Unexpected Sodium Methoxide-catalyzed Rearrangement of 6-Amino-5-aroyl-1,3-dimethyluracils to Form Novel Cinnamoamides

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

A synthetic access to novel cinnamoamides **6** was discovered by chance and explored following a two-step route. Compounds **3** were available from 6-amino-1,3-dimethyluracil (**1**) by acylation using benzoyl chlorides **2** and subsequently converted to 2-cyano-3-(*N*-methylamino)cinnamic acid methyl amides **6**. This sodium methoxide-catalyzed reaction involves ring opening of the pyrimidine ring followed by elimination of CO to form dimethyl carbonate and rearrangement. The application of **6** as potential catecholamine-*O*-methyl transferase (COMT) inhibitors for the treatment of Parkinson's disease is discussed.

Key words: Acylation, Rearrangement, 6-Amino-5-aroyl-1,3-dimethyluracil, Cinnamonitriles, COMT Inhibitor

Introduction

In the past 10 years, great efforts by medicinal chemists and pharmacologists have been devoted to the design of potent and selective ligands for adenosine receptors. In our research we established the 1,3-dimethylpyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-dione ring system instead of the xanthine scaffold [1 – 3]. Within the scope of our structure-activity studies concerning the affinity of these compounds for A_1- and A_{2A}-adenosine receptors we found that the structural features include a monosubstituted exocyclic amino function in positions 5 or 7 and electron-withdrawing groups at position 6. Within the group of xanthine derivatives several 8-styryl xanthines with selective A_{2A}-receptor antagonistic properties were developed [4]. The main drawback specific for this series was the low stability. Therefore, imidazo-, pyrimido-, and diazepinopurinediones as products of xanthine 7,8 annulation were designed representing constrained analogs of styrylxanthine derivatives [5]. Based on these tricyclic structures in connection with our successful displacement of the xanthine scaffold by pyrido[2,3-*d*]pyrimidine we decided to investigate annulated mono- and bicyclic pyrimidines such as pyrimido[4,5-*e*]diazepines, pyrimido[4,5-*b*]azepines, furo[2′,3′:4,5]pyrido[2,3-*d*]pyrimidines, and pyrazolo[3′,4′:4,5]pyrimido[4,5-*b*]azepines [6].

Results and Discussion

Our first approach to 7-membered ring-annulated uracil derivatives was a synthetic procedure analogous to that of benzodiazepines [7]. The planned synthetic sequence depicted in Scheme 1 would allow to gain structurally similar pyrimido[4,5-*e*]diazepines **5**.

Reviewing this concept, we acylated 6-amino-1,3-dimethyluracil (**1**) using benzoyl chloride (**2**) to form 6-amino-5-benzoyl-1,3-dimethyluracil (**3**) [8], but the following formation of the respective ketoxime **4** failed. The nucleophilic attack of hydroxylamine at the ketone function is obviously antagonized by the low electrophilicity of its carbonyl carbon atom. This negative result is explainable since compound **3** is characterized by the structure of a vinylogous amide or an acylated vinylogous amidine. Bredereck *et al.* [9] described the condensation of 6-amino-1,3-dimethyluracil-5-carbaldehyde with hy-

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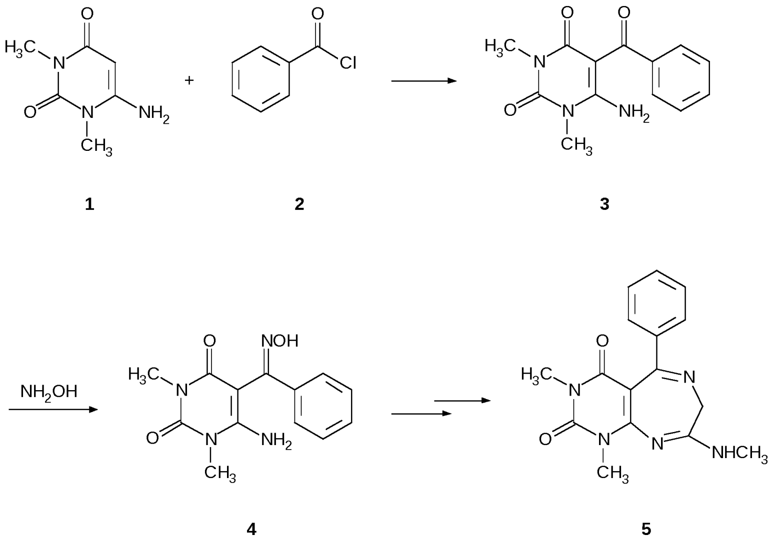
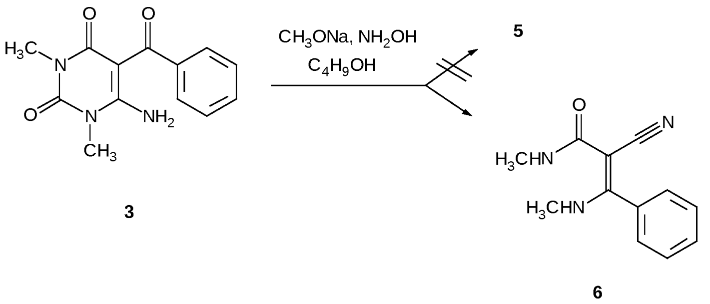


Scheme 1. Our concept of the pyrimido-diazepine synthesis.

