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Safe Cyano(nitro)methylating Reagent –Michael Addition of Cyano-*aci*-nitroacetate Leading to δ -Functionalized α -Nitronitriles–

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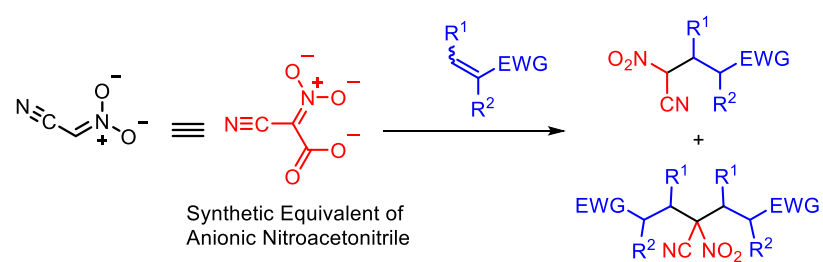
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ABSTRACT

A practical, convenient, and safe cyano(nitro)methylation method was developed, in which cyano-*aci*-nitroacetate served as a synthetic equivalent of anionic nitroacetonitrile. A control of the single/double Michael additions was achieved, which enabled the synthesis of unsymmetrical double Michael adducts. Moreover, the Michael adducts can be used as precursors of pyridine and naphthyridine frameworks.

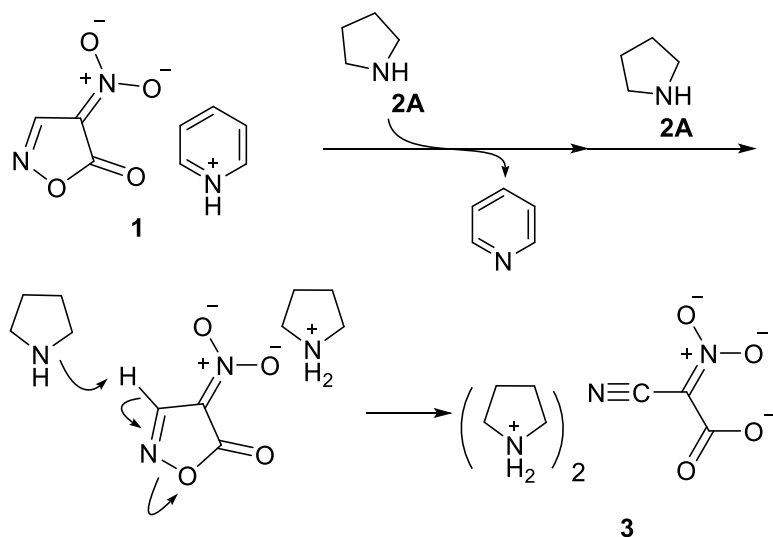
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INTRODUCTION

Nitroacetonitrile (NAN), a methylene connected with a nitro and a cyano functionalities, is used as a cyano(nitro)methylation agent, which serves as a building block for the synthesis of versatile polyfunctionalized compounds.^{1,2} Indeed, several reactions of NAN have been reported, such as Knoevenagel condensation with a ketone/aldehyde, addition reactions to polar multiple bonds, and Michael addition.¹⁻³ In spite of the great potential of NAN, it has not been widely used in organic syntheses because of its low thermodynamic stability and preparative methods for synthesizing this reagent suffer from somewhat troublesome manipulations and poor yield performance.⁴ Semenov overcame these drawbacks by using a two phase system, by which NAN is prepared in good yield.⁵ However, Thomas recently alerted on the explosive property of the NAN.⁶ In this context, the development of a safe alternative cyano(nitro)methylation agent is required.

Meanwhile, we have reported that the pyridinium salt of nitroisoxazolone **1** undergoes the ring opening reaction quantitatively under mild conditions upon treatment with pyrrolidine (**2A**) to give dianionic cyano-*aci*-nitroacetate **3**, which possesses three different functional groups on the same carbon atom (Scheme 1).⁷ The dianion **3** is thermally stable and is very soluble in common organic solvents, such as benzene, chloroform and ethanol. Since the dianion **3** is regarded as the masked framework of NAN, the above-mentioned features enabled its use as the easily treatable synthetic equivalent of the anionic form of NAN accompanied by decarboxylation. Indeed, the dianion **3** reacts with ketones and aldehydes to afford polyfunctionalized nitriles, such as glutaronitriles,^{7a} α -nitro- α,β -unsaturated nitriles^{7a} and α -nitro- δ -keto nitrile.^{7b} Herein we provide a new synthetic protocol for δ -functionalized α -nitronitriles **5** and **6** by a Michael addition reaction of cyano-*aci*-nitroacetate **3** to functionalized alkenes **4**. Additionally, we also demonstrate a single step conversion of the Michael adduct to a pyridine and a naphthyridine frameworks using the polyfunctionality of the Michael adducts.



