Butadienyl Ketene: An Unexplored Intermediate in Organic Synthesis

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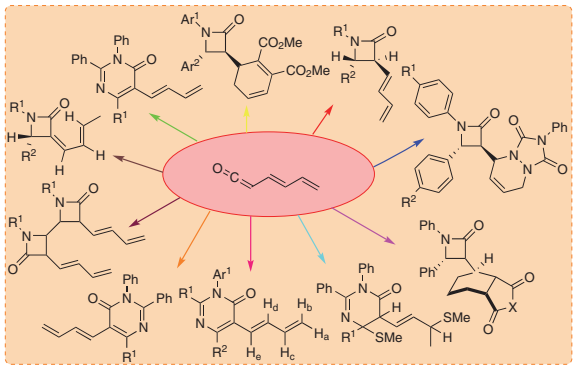

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Abstract Butadienyl ketene is a useful intermediate because of its role as a 2p-component in cycloaddition reactions with a variety of substrates such as simple or conjugated imines and dienes. This review article summarizes recent reports on the generation of butadienyl ketene in situ and their cycloaddition reactions to afford heterocyclic systems. The chemistry of butadienyl ketene is explored with a focus on its [2+2] and [4+2] cycloaddition reactions with a variety of imines and azadiene derivatives such as 1,3-diazabuta-1,3-dienes, for the synthesis of four- and six-membered heterocycles, respectively.

Key words ketenes, butadienyl ketene, dienyl ketene, [2+2] cycloaddition, [4+2] cycloaddition, lactams, pyrimidinones

1 Introduction

Ketenes are one of the most well-known and versatile organic synthetic intermediates (Figure 1). Ketenes, commonly presented as the 'neutral' cumulene form ($H_2C_\beta=C_\alpha=O$), are generally in resonance with the 'zwitterionic' form with the oxygen atom bearing a partially positive charge and the C_β atom bearing a partial negative charge.[1] Because of the fascinating electronic structure of ketenes, these species have been the subject of intense investigation,[1,2] and the appearance of ketenes in organic synthesis has become more frequent over the past few decades.[3,4] A very common reaction of ketenes – the Staudinger reaction – involves [2+2] cycloaddition of ketene derivatives and imines and proceeds via zwitterionic intermediate,[5] providing a useful method for the preparation of biologically potent lactams. The syntheses of carbo- and heterocyclic systems involving the [2+2] cycloaddition of ketenes with alkenes and iminic systems have been explored extensively.[3] Furthermore, there are many reports on the exploration of conjugated ketenes, namely vinyl and isopropenyl ketenes, for the synthesis of functionalized heterocyclic compounds.[6,7] The reactions of various Schiff bases with vinyl/isopropenyl ketenes resulted in β-lactams with *trans*-, *cis*-, or a mixture of *trans*- and *cis*-isomers.[8–10]

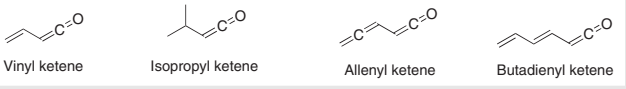

Figure 1 Ketenes explored in chemical reactions

However, compared with other conjugated ketenes such as vinyl and isopropenyl ketene, butadiene ketene has been less extensively explored in [*m*+*n*] cycloaddition reactions with different substrates acting as 2π- or 4π-components. There are some reports on [2+2] and [4+2] cycloaddition reactions of the butadienyl ketene with imines and dienes, respectively, to afford functionalized heterocycles with rich synthetic potential. In an effort to highlight the synthetic potential of butadienyl ketene and to arouse the interest of the synthetic community in capturing the unleashed potential of the butadienyl intermediate, this review article summarizes the generation of butadienyl ketene and applications of the cycloaddition reaction reported since 1982.

