Heterocycles

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

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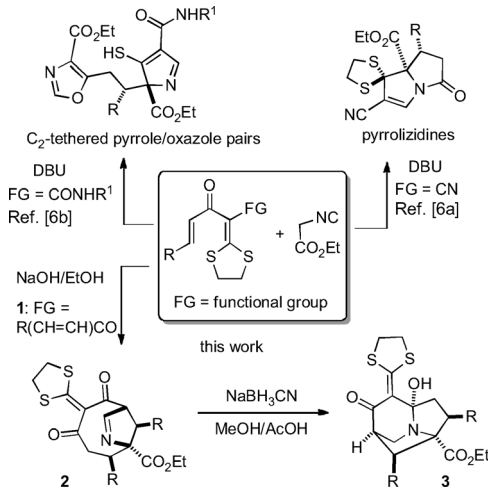
The indolizidine skeleton is one of the most important structural motifs found in numerous biologically active molecules.[1–4] The development of efficient methods for the synthesis of indolizidine alkaloids has been the subject of intense research.[1–4] Recently, we have been devoted to the research 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 C_7 1,7-dielectrophiles (Scheme 1).[5–8]

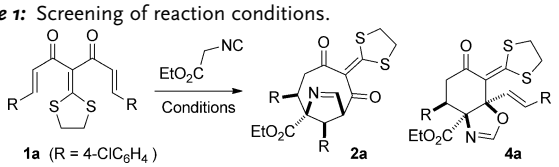
Initially, the reaction of the dialkenoyl ketene dithioacetal **1a** with ethyl isocyanoacetate was investigated to evaluate



Scheme 1. Heterocyclizations based on alkenoyl ketene dithioacetals.

a tandem process involving a [7C+1C] annulation with **1a** as a C_7 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_3CN	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_2CO_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.

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 C_7 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 C_7 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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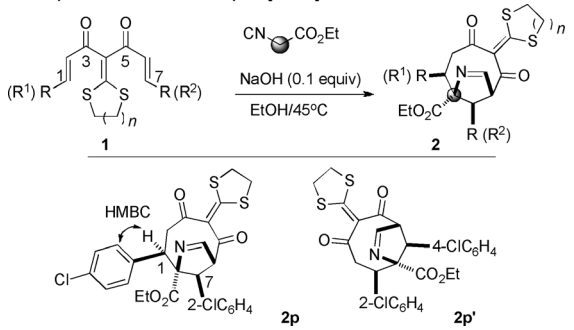
amount of NaOH in ethanol (Table 1, entry 6). Under identical reaction conditions as above, **2a** was produced in relatively lower yields with DBU (DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene) and K_2CO_3 as the catalysts (entries 9 and 10). In comparison, much lower yields of **2a** were obtained when 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 C_7 1,7-dielectrophiles was investigated and the results are summarized in Table 2. It was observed that the reactions of ethyl isocyanoacetate with symmetrical C_7 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).

