Fischer Indolization and Its Related Compounds. XXIII.[1a] Fischer Indolization of Ethyl Pyruvate 2-(2,6-Dimethoxyphenyl)phenylhydrazone

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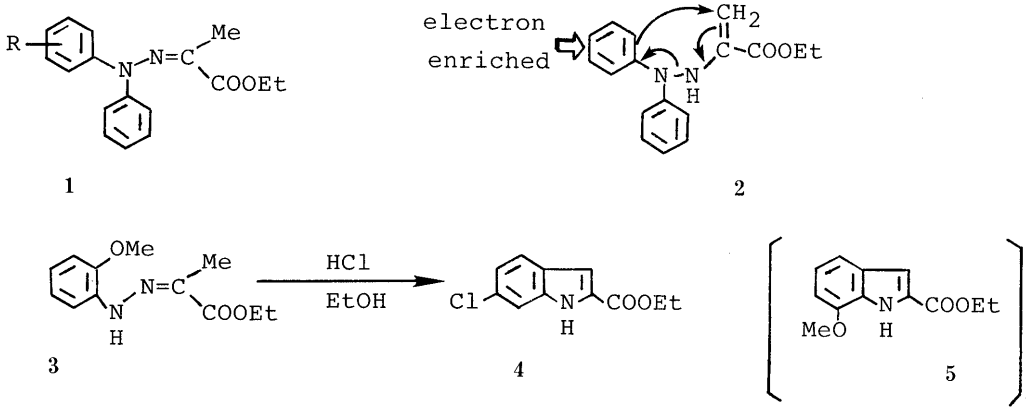
In order to clarify the mechanism of the abnormal Fischer indolization of 2-methoxyphenylhydrazones the Fischer indolization of ethyl pyruvate 2-(2,6-dimethoxyphenyl)phenylhydrazone (6) was undertaken using ethanolic hydrogen chloride and zinc chloride as an acid catalyst. The cyclization was found to take place predominantly on the 2,6-dimethoxyphenyl nucleus to give the corresponding indoles, although the yields of indoles formed were low. Some non-indolic by-products were also produced which might give information about the mechanism of Fischer indolization. In particular, the formation of 3,5-dimethoxy-4-anilinobenzaldehyde (15) suggests that the first cyclization step in Fischer indolization could take place at the *para* position of phenylhydrazone as a side reaction.

Keywords Fischer indolization; 2,6-dimethoxyphenylhydrazone; carbon unit migration; ^{13}C-experiment; ethanolic hydrogen chloride; zinc chloride

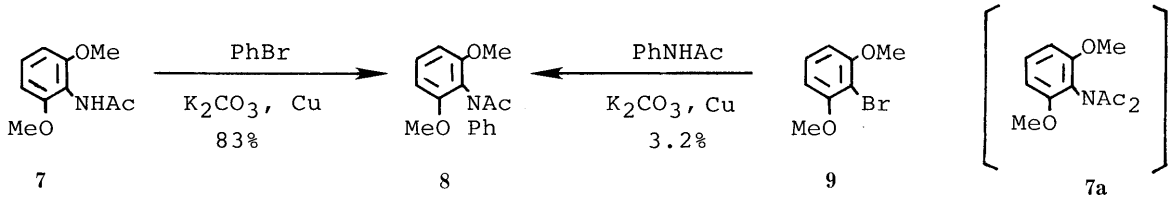
In the previous paper[1b] we reported that the first step of Fischer indolization has the character of an electrophilic attack by the enehydrazine moiety toward the benzene nucleus (**2**), on the basis of chemical evidence that cyclization of the ethyl pyruvate 2-(substituted phenyl)phenylhydrazone took place predominantly on the more electron-enriched nucleus between substituted and unsubstituted phenyl nuclei. We had previously found[2] that the Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)hydrazone (**3**) with refluxing ethanolic hydrogen chloride gave predominantly the 6-chloroindole (**4**) rather than the expected 7-methoxyindole (**5**). On the basis of the above result[1b] we decided to clarify why the Fischer indolization of the 2-methoxyphenylhydrazone (**3**) took place on the substituted *ortho* position rather than the unsubstituted one. We therefore examined the Fischer indolization of ethyl pyruvate 2-(2,6-dimethoxyphenyl)phenylhydrazone (**6**) in order to determine at which nucleus cyclization would take place.

The hydrazone (**6**) was prepared starting from 2,6-dimethoxyacetanilide (**7**) as shown in Chart 2. The Ullmann–Goldberg reaction[1b] of 2,6-dimethoxyacetani-

