Accepted Manuscript

Submission Date: 2024-02-13
Accepted Date: 2024-03-25
Accepted Manuscript online: 2024-04-09

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**Maninderjeet K Mann, Simranpreet K Wahan, Nitin Tandon, Gaurav Bhargava.**

Affiliations below.

**DOI: 10.1055/a-2302-3294**

**Please cite this article as:** Mann M K, Wahan S K, Tandon N et al. BUTADIENYL KETENE: AN UNEXPLORED INTERMEDIATE IN ORGANIC SYNTHESIS. SynOpen 2024. doi: 10.1055/a-2302-3294

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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Butadienyl ketene is a useful intermediate for its role as 2[5]- components in cycloaddition reactions with a variety of substrate such as simple/conjugated imines and dienes. The current review article summarizes the different reports on the in-situ generation of butadienyl ketene and their cycloaddition reactions to afford different heterocyclic systems. The chemistry of butadienyl ketene is explored only for their [2+2] and [4+2] cycloaddition with a variety of imines and azadiene such as 1,3-diazabuta-1,3-dienes for the synthesis of four- and six-membered heterocycles respectively.

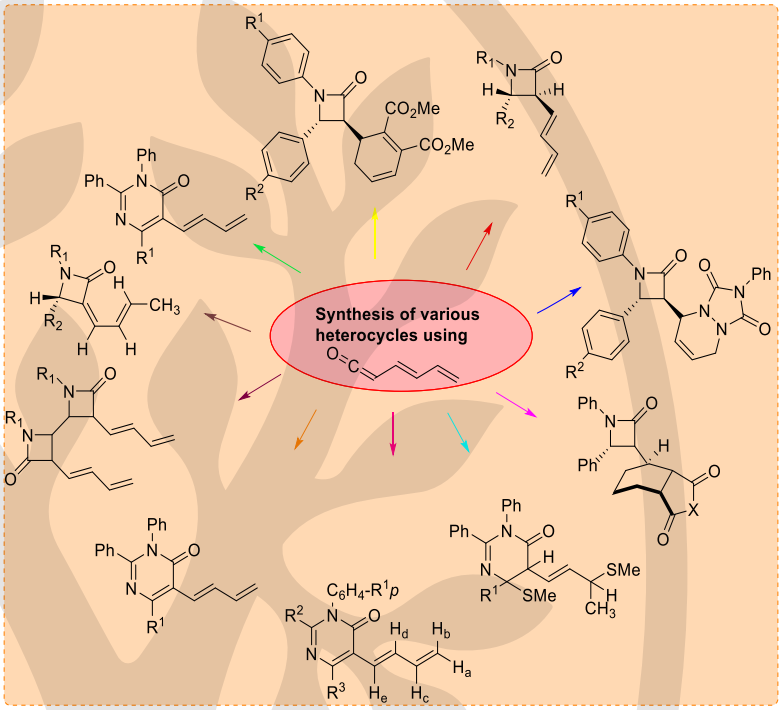
**Corresponding Author:**
Doctorate Gaurav Bhargava, Punjab Technical University, Kapurthala, Department of Applied Sciences, Jalandhar-Kapurthala Highway near Pushpa Gujral Science City, 144601 Kapurthala, India, gaurav@ptu.ac.in

**Affiliations:**
Maninderjeet K Mann, Punjab Technical University, Department of Applied Sciences, Kapurthala, India
Simranpreet K Wahan, IKGPTU, Chemistry, Kapurthala, India
Nitin Tandon, Lovely Professional University, Chemistry, Phagwara, India
Gaurav Bhargava, Punjab Technical University, Kapurthala, Department of Applied Sciences, Kapurthala, India

# BUTADIENYL KETENE: AN UNEXPLORED INTERMEDIATE IN ORGANIC SYNTHESIS

**Maninderjeet K. Mann[a#], Simranpreet K. Wahan[a#]**
**Nitin Tandon[b]**
**Gaurav Bhargava[a*]**

[a]Department of Chemistry, I. K. Gujral Punjab Technical University, Kapurthala, Punjab 144603, India
[b]School of Chemical Engineering and Physical Sciences, Lovely Professional University, Phagwara 144411, India
[#] Both authors contributed equally.




