

Heterocycles

Facile [7C+1C] Annulation as an Efficient Route to Tricyclic Indolizidine Alkaloids**

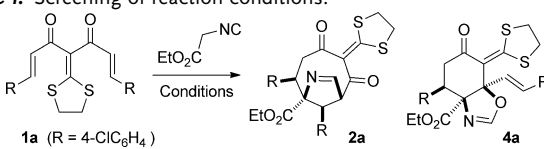
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The indolizidine skeleton is one of the most important structural motifs found in numerous biologically active molecules.^[1–4] The development of efficient methods for the synthesis of indolizidine alkaloids has been the subject of intense research.^[1–4] Recently, we have been devoted to the research of heterocyclizations using alkenoyl ketene dithioacetals as five-carbon 1,5-dielectrophiles^[5,6] and ethyl isocyanoacetate as both a double Michael donor and a 1,3-dipole in a [5C+1C] annulation process for the construction of complex heterocyclic systems (Scheme 1).^[6] As part of our studies in this area, we herein report a new synthetic strategy for the construction of the tricyclic indolizidine alkaloids **3** by an unprecedented [7C+1C] annulation to deliver the 8-azabicyclo[5.2.1]dec-8-enes **2** from the easily available dialkenoyl ketene dithioacetals **1** as C₇ 1,7-dielectrophiles (Scheme 1).^[5–8]

Initially, the reaction of the dialkenoyl ketene dithioacetal **1a** with ethyl isocyanoacetate was investigated to evaluate

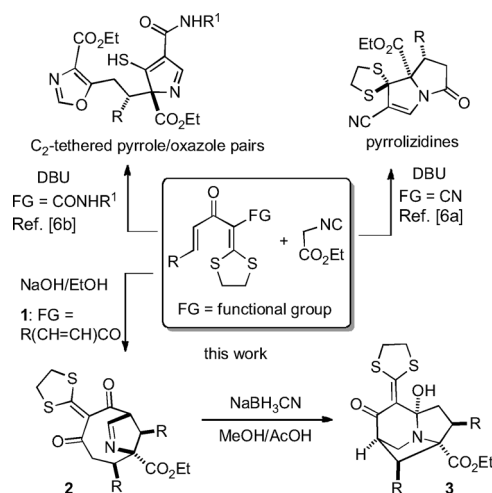
a tandem process involving a [7C+1C] annulation with **1a** as a C₇ 1,7-dielectrophile (Table 1). It was found that treatment

Table 1: Screening of reaction conditions.



Entry	Solvent	Base (equiv)	T [°C]	t [h]	Yield [%] ^[a]	
					2a	4a
1	THF	NaOH (1.0)	RT	0.5	17	71
2	DMF	NaOH (1.0)	RT	4	57	35
3	CH ₃ CN	NaOH (1.0)	RT	11	65	30
4	EtOH	NaOH (1.0)	RT	11	93	–
5	EtOH	NaOH (1.0)	45	4	92	–
6	EtOH	NaOH (0.1)	45	9	90	–
7 ^[b]	EtOH	NaOH (0.05)	45	24	24	–
8	EtOH	NaOH (0.3)	45	7	90	–
9	EtOH	DBU (0.1)	45	15	83	10
10 ^[c]	EtOH	K ₂ CO ₃ (0.1)	45	24	71	–

[a] Yields of isolated products. [b] Substrate **1a** was recovered in 70 % yield. [c] Substrate **1a** was recovered in 20 % yield. DMF = N,N-dimethylformamide, THF = tetrahydrofuran.



Scheme 1. Heterocyclizations based on alkenoyl ketene dithioacetals.

of the mixture of **1a** (1.0 mmol) and ethyl isocyanoacetate (1.1 equiv) with NaOH (1.0 equiv) in THF at room temperature for 0.5 hours gave the fused oxazoline **4a**^[8a] in 71 % yield and 8-azabicyclo[5.2.1]dec-8-ene **2a** in 17 % yield (entry 1). According to our previous reports,^[5a,b,6] the formation of **2a** would involve a [7C+1C] annulation process.