2 Generation of Butadienyl Ketene

Butadienyl ketene was first observed during the preparation of 3,5-hexadienoic esters by Thomas R. Hoye et al. in 1982.[3g] Sorboyl chloride **2** was prepared by refluxing sorbic acid and thionyl chloride. For the preparation of conjugated methallyl ester **1a**, triethylamine was used to catalyze the acylation of sorboyl chloride **2** using methallyl alcohol. However, the formation of a substantial portion of conjugated isomer **5a** was observed in addition to **1a** (Table 1). This side reaction proceeded via butadienyl ketene **4**. The addition of one equivalent of triethylamine to sorboyl chloride resulted in the formation of acyl triethylammonium ion **3**.[2] Acyl triethylammonium ion **3** then underwent direct

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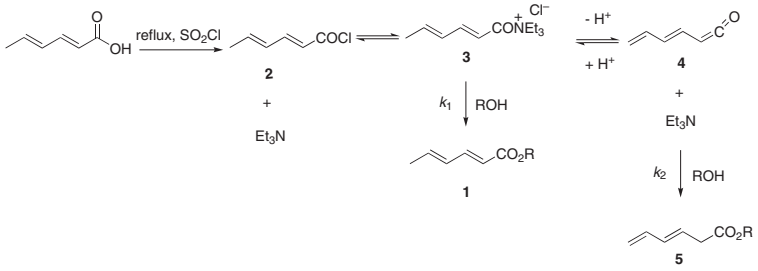
Table 1 Generation of Butadienyl Ketene **4** and Conversion into Conjugated Ester **5**



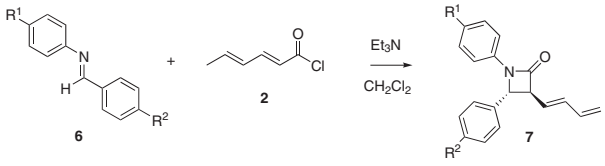
Compound	ROH	Yield (%)	Ratio **1**/**5**
a	CH_2=C(CH_3)CH_2OH	76	1:>10
b	CH_2=$CHCH_2$OH	68	1:>10
c	MeOH	100	1:2
d	EtOH	88	1:>10
e	*t*BuOH	70	1:>10
f	PhOH	100	1:0
g	CH_2=$CHCH_2NH_2$	0	~10:1
h	(*i*Pr)$_2$NH	84	1:1
i	H_2O	0	conjugated anhydride

addition reaction with alcohol to afford conjugated ester **1**; however, acyl triethylammonium ion **3** also formed ketene **4**, which, on reaction with a second molecule of triethylamine, resulted in the formation of conjugated ester **5** on reaction with alcohol.[3]

2.1 [2+2] Cycloaddition Reactions of Butadienyl Ketene

Nitrogen-containing organic molecules such as amino alkaloids have immense significance in organic chemistry.[11] The synthesis of such nitrogenous compounds by employing cycloadditions of functionalized ketene is a vital methodology in organic chemistry.[12,13] In 1995, Mahajan and coworkers explored the [2+2] cycloaddition reactions of Schiff bases **6** with butadienyl ketene, generated in situ from sorboyl chloride **2** in the presence of a mild base, to yield *trans*-3-butadienyl β-lactam derivatives **7** diastereoselectively (48–63%; Table 2).[14] The synthetic potential of the 3-dienyl-2-azetidinones **7** was explored by employing catalyzed and uncatalyzed Diels–Alder cycloaddition reactions with electron-deficient dienophiles such as dimethylacetylene dicarboxylate (DMAD),[15–17] maleic anhydride (MA), *N*-phenylmaleimide (NPM), and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). The cycloaddition reactions of butadienyl ketene with various imines and 1-azabuta-1,3-dienes proved to be a general method for the synthesis of butadienyl-substituted functionalized lactams in good yields.

