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$TiCl_4$ Promoted Formal [3 + 3] Cycloaddition of Cyclopropane 1,1-Diesters with Azides: Synthesis of Highly Functionalized Triazinines and Azetidines

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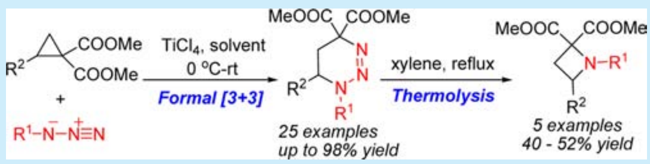
Supporting Information

ABSTRACT: A $TiCl_4$ promoted formal [3 + 3] cycloaddition of cyclopropane 1,1-diesters with azides has been developed for the synthesis of highly functionalized triazinines. Both stoichiometric and substoichiometric versions of this reaction were accomplished dependent on the choice of solvent. It is noteworthy that the corresponding products could be easily converted to biologically important azetidines by simple thermolysis.



Many heterocycles with NNN linkages in their cyclic arrangement embrace interesting biological activities.[1] Among them, 1,2,3-triazine represents a widely used lead structure with a multitude of interesting applications in numerous pharmacological fields. Various synthetic analogues of 1,2,3-triazine have been synthesized, and some of them have shown excellent pharmacological activity.[2] Combined with our interest in the cycloaddition of donor−acceptor cyclopropanes, we attempted to develop an efficient method for the straightforward synthesis of functionalized 1,4,5,6-tetrahydro-1,2,3-triazines, also named triazinines,[3] from azides and cyclopropanes under mild conditions.

To date, several reactions between azides and cyclopropanes have been reported.[4] Among which, Aubé and co-workers developed the reaction of alkyl azides with triethyl(1-methoxy-2,2-dimethyl-cyclopropoxy)silane to prepare a series of α-amino-α′-diazomethyl ketone.[4d,e] They speculated that a triazine intermediate was formed by [3 + 3] cycloaddition in this reaction but decomposed immediately (Figure 1). In addition, in several other reactions, some triazines were prepared from azides,[3,5] but the synthesis of triazinines via the cycloaddition of cyclopropane with azides has not been reported.

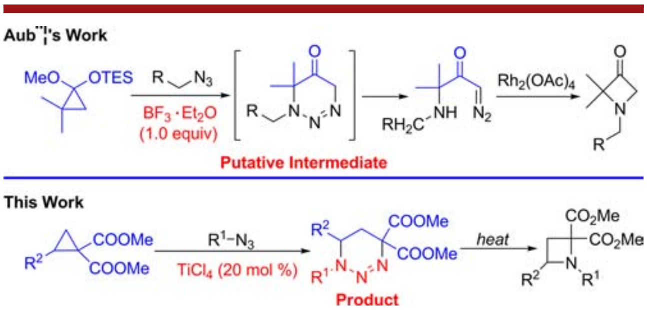
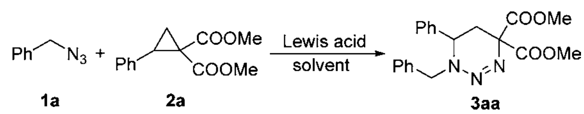


Figure 1. Cycloaddition of azide with cyclopropanes.

Cyclopropane 1,1-diesters, a kind of versatile three-carbon zwitterionic synthons, have been widely used to assemble various cyclic skeletons by means of [3 + *n*] cycloaddition reactions promoted by Lewis acid.[6] In these reactions, the scope and applicability of its [3 + 3] process are limited to a few 1,3-dipoles.[7,8] So far, alkyl azides have not been employed in this [3 + 3] process. Herein, we report an efficient synthesis of triazinines derivatives by the formal [3 + 3] cycloaddition of azides with cyclopropane 1,1-diesters.

In our initial trials, benzyl azide **1a** and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **2a** were employed to optimize the reaction conditions, and the results are summarized in Table 1. In order to activate **2a**, a variety of common Lewis acids were attempted. At first, a stoichiometric

Table 1. Optimization of the Reaction Conditions



entry[a]	Lewis acid (mol %)	solvent	time (h)	yield (%)[c]
1	$SnCl_4$ (100)	CH_2Cl_2	16	complex
2	$FeCl_3$ (100)	CH_2Cl_2	16	complex
3	$AlCl_3$ (100)	CH_2Cl_2	16	25
4[b]	$TiCl_4$ (100)	CH_2Cl_2	2	89
5[b]	$TiCl_4$ (50)	CH_2Cl_2	2	47
6[b]	$TiCl_4$ (20)	HFIP	12	87
7[b]	$TiCl_4$ (10)	HFIP	48	61

[a]Reaction conditions: unless otherwise noted, the reactions were carried out under a N_2 atmosphere with **1a** (0.5 mmol) and **2a** (0.5 mmol) in 5 mL of solvent at rt and stirred for the indicated time. [b]The reaction was carried out at 0 °C to rt. [c]Isolated yield.

