Tetrahedron Letters 59 (2018) 715–718

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes

Zhi-Yao Chu, Na Li, Dan Liang, Zheng-Hui Li, Yong-Sheng Zheng *, Ji-Kai Liu *

School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan 430074, China

ARTICLE INFO

Article history:
Received 21 November 2017
Revised 2 January 2018
Accepted 5 January 2018
Available online 6 January 2018

Keywords:
Pyrrolidines
3+2 cycloaddition
Donor-acceptor cyclopropanes
1,3,5-Triazinanes

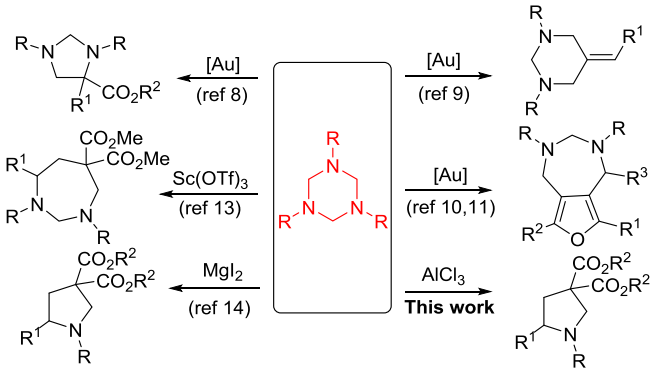
ABSTRACT

The formal [3+2] cycloaddition of 1,3,5-triaryl-1,3,5-triazinanes with donor-acceptor cyclopropanes has been found to provide pyrrolidines in good to excellent yields under mild reaction conditions. Preliminary mechanistic investigation indicates that this formal [3+2] cycloaddition reaction proceeds through competing S_N1 and S_N2 pathways.

Pyrrolidines are one of the most ubiquitous building blocks for a large number of natural products, pharmaceuticals and biologically active compounds.[1] They are also widely used as the core structure of synthetic catalysts.[2] Consequently, highly efficient strategies have been developed to construct pyrrolidine motifs.[3] Among the myriad of developed frameworks, the [3+2] cycloaddition of donor-acceptor cyclopropanes with various nitrogen-containing dipoles offers the most straightforward method and has received considerable attention with respect to atom economy and efficiency.[4] For example, Moshkin and co-workers employed spiroanthraceneoxazolidine as a synthetic equivalent of methanimine in the reaction with donor-acceptor cyclopropanes to afford pyrrolidines.[5]

1,3,5-Triaryl-1,3,5-triazinanes, which are readily available from the condensation of paraformaldehyde and various arylamines, are well-known as precursors of corresponding *N*-aryl formaldimines in the aminomethylation reactions with various nucleophiles in the presence of Lewis acids.[6] During the past few years, 1,3,5-triazinanes have attracted increasing attention in the synthesis of *N*-containing compounds due to their combination of nucleophilicity of the nitrogen atom and electrophilicity of the imine carbon. For example, Krische described the Ruthenium-catalyzed hydroaminomethylation of allenes/dienes by using 1,3,5-triazinanes as the surrogate of formaldimines.[7] Feng and co-workers reported the asymmetric Mannich-type reaction between *β*-keto-esters/amides and 1,3,5-triazinanes, in which 1,3,5-triazinanes were involved as bench stable Mannich reagents.[8]

Different from these aminomethylation protocols, triazinanes were also employed as dipolar adducts in cycloadditions to synthesize heterocycles (Scheme 1). For example, Sun and co-workers described gold-catalyzed [4+1]/[4+3] cycloaddition reactions of triazinanes with diazo esters to construct five- and seven-membered heterocycles.[9] Soon after, the same group reported [2+2+2] annulations of 1,3,5-triazinanes with functionalized allenes to provide the six-membered heterocycles.[10] In addition, Xu[11] and Sun[12] et al. developed the gold catalyzed [3+2+2] tandem dual heterocyclization reaction of enynones with 1,3,5-triazinanes to prepare



Scheme 1. Cycloadditions of 1,3,5-triazinanes.