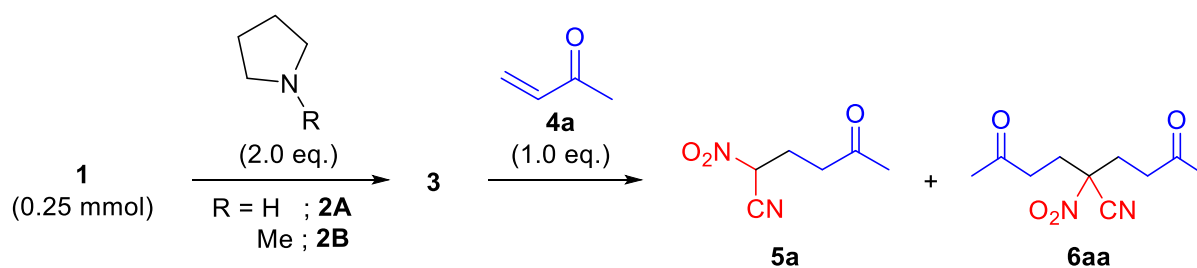
Scheme 1 Generation of cyano-*aci*-nitroacetate **3** derived from nitroisoxazolone **1**.

RESULTS AND DISCUSSION

Initially, the reaction of dianion **3** with 3-buten-2-one (**4a**) was chosen as a model reaction, and *N*-methylpyrrolidine (**2B**) was used as a base instead of **2A** to avoid the undesired Michael addition reaction of the amine to **4a** (Scheme 2). When the dianion **3** was subjected to reaction with equimolar **4a** in acetonitrile at 30 °C for 2 h, both single and double Michael adducts **5a**⁸ and **6aa**⁹ were obtained in 35 and 38% yields, respectively (Table 1, entry 1). In order to control the single/double Michael additions, the solvent, reaction time, and temperature were investigated (Table 1). Although the reaction proceeded efficiently in either nonpolar benzene or polar ethanol, the ratio of **5a**/**6aa** was not affected by the polarity of the solvent (entries 2-3). Chloroform was found to be somewhat effective for the predominant single addition; however, all attempts for complete synthesis of the single Michael adduct **5a** failed (entries 5-8). To our great surprise, the single Michael adduct **5a** was obtained as a sole product when **2A** was used as a base (entry 9). This suppression of the second Michael addition is probably due to the competitive Michael addition of **2A**, and the adduct releases **4a** gradually under equilibrium, which keeps the concentration of **4a** low in the reaction mixture (Scheme 2).¹⁰ On the other hand, double adduct **6aa** was exclusively obtained in 94% yield by using

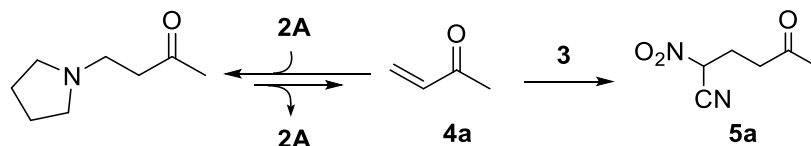
5 equivalents of **4a**. Consequently, the control of the single/double Michael addition was successfully achieved.

Table 1 Optimization of the reaction conditions for Michael addition of cyano-*aci*-nitroacetate **3** to 3-buten-2-one (**4a**).



Entry	Amine	Solv.	Temp. / °C	Time / h	Yield /% ^{a,b}			Ratio 5a:6aa
					Total	5a	6aa	
1	2B	MeCN	30	2	73	35	38	48:52
2	2B	PhH	30	2	100	40	60	40:60
3	2B	EtOH	30	2	93	40	52	44:56
4	2B	CHCl ₃	30	2	100	56	44	56:44
5	2B	CHCl ₃	30	0.5	56	38	18	68:32
6	2B	CHCl ₃	30	6	100	57	43	57:43
7	2B	CHCl ₃	0	2	39	19	20	49:51
8	2B	CHCl ₃	60	2	100	61	39	61:39
9	2A	CHCl ₃	30	2	100	>99	–	100:0
10 ^c	2B	CHCl ₃	50	2	94	–	94	0:100

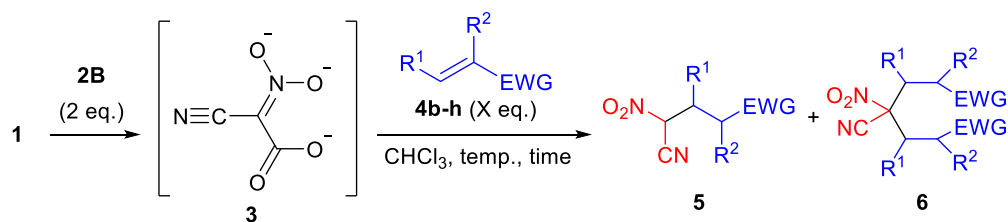
^a Determined by ¹H NMR. ^b Based on **4a**. ^c Five equivalents of **4a** were used.

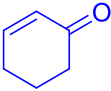
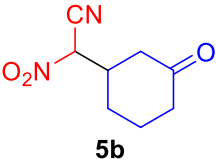
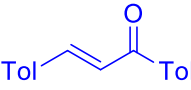
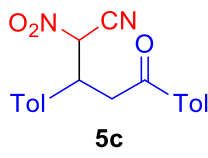
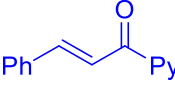
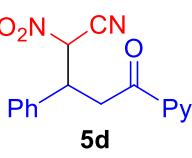
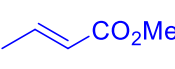
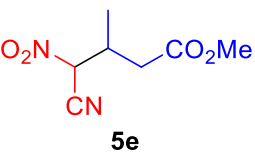
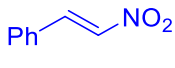
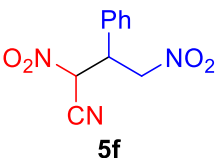
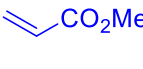
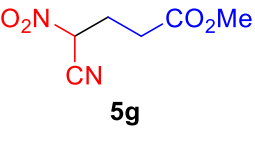
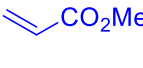
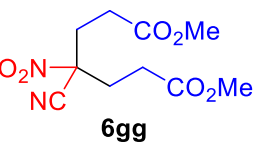
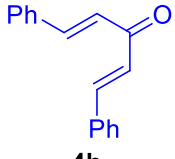
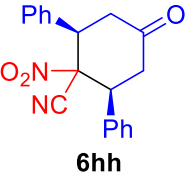


