Aminoenylesters. I. A New Synthesis of 1,2,3,4-Tetrahydropyrimidines by Heterocyclic Annelation Reactions of Aminoenylesters with Primary Amines and Acetaldehyde

Takeshi KOIKE,* Mituharu TANABE, Naoki TAKEUCHI, and Seisho TOBINAGA

Showa College of Pharmaceutical Sciences, Higashitamagawagakuen, Machida, Tokyo 194, Japan.

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The reactions of aminoenylesters **3**, which were prepared by the reactions of methyl propiolate (**1**) and primary amines **2**, with primary amines **2** and acetaldehyde afforded 1,2,3,4-tetrahydropyrimidines **4**. This provides a new heterocyclic annelation reaction.

Key words aminoenylester; acetaldehyde; 1,2,3,4-tetrahydropyrimidine; heterocyclic annelation reaction

In the preceding papers,^{1,2)} we reported that the cycloaddition reactions of methyl 5-(*N,N*-dimethylamino)-2,4-pentadienoate (*tert*-aminodienylester) with α,β -unsaturated carbonyl compounds gave aromatic compounds, and the heterocyclic annelation reaction of methyl 5-(alkylamino)-2,4-pentadienoate (*sec*-aminodienylester) with acetaldehyde gave 2,3-dihydro-6*H*-1,3-oxazines. Since we are interested in nitrodienamines and aminodienylesters with enaminic and diene moieties, the electronic "push-pull" character of which can lead to interesting cycloaddition reactions, we investigated the reactivities of the aminoenylesters **3** as well as those of aminodienylesters. The aminoenylesters **3** were prepared by the reaction of methyl propiolate (**1**) with primary amines **2**.³⁻⁵⁾ The reactions of **3** with primary amines **2** and acetaldehyde afforded 1,2,3,4-tetrahydropyrimidines **4**. This is a new heterocyclic annelation reaction.

The following aminoenylesters, namely, methyl *cis*- and *trans*-3-(benzylamino)acrylate (**3a**), methyl *cis*- and *trans*-3-(phenethylamino)acrylate (**3b**), methyl *cis*- and *trans*-3-(propylamino)acrylate (**3c**), methyl *cis*- and *trans*-3-(4-pyridylmethylamino)acrylate (**3d**), methyl *cis*- and *trans*-3-(3-pyridylmethylamino)acrylate (**3e**), and methyl *cis*- and *trans*-3-[2-(3-indolyl)ethylamino]acrylate (**3f**) were selected for investigation (Chart 1). They were prepared quantitatively by the reaction of methyl propiolate (**1**) with the corresponding primary amines **2**, namely, benzylamine (**2a**), phenethylamine (**2b**), propylamine (**2c**), 4-picolylamine (**2d**), 3-picolylamine (**2e**), and tryptamine (**2f**), respectively, at room temperature in tetrahydrofuran (THF) (Table 1).

First, we planned to prepare the heterocyclic annelation product, 3-benzyl-2,3-dihydro-5-methoxycarbonyl-2,6-dimethyl-6*H*-1,3-oxazine (**5**), by cycloaddition reaction of

Chart 1

* To whom correspondence should be addressed.

the aminoenylester **3a** with acetaldehyde. Unexpectedly, *trans*-1,3-dibenzyl-1,2,3,4-tetrahydro-5-methoxy-carbonyl-2,4-dimethylpyrimidine (**4a**) was obtained in low yield by the treatment of **3a** with acetaldehyde in THF in a sealed tube at room temperature. The structure of the product **4a** was proposed on the basis of the following spectroscopic analyses; the ^1H -NMR spectrum of **4a** showed proton signals due to a benzyl group, an aminoenylester, two methyl groups, and two methine groups. Next, the treatment of **3a** with benzylamine and acetaldehyde under similar conditions afforded the 1,2,3,4-tetrahydropyrimidine **4a** in 74% yield. The nuclear Overhauser and exchange spectroscopy (NOESY) spectrum of **4a** showed the presence of a cross-peak between the 2β methyl protons at δ 1.23 (d, $J=6.7$ Hz) and 4β methine proton at δ 4.44 (q, $J=6.7$ Hz). Therefore, it may be deduced that **4a** has an axial methyl group and an equatorial methyl group in *trans*-configuration.

