Pseudo-intramolecular Cyclization of α-Nitro-δ-keto Nitrile Leading to 2-Amino-3-nitro-1,4-dihydropyridines

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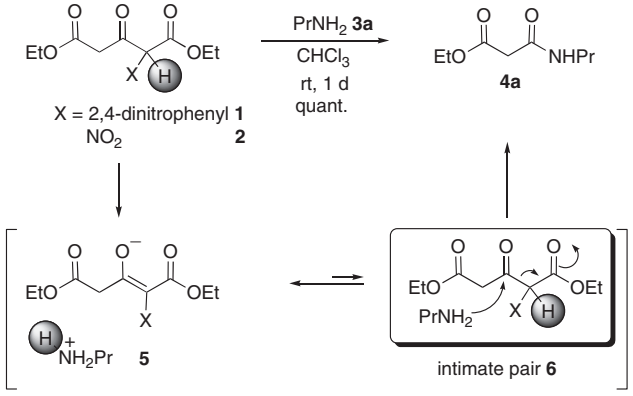
A novel concept—the pseudo-intramolecular process—is applied to the synthesis of multiply functionalized heterocyclic compounds. Acidic α-nitro-δ-keto nitrile easily forms an ammonium salt upon treatment with an amine. When the amine is liberated under equilibrium, an intimate pair, namely, a nucleophilic amine and an electrophilic keto nitrile are located close to each other, is formed; thus the amine efficiently attacks a cyano group of keto nitrile. As a result of subsequent cyclization, 1,4-dihydropyridines containing an amino and a nitro group at the vicinal positions as a partial structure are afforded.

Acyl groups of β-keto esters **1** and **2** are efficiently transferred to afford malonic acid amide esters **4** upon reaction with amines **3** (Scheme 1).[1] This transacylation proceeds via a pseudo-intramolecular process. The introduction of an aryl or a nitro group increases the acidity of an α-hydrogen, and thus, ammonium salt **5** is formed immediately after the addition of amine **3**. Salt **5** releases an amine under equilibrium to give an intimate pair **6**, in which a nucleophilic amine and an electrophilic keto ester are located close to each other. The spatial proximity of the reactants enhances the reactivity, and consequently, the reaction proceeds without any detectable by-product. Although the present reaction appears to proceed via an intramolecular process, it actually proceeds via an intermolecular process; this has been confirmed by NMR study and by carrying out reactions using amino alcohol in diluted conditions.[1]

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 not very difficult. From this viewpoint, we focused on



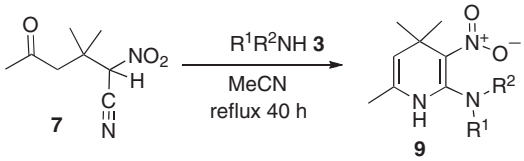
Scheme 1. Transacylation using α-substituted β-keto esters **1** and **2**.

α-nitro-δ-keto nitrile **7**[2] as a substrate for the present purpose and utilized it in the synthesis of vicinally functionalized heterocyclic compounds.

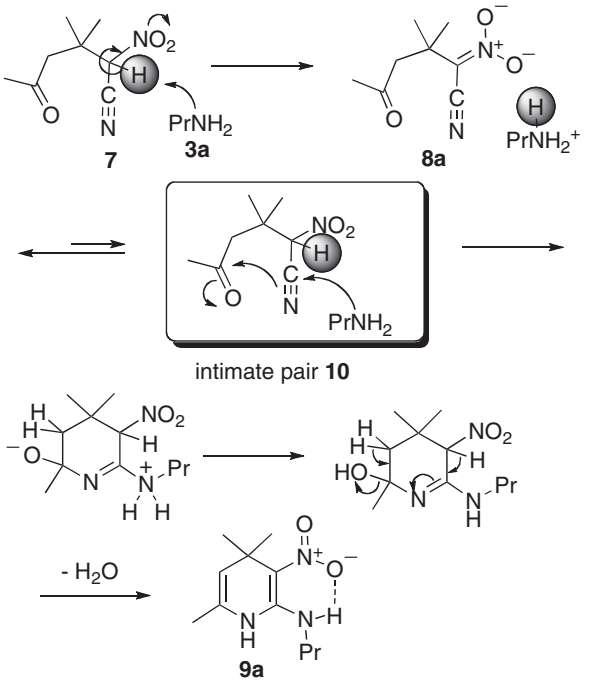
Keto nitrile **7** was easily transformed to ammonium salt **8a**[3] upon treatment with propylamine (**3a**); this was confirmed by ^{1}H NMR and IR spectra. Immediately after **3a** was added to a solution of keto nitrile **7** in acetonitrile-d_3, in the ^{1}H NMR spectrum, the singlet signal at 6.29 ppm assigned to an acidic α-proton immediately disappeared and the signals for a propyl group shifted to the downfield, indicating quantitative formation of ammonium salt **8a**. The absorption of a cyano group in the IR spectrum of **8a** was observed to be as strong as that of a carbonyl group; however, no cyano group absorption could be observed in the spectrum of starting keto nitrile **7**. The strong absorption of a cyano group is a typical feature of the α-cyanonitronate framework.[4]

