Convenient Synthesis of 4-Methylenecyclobutenones and Their Synthetic Utility as Allenylketene Precursors

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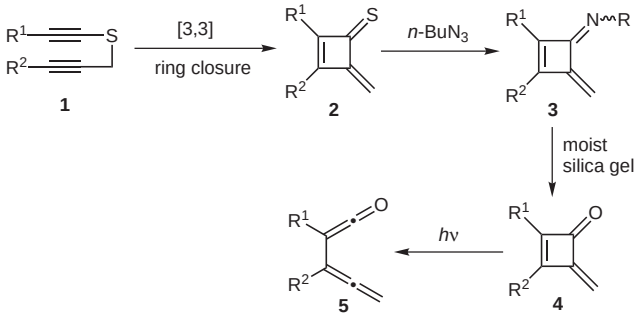
Abstract: Thermal reaction of alkynyl propargyl sulfides **1** in the presence of *n*-BuN_3 followed by moist silica gel treatment afforded 4-methylenecyclobutenones **4** in moderate yields. Photogeneration of allenylketenes **5** from **4** in the presence of amine or methanol gave 3,4-pentadienamides **6** or methyl 3,4-pentadienates **7**, respectively. Similar reaction in the presence of aldimines afforded unsaturated δ-lactams **9** in good yields.

Key words: alkynyl propargyl sulfides, 4-methylenecyclobutenones, allenylketenes, [4+2]-cycloaddition, unsaturated δ-lactams

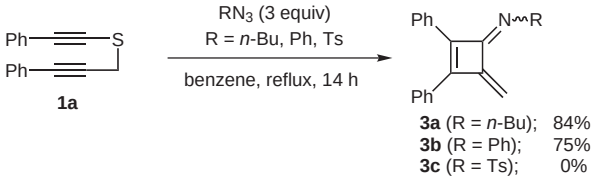
Cyclobutenones are recognized as useful synthetic equivalents of vinylketenes, and they have been considered as novel precursors for the formation of cyclic compounds via intermolecular [4+2]-[1] and [4+1]-cycloaddition[2] and intramolecular cyclization.[3,4] For these reasons, much research has been carried out on chemical conversion of these species. Tidwell reported a new preparation of 4-methylenecyclobutenones **4**, and used these products as precursors for allenylketenes **5**.[5] However, access to 2,3-unsymmetrically substituted 4-methylenecyclobutenones **4** has been limited due to low selectivity in the methylenation reaction of unsymmetrically substituted cyclobutene-1,2-diones.

In the course of our synthetic studies of chalcogenocarbonyl compounds,[6] we reported a new method for generating unstable 4-methylenecyclobutenethiones **2** via [3,3]-sigmatropic rearrangement of alkynyl propargyl sulfides **1** bearing various substituents. Further conversion of isolable 2-trimethylsilyl-3-phenyl-4-methylenecyclobutenethione (**2h**) via MCPBA oxidation gave the corresponding ketone **4h**.[6c] However, this protocol can only be used when **2** is isolable and bears a relatively bulky R^1 substituent. These results prompted us to develop a new general approach to the preparation of 4-methylenecyclobutenones **4** via a novel oxidative hydrolytic pathway from **2**. In this paper, we describe an efficient synthesis of **4** via formation of 4-methylenecyclobutenimines **3**, which are generated by treating in situ generated thiones **2** with *n*-butylazide. We also report photoinduced ring opening of **4** and efficient trapping of the resulting allenylketenes **5** (Scheme 1).



Scheme 1

We initially examined thermal reactions of alkynyl propargyl sulfide **1a**[6c] in the presence of azides (Equation 1). The use of *n*-butylazide or phenylazide resulted in the formation of imines **3a** and **3b** (84% and 75% yields), respectively.[7] An attempt to prepare *N*-tosylimine in an analogous procedure was unsuccessful. Imine **3a** was readily transformed into the corresponding ketone **4a** in 83% yield during purification by column chromatography, but **3b** was stable under similar conditions. Although treatment of **3b** with $TsOH·H_2O$ (2 equiv) in THF–H_2O (1:1) at room temperature for five hours also afforded **4a** in 68% yield, the relatively efficient preparation via **3a**, which proceeds under mild conditions, was preferable.