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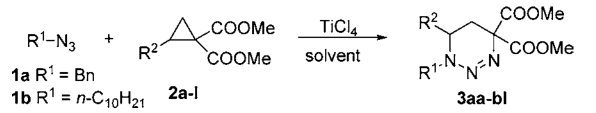
amount of Lewis acids was added and the reactions were carried out in dichloromethane. Using $SnCl_4$ and $FeCl_3$, the reaction mixture was very complex (entries 1, 2). Using $CeCl_3$ and $Ti(^iPrO)_4$, desired product was not detected. However, when $AlCl_3$ was added, triazinine **3aa** was obtained in 25% yield (entry 3). This result encouraged us to continue the study. Fortunately, we found that 1.0 equiv of $TiCl_4$ enabled full conversion of the starting materials to **3aa** in 89% yield after 2 h (entry 4). Further screening of the reaction solvents demonstrated that this reaction is sensitive to the solvent. Compound **3aa** could not be formed when the reaction was conducted in 1,2-dichloroethane, chloroform or tetrachloromethane.

Furthermore, on the basis of above results, we continued our efforts to develop substoichiometric version of this reaction. At first, the amount of $TiCl_4$ was reduced to 50 mol %, but the yield of **3aa** decreased dramatically (47%, entry 5). This result suggested that the generated product sequestered $TiCl_4$ in an unproductive manner and interrupted the circulation of $TiCl_4$. Thus, several other trifluoromethanesulfonate salts, such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$, $In(OTf)_3$ were examined with 20 mol % catalyst loading. However, no reaction was observed even by prolonging the reaction time or raising the temperature. Similar result was obtained in the presence of $Ni(ClO_4)_2$. Right at that moment, $TiCl_4$ catalyzed intramolecular Schmidt reaction was developed by Aubé and co-workers.[9] Using strong hydrogen-bond-donating solvent hexafluoro-2-propanol (HFIP) effectively overcame the inhabitation of product in catalysis. In this catalytic system, in situ-generated HCl from the reaction of HFIP with $TiCl_4$ is the catalytically active species. We were greatly inspired by this discovery and carried out our reaction in HFIP in the presence of 20 mol % $TiCl_4$. After 12 h, **3aa** was obtained in 87% yield (entry 6). Reducing the catalyst loading to 10 mol %, the reaction became very slow. After 48 h, **3aa** was obtained in 61% yield (entry 7). According to the above results, both stoichiometric and substoichiometric versions of this reaction have been developed. With the optimal conditions (entries 4, 6) in hand, we set forth to survey the substrate scope of this interesting reaction and demonstrate the utility of this process.

The scope of the reaction was investigated under stoichiometric and substoichiometric conditions, respectively. Various cyclopropane 1,1-diesters and azides were employed and the results are summarized in Table 2. The stoichiometric protocol was found to be tolerant to both electron-withdrawing and electron-donating substituents in cyclopropane 1,1-diesters, and all of them gave the corresponding triazinine derivatives **3aa**−**3bl** as a single product in moderate to high yields. No significant difference in reactivity was observed between the benzyl azides **1a** and decyl azides **1b** in the reaction. The position of the substituent on the aryl group slightly influences the reactivity and sterically demanding *ortho*-substituted cyclopropanes always gave relatively lower yields of the desired product. For example, the reaction of *o*-ClC_6H_4- and *p*-ClC_6H_4-substituted cyclopropanes **2d** and **2g** with **1a** gave the corresponding **3ad** and **3ag** in 77% and 88% yield respectively, probably due to the larger steric effect relative to the latter (entries 4, 7). A vinyl group could also be used as substituent, offering **3al** and **3bl** in good yield (entries 12, 24). Unfortunately, when the aryl group on cyclopropane was replaced by methyl or hexyl group, the reactions did not work. To examine the feasibility of this method on a larger preparative scale, the model reaction leading to **3aa** was also

