Synthetic Methods

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Tandem Double-Michael-Addition/Cyclization/Acyl Migration of 1,4-Dien-3-ones and Ethyl Isocyanoacetate: Stereoselective Synthesis of Pyrrolizidines**

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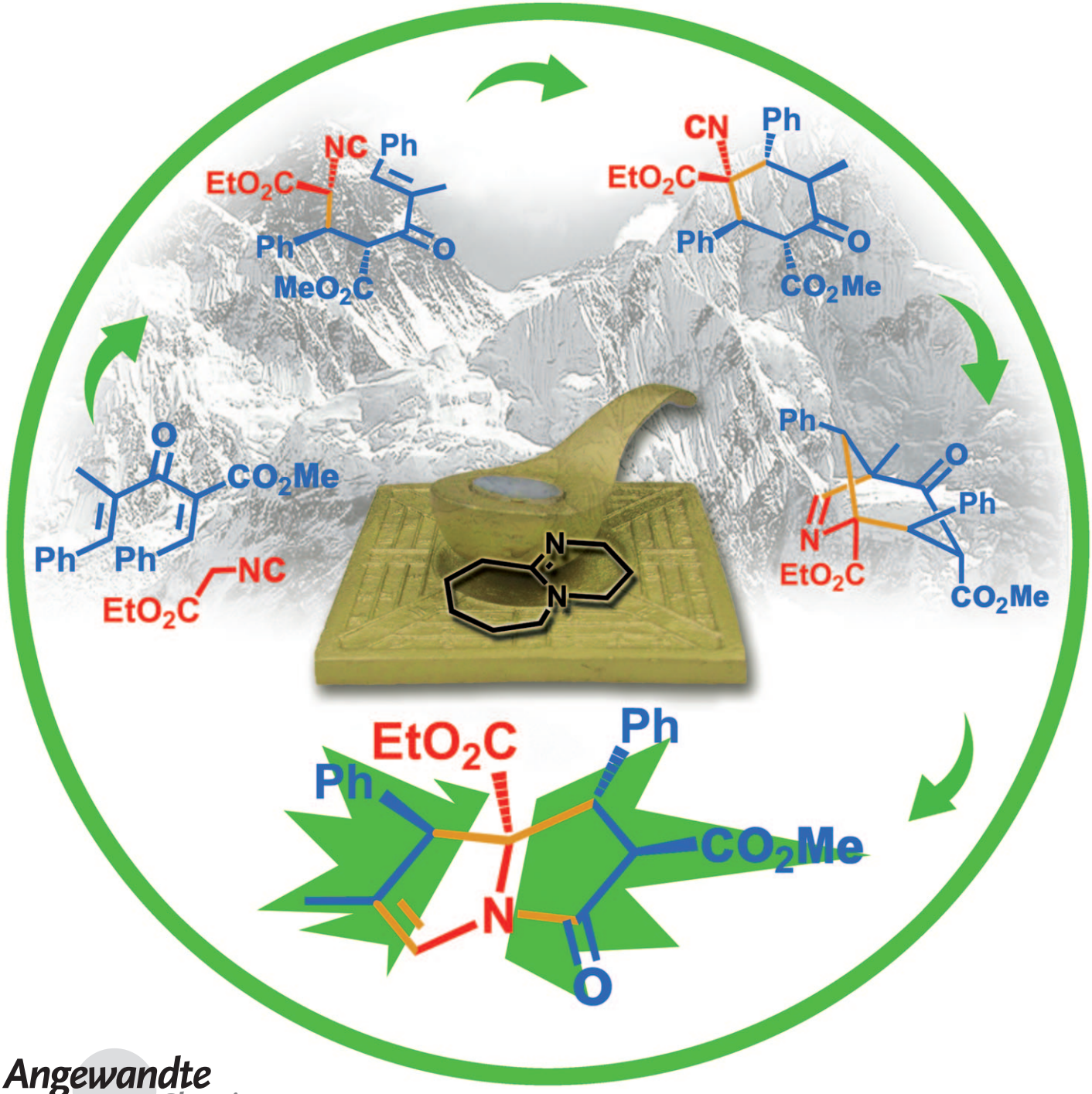
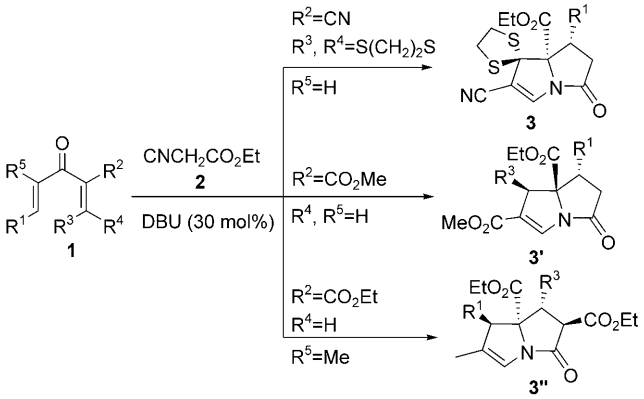