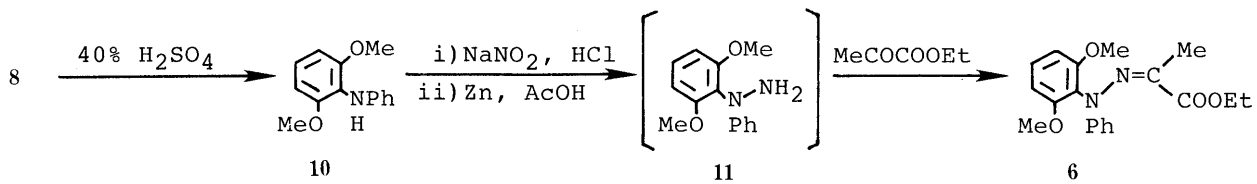


1 2 3 4 5

Chart 1



7 8 9 7a



8 10 11 6

Chart 2

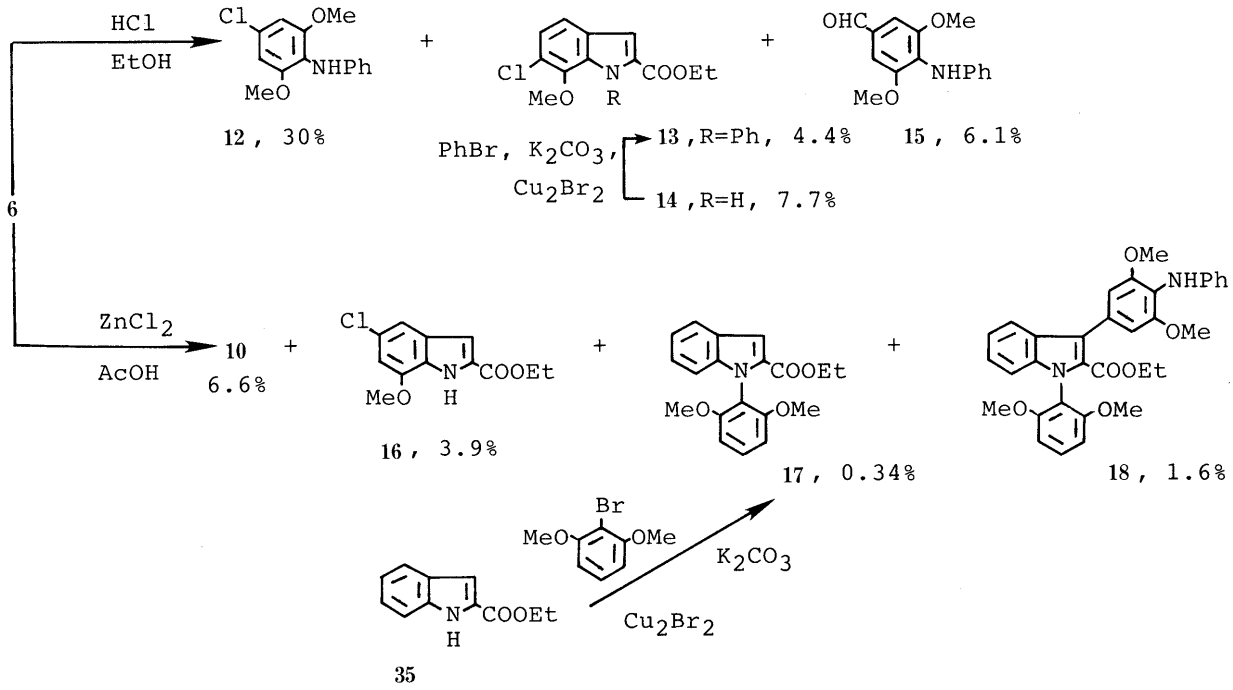


Chart 3

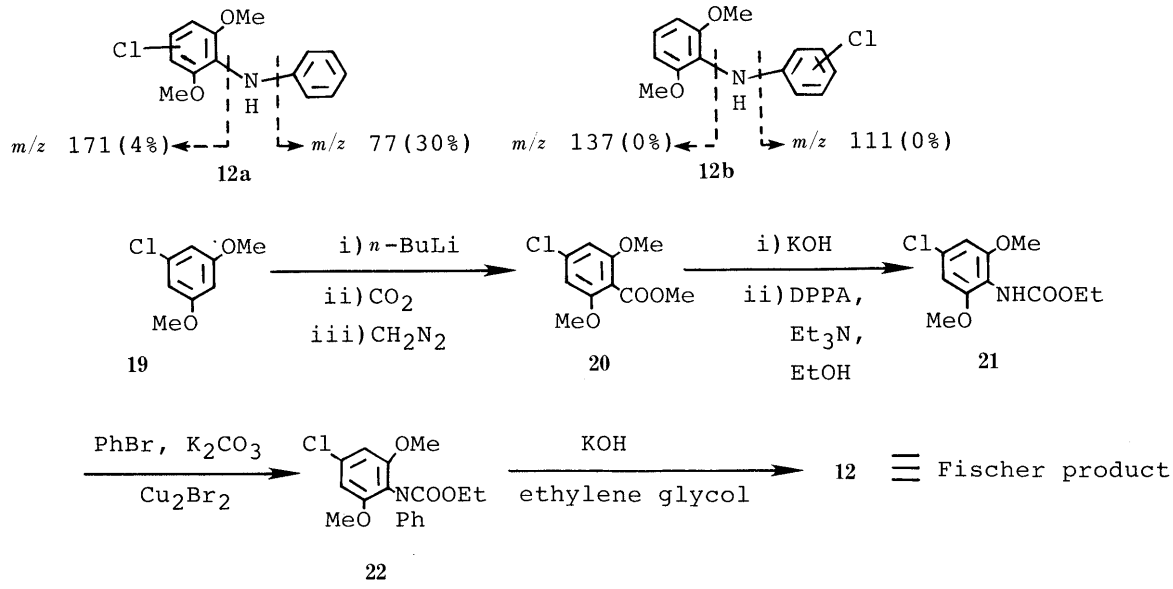


Chart 4

lide[3,4] (**7**) with bromobenzene gave the *N*-phenyl derivative (**8**) in a good yield, whereas the reaction of 1-bromo-2,6-dimethoxybenzene (**9**) with acetanilide gave **8** in only 3.2% yield. The diarylacetamide (**8**) was hydrolyzed to give the diarylamine (**10**), which was then converted to the diarylhydrazine (**11**) by nitrosation, followed by reduction. The hydrazine (**11**) was, without purification, treated with ethyl pyruvate to give the desired hydrazone (**6**).

The Fischer indolization of the hydrazone (**6**) with refluxing ethanolic hydrogen chloride gave four products as shown in Chart 3.

The first product (**12**), mp 115—116 °C, was found to have the formula $C_{14}H_{14}ClNO_2$ by elemental analysis and from the mass spectrum (MS) [*m/z* 265 ($M^+ + 2$, 36% intensity of M^+) and 263 (M^+)]. The infra red (IR) spectrum showed an absorption at 3375 cm^{-1} due to the NH group. The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum showed a 6H singlet at δ 3.78 due to two methoxy groups and a 7H multiplet at δ 6.60—7.15 due to aromatic protons. These data suggested us that **12** was a chlorinated derivative of the diphenylamine (**10**). The position of chlorine was determined as follows. In the mass spectrum the fragments at *m/z* 77 and 171 (shown in Chart 4) due to the structure **12a** were observed clearly, whereas the fragments at *m/z* 111 and 137 expected for the structure **12b** were not seen, suggesting that the chlorine atom was located on the dimethoxyphenyl nucleus (**12a**) but not on the unsubstituted phenyl one (**12b**). In the previous paper[1b] we obtained the same kind of chlorinated diphenylamine by the Fischer indolization of ethyl pyruvate 2-(4-methoxyphenyl)phenylhydrazone (**1**, R=4-OCH_3). Provided that the first product (**12**) is formed by the same mechanism as that of

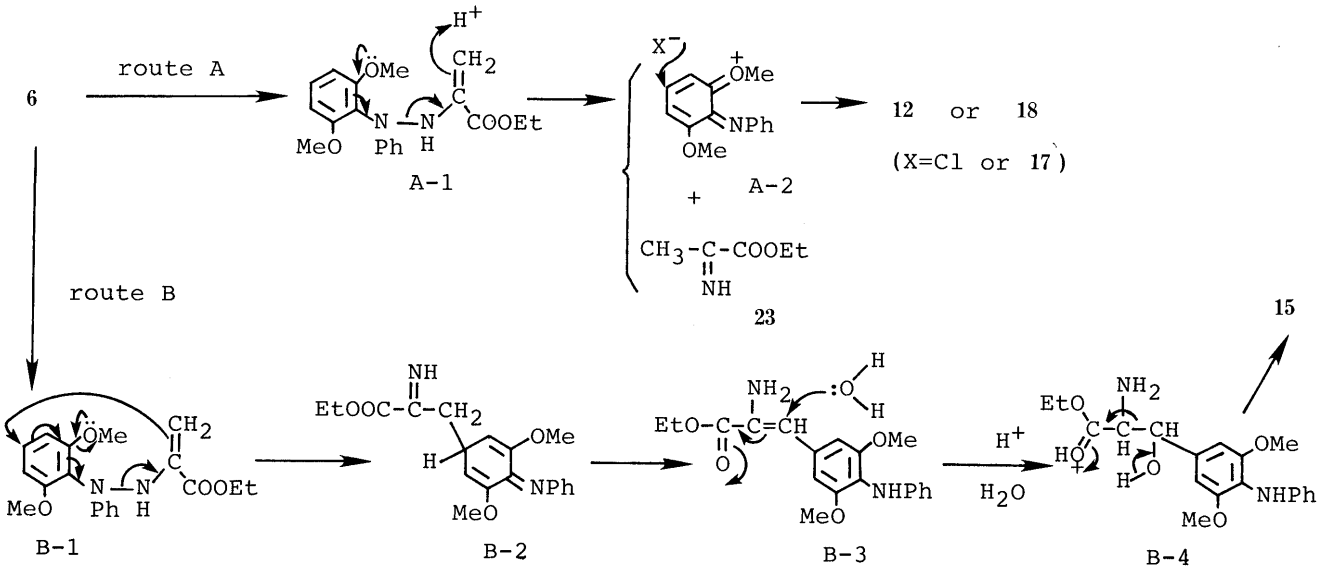


Chart 5. Suggested Mechanism of Formation of Abnormal Products

the formation of the above chlorinated diphenylamine from **1** (R=4-OCH_3), as shown in Chart 5 (route A), **12** should be 4-chloro-2,6-dimethoxy-*N*-phenylaniline. Thus, an alternative synthesis was conducted as shown in Chart 4. 1-Chloro-3,5-dimethoxybenzene (**19**) was carboxylated and esterified (for purification) to give methyl 4-chloro-2,6-dimethoxybenzoate (**20**). The ester (**20**) was hydrolyzed and treated with diphenyl phosphorazidate (DPPA) and triethylamine, followed by addition of ethanol to give the carbamate (**21**). The carbamate (**21**) was phenylated with bromobenzene by means of the Ullmann–Goldberg reaction, followed by decarboxylation to give the diphenylamine (**12**). The product was identical with the Fischer product (**12**).

The second product (**13**) and the third (**14**) had the formulae $C_{18}H_{16}ClNO_3$ and $C_{12}H_{12}ClNO_3$, respectively. Both compounds were suggested to be indolic compounds by their response to the Ehrlich reagent.[5,6] Since they contain a chlorine atom and only one methoxy group, they were readily supposed to be "*ortho*-C_6" abnormal Fischer indolization products,[2] ethyl 6-chloro-7-methoxyindole-2-carboxylate (**14**) and its *N*-phenyl derivative (**13**). Thus, the former (**14**) was identical with the sample which we had already obtained[7] in the Fischer indolization of ethyl pyruvate 2-(2,6-dimethoxyphenyl)hydrazone, and the latter (**13**) was characterized by alternative synthesis from the former (**14**), through *N*-phenylation by means of the Ullmann–Goldberg reaction.

The fourth product (**15**) had the formula $C_{15}H_{15}NO_3$ [*m/z* 257 (M^+)], and was not positive to the Erhlich reagent. The IR spectrum showed absorptions at 3300 and 1690 cm^{-1} due to NH and C=O groups. The ^{1}H-NMR spectrum showed a 6H singlet at δ 3.88 due to two methoxy groups, a 7H multiplet at δ 6.75—7.37 due to aromatic protons, and a 1H singlet at δ 9.88 due to a formyl group. These data suggested that it was a formyl derivative of 2,6-dimethoxy-*N*-phenylaniline (**10**). This suggestion was confirmed by decarbonylation of the aldehyde (**15**) with Pd–C to give **10**. However, the spectral data gave us no definite information about the position of the formyl group. The fact that the aldehyde (**15**) retains the 2,6-dimethoxy-*N*-phenylaniline structure (**10**) suggested to us at first that the first cyclization in Fischer indolization took place at the *ortho* position of the unsubstituted phenyl nucleus in the hydrazone (**6**) and the product immediately underwent some unknown degradative process before second-stage cyclization to give 2-(2,6-dimethoxyanilino)benzaldehyde (**26**). Thus, an authentic sample of **26** was prepared from 2,6-dimethoxyacetanilide (**7**) and ethyl 2-bromobenzoate as shown in Chart 6. However, the synthetic aldehyde (**26**) was not identical with the Fischer product (**15**).

The next possibility for the structure of the aldehyde (**15**) was 3,5-dimethoxy-4-anilinobenzaldehyde, which might be formed by replacement of the chlorine atom of 4-chloro-2,6-dimethoxy-*N*-phenylaniline (**12**) by a formyl group. Thus, 3,5-dimethoxy-4-anilinobenzaldehyde was synthesized as shown in Chart 6. 3,5-Dimethoxybenzyl alcohol (**27**) was carboxylated to the benzoic acid (**28**) in a usual manner, and **28** was converted to the carbamate (**29**). *N*-Phenylation of **29** by means of the Ullmann–Goldberg reaction, followed by hydrolysis and then oxidation with MnO_2 gave the desired benzaldehyde (**15**), which was identical with the Fischer product. This result means that the carbon residue of the phenylhydrazone (**6**) should attack the *para* position in Fischer indolization. As there has been no report about such a *para* substitution in Fischer indolization so far, we were interested in examining the origin of this C_1-unit.

