Synthesis of Vicinally Functionalized 1,4-Dihydropyridines and Diazabicycles via a Pseudo-Intramolecular Process

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Graphical Abstract

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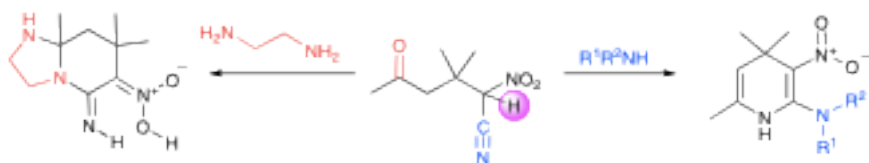
Abstract

An α-nitro-δ-keto nitrile readily forms the corresponding ammonium salt immediately upon treatment with an amine. When the amine liberated under equilibrium, the nucleophilic amine and the electrophilic keto nitrile come close to each other to afford so-called an intimate pair. The spatial proximity realized an efficient reaction to give a 2-amino-3-nitro-1,4-dihydropyridine; the reaction proceeded like an intramolecular reaction although it is actually an intermolecular reaction, namely the pseudo-intramolecular reaction. The bifunctionality of the keto nitrile also enabled the pseudo-intramolecular imination followed by tandem cyclization leading to diazabicyclic frameworks.

Introduction

The development of highly efficient synthetic methods for various organic compounds is crucial for the efficient utilization of carbon resources and for low environmental impact. Reactions not requiring a protecting group or a special reagent facilitate the simplification of manipulations from the viewpoint of atom economy.[1] The improvement of the efficiency of reactions is one of the main approaches to environmentally benign methods, in which the increase of the collision frequency of reactants should be considered as a significant factor. Intramolecular reactions proceed faster than do intermolecular reactions because of the high collision frequency of reaction sites, which can be attributed to the spatial proximity. With regard to an intermolecular process, employment of reaction fields such as capsules, cages, bowls, and micelles has been recognized as a useful method in organic synthesis to make reaction sites close to one another, so that the reaction proceeds rapidly to afford the product.[2] However, it is still difficult to achieve the high efficiency of the reaction under mild conditions without using any contrivance such as reaction field, catalyst, and activating agent. From this viewpoint, development of the efficient protocol is one of

the challenging subjects.

To the contrary, we 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 field.

Compounds having an acidic hydrogen as well as an appropriate functionality can be used as a substrate for the pseudo-intramolecular reaction, and the substrate readily form an ammonium salt upon treatment with an amine. 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 manner, 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).
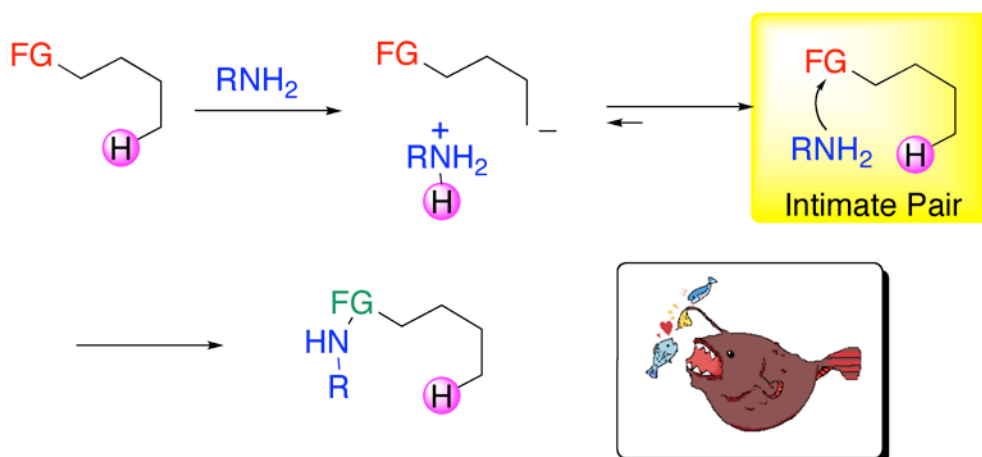
Scheme 1. The concept of the pseudo-intramolecular process

Indeed, the α-arylated and α-nitrated β-keto esters **1a** and **1b** underwent the transfer of an acyl group to the amines very smoothly yielding the amide **5** and deacylated ester **6**, which is named as the transacylation (Scheme 2).[3-5] In these reactions, the highly acidic keto ester reacted with the amine to form the corresponding ammonium salt **3** immediately. Then, under equilibrium, the electrophilic keto ester and the nucleophilic amine were regenerated simultaneously in close proximity. The spatial proximity of the reactants (the intimate pair **4**) enhanced the reactivity, and consequently, the reaction proceeded like an intramolecular process; this has been confirmed by NMR study and by carrying out the reaction using an amino alcohol in diluted conditions.[4]

The pseudo-intramolecular process is considered to be a novel method for

synthesizing polyfunctionalized compounds. In this process, it is crucial that suitable substrates –those containing both an acidic hydrogen and functionalities such as carbonyl and cyano groups– are available; molecular design for these substrates is considerably easy. From this viewpoint, we focused on the α-nitrated δ-keto nitriles **7**[6] and **8**[7] as substrates for the present pseudo-intramolecular reaction and utilized them in the synthesis of functionalized azaheterocyclic compounds.
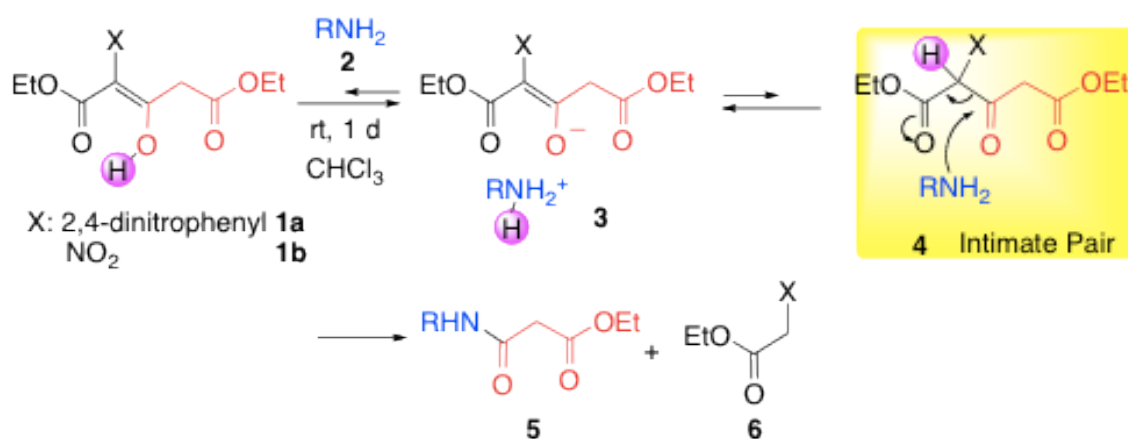
Scheme 2. Transacylation of the keto esters **1** with the amine **2**