Received:
Accepted:
Published online:
DOI:

**Abstract** Butadienyl ketene is a useful intermediate for its role as 2p- components in cycloaddition reactions with a variety of substrate such as simple/conjugated imines and dienes. The current review article summarizes the different reports on the *in-situ* generation of butadienyl ketene and their cycloaddition reactions to afford different heterocyclic systems. The chemistry of butadienyl ketene is explored only for their [2+2] and [4+2] cycloaddition with a variety of imines and azadiene 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 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 oxygen atom bearing partially positive charge and the $C_\beta$ atom with partial negative charge [1]. Because of the fascinating

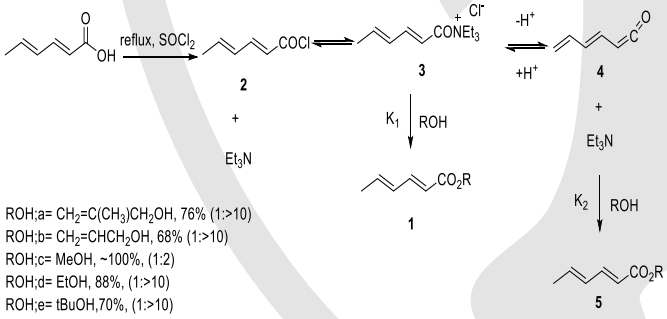
electronic structure of ketenes, these species have been the subject of intense investigation [1-2]. The appearance of ketenes in organic synthesis has gained enhanced frequency over the past few decades [3-4]. A very common reaction of ketene *i.e.* Staudinger reactions involving [2+2] cycloaddition of ketene and imines proceeded *via* zwitterionic intermediate [5] are useful reaction for the preparation of biologically potent lactams. The synthesis of carbo- and heterocyclic systems involving the [2+2] cycloaddition of ketenes with alkenes and iminic systems have been extensively explored [3]. Also, there are ample 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/isopropenylketenes resulted in *trans*, *cis*, or a mixture of *trans* and *cis* $\beta$ -lactams [8-10].


**Figure 1.** Ketenes explored in chemical reactions.

However, as compared to the other conjugated ketene such as vinyl and iso-propenyl ketene, butadiene ketene has relatively been less explored in (m+n) cycloaddition reactions with different substrates acting as 2π- or 4 π- component. 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 synthetic community for capturing the unleased potential of butadienyl intermediate, this review article summarizes the generation of butadienyl ketene and 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. 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, there is formation of a substantial portion of conjugated isomer **2a** in addition to **1a (Schene 1)**. This reaction was proceeded partially *via* butadienyl ketene **4**. Addition of one equivalent of triethylamine to sorboyl chloride resulted in the formation of acyl triethylammonium ion **5** [2]. Acyl triethylammonium ion **5** underwent direct addition reaction with alcohol to afford conjugated ester **1**. However, Acyl triethylammonium ion **3 f**ormed results into the formation of ketene **4** on reaction with another molecule of triethylamine which results in the formation of conjugated ester **5** on reaction with alcohol [3].

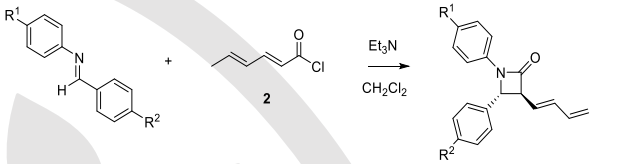



ROH;a= $CH_2$=C($CH_3$)$CH_2$OH, 76% (1:>10)
ROH;b= $CH_2$=$CHCH_2$OH, 68% (1:>10)
ROH;c= MeOH, ~100%, (1:2)
ROH;d= EtOH, 88%, (1:>10)
ROH;e= tBuOH,70%, (1:>10)
ROH;f= PhOH, ~100%, (1:0)
ROH;g= $CH_2$=$CHCH_2NH_2$, 0%, (~10:1)
ROH;h= $(iPr)_2NH$, 84%, (1:1)
ROH;i= $H_2O$, 0%, (conjugated anhydride)

**Scheme 1** Generation of butadienyl ketene **4** and conversion into conjugated methallyl ester **2.**

### 2.1 [2+2] cycloaddition reactions of butadienyl ketene

The nitrogen-containing organic molecules such as amino alkaloids have immense significance in organic chemistry [11]. The synthesis of such nitrogenous compounds *via* employing cycloadditions of functionalized ketene are a vital methodology in organic chemistry [12-13]. In 1995, Mahajan and coworkers have explored the [2+2] cycloaddition reactions of Schiff bases **6** with butadienylketene, generated *in situ* from sorboyl chloride **2** in the presence of mild base, to yield trans 3-butadienyl $\beta$-lactams **7** diastereoselectivly (48-63%; **Scheme 2)** [14]. The synthetic potential of the 3-dienyl-2-azetidinones **7** was explored *via* employing catalysed/ 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 cycloadditions of butadienylketene with various imines and 1-azabuta-1,3-dienes has proved to be a general method for the synthesis of various butadienyl substituted functionalized lactams in good yields.

