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doi: 10.1039/C1CC10705D

Journal Name

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Bicyclization Involving Pseudo-Intramolecular Imination with Diamines

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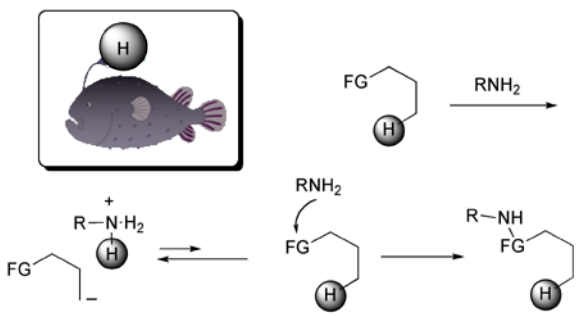
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

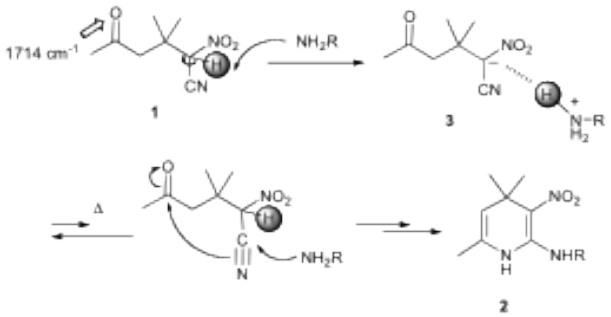
α-Nitro-δ-keto nitriles and α-nitro-δ-keto ester were readily converted to diazabicyclo compounds having vicinal functionalities upon treatment with diamines revealing. Keto nitrile attracts the diamine nearby by an acidic hydrogen to cause the pseudo-intramolecular imination which proceeds efficiently without any catalyst at room temperature.

Development of synthetic methods satisfying as many criteria as possible among the twelve principles of green chemistry[1] is highly demanded in organic chemistry. Improving the efficiency of reactions is one of the main approaches to environmentally benign methods, in which increase of the collision frequency of the reactants should be considered as a significant factor. Intramolecular reactions proceed faster than do intermolecular reactions because of the high collision frequency of the reaction sites, which can be attributed to the spatial proximity. With regard to intermolecular process, employment of reaction fields such as capsules, cages, bowls, and micelles has been recognized as a useful method in organic synthesis to come close to one another, so that the reaction proceeds rapidly to afford the product.[2]



Scheme 1. Pseudo-intramolecular process.

To the contrary, we previously proposed a new protocol, a pseudo-intramolecular reaction, which efficiently proceeds to completion under mild conditions even when no catalyst, additive, or special manipulation is employed; in particular, this reaction can be carried out even in the absence of the abovementioned reaction fields.[3,4] Compounds having an acidic hydrogen as well as an appropriate functionality can be used as substrates for the pseudo-intramolecular reaction, and they readily form ammonium salts upon treatment with amines. When the amine is liberated from the salt under equilibrium, the nucleophilic moiety (amine) and the electrophilic functionality come close to each other. Because of this spatial proximity, the reaction, which is actually intermolecular, behaves like an intramolecular reaction, and side reactions are suppressed. In the present process, the acidic hydrogen atom is used as a lure for attracting the amine, and the functional group bites it; this process is similar to the manner in which a football fish attracts its prey (Scheme 1). We considered this new concept is applicable to efficient syntheses of various kinds of polyfunctionalized compounds under mild conditions.



Scheme 2. Synthesis of 2,3-difunctionalized 1,4-dihydropyridine **2**.

For example, the pseudo-intramolecular reaction took place for substrates such as α-nitro-δ-keto nitrile **1** with amines,[5] which affords the corresponding 2-amino-3-nitro-1,4-dihydropyridine **2**[6] in the following manner. Treatment of **1** with an amine results in the formation of an intermediate ammonium salt **3**; then, the liberated amine attacks the nearby cyano group to cause cyclization (Scheme 2). From the point aimed at bifunctionality of the substrate **1**, we considered the pseudo-intramolecular reaction surely proceeds at the carbonyl group if amines having a nucleophilic functional group such as diamines **4** are employed, which leads to multiply functionalized 1,7-diazabicyclo[4.3.0]nonanes (DBNs) and their homologs.

