SYNTHESIS OF 1-CYANO-2-PHENYL-1,2,4,5-TETRAHYDRO-3H-3-BENZAZEPINES

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Abstract —— N-(2-Cyanomethyl-4,5-dimethoxyphenethyl)trifluoroacetamides 3, prepared by two step cyanomethylation of N-(3,4-dimethoxyphenethyl)trifluoroacetamides 1, were treated with benzaldehydes in the presence of EtONa to give the titled benzazepines 5. The structures of 5 were elucidated by ^{1}H nmr analysis, and the cyclization mechanism was also described.

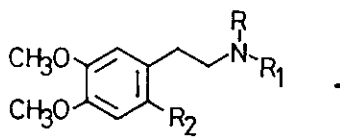
3-Benzazepines are of a considerable interest as skeletal features characteristic of some groups[1] of the isoquinoline alkaloids, and also as compounds having pharmacological activities.[2,3] In our previous studies,[4] the construction of the benz[d]indeno[1,2-b]azepine ring system has been efficiently achieved using the 2-oxo-3-benzazepines, which were prepared via the two step procedure for cyanomethylation of N-acetyl-3,4-dialkoxy-N-methylphenethylamines. The present paper deals with the preparation of the new type of 3-benzazepines from benzaldehydes and N-(2-cyanomethylphenethyl)-trifluoroacetamides by the base-catalyzed cyclization reaction.

RESULTS AND DISCUSSION

According to the method reported for the N-(2-cyanomethylphenethyl)acetamide,[3,4] N-trifluoroacetylhomoveratrylamine (**1a**) and its N-methyl derivative (**1b**) were treated with formalin and HCl gas at -15°C. The resulting benzyl chlorides **2a,b** were subsequently treated with sodium cyanide to afford the benzyl cyanides **3a,b** in good yields. When a mixture of **3a** and 2,3-dimethoxybenzaldehyde was warmed in EtONa-EtOH at 45-50°C, the benzazepine **5a** was obtained in 30% yield. Similarly, the reaction with 2-bromo-4,5-dimethoxybenzaldehyde gave **5b** (34%). From N-methyl amides **3c,d**, the corresponding 3-benzazepines **5c,d** were formed in the comparable yields.[5]

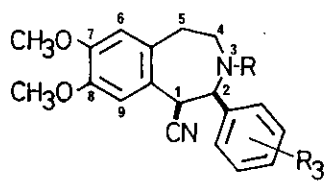
^{1}H Nmr spectra of **5a** revealed two sets of signals at δ 3.99 and 4.37 due to C_1 and C_2 protons. Irradiation of the broad singlet signal at δ 4.37 (C_2-H) caused the nuclear Overhouser enhancement

of the doublet signal at δ 3.99 (J=0.7 Hz, C_1-H) and the triplet-like double doublet signal at δ 2.92 (J=11.7, 12.8 Hz, 4α-H). It is reasonable to say that the configuration of C_1-H is cis to C_2-H, since these minimum coupling constant (J=0.7 Hz) were agreed with the Karplus calculation[6] for vicinal protons with the dihedral angle of 90°. It is also suggested that all the above three protons are in the same orientation, α in this case. In 5b, the C_2 proton appears as a doublet signal (J=1.1 Hz) at δ 4.32. When the 4α-H signal of 5a was irradiated, the double doublet signal at δ 3.50 was clearly enhanced as well as C_2-H at δ 4.37. Hence the signal at δ 3.50 was assigned to 4β-H. In case of the N-CH_3 derivative, irradiation of the N-CH_3 protons of 5c gave the positive NOE to each signal of C_2-H (δ 3.91), 4α-H (δ 2.44), 4β-H (δ 2.84) and $C_{6'}$-H (δ 7.36). Signals of the axial type C_2-H and 4α-H in 5c move to the higher field (Δ=0.46-0.48 ppm) than those in 5a. This may be accounted for by inductive effect of N-CH_3 group. In 5d, a singlet aromatic proton in the lowest field (δ 7.43) was found to be $C_{6'}$-H because its positive NOE on irradiation of N-methyl group was observed. Thus, the NOE experiments taking the difference spectra correlated $C_{1,2,4}$ and phenyl protons each other. Further the stereochemistry of C_4 and C_5 protons was examined in collaboration with the decoupling experiments, and assigned as noted in the Experimental section. These results suggest that the azepine molecules through 5a~d have the rigid conformations, which are essentially identical with those defined by Dreiding model analysis, as depicted for 5c in the figure. It is of interest that the dihedral angles of 4α-H − 5α-H (J=0 Hz) and 4β-H − 5β-H (J=0 Hz) appear both almost 90° as well as that of C_1-H − C_2-H (J=0~1.1 Hz).