Figure 1. α-Nitroketo nitriles **7** and **8**

Results and Discussion

A) Synthesis of vicinally functionalized 1,4-dihydropyridines

The keto nitrile **7** was easily transformed to the ammonium salt **9a** upon treatment with propylamine (**2a**); the formation was confirmed by ^{1}H NMR and IR spectra. Just after **2a** was added to a solution of the keto nitrile **7** in acetonitrile-d_3, in the ^{1}H NMR spectrum, the singlet signal at 6.29 ppm assigned to the acidic α-proton immediately disappeared, and the signals for the propyl group shifted to the downfield, indicating the formation of the ammonium salt **9a** (Figure 1). The absorption of the cyano group in the IR spectrum of **9a** was observed to be as strong as that of the carbonyl group, while, only very weak cyano group absorption could be detected in the spectrum of the starting keto nitrile **7**. The strong absorption of a cyano group is a typical feature of an α-cyanonitronate framework.[8]
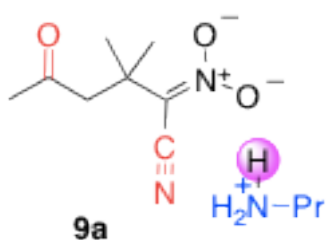

Figure 2. The ammonium salt **9a**

When an acetonitrile solution of **9a** was heated under reflux, the

3-nitro-2-propylamino-1,4-dihydropyridine **10a** was isolated in 71% yield (Table 1, run

1).[9] Although common transacylations via a pseudo-intramolecular process gave no

by-product (Scheme 1), several kinds of unidentified products were formed in this

reaction presumably due to side reactions caused by reactive multiple functionalities of

the keto nitrile **7**. The structure of the dihydropyridine **10a** was determined on the basis

of spectral and analytical data. The singlet signal at 7.51 ppm and the triplet signal at

12.12 ppm were exchangeable with D_2O; the former disappeared immediately and the

latter disappeared gradually. The different exchange rates indicate the presence of an

intramolecular hydrogen bond between an amino and a nitro group.   Furthermore, two

gem-methyl groups were equivalently observed despite a cyclic structure, suggesting

that the dihydropyridine ring is closely flat[10] or undergoes a facile ring flipping in an

NMR time scale.

Butylamine (**2b**) reacted in a similar manner with the keto nitrile **7** (Table 1,

run 2), however, bulkier amines such as isopropylamine (**2c**), *tert*-butylamine (**2d**),

aniline (**2e**), and dipropylamine (**2f**) did not cause the cyclization (runs 3-6). The high

sensitivity to steric hindrance is likely due to the congestion around the reaction site of

the intimate pair **11**. Hence, the insertion of a methylene group as a spacer between the

bulky group and the amino function facilitated the cyclization to afford the

dihydropyridines **10g-k**, respectively (runs 7-11).[9]

**Table 1.** Synthesis of the dihydropyridines **10**

run	R^1	R^2		Yield/%
1	Et-CH$_2$	H	**a**	71
2	Pr-CH$_2$	H	**b**	65
3	Me$_2$CH	H	**c**	0
4	Me$_3$C	H	**d**	0
5	Ph	H	**e**	0
6	Et-CH$_2$	Et-CH$_2$	**f**	0
7	*i*-Pr-CH$_2$	H	**g**	63
8	*t*-Bu-CH$_2$	H	**h**	48
9	*c*-Hex-CH$_2$	H	**i**	59
10	Ph-CH$_2$	H	**j**	80
11	(MeO)$_2$CH-CH$_2$	H	**k**	74

1,4-Dihydropyridines containing an amino group and a nitro group can also

be used in the synthesis of insecticides[11] and central nervous system potassium channel

modulators;[12] the dihydropyridine framework is constructed through a single procedure

by using nitroketene aminals (1,1-diamino-2-nitroethenes) or nitroketene dithioacetals

as building blocks.[13] However, this method has a serious drawback is difficulty in the

modification of the amino moiety. In sharp contrast, in our method, the amino group can

be easily modified by changing the amine **2**. Hence the present reaction will supplement

with the conventional reactions.


B) A plausible mechanism

   A plausible mechanism for the present reaction is illustrated in Scheme 3.

When the salt **9** is heated, the amine parts from **9** under equilibrium giving the intimate

pair **11**. The liberated amine immediately attacks the very close cyano group, and then

the cyano group attacks the acyl group to form a six-membered ring. Subsequent

dehydration and proton transfer lead to the formation of the dihydropyridine **10**.
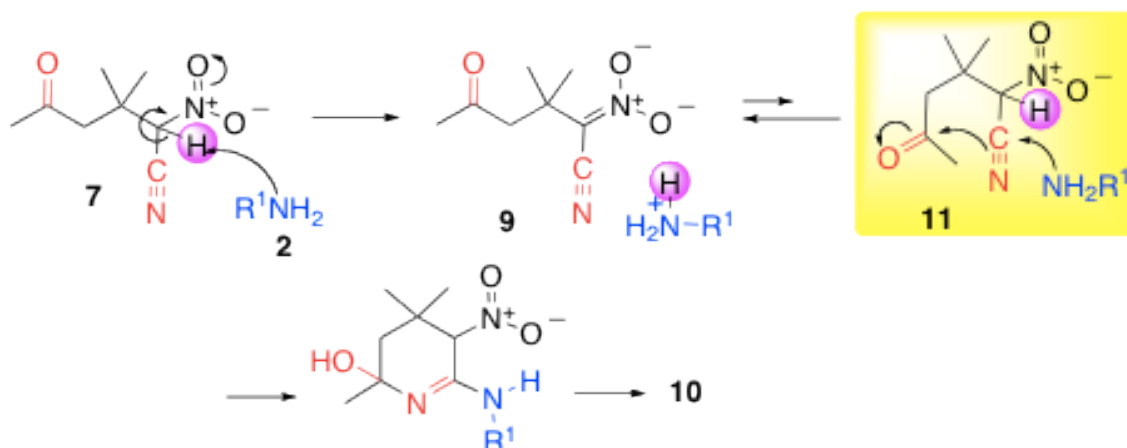
Scheme 3. A plausible mechanism for the formation of dihydropyridine **10**

