Highly efficient synthesis of 3-amino-/alkylthio-cyclobut-2-en-1-ones based on the cyclization of acyl ketene dithioacetals†

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A new strategy for the highly efficient one-pot synthesis of 3-amino-/alkylthio-cyclobut-2-en-1-ones based on the cyclization of acyl ketene dithioacetals is disclosed. In addition, the rearrangement of 3-amino-cyclobut-2-en-1-ones to 4-quinolone derivatives is described.

In recent research on the VLA-4 (very late activating antigen-4) antagonists,[1] 3-aminocyclobut-2-en-1-one derivatives have been described as potent VLA-4 antagonists.[2] However, to date synthesis of 3-amino-cyclobut-2-en-1-ones is limited to the following: condensation of cyclobutane-1,3-diones with primary amines;[2] [2 + 2] cycloaddition of ketenes with ynamides;[3] and the reaction of 3-ethoxycyclobut-2-enones with amino acids.[4] We report in this communication a novel and efficient synthesis of 3-aminocyclobut-2-en-1-ones **2** from the easily available acyl ketene dithioacetals **1**.[5]

In continuation of our studies on the application of ketene dithioacetals,[6,7] we found that the reaction of 4-(bis(methylthio)methylene)heptane-3,5-dione (**1a**) with 4-methylaniline under basic conditions afforded a cyclobutenone derivative,[8] 4-methyl-2-propionyl-3-(*p*-tolylamino)cyclobut-2-enone (**2a1**). Under optimal conditions, (*i.e.*, **1a** (1.0 mmol), 4-methylaniline (1.0 mmol) and Bu^{t}OK (2.0 equiv.) in DMSO (2.0 mL) at room temperature for 0.5 h), **2a1** was obtained in 76% yield (Table 1, entry 1).‡ Under the conditions described in Table 1, entry 1, a range of reactions of **1a** (R^2 = COEt) with amines were carried out (Table 1). As a result, various amines such as arylamines with either electron-rich (entry 1), electron-neutral (entry 2), or electron-deficient (entry 3) groups, heteroaromatic amine (entry 4), primary and secondary aliphatic amines (entries 5 and 6), reacted smoothly with **1a** to give the corresponding 3-aminocyclobut-2-en-1-ones **2a1–6** in good to high yields. In addition, 3-dimethylaminocyclobut-2-en-1-one **2a7** was obtained in 73% yield from the reaction of **1a** in DMF (entry 7, DMF as a dimethylamine equivalent). Similarly, reactions of acyl ketene dithioacetals **1b** (R^2 = CO_2Me) and **1c** (R^2 = Ph) in DMF gave the corresponding 3-dimethylaminocyclobut-2-en-1-ones **2b7** and **2c7** in 74% and 70% yields, respectively (entries 8 and 9).

In order to gain insight into the mechanism, the reaction of **1a** was investigated. Under conditions identical to those in Table 1, entry 1 but in the absence of an amine, 3-methylthiocyclobut-2-en-1-one **3a** was afforded in 82% yield (Scheme 1). Furthermore, reaction of **3a** with 4-methylaniline was carried out, which resulted in the formation of **2a1** in 72% yield (Scheme 1).

On the basis of the above experimental results and related reports,[4,6,7a,7b] a mechanism for the formation of **2** is proposed in Scheme 2. In the presence of Bu^{t}OK, a vinyl enolate anion intermediate **A** is formed by deprotonation of the methylene group of acyl ketene dithioacetals **1** (Scheme 2). Subsequently, a 4-electron electrocyclic ring closure of the vinyl enolate **A** to cyclobutanone **B** may occur. Under basic conditions, the elimination of an alkylthiol from **B** gives 3-alkylthiocyclobut-2-en-1-ones **3**.[6a] Whereas, in the presence of an amine, 3-aminocyclobut-2-en-1-ones **2** are thought to be produced *via* the nucleophilic amine addition and alkylthiol elimination processes.[6b]