Although synthetic approaches to five- and six-membered carbocycles are legion, encompassing both cyclization and cycloaddition approaches, the synthesis of medium-sized carbocycles from acyclic precursors is quite challenging because of unfavorable entropic and enthalpic factors which preclude ring formation.^[9] For the construction of eight-membered carbocycles, transition-metal-catalyzed/mediated higher-order cycloadditions involving [2+2+2+2], [4+4], [4+2+2], [5+2+1], and [6+2]^[9a] ring-closing metathesis,^[9b] and related intramolecular reactions have been reported.^[9,10] However, the synthesis of medium- and large-sized ring compounds from C₇ and larger carbon building blocks remains a formidable challenge.^[9a,10,11]

To the best of our knowledge, the synthesis of **2a** represents the first example involving the construction of an eight-membered carbocycle from simple acyclic C₇ precursors.^[9–11] Fortunately, optimization of the reaction conditions allowed us to obtain **2a** in excellent yield, where the mixture of **1a** and ethyl isocyanoacetate was treated with a catalytic

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amount of NaOH in ethanol (Table 1, entry 6). Under identical reaction conditions as above, **2a** was produced in relatively lower yields with DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) and K₂CO₃ as the catalysts (entries 9 and 10). In comparison, much lower yields of **2a** were obtained when DMF or acetonitrile was used as the solvent (entries 2 and 3 versus 4 and 5).

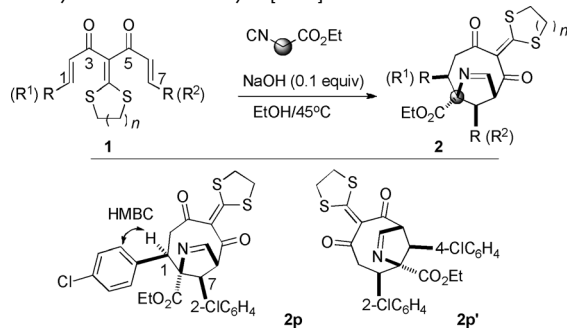
With the optimal reaction conditions (Table 1, entry 6) in hand, the scope of the tandem [7C+1C] annulation/intramolecular cyclization reaction with dialkenoyl ketene dithioacetals (**1**) as C₇ 1,7-dielectrophiles was investigated and the results are summarized in Table 2. It was observed that the reactions of ethyl isocyanoacetate with symmetrical C₇ 1,7-dielectrophiles (**1**) having electron-deficient aryl groups (entries 1, 2, 4 and 5), phenyl (entry 6), electron-rich aryl groups (entries 7–11), and heteroaryl groups (entries 12–14) at the 1,7-positions (β positions of the enone moiety) can afford the corresponding 8-azabicyclo[5.2.1]dec-8-enes **2** in high to excellent yields. It is important to note that all the above reactions (except for **1c**; entry 3) proceed in a highly

diastereoselective manner. In a few cases, such as for **1l** or **1m**, a higher NaOH loading (0.3 equiv) is required to get satisfactory results (entries 12 and 13). In addition, the 1,7-dielectrophiles **1** having electron-deficient aryl groups at the 1,7-positions appear to be more reactive than those bearing electron-rich aryl groups (entries 1, 2, 4 and 5 versus entries 7–11).

It was noted that substrates **1a** and **1b** bearing a chlorine atom at either the *para* or *meta* position of each phenyl ring resulted in the desired products **2a** and **2b**, respectively, in excellent yields (Table 2, entries 1 and 2). However, substrate **1c**, having a chlorine atom at the *ortho* position of each phenyl ring, was inert under identical reaction conditions even at 80 °C for 20 h (entry 3), thus indicating the sensitivity of the reaction to steric hindrance. Indeed, no reaction was detectable for the substrate **1r** bearing bulky *tert*-butyl groups at the 1,7-positions (entry 18). In contrast, the reaction of the substrate **1o** bearing two ferrocenyl groups at the electrophilic 1,7-positions gave the desired product **2o** in good yield (entry 15).^[12] To further examine the steric effect, nonsymmetrical substrates **1p** and **1q** were subjected to the reactions. As a result, **2p** and **2p'** were obtained as a mixture of diastereomers in high combined yield in a ratio of about 15:1 when the nonsymmetrical substrate **1p**, bearing two chlorine atoms at the *para*- and *ortho*-positions of the 1,7-phenyl rings, respectively, was used (entry 16). The structure of the dominant product **2p** was further confirmed by two-dimensional HMBC (heteronuclear multiple bond correlation) spectroscopy (for details, see the Supporting Information). In comparison, **2q** and **2q'** in a ratio of about 1:1 were obtained in excellent combined yield from the reaction of **1q** with ethyl isocyanoacetate (entry 17). In contrast, the ring sizes of the dithioacetal moiety of substrates **1s–v** seemed to have no significant effect on the formation of the eight-membered products **2s–v** (entries 19–22).