Equation 1

Next, we undertook the preparation of various other substituted 4-methylenecyclobutenones **4** via thermal reaction of **1** in the presence of *n*-BuN_3 followed by moist silica gel treatment. The results are summarized in Table 1. Alkyl-, aryl-, and silyl-substituted cyclobutenones **4a**–**i** were prepared with moderate to good yields,[8] despite the fact that intermediate thiones **2a**–**g** were not isolable. The structures of **4** were confirmed by mass, IR, ^1H and ^{13}C NMR spectroscopy and by elemental analysis. The spectral data of **4h** were in agreement with those previously reported.[5b,6c] It is noteworthy that, unlike Wittig-type methylenation of 3,4-unsymmetrically substituted

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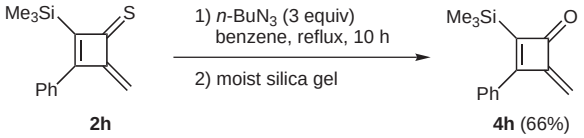
cyclobuten-1,2-dione,[5b] our method of preparing **4h** is completely regioselective.

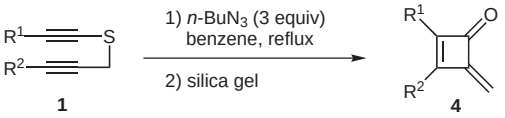
Compound **4h** was also obtained in 66% yield by heating the isolated cyclobutenethione **2h**[6c] with *n*-BuN_3 (3 equiv) in refluxing benzene for ten hours, followed by chromatographic purification (Equation 2).



2h **4h** (66%)

Equation 2

Table 1 Preparation of 4-Methylenecyclobutenones **4**



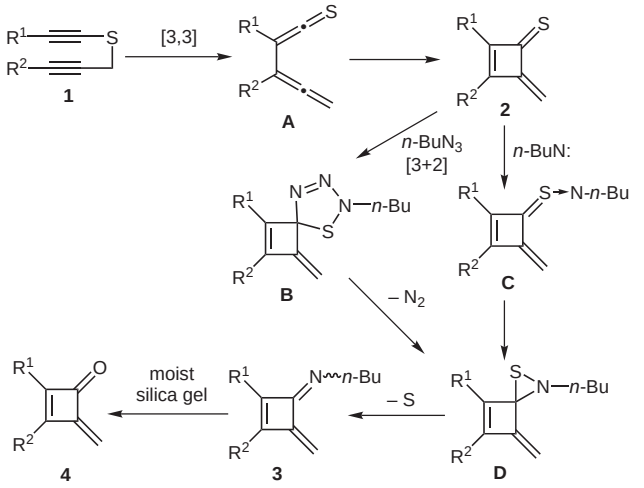
1 **4**

Entry	**1**	R^1	R^2	Time (h)	**4**	Yield (%)[a]
1	**1a**	Ph	Ph	14	**4a**	72
2	**1b**	Ph	4-BrC_6H_4	14	**4b**	77
3	**1c**	PMP[b]	Ph	14	**4c**	80
4	**1d**	DMP[c]	DMP[c]	14	**4d**	56
5	**1e**	Ph	*n*-Bu	18	**4e**	43
6	**1f**	Ph	Me_3Si	24	**4f**	62
7	**1g**	PMB[d]	Me_3Si	12	**4g**	77
8	**1h**	Me_3Si	Ph	24	**4h**	61
9	**1i**	Me_3Si	Me	12	**4i**	58

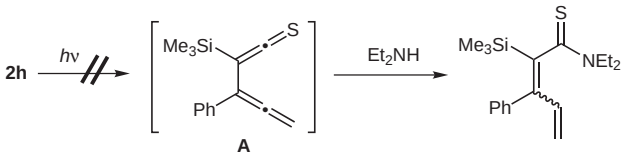
[a] Isolated yield.
[b] PMP: 4-Methoxyphenyl.
[c] DMP: 3,4-Dimethoxyphenyl.
[d] PMB: 4-Methoxybenzyl.