Since there are three carbons between the two functional groups (the cyano and the keto groups) in **7**, the nitro group should be unable to activate the carbonyl group by an electron-withdrawing inductive effect. The main role of the nitro group is to make the α-hydrogen acidic so that the abstraction of the hydrogen by the amine **2** takes place to form the ammonium salt **9**. Thus, the acidic hydrogen is essential for triggering the pseudo-intramolecular process, as shown in Scheme 4. Indeed, the simple prototype δ-keto nitrile **12**,[14] which has no nitro group, unreacted with the amine **2a** under the similar conditions used for the formation of **10a** (Scheme 4). Mulliken populations of atoms determined by DFT calculations (B3LYP 6-31+G**) reveal the electron density of the cyano group is not so decreased even though a nitro group is

introduced at the α-position (Figure 3), which well supports the above consideration.
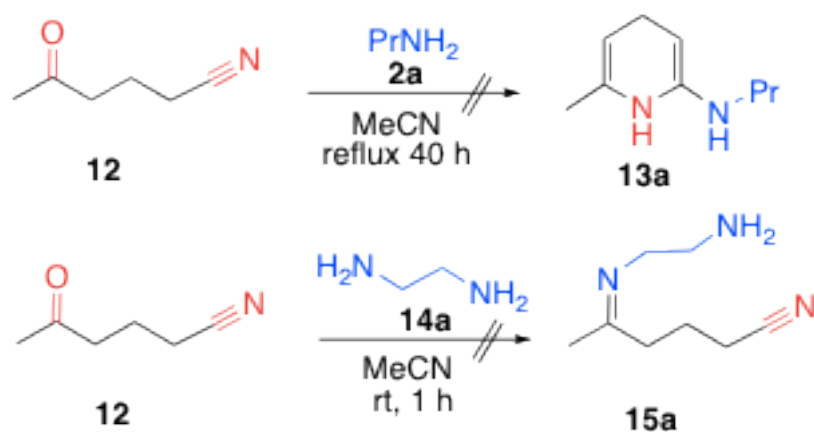
Scheme 4. Reactions of the keto nitrile **12** with propylamine (**2a**) and the diamine **14a**
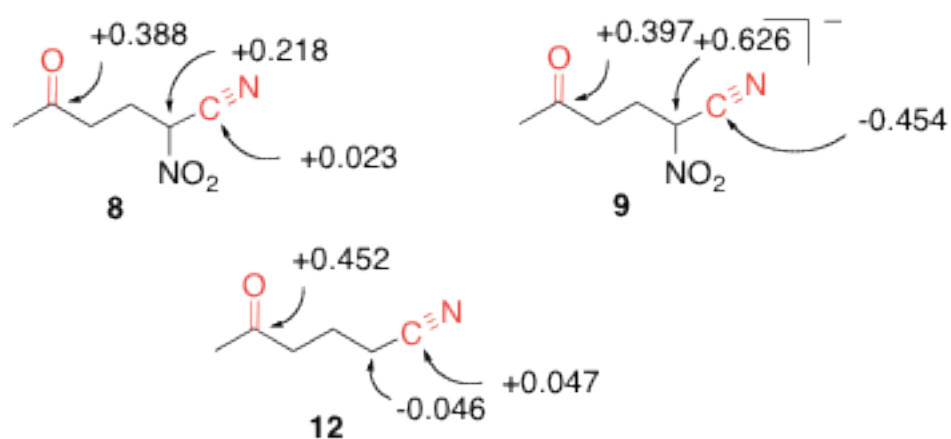

Figure 3. Mulliken population (au) determined by DFT calculations

In the case of the anionic keto nitrile **9**, the cyano group looses electrophilicity, which does not react with amine anymore. When the amine is liberated under equilibrium, the cyano group retrieves its electrophilicity, and the liberated amine attacks the cyano group efficiently because of spatial proximity, although the electrophilicity is lower than that of carbonyl group.

These calculated results strongly indicate that the carbonyl functionality of the keto nitrile is available for the pseudo-intramolecular process when the dinucleophilic diamine **14** is employed instead of the monoamine **2**. Namely, when one of the amino groups of **14** forms the salt **16** at the nitroacetonitrile moiety of **7**, the other functionalities, a nucleophilic amino group and an electrophilic keto group, are remained with spatial proximity, which will react easily with each other to cause the pseudo-intramolecular imination leading to a new framework via the iminoammonium salt **17** (Scheme 5). On the basis of this supposition, the reactions of the keto nitrile **7** with the dinucleophilic diamines **14** were studied.
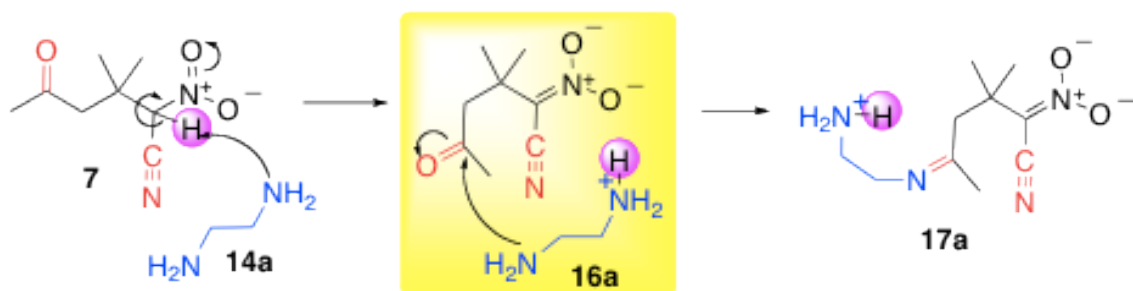
Scheme 5. The pseudo-intramolecular imination of the keto nitrile **7** with the diamine