Similarly, the analogous pyrimidines **4b–4f** were prepared from the corresponding **3b–3f** (Chart 1, Table 2).

Pyrimidine-ring-formation reaction of aminoenylesters **3** with primary amines **2** and acetaldehyde may proceed

as follows. Initially, the condensation reaction of **3** with the reactive **6** and subsequent condensation of the resulting amine **7** with acetaldehyde affords the intermediate **8**. Then, intramolecular ring closure of **8** may generate the 1,2,3,4-tetrahydropyrimidines **4**, as shown in Chart 2.

These results provide a new method of synthesizing 1,2,3,4-tetrahydropyrimidines **4**.

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 or JASCO FT/IR-8000 spectrometer, and ^1H -NMR spectra with a JEOL EX-90 or JEOL JNM- α 500 spectrometer, with tetramethylsilane as an internal standard. ^1H - ^1H , and ^1H - ^1H long-range correlation spectroscopy (COSY) and NOESY 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) and NH-DM 1020 (basic 100 Å type silica gel, Fuji Silysia Chemical Ltd.) and Merck aluminum oxide 90 (active neutral and activity II–III) were used for column chromatography and thin layer chromatography (TLC), respectively. All runs were carried out under argon.

General Procedure for Reactions of Methyl Propiolate (1**) with Primary Amines **2**** A solution of methyl propiolate (**1**) (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 a vacuum to afford the products **3** in quantitative yield without purification. The purity was confirmed by the NMR spectrum. The properties of the prepared compounds **3** are shown in Table 1.

Methyl *cis*- and *trans*-3-(Benzylamino)acrylate (3a**)** ^1H -NMR (500 MHz, CDCl_3) δ : 3.65 (9/4H, s, *cis*-Me), 3.66 (3/4H, s, *trans*-Me), 4.21 (1/2H, d, $J=5.2$ Hz, *trans*-methylene H), 4.35 (3/2H, d, $J=6.1$ Hz, *cis*-methylene H), 4.55 (3/4H, d, $J=8.2$ Hz, *cis*-olefinic H), 4.81 (1/4H, d, $J=13.4$ Hz, *trans*-olefinic H), 6.69 (3/4H, dd, $J=13.1$, 8.2 Hz, *cis*-olefinic H), 7.25–7.37 (5H, m, aromatic H), 7.59 (1/4H, dd, $J=13.4$, 7.9 Hz, *trans*-olefinic H). High-resolution electron impact (EI)-MS m/z : Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ (M^+): 191.0945. Found: 191.0940.

Methyl *cis*- and *trans*-3-(Phenethylamino)acrylate (3b**)** ^1H -NMR

Table 1. The Reactions of Methyl Propiolate **1** with Primary Amines **2**^{a)}

Initial compound	Reaction product ^{b)}	Appearance	IR (cm^{-1}) (neat)
2a	3a	Light yellow oil	3340, 1670, 1620
2b	3b	Light yellow oil	3337, 1672, 1618
2c	3c	Colorless oil	3335, 1672, 1614
2d	3d	Light red oil	3350, 1670, 1620
2e	3e	Light red oil	3360, 1680, 1610
2f	3f	Dark red oil	3414, 3317, 1658, 1606

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

Table 2. The Reactions of the Aminoenylesters **3** with Primary Amines **2** and Acetaldehyde

Initial compounds	Reaction product	Reaction time (h)	Reaction temp. ($^{\circ}\text{C}$)	Yield (%)	Appearance [solvent, mp ($^{\circ}\text{C}$)]	IR (cm^{-1})
2a and 3a	4a	5	60	74	Colorless prisms (ether–hexane, 117–119)	1670, 1620 (KBr)
2b and 3b	4b	6	60	80	Colorless oil	1680, 1614 (neat)
2c and 3c	4c	4	25	84	Light red oil	1684, 1614 (neat)
2d and 3d	4d	5	60	91	Light yellow oil	1680, 1620, 1600 (neat)
2e and 3e	4e	5	60	66	Light yellow oil	1680, 1610 (neat)
2f and 3f	4f	6	60	65	Light red oil	3404, 3333, 1662, 1606 (neat)