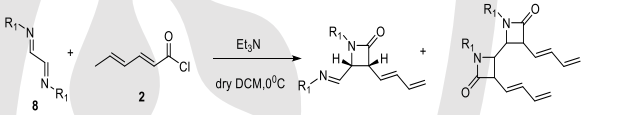



**6a**; $R^1$=$R^2$=H
**6b**; $R^1$=H, $R^2$=$OCH_3$
**6c**; $R^1$=$CH_3$, $R^2$=H
**6d**.;$R^1$=$CH_3$, $R^2$=$OCH_3$

**7a**; $R^1$=$R^2$=H, 59%
**7b**; $R^1$=H, $R^2$=$OCH_3$, 63%
**7c**; $R^1$=$CH_3$, $R^2$=H, 59%
**7d**.;$R^1$=$CH_3$, $R^2$=$OCH_3$, 48%

**Scheme 2** Synthesis of 3-butadienyl-$\beta$-lactams.

In 2015, Bhargava *et al.* have explored the [2+2] cycloaddition of *in situ* generated butadienylketene with variety of 1,4-diazadienes. The diastereoselective [2+2] cycloaddition afforded functionalized butadienyl-4-iminomethyl-azetidin-2-one and butenylidene-butadienyl-[2, 2′-biazetidine]-4, 4′-dione [18]. The butadienyl ketene generated *in situ* from sorboyl chloride **2** using mild base underwent [2+2] cycloadditions with different 1,4-diazabuta1,3-dienes **4a-e** yielded mono as well as bis-$\beta$-lactams **(Scheme 3).** The synthesis of mono-$\beta$-lactams 9**a–c** or bis-$\beta$-lactams **10a–c** was largely dependent on the concentration of the acid chloride used in the reaction medium. An equimolar amount of sorboyl chloride in [2+2] cycloadditions with 1,4-diazabuta-1,3-dienes afforded mono-$\beta$-lactam, i.e. *cis* butadienyl-4-iminomethyl-azetidin-2-ones **9**, as major product. The [2+2] cycloaddition reactions using high equivalents of sorboyl chloride with 1,4 diazabuta-1,3-dienes **8** afforded bis-$\beta$-lactams, i.e. **10a–c** as 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 major cycloadducts [19].



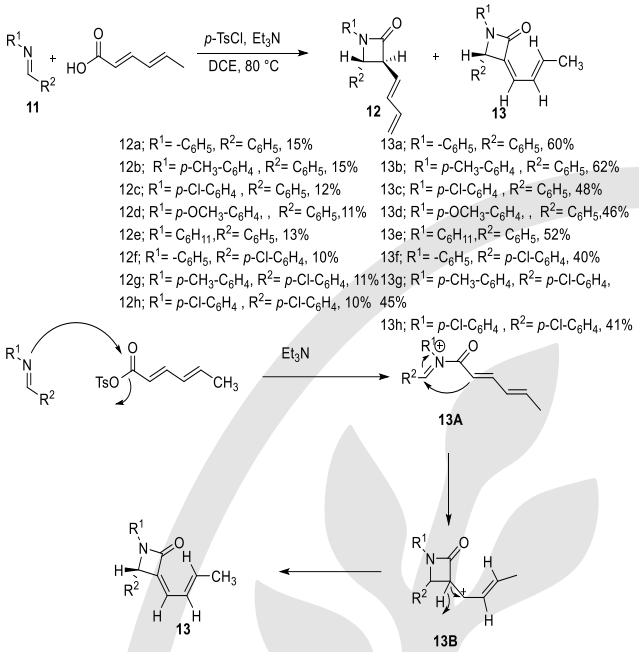

**8a**; $R_1$=*p*-$CH_3$-$C_6H_5$
**8b**; $R_1$=*o*-$CH_3$-$C_6H_5$
**8c**; $R_1$=$C_6H_5$
**8d**; $R_1$=*p*-$OCH_3$-$C_6H_5$
**8e**; $R_1$=$C_6H_{11}$