Scheme 2 A plausible mechanism of reaction of **4a** and **3** using pyrrolidine **2A** as a base.

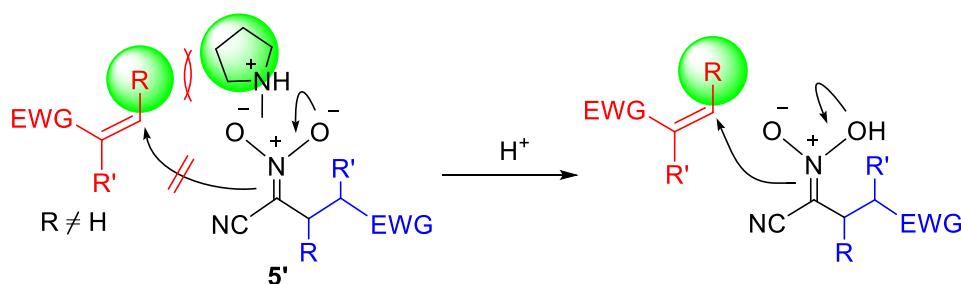
To explore the scope and limitations of the Michael addition reaction of **3**, various Michael acceptors were employed. The cyclic enone **4b**, the aromatic enones **4c** and **4d**, methyl crotonate **4e**, and the nitrostyrene **4f** underwent Michael additions to afford the corresponding single adducts **5b-f** in high to excellent yields without any detectable double adducts **6bb-ff** (Table 2, entries 1-5). These results suggested the substituent at the β -position of Michael acceptors suppressed the second Michael addition reaction. It can be attributed to the bulkiness of the counter cation which presents nearby the single adduct intermediate **5'** (Scheme 3). On the other hand, the reaction of **3** with methyl acrylate **4g**, which has no substituent at the β -position, gave the double adduct **6gg** in 9% yield besides the single adduct **5g** (49%) (entry 6). As expected, the double adduct **6gg** was afforded in 82% yield as a sole product upon treatment of **3** with 5 equivalents of **4g** (entry 7). In the case of the dibenzylideneacetone **4h**, functionalized cyclohexanone **6hh**¹¹ was obtained in 84% yield (entry 8).

Table 2 Reaction of cyano-*aci*-nitroacetate **3** to Michael acceptors **4b-h**.



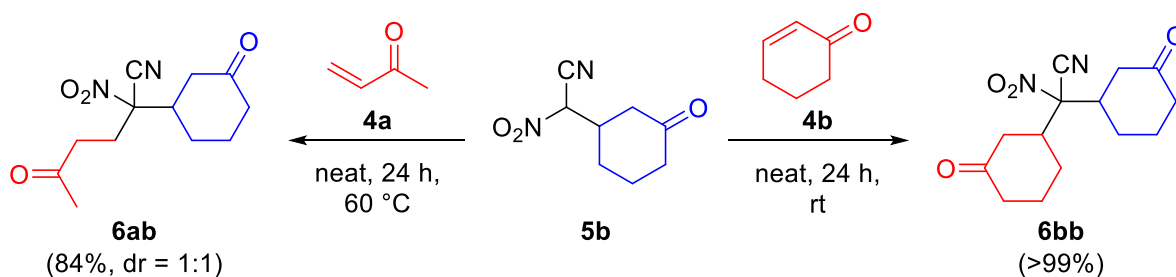
Entry	Substrates 4	Eq.	Temp. /°C	Time /h	Products 5	Yield /% ^{a,b}
1	 4b	1.0	60	4	 5b	>99% dr = 1:1
2	 4c^c	1.0	60	20	 5c	87% dr = 5:1
3	 4d^d	1.0	40	20	 5d	78% dr = 1.7:1
4	 4e^e	5.0	80	24	 5e	61% dr = 1.5:1
5	 4f	1.0	50	12	 5f	75% ^f dr = 1.3:1
6	 4g	1.0	50	24	 5g	49% (6gg , 9%)
7	 4g	5.0	60	24	 6gg	82% (5g , 0%)
8	 4h	1.0	80	24	 6hh	81% ^g

^a Isolated yield. The diastereomers were not separable, and this represents the total yield. ^b The diastereomeric ratio was determined by ¹H NMR of the crude product. ^c Tol: 4-MeC₆H₄. ^d Py: 2-Pyridyl. ^e Ethanol was used as a solvent. ^f The yield was determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard without isolation of **5f** because of its instability. ^g Isolated yield for *cis* isomer after purified by recrystallization.