Indeed, 3-nitro-2-propylamino-1,4-dihydropyridine (**9a**)[5] was isolated in 71% yield when an acetonitrile solution of **8a** was heated under reflux (Table 1, Run 1). Although the transacylation gave no by-product (Scheme 1), several kinds of unidentified products were formed in this reaction. This is presumably due to side reactions caused by multiple functionalities of keto nitrile **7**. The structure of dihydropyridine **9a** was determined on the basis of spectral and analytical data.[5] In the ^{1}H NMR, the singlet signal at 7.51 ppm and the triplet one at 12.12 ppm were exchangeable with D_2O; the former signal disappeared immediately and the latter one disappeared gradually. The different exchange rates indicate the presence of intramolecular hydrogen bonding between an amino and a nitro group. Furthermore, two *gem*-methyl groups were equivalently observed despite cyclic

Table 1. Synthesis of dihydropyridines **9**



Run	R^1	R^2		Yield/%
1	Et–CH_2	H	**a**	71
2	Pr–CH_2	H	**b**	65
3	Me_2CH	H	**c**	0
4	Me_3C	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	$(MeO)_2CH$–CH_2	H	**k**	74



Scheme 2. A plausible mechanism.

structure, which suggests the dihydropyridine ring is closely flat or undergoes a facile ring flipping on the NMR time scale.

A plausible mechanism for the present pseudo-intramolecular reaction is illustrated in Scheme 2. When salt **8a** is heated, the amine is removed under equilibrium giving an intimate pair **10**. The liberated amine attacks an immediate cyano group, and then the cyano group attacks an acyl group to form a six-membered ring. Subsequent dehydration and proton transfer lead to the formation of dihydropyridine **9a**.

Butylamine (**3b**) reacted in a similar manner with keto nitrile **7** (Table 1, Run 2), however, bulkier amines such as isopropylamine (**3c**), *tert*-butylamine (**3d**), aniline (**3e**), and dipropylamine (**3f**) did not cause cyclizations (Runs 3–6).[6] The high sensitivity to steric hindrance is due to the congestion around the reaction site of intimate pair **10**. Hence, the insertion of a methylene group as a spacer between the bulky group and the amino function facilitated the cyclization to afford dihydropyridines **9g–9k**,[12] respectively (Runs 7–11).

The frameworks containing both donor and acceptor moieties are often found as partial structures of functional materials such as molecular electronic devices,[7] chromophores for dyes,[8] and nonlinear optics.[7,8] Although 1,4-dihydropyridines containing an amino and a nitro group can also be used in insecticides[9] and central nervous system potassium channel modulators,[10] this framework is synthesized by a single procedure only, in which nitroketene aminals (1,1-diamino-2-nitroethenes) are used as building blocks,[11] however, a drawback of this method is that it is difficult to modify an amino moiety. In contrast, in our method, an amino group can be easily modified by changing amine **3**. Hence the present reaction will supplement the conventional one.

As mentioned thus far, multiply functionalized 1,4-dihydropyridines are prepared via pseudo-intramolecular process. This concept is applicable to the syntheses of various polyfunctionalized compounds.

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2 Keto nitrile **7** is easily prepared from nitroisoxazolone in one pot, in which intermediate cyano-*aci*-nitroacetate reacts with only acetone leading to β,β-dimethyl-δ-keto nitrile. Experimental details are shown in the following literature. a) N. Nishiwaki, T. Nogami, M. Ariga, *Heterocycles* **2008**, *75*, 675. b) N. Nishiwaki, T. Nogami, C. Tanaka, F. Nakashima, Y. Inoue, N. Asaka, Y. Tohda, M. Ariga, *J. Org. Chem.* **1999**, *64*, 2160.

3 To a solution of keto nitrile **7** (92 mg, 0.5 mmol) in acetonitrile (10 mL), propylamine (**3a**) (41 μL, 0.5 mmol) was added. After stirring at room temperature for 10 min., the solvent was evaporated to afford propylammonium salt **8a** (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).

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5 To a solution of keto nitrile **7** (92 mg, 0.5 mmol) in acetonitrile (10 mL), propylamine (**3a**) (41 μL, 0.5 mmol) was added, and heated under reflux for 40 h. After removal of the solvent, the residue was treated with column chromatography on silica gel to afford dihydropyridine **9a** (eluted with ethyl acetate, 80 mg, 0.35 mmol, 71%). Pale yellow needles (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) m/z; 226 ($[M + 1]^+$100). Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65%. Found: C, 58.49; H, 8.51; N, 18.59%.

6 Formations of ammonium salts **8b–8f** were confirmed by ^{1}H NMR.

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