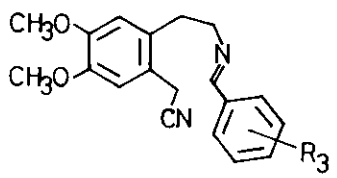


a: R=H, b: R=CH_3

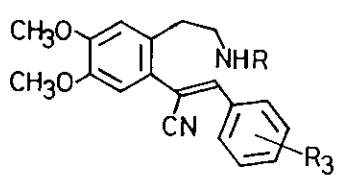
1. R_1=$COCF_3$, R_2=H
2. R_1=$COCF_3$, R_2=CH_2Cl
3. R_1=$COCF_3$, R_2=CH_2CN
4. R_1=H, R_2=CH_2CN



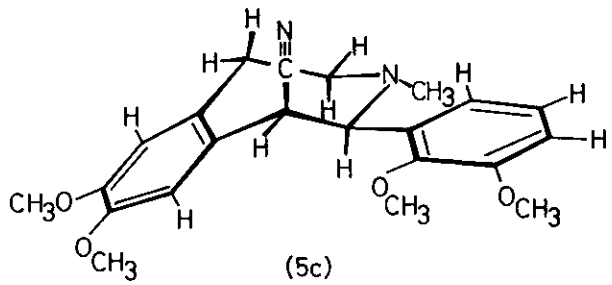
5a. R=H, R_3=2',3'-$(OCH_3)_2$
5b. R=H, R_3=2'-Br-4',5'-$(OCH_3)_2$
5c. R=CH_3, R_3=2',3'-$(OCH_3)_2$
5d. R=CH_3, R_3=2'-Br-4',5'-$(OCH_3)_2$



6a. R_3=2',3'-$(OCH_3)_2$
6b. R_3=2'-Br-4',5'-$(OCH_3)_2$



7.



(5c)

In order to explain the reaction mechanism, first, the intramolecular addition of the cyanomethyl anion to the imino group of 6 was examined. The amine **4a**, prepared by treatment of the trifluoroacetamide **3a** with H_2O-K_2CO_3, was condenced with 2,3-dimethoxybenzaldehyde or 2-bromo-4,5-dimethoxybenzaldehyde by heating in ^tBuOH. The resulting imino compounds **6a,b** (88 and 85%) were subsequently treated under the same condition (EtONa-EtOH) as noted for the azepines **5**. However, **5a** or **5b** formed only in 11 or 13% yield, together with the corresponding benzaldehyde, and the starting imine was not recovered. On the other hand, when the amine **4a** was treated with 2,3-dimethoxybenzaldehyde in the same manner, **5a** was obtained in the better yield (15 ∿ 25%),[7] but somehow lower than the yield (30%) for the preparation of **5a** starting with **3a**. These may suggest that **6a** or **6b** was hydrolyzed to the amine (**4a**) and each benzaldehyde, from which **5a** or **5b** was obtained. Accordingly, it is assumed that the cyclization reaction proceeds by the condensation of cyanomethyl group with the appropriate benzaldehyde, and finishes by the intramolecular Michael addition of the simultaniously and/or subsequently formed amino group to the resulting α-phenylcinnamonitrile derivative (7).[8,9]

EXPERIMENTAL

Melting points were determined on a MEL-TEMP (Laboratory Devices), and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Hitachi-Perkin Elmer Model 125 spectrophotometer. ^1H Nmr spectra were run on $CDCl_3$ solution with Me_4Si as an internal standard (δ=0 ppm) and resistered on a Hitachi R-22 (90 MHz) or JEOL JNM-FX 270 (270 MHz) spectrometer. Mass spectra were obtained on JEOL JMS-D300 at 70 eV under electron impact conditions. Preparative TLC was performed on Merck Kieselgel 60 PF_{254} (N0.7749).