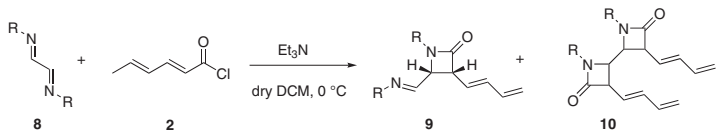
Table 2 Synthesis of 3-Butadienyl-β-lactams



Compound	R^1	R^2	Yield of **7** (%)
a	H	H	59
b	H	OCH_3	63
c	CH_3	H	59
d	CH_3	OCH_3	48

In 2015, Bhargava et al. explored the [2+2] cycloaddition of butadienyl ketene, generated in situ, with a variety of 1,4-diazadienes.[18a] The diastereoselective [2+2] cycloaddition afforded functionalized butadienyl-4-iminomethyl-azetidin-2-one and butenylidene-butadienyl-[2, 2′-biazetidine]-4, 4′-dione. The butadienyl ketene, generated in situ from sorboyl chloride **2** using a mild base, underwent [2+2] cycloadditions with 1,4-diazabuta-1,3-dienes **4a–e** to yield mono- as well as bis-β-lactams (Table 3). The synthesis of mono-β-lactams **9a–c** or bis-β-lactams **10a–c** was highly dependent on the concentration of the acid chloride used in the reaction medium. The use of an equimolar amount of sorboyl chloride in [2+2] cycloadditions with 1,4-diazabuta-1,3-dienes afforded mono-β-lactam, i.e., *cis*-butadienyl-

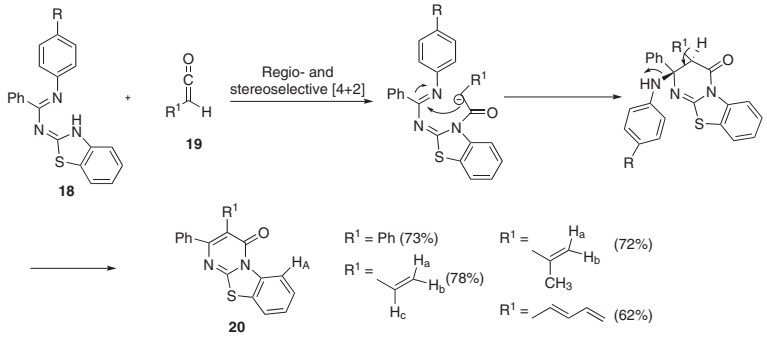
Table 3 Formation of *cis*-Butadienyl-4-iminomethyl-azetidin-2-ones and Bis-β-lactams



8 2 9 10

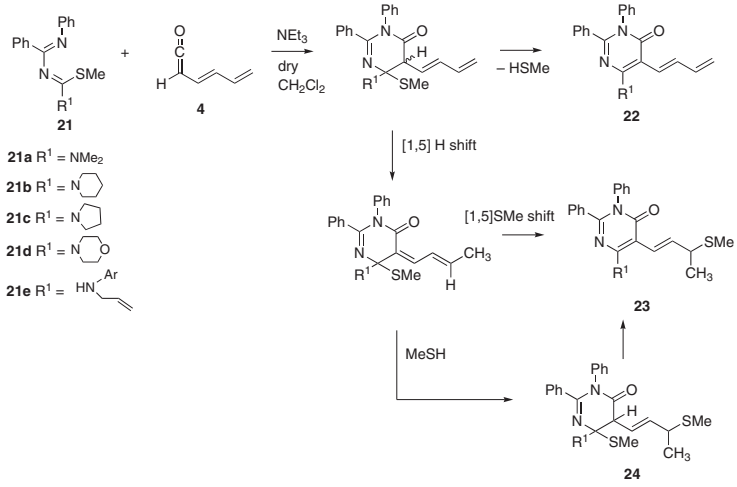
Compound	R	Yield (%)	
		9	**10**
a	*p*-CH_3-C_6H_5	47	15
b	*o*-CH_3-C_6H_5	41	13
c	C_6H_5	25	0
d	*p*-OCH_3-C_6H_5	5	0
e	C_6H_{11}	0	0

