Aminoacrylates. II. An Efficient Synthesis of α-Pyridones by Heterocyclic Annelation Reactions of Magnesium Amides Derived from *sec*-Aminoacrylates with Methyl Propiolate

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The reactions of magnesium amides 4 derived from *sec*-aminoacrylates 3 and ethylmagnesium bromide with methyl propiolate (2) afforded α-pyridones. This provides an efficient heterocyclic annelation reaction.

Key words aminoacrylate; methyl propiolate; pyridone; magnesium amide; heterocyclic annelation reaction

In proceeding papers, we reported the synthesis of naphthoquinones and anthraquinones,[1a] 2,3-dihydro-6*H*-1,3-oxazines,[1b] 1,2,3,4-tetrahydropyrimidines,[1c] and 1,4-dihydropyridines,[1d] by cycloaddition and heterocyclic annelation reactions. We are interested in the reactivities of *sec*-aminoacrylates **3** containing enaminic, olefinic, and other electron attracting moieties, as well as nitrodienamines and aminodienyl ester synthons because the electronic "push-pull" character of these compounds can lead to interesting cycloaddition reactions.[2—4] Although several reactions of related aminoacrylates with methyl propiolate (**2**) have been reported,[5] reactions of magnesium amides derived from *sec*-aminoacrylates are almost unknown. We have now found that treatment of the magnesium amides **4**, derived from *sec*-aminoacrylates **3** with methyl propiolate (**2**) afforded α-pyridones in a highly efficient heterocyclic annelation reaction.

The starting *sec*-aminoacrylates **3** were prepared quantitatively by reaction of methyl propiolate (**2**) with the corresponding primary amines **1**, namely, β-phenethylamine (**1a**), 4-methoxybenzylamine (**1b**), 3,4-dimethoxybenzylamine (**1c**), 2-(4-methoxyphenyl)ethylamine (**1d**), 2-(2,5-dimethoxyphenyl)ethylamine (**1e**), and 5-methoxytryptamine (**1f**), respectively, at room temperature in tetrahydrofuran (THF) (Chart 1 and Table 1).

The magnesium amides **4** were prepared by reaction of methyl *cis*- and *trans*-3-(phenethylamino)acrylates and methyl *cis*- and *trans*-3-(benzylamino)acrylates **3a**—**e**, and methyl *cis*- and *trans*-3-[2-(3-indolyl)ethylamino]acrylate **3f** with ethylmagnesium bromide, respectively.

Many syntheses of α-pyridones have been reported,[6] however synthetic methods using magnesium amides derived from *sec*-aminoacrylates with methyl propiolate (**2**) have not been studied extensively. One of the most general reported methods is the reaction of cyanoacetamide with 1,3-dicarbonyl compounds.[7] This reaction involves aldol type dehydrative condensation of the active methylene compound, cyanoacetamide, with 1,3-dicarbonyl compounds followed by intramolecular cyclization and dehydration. On the other hand, Kozikowski *et al*. reported the synthesis of related α-pyridone derivatives by aza-annulation reaction of enamines with methyl propiolate.[5c]