N-(3,4-Dimethoxyphenethyl)trifluoroacetamide (1a). A mixture of homoveratrylamine (9.05 g, 50 mmol), trifluoroacetic anhydride (11.6 g) and pyridine (4.3 g) in dry benzene (50 ml) was allowed to stir at room temperature for 20 h. The mixture was then washed with water (50 ml × 3), dried (Na_2SO_4), and evaporated. The residue was crystallized from ether to give the acetamide **1a** (11.9 g, 86%), mp 81-83°C, as a colorless solid. Recrystallization from ether gave an analytical sample, mp 83-84°C. Ir (nujol) 3330, 1702, 1610, 1595, 1577, 1518 cm^{-1}; ^1H nmr (90 MHz) δ 2.83(2H, t J=6.5

Hz, CH_2CH_2N), 3.59, 3.62 (each 1H, t J=6.5 Hz, CH_2N), 3.99, 3.91 (each 3H, s, CH_3O 2), 6.50 (1H, br, NH), 6.65-6.90 (3H, m, Ar-H). Anal. Calcd for $C_{12}H_{14}O_3NF_3$: C, 51.99; H, 5.09; N, 5.05. Found: C, 52.01; H, 5.07; N, 5.16.

N-(3,4-Dimethoxyphenethyl)-N-methyltrifluoroacetamide (1b). Trifluoroacetylation of 3,4-dimethoxy-N-methylphenethylamine (9.75 g) in the same manner as noted above afforded the crude product (13.1 g). Distillation gave 1b (12.1 g, 83%), bp 125-128°C/0.1 torr, as a light yellow oil, which on crystallization from benzene-petroleum ether afforded a white solid, mp 63-65°C. Ir (nujol) 1695, 1609, 1596, 1578 cm^{-1}; ^1H nmr (90 MHz) δ 2.76-3.05 (2H, m, CH_2CH_2N), 3.00, 3.05 (3H, each s, about 1:1, N-CH_3), 3.63 (2H, br t, J=7.0 Hz, CH_2N), 3.89 (6H, s, CH_3O×2), 6.65-6.90 (3H, m, Ar-H). Anal. Calcd for $C_{13}H_{16}O_3NF_3$: C, 53.61; H, 5.54; N, 4.81. Found: C, 53.62; H, 5.52; N, 4.66.

N-(2-Chloromethyl-4,5-dimethoxyphenethyl)trifluoroacetamide (2a). A mixture of 1a (11.1 g, 40 mmol), 37%-formaldehyde solution (26 ml) and $CHCl_3$ (95 ml) was stirred and cooled at -15°C. Dry HCl gas was introduced through the stirred mixture keeping the temperature at -20 to -15°C for 1.5 h. The resulting paste was poured into ice-water (300 ml) and extracted with $CHCl_3$ (100 ml×3). Extracts were combined, dried (Na_2SO_4), and evaporated. A crystalline residue (14.6 g) was recrystallized twice from benzene to give 2a (9.7 g, 92 %), mp 137-138°C. Ir (nujol) 3330, 1725, 1610, 1596, 1565, 1522 cm^{-1}; ^1H nmr (90 MHz) δ 2.98 (2H, t, J=6.5 Hz, CH_2CH_2N), 3.67, 3.73 (each 1H, t, J=6.5 Hz, CH_2N), 3.90, 3.92 (each 3H, s, CH_3O×2), 4.65 (2H, s, CH_2Cl), 6.60 (1H, br, NH), 6.72, 6.90 (each 1H, s, Ar-H). Anal. Calcd for $C_{13}H_{15}O_3NF_3Cl$: C, 47.94; H, 4.64; N, 4.30. Found: C, 48.14; H, 4.67; N, 4.49.