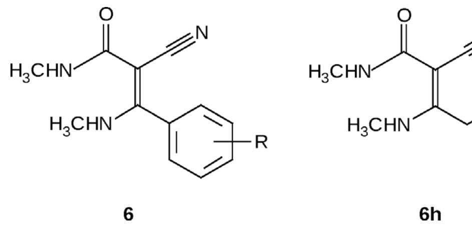


Scheme 2. Unexpected formation of 2-cyano-3-(*N*-methyl)aminocinnamic acid *N*-methyl amide.

droxylamine hydrochloride in the presence of sodium ethanolate in butanol to give the appropriate carbaldehyde oxime. However, the application of this method to the ketone **3** gave rise to a crystalline product the analytical and spectroscopic data of which identified the structure of this unexpected compound as 2-cyano-3-(*N*-methylamino)cinnamic acid methyl amide (**6**) (Scheme 2).

Later on, the reaction turned out to be independent of hydroxylamine hydrochloride, and the same product could be obtained by simply refluxing the ketone **3** with sodium methoxide in butanol. We would like to discuss the following reaction mechanism depicted in Scheme 3.

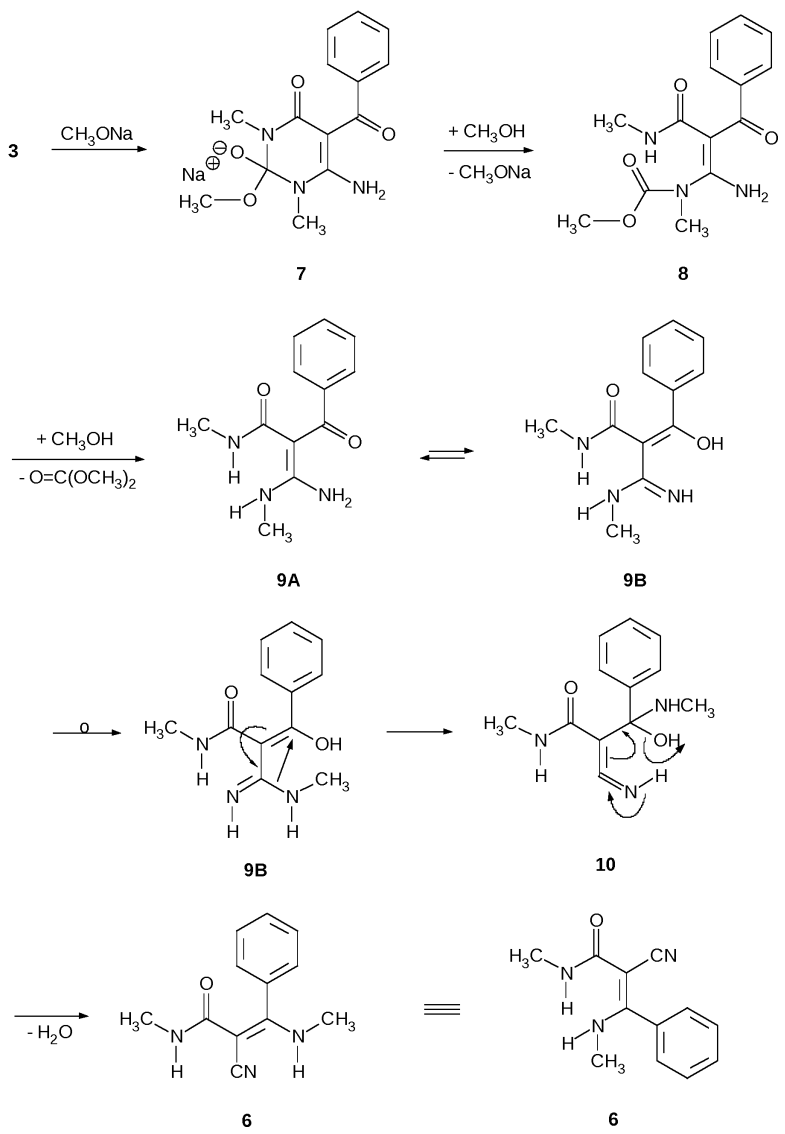
Nucleophilic attack of the methoxide anion selectively at C2 of the pyrimidine ring to afford **7** is followed by addition of methanol, ring opening and elimination of the methoxide anion giving the carbaminic acid ester **8**. An analogous process was described for the so-called “theophyllidine reaction” [10, 11]. Further addition of methanol leads to formation of



6	R	6	R
a	H	**e**	3,4-$(OCH_3)_2$
b	4-CH_3	**f**	4-Cl
c	4-C_2H_5	**g**	4-F
d	4-OCH_3		

Fig. 1. Cinnamic acid amides **6** prepared.

dimethyl carbonate and the vinylogous urea **9**. Subsequent rearrangement is occurring by shifting the equilibrium to the enol **9B**, this being possible by simultaneous electron transfer, moving the methylamino group to the enol carbon atom. Then the semiaminale group of the ketene imine **10** is stabilized by elimination of water to form cinnamoamide **6**.