On the basis of our earlier report on the formation of

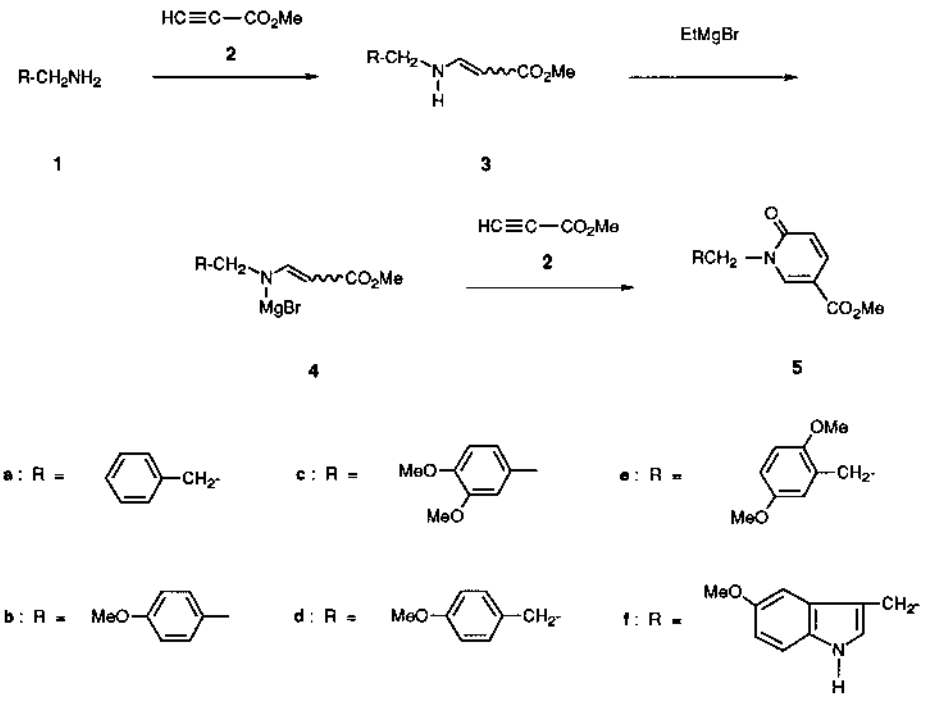

Chart 1

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1,2,3,4-tetrahydropyrimidines [aminoacrylates I (aminoenyl esters I)] by the reaction of *sec*-aminoacrylates with primary amines and acetaldehyde,[1c] we planned to prepare methyl 1-phenethyl-2-pyridone-5-carboxylate (**5a**) by cycloaddition reaction of the magnesium amide **4a** derived from *sec*-aminoacrylate **3a** with methyl propiolate (**2**). As expected, the heterocyclic annelation product **5a** was obtained in good yield by the treatment of **4a** with **2** in refluxing THF. The structure of the product **5a** was deduced from the following spectroscopic data. The ^{1}H-NMR spectrum showed the presence of three olefinic protons at δ 6.54 (1H, d, J=9.5 Hz), 7.81 (1H, dd, J=9.5, 2.4 Hz) and 7.84 (1H, d, J=2.1 Hz) due to a α-pyridone ring. The IR spectrum showed absorption bands at 1720 and 1680 cm^{-1} due to a methoxycarbonyl group and the 2-pyridone carbonyl group, respectively. The heteronuclear multiple bond correlation (HMBC) spectrum of **5a** showed a cross-peak between the methylene protons at δ 4.18 (t, J=7.3 Hz) and the pyridone carbonyl carbon at δ 162.2. Therefore, it may be deduced that **5a** is an α-pyridone.

In a similar manner, several other substituted α-pyridones **5b**—**f** were prepared from the corresponding **4b**—**f** (Chart 1 and Table 2).

The heterocyclic annelation reactions of magnesium amides **4**, derived from *sec*-aminoacrylates **3**, with methyl propiolate (**2**) may proceed as follows. Initially, condensation of the reactive magnesium amides **4** with methyl propiolate (**2**) may generate the intermediate **6**, followed by intramolecular ring closure with demethoxylation to form the α-pyridones **5**, as shown in Chart 2.

These results provide an efficient method for synthesizing α-pyridones **5** by utilizing the reactivity prepared magnesium amides **4** derived from *sec*-aminoacrylates **3**.