N-(2-Cyanomethyl-4,5-dimethoxyphenethyl)trifluoroacetamide (3a). To a solution of 2a (6.51 g, 20 mmol) in DMSO (50 ml) was dropwise added NaCN (2.45 g, 50 mmol). After stirring for 1 h at room temperature, the mixture was poured into water (150 ml), and extracted with $CHCl_3$ (20 ml×5). The extract was washed with saturated brine (50 ml×5), dried (Na_2SO_4) and evaporated. The residue was crystallized from benzene to give 3a (5.75 g, 91%), mp 135-137°C. Recrystallization from benzene afforded an analytical sample, mp 136-137°C. Ir (nujol) 3315, 2255, 1705, 1610, 1565, 1523 cm^{-1}; ^1H nmr (90 MHz) δ 2.91 (2H, t, J=7 Hz, CH_2CH_2N), 3.59, 3.68 (each 1H, t, J=7 Hz, CH_2N), 3.92, 3.94 (2H, each s, CH_3O×2), 6.75, 6.91 (each 1H, s, Ar-C_6-H and/or Ar-C_3-H)), 6.80 (1H, br, NH). Anal. Calcd for $C_{14}H_{15}N_2O_3F_3$: C, 53.17; H, 4.78; N, 8.86. Found: C, 53.28; H, 4.76; N, 8.88.

N-(2-Cyanomethyl-4,5-dimethoxyphenethyl)-N-methyltrifluoroacetamide (3b). Chloromethylation of 1b (6.3 g) gave N-(2-chloromethyl-4,5-dimethoxyphenethyl)-N-methyltrifluoroacetamide (2b) as a crude oily substance (8.4 g), whose ^1H nmr (270 MHz) spectrum displayed peaks at δ 2.90-3.05 (2H, m, CH_2CH_2N), 3.06, 3.11 (3H, each s, 5:2, N-CH_3), 3.60-3.85 (2H, m, CH_2N), 3.88, 3.98 (each 3H, s, CH_3O×2), 4.61, 4.67 (2H, each s, 2:5, CH_2Cl), 6.64, 6.69 (1H, each s, 2:5, Ar-C_6-H), 6.85, 6.86 (1H, each s, 2:5, Ar-C_3-H). This oil (7.9 g) was treated with NaCN (3.0 g) in DMSO (50 ml) in the same way as noted for 3a. The crude product (6.5 g) was distilled to give the benzyl cyanide 3b as

a colorless oil (6.0 g, 89% from 1b), bp 136-141°C/ 0.2 torr, which was crystallized from benzene to give an analytical sample, mp 77-84°C. Ir (nujol) 2260, 1780, 1610, 1590, 1520 cm^{-1}; ^1H nmr (270 MHz) δ 2.80-3.00 (2H, m, CH_2CH_2N), 3.12 (3H, br s, N-CH_3), 3.50-3.70 (2H, m, CH_2N), 3.77, 3.88 (2H, each s, 1:1, CH_2CN), 3.87, 3.90 (each 3H, s, CH_3O ×2), 6.70 (1H, br s, Ar-C_6-H), 6.86 (1H, br s, Ar C_3-H). Anal. Calcd for $C_{15}H_{17}O_3N_2F_3$: C, 54.54; H, 5.19; N, 8.48. Found: C, 54.32; H,5.19; N, 8.23.