Several synthetic routes to DBN frameworks have been established with the aim of studying the biological activities of these DBNs[7] and for producing DBN-based agrochemicals.[8] The DBN framework can be constructed by the intermolecular condensation of 1,2-diaminoethanes with 5-chloropentanal,[9] γ-acyl (or γ-cyano) butylates,[10] or glutaraldehyde.[11] Intramolecular cyclization of 5-amino-1-pentanols,[7] or dipeptides[12] is another for the direct synthesis of DBNs from acyclic starting materials. Pyridines and piperidines can be used as scaffolds for the synthesis of [*a*]-fused rings by intramolecular nucleophilic reaction,[13] 1,3-dipolar cycloaddition[14] *etc*. DBNs can also be synthesized by constructing a second ring on an imidazolidine ring, i.e., by the formation of a fused ring compound.[8,15] Although these methods are of great synthetic importance, they

are not effective for the synthesis of multifunctionalized DBN derivatives because of the following drawbacks: (1) these methods involve multistep reactions and (2) the starting materials are not readily available. To the best of our knowledge, there is only one report on the synthesis of DBNs possessing two functional groups at the 2- and the 3-positions.[8] Therefore, there is increased demand for the development of an easy synthetic method that affords vicinally functionalized DBNs via simple manipulations, even when no special reagents or reaction conditions are employed. In this study, we have developed a facile method for the synthesis of DBNs and their homologs; in our method, pseudo-intramolecular imination is a key step, and the diamines **4** used show acrobatic behavior.

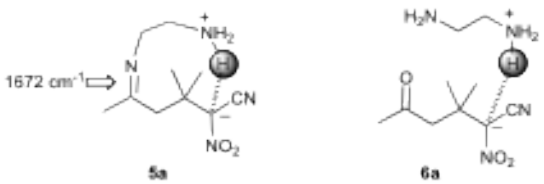


Figure 1. Plausible structures for the precipitates.

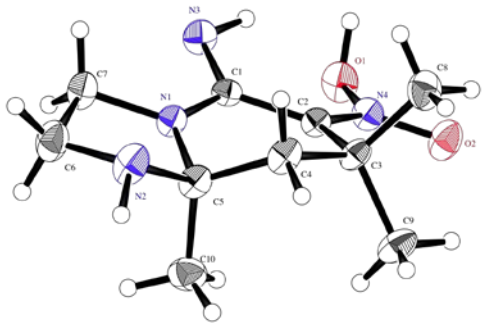
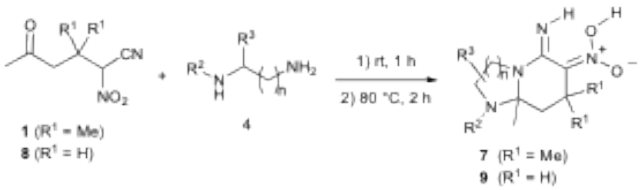


Figure 2. An ORTEP drawing of **7a** with 50% probability thermal ellipsoids.

When 1,2-diaminoethane **4a** was added to a solution of keto nitrile **1** in acetonitrile, a white precipitate was immediately formed. The results of elemental analyses and HRMS revealed that the molecular formula of the precipitated compound was $C_{10}H_{18}N_4O_2$, which corresponded to a dehydrated form of the adduct obtained from **1** and **4a**. The IR spectrum of the precipitate showed a strong absorption at 2190 cm^{-1} and a relatively weak absorption at 1672 cm^{-1}; these two absorptions could be assigned to the cyano group of α-cyanonitronate[9] and an imino group, respectively. On the basis of these spectral and analytical data, the product was confirmed to be the zwitterionic imine **5a**, and not the ammonium salt **6a** (Figure 1). However, when the ^{1}H NMR spectrum of the precipitate was recorded in DMSO-d_6 (in which the precipitate was readily soluble) instead of CD_3CN (in which the precipitate was insoluble), signals due to **5a** as well as **6a** were observed; these NMR signals could be ascribed to the equilibrium shift from **5a** to **6a** in DMSO. It is noteworthy that imination proceeded quantitatively at room temperature to afford **5a** even in the absence of a catalyst.