Table 1. Reactions of Primary Amines **1** with Methyl Propiolate (**2**)[a]

Starting material	Reaction product[b]	Appearance [solvent, mp (°C)]	IR (cm^{-1})
1a	**3a**	Light yellow oil	3337, 1672, 1618, 1500, 1480, 1456 (neat)
1b	**3b**	Colorless plates (Et_2O–hexane, 96—98)	3305, 1660, 1620, 1605, 1530, 1515 (KBr)
1c	**3c**	Light yellow oil	3370, 1690, 1680, 1630, 1620, 1515 (neat)
1d	**3d**	Light yellow oil	3330, 1680, 1610, 1510, 1480, 1460 (neat)
1e	**3e**	Light yellow oil	3330, 1670, 1610, 1505, 1480, 1460 (neat)
1f	**3f**	Light yellow oil	3400, 3330, 1670, 1615, 1490, 1450 (neat)

a) All reactions were run at room temperature for 5 h. *b*) All products were obtained in quantitative yield.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR-200 spectrometer, and ^{1}H-NMR spectra with a JEOL EX-90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. HMBC spectra were obtained with the usual pulse sequences and data processing was performed with the standard JEOL software. MS were recorded with a JEOL JMS-D 300 spectrometer. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. Wakogel C-200 (silica gel) and Merck Kieselgel G nach Stahl (silica gel) were used for column chromatography and thin layer chromatography (TLC), respectively. All reactions were carried out under an argon atmosphere.

General Procedure for Reactions of Primary Amines 1 with Methyl Propiolate (2) A solution of methyl propiolate (**2**) (1 mmol) and an amine (1 mmol) in THF (4 ml) was stirred at room temperature for 5 h. The reaction mixture was concentrated under vacuum to afford the products **3** in quantitative yield without purification. The purity was confirmed by the ^{1}H-NMR spectrum. The properties of the prepared compounds **3** are shown in Table 1.

Table 2. Reactions of the Magnesium Amides **4** Derived from *sec*-Aminoacrylates **3** with Methyl Propiolate (**2**)[a]

Starting materials	Reaction product	Reaction time (h)	Yield (%)	Appearance [solvent, mp (°C)]	IR (cm^{-1})
2 and **4a**	**5a**	3	95	Light yellow prisms (Et_2O–hexane, 64—66)	1720, 1680, 1610, 1545, 1500, 1450 (KBr)
2 and **4b**	**5b**	4	98	Colorless prisms (Et_2O–hexane, 96—97)	1710, 1680, 1610, 1590, 1540, 1510 (KBr)
2 and **4c**	**5c**	4	84	Light yellow prisms (Et_2O, 97—98)	1730, 1680, 1610, 1590, 1540, 1510 (KBr)
2 and **4d**	**5d**	3	75	Light yellow prisms (Et_2O–hexane, 102—103)	1710, 1680, 1615, 1590, 1530, 1510 (KBr)
2 and **4e**	**5e**	5	80	Colorless prisms (chloroform–hexane, 145—146)	1710, 1670, 1615, 1595, 1545, 1500 (KBr)
2 and **4f**	**5f**	3	56	Light yellow prisms (Et_2O, 142—144)	3360, 1730, 1670, 1660, 1605, 1590 (KBr)

a) All reactions were run in refluxing THF.

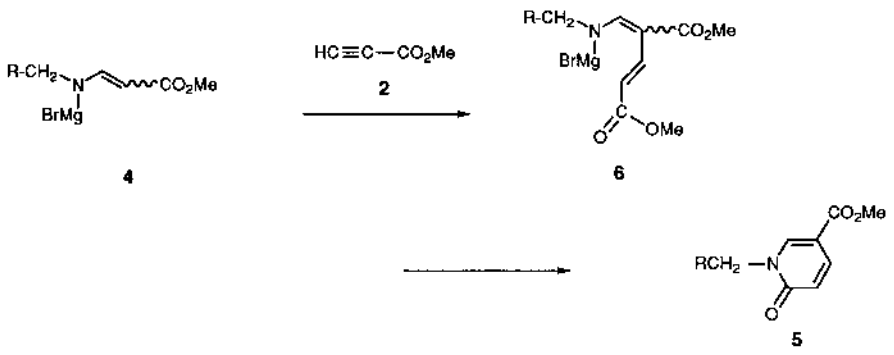

Chart 2

Methyl *cis*- and *trans*-3-(Phenethylamino)acrylate (3a)[1c] This product was identical with an authentic sample on the basis of IR, MS and NMR spectral comparisons.