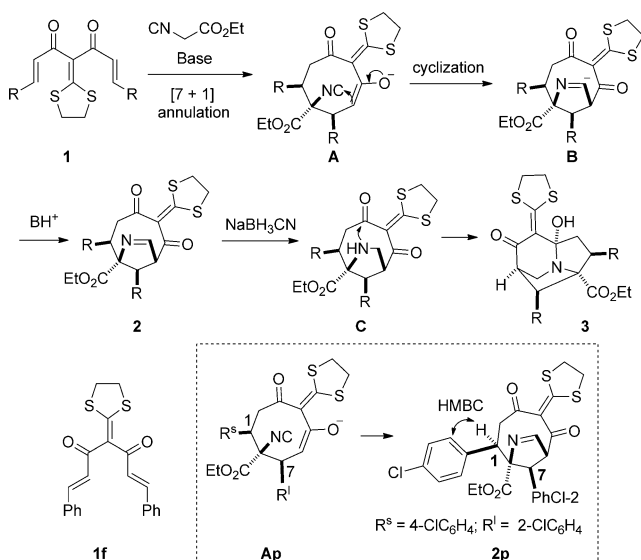
On the basis of the above results (Table 2) together with our previous observations,^[6,13] a possible mechanism for the formation of **2** from the symmetrical dialkenoyl ketene dithioacetals **1** is proposed in Scheme 2. The overall process would involve the diastereoselective double Michael addition ([7+1] annulation) of the active methylene of ethyl isocyanoacetate to the 1,7-dielectrophilic **1** under basic conditions to provide the enolate intermediate **A**. Intramolecular cyclization of **A** through C–C bond formation at the isocyanide carbon atom (**B**) and subsequent protonation would give **2** (Scheme 2).^[6a,13] This mechanism proves to be efficient to support the reactions of ethyl isocyanoacetate with nonsymmetrical dialkenoyl ketene dithioacetals as in the case of **1p** (Table 2, entry 16). In this case, the intermediate **Ap** should be formed through a double Michael addition by successive nucleophilic attack first at the less hindered C1 instead of the more hindered C7 as indicated in the dashed box in Scheme 2 (R^s = less hindered substituents; R^l = more hindered substituents). Thus, it is easy to understand not only why **2p** was formed dominantly (Table 2, entry 16), but also why **1c** and **1r** were inert to the [7+1] annulation (Table 2, entries 3 and 18). We can also understand why **2q** and **2q'** were obtained as a mixture of diastereomers in a ratio of about 1:1 (Table 2, entry 17), that is, because of the equal

Table 2: Synthesis of 8-azabicyclo[5.2.1]dec-8-enes **2**.



Entry	1	R or R ¹ /R ²	n	t [h]	2	Yield [%] ^[a]
1	1a	4-ClC ₆ H ₄	1	9	2a	90
2	1b	3-ClC ₆ H ₄	1	13	2b	90
3	1c	2-ClC ₆ H ₄	1	20	2c	0 ^[b]
4	1d	4-BrC ₆ H ₄	1	9	2d	91
5	1e	4-FC ₆ H ₄	1	5	2e	85
6	1f	Ph	1	12	2f	88
7	1g	4- <i>t</i> BuC ₆ H ₄	1	17	2g	91 ^[c]
8	1h	4-CH ₃ OC ₆ H ₄	1	36	2h	89
9	1i	3-CH ₃ OC ₆ H ₄	1	21	2i	88
10	1j	4-CH ₃ C ₆ H ₄	1	31	2j	90
11	1k	3-CH ₃ C ₆ H ₄	1	34	2k	90
12	1l	2-thienyl	1	24	2l	72 ^[c]
13	1m	2-furyl	1	25	2m	80 ^[c]
14	1n	3-pyridyl	1	5	2n	85
15	1o	2-ferrocenyl	1	7	2o	65 ^[d]
16	1p	4-ClC ₆ H ₄ /2-ClC ₆ H ₄	1	34	2p/2p'	73 ^[e,f]
17	1q	Me/4-ClC ₆ H ₄	1	10	2q/2q'	95 ^[g]
18	1r	<i>t</i> Bu	1	36	2r	0 ^[b]
19	1s	4-ClC ₆ H ₄	2	12	2s	90
20	1t	4-CH ₃ C ₆ H ₄	2	35	2t	89
21	1u	4-CH ₃ OC ₆ H ₄	2	40	2u	82
22	1v	4-CH ₃ C ₆ H ₄	3	46	2v	68

[a] Yields of isolated products. [b] 80 °C. [c] NaOH (0.3 equiv). [d] DBU (1.0 equiv), 80 °C. [e] A mixture of diastereomers in a ratio of about 15:1. [f] NaOH (1.0 equiv), 80 °C. [g] A mixture of diastereomers in a ratio of about 1:1. [h] NaOH (1.0 equiv) or DBU (1.0 equiv), 80 °C.



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