An alternative mechanism that can be considered for the formation of 3-alkylthiocyclobut-2-en-1-ones **3** from the vinyl enolate **A** is the involvement of intramolecular Michael addition (Scheme 2). Although this 4-*endo-trig* cyclization is disfavored according to Baldwin's rules, the validity of this assumption is open to question. For example, 5-*endo-trig* "anti-Baldwin" ring closure occurred in the cyclization of *gem*-difluoroolefins[9] or ketene dithioacetals (*gem*-dithioolefins)[10] bearing a homoallylic heteroatom nucleophile. In addition, the 3-*exo-dig* cyclization of propargylic halides possessing a suitably placed active methine was also observed.[11] Nevertheless, the preparation of 3-amino-/alkylthio-cyclobut-2-en-1-ones from the cyclization of acyl ketene dithioacetals provides a very convenient route to cyclobut-2-enones.[2–4,8]

It is well known that functionalized cyclobut-2-enones easily undergo thermal ring-expansion reaction to offer efficient access to functionalized monocyclic or ring-annelated carbo- and heterocycles.[8,12] To explore the synthetic potential of cyclobut-2-enones **2**, the ring-expansion reaction of **2** was examined (Scheme 3). As expected, the reaction of 3-arylamino-cyclobut-2-en-1-one **2a1** could proceed smoothly to give 4-quinolone derivative **4a1** in 56% yield in toluene at 110 °C for 16 h (Fig. 1).[13] To our satisfaction, the yield of **4a1** was increased to 72% under identical conditions with the addition of catalytic amounts of *p*-toluenesulfonamide (PTSA, 10%; Scheme 3). Similarly, 4-quinolones **4a2** and **4a3** were obtained in 70% yield from the reaction of 3-arylaminocyclobut-2-en-1-ones **2a2** and **2a3**, respectively (Scheme 3). Thus, the above thermal ring-expansion reaction of 3-arylaminocyclobut-2-en-1-ones provides an efficient approach to functionalized quinolin-4(1*H*)-ones.[14]

On the basis of the above experimental results together with the related reports,[8,12] a mechanism for the formation of 4-quinolones **4** is proposed and depicted in Scheme 4. Under thermal conditions, the 3-arylaminocyclobut-2-en-1-one **2**

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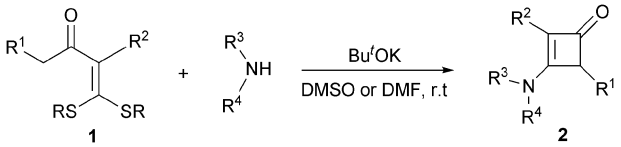
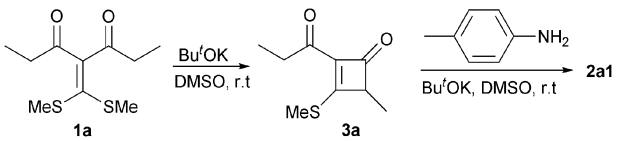
† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 781521 (**4a1**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc02470h

Table 1 Synthesis of 3-aminocyclobut-2-en-1-ones **2** from the reaction of **1** and amines[a]