Since we considered that the methyl group of the pyruvate moiety was the most likely candidate for the origin of the formyl group on the basis of the mechanism of normal Fischer indolization, we set out to examine the Fischer indolization of the "labeled" hydrazone (L-**6**), in which the methyl carbon concerned was enriched with ^{13}C-carbon. The labeled hydrazone (L-**6**) was prepared as shown in Chart 7. Commercially available $^{13}C_3$-enriched DL-alanine was diluted with the unlabeled compound to obtain 4.9% $^{13}C_3$-enriched[8] DL-alanine (L-**31**). The labeled alanine (L-**31**) thus obtained was converted to benzyl ester tosylate (L-**32**) and then to labeled benzyl pyruvate (L-**33**) by neutralization, followed by oxidation to the imine and hydrolysis. The labeled benzyl pyruvate (L-**33**) was treated

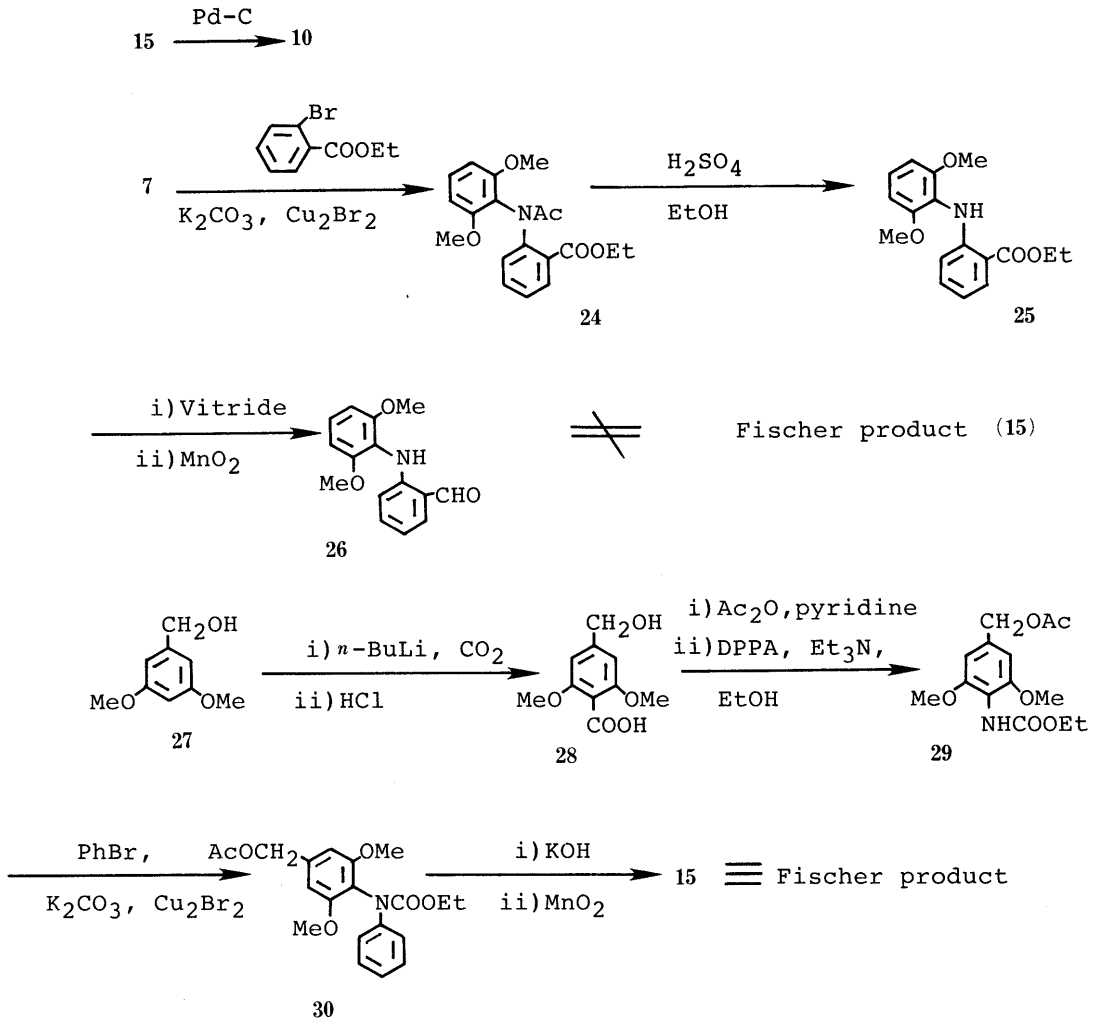
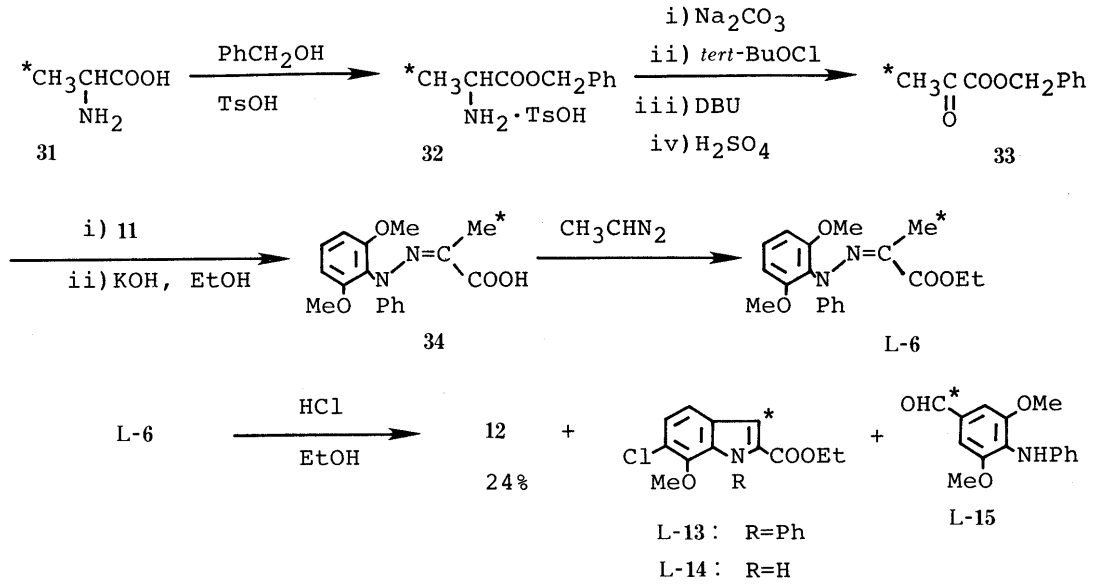


Chart 6



^{13}C-concentration in the labeled compounds

	32	6	13	14	15
yield (%) from L-6	—	—	7.9	7.7	3.5
concentration of enriched carbon (%)	4.9	4.6	4.6	4.7	4.8

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

Chart 7

TABLE I. ^{13}C-NMR Data for the Hydrazone (**6**) and the Fischer Products (**13**, **14**, and **15**)

Carbon	**6**	**13**	**14**	**15**
$OCH_2\underline{C}H_3$	14.44 (q)	14.02 (q)	14.36 (q)	—
$O\underline{C}H_2CH_3$	61.10 (t)	60.86 (t)	61.29 (t)	—
$=C-\underline{C}H_3$	12.74 (q)	—	—	—
$O\underline{C}H_3$	55.97 (q)	60.63 (q)	61.06 (q)	55.97 (q)
$-\underline{C}OO$	167.11 (s)	160.80 (s)	161.88 (s)	—
$N=\underline{C}-$	132.94 (s)	—	—	—
$\underline{C}HO$	—	—	—	190.88 (d)
$\underline{C}_3-$ of indole	—	111.98 (d)	109.29 (d)	—
Other	104.05 (d) × 2	118.73 (d)	118.73 (d)	106.32 (d) × 2
aromatic	115.49 (d) × 2	123.31 (d)	122.24 (s)	117.84 (d) × 2
carbon	119.19 (s)	124.35 (s)	123.12 (d)	121.00 (d)
	121.73 (d)	127.74 (s)	128.40 (s) × 2	127.16 (s)
	128.70 (d) × 2	128.01 (d) × 2	131.67 (s)	128.44 (d)[a] × 2
	130.56 (d)	128.21 (d)	142.23 (s)	130.56 (d)
	147.78 (s)	128.51 (d) × 2		143.00 (s)
	157.60 (s) × 2	130.83 (s)		151.78 (s) × 2
		134.02 (s)		
		139.96 (s)		
		143.23 (s)		

a) Long-range coupling.

with the hydrazine (**11**), followed by hydrolysis and esterification with diazoethane to give the desired labeled hydrazone (L-**6**). The ^{13}C-concentration in the labeled hydrazone (L-**6**) was 4.6%, meaning that no appreciable loss of ^{13}C-carbon had occurred during the conversion of labeled alanine (L-**31**) to the labeled hydrazone (L-**6**). Assignments of the ^{13}C-NMR signals of the labeled hydrazone are listed in Table I together with those of the Fischer indolization products.

