

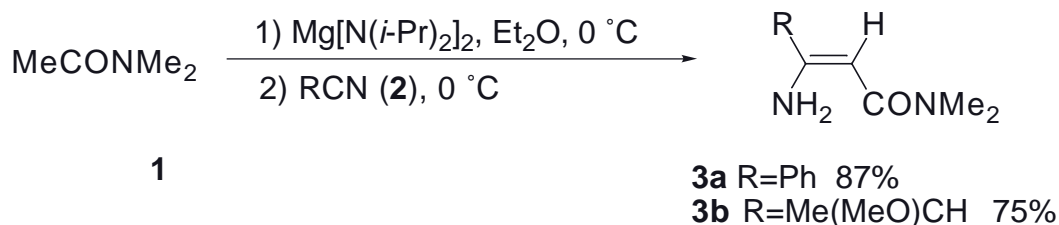
**CONVENIENT DIRECT SYNTHESIS OF VINYLOGOUS UREA  
DERIVATIVES USING MAGNESIUM AMIDE-INDUCED  
AMIDE/NITRILE COUPLING**

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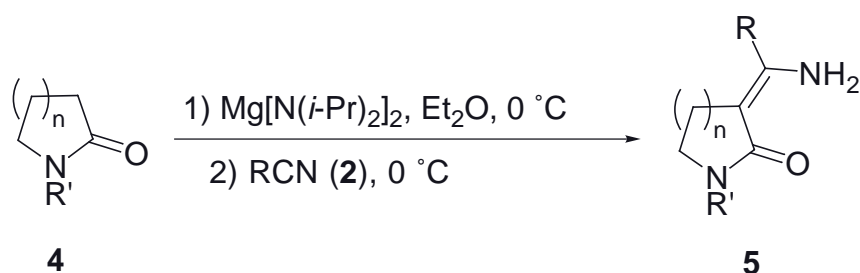
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**Abstract-** The magnesium enolates, generated by treatment of acyclic (**1**) and cyclic tertiary amides (**4**) with a (diisopropylamino)magnesium reagent, reacted efficiently with nitriles (**2**) to afford the corresponding  $\beta$ -aminoacrylamides (**3**) and  $\alpha$ -( $\alpha$ -aminoalkylidene)lactams (**5**). The formation of  $\alpha$ -(2-pyrrolidinylidene)lactams (**7**) from the reactions of *N*-methyl-2-pyrrolidone and *N*-methyl-2-piperidone with a  $\gamma$ -cyanopropyl *p*-toluenesulfonate (**6**) is also described.

As part of a program aimed at developing new synthetic methods utilizing magnesium amides,<sup>1-3</sup> we demonstrated that the ester magnesium enolates coupled efficiently with a range of nitriles to afford the corresponding vinylogous urethanes,<sup>2</sup> some of which could be elaborated to lead to useful biologically active natural products.<sup>3</sup> We planned to extend this nitrile coupling reaction to amide magnesium enolates<sup>4</sup> because of our interest in preparing vinylogous ureas including cyclic derivatives.<sup>5,6</sup> These compounds have been served as precursors to a number of useful organic compounds.<sup>5,7,8</sup> In this paper we wish to describe the results of our investigation, which offer a simple and general method for preparing  $\beta$ -aminoacrylamides (**3**) and  $\alpha$ -( $\alpha$ -aminoalkylidene)lactams (**5**). Previously, Suzuki *et al.*<sup>5b</sup> have reported that the lithium enolate of *N*-methylpyrrolidone reacts with benzonitrile to give 3-[amino(phenyl)methylene]-1-1-methyl-2-pyrrolidone in a good yield. The formation of a 1-alkyl-3-[amino(aryl)methylene]-2-pyrrolidone from the reaction of lithium enolate of a 1-alkyl-2-pyrrolidone with an aryl cyanide has also been reported by Hayes *et al.*<sup>5c</sup> We, however, found that the reactions of the lithium enolate of *N*-methylpyrrolidone with nitriles having  $\alpha$ -hydrogen(s) under each of their conditions did not afford the expected coupling products. An application of the present method to the preparation of  $\alpha$ -(2-pyrrolidinylidene)lactams (**7**) by using a  $\gamma$ -cyanopropyl *p*-toluenesulfonate (**6**) is also reported.