* Corresponding authors.
E-mail addresses: zhysh@mail.scuec.edu.cn (Y.-S. Zheng), jkliu@mail.kib.ac.cn (J.-K. Liu).

https://doi.org/10.1016/j.tetlet.2018.01.016
0040-4039/

3,4-fused bicyclic furan compounds, respectively. Werz reported the aza-[3+4] cycloaddition reactions of 1,3,5-triazinanes with donor-acceptor cyclopropanes to obtain seven-membered heterocycles.[13] During our preparation of this paper, the [3+2]/[4+2] cycloadditions of 1,3,5-triazinanes were disclosed by Werz to synthesize pyrrolidines and piperidines in the presence of MgI_2.[14] We herein describe the formal [3+2] cycloaddition of 1,3,5-triazinanes with donor-acceptor cyclopropanes catalyzed by $AlCl_3$, expediently delivering pyrrolidines in good to excellent yields under mild reaction conditions through competing S_N1 and S_N2 pathways (Scheme 1).

In our preliminary screening, the donor-acceptor cyclopropane **1a** and 1,3,5-triphenyl-1,3,5-triazinane **2a** were chosen as the model substrates to optimize the reaction conditions. Initially, the catalytic effects of Lewis acids on the cycloaddition reaction were evaluated in CH_2Cl_2 at room temperature. To our satisfaction, in the presence of 20 mol% $AlCl_3$, the desired product **3aa** was obtained in 70% isolated yield (Table 1, entry 1). However, other Lewis acids, such as $ZnCl_2$, $FeCl_3$ and $CuCl_2$, failed to catalyze the transformation even with prolonged time (Table 1, entries 2–4). $Cu(OTf)_2$ was also ineffective, and yielded only a trace amount of product by TLC analysis (Table 1, entry 5). $Sc(OTf)_3$ afforded full conversion of cyclopropane 1a, but delivered a complex mixture with 13% isolated yield (Table 1, entry 6). Thus $AlCl_3$ was determined to be the optimal catalyst and used in the subsequent investigation. Then various solvents were evaluated. Methanol and tetrahydrofuran delivered poor yields (Table 1, entries 7 and 8). When acetonitrile was used, moderate yield was obtained (Table 1, entry 9). Since the acceptable result was obtained in CH_2Cl_2, two other chlorinated solvents were screened to improve the yields. Unfortunately, reactions in dichloroethane and chloroform gave poor yields as well (Table 1, entries 11 and 12). Hence, dichloromethane was identified as the most favorable solvent in this reaction.

Having established the feasibility and optimal conditions, the generality of this formal [3+2] cycloaddition with a range of cyclopropanes and triazinanes was investigated. Firstly, the scope of 1,3,5-triazinanes was examined. As shown in Table 2, the electronic nature of the substituents on the 1,3,5-triazinanes had little influence on the yields (**3aa**–**3ae**). Substrates bearing either electron-donating or electron-withdrawing groups on the benzene part of triazinanes gave the corresponding cycloaddition products **3aa**–**3ae** in good to excellent yields (70–97%). However, substrates with sterically bulky group, such as 2-substituted 1,3,5-triazinanes, exerted more effect on the reaction efficiency, and gave inseparable mixtures (**3af**). When 1,3,5-tribenzyl-1,3,5-triazinane was employed, no desired product was observed (**3ag**).

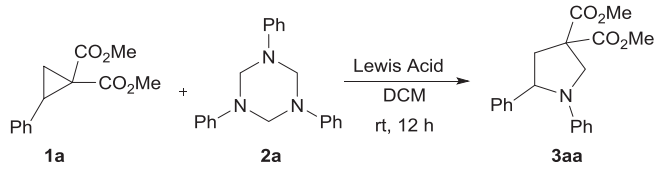
Subsequently, further substrate scope was investigated (Table 3). To our delight, the reaction of 1,3,5-triphenyl-1,3,5-triazinanes with different substituted donor-acceptor cyclopropanes proceeded smoothly to afford the cycloaddition product in good to excellent yields (**3aa**, **3ba**–**3ea**). However, donor-acceptor cyclopropane with a cyano group (—CN) on the benzene part gave an inseparable mixture (**3fa**). Ethyl-substituted donor-acceptor cyclopropane was also tolerated and led to the corresponding products in good to excellent yields (**3gb**–**3gd**). Finally, various *para*-substituted 1,3,5-triazinanes and different cyclopropanes were subjected to the reaction and gave structurally diverse pyrrolidines in excellent yields (**3bb**–**3be**, **3cb**–**3cd**, **3db**–**3dd**).