The labeled hydrazone (L-**6**) was treated with ethanolic hydrogen chloride in the same way as to the unlabeled one (**6**). The same products as in the case of the unlabeled hydrazone (**6**) were formed in similar yields. Incorporation of ^{13}C-carbon into each product was estimated by integration of the relevant ^{13}C-NMR signal and comparison with the corresponding unlabeled one (**6**) and the results are listed in the table in Chart 7. The results indicate that the methyl group of the hydrazone (**6**) was completely incorporated into the formyl carbon of the aldehyde (**15**) as well as into the C_3-carbon of the two indoles (**13** and **14**). Thus the formation mechanism of the aldehyde (**15**) shown in Chart 5 (route B) seems likely. The C_3-carbon of the pyruvate moiety in the enehydrazine (B-**1**) would attack the *para* position with the assistance of the mesomeric effect of the *ortho* methoxy groups, with simultaneous cleavage of the N–N bond to give B-**3** *via* B-**2**. The B-**3** intermediate would be attacked by water and would decompose to the aldehyde (**15**). Supposing that Fischer indolization of 2,6-disubstituted phenylhydrazones might give the *para*-rearrangement product of enehydrazine moiety, Carlin and Fisher[9] examined Fischer indolization of several kinds of 2,6-dichlorophenylhydrazones in detail. However, they did not obtain such products at all but obtained indoles formed by migration of chlorine. There has been no subsequent report concerning the former type of product. The present result seems to be the first example showing that the first step of Fischer indolization can take place at the *para* position of phenylhydrazones, although we have no further evidence that the reaction proceeded intramolecularly as shown in route B of Chart 5. At the present time we cannot rule out an intermolecular mechanism in which the intermediate (A-**2**) would react with the pyruvate derivative (**23**) to form the aldehyde (**15**).

The above mentioned result shows that Fischer indolization of the hydrazone (**6**) took place exclusively on the aromatic nucleus having the methoxy groups rather than on the unsubstituted one. However, as the yields of indoles were too low to allow a clear conclusion, we again examined the Fischer indolization with anhydrous zinc chloride in acetic acid. This reaction gave four products different from those in the reaction with ethanolic hydrogen chloride, as shown in Chart 3.

The first product was found to be 2,6-dimethoxy-*N*-phenylaniline (**10**) and the second to be ethyl 5-chloro-7-methoxyindole-2-carboxylate (**16**), which we have already obtained[7] as the *ortho*-C_5 abnormal Fischer indolization products.

The third product (**17**) was positive to the Ehrlich reagent and appeared to have the formula $C_{19}H_{19}NO_4$ from the MS [*m/z* 325 (M^+)]. The IR spectrum showed no NH band. As this compound was obtained in minute yield, we could not get any further spectral data. However, the tentative formula and lack of NH group suggested that **17** was one of the indoles expected from the hydrazone (**6**), ethyl 1-(2,6-dimethoxyphenyl)indole-2-carboxylate. Indeed, **17** was identical with an authentic sample prepared by the Ullmann–Goldberg reaction of ethyl indole-2-carboxylate (**35**) with 1-bromo-2,6-dimethoxybenzene.

The fourth product (**18**) had the formula $C_{33}H_{32}N_2O_6$ [*m/z* 552 (M^+)]. The IR spectrum and the ^{1}H-NMR spectrum (see Experimental) suggested that this product (**18**) was composed of the diphenylamine (**10**) and the indole (**17**). The binding position between these two compounds was presumed as follows. The diphenyl amine part would bind at the C_4-position of the 2,6-dimethoxyphenyl nucleus by analogy with the formation of 4-chloro-2,6-dimethoxy-*N*-phenylaniline (**12**) and 3,5-dimethoxy-4-anilinobenzaldehyde (**15**). The indole (**17**) part would bind at its C_3-position, because indoles usually react with electrophiles at the C_3-position and the ^{1}H-NMR spectrum of **18** showed no C_3-H. Thus, we suggest that **18** is ethyl 1-(2,6-dimethoxyphenyl)-3-(4′-anilino-3′,5′-dimethoxyphenyl)-indole-2-carboxylate. In conclusion, the reaction with zinc chloride also gave indoles only in miserable yields.

In the present study, the Fischer indolization of ethyl pyruvate 2-(2,6-dimethoxyphenyl)phenylhydrazone (**6**) was examined with two kinds of acid catalyst in order to clarify the direction of cyclization. The hydrazone (**6**) cyclized to the 2,6-dimethoxyphenyl nucleus exclusively with ethanolic hydrogen chloride, and predominantly with zinc chloride in acetic acid. However, the yields of indoles in both cases were too low to allow definitive conclusions. On the other hand, many non-indolic by-products were formed. These kinds of products have not been reported in Fischer indolization of NH-arylhydrazones, probably because they and the intermediates leading to them might be too unstable or water-soluble to be isolated. The present result, together with the previous one[1b] on *N*-aryl-4-methoxyphenylhydrazones, indicates that under Fischer indolization conditions, 2- and 4-methoxyphenylhydrazones potentially undergo

side reactions.

We will report in subsequent papers the Fischer indolization of other diarylhydrazones.

Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra were obtained with Hitachi EPI-G3 and Shimadzu IR-400, JEOL JMN-4H-100 (100 MHz) and Hitachi R-24B (60 MHz), Hitachi R-900, and Hitachi RMU-6E and JEOL JMS-01-SG-2 spectrometers, respectively. IR spectra were measured in Nujol and ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ unless otherwise stated. The NMR chemical shifts are given in δ-values referred to internal tetramethylsilane, and the assignments of all NH and OH signals were confirmed by the disappearance of their signals after addition of D_2O. Mass spectra were measured by the direct inlet system. For column chromatography, silicic acid (SiO_2; 100 mesh, Mallinckrodt Chemical Works) and for preparative thin layer chromatography (TLC), Kiesel gel GF_{254} (Merck), were used. Identification of products was done by IR spectroscopy, mixed melting point determination, and TLC examination.

2,6-Dimethoxyacetanilide[3,4] **(7)** A mixture of commercial 2,6-dimethoxyaniline (8.0 g) and Ac_2O (16 ml) was stirred at room temperature for 100 min. Then the reaction mixture was poured into ice-water, basified with diluted NH_4OH, and extracted with $CHCl_3$. The extract was dried over anhydrous K_2CO_3. Removal of the solvent *in vacuo* gave a solid (10.4 g), which was recrystallized from cyclohexane–benzene (10 : 1) to give colorless plates (9.91 g, 97%), mp 130—132 °C. *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.73; H, 6.82; N, 7.06. IR ν_{max} cm^{-1}: 3250 (NH), 1660 (C=O). ^{1}H-NMR δ: 2.07 (3H, dif s, $COCH_3$), 3.85 (6H, s, $2\times OCH_3$), 6.55 (2H, d, J=7.5 Hz, C_3- and C_5-H), 7.18 (2H, m, C_4-H and NH). MS *m/z*: 195 (M^+).

***N,N*-Diacetyl-2,6-dimethoxyaniline**[4] **(7a)** A mixture of 2,6-dimethoxyaniline (100 mg) and Ac_2O (1 ml) was heated at 100 °C for 1 h. Then the reaction mixture was worked up according to the same procedure as the case of the anilide (**7**). The crude product was recrystallized from hexane to give colorless plates (129 mg, 83%), mp 88—90 °C (lit., [4] mp 81 °C, reported as *N*-acetyl-2,6-dimethoxyaniline). *Anal.* Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.89; H, 6.60; N, 5.90. IR ν_{max} cm^{-1}: 1715 (C=O). ^{1}H-NMR δ: 2.27 (6H, s, $2\times COCH_3$), 3.83 (6H, s, $2\times OCH_3$), 6.60 (2H, d, J=7.5 Hz, C_3- and C_5-H), 7.31 (1H, t, J=7.5 Hz, C_4-H). MS *m/z*: 237 (M^+).

2,6-Dimethoxy-*N*-phenylacetanilide (8) i) From 1-Bromo-2,6-dimethoxybenzene (**9**). General Procedure of the Ullmann–Goldberg[1b] Reaction: A mixture of 1-bromo-2,6-dimethoxybenzene (**9**) (500 mg), acetanilide (542 mg), Cu powder (19 mg), anhydrous K_2CO_3 (194 mg), and a catalytic amount of I_2 in nitrobenzene (2 ml) was refluxed for 24 h under Ar. The reaction mixture was poured into water and steam-distilled to remove nitrobenzene. The residue was extracted with Et_2O, and the extract was washed with water, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue (507 mg) was chromatographed over silicic acid using AcOEt–benzene (1 : 5) as an eluent to give crystals (87 mg). Recrystallizations from benzene–hexane gave colorless needles (20 mg, 3.2%), mp 118—119 °C. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.92; H, 6.37; N, 5.11. IR ν_{max} cm^{-1}: 1664 (C=O). ^{1}H-NMR δ: 1.95 (3H, dif s, $COCH_3$), 3.85 (6H, s, $2\times OCH_3$), 6.50—7.50 (8H, m, ArH). MS *m/z*: 271 (M^+).

ii) From 2,6-Dimethoxyacetanilide (**7**): A mixture of 2,6-dimethoxyacetanilide (**7**) (2.00 g), bromobenzene (2.8 g), anhydrous K_2CO_3 (0.84 g), Cu powder (84 mg), and a catalytic amount of I_2 in nitrobenzene (9 ml) was refluxed for 10 h under Ar. Work-up according to the general procedure of the Ullmann–Goldberg reaction gave the residue (3.27 g), which was chromatographed over silicic acid using benzene, followed by AcOEt–benzene (1 : 4) as eluents. The eluate with the latter solvent gave a solid (2.50 g), which was recrystallized from hexane–benzene to give colorless needles (2.29 g, 83%), mp 118—119 °C. This compound was identical with the sample prepared in i).