Scheme 3. Reaction mechanism for the formation of the cinnamic acid amide **6**.

This condensation of **3** with sodium methanolate in butanol offered potential for further elaboration of the system, and a number of cinnamonitriles **6** have been obtained (Fig. 1).

It is noteworthy to point out that ketones **3** with benzoyl groups substituted by electron-withdrawing groups fail to undergo this rearrangement, *e. g.* 6-amino-5-(*p*-nitrobenzoyl)-1.3-dimethyluracil **3i**.

The structure of compound **6a** was unambiguously identified by comprehensive and detailed structure elucidation methods, particularly by means of one- and two-dimensional NMR spectroscopy as well as by X-ray crystallography (Fig. 2).

In the ^{1}H NMR spectrum of **6a** the signals of the protons of the methyl groups are split up to two doublets. After addition of D_2O two singlets are generated. The cyano group could be evidenced by IR as well as by ^{13}C NMR spectroscopy. According to the NOESY spectrum, the protons of the methyl group of the methylamino function are near to the aromatic protons.

2-Cyano-3-(*N*-methylamino)cinnamic acid methyl amides **6** are structurally related to the catecholamine-*O*-methyl transferase (COMT) inhibitor Entacapone (Fig. 3) which is used for the treatment of Parkinson's disease by reducing the speed of the degradation of

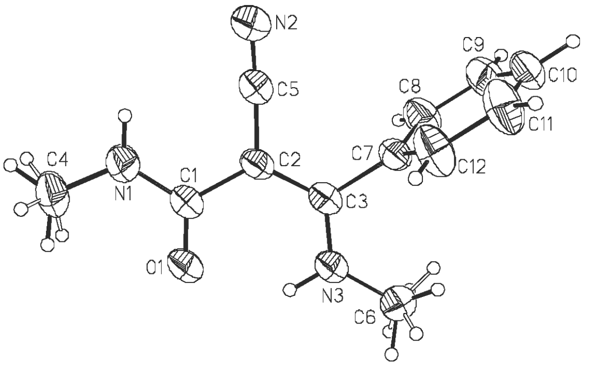


Fig. 2. Molecular structure of **6a** in the crystal and crystallographic labelling scheme used (displacement ellipsoids at the 50 % probability level).

dopamine. This is why the rearrangement discovered incidentally by us offers a good chance for the simple and efficient preparation of novel potential COMT inhibitors.

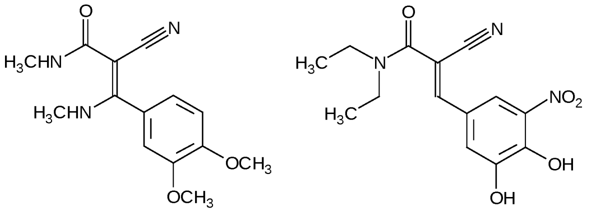
Conclusions

We have demonstrated that pyrimidodiazepines **5** are not available by application of Sternberg's benzodiazepine synthesis based on analogous pyrimidine derivatives. Within experiments for the preparation of the ketoxime **4** as an important intermediate, the unexpected formation of novel 2-cyano-3-(*N*-methylamino)cinnamic acid methyl amides **6** was discovered and a sound reaction mechanism proposed. To the best of our knowledge this type of base-catalyzed degradation of 6-amino-5-benzoyl-1,3-dimethyluracil **3** is described for the first time in pyrimidine chemistry. Since amides **6** are structurally related to Entacapone, this synthetic sequence might be useful for the development of novel COMT inhibitors.

Experimental Section

General methods

Melting points are uncorrected and were recorded with a Stuart Scientific SMP03 melting point apparatus. 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra (internal Me_4Si) were recorded using a Bruker Avance III 300 spectrometer (δ given in ppm, J in Hz). IR spectra (KBr pellets) were measured on a Perkin-Elmer FT-IR 16 PC spectrometer. ESI-MS spectra were taken on a Bruker LC esquire mass spectrometer (ESI) in a MeOH/water mixture by direct infusion. EI (electron impact) mass spectra were obtained with an ionization energy of 70 eV using a HP 5989 mass spectrometer and a direct inlet probe with a tungsten wire; *m/z* values are reported



6e **Entacapone**

Fig. 3. The structural similarity of **6e** with Entacapone.

followed by the relative intensity in parentheses. Elemental analyses were obtained from the Microanalytical laboratory of the Institute of Inorganic Chemistry, University of Kiel. Macherey-Nagel Polygram® SIL G/UV_{254} on plastic sheets was used for TLC monitoring.