**9a**; $R_1$=*p*-$CH_3$-$C_6H_5$, 47%
**9b**; $R_1$=*o*-$CH_3$-$C_6H_5$, 41%
**9c**; $R_1$=$C_6H_5$, 25%
**9d**; $R_1$=*p*-$OCH_3$-$C_6H_5$, 5%
**9e**; $R_1$=$C_6H_{11}$, 0%

**10a**; $R_1$=*p*-$CH_3$-$C_6H_5$, 15%
**10b**; $R_1$=*o*-$CH_3$-$C_6H_5$, 13%
**10c**; $R_1$=$C_6H_5$, 0%
**10d**; $R_1$=*p*-$OCH_3$-$C_6H_5$, 0%
**10e**; $R_1$=$C_6H_{11}$, 0%

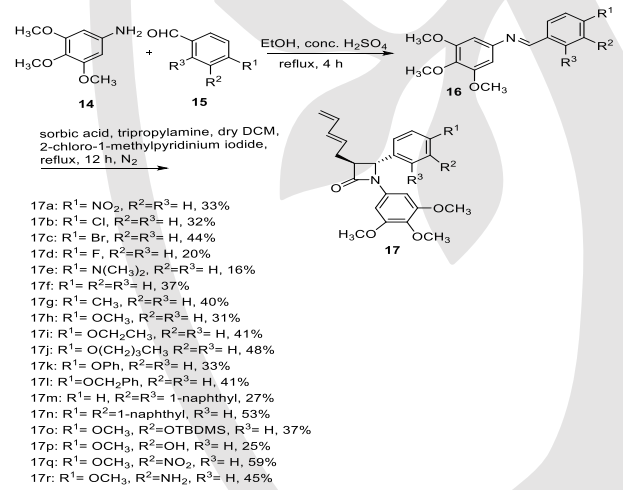
**Scheme 3** Formation of *cis* butadienyl-4-iminomethyl-azetidin-2-ones and bis-$\beta$-lactams.

In 2018, Bhargava *et al.* explored the reactions of sorboyl tosylate at high temperature (80 °C) with variety of imines to yield mixture of 3-dienyl lactam **12** and $\alpha$–alkylidene–$\beta$–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 $\alpha$–alkylidene–$\beta$–lactams **13** involved the addition of the sorbic tosylate to the imine nitrogen **11** to afford a zwitterionic intermediate **13A** which collapsed to an another intermediate **13B** by ring closure electrocyclizations. An abstraction of acidic ring proton by base led to the formation of 3-but-2-enylidene-azetidin-2-ones **13** as major adduct (**Scheme 4).** The density functional theory on the outcome of the cycloaddition reaction was also explored to predict the plausible mechanism of the reaction which afforded a mixture of 3-butadienyl-azetidin-2-ones **12** and 3-but-2-azetidin-2-ones **13** in appreciable yield at elevated temperature [19].




**Scheme 4** Synthesis of a series of *α*-alkylidene-*β*-lactam derivatives.

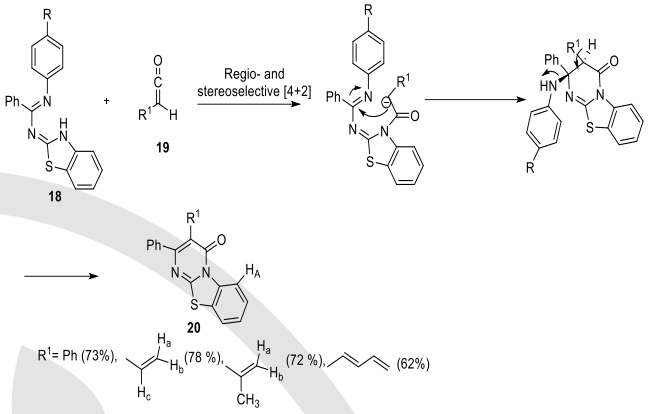
Wang *et al.* designed and synthesized three series of 3-dienyl-*β*-lactams as colchicine-binding-site-targeting inhibitors. The imines **16** were reacted with butadienyl ketene generated *in situ* by action of sorbic acid and suitable base in dichloromethane to afford 3-(buta-1,3-dien-1-yl)azetidin-2-ones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