Scheme 1.



Scheme 2.

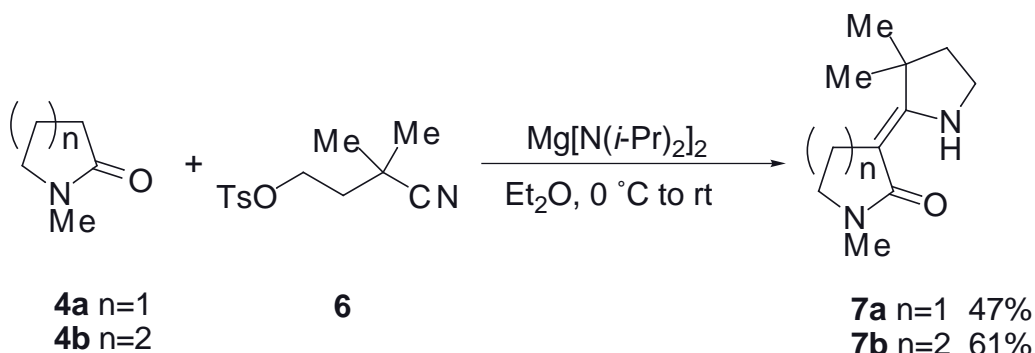
*N,N*-Dimethylacetamide (**1**) was treated with a magnesium amide, generated by the treatment of diisopropylamine with EtMgBr, in diethyl ether at 0 °C to generate a magnesium enolate. This was then allowed to react with benzonitrile (**2a**) or 2-methoxypropanenitrile (**2d**). Usual workup, followed by distillation using a Kugelrohr apparatus, gave (*Z*)- $\beta$ -aminoacrylamide derivatives (**3a**) or (**3b**) in good yields, as shown in Scheme 1. The formation of **3** was completely stereoselective, none of the corresponding *E* isomer being detected in each case. The stereochemistry was determined on the basis of their spectral data (IR and <sup>1</sup>H NMR). For example, the IR spectrum of **3a** showed absorption bands assignable to the amino group at 3383 and 3278 cm<sup>-1</sup> and the amide carbonyl group at 1613 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectrum exhibited very broad signals at  $\delta$  6.1–7.1 due to the NH<sub>2</sub>. These are attributable to the hydrogen bonding interaction between the amide carbonyl and the 3-amino group (see EXPERIMENTAL).<sup>9</sup>

Having shown that the (diisopropylamino)magnesium was effective for the coupling of amides with nitriles, we anticipated that *N*-alkylated lactams (**4**) would also show similar reactivity and examined the reactions of magnesium enolates of **4** with various nitriles in order to prepare  $\alpha$ -(*Z*)-( $\alpha$ -aminoalkylidene)lactams (**5**). As illustrated in Scheme 2, the lactams (**4**) were deprotonated with the magnesium amide under the conditions employed for **1**. The enolates thus generated were treated with a range of nitriles (**2**) to afford **5** in good yields. The results are summarized in the Table, which indicates that nitriles having  $\alpha$ -hydrogen(s), including propanenitrile or 2-methylpropanenitrile, could be used in the present reaction (Entries 3, 4, 7, 9, 10, and 11). Acetonitrile and phenylacetnitrile were examined in this transformation but failed to provide the desired products. Nitriles with steric bulk (**2b**) and (**2f**) also

**Table.** Coupling of magnesium enolates of lactams (**4**) with nitriles (**2**) yielding  $\alpha$ -( $\alpha$ -aminoalkylidene)lactams (**5**)