*General procedure for the synthesis of 5-acyl-6-amino-1,3-dimethyluraciles **3***

To a suspension of 6-amino-1,3-dimethyluracil (**1**) (0.1 mol) in pyridine (100 mL) the substituted carboxylic acid chloride **2** (0.1 mol) was added slowly dropwise at r. t. The mixture was subsequently refluxed, monitoring by TLC (DCM-MeOH, 9 : 1). Evaporation of the solvent was followed by addition of water to the resulting residue, and the mixture was heated for a short time. After cooling to r. t. the solid formed was purified by crystallization from dioxane.

*6-Amino-5-benzoyl-1,3-dimethyluracil (**3a**)*

This compound was prepared according to ref. [8].

*6-Amino-1,3-dimethyl-5-(p-methylbenzoyl)uracil (**3b**)*

The mixture of **1** and **2b** was refluxed for 3 h. M. p. 278.2 °C (dioxane); yield 18.38 g (70 mmol, 67 %). – ^{1}H NMR ([D_6]DMSO): δ = 2.33 (s, 3H, CH_3), 3.07 (s, 3H, N^3-CH_3), 3.37 (s, 3H, N^1-CH_3), 7.12 (m_c, 2H, 3-H, 5-H), 7.29 (m_c, 2H, 2-H, 6-H), 9.12 (br s, 1H, $HNCH_3$). – ^{13}C NMR ([D_6]DMSO): δ = 20.93 (CH_3), 27.42 (N^3-CH_3), 29.60 (N^1-CH_3), 89.53 (C-5), 126.66 (2C, C-2′, C-6′), 127.39 (2C, C-3′, C-5′), 139.98 (C-1′), 144.57 (C-4′), 150.05 (C-2), 157.89 (C-6), 160.66 (C-4), 194.44 (CO). – ESI-MS: *m/z* = 182 $[M–C_6H_4CH_3]^+$, 274 $[M+H]^+$, 569 $[2M+Na]^+$. – $C_{14}H_{15}N_3O_3$ (273.29): calcd. C 61.53, H 5.53, N 15.38; found C 61.41, H 5.63, N 15.57.

*6-Amino-1,3-dimethyl-5-(p-ethylbenzoyl)uracil (**3c**)*

The mixture of **1** and **2c** was refluxed for 3 h. M. p. 274.8 °C (dioxane); yield 14.44 g (50 mmol, 50 %). – ^{1}H NMR ([D_6]DMSO): δ = 1.20 (t, ^3J = 7.6 Hz, 3H, CH_2CH_3), 2.63 (q, ^3J = 7.6 Hz, 2H, CH_2CH_3), 3.07 (s, 3H, N^3-CH_3), 3.37 (s, 3H, N^1-CH_3), 7.16 (d, ^3J = 8.3 Hz, 2H, 3′-H, 5′-H), 7.31 (d, ^3J = 8.2 Hz, 2H, 2′-H, 6′-H), 8.91 (br s, 1H, NH_2). – ^{13}C NMR ($[D_6]$DMSO): δ = 15.26 ($CH_2\mathit{C}H_3$), 27.41 (N^3-CH_3), 28.01 ($\mathit{C}H_2CH_3$), 29.55 (N^1-CH_3), 89.53 (C-5), 126.53 (2C, C-2′, C-6′), 127.46 (2C, C-3′, C-5′), 140.21 (C-1′), 145.44 (C-4′), 150.05 (C-2), 157.89 (C-6), 160.67 (C-4), 194.41 (CO). – ESI-MS: *m/z* = 182 $[M–C_6H_4CH_2CH_3]^+$, 288 $[M+H]^+$, 597 $[2M+Na]^+$. – $C_{15}H_{17}N_3O_3$ (287.32): calcd. C 62.71, H 5.96, N 14.62; found C 62.98, H 6.05, N 14.71.

*6-Amino-1,3-dimethyl-5-(p-methoxybenzoyl)uracil (**3d**)*

The mixture of **1** and **2d** was refluxed for 3.5 h. M. p. 263.1 °C (dioxane); yield 16.03 g (60 mmol, 55 %). – ^1H NMR ($[D_6]$DMSO): δ = 3.08 (s, 3H, N^3-CH_3), 3.36 (s, 3H, N^1-CH_3), 3.79 (s, 3H, OCH_3), 6.88 (m_c, ^3J = 8.8 Hz, 2H, 3′-H, 5′-H), 7.41 (m_c, ^3J = 8.8 Hz, 2H, 2′-H, 6′-H), 8.95 (br s, 1H, NH_2). – ^{13}C NMR ($[D_6]$DMSO): δ = 27.45 (N^3-CH_3), 29.57 (N^1-CH_3), 55.16 (OCH_3), 89.37 (C-5), 112.48 (2C, C-3′, C-5′), 129.77 (2C, C-2′, C-6′), 134.67 (C-1′), 150.10 (C-2), 157.71 (C-6), 160.69 (C-4′), 160.88 (C-4), 193.50 (CO-Ar). – ESI-MS: *m/z* = 182 $[M–C_6H_4OCH_3]^+$, 290 $[M+H]^+$, 601 $[2M+Na]^+$. – $C_{14}H_{15}N_3O_4$ (289.29): calcd. C 58.13, H 5.23, N 14.53; found C 57.97, H 5.29, N 14.46.