14a

C) Tandem cyclization including a pseudo-intramolecular imination

When the 1,2-diaminoethane (**14a**) was added to a solution of the keto nitrile

7 in acetonitrile, a white precipitate was immediately formed. The results of an

elemental analysis and HRMS revealed that the molecular formula of the precipitated

compound was $C_{10}H_{18}N_4O_2$, which corresponds to a dehydrated form of an adduct

obtained from **7** and **14a**. 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 a cyano group in an α-cyanonitronate structure[8] and an imino group,

respectively. On the basis of these spectral and analytical data, the product was

confirmed to be the zwitterionic imine **17a**, rather than the ammonium salt **16a** (Scheme

5). It is noteworthy that the imination proceeded quantitatively at room temperature to afford **17a** even in the absence of a catalyst. In the case of the keto nitrile **12**, the corresponding imine **15a** was not formed upon treatment with the diamine **14a** under similar conditions (Scheme 4), which revealed the imination of the keto nitrile **7** proceeded in a pseudo-intramolecular manner.
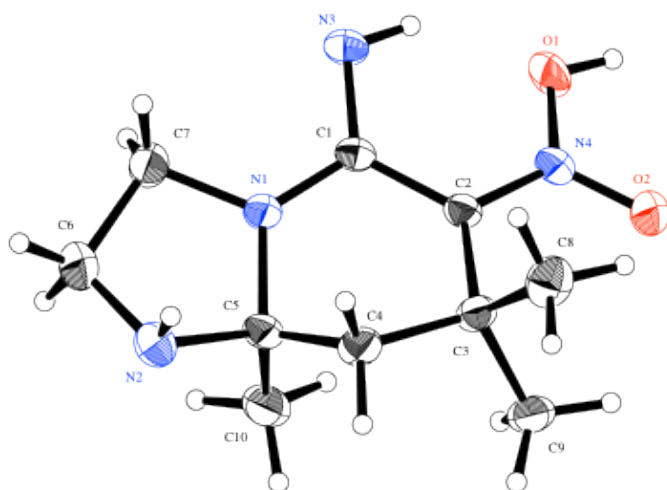
Figure 4. An ORTEP drawing of **18a** with 50% probability thermal ellipsoids. Selected bond lengths [Å] and angles [°]: N1-C1 1.320(3), N1-C5 1.482(3), N1-C7 1.468(3), C1-C2 1.457(3), C1-N3 1.331(3), N4-O1 2.567(3), C2-N4 1.351(3); C1-N1-C5 123.3(2), C1-N1-C7 125.0(2), C5-N1-C7 111.5(2), N1-C1-N3 119.2(2), N3-C1-C2 122.7(2), N1-C1-C2 118.2(2)

Upon refluxing a suspension in acetonitrile, the imine **17a** could be easily transformed to the diazabicyclononane derivative **18a** (yield: 76%; Table 2, run 1).[7] The

structure of **18a** was determined by X-ray crystallography (Figure 4) as well as by spectral analyses. Interestingly, the bridgehead nitrogen and the three adjacent carbons in **18a** were located in a plane with a derivation of only 0.025 Å; this was thought to be owing to the conjugation with the α-iminonitronic acid moiety.

The formation of a bicyclic framework is considered to proceed as illustrated in Scheme 6. When the imine **18a** is heated, a small amount of the imino amine **19a** is formed under equilibrium, and the nucleophilicity of the amino group and the electrophilicity of the cyano group are reverted. As a result, two rings are simultaneously constructed by the nucleophilic attack of the amino group to the imino carbon and the subsequent attack of the imino nitrogen to the cyano group to give the resulting product **18a** with a bicyclic structure.

Table 2. Synthesis of bicyclic compounds **18** using the diamines **14**

7 (R^1 = Me)
8 (R^1 = H)

18 (R^1 = Me)
20 (R^1 = H)
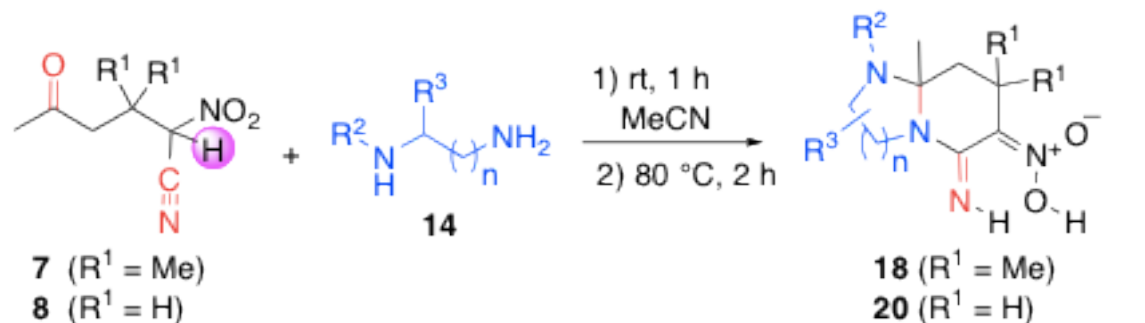
run	R^1	R^2	R^3	n	diamine	product	yield/%
1	Me	H	H	1	**14a**	**18a**	76
2	H	H	H	1	**14a**	**20**	26
3	Me	H	Me	1	**14b**	**18b** and **18b'**[a]	65[a]
4	Me	Et	H	1	**14c**	**18c**	79
5	Me	H	H	2	**14d**	**18d**	85
6	Me	H	H	3	**14e**	**18e**	23

[a] A mixture of two regioisomers **18b** (8-methyl isomer) and **18b'** (9-methyl isomer) was formed in a 1:1 ratio.
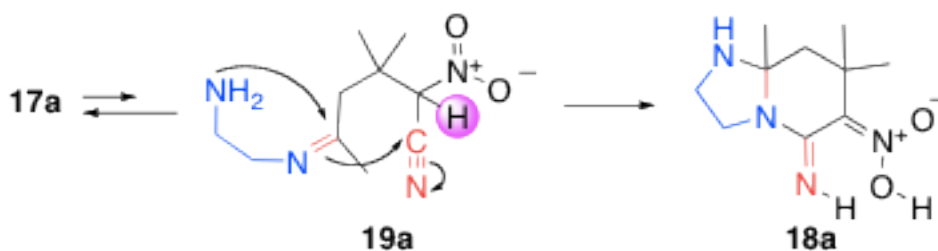
Scheme 6. Tandem cyclization leading to the bicyclic product **18a**