**Scheme 5** Synthesis of 3-dienyl-β-lactams as colchicine-binding-site-targeting inhibitors.

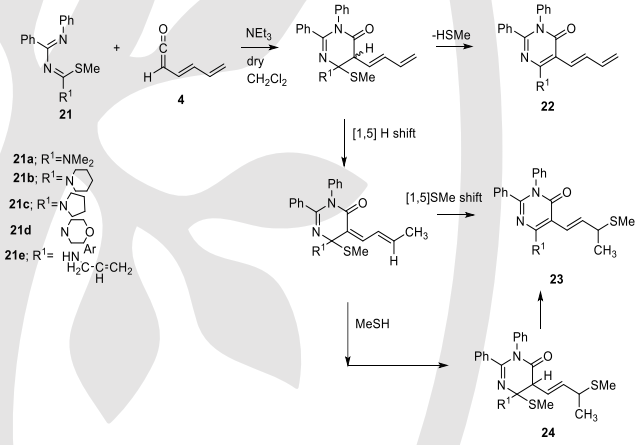
### 2.2 [4+2] cycloaddition reactions of butadienyl ketene.

Regioselective [4+2] cycloaddition reaction of *N*-benzothiazolyl fused 1,3-diazabuta-1,3-dienes was explored for the synthesis of pyrimidinones fused benzathiazoles. The [ 4+2] cycloaddition reaction between benzothiazolyl clubbed 1,3-diazabuta-1,3-dienes **18** and *in situ* generated butadienylketene **19** resulted in the formation of 5-butadienyl pyrimidinones **20 (Scheme 6)**. The mechanistic approach for [4+2] cycloadditions involved the nucleophilic attack by the benzothiazole nitrogen to carbonyl of ketene to form an intermediate which *via* internal rearrangement and tandem cyclization afforded tricyclic condensed pyrimidinones [21].



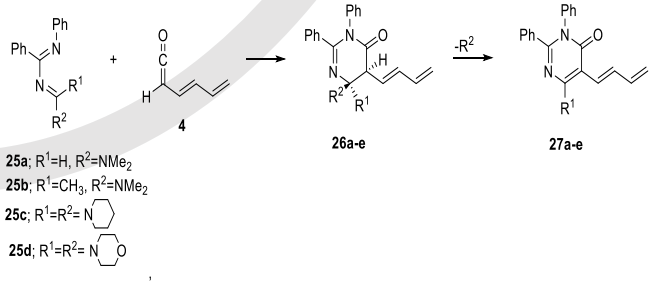

**Scheme 6** Regioselective [4+2] cycloadditions reaction for the synthesis of 5-butadienyl pyrimidinones.

There are further reports on the synthesis of 5-dienyl pyrimidinones **22** using [4+2] cycloadditions of 1,3-diazabuta-1,3 dienes **21** with butadienylketene. The [4+2] cycloadditions of various 1-aryl-2-phenyl-4-methylthio-4-secondary amino-l,3-diazabuta-l,3-dienes **21a-d** with butadienylketene **2**, generated in situ from sorboyl chloride and triethylamine, involved the initial formation of 5-dienyl-6-methylsulfanyl-2,3-diaryl-5,6-dihydro-3H-pyrimidin-4-ones, which *via* -SMe elimination afforded 5-dienyl pyrimidinones **22**. 5-Dien0yl-6-methylsulfanyl-2,3-diaryl-5,6-dihydro-3H-pyrimidin-4-ones have also exhibited the tandem 1,5-hydride and 1,5-SMe shift to yield the mixture of 5-(l',Y-butadienyl)pyrimidinones **23** and 5-(l'-butenyl)pyrimidinones **24** (**Scheme 7**) [15].




**Scheme 7** Cycloaddition of 1,2-diaryl-4-methylthio-4-secondary amino-l,3-diazabuta-l,3-dienes **17** with butadienylketene **2**.