4-iminomethyl-azetidin-2-one derivatives **9**, as the major product. The [2+2] cycloaddition reactions using a higher number of equivalents of sorboyl chloride with 1,4 diazabuta-1,3-dienes **8** afforded bis-β-lactams, i.e., **10a–c**, as the major product. This is probably due to the tandem [2+2] cycloaddition of the in-situ generated butadienyl ketene with the second imine of the 1,4-diazabuta-1,3-dienes to afford butenylidene-butadienyl-[2,2′-biazetidine]-4,4′-dione **10** as the major cycloadduct.[19]



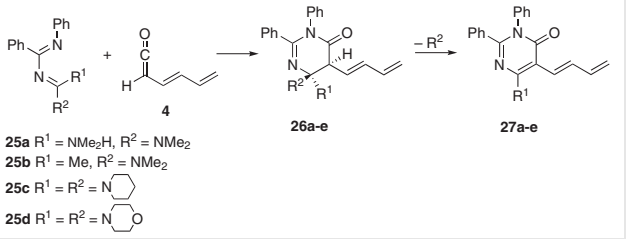
18 19 20

Scheme 1 Regioselective [4+2] cycloaddition reactions for the synthesis of 5-butadienyl pyrimidinones



21 4 22 23 24

Scheme 2 Cycloaddition of 1,2-diaryl-4-methylthio-4-secondary amino-l,3-diazabuta-l,3-dienes **21** with butadienyl ketene **4**

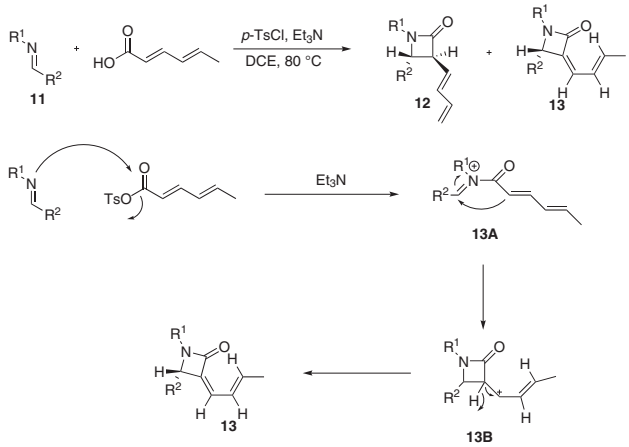


Scheme 3 [4+2] cycloaddition of butadienyl ketene **4** and 1,3-diazabuta-l,3-dienes **25**

In 2018, Bhargava et al. explored the reactions of sorboyl tosylate at high temperature (80 °C) with a variety of imines to yield mixtures of 3-dienyl lactam **12** and α-alkylidene-β-lactams **13**. The formation of dienyl lactam at elevated temperature was mediated through a [2+2] cycloaddition of in-situ generated butadienyl ketene and imines. However, the formation of α-alkylidene-β-lactams **13** involved the addition of the sorbic tosylate to the imine nitrogen of **11** to afford a zwitterionic intermediate **13A**, which collapsed to intermediate **13B** by ring-closure electrocyclization. Abstraction of an acidic ring proton by the base led to the formation of 3-but-2-enylidene-azetidin-2-ones **13** as the major adduct (Table 4). Density functional theory calculations were performed to understand the outcome of the cycloaddition reaction and the results were used to predict a plausible mechanism for the reaction. As a result, a mixture of 3-butadienyl-azetidin-2-ones **12** and 3-but-2-azetidin-2-ones **13** was afforded in appreciable yield at elevated temperature.[19]

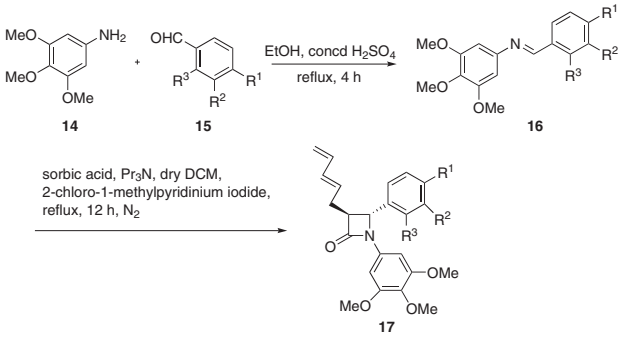
Wang et al. designed and synthesized three series of 3-dienyl-β-lactams as inhibitors targeting a binding site of colchicine.[20] The imines **16** were accessed via butadienyl ketene generated in situ by the action of sorbic acid and suitable base in dichloromethane to afford 3-(buta-1,3-dien-1-yl)azetidin-2-ones **17** (Table 5). Derivatives **17** also exhibited in vitro antitumor activity against the MCF-7 breast cancer cell line, with IC_{50} values of 23–33 nM.[20]