Chart 2

(500 MHz, CDCl_3) δ : 2.82 (1H, t, $J=7.0$ Hz, *cis*-methylene H), 2.86 (1H, t, $J=7.0$ Hz, *trans*-methylene H), 3.32 (1H, q, $J=7.0$ Hz, *trans*-methylene H), 3.40 (1H, q, $J=7.0$ Hz, *cis*-methylene H), 3.63 (3/2H, s, *cis*-Me), 3.66 (3/2H, s, *trans*-Me), 4.43 (1/2H, d, $J=8.2$ Hz, *cis*-olefinic H), 4.51 (1/2H, br, *trans*-NH), 4.79 (1/2H, d, $J=13.4$ Hz, *trans*-olefinic H), 6.51 (1H, dd, $J=13.1$, 8.2 Hz, *cis*-olefinic H), 7.17–7.19 (2H, m, aromatic H), 7.21–7.26 (1H, m, aromatic H), 7.29–7.33 (2H, m, aromatic H), 7.46 (1H, dd, $J=13.4$, 8.2 Hz, *trans*-olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ (M^+): 205.1103. Found: 205.1141.

Methyl *cis*- and *trans*-3-(Propylamino)acrylate (3c) ^1H -NMR (500 MHz, CDCl_3) δ : 0.94 (9/4H, t, $J=7.3$ Hz, *cis*-Me), 0.95 (3/4H, t, $J=7.3$ Hz, *trans*-Me), 1.56 (3/2H, dd, $J=14.4$, 7.3 Hz, *cis*-methylene H), 1.60 (1/2H, dd, $J=14.3$, 7.3 Hz, *trans*-methylene H), 3.01 (1/2H, q, $J=6.7$ Hz, *trans*-methylene H), 3.13 (3/2H, q, $J=6.7$ Hz, *cis*-methylene H), 3.64 (9/4H, s, *cis*-Me), 3.66 (3/4H, s, *trans*-Me), 4.46 (3/4H, d, $J=7.9$ Hz, *cis*-olefinic H), 4.54 (1/4H, br, *trans*-NH), 4.73 (1/4H, d, $J=12.8$ Hz, *trans*-olefinic H), 6.63 (3/4H, dd, $J=13.4$, 7.9 Hz, *cis*-olefinic H), 7.51 (1/4H, dd, $J=12.8$, 8.5 Hz, *trans*-olefinic H), 7.84 (3/4H, br, *cis*-NH). High-resolution EI-MS m/z : Calcd for $\text{C}_7\text{H}_{13}\text{NO}_2$ (M^+): 143.0944. Found: 143.0944.

Methyl *cis*- and *trans*-3-(4-Pyridylmethylamino)acrylate (3d) ^1H -NMR (500 MHz, CDCl_3) δ : 3.64 (9/5H, s, *cis*-Me), 3.68 (6/5H, s, *trans*-Me), 4.28 (6/5H, d, $J=5.8$ Hz, *cis*-methylene H), 4.37 (4/5H, d, $J=6.1$ Hz, *trans*-methylene H), 4.63 (3/5H, d, $J=7.9$ Hz, *cis*-olefinic H), 4.72 (2/5H, d, $J=13.1$ Hz, *trans*-olefinic H), 5.31 (2/5H, br, *trans*-NH), 6.65 (3/5H, dd, $J=13.1$, 7.9 Hz, *cis*-olefinic H), 7.19–7.21 (2H, m, aromatic H), 7.61 (2/5H, dd, $J=13.1$, 7.7 Hz, *trans*-olefinic H), 8.16 (3/5H, br, *cis*-NH), 8.56–8.58 (2H, m, aromatic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$ (M^+): 192.0898. Found: 192.0918.

Methyl *cis*- and *trans*-3-(3-Pyridylmethylamino)acrylate (3e) ^1H -NMR (500 MHz, CDCl_3) δ : 3.65 (3H, s, -Me), 4.27 (4/3H, d, $J=5.5$ Hz, *trans*-methylene H), 4.38 (2/3H, d, $J=6.4$ Hz, *cis*-methylene H), 4.60 (1/3H, d, $J=7.9$ Hz, *cis*-olefinic H), 4.79 (2/3H, d, $J=13.4$ Hz, *trans*-olefinic H), 5.23 (2/3H, br, *trans*-NH), 6.69 (1/3H, dd, $J=13.0$, 7.9 Hz, *cis*-olefinic H), 7.26–7.30 (1H, m, aromatic H), 7.59 (2/3H, dd, $J=13.4$, 7.7 Hz, *trans*-olefinic H), 7.60–7.63 (1H, m, aromatic H), 8.51–8.55 (2H, m, aromatic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$ (M^+): 192.0896. Found: 192.0895.