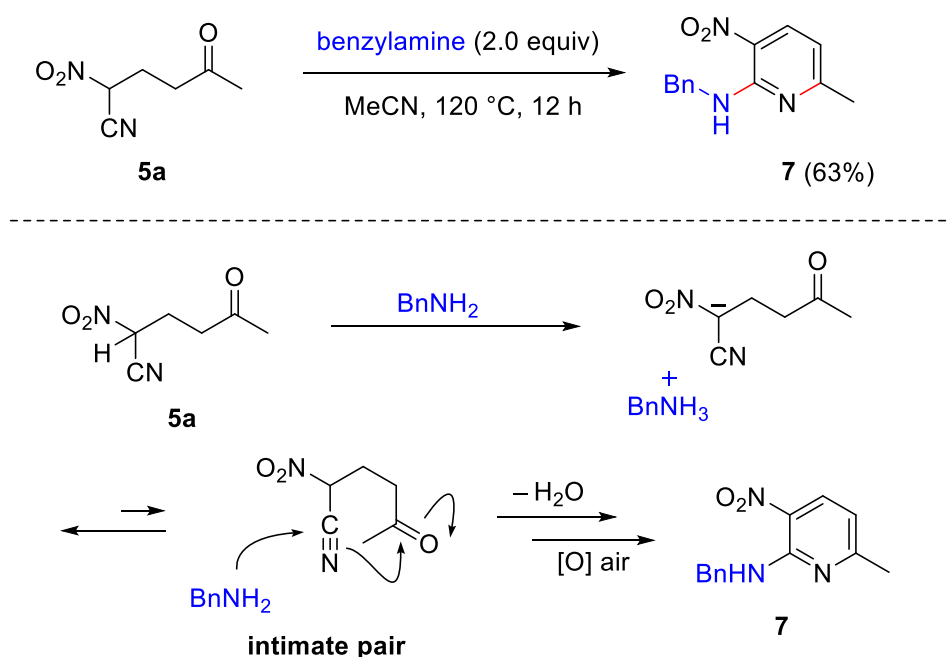
Scheme 3 Steric hindrance of the Michael acceptor preventing the second addition.

As mentioned above, double Michael adduct **6bb** was not detected even under the severe conditions; employing the excess amounts of **4b**, higher temperature (>150 °C), and longer reaction time (48 h). Contrary to this, double adduct **6bb** was obtained quantitatively, when a mixture of isolated single adduct **5b** and the excess amounts of **4b** was left standing without solvent at ambient temperature for 24 h even in the absence of an amine (Scheme 4, right). This is probably because the congestion around the active methine group is relieved by the removal of the counter cation through acidification (Scheme 3). This interesting result encouraged us to investigate the synthesis of an unsymmetrical double Michael adducts. Indeed, desired unsymmetric double Michael adducts **6ab** were obtained in high yield (Scheme 4, left).



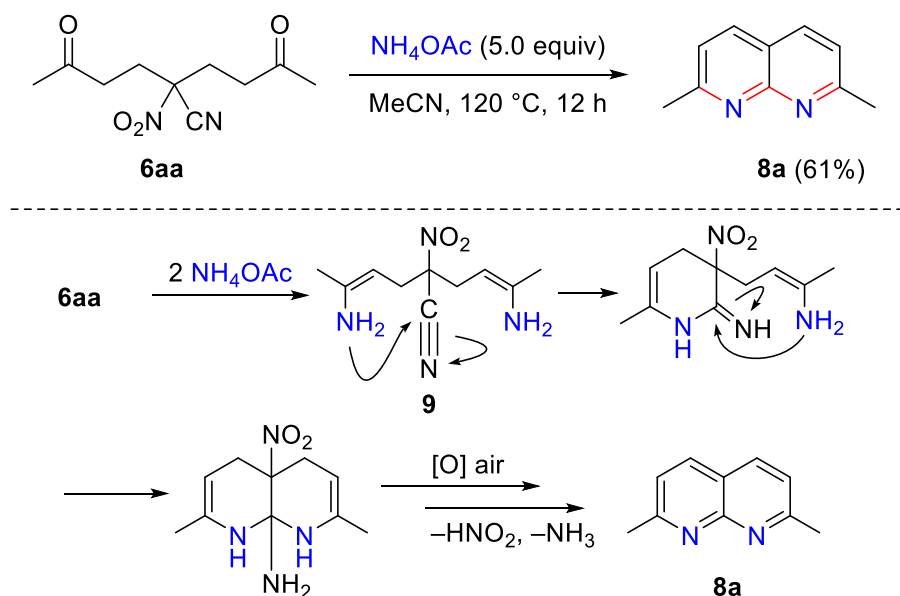
Scheme 4 Reaction of single adduct **5b** to Michael acceptors **4a,b**.