Although the intermediates 1-thia-2,3,4-triazole **B**, thione *S*-imide **C** and thiaziridine **D** could not be isolated, the formation mechanism illustrated in Scheme 2 is plausible: [3,3]-sigmatropic rearrangement of **1** followed by ring closure of the intermediate allenylthioketene **A** affords cyclobutenethione **2**; subsequent [3+2]-cycloaddition of **2** with azide gives intermediate **B**, and extrusion of N_2 and sulfur via **D** produces imine **3**. It is well known that thiones undergo [3+2]-cycloaddition with 1,3-dipoles,[9] including nitrones, nitrile oxides and sulfines; thus, an alternative reaction pathway via **C**, involving a nitrene derived from *n*-BuN_3, is also possible.[10]

Next, we investigated photoinduced ring-opening reactions of the series of compounds **4** to generate allenylketenes **5**, which were then trapped with amines or methanol. Tidwell reported a photoinduced ring-opening reaction of **4h** at –50 °C and analysis of the resulting **5h** by ^{1}H NMR and IR at low temperature.[5b] We previously attempted to photogenerate allenylthioketene **A** via ring opening of thione **2**; however, photoirradiation of **2h** in the presence of Et_2NH as a trapping reagent resulted in the recovery of thione **2h** in place of α,β,γ,δ-unsaturated thioamide (Equation 3).



Scheme 2 Plausible formation pathway of 4-methylenecyclobutenone **4**



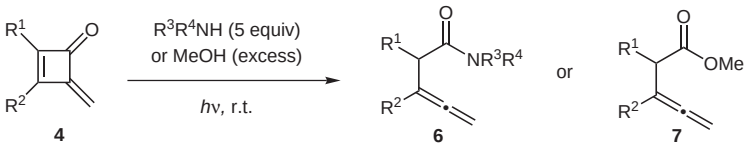
Equation 3

In contrast, photoirradiation of **4** in the presence of amine or MeOH at room temperature afforded the corresponding 3,4-pentadienamides **6**[11] or methyl 3,4-pentadienates **7**,[12] which are the trapping products of allenylketenes **5**, in moderate to good yields (Table 2).

When photogeneration of allenylketene **5h** from **4h** was carried out in the presence of Et_2NH, the desilylated product **6h**–**Et′** was also obtained in 72% yield. It is noteworthy that **4a** and **4e**, which lack a silyl group at R^1, resulting in destabilization of the ketene moiety, also serve as precursors for allenylketenes **5**.

Finally, we examined the photoinduced ring opening of 4-methylenecyclobutenone **4h** in the presence of imines **8**. We previously reported that [4+2]-cycloaddition of the thermally generated allenyltrimethylsilylthioketene **A** (R^1 = Me_3Si) with imines afforded unsaturated δ-thiolactams.[14] However, the application of thermally unstable imines pyrroline (**8b**) and piperideine (**8c**)[13] in this reaction was limited; they could only be used in conjunction with allenyltrimethylsilylthioketene **A** (R^1 = Me_3Si, R^2 = H), as this could be generated at room temperature. A thermal reaction of **1h**, which undergoes [3,3]-sigmatropic rearrangement at 80 °C and above, in the presence of **8c** did not give the expected 4-substituted indolizidinthione