Table 2. Investigation of the Reaction Scope



entry	1	2	R^2	3	yield (%)[a] A[b]	yield (%)[a] B[c]
1	**1a**	**2a**	C_6H_5	**3aa**	89	87
2	**1a**	**2b**	*o*-$MeOC_6H_4$	**3ab**	75	57
3	**1a**	**2c**	*o*-MeC_6H_4	**3ac**	79	80
4	**1a**	**2d**	*o*-ClC_6H_4	**3ad**	77	49
5	**1a**	**2e**	*p*-$MeOC_6H_4$	**3ae**	86	41
6	**1a**	**2f**	*p*-MeC_6H_4	**3af**	89	86
7	**1a**	**2g**	*p*-ClC_6H_4	**3ag**	88	85
8	**1a**	**2h**	*p*-BrC_6H_4	**3ah**	87	74
9	**1a**	**2i**	*p*-FC_6H_4	**3ai**	89	80
10	**1a**	**2j**	*m*-MeC_6H_4	**3aj**	85	89
11	**1a**	**2k**	*m*-BrC_6H_4	**3ak**	85	70
12	**1a**	**2l**	$H_2C{=}CH$	**3al**	81	58
13	**1b**	**2a**	C_6H_5	**3ba**	91	91
14	**1b**	**2b**	*o*-$MeOC_6H_4$	**3bb**	78	74
15	**1b**	**2c**	*o*-MeC_6H_4	**3bc**	84	81
16	**1b**	**2d**	*o*-ClC_6H_4	**3bd**	83	83
17	**1b**	**2e**	*p*-$MeOC_6H_4$	**3be**	85	87
18	**1b**	**2f**	*p*-MeC_6H_4	**3bf**	90	88
19	**1b**	**2g**	*p*-ClC_6H_4	**3bg**	87	87
20	**1b**	**2h**	*p*-BrC_6H_4	**3bh**	88	84
21	**1b**	**2i**	*p*-FC_6H_4	**3bi**	89	94
22	**1b**	**2j**	*m*-MeC_6H_4	**3bj**	91	98
23	**1b**	**2k**	*m*-BrC_6H_4	**3bk**	85	87
24	**1b**	**2l**	$H_2C{=}CH$	**3bl**	86	61

[a]Isolated yield. [b]Stoichiometric conditions: cyclopropane (0.5 mmol), azide (0.5 mmol), $TiCl_4$ (0.5 mmol, 100 mol %), CH_2Cl_2 (5 mL), 0 °C to rt, 2 h. [c]Substoichiometric conditions: cyclopropane (0.3 mmol), azide (0.3 mmol), $TiCl_4$ (0.06 mmol, 20 mol %), HFIP (3 mL), 0 °C to rt, 12 h. See Supporting Information for more details.

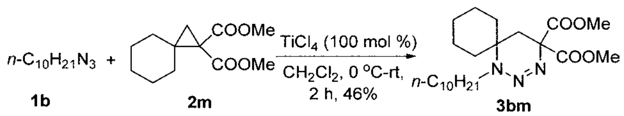
performed on a 5.0 mmol (1.17 g) scale. The reaction proceeded similarly to the small-scale experiment and provided **3aa** in 82% yield after 4 h. The molecular structure of **3ab** was unambiguously established by X-ray crystallographic analysis (see Supporting Information).[10]

When the reaction was conducted in HFIP with 20 mol % $TiCl_4$, benzyl azide generally gave lower yields than decyl azide probably due to the partial decomposition of benzyl azide under this conditions.[11] When vinyl substituted cyclopropane was employed, the yields reduced dramatically (entries 12, 24). This may be attributed to the electrophilic addition of carbocation to the vinyl group on cyclopropane. When *o*-$MeOC_6H_4$- and *p*-$MeOC_6H_4$-substituted cylcopropanes reacted with benzyl azide, the lower yields were obtained due to cyclodimerization of cyclopropanes (entries 2, 5).[12] Because of steric effect, *o*-ClC_6H_4-substituted cyclopropane also gave lower yield than *p*-ClC_6H_4- substituted ones (entries 4, 7).

An attractive feature of this cycloaddition reaction is the opportunity for ready access to *spiro*-triazinines. We were pleased to find that the [3 + 3] cycloaddition of cyclopropane 1,1-diester **2m**[13] with **1b** under the stoichiometric conditions also proceeded well to give *spiro*-triazinine **3bm**, albeit with a modest yield (46%) (Scheme 1).

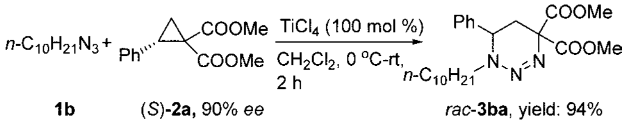
In an effort to gain knowledge on the mechanism of our reaction, the reaction between (*S*)-**2a**[14] and **1b** was carried out