Table 4 Synthesis of a Series of α-Alkylidene-β-lactam Derivatives



Entry	R^1	R^2	Yield (%)	
			12	**13**
a	C_6H_5	C_6H_5	15	60
b	*p*-CH_3-C_6H_4	C_6H_5	15	62
c	*p*-Cl-C_6H_4	C_6H_5	12	48
d	*p*-OCH_3-C_6H_4	C_6H_5	11	46
e	C_6H_{11}	C_6H_5	13	52
f	C_6H_5	*p*-Cl-C_6H_4	10	40
g	*p*-CH_3-C_6H_4	*p*-Cl-C_6H_4	11	15
h	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	10	41

Table 5 Synthesis of 3-Dienyl-β-lactams as Inhibitors Targeting a Colchicine Binding Site



Entry	R^1	R^2	R^3	Yield (%)
a	NO_2	H	H	33
b	Cl	H	H	32
c	Br	H	H	44
d	F	H	H	20
e	$N(CH_3)_2$	H	H	16
f	H	H	H	37
g	CH_3	H	H	40
h	OCH_3	H	H	31
i	OCH_2CH_3	H	H	41
j	$O(CH_2)_3CH_3$	H	H	48
k	OPh	H	H	33
l	OCH_2Ph	H	H	41
m	H	1-naphth	1-naphth	27
n	1-naphth	1-naphth	H	53
o	OCH_3	OTBDMS	H	37
p	OCH_3	OH	H	25
q	OCH_3	NO_2	H	59
r	OCH_3	NH_2	H	45

2.2 [4+2] Cycloaddition Reactions of Butadienyl Ketene

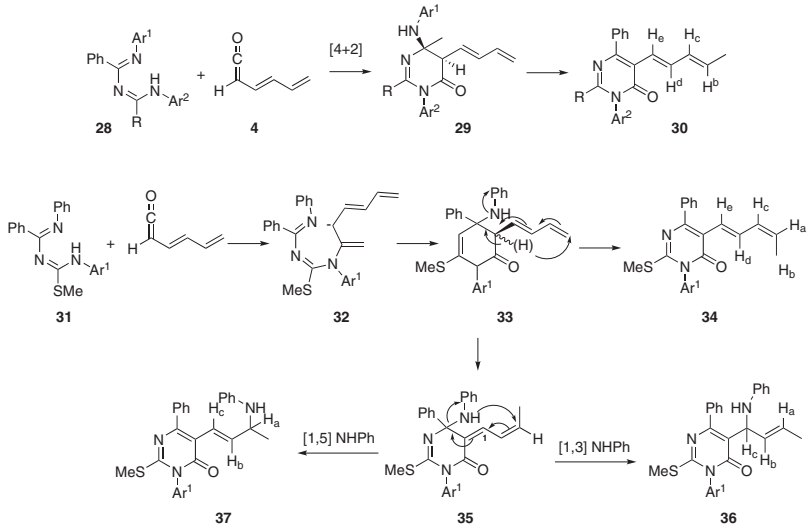
Regioselective [4+2] cycloaddition reaction of *N*-benzothiazolyl-fused 1,3-diazabuta-1,3-dienes was explored for the synthesis of pyrimidinone-fused benzathiazoles.[21] The [4+2] cycloaddition reaction between benzothiazolyl linked 1,3-diazabuta-1,3-dienes **18** and butadienyl ketene **19**, generated in situ, resulted in the formation of 5-butadienyl pyrimidinones **20** (Scheme 1). The mechanistic approach for the [4+2] cycloadditions involved a nucleophilic attack by the benzothiazole nitrogen on the carbonyl of ketene to form an intermediate that afforded tricyclic condensed pyrimidinones via internal rearrangement and tandem cyclization.[21]