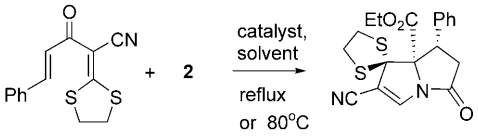
Pyrrolizidine alkaloids are widespread among various plants and insects and display important biological activities.[1,2] The formation of the pyrrolizidine framework generally involves building a second five-membered ring onto a preformed pyrrolidine moiety.[1–3] Therefore, the development of a new strategy for the efficient construction of the azabicyclic skeleton from simple acyclic starting materials in a single step is highly desirable.[3,4] Herein, we report an organocatalytic domino reaction of 1,4-dien-3-ones **1** with ethyl isocyanoacetate (**2**; Scheme 1). This new general approach allows, in a single reaction, the formation of three C–C and one C–N bonds in a regio- and diastereoselective manner, which provides efficient access to the azabicyclic compounds **3**—the motif in pyrrolizidine alkaloids.[1–3]



Scheme 1. Synthesis of pyrrolizidines from 1,4-dien-3-ones **1** and ethyl isocyanoacetate (**2**). R^1 = aryl or alkyl group.

In general, the one-pot tandem strategy is used to improve the efficiency of a chemical reaction whereby multiple bonds and stereocenters are formed in a single reaction without the need to isolate intermediates.[4] Our research in this area[5,6] has shown that 1,4-dien-3-ones of the type **1** can be used as versatile building blocks for the efficient construction of a wide variety of carbo- and heterocycles.[6] In the present study, treatment of 1,4-dien-3-one **1a** with ethyl isocyanoacetate (**2**) was performed under basic conditions to test our [5+1] annulation reactions, where **1a** acted as the dielectrophile (Table 1).[6a,b] Pyrrolizidine **3a** was obtained in 83% yield under optimized reaction conditions, where **1a** (1.0 mmol) was treated with **2** (1.2 mmol) and the reaction catalyzed by DBU (30 mol%) in acetonitrile (5 mL) at 80°C in air for 0.3 hours (Table 1, entry 1). The yield of **3a** was not improved neither by prolonging the reaction time (Table 1, entry 2) nor by decreasing the amount of DBU to 10–20 mol% (Table 1, entries 3 and 4). The reaction between **1a** and **2** did not occur in the presence of bases such as K_2CO_3 or Et_3N (Table 1, entries 5 and 6). Different solvents were also tested, for example CH_2Cl_2 or THF at reflux, but unfortunately these resulted in very low yields (Table 1, entries 7 and 8). Although, in DMF at 80°C a 72% yield of **3a** was obtained (Table 1, entry 9).

Table 1: Optimization of reaction conditions.