Entry	Lactam ( <b>4</b> )	Nitrile ( <b>2</b> )	<b>5</b> (Yield/%) <sup>a</sup>
1	<b>4a</b> (R'=Me, n=1)	<b>2a</b> (R=Ph)	<b>5a</b> (84)
2	<b>4a</b>	<b>2b</b> (R= <i>o</i> -Tol)	<b>5b</b> (75)
3	<b>4a</b>	<b>2c</b> (R= <i>i</i> -Pr)	<b>5c</b> (88)
4	<b>4a</b>	<b>2d</b> [R=Me(MeO)CH]	<b>5d</b> (87)
5	<b>4a</b>	<b>2e</b> [R=(MeO) <sub>2</sub> CH]	<b>5e</b> (88)
6	<b>4a</b>	<b>2f</b> (R= <i>t</i> -Bu)	<b>5f</b> (59)
7	<b>4b</b> (R'=c-Hex, n=1)	<b>2c</b>	<b>5g</b> (77)
8	<b>4c</b> (R'=Me, n=2)	<b>2a</b>	<b>5h</b> (75)
9	<b>4c</b>	<b>2g</b> (R=Et)	<b>5i</b> (50)
10	<b>4c</b>	<b>2c</b>	<b>5j</b> (88)
11	<b>4c</b>	<b>2d</b>	<b>5k</b> (86)
12	<b>4d</b> (R'=Me, n=3)	<b>2a</b>	<b>5l</b> (67)

<sup>a</sup>Yields refer to isolated materials purified by distillation or recrystallization.



**Scheme 3.**

coupled efficiently to give the corresponding products (**5b**) and (**5f**) (Entries 2 and 6). The products (**5**) were somewhat unstable under chromatographic separation on silica gel and resulted in contamination by the corresponding  $\beta$ -keto amide. However, they could be isolated by recrystallization or Kugelrohr distillation in pure forms. Each of the products was obtained in a stereochemically pure form, and the stereochemistry was also determined in a manner similar to that described for the products (**3**) (see EXPERIMENTAL). The *Z* configuration of **5a** was unambiguously determined on the basis of a NOE experiment. Thus, irradiation of the signal at  $\delta$  2.62 due to of the 4-methylene protons resulted in a 4.2%

enhancement of the signal at  $\delta$  7.3–7.5 due to the phenyl protons.

Next, 2-(pyrrolidinylidene)lactam formation was attempted by using 3-cyano-3-methylbutyl *p*-toluenesulfonate (**6**). On treating this nitrile with the magnesium enolates of *N*-methylpyrrolidone or *N*-methylpiperidone under the above conditions, the enolate–nitrile coupling was followed by a cyclization to lead to the formation of the corresponding  $\alpha$ -(2-pyrrolidinylidene)lactams (**7**) as the thermodynamically favored *Z*-isomers in fair yields, as outlined in Scheme 3. In these cases the products could be isolated by preparative TLC on silica gel in pure forms. The stereochemistry of these products was also established in a manner similar to that described for the products (**3**) and (**5**) (see EXPERIMENTAL).

Overall, we have demonstrated that the magnesium amide was effective for the coupling of cyclic and acyclic tertiary amides with various nitriles, affording vinylogous urea derivatives. The bivalent magnesium ion may be responsible for the success of the present reactions and the predominant formation of the *Z* isomer in each reaction. This method is useful because of its efficiency, the ready availability of the starting materials and the ease of operation, and its applicability to the preparation of  $\alpha$ -(*Z*)-(2-pyrrolidinylidene)lactams.

## EXPERIMENTAL

The mps were determined on a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The IR spectra were determined with a Perkin-Elmer 1600 Series FT IR spectrophotometer. The <sup>1</sup>H NMR spectra were determined using SiMe<sub>4</sub> as an internal reference with either a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in CDCl<sub>3</sub> or a JNX-PMX 60 NMR spectrometer operating at 60 MHz in CCl<sub>4</sub>. *J* Values are given in Hz. Low-resolution MS spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). High-resolution MS analyses were performed with a JEOL JMX-AX505HA spectrometer (Faculty of Agriculture, this University). 2-Methoxypropanenitrile (**2d**) and 2,2-dimethoxyethanenitrile (**2e**) were prepared following the method reported by Utimoto *et al.*<sup>10</sup> 3-Cyano-3-methylbutyl 4-methylbenzenesulfonate (**6**) was prepared following the procedure previously reported by one of the present authors.<sup>2b</sup> All of the other chemicals used in this study were commercially available.