There are reports on the synthesis of 5-dienyl pyrimidinones **22** using [4+2] cycloadditions of 1,3-diazabuta-1,3-dienes **21** with butadienyl ketene.[15] The [4+2] cycloadditions of various 1-aryl-2-phenyl-4-methylthio-4-secondary amino-l,3-diazabuta-l,3-dienes **21a–d** with butadienyl ketene **4**, generated in situ from sorboyl chloride and triethylamine, involved the initial formation of 5-dienyl-6-methylsulfanyl-2,3-diaryl-5,6-dihydro-3*H*-pyrimidin-4-ones, which afforded 5-dienyl pyrimidinones **22** via SMe elimination. 5-Dienyl-6-methylsulfanyl-2,3-diaryl-5,6-dihydro-3*H*-pyrimidin-4-ones also underwent tandem 1,5-hydride and 1,5-SMe shift to yield mixtures of 5-buta-1,3-dienyl-2,3-diaryl-3*H*-pyrimidin-4-one **23** and 5-(l′-butenyl)pyrimidinones **24** (Scheme 2).[15]

The interactions of butadienyl ketene with 1,3-diazabuta-l,3-dienes **25**, containing one or two secondary amino functionalities at the 4-position, resulted in functionalized 5-dienylpyrimidinones **27**. Removal of the secondary amine/-SMe from the initially produced intermediate **26** through [4+2] cycloaddition of butadienyl ketene and 1,3-diazabuta-l,3-dienes **25** resulted in more stable 5-dienylpyrimidinones **27** in high yields (Scheme 3).[15]

When dialkylamino-substituted *N*-arylamino-1,3-diazabuta-1,3dienes **28** were treated with butadienyl ketene **4**, generated in situ, only 2-dialkylamino-5-(buta-1,3-dienyl)pyrimidinone **30** was produced. However, the reactions between methylthio-modified *N*-arylamino-1,3-diazabuta-1,3-dienes **31** and **4** resulted in the isolation of a mixture consisting of 5-(buta-1,3-dienyl)-2-methylthiopyrimidin-4(3*H*)-one **34**, 2-methylthio-5-[1-(*N*-phenylamino)but-2-enyl]pyrimidin-4(3*H*)-one **36** and 2-methylthio-5-[3-(*N*-phenylamino)but-1-enyl]pyrimidin-4(3*H*)-one **37** (Table 6).[16]

Table 6 Preparation of 2-Dialkylamino-5-(buta-1,3-dienyl)pyrimidinone Derivatives



Compound	Ar^1	Ar^2	R	Yield (%)			
				30	**34**	**36**	**37**
a	Ph	Ph	Piperidino	86	33	21	30
b	4-Tol	Ph	Piperidino	82	29	26	29
c	4-Tol	4-Tol	Piperidino	80	25	21	27

Conclusion

This mini-review has focused on the reactivity of dienyl ketenes. Ketene chemistry is an area of interest for chemists due to the atom-economical formation of cycloadducts with a variety of functionalities at different positions. [2+2] and [4+2] cycloaddition reactions of dienyl ketene with imines and heterodienes, respectively, are well-established methods that afford a variety of four- and six-membered heterocycles. However, the synthesis of carbo- and heterocyclic systems through cycloaddition reactions of dienyl ketene are less extensively explored and cycloaddition reactions of butadienyl ketene with aldehyde, enamine, and ynamines, etc. are potentially useful for the development of new routes to functionalized heterocycles. Moreover, the synthetic potential of dienyl ketene as a 4π-component in cycloadditions with various substrates has not yet been tested. We hope that this mini-review has highlighted the work carried out using butadienyl ketene and underscored the synthetic potential of this important compound in organic chemistry.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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