Both the single and double Michael adducts are useful synthetic precursors due to their polyfunctionality. For example, single adduct **5a**, which has both an acidic hydrogen and an appropriate functionality, can be used as a substrate for the pseudo-intramolecular process.¹² Indeed, 63% of 2-amino-3-nitropyridine **7**¹² was formed when a mixture of keto nitrile **5a** and 2 equivalents of benzylamine in acetonitrile was heated in a sealed tube at 120 °C for 12 h (Scheme 5).¹³ The reaction proceeds in a similar manner to the dihydropyridine synthesis, reported previously.¹² The ammonium salt, immediately formed upon treatment of the single adduct **5a** with an amine, liberates the amine under equilibrium. In this stage, the amine is in close proximity to the cyano group of **5a** (intimate pair), and attacks the cyano group to construct a six-membered ring as a result of the tandem cyclization. The subsequent dehydration and air oxidation gives 2-amino-3-nitropyridine **7**.¹³

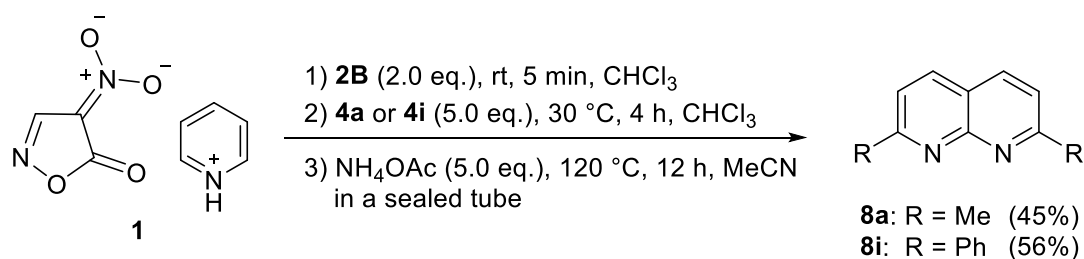


Scheme 5 Synthesis of vicinally functionalized pyridine **7** from single adduct **5a** via pseudo-intramolecular process.

Additionally, the double Michael adduct **6aa** provided 2,7-dimethyl-[1,8]-naphthyridine (**8a**)¹⁴ in 61% yields upon heating with 5 equivalents of ammonium acetate in acetonitrile at 120 °C for 12 h. A plausible mechanism is also depicted in Scheme 6. The reaction between the two carbonyl groups with ammonium acetate gives the intermediate enamine **9**, an intramolecular double cyclization followed by aromatization to give the product **8a**. To enhance the utility of this method, we also examined the synthesis of [1,8]-naphthyridine from the pyridinium salt of isoxazolone **1** and Michael acceptor **4a** without purification of the double Michael adduct (Scheme 7). After normal workup of Michael addition reaction, the residue was heated with 5 equivalents of NH₄OAc to afford [1,8]-naphthyridine **8a** in 45% overall yield. This method was also applicable to benzoyl ethene **4i** (R¹=R²=H, EWG=PhCO) leading to 2,7-diphenylnaphthyridine **8i**¹⁴ directly with 56% yield. The [1,8]-naphthyridine skeleton is widely found in a biologically active substances¹⁶ and used as a ligand for many metal complexes.¹⁷ This reaction is highly useful because the naphthyridine skeleton is constructed in a single step which was not easily achieved by conventional methods.^{18, 19} Additionally, this method is multi-component reaction which also fits the idea of highly efficient green synthesis methodology.²⁰



Scheme 6 A concise construction of [1,8]-naphthridine **8** via double cyclization/aromatization procedure from diketone **6aa**.



Scheme 7 Synthesis of [1,8]-naphthridine **8** from the pyridinium salt of nitroisoxazolone **1**.

CONCLUSIONS

In conclusion, we have demonstrated cyano-*aci*-nitroacetate **3** derived from nitroisoxazolone **1** can be regarded as a practically usable and safe cyano(nitro)methylation agent, which reacts with Michael acceptors **4** to afford both single/double adducts **5** and **6**. In addition, the synthesis of an unsymmetrical double Michael adduct **6ab** was demonstrated through the reaction of isolated single

adduct **5b** with Michael acceptor **4a** without solvent. As one of the applications of the single Michael adduct **5a**, polyfunctionalized pyridine **7** was easily prepared in good yield via a pseudo-intramolecular process. Additionally, the concise, double Michael addition reaction, followed by intramolecular double cyclization reaction upon treatment with ammonium acetate was successfully achieved to afford [1,8]-naphthyridine **8**.

EXPERIMENTAL SECTION

Typical Procedure for Michael Addition Reaction of Cyano-*aci*-nitroacetate with Michael Acceptor 4. To a solution of pyridinium salt **1** (0.25 mmol) in chloroform (2 mL), amine **2B** (0.5 mmol) was added and the resultant mixture was stirred several minutes until the salt was completely dissolved. And then Michael acceptor **4** was added. After stirring of the solution for 4 h at 30 °C, 1M HCl solution (1.5 mL) was added, and extracted with chloroform (2 × 5 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The yield and diastereomer ratio of the product were determined by ¹H NMR integration of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. Further purification was achieved by flash column chromatography on silica gel (hexane/EtOAc = 95/5). All products were isolated in almost pure form but not stable to the elemental analysis.

3-(Cyanonitromethyl)cyclohexan-1-one (5b): (46.0 mg, >99%); (1:1 diastereomer mixture), yellow oil. Diastereomer A: ¹H NMR (400 MHz, CDCl₃) δ 1.80–1.64 (m, 2H), 2.10–1.91 (m, 1H), 2.21–2.17 (m, 1H), 2.51–2.20 (m, 4H), 2.98–2.80 (m, 1H), 5.36 (d, *J* = 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.6 (CH₂), 26.2 (CH₂), 40.5 (CH₂), 40.9 (CH), 42.2 (CH₂), 80.4 (CH), 110.4 (C), 206.1 (C); Diastereomer B: ¹H NMR (400 MHz, CDCl₃) δ 1.80–1.64 (m, 2H), 2.10–1.91 (m, 1H), 2.21–2.17 (m, 1H), 2.51–2.20 (m, 4H), 2.98–2.80 (m, 1H), 5.27 (d, *J* = 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.8 (CH₂), 27.4 (CH₂), 40.4 (CH₂), 40.9 (CH), 43.3 (CH₂), 80.3 (CH), 110.5 (C), 206.1 (C); IR (neat) 1715, 1568, 1350 cm⁻¹. HRMS (CI, Magnetic field) *m/z* calcd. for C₈H₁₁N₂O₃:

183.0770 (M + H)⁺, found 183.0770.