Scheme 1. Synthesis of *spiro*-Triazinine

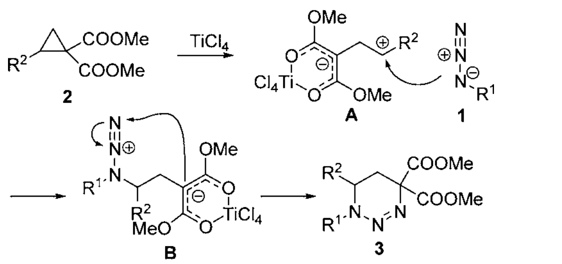


in the presence of 1.0 equiv of $TiCl_4$ and racemic mixture of **3ba** was obtained (Scheme 2). This indicated that the mechanism of this cycloaddition is stepwise, rather than concerted process. In view of this, plausible reaction mechanism for these transformations is proposed in Scheme 3. Initially, under the activation of $TiCl_4$, the ring-opening of cyclopropane **2** affords 1,3-zwitterionic intermediate **A**. Subsequently, a nucleophilic attack of an azide[15] happens to form a new zwitterion **B**, which then undergoes an intramolecular nucleophilic attack to form the product **3**.

Scheme 2. [3 + 3] Cycloaddition of Enantioenriched Cyclopropane



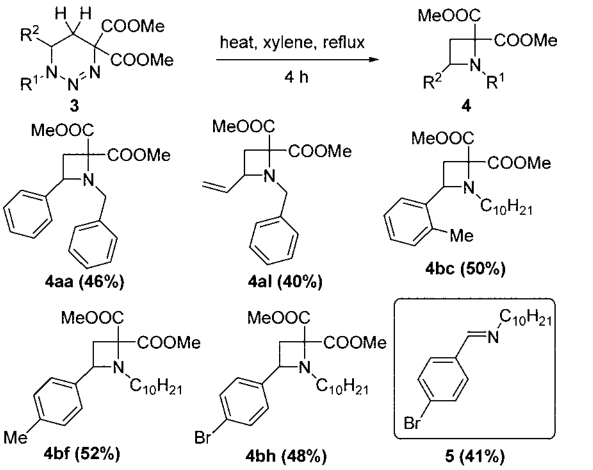
Scheme 3. Proposed Mechanism for [3 + 3] Cycloaddition



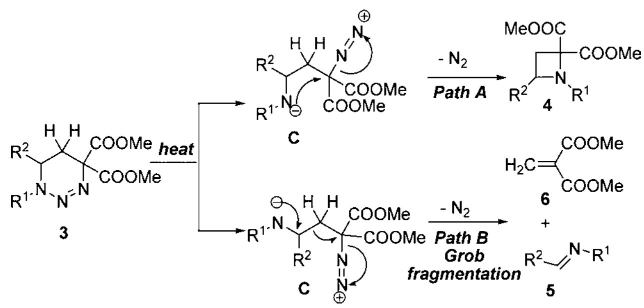
As early as 1989, Dunkin and co-workers reported that the thermal decomposition of 1-methyl-1,2,3-benzotriazin-4(1H)-one offered benzazetinone by loss of nitrogen.[16] If our products decomposed in the same way, azetidines, a class of useful molecular,[17] will be obtained. Therefore, the solution of **3aa** in xylene was heated to reflux. After 4 h, **3aa** was exhausted and **4aa** was obtained in 46% yield (Scheme 4). In order to improve the yield, we changed the solvent to toluene or dimethyl sulfoxide to promote the reaction. But no expected increase of yield developed. Thermolysis of **3al**, **3bc**, **3bf** and **3bh** offered **4al**, **4bc**, **4bf** and **4bh** respectively in 40–52% yield. Among these reactions, imine **5** was obtained along with **4bh**. This disclosed that the decomposition occurred via two pathways (Scheme 5). Under the thermolysis conditions, the cleavage of N–N bond affords intermediate **C**. Which undergoes an intramolecular nucleophilic substitution to furnish the desired azetidine **4** in path A or a Grob fragmentation to furnish the imine **5** in path B.

In conclusion, we have discovered the first $TiCl_4$ promoted [3 + 3] cycloaddition of 2-substituted cyclopropane-1,1-diesters with azides to devise complex triazinines with diverse substituent patterns in good yields. Both stoichiometric and substoichiometric versions of this reaction were investigated through judicious choice of solvent. Notably, this chemistry offers an efficient and practical strategy for the construction of medicinally valuable azetidines by means of simple thermolysis of the triazinine products. Further related studies utilizing this novel [3 + 3] cycloaddition for the development of other methodologies are currently underway in our laboratory.

Scheme 4. Thermolysis of Triazinines



Scheme 5. Proposed Pathways of Thermolysis



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization data for all products, including ^{1}H NMR and ^{13}C NMR spectra, X-ray structural information on **3ab** (CIF) and chiral HPLC chromatograms of (*S*)-**2a** and *rac*-**3ba**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Crystal data for **3ab** has been deposited in CCDC as deposition number 959858. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.com. According to the crystal structure and the ^{1}H NMR spectra, the conformations of triazinines **3** may be different in solid and solution state. See Supporting Information for more details.

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