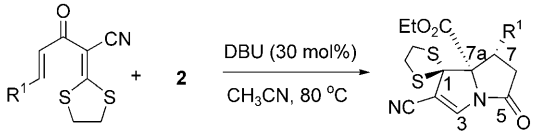


Entry	Solvent	Base (equiv)	*t* [h]	**3a** [%][a]	**1a** [%][b]
1	CH_3CN	DBU (0.3)	0.3	83	
2	CH_3CN	DBU (0.3)	1.0	81	
3	CH_3CN	DBU (0.2)	0.3	63	10
4	CH_3CN	DBU (0.1)	0.3	42	18
5	CH_3CN	K_2CO_3 (0.3)	0.3	–	95
6	CH_3CN	Et_3N (0.3)	0.3	–	97
7[c]	CH_2Cl_2	DBU (0.3)	0.3	7	85
8[c]	THF	DBU (0.3)	0.3	8	81
9	DMF	DBU (0.3)	0.3	72	

[a] Yield of isolated product **3a**. [b] Recovered starting material. [c] At reflux. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

Under the optimized reaction conditions (Table 1, entry 1), this tandem reaction showed broad tolerance for various R^1 substituents (Table 2). Substrates **1**, with either electron-rich or electron-deficient aryl groups, afforded the corresponding pyrrolizidines **3a**–**3f** in good to high yields (Table 2, entries 1–6). Heteroaryl- (Table 2, entries 7–9),

Table 2: Reactions of 1,4-dien-3-ones **1** with **2**.



Entry	Product	R^1	*t* [h]	Yield [%][a]
1	**3a**	Ph	0.3	83
2	**3b**	4-ClC_6H_4	0.2	72
3	**3c**	4-BrC_6H_4	0.3	78
4	**3d**	4-$NO_2C_6H_4$	0.2	64
5	**3e**	4-MeC_6H_4	1.5	76
6	**3f**	4-$MeOC_6H_4$	5.0	60
7	**3g**	2-furyl	5.0	56
8	**3h**	2-thienyl	5.0	58
9	**3i**	2-pyridyl	0.2	72
10[b]	**3j**	CH_3	5.0	53
11	**3k**	PhCH=CH	5.0	44

[a] Yield of isolated product. [b] 1.0 equivalent of DBU was used.

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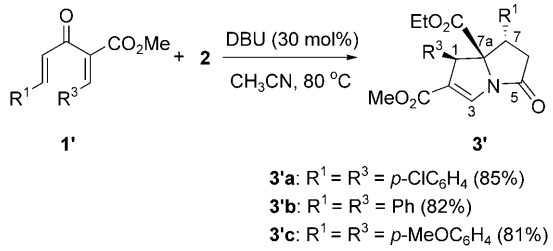
alkyl- (Table 2, entry 10), or alkenyl-substituents (Table 2, entry 11) were suitable substrates and gave **3g–3k** in moderate to good yields. According to ^{1}H and ^{13}C NMR spectroscopy data of the products, the tandem reaction proceeded in a highly regio- and diastereoselective manner and simultaneously set two adjacent stereocenters (no diastereoisomers of **3a–3k** were detected). The configurations of **3a–3k** were assigned based on the X-ray diffraction analysis of **3b**, where the CO_2Et group is *cis* to the R^1 group.[7]

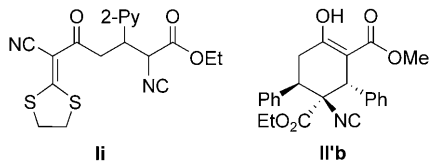
The tandem process mentioned above represents a very simple and efficient methodology for the construction of polyfunctionalized pyrrolizidine derivatives[3,8]—the starting materials are simple acyclic precursors and the reaction is highly atom-economic. To test the generality of this new reaction,[9] selected 1,4-dien-3-ones **1′a–1′c**[10] were treated with **2** under the optimized reaction conditions (Table 1, entry 1). Pleasingly, pyrrolizidines **3′a–3′c** (Scheme 2) were