3-Cyanonitromethyl-1,3-bis(4-methylphenyl)-1-propanone (5c): (70.8 mg, 87%); (5:1 diastereomer mixture), white solid, mp 126–127 °C. Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 2.34 (s, 3H), 2.43 (s, 3H), 3.57–3.68 (m, 2H), 4.40–4.45 (m, 1H), 6.20 (d, *J* = 5.2 Hz 1H), 7.17–7.19 (m, 2H), 7.22–7.30 (m, 4H), 7.83–7.87 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.1 (CH₃), 21.7 (CH₃), 40.1 (CH), 42.3 (CH₂), 80.3 (CH), 110.9 (C), 128.0 (CH), 128.2 (CH), 129.5 (CH), 130.1 (CH), 131.8 (C), 133.3 (C), 139.2 (C), 145.2 (C), 195.7 (C); Minor isomer: ¹H NMR (400 MHz, CDCl₃) δ 2.33 (s, 3H), 2.42 (s, 3H), 3.57–3.70 (m, 2H), 4.40–4.45 (m, 1H), 5.75 (d, *J* = 5.2 Hz 1H), 7.19–7.22 (m, 2H), 7.24–7.30 (m, 4H), 7.83–7.85 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.1 (CH₃), 21.7 (CH₃), 38.9 (CH), 43.3 (CH₂), 80.2 (CH), 111.3 (C), 127.8 (CH), 128.2 (CH), 129.6 (CH), 130.0 (CH), 132.2 (C), 133.6 (C), 139.1 (C), 144.9 (C), 195.6 (C); IR (KBr) 1684, 1572, 1410 cm⁻¹. HRMS (CI, Magnetic field) *m/z* calcd. for C₁₉H₁₉N₂O₃: 323.1396 (M + H)⁺, found 323.1394.

3-Cyanonitromethyl-1-(2-pyridyl)-3-phenyl-1-propanone (5d): (57.5 mg, 78%); (1.7:1 diastereomer mixture), yellow oil (The isolated product was easily decomposed by heating over 60 °C). Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 3.88 (dd, *J* = 9.2, 19.1 Hz, 1H), 4.07 (dd, *J* = 5.0, 19.1 Hz, 1H), 4.44 (ddd, *J* = 5.0, 5.7, 9.2 Hz 1H), 6.10 (d, *J* = 5.7 Hz, 1H), 7.33–7.40 (m, 5H), 7.51–7.53 (m, 1H), 7.82–7.85 (m, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 8.67–8.69 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 39.5 (CH₂), 42.8 (CH), 80.4 (CH), 110.8 (C), 122.0 (CH), 128.0 (CH), 128.2 (CH), 129.2 (CH), 129.2 (CH), 134.9 (C), 137.2 (CH), 149.2 (CH), 152.2 (C), 198.4 (C); Minor isomer: ¹H NMR (400 MHz, CDCl₃) δ 3.88 (dd, *J* = 6.7, 18.6 Hz, 1H), 4.18 (dd, *J* = 8.0, 18.6 Hz, 1H), 4.44 (ddd, *J* = 5.5, 6.7, 8.0 Hz 1H), 5.70 (d, *J* = 5.5 Hz, 1H), 7.33–7.40 (m, 5H), 7.51–7.53 (m, 1H), 7.82–7.85 (m, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.67–8.69 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 38.4 (CH₂), 43.6 (CH), 80.6 (CH), 111.3 (C), 122.0 (CH), 127.8 (CH), 128.1 (CH), 129.0 (CH), 129.4 (CH), 135.4 (C), 137.1 (CH), 149.1 (CH), 152.3 (C), 197.7 (C); IR (neat) 1691, 1571, 1396 cm⁻¹. HRMS (CI, Magnetic field) *m/z* calcd. for C₁₆H₁₄N₃O₃: 296.1035 (M + H)⁺, found 296.1033.

Methyl 4-cyano-3-methyl-4-nitrobutanoate (5e): (28.5 mg, 61%); (1.5:1 diastereomer mixture),

yellow oil. Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.19 (d, $J = 6.8$ Hz, 3H), 2.48–2.56 (m, 2H), 3.09–3.16 (m, 1H), 3.73 (s, 3H), 5.84 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 15.4 (CH_3), 33.6 (CH), 36.6 (CH_2), 52.4 (CH_3), 80.2 (CH), 110.5 (C), 171.1 (C); Minor isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.25 (d, $J = 6.9$ Hz, 3H), 2.54–2.66 (m, 2H), 2.97–3.02 (m, 1H), 3.72 (s, 3H), 5.59 (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.1 (CH_3), 34.2 (CH), 36.1 (CH_2), 52.3 (CH_3), 80.2 (CH), 111.3 (C), 171.0 (C); IR (neat) 1730, 1580, 1337 cm^{-1} . HRMS (CI, Magnetic field) m/z calcd. for $\text{C}_7\text{H}_{11}\text{N}_2\text{O}_4$: 187.0719 ($\text{M} + \text{H}$) $^+$, found 187.0722.

