a proximate, parallel arrangement of 1,4-dihydropyridines in *head-to-head* orientation. Previously, many regiochemical efforts have been directed toward solvent-free synthesis with molecular templates, host-guests, and large frameworks to control the photocycloaddition regioselectivity of olefinic substrates.[4] The progress of supramolecular chemistry has accelerated the development of intriguing templates that exploit noncovalent interactions such as hydrogen bonding, halogen bonding, π-π interactions, π-cation interactions, and transition metal coordination to influence the relative orientation of olefinic compounds.[5] This approach usually exploits the outstanding regularity and molecular orientation offered by a crystal lattice to control the regions electivity during reaction in solid state.[6]

2. Results and discussion

Unfortunately, our numerous attempts to produce a regioselective photodimerization of DHPs to 3,6-diazatetraasteranes with these solid-state synthesis methods were unsuccessful. The failed experiments clearly revealed a significant limitation for the synthesis of 3,6-diazatetraasteranes in this solid-state way. In spite of the overall success with solid-state photodimerizations, the packing motive and the relative orientation of substrates DHPs remain difficult to control. Because that a proximate, parallel arrangement in *head-to-head* orientation of DHPs requires entropic decrease, and reduction in the degrees of freedom of the unimolecular transition

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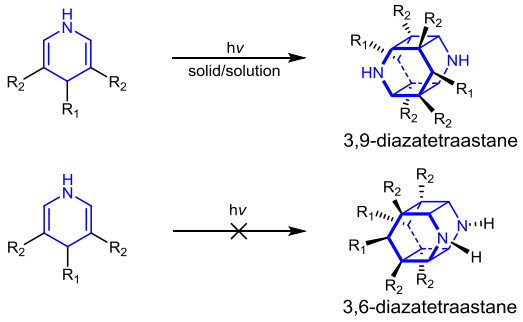


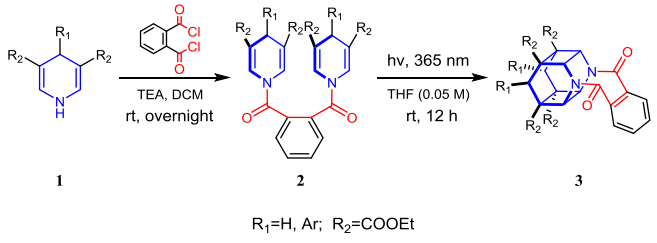
Scheme 1. Previous work of photodimerization of DHPs.

state.[7] So it is indeed difficult and inefficient to regionally control the unimolecular DHPs to form a desired arrangement by utilizing noncovalent interactions.

Herein, we report a strategy for constructing the novel 3,6-diazatetraasterane polycyclic system by a photodimerization of covalently attached DHPs (Scheme 2). The key point of the strategy was the introduction of a rigid linker to tether DHPs and to direct a *head-to-head* orientation firstly. And then, an intramolecular [2 + 2] photocycloaddition followed by the formation of a proximate, parallel arrangement to produce the desired 3,6-diazatetraasteranes.

Table 1 summarizes the results of the synthesis of bis-DHPs **2** and 3,6-diazatetraasteranes **3** from various substrates with different conditions. We initially investigated the nucleophilic substitution with model substrate 1,4-dihydropyridine (**1a**) using TEA as the deacid reagent. Different ratios of phthaloyl dichloride/**1a** were tested, and when phthaloyl dichloride (1.3 mmol) was added dropwise into the solution of **1a** (2 mmol in 10 mL dried DCM), the corresponding bis-DHPs **2a** was obtained in high yield (82%, Table 1, entry 1). Next, the photocycloaddition of bis-DHPs **2a** was tested in THF under different UV light sources. The photoreaction of **2a** under irradiation for 12 h by UV light of 365 nm furnished corresponding 3,6-diazatetraasterane **3a** in high yield (93%, Table 1, entry 1). After the optimal conditions were established, we focused attention on investigating the scope of the regiocontrolled [2 + 2] photocycloaddition. As shown in Table 1, a series of DHPs were subjected to the optimal conditions. All of the reactions proceeded smoothly to produce the desired products **3a-h**, showing extremely high regioselectivity (yields > 92%). The experimental outcome revealed that a wide range of substituents in DHPs (**1**) were well-tolerated, affording the exclusive desired *head-to-head* 3,6-diazatetraasteranes derivatives (**3**).