1-Cyano-7,8-dimethoxy-2-(2,3-dimethoxyphenyl)-1,2,4,5-tetrahydro-3H-3-benzazepine (5a). To a solution of 3a (316 mg, 1 mmol) and 2,3-dimethoxybenzaldehyde in THF (4 ml) and 95%-EtOH (1 ml) was added a sodium ethoxide solution [prepared from Na (40 mg) and abs. EtOH (1 ml)], and the mixture was stirred at 45-50°C for 20 h. After evaporation of the solvent, 1N-HCl (10 ml) was added. The resulting acidic solution was washed with ether (10 ml×2), and extracted with CH_2Cl_2 (10 ml×3). The CH_2Cl_2 layers were combined, washed with diluted NaOH solution and water, dried (Na_2SO_4), and evaporated. The residue (209 mg) was subjected to preparative TLC on silica gel plates developing with 3%-MeOH-CH_2Cl_2. A fraction with Rf.0.55 (152 mg) was crystallized from EtOH to give the benzazepine 5a (110 mg, 30%), mp 111-113°C. Recrystallization from EtOH afforded an analytical sample, mp 113-114°C. Ir (neat) 3330, 2230, 1610, 1590, 1515 cm^{-1}; ^1H nmr (270 MHz) δ 2.74 (1H, dd, J=5.1, 15.4 Hz, 5α-H), 2.92 (1H, triplet-like dd, J=11.7, 12.8 Hz, 4α-H), 3.50 (1H, dd, J=5.1, 12.8 Hz, 4β-H), 3.52 (1H, dd, J=11.7, 15.4 Hz, 5β-H), 3.84, 3.85, 3.89, 3.90 (each 3H, s, CH_3O×4), 3.99 (1H, d, J= 0.7 Hz, C_1-H), 4.37 (1H, br s, C_2-H), 6.65, 6.69 (each 1H, s, C_6-H and/or C_9-H), 6.92 (1H, dd, J=1.5, 8.1 Hz, $C_{4'}$-H), 7.14 (1H, t, J=8.1 Hz, $C_{5'}$-H), 7.25 (1H, dd, J=1.5, 8.1 Hz, $C_{6'}$-H). Ms m/z (relative intensity) 368 (M^+, 96), 352 (M^+-CH_3, 17), 203 (43), 178 (100). Anal. Calcd for $C_{21}H_{24}O_4N_2$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.44; H, 6.66; N, 7.48.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-cyano-7,8-dimethoxy-1,2,4,5-tetrahydro-3H-3-benzazepine (5b). Similar treatment of 3a (632 mg, 2 mmol) with 2-bromo-4,5-dimethoxybenzaldehyde (490 mg, 2 mmol) afforded the crude product (1.0 g), which was separated by TLC and crystallized from EtOH to give the benzazepine 5b (310 mg, 35%), mp 200-202°C. Analytical sample was prepared on recrystallization from EtOH, and melted at 207-209°C. Ir (neat) 3330, 2235, 1605, 1505 cm^{-1}; ^1H nmr (270 MHz) δ 2.77 (1H, dd, J=5.9, 15.4 Hz, 5α-H), 2.90 (1H, triplet-like dd, J=11.4, 11.7 Hz, 4α-H), 3.47 (1H, dd, J=5.9, 11.7 Hz, 4β-H), 3.53 (1H, dd, J=11.4, 15.4 Hz, 5β-H), 3.86, 3.88, 3.89, 3.96 (each 3H, s, CH_3O×4), 3.91 (2H, hiding d, J=1.1 Hz, C_1-H), 4.32 (2H, dd, J=1.1 Hz, C_2-H), 6.69, 6.70 (each 1H, s, C_6-H and/or C_9-H), 7.05, 7.40(each 1H, s, $C_{3'}$-H and $C_{6'}$-H). Ms m/z (relative intensity) 448 (M^+, 61), 446 (M^+, 61), 433 (M^+-CH_3, 6), 431 (M^+-CH_3, 6), 367 (M^+-Br, 9), 258 (50), 256 (50), 203 (41). Anal. Calcd for $C_{21}H_{23}O_4N_2Br$: C, 56.38; H, 5.20; N, 5.26; Br, 17.86. Found: C, 56.18; H, 5.09; N, 5.97; Br, 18.08.

1-Cyano-7,8-dimethoxy-2-(2,3-dimethoxyphenyl)-3-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine (5c). The reaction of 3b (990 mg, 3 mmol) with 2,3-dimethoxybenzaldehyde (498 mg, 3 mmol) gave the crude product (720 mg). Purification by TLC and crystallization in the same manner as noted above