*6-Amino-1,3-dimethyl-5-(3′,4′-dimethoxybenzoyl)uracil (**3e**)*

The mixture of **1** and **2e** was refluxed for 3.0 h. M. p. 226.5 °C (dioxane); yield 20.94 g (70 mmol, 66 %). – ^1H NMR ($[D_6]$DMSO): δ = 3.09 (s, 3H, N^3-CH_3), 3.37 (s, 3H, N^1-CH_3), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.90 (m_c, 1H, 5′-H), 7.07 (m_c, 2H, 2′-H, 6′-H), 8.89 (br s, 2H, NH_2). – ^{13}C NMR ($[D_6]$DMSO): δ = 27.44 (N^3-CH_3), 27.55 (N^1-CH_3), 55.48 (2C, 2× OCH_3), 89.41 (C-5), 110.22 (C-2′), 111.66 (C-5′), 121.47 (C-6′), 134.67 (C-1′), 147.52 (C-2), 150.13 (C-4′), 150.70 (C-3′), 157.58 (C-6), 160.66 (C-4), 193.52 (CO-Ar). – ESI-MS: *m/z* = 182 $[M–C_6H_4(OCH_3)_2]^+$, 320 $[M+H]^+$, 661 $[2M+Na]^+$. – $C_{15}H_{14}N_3O_5$ (319.32): calcd. C 56.42, H 5.37, N 13.16; found C 56.39, H 5.50, N 12.85.

*6-Amino-1,3-dimethyl-5-(p-chlorobenzoyl)uracil (**3f**)*

This compound was prepared according to ref. [8].

*6-Amino-1,3-dimethyl-5-(p-fluorobenzoyl)uracil (**3g**)*

The mixture of **1** and **2g** was refluxed for 2.5 h. M. p. 238.1 °C (dioxane); yield 16.34 g (0.06 mol, 59 %). – ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 3.07 (s, 3H, N^3-CH_3), 3.37 (s, 3H, N^1-CH_3), 7.13 (m_c, 2H, 3-H, 5-H), 7.44 (m_c, 2H, 2-H, 6-H), 9.17 (br s, 2H, NH_2). – ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 27.44 (N^3-CH_3), 29.58 (N^1-CH_3), 89.53 (C-5), 113.89 (C-3′), 114.18 (C-5′), 129.64 (2C, C-2′, C-6′), 139.25 (C-1′), 149.98 (C-2), 158.02 (C-6), 160.95 (C-4), 164.43 (C-4′), 193.16 (CO). – ESI-MS: *m/z* = 182 $[M–C_6H_4(OCH_3)_2]^+$, 278 $[M+H]^+$, 577 $[2M+Na+]^+$. – $C_{13}H_{12}N_3O_3F$ (277.26): calcd. C 56.32, H 4.36, N 15.16; found C 56.33, H 4.63, N 15.33.

*6-Amino-1,3-dimethyl-5-(2-phenylacetyl)uracil (**3h**)*

This compound was prepared according to ref. [8].

*General procedure for the synthesis of 2-cyano-3-(N-methylamino)cinnamic acid methyl amides **6***

A mixture of 6-amino-5-aroyl-1,3-dimethyluracil **3** (5 mmol) and sodium methoxide (2.7 g, 50 mmol) in butanol (25 mL) was refluxed, monitoring by TLC (DCM-MeOH, 9 : 1). After evaporation of the solvent, water was added to the resulting residue followed by azeotropic distillation for the removal of butanol. The water was concentrated, and ice was added to the resulting residue.

Method A: The product formed was filtered and purified by crystallization from ethanol.

Method B: After cooling to r. t. the solution was extracted three times with dichloromethane (50 mL). After drying over sodium sulfate followed by evaporation of the solvent, diethyl ether was added to the oily residue for crystallization and again removed. The product formed was purified by crystallization from ethanol.