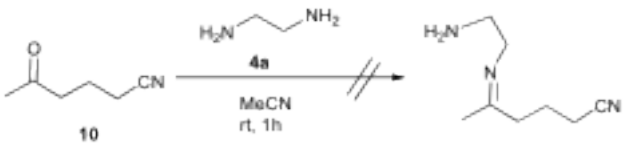
Under reflux conditions, imine **5a** could be easily transformed to the DBN derivative **7a** (yield: 76%; Table, run 1), whose structure was determined by X-ray crystallography (Figure 2) as well as from spectral and analytical data. Interestingly, the bridgehead nitrogen and the three adjacent carbons in **7a** were located in a plane within 0.025 Å; this was thought to be due to the conjugation with the α-iminonitronic acid moiety. For the formation of **9** via bicyclization (run 2), the two methyl groups at the β-position of the δ-keto nitrile were replaced with hydrogen atoms (i.e. compound **8**); however, **8** was unstable and decomposed within a few days even when stored in a refrigerator. When 1,2-diaminopropane **4b** was employed, an equimolar mixture regioisomers **7b** and **7b'** was formed, indicating that the initial imination was unaffected by the presence of the methyl group on the ethylene chain (run 3). The reactivity of diamine **4c**, which had an *N*-ethyl group, was similar to that of the unsubstituted diamine **4a**; the *N*-ethyl group in **4c** did not interfere with the reaction, and a bicyclic product **7c** was obtained (run 4). This is notable because the present reaction completely recoginized the primary amino group from the secondary amino one having similar basicity. It was also possible to construct relatively larger condensed rings by employing diamines **4d** and **4e**. When using 1,3-diaminopropane **4d**, bicyclization proceeded in the same way to afford diazabicyclo[4.4.0]decane **7d** in 85% yield (run 5). The use of 1,4-diaminobutane **4e** resulted in the formation of a seven-membered ring (run 6).

Table. Bicyclization using other diamines.



run	R^1	R^2	R^3	n	Diamine	Product	Yield / %
1	Me	H	H	1	**4a**	**7a**	76
2	H	H	H	1	**4a**	**9**	26
3	Me	H	Me	1	**4b**	**7b, 7b'**[a]	65[a]
4	Me	Et	H	1	**4c**	**7c**	79
5	Me	H	H	2	**4d**	**7d**	85
6	Me	H	H	3	**4e**	**7e**	23

[a] A mixture of two regioisomers **7b** (8-methyl isomer) and **7b'** (9-methyl isomer) was formed in a 1:1 ratio.