furnished 5c (390 mg, 34%), mp 173-176°C, as white crystals which on recrystallization from EtOH provided an analytical sample, mp 175-177°C. Ir (neat) 2240, 1610, 1590, 1520 cm^{-1}; ^1H nmr (270 MHz) δ 2.18 (3H, s, N-CH_3), 2.44 (1H, triplet-like dd, J=11.0, 11.7 Hz, 4α-H), 2.84 (1H, dd, J=7.0, 15.8 Hz, 5α-H), 3.35 (1H, dd, J=7.0, 11.7 Hz, 4β-H), 3.58 (1H, dd, J=11.0, 15.8 Hz, 5β-H), 3.80, 3.81 (each 3H, s, CH_3O×2), 3.87 (1H, br s, C_1-H), 3.89 (6H, s, CH_3O×2), 3.91 (1H, br s, C_2-H), 6.60, 6.70 (each 1H, s, C_6-H and/or C_9-H), 6.88 (1H, dd, J=1.5, 8.1 Hz, $C_{4'}$-H), 7.12 (1H, t, J=8.1 Hz, $C_{5'}$-H), 7.36 (1H, br d, J= 8.1 Hz, $C_{6'}$-H). Ms m/z (relative intensity) 382 (M^+, 100), 367 (M^+-CH_3, 19), 351 (M^+-OCH_3, 13), 203 (32), 192 (69). Anal. Calcd for $C_{22}H_{26}O_4N_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.98; H, 7.03; N, 7.41.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-cyano-7,8-dimethoxy-3-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine (5d). The reaction of 3b (660 mg, 2 mmol) with 2-bromo-4,5-dimethoxybenzaldehyde (490 mg, 2 mmol) gave the crude product (610 mg), which was further treated in the same way as noted above to afford the benzazepine 5d (317 mg, 34%), mp 148-151°C. Recrystallization from EtOH provided a pure sample, mp 155-156°C. Ir (neat) 2235, 1610, 1512 cm^{-1}; ^1H nmr (270 MHz) δ 2.16 (3H, s, N-CH_3), 2.49 (1H, triplet-like dd, J=11.4, 11.7 Hz, 4α-H), 2.85 (1H, dd, J=7.0, 15.8 Hz, 5α-H), 3.38 (1H, dd, J=7.0, 11.7 Hz, 4β-H), 3.58 (1H, dd, J=11.4, 15.8 Hz, 5β-H), 3.84 (3H, s, CH_3O), 3.88 (1H, s, C_1-H), 3.89 (7H, s, CH_3O×2 and C_2-H), 3.93 (3H, s, CH_3O), 6.65, 6.70 (each 1H, s, C_6-H and/or C_9-H), 7.03 (1H, s, $C_{3'}$-H), 7.43 (1H, br s, $C_{6'}$-H). Ms m/z (relative intensity) 462 (M^+, 100), 460 (M^+, 99), 447 (M^+-CH_3, 14), 445 (M^+-CH_3, 14), 381 (M^+-Br, 50), 272 (29), 270 (29), 203 (60). Anal. Calcd for $C_{22}H_{25}O_4N_2Br$: C, 57.27; H, 5.46; N, 6.07; Br, 17.32. Found: C, 57.09; H, 5.47; N, 5.93; Br, 17.25.

2-Cyanomethyl-N-(2,3-dimethoxybenzylidene)-4,5-dimethoxyphenethylamine (6a). To a stirred solution of 3b (200 mg) in MeOH 2: H_2O 1 (4 ml), was added K_2CO_3 (500 mg). After stirring at room temperature for 1 h, the mixture was acidified with 2N-HCl solution, and washed with ether (20 ml). The water layer was basified with 2N-NaOH solution, and extracted with $CHCl_3$ (10 ml×2). The $CHCl_3$ extracts were washed with saturated brine (20 ml), dried (Na_2SO_4), and evaporated to dryness to leave the amine **4a**, as a colorless oil (108 mg, 81%). Ir (neat) 3370, 2250, 1610, 1590, 1515 cm^{-1}; ^1H nmr (90 MHz) δ 2.16 (2H, br, NH_2), 2.26, 3.00 (each 2H, each deformed t, J=7 Hz, CH_2CH_2N), 3.76 (2H, s, CH_2CN), 3.91 (6H, s, CH_3O×2)), 6.78, 6.92 (each 1H, s, Ar-C_6-H and/or Ar-C_3-H)). This was used in the following step without further purification.

A solution of **4a** (105 mg, 0.5 mmol) and 2,3-dimethoxybenzaldehyde (83 mg, 0.5 mmol) in ^tBuOH (4 ml) was refluxed for 5h. Evaporation of the solvent left an oil, which was crystallized from EtOH to give a white solid (140 mg, 88%), mp 83-84°C. Recrystallization from EtOH afforded an analytical sample for **6a**, mp 84.5-85.5°C. Ir (neat) 2240, 1638, 1610, 1580, 1520 cm^{-1}; ^1H nmr (90 MHz) δ 2.93 (2H, t, J=6.5 Hz, CH_2CH_2N), 3.70-3.95 (2H, hiding, CH_2N), 3.71 (5H, s, CH_3O and CH_2CN), 3.81, 3.82, 3.83 (each 3H, s, CH_3O×3), 6.63, 6.85 (each 1H, s, C_3-H and/or C_6-H), 6.95 (1H, dd, J=7.2, 1.4 Hz, $C_{4'}$-H), 7.06 (1H, d, J=7.2 Hz, $C_{5'}$-H), 7.48 (1H, dd, J=7.2, 1.4 Hz, $C_{6'}$-H), 8.37 (1H, s, H-C=N)

Anal. Calcd for $C_{21}H_{24}O_4N_2$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.56; H, 6.57; N, 7.43.