We next tried to use other diamines **14**. Except for run 2, the reactions proceeded smoothly to give the corresponding bicyclic compounds **18**, as was expected

(Table 2). The yield of the product **20** having the same bicyclic structure is rather low

(run 2), when a substrate with no substituent at the β-position of the δ-keto nitrile

skeleton (i.e. the compound **8**) was used. This result would arise from the instability of

8 at the reaction temperature; **8** decomposed within a few days even when stored in a

refrigerator. When 1,2-diaminopropane (**14b**) was employed, an equimolar mixture of

the regioisomers **18b** (8-methyl isomer) and **18b'** (9-methyl isomer) was formed,

indicating that the initial imination unfortunately could not be controlled by the

presence of the methyl group on the ethylene chain (run 3).

The reactivity of the diamine **14c**, which has an *N*-ethyl group, was similar to

that of the unsubstituted diamine **14a**; the *N*-ethyl group in **14c** did not interfere the

reaction, and the bicyclic product **18c** was obtained (run 4). Worth to note is that the

present reaction completely recoginized the difference in reactivity between the primary

amino group and the secondary amino group even though they have similar basicity. It

was also possible to construct relatively larger condensed rings by employing the

diamines **14d** and **14e**. When using 1,3-diaminopropane (**14d**), the bicyclization

proceeded in the same way to afford the diazabicyclo[4.4.0]decane **18d** in 85% yield

(run 5). The use of 1,4-diaminobutane (**18e**) resulted in the formation of a seven-membered ring (run 6).

Although several synthetic methods[15] for diazabicyclic compounds have been established with the aim of studying the biological activities[16] and of producing agrochemicals,[17] these methods are not effective for synthesizing multiply functionalized systems 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 diazabicyclononanes possessing two functional groups at the 2- and 3-positions.[17] In contrast, the present method is a valuable synthetic method that affords the vicinally functionalized diazabicyclic compounds **18** and **20** via simple manipulations without no special reagents nor reaction conditions.

Conclusions

We successfully synthesized vicinally functionalized azaheterocyclic compounds such as the 1,4-dihydropyridines **10** and the diazabicyclic compounds **18**

and **20** upon treatment of the keto nitriles **7** with the amines **2** and the diamines **14** under mild conditions, in which the pseudo-intramolecular process is a key step. Molecular design of the substrates with an acidic hydrogen and a functionality, is not difficult. Hence, the pseudo-intramolecular reaction is expected to emerge as a powerful tool for the synthesis of polyfunctionalized compounds that cannot be prepared by conventional methods.

Experimental

General

The melting points were determined on a Yanaco micro-melting- points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker DPX-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker DPX-400 at 100 MHz, and the assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a Horiba FT-200 IR spectrometer. The mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer. The high resolution mass spectra were measured on a JEOL JMS-DX303HF. The elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

Conversion of 3,3-dimethyl-2-nitro-5-oxohexanenitrile (7) to propylammonium 3,3-dimethyl-5-oxohexanenitrile-2-nitronate 9a

To a solution of keto nitrile **7** (92 mg, 0.5 mmol) in acetonitrile (10 mL), propylamine (**2a**) (41 μL, 0.5 mmol) was added. After stirring at room temperature for 10 min., the solvent was evaporated to afford the propylammonium salt **9a** (122 mg, 0.5 mmol,

quant.).

Pale brown oil. IR (neat / cm^{-1}) 3200-2900 (br), 2198 (strong), 1711, 1341, 1228, 733; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.99 (t, J = 7.4 Hz, 3H), 1.26 (s, 6H), 1.71 (dt, J = 7.5, 7.4 Hz, 2H), 2.10 (s, 3H), 2.97 (s, 2H), 3.00 (t, J = 7.5 Hz, 2H), 7.2-8.2 (br, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 9.0 (CH$_3$), 19.3 (CH$_2$), 24.2 (CH$_3$), 29.0 (CH$_3$), 32.3 (CH$_2$), 39.6 (CH$_2$), 48.6 (CH$_2$), 103.6 (C), 116.1(C), 206.0 (C).

1,4-Dihydro-4,4,6-trimethyl-3-nitro-2-(1-propylamino)pyridine (10a)

To a solution of keto nitrile **7** (92 mg, 0.5 mmol) in acetonitrile (10 mL), propylamine (**2a**) (41 μL, 0.5 mmol) was added, and the solution was heated under reflux for 40 h. After removal of the solvent, the residue was purified by column chromatography on silica gel to afford the dihydropyridine **10a** (eluted with ethyl acetate, 80 mg, 0.35 mmol, 71%). Pale yellow needles (recrystallized from ethyl acetate). Mp 202-204 °C. IR (Nujol / cm^{-1}) 1720, 1626, 1535, 1333; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.48 (s, 6H), 1.72 (tq, J = 7.2, 7.2 Hz, 2H), 1.83 (s, 3H), 3.36 (dt, J = 7.2, 5.2 Hz, 2H), 4.47 (s, 1H), 7.51 (s, 1H), 12.14 (t, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 11.4 (CH$_3$), 18.4 (CH$_3$), 22.0 (CH$_2$), 27.0 (CH$_3$), 36.0 (C), 43.5 (CH$_2$), 113.7

(C), 114.4 (CH), 124.7 (C), 152.5 (C); MS (FAB) 226 (M$^+$+1, 100). Anal. Calcd for

C$_{11}$H$_{19}$N$_3$O$_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.49; H, 8.51; N, 18.59.

The other dihydropyridines were synthesized in a similar manner.