Scheme 2. Reactions of 1,4-dien-3-ones **1′** with **2**.

produced in high yields (85%, 82%, and 81%, respectively) and in a highly regio- and diastereoselective manner. In these cases three adjacent stereocenters were created simultaneously and no diastereoisomers were formed (for details see the Supporting Information). The configurations of **3′a–3′c** were assigned based on the X-ray diffraction analysis of **3′b**.[11] Notably, upon comparison it was discovered that the configuration of **3** (Table 2) and **3′** (Scheme 2) were different. For **3** the CO_2Et group at C7a is *cis* to the R^1 group at C7, whereas for **3′** there is a *trans* relationship between the substituents.

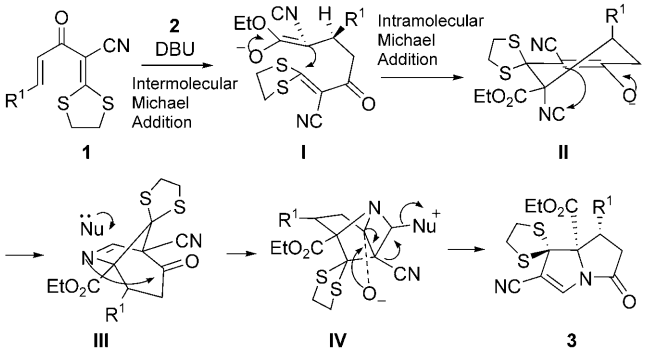
To gain insight into the mechanism of this tandem process, we examined reactions of **1** with **2** at a lower temperature and/or at a different catalyst loading. By treating **1i** with **2** at 0 °C for 2 hours in the presence of 0.1 equivalent of DBU, the Michael adduct **Ii** (Scheme 3) could be isolated in 49% yield as a mixture of two diastereomers (along with 18% of **3i**). Subsequent treatment of **Ii** with 0.3 equivalents of DBU in acetonitrile at 80 °C for 0.5 hours afforded **3i** in 69% yield. Comparatively, **Ii** remained intact in the absence of DBU. When substrate **1′b** and **2** were treated with 0.3 equivalents



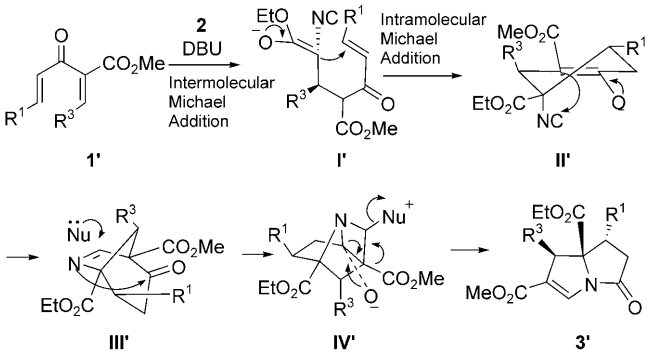
Scheme 3. Intermediates **Ii** and **II′b**.

DBU at room temperature for 10 minutes, the intermediate **II′b** was produced in 82% yield as a single diastereomer through a double Michael addition.

On the basis of these observations, plausible mechanisms for the formation of **3** and **3′** are proposed in Schemes 4 and 5, respectively. The overall process for the formation of **3** may



Scheme 4. Proposed mechanism for the formation of **3**.



