Fischer Indolization of Ethyl Pyruvate 2-[2-(Trifluoromethyl)phenyl]-phenylhydrazone and New Insight into the Mechanism of the Goldberg Reaction. (Fischer Indolization and Its Related Compounds. XXVI[1])

Yasuoki MURAKAMI,*,[a] Toshiko WATANABE,[a] Takao HAGIWARA,[b] Yohko AKIYAMA (née KONDO),[b] and Hisashi ISHII*,[b]

School of Pharmaceutical Sciences, Toho University,[a] 2–2–1 Miyama, Funabashi, Chiba 274, Japan and Faculty of Pharmaceutical Sciences, Chiba University,[b] 1–33 Yayoicho, Inage-ku, Chiba 263, Japan.

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The Fischer indolization of ethyl pyruvate 2-[2-(trifluoromethyl)phenyl]phenylhydrazone (5) gave two indolic products, ethyl 7-(trifluoromethyl)-1-phenylindole-2-carboxylate (12) as a minor product and ethyl 1-[2-(trifluoromethyl)phenyl]indole-2-carboxylate (13) as a major product. This result shows that the Fischer indolization occurred on the more electron-rich phenyl group. In the Goldberg reaction to prepare 13 from ethyl indole-2-carboxylate (15) and *o*- (21) or *m*-bromo-α,α,α-trifluorotoluene (23), it was found that Goldberg reaction proceeds *via* a benzyne mechanism, at least in part, in a sterically crowded situation.

Key words Fischer indolization; diarylhydrazone; indole; trifluoromethyl; Goldberg reaction; benzyne

In a previous paper[2] we reported the result of Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (**1**). The main indolic product was ethyl 1-(2-methoxyphenyl)indole-2-carboxylate (**2**), which resulted from the cyclization towards the electron-poorer B ring in **1**. This result is in contrast to that of the Fischer indolization of ethyl pyruvate 2-(4-methoxyphenyl)phenylhydrazone[3] (**3**) and 2-(2,6-dimethoxyphenyl)phenylhydrazone[4] (**4**), in which the cyclization occurred predominantly to the electron-richer A ring. In order to clarify the reason for this discrepancy, we investigated the Fischer indolization of a phenylhydrazone with an electron-attracting group in place of the methoxy group of **1**. In this paper we report on the Fischer indolization of ethyl pyruvate 2-[2-(trifluoromethyl)phenyl]phenylhydrazone (**5**).

Preparation of Starting Hydrazone (5) The starting hydrazone (**5**) was prepared according to the route shown in Chart 2. The diphenylamine (**9**) is a known compound.[5] In order to prepare **9** α,α,α-trifluoro-*o*-toluidine (**6**) was heated in acetic anhydride/pyridine according to the known method[6] to give a product whose melting point (mp 96—97 °C) was identical with that reported for the corresponding acetanilide.[6] However, our product was