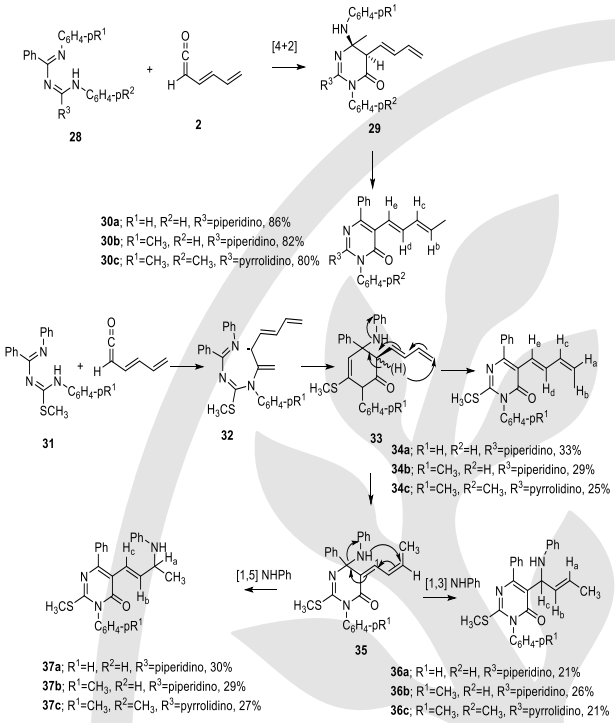
The interactions of butadienylketene with 1,3-diazabuta-l,3-dienes **25** containing one or two secondary amino functionalities at the 4-position resulted in functionalized 5-dienylpyrimidinones **27**. The removal of secondary amine/-SMe from the initially produced intermediate **26** *via* [4+2] cycloaddition of butadienyl ketene and 1,3-diazabuta-l,3-dienes **25** resulted in more stable 5-dienylpyrimidinones **27** in high yields (**Scheme 8**) [15].




**Scheme 8** (4+2) cycloaddition of butadienyl ketene **2** and1,3-diazabuta-l,3-dienes **20**

When dialkylamino substituted N-arylamino-1,3-diazabuta-1,3dienes **28** were treated with in situ created butadienylketene **2**, 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(3H)-one **34**, 2-methylthio-5-[1-(N-phenylamino)but-2-enylpyrimidin-4(3H)-one **36** and 2-methylthio5-[3-(N-phenylamino)but-1-enyl].pyrimidin-4(3H)-one **37** [16] (see **Scheme 9**).




**Scheme 9** Preparation of 2-dialkylamino-5-(buta-1,3-dienyl)pyrimidinone derivatives.

## 3. CONCLUSION

The mini review aims to focus on earlier explored reactivity aspects of dienyl ketenes. Ketenes chemistry is an area of interest for chemists due to the atom economical formation of cycloadducts having variety of functionality at different positions. [2+2] and [4+2] cycloaddition reactions of dienylketene with imines and heterodienes respectively are well illustrated to afford variety of four and six membered heterocycles. However, the synthesis of carbo- and heterocyclic systems involved the cycloaddition reactions of dienyl ketene are comparatively less explored and cycloaddition reaction of butadienyl ketene with aldehyde, enamine ynamines etc. can potentially be useful for the development of new route for functionalized heterocycles. Moreover the synthetic potential of dienyl ketene as 4π-component in its cycloadditions with various substrates is note been even tested so far. The purpose of the mini-review is to highlight the earlier work carried out using butadienyl ketes as well as the anticipated synthetic potential of butadienyl ketene in organic chemistry.

## Acknowledgment

We gratefully acknowledge I. K. Gujral Punjab Technical University, Kapurthala for generous support of this work.

## Conflict of Interest

The authors declare no conflict of interest.

**Author details**

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**Maninderjeet Kaur Mann** has completed Ph.D in chemical sciences under the supervision of Dr. Gaurav Bhargava at IK Gujral Punjab Technical University, Jalandhar**.** She has research experience in synthetic chemistry.

**Simranpreet K. Wahan** is DST Inspire JRF at IK Gujral Punjab Technical University, Jalandhar. She is gold medalist in Masters of Science (Chemistry) at Punjab University, Chandigarh. She has many publications in various reputed journals.

**Nitin Tandon** works as Associate Professor at Lovely Professional University, Jalandhar. His research work includes synthesis of active pharmaceutical ingredients and synthesis of novel organic molecules of medicinal use.

**Gaurav Bhargava** is head of department in the Department of Applied Sciences, IK Gujral Punjab Technical University, Jalandhar**.** He has rich research experience in green chemistry and organic synthetic chemistry and various publications in reputed international journals.