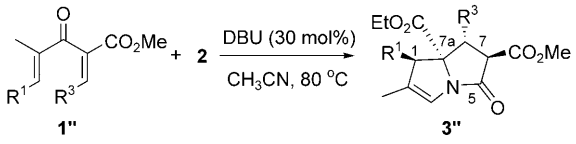
Scheme 5. Proposed mechanism for the formation of **3′**.

involve the following steps: 1) the double Michael addition of **2** to a dielectrophile **1** to provide cyclohexene intermediate **II** in a highly regio- and diastereoselective manner owing to the intramolecular Michael addition of **I** that leads to **II** (through a preliminary enolization of the isocyanoacetate moiety) in a stereoelectronically favored manner;[6a,c] 2) intramolecular cyclization in a stereospecific manner (controlled by chiral centres in **II**) to form intermediate **III**; 3) an acyl migration similar (in form) to a transannular attack of the imine nitrogen atom to the carbonyl carbon atom (**II**→**III**),[12] and subsequent C–C bond breakage (**III**→**IV**) to afford pyrrolizidines **3**.

According to the proposed mechanism for the formation **3**, it is easy to understand that the relative configuration at C7a and C7 would be dictated by the configuration of the cyclohexene intermediate **II**. Therefore, the difference in the relative configuration at C7a and C7 between **3** and **3′** should be dictated by the nature of the double Michael addition. Thus, a difference in the sequence of events; namely between 1) a double Michael addition of **2** to **1′** (Schemes 2 and 3, an intermolecular addition at the carbon center bearing R^3 and

subsequent intramolecular reaction at the carbon center bearing R^1)[10] and 2) the double Michael addition of **2** to **1** (Table 2 and Scheme 4, an intermolecular reaction at the carbon center bearing R^1 and subsequent intramolecular reaction at the carbon center bearing the (*S*,*S*)-acetal)[6a,c] would account for the contrast in configurations. Accordingly, a possible mechanism for the formation of **3′** is depicted in Scheme 5.

To our surprise the pyrrolizidines **3″a–c**, which bear four adjacent stereocenters, were produced in good yields under identical reaction conditions (Table 1, entry 1) by the treatment of selected 1,4-dien-3-ones **1″** with **2** (Scheme 6).[13]



3″a: $R^1 = R^3 = p\text{-}ClC_6H_4$ (71%)
3″b: $R^1 = R^3 = Ph$ (69%)
3″c: $R^1 = R^3 = p\text{-}MeOC_6H_4$ (65%)

Scheme 6. Reactions of 1,4-dien-3-ones **1″** with **2**.

Clearly, the four adjacent stereocenters of **3″** were created through the double Michael addition in a manner similar to **3′** and according to the mechanisms for the formation of **3** (Scheme 4) and **3′** (Scheme 5). The transformations would be initiated by the attack of the carbon atom adjacent to the methyl group in **1″** (R^5 of **1** in Scheme 1) on the electrophilic carbon atom of the isocyano group.

In conclusion, we have described a general method for the divergent synthesis of pyrrolizidine derivatives from reactions of various easily available acyclic 1,4-dien-3-ones with ethyl isocyanoacetate. This new strategy allows the formation of one C–N and three C–C bonds in a regio- and diastereoselective manner. This single step process involves a novel tandem double-Michael-addition/cyclization/1,3-acyl migration [1–3,8,14] where up to four adjacent stereocenters are created simultaneously in one-pot in an atom-economic manner. This strategy exhibits a highly efficient use of the reactive sites of the 1,4-dien-3-one substrate.

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Keywords: domino reactions · Michael addition · pyrrolizidines · synthetic methods

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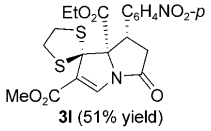
[9] The scope of the reaction was also demonstrated by the synthesis of pyrrolizidine **3l**, which was carried out by treatment of **1l** ($R^1 = p\text{-}NO_2Ph$; $R^2 = CO_2Et$, 1.0 mmol) and **2** (1.2 mmol) with KOH (1.0 equiv) in THF (5 mL) at 60 °C for 0.5 hours. Whereas, under identical reaction conditions as those used for the preparation of **3a–3k**, no desired product **3l** was formed.



3l (51% yield)

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[13] The configurations of **3″a**–**3″c** was assigned based on the X-ray diffraction analysis of **3″b**. CCDC 709063 (**3″b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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