**General Procedure for the Preparation of the  $\beta$ -Aminoacrylamides (**3**) and  $\alpha$ -( $\alpha$ -Aminoalkylidene)lactams (**5**).** To a stirred solution of EtMgBr (2.0 mmol) in Et<sub>2</sub>O (7 mL) at 0 °C in an atmosphere of argon was added *i*-Pr<sub>2</sub>NH (0.40 g, 4 mmol), and the mixture was refluxed for 1 h. To the cooled (0 °C) turbid solution, *N,N*-dimethylacetamide (**1**) or one of the lactams (**4**) (1.0 mmol) was added. After stirring for 5 min, one of the nitriles (**2**) (1.0 mmol) was added and stirring was continued for 6 h at the same temperature. The resulting mixture was quenched by adding saturated aqueous NH<sub>4</sub>Cl and the layers were separated. The aqueous phase was extracted with Et<sub>2</sub>O twice. The combined extracts were washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvent the crude product

was subjected to purification by distillation using Kugelrohr or by recrystallization.

***N,N*-Dimethyl-3-amino-3-phenylpropenamide (3a):**<sup>11</sup> bp 180 °C (bath temp)/0.38 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3383, 3278, 1613;  $\delta_{\text{H}}$  (60 MHz) 2.91 (6H, s), 4.87 (1H, s), 6.1–7.1 (2H, br), 7.1–7.55 (5H, m); MS  $m/z$  190 ( $\text{M}^+$ ).

***N,N*-Dimethyl-3-amino-4-methoxy-2-butenamide (3b):** bp 150 °C (bath temp)/1.7 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3404, 3294, 1627;  $\delta_{\text{H}}$  (60 MHz) 1.33 (3H, d,  $J = 6.8$ ), 2.90 (6H, s), 3.23 (3H, s), 3.57 (1H, q,  $J = 6.8$ ), 4.56 (1H, s), 5.9–6.3 (2H, br); MS  $m/z$  172 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$ : C, 55.79; H, 9.36; N, 16.27. Found: C, 55.51; H, 9.28; N, 16.17.

**(*Z*)-3-[Amino(phenyl)methylidene]-1-methyl-2-pyrrolidone (5a):** this product had spectral (IR, <sup>1</sup>H NMR, and MS) properties identical to those reported previously;<sup>5b</sup> bp 175 °C (bath temp)/0.4 mmHg (lit.,<sup>5b</sup> 250 °C/2.5 mmHg); mp 101–102 °C (hexane- $\text{CHCl}_3$ ) (lit.,<sup>5b</sup> 101–103 °C).

**(*Z*)-3-[Amino(2-methylphenyl)methylidene]-1-methyl-2-pyrrolidone (5b):** bp 180 °C (bath temp)/0.4 mmHg; mp 98–99 °C (hexane);  $\nu_{\max}/\text{cm}^{-1}$  (KBr disk) 3400, 3303, 1657, 1602;  $\delta_{\text{H}}$  (270 MHz) 2.27 (2H, t,  $J = 7.4$ ), 2.34 (3H, s), 2.86 (3H, s), 3.26 (2H, t,  $J = 7.4$ ), 5.73 (2H, br s), 7.15–7.3 (4H, m); MS  $m/z$  216 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$ : C, 72.19; H, 7.46; N, 12.95. Found: C, 72.15; H, 7.36; N, 12.87.

**(*Z*)-3-(1-Amino-2-methylpropylidene)-1-methyl-2-pyrrolidone (5c):** bp 130 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3423, 3319, 1652;  $\delta_{\text{H}}$  (270 MHz) 1.17 (6H, d,  $J = 6.9$ ), 2.51 (1H, sept,  $J = 6.9$ ), 2.61 (2H, t,  $J = 6.6$ ), 2.81 (3H, s), 3.31 (2H, t,  $J = 6.6$ ), 5.73 (2H, br s); MS  $m/z$  216 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_9\text{H}_{16}\text{N}_2\text{O}$ : MW, 168.1264. Found:  $m/z$  168.1261 ( $\text{M}^+$ ).