Methyl *cis*- and *trans*-3-(4-Methoxybenzylamino)acrylate (3b) ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.64 (2H, s, *cis*-Me), 3.66 (1H, s, *trans*-Me), 3.79 (2H, s, *cis*-Me), 3.80 (1H, s, *trans*-Me), 4.14 (2/3H, d, J=5.2 Hz, *trans*-methylene H), 4.29 (4/3H, d, J=5.8 Hz, *cis*-methylene H), 4.53 (2/3H, d, J=7.9 Hz, *cis*-olefinic H), 4.82 (1/3H, d, J=13.4 Hz, *trans*-olefinic H), 6.68 (2/3H, dd, J=13.1, 7.9 Hz, *cis*-olefinic H), 6.87 (4/3H, d, J=8.5 Hz, *cis*-aromatic H), 6.88 (2/3H, d, J=8.5 Hz, *trans*-aromatic H), 7.17 (4/3H, d, J=8.5 Hz, *cis*-aromatic H), 7.20 (2/3H, d, J=8.5 Hz, *trans*-aromatic H), 7.58 (1/3H, dd, J=13.4, 7.9 Hz, *trans*-olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{12}H_{15}NO_3$ (M^+): 221.1049. Found: 221.1028. *Anal*. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; Found: C, 64.93; H, 6.82; N, 6.15.

Methyl *cis*- and *trans*-3-(3,4-Dimethoxybenzylamino)acrylate (3c) ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.62 (1.5H, s, -Me), 3.63 (1.5H, s, -Me), 3.84 (3H, s, -Me), 3.85 (3H, s, -Me), 4.12 (2/3H, s, *trans*-methylene H), 4.27 (4/3H, d, J=4.6 Hz, *cis*-methylene H), 4.54 (2/3H, d, J=7.9 Hz, *cis*-olefinic H), 4.78 (1/3H, d, J=12.8 Hz, *trans*-olefinic H), 6.69 (2/3H, dd, J=12.8, 7.9 Hz, *cis*-olefinic H), 6.81—6.67 (3H, m, aromatic H), 7.57 (1/3H, dd, J=12.8, 7.9 Hz, *trans*-olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{13}H_{17}NO_4$ (M^+): 251.1155. Found: 251.1155.

Methyl *cis*- and *trans*-3-[2-(4-Methoxyphenyl)ethylamino]acrylate (3d) ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.73-2.79 (2H, m, methylene H), 3.22—3.36 (2H, m, methylene H), 3.62 (3/2H, s, *cis*-Me), 3.64 (3/2H, s, *trans*-Me), 3.76 (3/2H, s, *cis*-Me), 3.77 (3/2H, s, *trans*-Me), 4.42 (1/2H, d, J=7.9 Hz, *cis*-olefinic H), 4.76 (1/2H, d, J=13.1 Hz, *trans*-olefinic H), 6.49 (1/2H, dd, J=13.4, 7.9 Hz, *cis*-olefinic H), 6.83 (2H, d, J=8.6 Hz, aromatic H), 7.08 (2H, d, J=8.6 Hz, aromatic H), 7.46 (1/2H, dd, J=13.1, 7.9 Hz, *trans*-olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{13}H_{17}NO_3$ (M^+): 235.1209. Found: 235.1211.