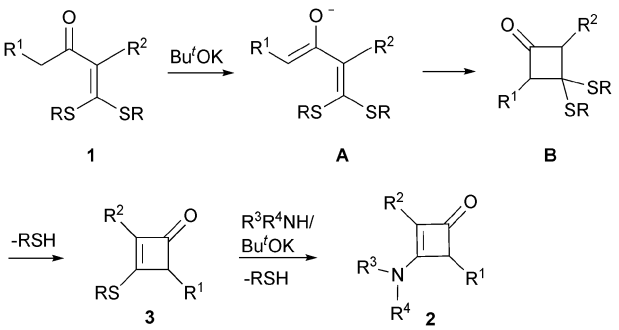


Entry	Substrate	R, R	R^1	R^2	R^3	R^4	Solvent	Yield (%)[b]
1	**1a**	Me	Me	COEt	H	4-MeC_6H_4	DMSO	**2a1** (76)
2	**1a**	Me	Me	COEt	H	C_6H_5	DMSO	**2a2** (70)
3	**1a**	Me	Me	COEt	H	4-ClC_6H_4	DMSO	**2a3** (66)
4	**1a**	Me	Me	COEt	H	2-Pyridyl	DMSO	**2a4** (69)
5	**1a**	Me	Me	COEt	H	$CH_3(CH_2)_3$	DMSO	**2a5** (75)
6	**1a**	Me	Me	COEt		$(CH_2)_5$	DMSO	**2a6** (70)
7	**1a**	Me	Me	COEt	Me	Me	DMF	**2a7** (73)
8	**1b**	Et	Me	CO_2Me	Me	Me	DMF	**2b7** (74)
9	**1c**	Et	C_6H_5	C_6H_5	Me	Me	DMF	**2c7** (70)

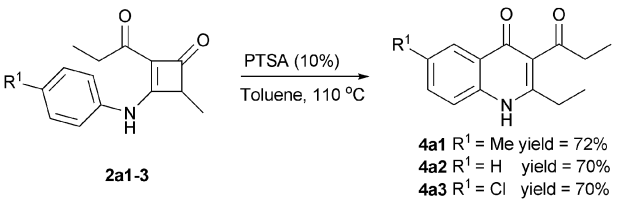
[a] Reaction conditions: **1** (1.0 mmol), amine (1.0 mmol), Bu^{t}OK (2.0 mmol), DMSO/DMF (2.0 mL), room temperature. [b] Isolated yield.



Scheme 1 Synthesis of 3-methylthiocyclobutenone **3a** and its reaction with 4-methylaniline.



Scheme 2 Proposed mechanism for the formation of **2** and **3**.



Scheme 3 Synthesis of 4-quinolones **4a1–3** from **2a1–3**.

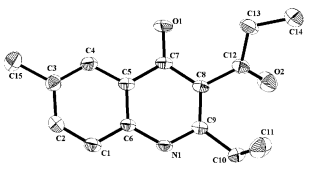
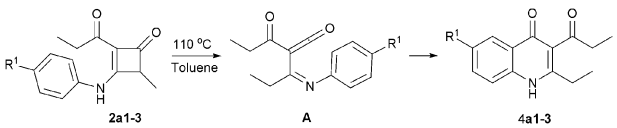


Fig. 1 ORTEP drawing of **4a1**.

undergoes a 4π electrocyclic cleavage to generate vinylketene intermediate **A**, which rapidly cyclizes *via* 6π electrocyclic ring closure, followed by tautomerization to give the coresponding



Scheme 4 Proposed mechanism for the formation of **4**.

4-quinolones **4** (Scheme 4). As to the role of PTSA in increasing the yield of 4-quinolones **4**, it may be due to a weak base effect to accelerate the formation of vinylketene intermediate **A**.

In conclusion, we have developed a new strategy for the highly efficient one-pot synthesis of 3-amino-/alkylthio-cyclobut-2-en-1-ones **2** and **3** *via* a base-promoted cyclization of acyl ketene dithioacetals **1**. The simplicity of execution, readily available substrates, mild reaction conditions, short reaction time make this synthetic strategy most attractive for practical applications. As a synthetic application, 4-quinolones **4** were prepared in high yields through a tandem ring-opening/recyclization of **2**. Further studies to expand the synthetic utility of these functionalized cyclobutenones are in progress.

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Notes and references

‡ **General procedure for the synthesis of cyclobutenones 2 (taking 2a1 as an example):** To a solution of 4-(bis(methylthio)methylene)-heptane-3,5-dione **1a** (1.0 mmol, 232 mg) and 4-methylaniline (1.0 mmol, 107 mg) in DMSO (2.0 mL) was added Bu^{t}OK (2.0 mmol, 224 mg) in one portion. The reaction mixture was stirred for 0.5 h at room temperature. After **1a** was consumed (monitored by TLC), the reaction mixture was poured into saturated aqueous NaCl (25 mL), neutralized with aqueous HCl and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (ethyl acetate–hexane = 1/9, v/v) to give **2a1** (185 mg, 76%) as a white solid.

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