2,6-Dimethoxy-*N*-phenylaniline (10) The acetanilide (**8**) (1.00 g) was added to 40% H_2SO_4 (10 ml) and the whole was refluxed for 13 h. The reaction mixture was poured into water, and extracted with Et_2O, then the extract was washed with aqueous 5% $NaHCO_3$, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue was chromatographed over silicic acid using benzene as an eluent to give crystals (780 mg), which were recrystallized from hexane to give colorless plates (770 mg, 91%), mp 76—78 °C. *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.45; H, 6.60; N, 5.90. IR ν_{max} cm^{-1}: 3420 (NH). ^{1}H-NMR δ: 3.80 (6H, s, $2\times OCH_3$), 4.80 (1H, br s, NH), 6.57—7.20 (9H, m, ArH). MS *m/z*: 229 (M^+).

Ethyl Pyruvate 2-(2,6-Dimethoxyphenyl)phenylhydrazone (6) A solution of $NaNO_2$ (661 mg) in water (3.3 ml) was added to a solution of the aniline (**10**) (2.00 g) in a mixture of EtOH (100 ml) and concentrated HCl (0.88 ml) at 0—4 °C during 10 min, and the mixture was stirred for a further 30 min. The reaction mixture was poured into water, and extracted with Et_2O, then the extract was washed with water, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue (2.16 g) was recrystallized from cyclohexane to give 2,6-dimethoxy-*N*-nitroso-*N*-phenylaniline as pale yellow plates (2.04 g, 90%), mp 97—98 °C. *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.23; H, 5.56; N, 10.78. IR ν_{max} cm^{-1}: 1490 (NO), no NH. ^{1}H-NMR δ: 3.70 (6H, s, $2\times OCH_3$), 6.59—7.52 (8H, m, ArH). MS *m/z*: 229 (M^+-29).

A solution of 2,6-dimethoxy-*N*-nitroso-*N*-phenylaniline (2.00 g) in AcOH (14 ml) was added dropwise to an ice-cooled suspension of Zn powder (2.12 g) in water (6 ml). The reaction mixture was poured into ice-water and the precipitates were filtered off. The filtrate was basified with 10% NaOH, and extracted with Et_2O. The extract was washed with water, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue (2.06 g), which was crude 1-(2,6-dimethoxyphenyl)-1-phenylhydrazine (**11**), was dissolved in EtOH (16 ml) containing ethyl pyruvate (1.43 g) and one drop of AcOH without further purification. The mixture was refluxed for 5 min, and then concentrated to dryness *in vacuo*. The residue (2.79 g) was chromatographed over silicic acid using Et_2O–cyclohexane (1 : 1) as an eluent to give a solid (2.20 g, 83%), which was recrystallized from benzene–hexane to give colorless plates, mp 118—119 °C. *Anal.* Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.65; H, 6.52; N, 8.06. IR ν_{max} cm^{-1}: 1690 (C=O). ^{1}H-NMR δ: 1.38 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.52 (3H, s, $=CC\underline{H}_3$), 3.72 (6H, s, $2\times OCH_3$), 4.28 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.55—7.52 (8H, m, ArH). MS *m/z*: 342 (M^+).

Fischer Indolization of Ethyl Pyruvate 2-(2,6-Dimethoxyphenyl)phenylhydrazone (6) with HCl/EtOH A solution of the hydrazone (**6**) (1.30 g) in EtOH (50 ml) saturated with dry HCl gas was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water, and extracted with Et_2O, then the extract was washed with 5% aqueous $NaHCO_3$, dried over anhydrous K_2CO_3 and evaporated to dryness *in vacuo*. The residue (1.20 g) was chromatographed over silicic acid using benzene as an eluent to give four eluates, A, B, C, and D, in order of elution.

i) 4-Chloro-2,6-dimethoxy-*N*-phenylaniline (**12**): Eluate A was recrystallized from benzene–hexane to give colorless plates (299 mg, 30%), mp 108—110 °C. *Anal.* Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.81; H, 5.29; N, 5.44. IR ν_{max} cm^{-1}: 3375 (NH). ^{1}H-NMR δ: 3.78 (6H, s, $2\times OCH_3$), 5.52 (1H, br s, NH), 6.60 (2H, s, C_3- and C_5-H), 6.64 (2H, d, J=8 Hz, $C_{1'}$- and $C_{6'}$-H), 6.84 (1H, d, J=8.0 Hz, $C_{4'}$-H), 7.15 (2H, t, J=8.0 Hz, $C_{3'}$- and $C_{5'}$-H). MS *m/z*: 265 (M^++2, 36% intensity of M^+) and 263 (M^+). This compound was identical with an authentic sample prepared by the alternative route described later.

ii) Ethyl 6-Chloro-7-methoxy-1-phenylindole-2-carboxylate (**13**): Eluate B was recrystallized from pentane to give colorless plates (55 mg, 4.4%), mp 73—75 °C. *Anal.* Calcd for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.70; H, 4.84; N, 4.31. IR ν_{max} cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 1.18 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.22 (3H, s, OCH_3), 4.18 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.10—7.60 (8H, m, ArH). This compound was identical with an authentic sample prepared by the alternative route described later.

iii) Ethyl 6-Chloro-7-methoxyindole-2-carboxylate (**14**): Eluate C was recrystallized from hexane–benzene to give colorless plates (75 mg, 7.7%), mp 90—92 °C. *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.75; N, 5.52. Found: C, 57.06; H, 4.70; N, 5.71. IR ν_{max} cm^{-1}: 3400 (NH), 1680 (C=O). This compound was identical with the sample which we had already obtained.[2]

iv) 4-Anilino-3,5-dimethoxybenzaldehyde (**15**): Eluate D was recrystallized from pentane to give pale yellow prisms (59 mg, 6.0%), mp 138—139 °C. *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.97; H, 5.91; N, 5.35. IR ν_{max} cm^{-1}: 3300 (NH), 1690 (C=O). ^{1}H-NMR δ: 3.88 (6H, s, $2\times OCH_3$), 5.42 (1H, br s, NH), 6.75—7.37 (7H, m, ArH), 9.88 (1H, s, CHO). MS *m/z*: 257 (M^+).

Fischer Indolization of Ethyl Pyruvate 2-(2,6-Dimethoxyphenyl)phenylhydrazone (6) with $ZnCl_2$/AcOH A solution of the hydrazone (**6**) (1.50 g) in AcOH (15 ml) containing anhydrous $ZnCl_2$ (1.18 g) was refluxed for 35 min. Then the reaction mixture was poured into ice-water, and

extracted with Et_2O. The extract was washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (1.465 g) was chromatographed over silicic acid using benzene, then AcOEt–benzene (3 : 20) as eluents to give four eluates, A, B, C, and D, in order of elution.

i) 2,6-Dimethoxy-*N*-phenylaniline (**10**): Eluate A was recrystallized from hexane to give colorless plates (66 mg, 6.6%), mp 78—79 °C. IR ν_{max} cm^{-1}: 3420 (NH). This compound was found to be identical with an authentic sample of 2,6-dimethoxy-*N*-phenylaniline (**10**).

ii) Ethyl 5-Chloro-7-methoxyindole-2-carboxylate (**16**): Eluate B was recrystallized from hexane to give colorless plates (44 mg, 3.9%), mp 139—140 °C. IR ν_{max} cm^{-1}: 1705 (C=O). This compound was identical with the sample[2] which we had already obtained.

iii) Ethyl 1-(2,6-Dimethoxyphenyl)indole-2-carboxylate (**17**): Eluate C was recrystallized from hexane to give colorless needles (5 mg, 0.34%), mp 140.5—141.5 °C. IR ν_{max} cm^{-1}: 1725 (C=O). MS *m/z*: 325 (M^+). This compound was identical with the sample prepared by the alternative route described later.

iv) Ethyl 1-(2,6-Dimethoxyphenyl)-3-(4′-anilino-3′,5′-dimethoxyphenyl)-indole-2-carboxylate (**18**): Eluate D was recrystallized from hexane–benzene to give colorless plates (37 mg, 1.6%), mp 208—209 °C. *Anal.* Calcd for $C_{33}H_{32}N_2O_6$: C, 71.72; H, 5.84; N, 5.07. Found: C, 71.41; H, 6.02; N, 4.96. IR ν_{max} cm^{-1}: 3355 (NH), 1680 (C=O). ^{1}H-NMR δ: 1.30 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.62 (6H, s, 2×OCH_3), 3.65 (6H, s, 2×OCH_3), 3.98 (1H, br s, NH), 4.33 (2H, q, J=7.5 Hz, $OC\underline{H}_2$–CH_3), 6.50—8.32 (14H, m, ArH). MS *m/z*: 552 (M^+).