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

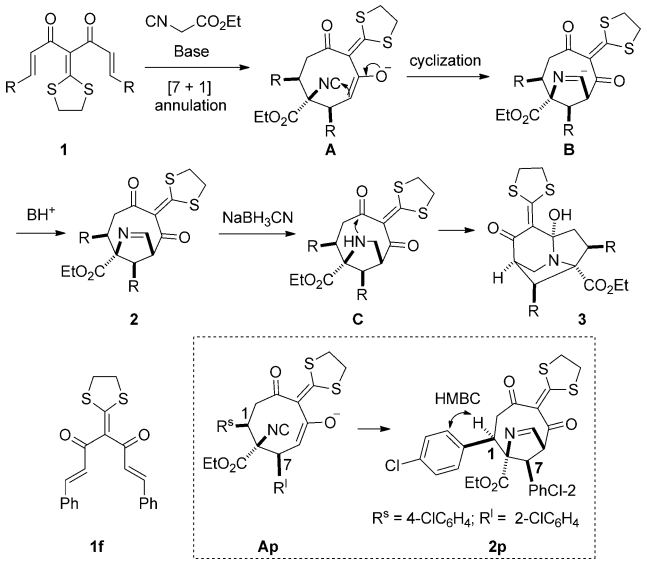


Entry	1	R or R^1/R^2	n	t [h]		Yield [%][a]
1	**1a**	4-ClC_6H_4	1	9	**2a**	90
2	**1b**	3-ClC_6H_4	1	13	**2b**	90
3	**1c**	2-ClC_6H_4	1	20	**2c**	0[b]
4	**1d**	4-BrC_6H_4	1	9	**2d**	91
5	**1e**	4-FC_6H_4	1	5	**2e**	85
6	**1f**	Ph	1	12	**2f**	88
7	**1g**	4-*t*BuC_6H_4	1	17	**2g**	91[c]
8	**1h**	4-$CH_3OC_6H_4$	1	36	**2h**	89
9	**1i**	3-$CH_3OC_6H_4$	1	21	**2i**	88
10	**1j**	4-$CH_3C_6H_4$	1	31	**2j**	90
11	**1k**	3-$CH_3C_6H_4$	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_6H_4/2-ClC_6H_4	1	34	**2p/2p′**	73[e,f]
17	**1q**	Me/4-ClC_6H_4	1	10	**2q/2q′**	95[g]
18	**1r**	*t*Bu	1	36	**2r**	0[h]
19	**1s**	4-ClC_6H_4	2	12	**2s**	90
20	**1t**	4-$CH_3C_6H_4$	2	35	**2t**	89
21	**1u**	4-$CH_3OC_6H_4$	2	40	**2u**	82
22	**1v**	4-$CH_3C_6H_4$	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.

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 groups, 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 substitutes; R^l = more hindered substitutes). 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



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

chance of the conjugate addition of ethyl isocyanoacetate at both of C1 and C7 carbon atoms of **1**.

Unlike the synthesis of pyrrolizidines and C_2-tethered pyrrole/oxazole pairs (Scheme 1) in which [5C+1C] annulation intermediates can be obtained,[6,13] the synthesis of **2** does not result in an intermediate corresponding to the [7C+1C] annulation of **1a** with ethyl isocyanoacetate under optimal reaction conditions (Table 1, entry 6), even at a temperature of 0 °C. To the best of our knowledge, no report has been published on the [7C+1C] annulation using a seven-carbon acyclic precursor.[9–11] Asokan and co-workers observed that the two cinnamoyl moieties of the dicinnamoyl ketene dithioacetal **1f** (Scheme 2 and Table 2, entry 6) are aligned in parallel and close to each other in the crystal structure because of the existence of the cyclic dithiolane moiety and the push-pull nature of the α-oxo ketene dithioacetals.[5,14] This structural feature may be important in determining the tendency of the [7+1] annulation because of the proper conformation of the dicinnamoyl ketene dithioacetals **1** for [7+1] annulation. Therefore, the tandem [7+1] annulation/intramolecular cyclization cascade provides an efficient route to eight-membered carbocycles[9–11] and a novel tandem cyclization for a highly efficient use of the reactive sites of both dialkenoyl ketene dithioacetals and methyl isocyanides.[5–8,15,16]

The tandem process mentioned above represents a very simple and efficient methodology for the construction of 8-azabicyclo[5.2.1]dec-8-enes (**2**) where the starting materials are simple acyclic precursors and the reaction is highly atom-economic. To highlight the synthetic potential of **2**, the transformation of **2** into tricyclic indolizidine alkaloids (**3**; Scheme 1) through a transannular attack of the imine nitrogen atom on the nearby carbonyl carbon atom of **2** was envisioned.[6a] Treatment of the selected 8-azabicyclo-[5.2.1]dec-8-enes **2a**, **2g**, **2h**, **2n**, and **2o** with $NaBH_3CN$ (10 equiv) led to the formation of the corresponding tricyclic indolizidine derivatives [**3a** (R = 4-ClC_6H_4, 98 %), **3g** (R = 4-*t*BuC_6H_4, 94 %), **3h** (R = 4-$CH_3OC_6H_4$, 94 %), **3n** (R = 3-pyridyl, 99 %), **3o** (R = 2-ferrocenyl, 96 %)].[12] Clearly, the formation of **3** would involve the selective reduction of the imine bond of **2** to the amine intermediate **C** followed by the nucleophilic attack of the amine nitrogen atom onto the nearby carbonyl group in a regiospecific fashion (Scheme 2).[6a]

In conclusion, we have developed an efficient and practical [7C+1C] annulation strategy from the reaction of ethyl isocyanoacetate with dialkenoyl ketene dithioacetals as C_7 1,7-dielectrophiles. This reaction features high to excellent yields, mild reaction conditions, high diastereoselectivity in most cases, perfect atom economy, readily available starting materials, and no need for transition metals. Furthermore, a series of tricyclic indolizidine alkaloids were prepared in excellent yields in a two-step procedure based on the novel and efficient [7C+1C] annulation strategy. This [7C+1C] annulation strategy opens a way to explore the construction of medium-sized rings from easily available acyclic building blocks.

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