Methyl *cis*- and *trans*-3-[2-(3-Indolyl)ethylamino]acrylate (3f) ^1H -NMR (500 MHz, CDCl_3) δ : 2.98 (3/2H, t, $J=6.7$ Hz, *cis*-methylene H), 3.02 (1/2H, t, $J=6.7$ Hz, *trans*-methylene H), 3.37 (1/2H, q, $J=6.7$ Hz, *trans*-methylene H), 3.46 (3/2H, q, $J=6.7$ Hz, *cis*-methylene H), 3.63 (9/4H, s, *cis*-Me), 3.67 (3/4H, s, *trans*-Me), 4.41 (3/4H, d, $J=7.9$ Hz, *cis*-olefinic H), 4.55 (1/4H, br, *trans*-NH), 4.79 (1/4H, d, $J=13.1$ Hz, *trans*-olefinic H), 6.52 (3/4H, dd, $J=13.1$, 7.9 Hz, *cis*-olefinic H), 6.99–7.01 (1H, m, aromatic H), 7.10–7.15 (1H, m, aromatic H), 7.18–7.25 (1H, m, aromatic H), 7.34–7.38 (1H, m, aromatic H), 7.46 (1/4H, dd, $J=13.1$, 8.2 Hz, *trans*-olefinic H), 7.56–7.58 (1H, m, aromatic H), 7.89 (3/4H, br, *cis*-NH), 8.16 (3/4H, br, *cis*-NH), 8.22 (3/4H, br, *trans*-NH). High-resolution EI-MS m/z : Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$ (M^+): 244.1210. Found: 244.1190.

General Procedure for Reactions of Aminoenoylesters 3 with Primary Amines 2 and Acetaldehyde A solution of an aminoenoylester (1 mmol), an amine (1.5 mmol) and excess acetaldehyde (8 ml) in THF (4 ml) in a sealed tube was stirred at room temperature or heated at 60 °C for an appropriate period until the aminoenoylester was no longer detectable by TLC. The reaction mixture was concentrated under a vacuum, and then the residue was subjected to column chromatography on N-H silica gel or aluminum oxide with appropriate solvents. The reaction conditions and properties of the prepared compounds 4 are shown in Table 2.

***trans*-1,3-Dibenzyl-1,2,3,4-tetrahydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (4a)** Solvent for chromatography: 50% ethyl acetate

in hexane. Product: 259 mg. ^1H -NMR (500 MHz, CDCl_3) δ : 1.23 (3H, d, $J=6.7$ Hz, -Me), 1.33 (3H, d, $J=6.7$ Hz, -Me), 3.19 (1H, d, $J=14.6$ Hz, methylene H), 3.52 (1H, q, $J=6.7$ Hz, methine H), 3.65 (3H, s, -Me), 3.84 (1H, d, $J=14.6$ Hz, methylene H), 4.40 (2H, s, methylene H), 4.44 (1H, q, $J=6.7$ Hz, methine H), 7.28 (10H, m, aromatic H), 7.66 (1H, s, olefinic H). ^{13}C -NMR (125 MHz, CDCl_3) δ : 16.77, 22.80, 50.11, 50.49, 50.99, 55.73, 63.80, 99.32, 126.53, 126.77, 127.63, 128.08, 128.14, 128.83, 137.89, 140.36, 146.53, 168.60. Chemical ionization (CI)-MS m/z : 351 ($M^+ + 1$). Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.50; N, 7.82.