2,4-Dinitro-3-phenylbutanenitrile (5f): (NMR yield, 75%); (1.3:1 diastereomer mixture), yellow oil. Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 4.56–4.62 (m, 1H), 4.86–5.00 (m, 1H), 5.01–5.05 (m, 1H), 5.96 (d, $J = 5.6$ Hz, 1H), 7.25–7.31 (m, 2H), 7.40–7.44 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 44.8 (CH), 74.6 (CH_2), 78.3 (CH), 109.9 (C), 128.0 (CH), 129.9 (CH), 130.3 (C), 130.4 (CH). Minor isomer: ^1H NMR (400 MHz, CDCl_3) δ 4.48–4.51 (m, 1H), 4.86–5.00 (m, 1H), 5.01–5.05 (m, 1H), 5.76 (d, $J = 5.6$ Hz, 1H), 7.25–7.31 (m, 2H), 7.40–7.44 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 45.3 (CH), 74.4 (CH_2), 78.1 (CH), 110.3 (C), 127.7 (CH), 130.0 (CH), 130.3 (CH), 130.8 (C). Satisfactory analytical data were not given because of the instability of **5f**.

Methyl 4-cyano-4-nitro-butanoate (5g): (21.2 mg, 49%); brown oil. ^1H NMR (400 MHz, CDCl_3) δ 2.54–2.71 (m, 4H), 3.73 (s, 3H), 5.59 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 27.6 (CH_2), 28.9 (CH_2), 52.5 (CH_3), 74.8 (CH), 111.7 (C), 171.4 (C); IR (neat) 1738, 1601, 1370 cm^{-1} . HRMS (CI, Magnetic field) m/z calcd. for $\text{C}_6\text{H}_9\text{N}_2\text{O}_4$: 173.0562 ($\text{M} + \text{H}$) $^+$, found 173.0563.

5-Cyano-5-nitro-nonane-2,8-dione (6aa): (53.3 mg, 94%); white solid, mp 77–78 $^\circ\text{C}$ (from hexane/chloroform). ^1H NMR (400 MHz, CDCl_3) δ 2.18 (s, 6H), 2.36–2.47 (m, 2H), 2.48–2.61 (m, 4H), 2.71–2.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 30.0 (CH_3), 32.4 (CH_2), 38.1 (CH_2), 88.9 (C), 113.8 (C), 204.1 (C); IR (KBr) 1703, 1560, 1370 cm^{-1} . HRMS (CI, Magnetic field) m/z calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_4$: 227.1032 ($\text{M} + \text{H}$) $^+$, found 227.1033.

Dimethyl 4-cyano-4-nitro-heptanedioate (6gg): (53.0 mg, 82%); yellow solid, mp 33–34 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 2.39–2.54 (m, 4H), 2.61–2.71 (m, 4H), 3.72 (s, 6H); ^{13}C NMR (100 MHz,

CDCl₃) δ 29.2 (CH₂), 33.7 (CH₂), 52.5 (CH₃), 88.5 (C), 113.3 (C), 170.8 (C); IR (KBr) 1738, 1568, 1381 cm⁻¹. HRMS (CI, Magnetic field) m/z calcd. for C₁₀H₁₅N₂O₆: 259.0930 (M + H)⁺, found 259.0931.

***cis*-4-Cyano-4-nitro-3,5-diphenylcyclohexanone (6hh)**: After workup, 13:1 of *cis:trans* mixture was obtained and *cis* isomer was isolated by recrystallization from hexane/chloroform (64.9 mg, 81%); brown solid, mp 177–178 °C. ¹H NMR (400 MHz, CDCl₃) δ 2.89 (dd, J = 4.0, 15.6 Hz, 2H), 3.32 (dd, J = 14.5, 15.6 Hz, 2H), 4.08 (dd, J = 4.0, 14.5 Hz, 2H), 7.33–7.37 (m, 2H), 7.38–7.40 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 43.7 (CH₂), 50.5 (CH), 97.5 (C), 111.5 (C), 128.1 (CH), 129.6 (CH), 130.0 (CH), 133.4 (C), 202.3 (C); IR (KBr) 1717, 1563, 1361 cm⁻¹. HRMS (CI, Magnetic field) m/z calcd. for C₁₉H₁₇N₂O₃: 321.1239 (M + H)⁺, found 321.1240.

Typical Procedure for Michael Addition Reaction of Single Adduct 5b with 4a,b. To a single adduct **5b** (0.25 mmol), Michael acceptor **4** (0.3 mmol) was added. The resulting mixture was stirred for 24 h at 60 °C, and unreacted Michael acceptor was evaporated under vacuo to afford pure double adduct **6**. Further purification was performed by recrystallization from hexane/chloroform.