*2-Cyano-3-(N-methylamino)cinnamic acid N-methylamide (**6a**)*

The mixture of **3a** and sodium methoxide was refluxed for 2 h (method A). M. p. 173 °C (ethanol); yield 0.8 g (3.7 mmol, 73 %). – ^1H NMR ($CDCl_3$): δ = 2.75 (d, ^3J = 5.2 Hz, 3H, $HNC\mathit{H}_3$), 2.85 (d, ^3J = 5.0 Hz, 3H, H_3CNHCO), 5.95 (br s, 1 H, $H_3CN\mathit{H}CO$), 7.33 (m_c, 2H, H-2′, H-6′), 7.49 (m_c, 3H, H-3′, H-4′, H-5′), 10.62 (br s, 1H, $\mathit{H}NCH_3$). – ^{13}C NMR ($CDCl_3$): δ = 26.00 ($H_3\mathit{C}NHCO$), 31.62 ($HN\mathit{C}H_3$), 72.92 (C-2), 120.64 (CN), 127.54 (2C, C-2′, C-6′), 128.93 (2C, C-3′, C-5′), 130.31 (C-4′), 132.18 (C-1′), 168.70 (C-1), 170.24 (C-3). – ^1H, ^1H NOESY ($CDCl_3$): cross peaks = 2.75/7.33, 2.75/10.62, 2.85/5.95. – ^1H, ^{13}C HSQC ($CDCl_3$): cross peaks = 2.75/31.62, 2.85/26.06, 7.33/127.54, 7.49/128.93, 7.49/130.41. – ^1H, ^{13}C HMBC ($CDCl_3$): cross peaks: 2.75/31.62 (^1J), 2.85/26.06 (^1J), 2.85/168.70 (^3J), 2.75/170.24 (^3J), 5.95/168.70 (^2J), 7.33/130.31 (^3J), 7.33/170.24 (^3J), 7.49/127.54 (^3J, ^2J), 7.49/128.93 (^2J), 7.49/132.18 (^3J). – IR: ν = 3338 (m), 2196 (s), 1630 (m), 1604 (s), 1532 (m), 810 (m) cm^{-1}. – EI-MS: *m/z* (%) = 215 (38) $[M]^+$, 214 (100), 185 (42), 158 (25), 118 (47), 91 (13), 77 (36), 58 (22), 51 (19). – $C_{12}H_{13}N_3O$ (215.26): calcd. C 66.96, H 6.09, N 19.52; found C 67.07, H 6.25, N 19.51.

*2-Cyano-p-methyl-3-(N-methylamino)cinnamic acid N-methylamide (**6b**)*

The mixture of **3b** and sodium methoxide was refluxed for 1.5 h (method A). M. p. 217 °C (ethanol); yield 0.45 g (2 mmol, 39 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.39 (s, 3H,$\mathrm{CH_3}$), 2.76 (d, ^3J = 5.2 Hz, 3H, $\mathrm{HNC}H_3$), 2.85 (d, ^3J = 5.0 Hz, 3H, $H_3\mathrm{CNHCO}$), 5.92 (br s, 1 H, $\mathrm{H_3CN}H\mathrm{CO}$), 7.25 (m$_c$, 4H, Ar-H), 10.60 (br s, 1H, $H\mathrm{NCH_3}$). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 18.95 ($\mathrm{CH_3}$), 23.55 ($\mathrm{H_3}C\mathrm{NHCO}$), 29.20 ($\mathrm{HN}C\mathrm{H_3}$), 70.42 (C-2), 118.51 (CN), 125.10 (2C, C-2′, C-6′), 126.80 (2C, C-3′, C-5′), 127.17 (C-1′), 138.15 (C-4′), 166.37 (C-1), 168.12 (C-3). – EI-MS: *m/z* (%) = 229 (85) [M]$^+$, 198 (86), 169 (41), 141 (16), 138 (37), 91 (82), 82 (100). – $\mathrm{C_{13}H_{15}N_3O}$ (229.28): calcd. C 68.10 H 6.59 N 18.33; found C 68.01 H 6.71 N 18.38.

*2-Cyano-p-ethyl-3-(N-methylamino)cinnamic acid N-methylamide (**6c**)*

The mixture of **3c** and sodium methoxide was refluxed for 1.5 h (method A). M. p. 131 °C (ethanol); yield 0.48 g (2 mmol, 39 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 1.22 (t,^3J = 7.6 Hz, 3H, $\mathrm{CH_2C}H_3$), 2.68 (m$_c$, 8H, $\mathrm{HNC}H_3$, $H_3\mathrm{CNHCO}$, $\mathrm{C}H_2\mathrm{CH_3}$), 7.15 (br s, 1 H, $\mathrm{H_3CN}H\mathrm{CO}$), 7.29 (d, ^3J = 8.0 Hz, 2H, H-3′, H-5′), 7.37 (d, ^3J = 8.0 Hz, 2H, H-2′, H-6′), 10.62 (br s, 1H, $H\mathrm{NCH_3}$). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 15.03 ($\mathrm{CH_2}C\mathrm{H_3}$), 25.89 ($\mathrm{H_3}C\mathrm{NHCO}$), 27.87 ($C\mathrm{H_2CH_3}$), 31.43 ($\mathrm{HNCH_3}$), 71.77 (C-2), 120.05 (CN), 128.04 (2C, C-2′, C-6′), 130.41 (2C, C-3′, C-5′), 129.83 (C-1′), 145.67 (C-4′), 167.98 (C-1), 169.70 (C-3). – ESI-MS: *m/z* = 244 [M+H]$^+$, 509 [2M+Na]$^+$. – $\mathrm{C_{14}H_{17}N_3O}$ (243.31): calcd. C 69.11 H 7.04 N 17.27; found C 69.34 H 7.13 N 17.14.