2-(1-Butylamino)-1,4-dihydro-4,4,6-trimethyl-3-nitro-pyridine (10b)

Yield (78 mg, 0.33 mmol, 65%). Yellow plates (recrystallized from acetonitrile). Mp

192-193 °C.   IR (Nujol / cm^{-1}) 1720, 1626, 1531, 1331; ^{1}H NMR (400 MHz, CDCl$_3$) δ

0.94 (t, J = 7.3 Hz, 3H), 1.43 (tq, J = 7.3, 7.3 Hz, 2H), 1.48 (s, 6H), 1.67 (tt, J = 7.3, 7.3

Hz, 2H), 1.83 (s, 3H), 3.42 (dt, J = 7.3, 5.1 Hz, 2H), 4.45 (s, 1H), 7.85 (s, 1H), 12.12 (t,

J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.6 (CH$_3$), 18.4 (CH$_3$), 20.1 (CH$_2$),

27.0 (CH$_3$), 30.6 (CH$_2$), 36.0 (C), 41.5 (CH$_2$), 113.6 (C), 114.4 (CH), 124.7 (C), 152.4

(C). Anal. Calcd for C$_{12}$H$_{21}$N$_3$O$_2$: C, 60.23; H, 8.84; N, 17.56. Found: C, 60.27; H, 8.91;

N, 17.43.

1,4-Dihydro-4,4,6-trimethyl-2-(2-methyl-1-propyl)amino-3-nitropyridine (10g)

Yield (75 mg, 0.32 mmol, 63%). Yellow needles (recrystallized from acetonitrile). Mp

201-205 °C.   IR (Nujol / cm^{-1}) 1724, 1620, 1537, 1313; ^{1}H NMR (400 MHz, CDCl$_3$) δ

1.04 (d, J = 6.6 Hz, 6H), 1.49 (s, 6H), 1.83 (s, 3H), 2.0-2.1 (m, 1H), 3.13 (dd, J = 6.6,

5.1 Hz, 2H), 4.50 (s, 1H), 7.27 (s, 1H), 12.19 (t, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz,

CDCl$_3$) δ 18.4 (CH$_3$), 20.2 (CH$_3$), 27.0 (CH$_3$), 27.8 (CH), 36.0 (C), 49.2 (CH$_2$), 113.6

(C), 114.5 (CH), 124.5 (C), 152.5 (C). Anal. Calcd for C$_{12}$H$_{21}$N$_3$O$_2$: C, 60.23; H, 8.84;

N, 17.56. Found: C, 59.86; H, 8.95; N, 17.29.

1,4-Dihydro-2-(2,2-dimethyl-1-propyl)amino-3-nitro-4,4,6-trimethylpyridine (10h)

Yield (61 mg, 0.24 mmol, 48%). Pale yellow needles (recrystallized from acetonitrile).

Mp 219-222 °C.   IR (Nujol / cm^{-1}) 1722, 1620, 1543, 1313; ^{1}H NMR (400 MHz,

CDCl$_3$) δ 1.07 (s, 9H), 1.50 (s, 6H), 1.83 (s, 3H), 3.08 (d, J = 7.0 Hz, 2H), 4.52 (s, 1H),

5.73 (s, 1H), 12.37 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.4 (CH$_3$),

25.0 (CH$_3$), 25.3 (CH$_3$), 29.4 (C), 33.5 (C), 51.0 (CH$_2$), 110.4 (C), 111.5 (CH), 123.0

(C), 150.3 (C). Anal. Calcd for C$_{13}$H$_{23}$N$_3$O$_2$: C, 61.63; H, 9.15; N, 16.59. Found: C,

61.40; H, 9.29; N, 16.51.

2-(Cyclohexylmethyl)amino-1,4-dihydro-4,4,6-trimethyl-3-nitropyridine (10i)

Yield (109 mg, 0.40 mmol, 80%). Yellow needles (recrystallized from acetonitrile). Mp

202-203 °C.   IR (Nujol / cm^{-1}) 1720, 1626, 1537, 1313; ^{1}H NMR (400 MHz, CDCl$_3$) δ

1.40 (s, 6H), 1.76 (s, 3H), 4.53 (s, 1H), 4.61 (d, J = 5.4 Hz, 2H), 7.32-7.44 (m, 5H), 8.33

(s, 1H), 12.15 (t, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.5 (CH$_3$), 27.2

(CH$_3$), 36.1 (C), 45.9 (CH$_2$), 113.4 (C), 115.1(CH), 123.4 (C), 127.1 (CH), 127.5 (CH),

128.5 (CH), 128.8 (CH), 129.4 (CH), 135.1 (C), 152.4 (C); MS (FAB) 274 (M$^+$+1, 100).

Anal. Calcd for C$_{15}$H$_{19}$N$_3$O$_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 66.13; H, 7.07; N,

15.43.

2-Benzylamino-1,4-dihydro-4,4,6-trimethyl-3-nitropyridine (10j)

Yield (109 mg, 0.40 mmol, 80%). Yellow needles (recrystallized from acetonitrile). Mp

202-203 °C.   IR (Nujol / cm^{-1}) 1720, 1626, 1537, 1313; ^{1}H NMR (400 MHz, CDCl$_3$) δ

1.40 (s, 6H), 1.76 (s, 3H), 4.53 (s, 1H), 4.61 (d, J = 5.4 Hz, 2H), 7.32-7.44 (m, 5H), 8.33

(s, 1H), 12.15 (t, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.5 (CH$_3$), 27.2

(CH$_3$), 36.1 (C), 45.9 (CH$_2$), 113.4 (C), 115.1(CH), 123.4 (C), 127.1 (CH), 127.5 (CH),

128.5 (CH), 128.8 (CH), 129.4 (CH), 135.1 (C), 152.4 (C); MS (FAB) 274 (M$^+$+1, 100).

Anal. Calcd for C$_{15}$H$_{19}$N$_3$O$_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 66.13; H, 7.07; N,

15.43.

1,4-Dihydro-2-[(2,2-dimethoxy)ethyl]amino-4,4,6-trimethyl-3-nitropyridine (10k)

Yield (100 mg, 0.37 mmol, 74%). Yellow needles (recrystallized from ethyl acetate).