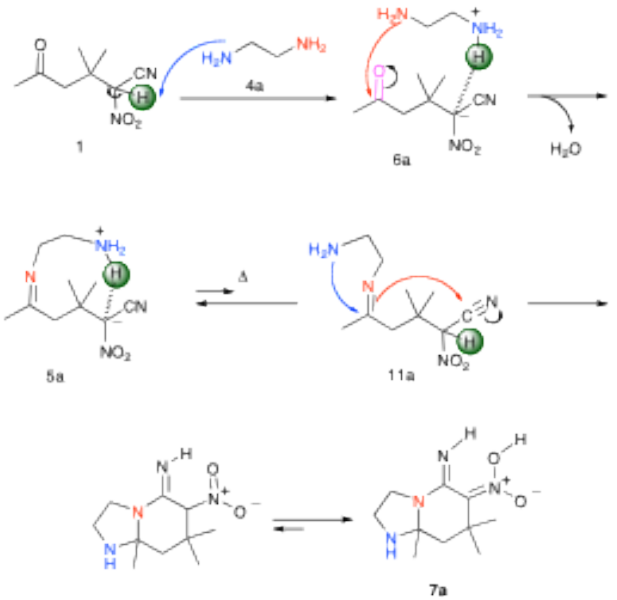


Scheme 3. Reaction of keto nitrile **10** with diamine **4a**

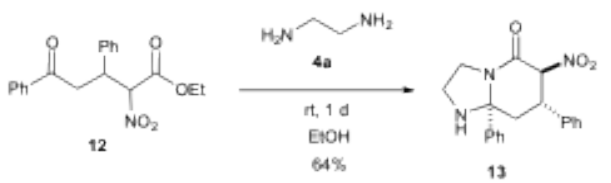
While α-nitro-δ-keto nitrile **1** quantitatively affords **5a**, δ-keto nitrile **10**, which has no nitro group, remains unreacted even after treatment with diamine **4a** under the same conditions used for the formation of **5a** (Scheme 3). This result indicates that the presence of a nitro group is necessary for the initial imination step. Since there are three carbons between the two functional groups (the cyano group and the keto group) in **1**, the nitro group cannot activate the carbonyl group by the electron-withdrawing

inductive effect. The main role of the nitro group is to make the α-hydrogen acidic so that it can attract diamine **4a** to form ammonium salt **6a**, which is essential for triggering the pseudo-intramolecular process, as shown in Scheme 1.

A plausible mechanism for the present reaction is illustrated in Scheme 4. One of the amino groups (blue) in **4a** deprotonates the α-carbon of δ-keto nitrile **1** to afford ammonium salt **6a**, which realizes two reactants, **1** and **4a**, are closed together to cause the pseudo-intramolecular imination. Ammonium salt **3**, which is derived from a monoamine (Scheme 2), has no nucleophilic site, but ammonium salt **6a** has an additional nucleophilic amino group (shown in red) that attacks the electrophilic carbonyl group in preference to the anionic cyano group to afford imine **5a** efficiently. The result shown in Scheme 3 well supports this mechanism. When imine **5a** is heated, a small amount of amine **11a** is formed under equilibrium, and the nucleophilicity of the amino group (blue) and the electrophilicity of the cyano group are reverted. Two rings are simultaneously constructed by the nucleophilic attack of the amino group (blue) on the imino carbon and the subsequent attack of the imino nitrogen (red) on the cyano group, and the resulting product **7a** is a bicyclic compound.



Scheme 4. A plausible mechanism for bicyclization of **1**.



Scheme 5. Reaction of keto ester **12** with diamine **4a**.

Next, α-nitro-δ-keto ester **12**, which was easily prepared by the Michael addition of ethyl nitroacetate to chalcone, was treated with diamine **4a**. As expected, DBN derivative **13** was precipitated as a white solid from a solution of **12** and **4a** in ethanol (Scheme 5). Thus, it is apparent that the present bicyclization method involving a pseudo-intramolecular process is applicable not only to α-nitro-δ-keto nitriles **1** and **8** but also to α-nitro-δ-keto ester **12**.

Conclusions

The pseudo-intramolecular process is well suited for the synthesis of vicinally bifunctional compounds, which can be converted into a variety of new compounds.[16] Molecular design of the substrates with an acidic hydrogen and a functionality, is easy. Hence, the pseudo-intramolecular reaction is expected to emerge as a powerful tool for the synthesis of polyfunctionalized compounds that cannot be prepared by alternative methods.

This work was supported by Grants-in-Aid for Scientific Research (No. 22550043) and by Kyoto-Advanced Nanotechnology Network from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

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† Electronic Supplementary Information (ESI) available: Spectral and analytical data of compounds **1**, **5a**, **7**, **8**, **9** and **13**. X-ray crystallographic data of **7a** and **13**. See DOI: 10.1039/b000000x/

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