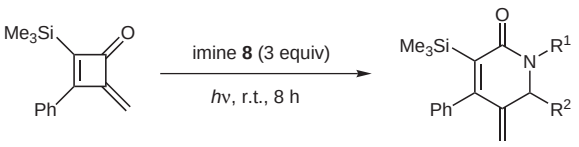
Table 2 Photoreaction of 4-Methylenecyclobutenones **4** in the Presence of an Amine or Methanol

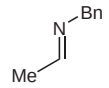
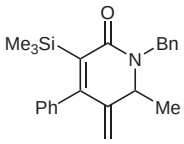
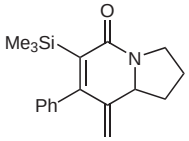
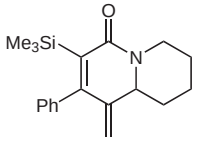
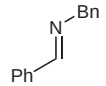
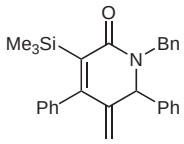


Entry	Substrate	R^1	R^2	Reagent	Solvent	Time (h)	Product	Yield (%)[a]
1	**4a**	Ph	Ph	$BnNH_2$	THF	9	**6a-Bn**	44
2	**4a**	Ph	Ph	Et_2NH	THF	7	**6a-Et**	24
3	**4e**	Ph	Me_3Si	$BnNH_2$	THF	8	**6e-Bn**	62
4	**4e**	Ph	Me_3Si	MeOH	MeOH	5	**7e**	68
5	**4h**	Me_3Si	Ph	$BnNH_2$	THF	8	**6h-Bn**	72
6	**4h**	Me_3Si	Ph	Et_2NH	THF	5	**6h-Et**	17[b]
7	**4h**	Me_3Si	Ph	MeOH	MeOH	5	**7h**	94

[a] Isolated yield.
[b] *N*,*N*-Diethyl-3-phenyl-3,4-pentadienamide (**6h-Et′**) was also afforded in 72% yield.

Table 3 Photoreaction of **4h** in the Presence of Imine **8**



Entry	Imine	Solvent	Cycloadduct	Yield (%)[a]
1	 **8a**	THF	 **9a**	72
2	 **8b**[b]	Et_2O	 **9b**	67
3	 **8c**[b]	Et_2O	 **9c**	71
4	 **8d**	THF	 **9d**	13

[a] Isolated yield.
[b] The imine was prepared according to the reported procedure[13] and was used without further purification.

due to decomposition of the thermally unstable **8c**. Therefore, we attempted to develop a versatile aza-Diels–Alder reaction to obtain 4-substituted indolizidinone **9b** and quinolizidinone **9c**, respectively, from **8b**/**8c** and **4h**. To achieve this, allenyltrimethylsilylketene **5h** was generated from **4h** via photoirradiation in the presence of imines **8**, and the resulting [4+2]-cycloaddition reactions were examined; the results are summarized in Table 3. The photoreaction of **4h** in the presence of imine **8a** (3 equiv) in THF at room temperature afforded the unsaturated δ-lactam **9a** in 72% yield. Similar reactions employing thermally unstable cyclic imines **8b** and **8c** afforded indolizidinone **9b** and quinolizidinone **9c** in 67% and 71% yields, respectively.[15] The reaction of **5h** with *N*-benzylbenzylideneimine **8d** was sluggish, and the isolated yield of [4+2]-cycloadduct **9d** was 13%. Unfortunately, **5h** did not react with ketimines *N*-benzyl-2-propylideneimine and 2-methylpyrroline. As expected, photoirradiation of **4a** (which lacks a silyl group at R^1) in the presence of imine **8a** gave neither the [4+2]- nor the [2+2]-cycloadduct and instead 3,4-pentadienamide **6a-Bn**, derived from allenylketene **5h** and $BnNH_2$ via photodecomposition of imine **8a**, was afforded in 25% yield.