Alternative Synthesis of 4-Chloro-2,6-dimethoxy-*N*-phenylaniline (12) i) 1-Chloro-3,5-dimethoxybenzene (**19**): A suspension of commercial 3,5-dimethoxyaniline (3.00 g) in 35% HCl (6.72 ml) was treated with a solution of $NaNO_2$ (1.38 g) in water (6 ml) under ice-cooling. The resulting diazonium solution was added at once to a solution of Cu_2Cl_2[10] [freshly prepared from $CuSO_4 \cdot 5H_2O$ (6.12 g)] in 35% HCl (7 ml) under ice-cooling. After generation of N_2 gas had ceased, the mixture was slowly heated to 60 °C, stirred for 1 h, poured into water, and extracted with Et_2O. The extract was washed with water, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave the oily residue (2.549 g), which was purified by column chromatography over silica gel using benzene–hexane (3 : 1) as an eluent to give colorless prisms (2.278 g, 67%), mp 33—34 °C (lit.[11] mp 38 °C).

ii) Methyl 4-Chloro-2,6-dimethoxybenzoate (**20**): A solution of 15% *n*-BuLi in hexane (17.6 ml) was added to a solution of 1-chloro-3,5-dimethoxybenzene (**19**) (3.597 g) in dry tetrahydrofuran (THF) (150 ml) at −23 °C (bath temperature) under Ar and the whole was stirred at −25—−20 °C for 1 h. Then dry ice (10 g) was added, and the resulting mixture was allowed to stand until the temperature went up to room temperature. The solvent was removed *in vacuo* and water was added to the residue. The mixture was extracted off with Et_2O. The aqueous layer was acidified with diluted HCl, and extracted with $CHCl_3$, then the extract was dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The resulting brown oily residue was dissolved in AcOEt and allowed to react with excess ethereal CH_2N_2 under ice-cooling for 1 h. Removal of the solvent *in vacuo* gave an oily residue (4.350 g), which was purified by column chromatography over silica gel using benzene as an eluent to give colorless crystals (0.479 g, 10%). Recrystallization from benzene–hexane gave colorless needles, mp 78—80 °C. *Anal.* Calcd for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4.81. Found: C, 52.06; H, 4.84. IR ν_{max} cm^{-1}: 1730 (C=O), 1260 (C–O–C). ^{1}H-NMR δ: 3.78 (6H, s, 2×OCH_3), 3.85 (3H, s, OCH_3), 6.52 (2H, s, ArH). MS *m/z*: 232 (M^++2, 37% intensity of M^+), 230 (M^+), 199 (100%).

iii) Ethyl 4-Chloro-2,6-dimethoxycarbanilate (**21**): A mixture of the ester (**20**) (109 mg) and powdered KOH (500 mg) in ethylene glycol (2 ml) was heated at 150 °C for 30 min. Then the mixture was poured into water, and extracted with Et_2O. The aqueous layer was acidified with diluted HCl, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a solid (87 mg, 85%). Recrystallizations from water–EtOH gave 4-chloro-2,6-dimethoxybenzoic acid as colorless prisms, mp 181—183 °C (lit.[12] mp 189—190 °C). MS *m/z*: 218 (M^++2, 37% of M^+), 216 (M^+).

Diphenyl phosphorazidate[13] (DPPA) (0.16 ml) and Et_3N (0.12 ml) were added to a solution of 4-chloro-2,6-dimethoxybenzoic acid (87 mg) in dioxane (1.5 ml), and the mixture was refluxed for 5 h. Then EtOH (1 ml) was added, and the whole was refluxed for a further 10 h. At the end of the reaction, the solvent was removed *in vacuo*. The residue was dissolved in benzene (10 ml), and the resultant solution was washed with 5% aqueous citric acid, water, and 5% aqueous $NaHCO_3$ successively, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a brown solid (158 mg), which was purified by column chromatography over silica gel using benzene–AcOEt (10 : 1) as an eluent to give crystals (100 mg, 96%). Recrystallizations from benzene–hexane gave colorless needles, mp 123—125 °C. *Anal.* Calcd for $C_{11}H_{14}ClNO_4$: C, 50.87; H, 5.43; N, 5.39. Found: C, 51.18; H, 5.32; N, 5.20. IR ν_{max} cm^{-1}: 3240 (NH), 1705 (C=O). ^{1}H-NMR δ: 1.38 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 3.80 (6H, s, 2×OCH_3), 4.17 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 4.86 (1H, br s, NH), 6.55 (2H, s, ArH). MS *m/z*: 261 (M^++2, 36% intensity of M^+), 259 (M^+).

iv) Ethyl 4-Chloro-2,6-dimethoxy-*N*-phenylcarbanilate (**22**): A mixture of the carbanilate (**21**) (72 mg), powdered anhydrous K_2CO_3 (51 mg), Cu_2Br_2 (11 mg), and bromobenzene (1 ml) was heated at 160—170 °C (bath temperature) for 2 h under Ar. Work-up according to the general procedure of the Ullmann–Goldberg reaction gave crystals (87 mg), which were purified by column chromatography over silica gel using benzene, then benzene–AcOEt (10 : 1) as eluents to give colorless prisms (65 mg, 70%), mp 135—140 °C. Recrystallizations from benzene–hexane gave an analytical sample as colorless prisms, mp 139—141 °C. *Anal.* Calcd for $C_{17}H_{18}ClNO_4$: C, 60.80; H, 5.40; N, 4.17. Found: C, 61.07; H, 5.54; N, 4.20. IR ν_{max} cm^{-1}: 1705 (C=O). ^{1}H-NMR δ: 1.17 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 3.73 (6H, s, 2×OCH_3), 4.15 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.55 (2H, s, C_3- and C_5-H), 6.90—7.40 (5H, m, ArH). MS *m/z*: 337 (M^++2, 44% intensity of M^+), 335 (M^+).

v) 4-Chloro-2,6-dimethoxy-*N*-phenylaniline (**12**): A mixture of the *N*-phenyl carbamate (**22**) (62 mg) and powdered KOH (113 mg) in ethylene glycol (1 ml) was heated at 150 °C (bath temperature) for 4 h. The reaction mixture was poured into water, and extracted with $CHCl_3$, then the extract was washed with saturated aqueous NaCl, and dried over $MgSO_4$. Removal of solvent *in vacuo* gave a crystalline residue (48 mg), which was chromatographed over silica gel using benzene as an eluent to give a colorless solid (37 mg, 76%). Recrystallization from benzene–hexane gave colorless needles, mp 109—112 °C. This compound was identical with the Fischer product.

Preparation of Authentic Ethyl 6-Chloro-7-methoxy-1-phenylindole-2-carboxylate (13) A mixture of the NH-indole (**14**) (84 mg), bromobenzene (1 ml), anhydrous K_2CO_3 (80 mg), Cu_2Br_2 (8 mg), and pyridine (0.2 ml) in nitrobenzene (3 ml) was refluxed for 20 h under Ar. The reaction mixture was worked up according to the general procedure of the Ullmann–Goldberg reaction. The crude product was purified by column chromatography over silica gel using benzene as an eluent to give a solid (69 mg). Recrystallizations from hexane gave colorless plates, mp 73—74 °C. This compound was identical with the Fischer product, ethyl 6-chloro-7-methoxy-1-phenylindole-2-carboxylate (**13**).

2,6-Dimethoxy-*N*-phenylaniline (10) from 4-Anilino-3,5-dimethoxybenzaldehyde (15) The aldehyde (**15**) (71 mg) was well mixed with 5% Pd–C[14] (178 mg) and heated at 190—200 °C (bath temperature) for 2 h. The reaction mixture was extracted with benzene and filtered. The benzene layer was evaporated to dryness *in vacuo* to give a pale brown solid (51 mg). Purification by column chromatography over silica gel using benzene as an eluent gave colorless crystals (46 mg, 73%). Recrystallizations from benzene–hexane gave colorless plates, mp 77—78.5 °C. This sample was identical with an authentic sample of 2,6-dimethoxy-*N*-phenylaniline (**10**).

Ethyl 2-(*N*-Acetyl-2,6-Dimethoxyanilino)benzoate (24) A mixture of 2,6-dimethoxyacetanilide (**7**) (0.700 g), ethyl *o*-bromobenzoate[15] (8.586 g), Cu_2Br_2 (0.065 g), anhydrous K_2CO_3 (0.549 g), and pyridine (2.9 ml) was heated at 150—160 °C for 8 h under Ar. Work-up according to the general procedure of the Ullmann–Goldberg reaction gave the crude prŏduct, which was prurified by 'column chromatography over silica gel using benzene then AcOEt as eluents to give crystals (0.706 g, 87%). Recrystallizations from $CHCl_3$–cyclohexane gave colorless fine prisms, mp 144—145 °C. *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.49; H, 6.17; N, 4.32. IR ν_{max} cm^{-1}: 1710, 1680 (C=O). ^{1}H-NMR δ: 1.36 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.96 (9/5H, s, $COCH_3$),[16] 2.02 (6/5H, s, $COCH_3$),[16] 3.76 (6H, s, 2×OCH_3), 4.36 (2H, m, $OC\underline{H}_2CH_3$), 6.55 (2H, d, J=8.0 Hz, $C_{3'}$- and $C_{5'}$-H), 7.04—7.50 (4H, m, ArH), 7.84 (1H, m, C_6-H).