*2-Cyano-p-methoxy-3-(N-methylamino)cinnamic acid N-methylamide (**6d**)*

The mixture of **3d** and sodium methoxide was refluxed for 2 h (method A). M. p. 208 °C (ethanol); yield 0.8 g (3.3 mmol, 65 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.66 (d, ^3J = 3.0 Hz, 3H, $\mathrm{HNC}H_3$), 2.69 (d, ^3J = 3.0 Hz 3H, $H_3\mathrm{CNHCO}$), 3.82 (s, 1H, $\mathrm{OCH_3}$), 7.07 (m$_c$, 2H, H-3′, H-5′), 7.14 (br s, 1 H, $\mathrm{H_3CN}H\mathrm{CO}$), 7.33 (m$_c$, 2H, H-2′, H-6′), 10.61 (br s, 1H, $H\mathrm{NCH_3}$). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 26.03 ($\mathrm{H_3}C\mathrm{NHCO}$), 31.70 ($\mathrm{HNCH_3}$), 55.32 ($\mathrm{OCH_3}$), 72.94 (C-2), 114.36 (2C, C-3′, C-5′), 121.15 (CN), 124.22 (C-1′), 129.36 (2C, C-2′, C-6′), 161.13 (C-4′), 168.87 (C-1), 170.32 (C-3). – ESI-MS: *m/z* = 246 [M+H]$^+$, 268 [M+Na]$^+$. – $\mathrm{C_{13}H_{15}N_3O_2}$ (245.28): calcd. C 63.66 H 6.16 N 17.13; found C 63.73 H 6.28 N 17.22.

*2-Cyano-3′,4′-dimethoxy-3-(N-methylamino)cinnamic acid N-methylamide (**6e**)*

The mixture of **3e** and sodium methoxide was refluxed for 4 h (method B). M. p. 172 °C (ethanol); yield 0.17 g (0.62 mmol, 12 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.66 (d, ^3J = 4.5 Hz, 3H, $\mathrm{HNC}H_3$), 2.71 (d, ^3J = 5.0 Hz 3H, $H_3\mathrm{CNHCO}$), 3.79 (s, 3H, $\mathrm{OCH_3}$), 3.82 (s, 3H, $\mathrm{OCH_3}$), 6.94 (m$_c$, 2H, H-2′, H-5′), 7.08 (m$_c$, 1H, H-6′), 7.14 (br s, 1H, $\mathrm{H_3CN}H\mathrm{CO}$), 10.61 (br s, 1H, $H\mathrm{NCH_3}$). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 25.90 ($\mathrm{H_3}C\mathrm{NHCO}$), 31.45 ($\mathrm{HNCH_3}$), 55.47 ($\mathrm{OCH_3}$), 55.70 ($\mathrm{OCH_3}$), 71.86 (C-2), 111.34 (C-2′), 111.59 (C-5′), 120.23 (CN), 120.61 (C-6′), 124.98 (C-1′), 148.61 (C-4′), 149.93 (C-3′), 168.07 (C-1), 169.54 (C-3). – ESI-MS: *m/z* = 276 [M+H]$^+$, 573 [2M+Na]$^+$. – $\mathrm{C_{14}H_{17}N_3O_3}$ (275.31): calcd. C 61.08 H 6.22 N 15.26; found C 60.70 H 6.32 N 15.27.

*p-Chloro-2-cyano-3-(N-methylamino)cinnamic acid N-methylamide (**6f**)*

The mixture of **3f** and sodium methoxide was refluxed for 2 h (method A). M. p. 206 °C (ethanol); yield 1.1 g (4.4 mmol, 88 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.66 (d, ^3J = 4.5 Hz, 3H, $\mathrm{HNC}H_3$), 2.67 (d, ^3J = 5.13 Hz, 3H, $H_3\mathrm{CNHCO}$), 7.21 (br s, 1H, $\mathrm{H_3CN}H\mathrm{CO}$), 7.44 (m$_c$, 2H, H-3′, H-5′), 7.61 (m$_c$, 2H, H-2′, H-6′), 10.59 (br s, 1H, $H\mathrm{NCH_3}$). – ^{13}C NMR ($\mathrm{CDCl_3}$): δ = 25.90 ($\mathrm{H_3}C\mathrm{NHCO}$), 31.49 ($\mathrm{HNCH_3}$), 71.99 (C-2), 119.75 (CN), 128.93 (2C, C-2′, C-6′), 129.68 (2C, C-3′, C-5′), 131.35 (C-1′), 134.80 (C-4′), 167.69 (C-1), 168.40 (C-3). – ESI-MS: *m/z* = 250 [M+H]$^+$, 272 [M+Na]$^+$. – EI-MS: *m/z* (%) = 251 (13) [M, ^{37}Cl]$^+$, 249 (39) [M, ^{35}Cl]$^+$, 250 (34) [^{35}Cl], 248 (100) [^{35}Cl], 221 (15) [^{37}Cl], 219 (45) [^{35}Cl], 194 (10) [^{37}Cl], 192 (29) [^{35}Cl], 154 (15) [^{37}Cl], 152 (45) [^{35}Cl], 113 (5) [^{37}Cl], 111 (16) [^{35}Cl], 58 (43). – $\mathrm{C_{12}H_{12}N_3OCl}$ (249.70): calcd. C 57.72 H 4.84 N 16.83; found C 58.03 H 5.02 N 16.93.