In conclusion, the thermal reaction of alkynyl propargyl sulfides **1** in the presence of *n*-BuN_3 followed by moist silica gel treatment afforded 4-methylenecyclobutenones **4**, which are considered to have synthetic potential. Generation of allenylketenes **5** by photoinduced ring opening of 4-methylenecyclobutenone **4** followed by trapping with amine or MeOH gave 3,4-pentadienamide **6** or methyl 3,4-pentadienate **7** in moderate to good yields. Similar reactions of **4h** in the presence of aldimines **8** furnished unsaturated δ-lactams **9** in good yield. Further examination of this method, including mechanistic investigations, is underway.

References and Notes

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(7) A benzene solution (20 mL) of **1a** (500 mg, 2.01 mmol) and *n*-BuN_3 (598 mg, 6.04 mmol) was heated to reflux for 14 h. Decantation (hexane) of the residue after removal of solvent and excess amount of *n*-BuN_3 followed by evaporation afforded **3a**; yield: 4.87 mg (84%); pale yellow oil. MS: *m*/*z* = 287 (95) [M^+], 230 (100) [M^+ – *n*-Bu]. IR (neat): 2957, 2930, 1708, 1444, 1361, 867, 764, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3 H), 1.51–1.61 (m, 2 H), 1.71–1.76 (m, 2 H), 3.81 (t, *J* = 7.2 Hz, 2 H), 5.09 (d, *J* = 1.5 Hz, 1 H), 5.17 (d, *J* = 1.5 Hz, 1 H), 7.32–7.47 (m, 6 H), 7.61–7.65 (m, 2 H), 7.90–7.94 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (q), 20.5 (t), 33.7 (t), 51.6 (t), 98.5 (dd), 127.2 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.7 (d), 129.1 (d), 129.3 (s), 130.8 (s), 151.1 (s), 151.8 (s), 157.8 (s), 161.9 (s). Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.87. Found: C, 87.44; H, 7.41; N, 4.67.

(8) A benzene solution (20 mL) of **1a** (500 mg, 2.01 mmol) and *n*-BuN_3 (598 mg, 6.04 mmol) was heated to reflux for 14 h. The resulting solution was subjected to column chromatography on silica gel (hexane–EtOAc = 20:1) to yield **4a** (337 mg, 72%) as a pale yellow oil. UV (hexane): λ_{max} = 332 (ε = 10500), 283 (ε = 13500) nm. MS: *m*/*z* = 232 (100) [M^+], 204 (79) [M^+ – CO]. IR (neat): 3062, 1773, 1751, 1445, 1360, 722, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.02 (d, *J* = 1.7 Hz, 1 H), 5.27 (d, *J* = 1.7 Hz, 1 H), 7.35–7.37 (m, 3 H), 7.50–7.51 (m, 3 H), 7.76–7.78 (m, 2 H), 7.82–7.85 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 95.7 (dd), 127.5 (d), 127.83 (d), 128.78 (d), 129.1 (d), 129.4 (s), 130.1 (d), 131.0 (s), 131.5 (d), 155.5 (s), 157.0 (s), 172.4 (s), 188.2 (s). Anal. Calcd for $C_{17}H_{12}O$: C, 87.90; H, 5.21. Found: C, 87.81; H, 5.33.