N-(2-Bromo-4,5-dimethoxybenzylidene)-2-cyanomethyl-4,5-dimethoxyphenethylamine (6b). Similarly, the reaction of **4a** with 2-bromo-4,5-dimethoxybenzaldehyde gave **6b**, mp 203-205°C (EtOH) in 85% yield. Ir (neat) 2250, 1635, 1605, 1575, 1505 cm^{-1}; ^1H nmr (90 MHz) δ 2.94 (2H, t, J=6.5 Hz, CH_2CH_2N), 3.70-3.95 (2H, hiding, CH_2N), 3.73 (2H, s, CH_2CN), 3.85, 3.87, 3.89, 3.92 (each 3H, s, $CH_3O\times4$), 6.73, 6.82, 7.00, 7.46 (each 1H, s, Ar-H), 8.31 (1H, s, H-C=N). Anal. Calcd for $C_{21}H_{23}O_4N_2Br$: C, 56.38; H, 5.20; N, 6.26; Br, 17.86. Found: C, 56.49; H, 5.09; N, 6.12; Br, 17.60.

Treatment of 6 with EtONa-EtOH. A mixture of **6a** (37 mg, 0.1 mmol), THF (0.4 ml), 95% EtOH (0.1 ml) and a EtONa solution [prepared from Na (4 mg) and abs. EtOH (0.1 ml)] was warmed under nitrogen at 45-50°C for 20 h. After evaporation of the solvents, the residue was treated with water and CH_2Cl_2 (5 ml×2). The CH_2Cl_2 extracts were washed with water, dried and evaporated. Separation of the oily residue (37 mg) by silica gel TLC (3%-MeOH-CH_2Cl_2) gave **5a** (4 mg, Rf. 0.5, 11%) and 2,3-dimethoxybenzaldehyde (7 mg, Rf. 0.9, 43 %). From the similar treatment of **6b** (45 mg, 0.1 mg), **5b** (6 mg, Rf. 0.5, 13 %) and 2-bromo-4,5-dimethoxybenzaldehyde (11 mg, Rf. 0.9, 45 %) were obtained.

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5. The corresponding N-methyltrichloroacetyl derivative gave also **5a**, but in the lower yield.
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9. In the same manner, the reaction of N-(2-cyanomethyl-4,5-dimethoxyphenethyl)-N-methylacetamide (see ref. 4) with 2,3-dimethoxybenzaldehyde gave quantitatively the α-phenylcinnamonitrile [7: $COCH_3$ for H, R=CH_3, R_3=2',3'-$(OCH_3)_2$], mp 68-73°C (aq. EtOH). Ir (nujol) 2200, 1660, 1600, 1575, 1515 cm^{-1}; ^1H nmr (90 MHz) δ 1.89, 2.06 (3H, each s, 1:2, $COCH_3$), 2.85-3.13 (2H, hiding, CH_2CH_2N), 2.92, 2.95 (3H, each s, 2:1, N-CH_3), 3.55, 3.64 (2H, each t, J=7.5 Hz, CH_2N), 3.86 (3H, s, OCH_3), 3.90 (9H, s, $CH_3O\times3$), 6.64, 6.80 (1H, each s, 1:2, C_6-H and/or C_3-H), 6.82, 6.88 (1H, each s, 1:2, C_3-H and /or C_6-H), 7.01 (1H, dd, J=7.8, 1.8 Hz, $C_{4'}$-H), 7.19 (1H, t, J=7.8 Hz, $C_{5'}$-H), 7.51 (1H, s, H-C=N), 7.82 (1H, dd, J=7.8, 1.8 Hz, $C_{6'}$-H).

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