Methyl *cis*- and *trans*-3-[2-(2,5-Dimethoxyphenyl)ethylamino]acrylate (3e) ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.84—2.78 (2H, m, methylene H), 3.36—3.22 (2H, m, methylene H), 3.62 (2H, s, *cis*-Me), 3.64 (1H, s, *trans*-Me), 3.73 (2H, s, *cis*-Me), 3.74 (1H, s, *trans*-Me), 3.76 (2H, s, *cis*-Me), 3.78 (1H, s, *trans*-Me), 4.41 (2/3H, d, J=7.9 Hz, *cis*-olefinic H), 4.76 (1/3H, d, J=13.1 Hz, *trans*-olefinic H), 6.52 (2/3H, dd, J=13.1, 7.9 Hz, *cis*-olefinic H), 6.78—6.68 (3H, m, aromatic H), 7.47 (1/3H, dd, J=13.1, 8.2 Hz, *trans*-olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{14}H_{19}NO_4$ (M^+): 265.1314. Found: 265.1334.

Methyl *cis*- and *trans*-3-[2-[3-(5-Methoxyindolyl)]ethylamino]acrylate (3f) ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.91—2.87 (2H, m, methylene H), 3.41—3.25 (2H, m, methylene H), 3.60 (2H, s, *cis*-Me), 3.65 (1H, s, *trans*-Me), 3.82 (1H, s, *trans*-Me), 3.83 (2H, s, *cis*-Me), 4.40 (2/3H, d, J=7.9 Hz, *cis*-olefinic H), 4.77 (1/3H, d, J=13.4 Hz, *trans*-olefinic H), 6.50 (2/3H, dd, J=13.4, 7.9 Hz, *cis*-olefinic H), 7.20—6.81 (4H, m, aromatic H), 7.43 (1/3H, dd, J=13.4, 8.2 Hz, *trans*-olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{15}H_{18}N_2O_3$ (M^+): 274.1316. Found: 274.1306.

General Procedure for Reactions of Magnesium Amides 4 Derived from *sec*-Aminoacrylates 3 with Methyl Propiolate (2) A solution of 1 M ethylmagnesium bromide (EtMgBr) in THF solution (1.5 ml, 1.5 mmol) was added dropwise to a solution of *sec*-aminoacrylate **3** (1.5 mmol) in dry THF (1 ml) with stirring at 0 °C. The whole was stirred at room temperature for 2 h. Methyl propiolate (**2**) (44.5 μl, 0.5 mmol) was added to the reaction mixture and the whole was refluxed for an appropriate period. The reaction mixture was poured into saturated aqueous NH_4Cl and the whole was stirred at room temperature for 5 min, then extracted with ethyl acetate. The organic layer was washed with brine, then dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel chromatography. The reaction conditions and properties of the prepared compounds **5** are shown in Table 2.

Methyl 1-Phenethyl-2-pyridone-5-carboxylate (5a) Solvent for chromatography: 40% ethyl acetate in hexane. Product: 123 mg. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.06 (2H, t, J=7.3 Hz, methylene H), 3.80 (3H, s, -Me) , 4.18 (2H, t, J=7.3 Hz, methylene H), 6.54 (1H, d, J=9.5 Hz, olefinic H), 7.16 (2H, d, J=7.3 Hz, aromatic H), 7.23 (1H, t, J=7.3 Hz, aromatic H), 7.29 (2H, t, J=7.3 Hz, aromatic H), 7.81 (1H, dd, J=9.5, 2.4 Hz, olefinic H), 7.84 (1H, d, J=2.4 Hz, olefinic H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 35.0, 51.9, 52.3, 109.2, 119.6, 126.9, 128.7, 128.7, 128.8, 128.8, 137.2, 138.5, 143.0, 162.2, 164.6. High-resolution EI MS *m/z*: Calcd for $C_{15}H_{15}NO_3$ (M^+): 257.1052. Found: 257.1073. *Anal*. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44; Found: C, 69.78; H, 5.99; N, 5.32.