Mp 171-174 °C. IR (Nujol / cm^{-1}) 1724, 1622, 1531, 1311; ^{1}H NMR (400 MHz,

CDCl$_3$) δ 1.40 (s, 6H), 1.76 (s, 3H), 3.45 (dd, J = 5.8, 4.8 Hz, 2H), 3.51 (s, 6H), 4.45 (t,

J = 4.8 Hz, 1H), 4.50 (s, 1H), 7.38 (s, 1H), 11.89 (t, J = 5.8 Hz, 1H); ^{13}C NMR (100

MHz, CDCl$_3$) δ 18.6 (CH$_3$), 27.2 (CH$_3$), 36.1 (C), 45.5 (CH$_2$), 55.6 (CH$_3$), 104.4 (CH),

113.6 (C), 115.0 (CH), 123.8 (C), 154.0 (C). Anal. Calcd for C$_{12}$H$_{21}$N$_3$O$_4$: C, 53.12; H,

7.80; N, 15.49. Found: C, 52.94; H, 7.92; N, 15.33.

1,7-Diaza-2-imino-4,4,6-trimethyl-3-*aci*-nitrobicyclo[4.3.0]nonane (18a)

To a solution of the keto nitrile **7** (184 mg, 1.0 mmol), in acetonitrile (15 mL),

1,2-diaminoethane **14a** (67 μL, 1.0 mmol) was added; the imine **17a** was immediately

precipitated as a pale yellow solid. The resultant mixture was heated under reflux for 2

h and concentrated under reduced pressure. The brown residual oil was purified by

column chromatography on silica gel to afford the diazabicyclononane **18a** (172 mg,

0.76 mmol, 76%, eluted with AcOEt/methanol (70:30, v/v)) as a colorless solid. Single

colorless crystals for X-ray analysis were obtained by recrystallization from a mixed

solvent of methanol and acetonitrile (1:2, v/v). Mp 241-243 °C (dec.). IR (KBr) 3271,

3093, 1641, 1566, 1392, 1371, 1348 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.22 (s, 3H), 1.32 (s,

3H), 1.47 (s, 3H), 1.69 (d, J = 13.3 Hz, 1H), 2.04 (d, J = 13.3 Hz, 1H), 2.9-3.0 (br, 1H),

3.2-3.3 (m, 3H), 3.4-3.5 (m, 1H), 7.3-7.6 (br, 1H), 10.4-10.7 (br, 1H); ^{13}C NMR

(DMSO-d_6) δ 23.9 (CH$_3$), 26.3 (CH$_3$), 29.0 (CH$_3$), 33.2 (C), 42.2 (CH$_2$), 46.6 (CH$_2$),

50.5 (CH$_2$), 75.7 (C), 112.3 (C), 152.7 (C); MS (FAB) 227 (M$^+$+1, 100). Anal. Calcd for

C$_{10}$H$_{18}$N$_4$O$_2$: C, 53.08; H, 8.02; N, 24.76%. Found: C, 53.18; H, 8.33; N, 24.69%.

CCDC 804331 contains the supplementary crystallographic data for this compound.

These data can be obtained free of charge from the Cambridge Crystallographic Data

Centre via www.ccdc.cam.ac.uk/data_request/cif.

By using the other diamines **14b-e** and the keto nitrile **8**, the diazabicyclo compounds

18b-e and **20** were synthesized in a similar way.

1,5-Diaza-2-imino-4,4,6,8-tetramethyl-3-*aci*-nitrobicyclo[4.3.0]nonane (18b)

1,5-Diaza-2-imino-4,4,6,9-tetramethyl-3-*aci*-nitrobicyclo[4.3.0]nonane (18b')

Yield of **18b** and **18b'** (1:1) (eluted with a mixed solvent of dichloromethane and

methanol (9:1, v/v), 156 mg, 0.65 mmol, 65%). Colorless prisms (recrystallized from a

mixed solvent of acetonitrile and methanol (1:2, v/v)). Mp 237-238 °C (dec.). IR (KBr)

3258, 2978, 2398, 1618, 1557, 1389, 1356, 1315,1196, 1069 cm^{-1}; ^{1}H NMR (CD$_3$OD) δ

1.30 (d, J = 6.5 Hz, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.86 (d, J = 13.5 Hz, 1H), 1.96 (d, J = 13.5 Hz, 1H), 3.10 (10.8, 9.4 Hz, 1H), 3.3-3.4 (m, 1H), 3.83 (dd, J = 10.8, 6.0 Hz, 1H); ^{13}C NMR (CD$_3$OD) δ 16.4 (CH$_3$), 23.7 (CH$_3$), 25.7 (CH$_3$), 28.1 (CH$_3$), 33.9 (C), 50.4 (CH), 50.9 (CH$_2$), 53.3 (CH$_2$), 77.2 (C), 154.8 (C), 188.6 (C); MS (EI) 240 (M$^+$, 21), 225 (100), 208 (40), 179 (47), 164 (95), 99 (86). HRMS (EI, magnetic field) Calcd for C$_{11}$H$_{20}$N$_4$O$_2$: 240.1586. Found: 240.1582. A correlation between a proton of the methyl group at the 5-position and a methyne proton at the 7-position was observed in the ^{1}H-^{1}H NOESY 2D spectrum.

18b' (measured using a mixture with **18b**) ^{1}H NMR (CD$_3$OD) δ 1.34 (d, J = 6.1 Hz, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.59 (s, 3H), 1.85 (d, J = 13.4 Hz, 1H), 2.12 (d, J = 13.4 Hz, 1H), 2.99 (dd, J = 10.4, 8.5 Hz, 1H), 3.73 (dd, J = 10.4, 7.1 Hz, 1H), 3.7-3.8 (m, 1H).

1,7-Diaza-1-ethyl-2-imino-4,4,6-trimethyl-3-*aci*-nitrobicyclo[4.3.0]nonane (18c)

Yield (201 mg, 0.79 mmol, 79%). Colorless prisms (recrystallized from a mixed solvent of acetonitrile and methanol (1:1, v/v)). Mp 201-204 °C (dec.). IR (KBr) 3250, 1605, 1564, 1389, 1338, cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.05 (t, J = 7.1 Hz, 3H), 1.09 (s, 3H),

1.31 (s, 3H), 1.44 (s, 3H), 1.51 (d, J = 13.2 Hz, 1H), 2.15 (d, J = 13.2 Hz, 1H),

2.20-2.25 (m, 1H), 2.6-2.7 (m, 2H), 3.3-3.45 (m, 2H), 3.5-3.6 (m, 1H), 7.3-7.7 (br, 1H),

10.4-10.8 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 13.7 (CH$_3$), 16.8 (CH$_3$), 26.4 (CH$_3$), 29.0

(CH$_3$), 32.6 (C), 41.4 (CH$_2$), 44.0 (CH$_2$), 45.5 (CH$_2$), 50.9 (CH$_2$), 75.1 (C), 112.3 (C),

153.1 (C); MS (EI) 254 (M$^+$, 20), 239 (100), 222 (36), 193 (36), 178 (91), 113 (63).