Ethyl 2-(2,6-Dimethoxyanilino)benzoate (25) A solution of the acetanilide (**24**) (350 mg) in 40% alcoholic H_2SO_4 (3.5 ml) was refluxed for 4 h. Then the reaction mixture was diluted with Et_2O, washed with water and 5% aqueous $NaHCO_3$, and dried over anhydrous K_2CO_3. Removal of solvent *in vacuo* gave the residue, which was purified over Al_2O_3 (Merck, neutral, grade I) using benzene as an eluent to give a solid. Recrystallizations from hexane gave colorless needles (250 mg, 81%), mp 99—100 °C. *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found:

C, 67.80; H, 6.34; N, 4.61. IR ν_{max} cm^{-1}: 3340 (NH), 1680 (C=O). ^{1}H-NMR δ: 1.39 (3H, t, J=7.0 Hz, CH_2CH_3), 3.78 (6H, s, 2×OCH_3), 4.36 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.40 (1H, dif d, J=8.0 Hz, C_3-H), 6.60 (2H, d, J=8.0 Hz, $C_{3'}$- and $C_{5'}$-H), 6.62 (1H, t, J=8.0 Hz, $C_{4'}$-H), 7.00—7.28 (2H, m, C_4- and C_5-H), 7.92 (1H, dd, J=8.0 and 2.0 Hz, C_6-H), 8.10—9.40 (1H, br s, NH).

2-(2,6-Dimethoxyanilino)benzaldehyde (26) Vitride[17] (0.95 ml) was added to a solution of the NH-benzoate (**25**) (101 mg) in dry benzene (1 ml) under ice-cooling and the resulting mixture was stirred at room temperature for 40 min. Then, 10% aqueous H_2SO_4 (10 ml) was added to the reaction mixture under ice-cooling. The organic layer was separated, washed with 5% aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The crude product (85 mg, 98%), was recrystallized from MeOH to give 2-(2,6-dimethoxyanilino)benzyl alcohol as colorless prisms, mp 164—165 °C. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.32; H, 6.63; N, 5.31. IR ν_{max} cm^{-1}: 3370 (NH and OH). ^{1}H-NMR δ: 2.06 (1H, br s, OH), 3.76 (6H, s, 2×OCH_3), 4.78 (2H, br s, $ArCH_2O$), 6.46 (1H, d, J=8.0 Hz, C_3-H), 6.60 (2H, d, J=8.0 Hz, $C_{3'}$- and $C_{5'}$-H), 6.73 (1H, t, J=8.0 Hz, $C_{4'}$-H), 6.40—6.90 (1H, br s, NH), 6.92—7.20 (3H, m, C_4-, C_5-, and C_6-H). MS *m/z*: 259 (M^+), 210 (100%).

Active MnO_2[18] (237 mg) was added to a solution of the benzyl alcohol (71 mg) in benzene (3.5 ml) and the resulting mixture was refluxed for 30 min. More MnO_2 (237 mg) was then added and the whole was refluxed for a further 40 min. The reaction mixture was diluted with benzene and filtered. The filtrate was dried over anhydrous K_2CO_3 and evaporated to dryness *in vacuo*. The residue (66 mg, 95%) was purified by column chromatography using benzene as an eluent and recrystallized from MeOH–$CHCl_3$ to give pale yellow fine needles (41 mg, 58%), mp 189—190 °C.[19] *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.99; H, 5.81; N, 5.31. IR ν_{max} cm^{-1}: 3280 (NH), 1660 (C=O). ^{1}H-NMR δ: 3.78 (6H, s, 2×OCH_3), 6.41 (1H, d, J=8.0 Hz, C_3-H), 6.61 (2H, d, J=8.0 Hz, $C_{3'}$- and $C_{5'}$-H), 6.73 (1H, t, J=8.0 Hz, $C_{4'}$-H), 7.16 (1H, dif t, J=8.0 Hz, C_5-H), 7.24 (1H, dif t, J=8.0 Hz, C_4-H), 7.51 (1H, dd, J=8.0 and 2.0 Hz, C_6-H), 9.43 (1H, br s, NH), 9.90 (1H, s, CHO). MS *m/z*: 257 (M^+, 100%).

4-(Hydroxymethyl)-2,6-dimethoxybenzoic Acid (28) A solution of 15% *n*-BuLi in hexane (17.8 ml) was added to a solution of 3,5-dimethoxybenzyl alcohol (**27**) (2.00 g) in dry THF (100 ml) at 0 °C under Ar, and the mixture was stirred at room temperature for 1 h. At the end of the reaction, dry ice (10 g) was added and the reaction mixture was allowed to stand at room temperature for 2 h. THF was evaporated off *in vacuo* and water was added to the residue, which was extracted with Et_2O. The aqueous layer was acidified with diluted HCl and the separated crystals (1.940 g, 77%), mp 205—207 °C, were collected with suction. Recrystallizations from MeOH gave colorless needles, mp 210—212 °C. *Anal.* Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.75; H, 5.64. IR ν_{max} cm^{-1}: 3360 (OH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 3.60 (1H, br s, COH or COOH), 3.73 (6H, s, 2×OCH_3), 4.50 (2H, s, $ArCH_2O$), 5.25 (1H, br s, COOH or COH), 6.61 (2H, s, ArH). MS *m/z*: 212 (M^+, 100%). The structure, specifically the position of the carboxyl group, was further confirmed by converting the benzyl alcohol (**28**) to known 2,6-dimethoxy-4-methylbenzoic acid, mp 183—185 °C (authentic sample prepared from orcinol dimethyl ether: mp 184—187 °C, lit.[20] mp 189—190 °C) by hydrogenolysis (98% yield) with 10% Pd–C in AcOH.

Ethyl 4-(Acetoxymethyl)-2,6-dimethoxycarbanilate (29) Acetic anhydride (Ac_2O) (1.13 ml) was added to a solution of the benzyl alcohol (**28**) (2.14 g) in pyridine (20 ml) and the mixture was stirred at room temperature for 4 h. Then the reagents were evaporated off *in vacuo* and the residue was treated with diluted HCl. The separated crystals were collected with suction and washed with water. The yield was 2.17 g (85%). Recrystallizations from EtOH gave 4-(acetoxymethyl)-2,6-dimethoxybenzoic acid as colorless prisms (1.92 g, 75%), mp 174—176 °C. *Anal.* Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.52; H, 5.65. IR ν_{max} cm^{-1}: 3300—2800 (br s, OH), 1730 (C=O). MS *m/z*: 254 (M^+).

DPPA (2.7 ml) and then Et_3N (1.98 ml) were added to a solution of 4-(acetoxymethyl)-2,6-dimethoxybenzoic acid (1.80 g) in dioxane (30 ml) at room temperature. The mixture was heated at 110 °C (bath temperature) for 5 h, and absolute EtOH (10 ml) was then added to it. The whole was heated at 100 °C (bath temperature) for 10 h. The solvent was evaporated off *in vacuo* and the residue was diluted with benzene. The organic layer was washed with 10% aqueous citric acid, water, 5% aqueous $NaHCO_3$, and saturated NaCl successively, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (2.78 g) was purified by column chromatography over silica gel using benzene–AcOEt (5:1) to give a solid (1.59 g, 76%), mp 116—119 °C. Recrystallizations from benzene–hexane gave colorless prisms, mp 116—118 °C. *Anal.* Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.59; H, 6.38; N, 4.60. IR ν_{max} cm^{-1}: 3280 (NH), 1720, 1710 (C=O). ^{1}H-NMR δ: 1.28 (3H, t, J=8.0 Hz, CH_2CH_3), 2.10 (3H, s, $COCH_3$), 3.83 (6H, s, 2×OCH_3), 4.18 (2H, q, J=8.0 Hz, OCH_2CH_3), 5.03 (2H, s, $ArCH_2O$), 5.95 (1H, br s, NH), 6.55 (2H, s, ArH). MS *m/z*: 297 (M^+, 100%).

Ethyl 4-(Acetoxymethyl)-2,6-dimethoxy-*N*-phenylcarbanilate (30) A mixture of the NH-carbanilate (**29**) (85 mg), anhydrous K_2CO_3 (55 mg), Cu_2Br_2 (13 mg), and bromobenzene (1 ml) was heated at 170 °C (bath temperature) for 3 h under Ar. The reaction mixture was worked up according to the general procedure of the Ullmann–Goldberg reaction gave an oily residue, which was purified by column chromatography over silica gel using benzene then benzene–AcOEt (5:1) as eluents to give colorless crystals (86 mg, 80%). Recrystallizations from benzene–hexane gave colorless prisms, mp 125—127 °C. *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.28; H, 6.21; N, 3.60. IR ν_{max} cm^{-1}: 1720, 1695 (C=O). ^{1}H-NMR δ: 1.18 (3H, t, J=8.0 Hz, CH_2CH_3), 2.12 (3H, s, $COCH_3$), 3.78 (6H, s, 2×OCH_3), 4.17 (2H, q, J=8.0 Hz, OCH_2CH_3), 5.06 (2H, s, $ArCH_2O$), 6.55 (2H, s, C_3- and C_5-H), 7.00—7.40 (5H, m, ArH). MS *m/z*: 373 (M^+, 100%).