Methyl 1-(4-Methoxybenzyl)-2-pyridone-5-carboxylate (5b) Solvent for chromatography: 40% ethyl acetate in hexane. Product: 134 mg. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.79 (3H, s, -Me), 3.82 (3H, s, -Me), 5.09 (2H, s, methylene H), 6.55 (2H, d, J=9.5 Hz, olefinic H), 6.87 (2H, d, J=8.6 Hz, aromatic H), 7.29 (2H, d, J=8.6 Hz, aromatic H), 7.82 (1H, d, J=9.5 Hz, olefinic H), 8.16 (1H, s, olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{15}H_{15}NO_4$ (M^+): 273.1001. Found: 273.1021. *Anal*. Calcd for $C_{15}H_{15}NO_4$: C, 65.92. H, 5.53. N, 5.13. Found: C, 65.76; H, 5.62; N, 4.96.

Methyl 1-(3,4-Dimethoxybenzyl)-2-pyridone-5-carboxylate (5c) Solvent for chromatography: 50% ethyl acetate in hexane. Product: 127 mg. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.83 (3H, s, -Me), 3.87 (6H, s, -Me), 5.09 (2H, s, methylene H), 6.57 (1H, d, J=9.5 Hz, olefinic H), 6.90—6.86 (3H, m, aromatic H), 7.82 (1H, dd, J=9.5, 2.4 Hz, olefinic H), 8.18 (1H, d, J=2.4 Hz, olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{16}H_{17}NO_5$ (M^+): 303.1107. Found: 303.1137. *Anal*. Calcd for $C_{16}H_{17}NO_5$: C, 63.36: H, 5.65; N, 4.62; Found: C, 63.18; H, 5.71; N, 4.50.

Methyl 1-[2-(4-Methoxyphenyl)ethyl]-2-pyridone-5-carboxylate (5d) Solvent for chromatography: 40% hexane in ethyl acetate. Product: 108 mg. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.00 (2H, t, J=7.3 Hz, methylene H), 3.78 (3H, s, -Me), 3.81 (3H, s, -Me), 4.14 (2H, t, J=7.3 Hz, methylene H), 6.54 (1H, d, J=9.5 Hz, olefinic H), 6.83 (2H, d, J=8.9 Hz, aromatic H), 7.07 (2H, d, J=8.9 Hz, aromatic H), 7.81 (1H, dd, J=9.5, 2.4 Hz, olefinic H), 7.85 (1H, d, J=2.4 Hz, olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{16}H_{17}NO_4$ (M^+): 287.1158. Found: 287.1168. *Anal*. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.66; H, 6.02; N, 4.67.

Methyl 1-[2-(2,5-Dimethoxyphenyl)ethyl]-2-pyridone-5-carboxylate (5e) Solvent for chromatography: 50% hexane in ethyl acetate. Product: 128 mg. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.05 (2H, t, J=7.0 Hz, methylene H), 3.70 (3H, s, -Me), 3.78 (3H, s, -Me), 3.80 (3H, s, -Me), 4.19 (2H, t, J=7.0 Hz, methylene H), 6.51 (1H, d, J=8.6 Hz, olefinic H), 6.77—6.61 (3H, m, aromatic H), 7.78 (1H, dd, J=8.6, 2.4 Hz, olefinic H), 7.84 (1H, s, olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{17}H_{19}NO_5$ (M^+): 317.1178. Found: 317.1219. *Anal*. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.06; H, 6.08: N, 4.42.

Methyl 1-[2-[3-(5-Methoxyindolyl)]ethyl]-2-pyridone-5-carboxylate (5f) Solvent for chromatography: 40% hexane in ethyl acetate. Product: 90 mg. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.19 (2H, t, J=7.3 Hz, methylene H), 3.75 (3H, s, -Me), 3.87 (3H, s, -Me), 4.25 (2H, t, J=7.3 Hz, methylene H), 6.55 (1H, d, J=9.9 Hz, olefinic H), 7.26—6.91 (4H, m, aromatic H), 7.77 (1H, s, olefinic H), 7.82 (1H, d, J=9.9 Hz, olefinic H). High-resolution EI MS *m/z*: Calcd for $C_{18}H_{18}N_2O_4$ (M^+): 326.1267. Found: 326.1267. *Anal*. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.02; H, 5.73; N, 8.48.

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