**(*Z*)-3-(1-Amino-2-methoxypropylidene)-1-methyl-2-pyrrolidone (5d):** bp 135 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3436, 3316, 1660;  $\delta_{\text{H}}$  (270 MHz) 1.31 (3H, d,  $J = 6.9$ ), 2.61 (2H, t,  $J = 7.3$ ), 2.83 (3H, s), 3.29 (3H, s), 3.35 (2H, t,  $J = 7.3$ ), 3.84 (1H, q,  $J = 6.9$ ), 5.88 (2H, br s); MS  $m/z$  184 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_2$ : C, 58.67; H, 8.75; N, 15.21. Found: C, 58.66; H, 8.81; N, 15.31.

**(*Z*)-3-(1-Amino-2,2-dimethoxyethylidene)-1-methyl-2-pyrrolidone (5e):** bp 145 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3478, 3325, 1667;  $\delta_{\text{H}}$  (270 MHz) 2.63 (2H, t,  $J = 7.4$ ), 2.84 (3H, s), 3.34 (6H, s), 3.33 (2H, t,  $J = 7.4$ ), 4.90 (1H, s), 6.02 (2H, br s); MS  $m/z$  200 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_3$ : C, 53.98; H, 8.05; N, 13.99. Found: C, 53.96; H, 8.11; N, 13.99.

**(*Z*)-3-(1-Amino-2,2-dimethylpropylidene)-1-methyl-2-pyrrolidone (5f):** bp 150 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3423, 3292, 1661;  $\delta_{\text{H}}$  (270 MHz) 1.23 (9H, s), 2.81 and 2.82 (combined 5H, t,  $J = 6.9$  and s, respectively), 3.27 (2H, t,  $J = 6.9$ ), 6.41 (2H, br s); MS  $m/z$  182 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}$ : MW, 182.1420. Found:  $m/z$  182.1419 ( $\text{M}^+$ ).

**(Z)-3-(Amino-2-methylpropylidene)-1-cyclohexyl-2-pyrrolidone (5g):** bp 180 °C (bath temp)/0.6 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3419, 3314, 1651;  $\delta_{\text{H}}$  (270 MHz) 1.11 (6H, d,  $J = 7.0$ ), 1.35–1.8 (10H, m), 2.51 (1H, sept,  $J = 7.0$ ), 2.58 (2H, t,  $J = 7.0$ ), 3.31 (2H, t,  $J = 7.0$ ), 3.9–3.95 (1H, m), 5.72 (2H, br s); MS  $m/z$  236 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}$ : MW, 236.3574. Found:  $m/z$  236.3580 ( $\text{M}^+$ ).

**(Z)-3-[1-Amino(phenyl)methylidene]-1-methyl-2-piperidone (5h):** mp 77–78 °C (hexane);  $\nu_{\max}/\text{cm}^{-1}$  (KBr disk) 3387, 3264, 1610, 1596;  $\delta_{\text{H}}$  (270 MHz) 1.72 (2H, quint,  $J = 6.2$ ), 2.21 (2H, t,  $J = 6.2$ ), 3.00 (3H, s), 3.29 (2H, t,  $J = 6.2$ ), 6.25 (2H, br), 7.3–7.4 (5H, m); MS  $m/z$  216 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$ : C, 72.19; H, 7.46; N, 12.95. Found: C, 72.26; H, 7.61; N, 12.87.

**(Z)-3-(1-Aminopropylidene)-1-methyl-2-piperidone (5i):** bp 130 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3357, 3234, 1610;  $\delta_{\text{H}}$  (270 MHz) 1.13 (3H, t,  $J = 7.4$ ), 1.81 (2H, quint,  $J = 6.3$ ), 2.17 (2H, q,  $J = 7.4$ ), 2.39 (2H, t,  $J = 6.3$ ), 2.95 (3H, s), 3.27 (2H, t,  $J = 6.2$ ), 4.04 (2H, br); MS  $m/z$  168 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_9\text{H}_{16}\text{N}_2\text{O}$ : MW, 168.1264. Found:  $m/z$  168.1281 ( $\text{M}^+$ ).