*2-Cyano-p-fluoro-3-(N-methylamino)cinnamic acid N-methylamide (**6g**)*

The mixture of **3g** and sodium methoxide was refluxed for 1.5 h (method A). M. p. 163 °C (ethanol); yield 125 mg (0.5 mmol, 11 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.66 (m$_c$, 6H, $\mathrm{HNC}H_3$, $H_3\mathrm{CNHCO}$), 7.20 (br s, 1 H, $\mathrm{H_3CN}H\mathrm{CO}$), 7.36 (m$_c$, 2H, H-3′, H-5′), 7.48 (m$_c$, 2H, H-2′, H-6′), 10.61 (br s, 1H, $H\mathrm{NCH_3}$). – ^{13}C NMR (75 MHz): δ = 26.03 ($\mathrm{H_3}C\mathrm{NHCO}$), 31.70 ($\mathrm{HNCH_3}$), 55.32 ($\mathrm{OCH_3}$), 72.94 (C-2), 114.36 (2C, C-3′, C-5′), 121.15 (CN), 124.22 (C-1′), 129.36 (2C, C-2′, C-6′), 161.13 (C-4′), 168.87 (C-1), 170.32 (C-3). – ESI-MS: *m/z* = 234 [M+H]$^+$, 256 [M+Na]$^+$. – $\mathrm{C_{12}H_{12}N_3OF}$ (233.25): calcd. C 61.79 H 5.19 N 18.02; found C 61.79 H 5.19 N 18.02.

*2-Cyano-3-(N-methyl)amino-4-phenylbut-2-enic acid N-methylamide (**6h**)*

The mixture of **6h** and sodium methoxide was refluxed for 2 h (method A). M. p. 210 °C (ethanol); yield 0.65 g (2.8 mmol, 57 %). – ^{1}H NMR ($\mathrm{CDCl_3}$): δ = 2.64 (d, ^3J =

6.0 Hz, 3H, HNCH_3), 2.85 (d, ^3J = 6.0 Hz, 3H, H_3CNHCO), 3.92 (s, 2H, CH_2), 7.18 (br s, 1 H, H_3CN*H*CO), 7.28 (m_c, 3H, H-3′,H-4′, H-5′), 7.37 (m_c, 2H, H-2′, H-6′), 10.68 (br s, 1H, *H*NCH_3). – ^{13}C NMR ($CDCl_3$): δ = 25.99 (H_3*C*NHCO), 30.32 (HNCH_3), 37.01 (CH_2), 72.84 (C-2), 121.18 (CN), 127.25 (C-4′), 127.97 (2C, C-3′, C-5′), 129.01 (2C, C-2′, C-6′), 133.92 (C-1′), 168.85 (C-1), 169.17 (C-3). – ESI-MS: *m/z* = 230 [M+H]$^+$, 252 [M+Na]$^+$. – $C_{13}H_{15}N_3O$ (229.28): calcd. C 68.10 H 6.59 N 18.33; found C 68.13 H 6.50 N 18.58.

X-Ray structure determination of ***6a***

Crystal size: 0.3 × 0.2 × 0.2 mm^3, monoclinic crystal system, space group $P2_1/n$, a = 7.4436(4), b = 10.0228(6), c = 15.7108(11) Å, β = 103.337(8)°, V = 1140.50(12) Å^3, Z = 4, T = 293(2) K, $\mu(\mathrm{Mo}K_\alpha)$ = 0.083 mm^{-1}, θ range for data collection 3.35 – 26.02°, index ranges (h, k, l) = ±8, ±12, ±19, 6852 measured reflections, 2167 independent reflections, R_int = 0.0389, GOF (F^2) = 1.018, R_1/wR_2 [$I \geq 2\sigma(I)$] = 0.0431/0.1051, R_1/wR_2 (all data) = 0.0668/0.1178, $\Delta\rho_\mathrm{fin}$ (max/min) = 0.126/−0.135 e Å^{-3}. Remarks: Data collection was performed using a Stoe IPDS-1 (Imaging Plate Diffraction System) with MoK_α radiation at r. t. The structure was solved with Direct Methods using SHELXS-97 and refined against F^2 with SHELXL-97. All non-hydrogen atoms were refined anisotropically. The C–H H atoms were positioned in idealized geometry and were refined using a riding model. The H atoms in both methyl groups are disordered and were refined using a split model. The N–H H atoms were located in the difference map; their bond lengths were set to ideal values, and finally they were refined using a riding model.

CCDC 726715 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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