To evaluate the synthetic value of this formal [3+2] cycloaddition reaction, a gram-scale reaction was performed under the optimized conditions. As shown in Scheme 2, in the presence of 20 mol% $AlCl_3$, the reaction between **1e** and **2d** proceeded smoothly and gave the corresponding product in 95% yield, this results reflected the present protocol was amenable to large scale production.

To further understand the cycloaddition process, we conducted this reaction using enantioenriched (98% ee) cyclopropane (*S*)-**1a′** to explore the stereochemistry of this transformation (Scheme 3). The corresponding **3a′a** was obtained with significant loss in the stereochemical information from the enantioriched cyclopropane.

Based on the key piece of mechanistic evidence obtained and related studies on formal [3+2] cycloaddition of donor-acceptor cyclopropanes,[15] a plausible mechanism was proposed. As shown in Scheme 4, in the presence of $AlCl_3$, in situ generated *N*-phenyl formaldimine **2a′** attacked the activated cyclopropane A through

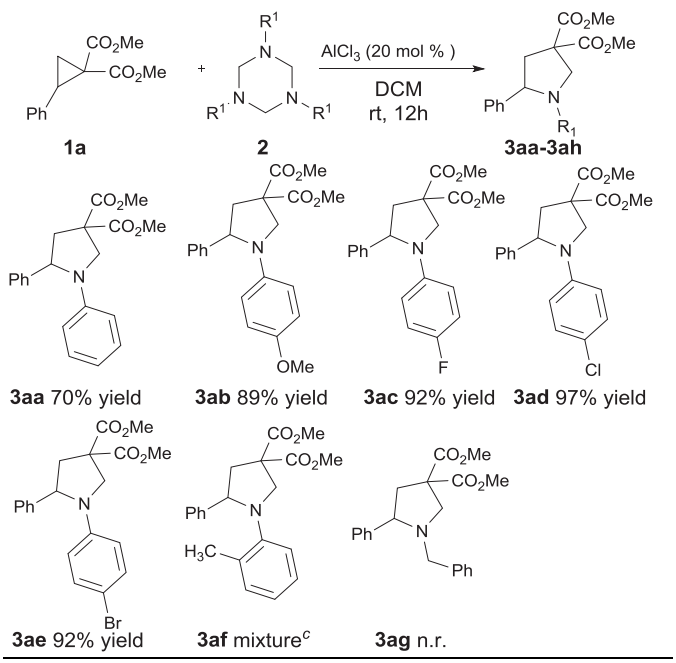
Table 1
Optimization of the reaction conditions.[a]



Entry	Lewis acid	Solvent	Time (h)	Yield %[b]
1	$AlCl_3$	DCM	12	70
2	$ZnCl_2$	DCM	48	NR
3	$FeCl_3$	DCM	48	NR
4	$CuCl_2$	DCM	48	NR
5	$Cu(OTf)_2$	DCM	48	Trace
6	$Sc(OTf)_3$	DCM	12	13[c]
7	$AlCl_3$	MeOH	12	38
8	$AlCl_3$	THF	12	28
9	$AlCl_3$	CH_3CN	12	58
10	$AlCl_3$	Toluene	48	NR
11	$AlCl_3$	DCE	12	39
12	$AlCl_3$	$CHCl_3$	12	36

[a] Unless otherwise noted, the reactions were performed with **1a** (0.40 mmol), **2a** (0.40 mmol) and Lewis acid (0.08 mmol) in 4.0 ml solvent.
[b] Isolated yield of the product.
[c] Isolated by preparative thin layer chromatography.

Table 2
Substrate scope of 1,3,5-triazinanes.[a,b]



[a] See Supporting information for experimental detail.
[b] Isolated yield.
[c] Inseparable mixture was obtained.