**(Z)-3-(1-Amino-2-methylpropylidene)-1-methyl-2-piperidone (5j):** bp 150 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3414, 3255, 1606;  $\delta_{\text{H}}$  (270 MHz) 1.09 (6H, d,  $J = 6.9$ ), 1.82 (2H, quint,  $J = 5.9$ ), 2.41 (2H, t,  $J = 5.9$ ), 2.85 (1H, sept,  $J = 6.9$ ), 2.95 (3H, s), 3.27 (2H, t,  $J = 5.9$ ), 6.88 (2H, br s); MS  $m/z$  182 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}$ : MW, 182.1420. Found:  $m/z$  182.1428 ( $\text{M}^+$ ).

**(Z)-3-(1-Amino-2-methoxypropylidene)-1-methyl-2-piperidone (5k):** bp 145 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3472, 3270, 1621;  $\delta_{\text{H}}$  (270 MHz) 1.30 (3H, d,  $J = 6.5$ ), 1.83 (2H, quint,  $J = 6.3$ ), 2.24 (1H, dt,  $J = 14.2, 6.3$ ), 2.40 (1H, dt,  $J = 14.2, 6.3$ ), 2.96 (3H, s), 3.28 and 3.29 (combined 5H, t,  $J = 6.3$  and s, respectively), 4.13 (1H, q,  $J = 6.5$ ), 6.88 (2H, br s); MS  $m/z$  198 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2$ : C, 60.58; H, 9.15; N, 14.13. Found: C, 60.59; H, 9.13; N, 14.23.

**(Z)-3-[Amino(phenyl)methylidene]-1-methyl-6-hexanelactam (5l):** bp 190 °C (bath temp)/0.4 mmHg;  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3418, 3327, 1607, 1597;  $\delta_{\text{H}}$  (270 MHz) 1.5–1.75 (4H, m), 2.0–2.1 (2H, m), 3.00 (3H, s), 3.35–3.4 (2H, m), 5.49 (2H, br s), 7.35–7.45 (5H, m); MS  $m/z$  230 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$ : MW, 230.1420. Found:  $m/z$  230.1419 ( $\text{M}^+$ ).

**(Z)-1-Methyl-3-(3,3-dimethyl-2-pyrrolidinylidene)-2-pyrrolidone (7a).** To a stirred solution of EtMgBr (2.6 mmol) in Et<sub>2</sub>O (6.5 mL) under argon at 0 °C was added *i*-Pr<sub>2</sub>NH (0.53 g, 5.3 mmol) and the mixture was heated under reflux for 1 h. *N*-Methylpyrrolidone (65 mg, 0.66 mmol) and the cyano tosylate (**6**) were successively added to the cooled (0 °C) turbid solution of the magnesium amide. The mixture was allowed to warm to rt and stirring was continued for 6.5 h before it was quenched by adding saturated aqueous NH<sub>4</sub>Cl. The layers were separated and the aqueous was extracted with Et<sub>2</sub>O three times. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated

under reduced pressure. The residue was purified by preparative TLC on silica gel to give the product (**7a**) (60 mg, 47%);  $R_f$  0.17 (1:2 hexane–THF);  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3341, 1655, 1613;  $\delta_{\text{H}}$  (270 MHz) 1.22 (6H, s), 1.78 (2H, t,  $J = 6.9$ ), 2.73 (2H, t,  $J = 6.9$ ), 2.80 (3H, s), 3.31 (2H, t,  $J = 6.9$ ), 3.36 (2H, t,  $J = 6.9$ ), 7.85 (1H, br s); MS  $m/z$  194 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}$ : MW, 194.1420. Found:  $m/z$  230.1417 ( $\text{M}^+$ ).

**(Z)-1-Methyl-3-(3,3-dimethyl-2-pyrrolidinylidene)-2-piperidone (7b):**  $R_f$  0.28 (1:2 hexane–THF);  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3422, 1610;  $\delta_{\text{H}}$  (270 MHz) 1.29 (6H, s), 1.7–1.85 (4H, m), 2.53 (2H, t,  $J = 6.0$ ), 2.94 (3H, s), 3.26 (2H, t,  $J = 6.0$ ), 3.34 (2H, t,  $J = 6.9$ ), 9.31 (1H, br s); MS  $m/z$  208 ( $\text{M}^+$ ). HR-MS Calcd for  $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}$ : MW, 208.1577. Found:  $m/z$  208.1561 ( $\text{M}^+$ ).

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