Authentic Sample of 4-Anilino-3,5-dimethoxybenzaldehyde (15) A mixture of the carbanilate (**30**) (0.500 g) and powdered KOH (0.80 g) in ethylene glycol (8 ml) was heated at 130 °C for 9 h under Ar. Then the mixture was poured into water, and extracted with $CHCl_3$. The extract was washed with saturated NaCl, and dried over $MgSO_4$. Removal of solvent *in vacuo* gave a brown oily residue (0.317 g), which was purified by column chromatography over silica gel using benzene–AcOEt (10:1) as an eluent to give colorless crystals (0.262 g, 76%). Recrystallizations from benzene–hexane gave 4-anilino-3,5-dimethoxybenzyl alcohol as colorless needles, mp 81—82.5 °C. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.45; H, 6.60; N, 5.24. IR ν_{max} cm^{-1}: 3400, 3330 (OH and NH). ^{1}H-NMR δ: 2.00 (1H, br s, OH), 3.77 (6H, s, 2×OCH_3), 4.63 (2H, s, $ArCH_2O$), 5.60 (1H, br s, NH), 6.55—7.37 (5H, m, ArH), 6.61 (2H, s, C_3- and C_5-H). MS *m/z*: 259 (M^+, 100%).

Active MnO_2[18] (1.01 g) was added to a solution of 4-anilino-3,5-dimethoxybenzyl alcohol (101 mg) in dry benzene (1 ml) and the whole was stirred at room temperature for 1 h. After addition of more MnO_2 (0.20 g), the reaction mixture was stirred at the same temperature for a further 1.5 h. The MnO_2 was filtered off and the filtrate was evaporated to dryness *in vacuo* to give a brown solid. Column chromatography over silica gel using benzene as an eluent gave pale yellow crystals (73 mg, 73%). Recrystallizations from benzene–hexane gave pale yellow prisms, mp 140—141.5 °C. *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.17; H, 5.85; N, 5.38. IR ν_{max} cm^{-1}: 3390 (NH), 1670 (C=O). This compound was identical with the Fischer product, 4-anilino-3,5-dimethoxybenzaldehyde (**15**).

Authentic Sample of Ethyl 1-(2,6-Dimethoxyphenyl)indole-2-carboxylate (17) A mixture of ethyl indole-2-carboxylate (**35**) (1.00 g), 2,6-dimethoxybromobenzene (**9**) (3.46 g), anhydrous K_2CO_3 (1.00 g), and Cu_2Br_2 (100 mg) in a mixture of pyridine (2 ml) and nitrobenzene (10 ml) was refluxed for 18 h. The reaction mixture was worked up according to the general procedure of the Ullmann–Goldberg reaction to give a crude product (1.498 g). Column chromatography over silicic acid using benzene as an eluent gave a colorless solid (571 mg, 33%). Recrystallizations from hexane–benzene gave colorless needles, mp 140 °C. *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.14; H, 5.87; N, 4.28. IR ν_{max} cm^{-1}: 1720 (C=O). ^{1}H-NMR δ: 1.19 (3H, t, J=7.2 Hz, CH_2CH_3), 3.62 (6H, s, 2×OCH_3), 4.17 (2H, q, J=7.2 Hz, OCH_2CH_3), 6.58—7.63 (8H, m, ArH). MS *m/z*: 325 (M^+).

Experiment with ^{13}C-Enriched (Labeled) Compounds The starting material for the ^{13}C experiment was a commercial DL-alanine-3-^{13}C (**31**) (90% atom% ^{13}C, Merck Sharp & Dohme Limited, Montreal, Canada) (0.486 g), which was diluted with unlabeled DL-alanine (10.625 g) to 4.9% ^{13}C-enriched concentration at C-3. The ^{13}C concentration of enriched carbon in the present series was determined by comparison of ^{13}C-NMR spectra of the labeled compound and the corresponding unlabeled compound on the basis of appropriate non-enriched carbons (see the table in Chart 7). All labeled compounds were characterized by comparison of their spectra, melting point, and TLC behavior with those of the corresponding unlabeled compound. Elemental analyses and spectral data for characterization were performed on the unlabeled compound.

Labeled DL-Alanine Benzyl Ester *p*-Toluenesulfonate (L-32) The procedure follows the method of Winitz *et al.*[21] A mixture of the labeled DL-alanine (11.11 g), $TsOH \cdot H_2O$ (26.16 g), and benzyl alcohol (80 ml) was

slowly heated to 100 °C at 4 mmHg. When the benzyl alcohol was distilled off, more benzyl alcohol (80 ml) was added to the mixture, and similar distillation was performed. This procedure was repeated three times. Finally, the residue was dissolved in EtOH (50 ml), and then Et_2O was added to this solution. The precipitated crystals were collected, washed with Et_2O, and dried to give colorless needles (25.89 g, 82%), mp 107—112 °C. IR ν_{max} cm^{-1}: 1745 (C=O). ^{1}H-NMR δ (free base): 1.29 (3H, d, J=8.0 Hz, C_3-H), 1.70 (2H, br s, NH_2), 3.53 (1H, q, J=8.0 Hz, C_2-H), 5.08 (2H, s, $ArCH_2O$), 7.24 (5H, s, ArH).

Labeled Benzyl Pyruvate (L-33) *tert*-Butyl hypochlorite (*tert*-BuOCl) (1.50 ml) was added dropwise to a solution of labeled DL-alanine benzyl ester (**32**) (2.27 g), the free base prepared from the *p*-toluenesulfonate (**32**) with 10% aqueous Na_2CO_3, under ice-cooling, and the whole was stirred for 10 min. The reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in CH_2Cl_2. The organic layer was washed with 0.1 N HCl and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. A pale yellow oily residue was dissolved in Et_2O (30 ml). To this solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.90 ml) was added dropwise under ice-cooling, and the whole was stirred at the same temperature for 30 min. Then the reaction mixture was filtered to remove insoluble material (DBU·HCl). The filtrate was mixed with concentrated H_2SO_4 (1.24 g), Et_2O (20 ml), water (0.23 g), and THF (5 ml) and refluxed for 1.5 h. Then the reaction mixture was concentrated *in vacuo* to dryness and the residue was dissolved in CH_2Cl_2. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a pale yellow oil (1.41 g, 63%). IR ν_{max} cm^{-1}: 1730 (C=O). This compound was used for next reaction without further purification.

Labeled Pyruvic Acid 2-(2,6-Dimethoxyphenyl)phenylhydrazone (L-34) A solution of the benzyl pyruvate (L-**33**) (2.113 g) in a mixture of EtOH (15 ml) and AcOH (0.5 ml) was added to a solution of 1-(2,6-dimethoxyphenyl)-1-phenylhydrazine (**11**) in EtOH (15 ml), and the whole was stirred at room temperature for 1.5 h. The reaction mixture was poured into water, and the precipitated crystals (2.78 g) were collected with suction. These crystals were chromatographed over silica gel using benzene–AcOEt (20:1) as an eluent to give benzyl pyruvate 2-(2,6-dimethoxyphenyl)-phenylhydrazone as colorless prisms [2.36 g, 75%, based on the hydrazine (**11**)], mp 150—154 °C. Recrystallizations from benzene–MeOH gave colorless prisms, mp 155.5—157 °C. *Anal.* Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.38; H, 5.94; N, 6.89. IR ν_{max} cm^{-1}: 1690 (C=O). ^{1}H-NMR δ: 1.58 (3H, s, $=CCH_3$), 3.74 (6H, s, $2\times OCH_3$), 5.32 (2H, s, OCH_2Ph), 6.60 (2H, d, J=8.0 Hz, C_3- and C_5-H), 6.85—7.65 (11H, m, ArH). MS m/z: 404 (M^+, 93%), 228 (100%).

The benzyl pyruvate 2-(2,6-dimethoxyphenyl)phenylhydrazone (2.36 g) was added to a solution of KOH (7.16 g) in EtOH (60 ml) and the mixture was stirred at 60 °C (bath temperature) for 30 min. The reaction mixture was poured into water, and extracted with Et_2O. The aqueous layer was acidified with concentrated HCl and extracted with $CHCl_3$. The chloroform layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crystalline residue (1.83 g, 100%), mp 155—159 °C, was recrystallized from benzene–hexane to give pale yellow prisms, mp 160—162.5 °C. *Anal.* Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.98; H, 5.67; N, 8.82. IR ν_{max} cm^{-1}: 3270 (OH), 1740 (C=O). ^{1}H-NMR δ: 1.54 (3H, s, $=CCH_3$), 3.72 (6H, s, $2\times OCH_3$), 6.50—7.55 (8H, m, ArH), 10.05 (1H, br s, COOH). MS m/z: 314 (M^+, 96%), 111 (100%).

Labeled Ethyl Pyruvate 2-(2,6-Dimethoxyphenyl)phenylhydrazone (L-6) Excess CH_3CHN_2 in Et_2O was added to a solution of the labeled carboxylic acid (L-**34**) (354 mg) in AcOEt under ice-cooling, and the mixture was stirred for 30 min. Removal of the solvent gave a solid, which was purified over silica gel using benzene–AcOEt (20:1) as an eluent to give pale yellow crystals (369 mg, 96%). Recrystallizations from benzene–hexane gave pale yellow prisms, mp 114—115.5 °C. IR ν_{max} cm^{-1}: 1690 (C=O). This compound was identical with the unlabeled hydrazone (**14**).

Fischer Indolization of Labeled Ethyl Pyruvate 2-(2,6-Dimethoxyphenyl)-phenylhydrazone (L-6) with HCl/EtOH The labeled hydrazone (L-**6**) (1.60 g) was dissolved in absolute EtOH saturated with dry HCl gas and stirred at room temperature for 50 min. The reaction mixture was worked up in the same way as in the reaction of the unlabeled hydrazone (**6**) with HCl/EtOH. The results are shown in Chart 7, and ^{13}C-NMR assignments in Table I.

References and Notes

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