***trans*-1,2,3,4-Tetrahydro-5-methoxycarbonyl-2,4-dimethyl-1,3-diphenylethylpyrimidine (4b)** Solvent for chromatography: 30% ethyl acetate in hexane. Product: 301 mg. ^1H -NMR (500 MHz, CDCl_3) δ : 1.20 (3H, d, $J=6.7$ Hz, -Me), 1.25 (3H, d, $J=6.7$ Hz, -Me), 2.23–2.29 (1H, m, methylene H), 2.63–2.83 (5H, m, methylene H), 3.22–3.29 (1H, m, methylene H), 3.34–3.40 (1H, m, methylene H), 3.65 (1H, q, $J=6.7$ Hz, methine H), 3.66 (3H, s, -Me), 4.28 (1H, q, $J=6.7$ Hz, methine H), 7.12–7.28 (10H, m, aromatic H), 7.36 (1H, s, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2$ (M^+): 378.2313. Found: 378.2343.

***trans*-1,2,3,4-Tetrahydro-5-methoxycarbonyl-2,4-dimethyl-1,3-dipropylpyrimidine (4c)** Solvent for chromatography: 30% ethyl acetate in hexane. Product: 214 mg. ^1H -NMR (90 MHz, CDCl_3) δ : 0.54 (3H, t, $J=6.6$ Hz, -Me), 0.76–1.55 (13H, m, -Me and methylene H), 1.94–2.70 (4H, m, methine H), 3.61 (3H, s, -Me), 3.89 (1H, q, $J=6.6$ Hz, methine H), 4.17 (1H, q, $J=6.6$ Hz, methine H), 7.51 (1H, s, olefinic H). High-resolution EI-MS m/z : Calcd for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_2$ (M^+): 254.1991. Found: 254.1980.

***trans*-1,2,3,4-Tetrahydro-5-methoxycarbonyl-2,4-dimethyl-1,3-di(4-pyridylmethyl)pyrimidine (4d)** Solvent for chromatography: 30% hexane in ethyl acetate. Product: 319 mg. ^1H -NMR (90 MHz, CDCl_3) δ : 1.29 (6H, d, $J=5.9$ Hz, -Me), 3.15 (1H, s, methylene H), 3.43 (1H, q, $J=5.9$ Hz, methine H), 3.66 (3H, s, -Me), 3.94 (1H, s, methylene H), 4.40 (2H, s, methylene H), 4.46 (1H, q, $J=5.9$ Hz, methine H), 7.13–7.24 (4H, m, aromatic H), 7.61 (1H, s, olefinic H), 8.59 (4H, m, aromatic H). CI-MS m/z : 353 ($M^+ + 1$).

***trans*-1,2,3,4-Tetrahydro-5-methoxycarbonyl-2,4-dimethyl-1,3-di(3-pyridylmethyl)pyrimidine (4e)** Solvent for chromatography: 30% hexane in ethyl acetate. Product: 233 mg. ^1H -NMR (90 MHz, CDCl_3) δ : 1.22 (3H, d, $J=6.6$ Hz, -Me), 1.36 (3H, d, $J=6.6$ Hz, -Me), 3.31 (1H, s, methylene H), 3.39 (1H, q, $J=6.6$ Hz, methine H), 3.66 (3H, s, -Me), 3.93 (1H, s, methylene H), 4.40 (1H, q, $J=6.6$ Hz, methine H), 4.42 (2H, s, methylene H), 7.13–7.24 (4H, m, aromatic H), 7.63 (1H, s, olefinic H), 8.54 (4H, m, aromatic H). CI-MS m/z : 353 ($M^+ + 1$).

***trans*-1,2,3,4-Tetrahydro-1,3-di[2-(3-indolyl)ethylamino]-5-methoxycarbonyl-2,4-dimethylpyrimidine (4f)** Solvent for chromatography: 50% hexane in ethyl acetate. Product: 287 mg. ^1H -NMR (90 MHz, CDCl_3) δ : 1.25 (6H, d, $J=6.6$ Hz, -Me), 2.28–3.46 (8H, m, methylene H), 3.66 (3H, s, -Me), 3.70 (1H, q, $J=6.6$ Hz, methine H), 4.38 (1H, q, $J=6.6$ Hz, methine H), 6.85–7.61 (11H, m, aromatic H and olefinic H), 8.02 (2H, br, -NH). High-resolution FAB-MS m/z : Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_4\text{O}_2$ ($M + H$) $^+$: 457.2613. Found: 457.2596.

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