3-(1-Cyano-1-nitro-4-oxopentyl)-cyclohexanone (6ab): (53.1 mg, 84%); (1:1 diastereomer mixture), white solid, mp 124–125 °C. Diastereomer A: ¹H NMR (400 MHz, CDCl₃) δ 1.60–1.77 (m, 2H), 2.17 (s, 3H), 2.14–2.78 (m, 11H); ¹³C NMR (100 MHz, CDCl₃) δ 23.8 (CH₂), 26.4 (CH₂), 30.0 (CH₃), 30.3 (CH₂), 38.1 (CH₂), 40.4 (CH₂), 42.5 (CH₂), 45.6 (CH), 93.8 (C), 112.8 (C), 204.2 (C), 206.0 (C); Diastereomer B: ¹H NMR (400 MHz, CDCl₃) δ 1.60–1.77 (m, 2H), 2.15 (s, 3H), 2.14–2.78 (m, 11H); ¹³C NMR (100 MHz, CDCl₃) δ 23.5 (CH₂), 26.5 (CH₂), 30.0 (CH₃), 30.3 (CH₂), 38.0 (CH₂), 40.5 (CH₂), 42.3 (CH₂), 45.5 (CH), 93.9 (C), 112.6 (C), 204.0 (C), 206.1 (C); IR (KBr) 1713, 1562, 1355 cm⁻¹. HRMS (CI, Magnetic field) m/z calcd. for C₁₉H₁₅Cl₂NO: 343.0531 (M + H)⁺, found 343.0534.

Cyanonitro-di-(3-oxocyclohexyl)methane (6bb): (70.1 mg, >99%); pale yellow solid, mp 145–146 °C. ¹H NMR (400 MHz, CDCl₃) δ 1.45–1.61 (m, 1H), 1.62–1.83 (m, 3H), 1.84–1.95 (m, 1H), 2.15–2.38 (m, 7H), 2.44–2.65 (m, 3H), 2.68–2.78 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 23.7

(CH₂), 23.8 (CH₂), 26.1 (CH₂), 27.0 (CH₂), 40.6 (CH), 40.7 (CH), 41.1 (CH₂), 41.9 (CH₂), 42.3 (CH₂), 42.5 (CH₂), 97.2 (C), 112.9 (C), 205.6 (C), 205.7 (C); IR (KBr) 1715, 1562, 1348 cm⁻¹. HRMS (CI, Magnetic field) *m/z* calcd. for C₁₄H₁₉N₂O₄: 279.1345 (M + H)⁺, found 279.1344.

Procedure for the Synthesis of 2-amino-3-nitropyridine 7. To a solution of single adduct **5b** (0.25 mmol) in acetonitrile (3 mL), benzylamine (0.5 mmol) was added, and heated at 120 °C in a sealed tube for 12 h. After removal of the solvent, the residue was treated with column chromatography on silica gel to afford 2-amino-3-nitropyridine **7** (38.2 mg, 63%, eluted with dichloromethane). The product **7** was identified by comparison of spectral data with authentic sample.

Synthesis of [1,8]-naphthyridine 8 from Double Michael Adduct 6. To a solution of double adduct **6aa** (0.20 mmol) in acetonitrile (3 mL), ammonium acetate (1.0 mmol) was added, and heated at 120 °C in a sealed tube for 12 h. After removal of the solvent, the residue was treated with column chromatography on silica gel to afford [1,8]-naphthyridine **8a**¹⁴ (19.4 mg, 61%, eluted with hexane/EtOAc = 80/20). The product **8a** was identified by comparison of NMR spectra to those reported in the literature.

Synthesis of [1,8]-naphthyridine 8 from Pyridinium Salt 1. To a solution of pyridinium salt **1** (0.25 mmol) in chloroform (2 mL), amine (0.5 mmol) was added and the resultant mixture was stirred several minutes until the salt was completely dissolved. And then Michael acceptor **4** (1.3 mmol) was added. After stirring of the solution for 4 h at 30 °C, 1M HCl solution (1.5 mL) was added, and extracted with chloroform (2 × 5 mL). The combined organic layer were dried over MgSO₄, filtered, and evaporated to give double Michael adduct **6** which was used for the next step without purification. The solution of **6** in acetonitrile (3 mL), ammonium acetate (1.25 mmol) was added. The mixture was stirred at 120 °C in a sealed tube for 12 h. After removal of the solvent, the residue was treated with column chromatography on silica gel to afford [1,8]-naphthyridine **8a**¹⁴ (17.8 mg, 45%, eluted with hexane/EtOAc = 80/20) and **8i**¹⁵ (39.5 mg, 56%, eluted with hexane/EtOAc = 80/20), respectively. The product **8i** was identified by comparison of NMR spectra to those reported in the literature.

ASSOCIATED CONTENT:

Supporting Information

^1H and ^{13}C NMR spectra of products **5b-5g**, **6aa**, **6ab**, **6bb**, **6hh**, and **6gg**, and crystallographic data of **6aa**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (10) Michael adduct between pyrrolidine **2a** with **4a** was detected by ¹H NMR spectrum, see Supporting Information.
- (11) It is reported that *cis* isomer is thermodynamically stable and predominantly formed in the case of two substituents at the 1-position of 2,5-diphenylcyclohexan-4-one were different. Indeed, the *cis* structure was assigned by the comparison of ¹H NMR spectra between **6hh** and a reported analogue. For reference, see: Rowland, A. T.; Filla, S. A.; Coutlangus, M. L.; Winemiller, M. D.; Chamberlin, M. J.; Czulada, G.; Johnson, S. D. *J. Org. Chem.* **1998**, *63*, 4359–4365.
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