To expand the utility of DHPs as building blocks for synthesis, we hypothesized that this method would also be applied to the regioselective intramolecular [2 + 2] cross-photodimerization of different DHPs to affording polysubstituted 3,6-diazatetraasterane derivatives. Satisfactorily, the representative photoproducts (**3be**



Scheme 2. Synthetic strategy to novel 3,6-diazatetraasterane polycyclic system by in-solution photodimerization of covalently attached DHPs.

Table 1
Optimization of reaction conditions in the preparation of bis-DHPs **2**[a] and 3,6-diazatetraasteranes **3**.[b]

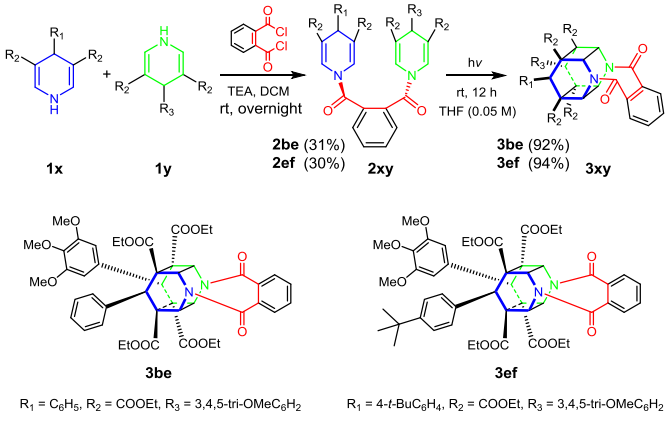
Entry	R_1	yield[c] (%) of **2**	yield[c] (%) of **3**
1	H	82 (**2a**)	93 (**3a**)
2	H	63[d] (**2a**)	80[f] (**3a**)
3	H	82[e] (**2a**)	93[g] (**3a**)
4	C_6H_5	85 (**2b**)	95 (**3b**)
5	4-$MeOC_6H_4$	86 (**2c**)	95 (**3c**)
6	3,4-di-$MeOC_6H_3$	81 (**2d**)	94 (**3d**)
7	3,4,5-tri-$MeOC_6H_2$	86 (**2e**)	95 (**3e**)
8	4-*t*-BuC_6H_4	87 (**2f**)	97 (**3f**)
9	3-MeC_6H_4	84 (**2g**)	92 (**3g**)
10	4-ClC_6H_4	80 (**2h**)	94 (**3h**)

[a] Unless otherwise specified, DHPs (2 mmol) reacted with phthaloyl dichloride (1.3 mmol) in dried DCM at room temperature in the presence of TEA (5 mmol).
[b] Unless otherwise specified, reactions were conducted in THF (0.05 M) at room temperature under irradiation by UV light (365 nm) for 12 h.
[c] Isolated yields.
[d] Phthaloyl dichloride (1.0 mmol).
[e] Phthaloyl dichloride (1.6 mmol).
[f] UV light (365 nm) for 8 h.
[g] UV light (365 nm) for 16 h.

and **3ef**) were favorably obtained as expected, in high yields (95% and 93% respectively) (Scheme 3). This result demonstrated that the different 1,4-dihydropyridines can also be regiocontrolled by phthaloyl and give various polysubstituted 3,6-diazatetraasteranes derivatives in a concise and efficient way.

All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy and HRMS (see the Supporting Information for details). Slow evaporation of saturated solutions of **2e** and **3g** in ethyl acetate gave single crystals. Finally, the single-crystal X-ray analysis of **2e** (CCDC-1522995) and **3g** (CCDC-1522996) conclusively confirmed their structures, and by analogy, those of the other isolated products were confirmed too. (The ORTEP diagrams of **2e** and **3g** are shown in Figs. S1 and S2 respectively in Supporting Information).

To gain insight into the reaction mechanism, in this study, we have examined the photocycloaddition of **2** in solid state (powders and crystals). The results showed that the intramolecular photodimerization of **2** was not observed in these conditions. Generally, photodimerization of olefins requires a parallel alignment and a centroid-centroid distance of no more than 4.2 Å.[8] And the X-ray structure illustrated that **2e** was in its anti-conformation in solid state (5.9 Å > 4.2 Å) (Fig. 1), which didn't meet the requirements. While, in solution (THF), the **2** can result in the regiocontrolled



Scheme 3. Highly regiocontrolled [2 + 2] cross-photodimerization of for construction of polysubstituted 3,6-diazatetraasterane derivatives.