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(11) A THF solution (20 mL) of **4h** (300 mg, 1.31 mmol) and $BnNH_2$ (703 mg, 6.57 mmol) was irradiated using high pressure Hg lamp at r.t. for 8 h under N_2. The residue after removal of solvent was subjected to column chromatography on silica gel (hexane–EtOAc = 5:1) to give **6h-Bn** (317 mg, 72%) as a pale yellow oil. MS: *m*/*z* = 335 (3) [M^+], 262 (51) [M^+ – Me_3Si], 91 (100) [Bn]. IR (neat): 3304, 3062, 3031, 2956, 1938, 1636, 1515, 1495, 1249, 846, 733, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 2.97 (s, 1 H), 4.31 (d, *J* = 2.1 Hz, 1 H), 4.33 (d, *J* = 2.1 Hz, 1 H), 5.04 (d, *J* = 12.1 Hz, 1 H), 5.10 (d, *J* = 12.1 Hz, 1 H), 6.14 (br s, 1 H), 7.00–7.03 (m, 2 H), 7.07–7.14 (m, 3 H), 7.17–7.22 (m, 3 H), 7.27–7.30 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.5 (q), 41.2 (d), 43.4 (t), 79.9 (t), 103.1 (s), 126.0 (d), 127.0 (d), 127.1 (d), 127.3 (d), 128.3 (d), 128.4 (d), 136.5 (s), 138.4 (s), 171.7 (s), 210.0 (s). Anal. Calcd for $C_{21}H_{25}NOSi$: C, 75.18; H, 7.51; N, 4.17. Found: C, 75.11; H, 7.50; N, 4.27.

(12) A MeOH solution (20 mL) of **4h** (300 mg, 1.31 mmol) was irradiated using high pressure Hg lamp at r.t. for 5 h under N_2. The residue after removal of excess amount of MeOH was subjected to column chromatography on silica gel (hexane–EtOAc = 7:1) to provide **7h** (322 mg, 94%) as a pale yellow oil. MS: *m*/*z* = 260 (44) [M^+], 245 (77) [M^+ – Me], 187 (65) [M^+ – Me_3Si], 73 (100) [Me_3Si]. IR (neat): 2952, 1948, 1731, 1715, 1251, 1154, 850, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 9 H), 3.19 (s, 1 H), 3.69 (s, 3 H), 5.17 (d, *J* = 11.8 Hz, 1 H), 5.27 (d, *J* = 11.8 Hz, 1 H), 7.18–7.21 (m, 1 H), 7.25–7.30 (m, 2 H), 7.32–7.39 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.7 (q), 38.8 (d), 51.5 (q), 79.5 (t), 101.4 (s), 126.0 (d), 126.7 (d), 128.4 (d), 137.4 (s), 173.3 (s), 173.3 (s), 210.9 (s). Anal. Calcd for $C_{15}H_{20}O_2Si$: C, 69.19; H, 7.74. Found: C, 69.28; H, 7.96.

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(15) To an ethereal solution (50 mL) of **8c** prepared from piperidine (335 mg, 3.94 mmol) according to the reported procedure,[13] **4h** (300 mg, 1.31 mmol) was added and the mixture was irradiated using high pressure Hg lamp at r.t. for 8 h under N_2. The residue after removal of solvent was subjected to column chromatography on silica gel (hexane–EtOAc = 5:1) to give **9c** (291 mg, 71%) as a colorless oil. MS: *m*/z = 311 (10) [M^+], 296 (100) [M^+ – Me]. IR (neat): 2939, 1623, 1462, 1442, 1269, 1251, 878, 843 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = –0.15 (s, 9 H), 1.49–1.57 (m, 1 H), 1.67–1.74 (m, 3 H), 1.79–1.87 (m, 1 H), 1.95–1.99 (m, 1 H), 2.58 (td, *J* = 2.6, 12.8 Hz, 1 H), 4.14 (br d, 1 H), 4.64–4.71 (m, 1 H), 4.68 (s, 1 H), 5.18 (s, 1 H), 7.11–7.12 (m, 2 H), 7.33–7.36 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.93 (q), 25.1 (t), 25.7 (t), 36.2 (t), 43.9 (dd), 61.8 (d), 118.6 (d), 127.8 (d), 129.0 (d), 129.7 (d), 133.8 (s), 138.8 (s), 144.9 (s), 155.2 (s), 165.6 (s). Anal. Calcd for $C_{19}H_{25}NOSi$: C, 73.26; H, 8.09; N, 4.50. Found: C, 73.08; H, 8.15; N, 4.44.