HRMS (EI, magnetic field) Calcd for C$_{12}$H$_{22}$N$_4$O$_2$: 254.1743. Found: 254.1744.

1,7-Diaza-2-imino-4,4,6-trimethyl-3-*aci*-nitrobicyclo[4.4.0]decane (18d)

Yield (204 mg, 0.85 mmol, 85%). Pale yellow plates (eluted with chloroform). Mp

204-205 °C (dec.). IR (KBr) 3259, 1606, 1537, 1338 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.31

(s, 3H), 1.34 (s, 3H), 1.44 (s, 3H), 1.55-1.70 (m, 2H), 1.78 (d, J = 13.8 Hz, 1H), 1.83 (d,

J = 13.8 Hz, 1H), 2.44 (br, 1H), 2.70 (br d, J = 12.8 Hz, 1H), 2.91 (br dd, J = 11.8, 11.8

Hz, 1H), 3.09 (ddd, J = 12.8, 12.0, 3.6 Hz, 1H), 3.71 (br d, J = 12.0 Hz, 1H), 7.9-8.3 (s,

1H), 11.4-11.9 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 23.2 (CH$_3$), 27.5 (CH$_2$), 28.9 (CH$_3$),

31.3 (CH$_3$), 34.3 (C), 38.6 (CH$_2$), 41.8 (CH$_2$), 54.9 (CH$_2$), 70.5 (C), 116.1 (C), 158.3

(C); MS (EI) 240 (M$^+$, 3), 225 (88), 194 (63), 179 (93), 164 (100). HRMS (EI, magnetic

field) Calcd for C$_{11}$H$_{20}$N$_4$O$_2$: 240.1586. Found: 240.1585.

1,7-Diaza-2-imino-4,4,6-trimethyl-3-*aci*-nitrobicyclo[5.4.0]undecane (18e)

Yield (58 mg, 0.23 mmol, 23%). Orange granules (recrystallized from methanol). Mp

173-178 °C (dec.). IR (KBr) 3275, 2930, 1611, 1560, 1544, 1335 cm^{-1}; ^{1}H NMR

(DMSO-d_6) δ 1.31 (s, 3H), 1.33 (s, 3H), 1.35-1.40 (m, 2H), 1.39 (s, 3H), 1.50-1.55 (m,

1H), 1.56 (d, J = 14.3 Hz, 1H), 1.66-1.69 (m, 1H), 1.90 (d, J = 14.3 Hz, 1H), 2.49-2.53

(m, 1H), 2.6-2.7 (br, 1H), 2.75-2.80 (m, 1H), 3.45-3.50 (m, 2H), 7.4-7.8 (s, 1H),

11.4-11.9 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 25.7 (CH$_2$), 25.8 (CH$_3$), 26.2 (CH$_3$), 28.8

(CH$_2$), 29.5 (CH$_3$), 40.7 (CH$_2$), 41.5 (CH$_2$), 49.2 (CH$_2$), 71.9 (C), 112.8 (C), 154.8 (C);

MS (EI) 254 (M$^+$, 7), 239 (30), 208 (81), 178 (36), 110 (57), 70 (100). HRMS (EI,

magnetic field) Calcd for C$_{12}$H$_{22}$N$_4$O$_2$: 254.1743. Found: 254.1743.

1,7-Diaza-2-imino-6-methyl-3-*aci*-nitrobicyclo[4.3.0]nonane (20)

Yield (52 mg, 0.26 mmol, 26%). Colorless plates (recrystallized from acetonitrile). Mp

234-235 °C (dec.). IR (KBr) 3271, 3101, 1624, 1570, 1406 cm^{-1}; ^{1}H NMR (CD$_3$OD) δ

1.27 (s, 3H), 1.63 (ddd, J = 13.7, 12.8, 6.1 Hz, 1H), 2.19 (ddd, J = 12.8, 6.0, 1.8 Hz, 1H),

2.68 (ddd, J = 17.4, 13.7, 6.0 Hz, 1H), 3.05 (ddd, J = 17.4, 6.1, 1.9 Hz, 1H), 3.35-3.45

(m, 3H), 3.48-3.59 (m, 1H); ^{13}C NMR (CD$_3$OD) δ 22.3 (CH$_3$), 23.3 (CH$_2$), 32.6 (CH$_2$),

44.1 (CH_2), 46.8 (CH_2), 79.8 (C), 108.0 (C), 189.8 (C); MS (EI) 198 (M^+, 40), 181 (29), 166 (54), 152 (82), 85 (100). HRMS (EI, magnetic field) Calcd for $C_8H_{14}N_4O_2$: 198.1117. Found: 198.1113.

7-Ammonio-5-aza-1-cyano-2,2,4-trimethyl-4-heptenenitronate (17a)

To a solution of the keto nitrile **7** (184 mg, 1.0 mmol), in acetonitrile (15 mL), 1,2-diaminoethane (**14a**) (67 μL, 1.0 mmol) was added; a pale yellow solid was immediately precipitated, which was collected by filtration to give the imine **17a** (226 mg, 1.0 mmol, quant.). Pale yellow prisms (recrystallized from methanol). Mp 129-130 °C (dec.). IR (KBr) 2189, 1655, 1464, 1234, 1061 cm^{-1}; MS (EI) 226 (M^+, 28), 211 (95), 194 (94), 150 (97), 85 (100), 69 (99). HRMS Calcd for $C_{10}H_{18}N_4O_2$: 226.1430. Found: 226.1427. Anal. Calcd for $C_{10}H_{18}N_4O_2$: C, 53.08; H, 8.02; N, 24.76%. Found: C, 52.70; H, 8.18; N, 25.07%.

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