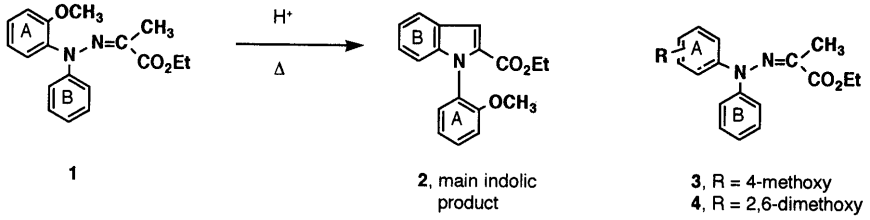


Chart 1

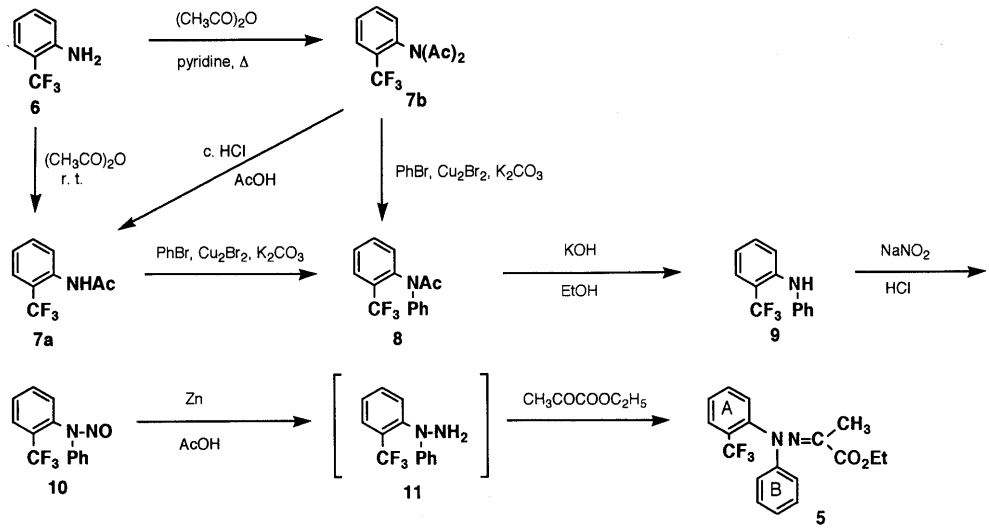


Chart 2

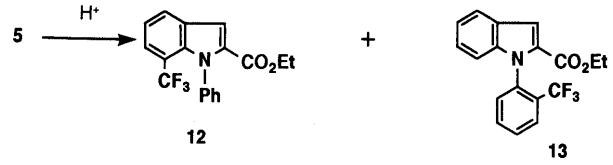
* To whom correspondence should be addressed.

found to be the diacetylaniline (**7b**) on the basis of the spectral data and elemental analysis ($C_{11}H_{10}F_3NO$). Thus, the aniline (**6**) was treated with acetic anhydride under milder conditions to give the desired acetanilide (**7a**), mp 99—100 °C, which was also obtained easily from **7b** by hydrolysis with concentrated HCl in AcOH. Compound **7a** was treated with bromobenzene in the presence of cuprous bromide under Goldberg reaction conditions[7] to give α,α,α-trifluoro-*N*-phenyl-*o*-acetotoluidide (**8**). The acetanilide (**8**) was also obtained directly from **7b** in the same Goldberg reaction. The success of conversion of **7b** into **8** might depend on the ease of hydrolysis of **7b**. Alkaline hydrolysis of the acetanilide (**8**) gave the diphenylamine (**9**), which was accompanied with ethyl *N*-phenylanthranilate as a by-product as a result of ethanolysis[8] of the trifluoromethyl group of **9**. Compound **9** was converted into the nitroso compound (**10**). The reduction of **10**, followed by treatment with ethyl pyruvate, gave the target hydrazone (**5**).

Fischer Indolization of the Hydrazone (5) The hydrazone (**5**) was submitted to Fischer indolization with two kinds of acid catalysts, ethanolic hydrogen chloride and zinc chloride in acetic acid, to give two indolic products (**12**, **13**) in high total yields, respectively. In both reactions the yields of **13** were much higher than those of **12**. The indolic structures for these compounds were deduced by elemental analysis and mass spectrum ($C_{18}H_{14}F_3NO_2$, M^+, 333), and other spectral data. However, the distinction between these two structures was not regarded as definitive, since the position of the trifluoromethyl group was difficult to determine spectroscopically. Thus, these two *N*-arylindoles were identified by alternative syntheses as described below. The results of the Fischer indolization are summarized in Chart 3, showing that the cyclization occurred predominantly on the more electron-rich B-ring of the hydrazone (**5**). Judging from these data, the previous result[2] on the Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (**1**) was abnormal, because **1** cyclized towards the electron-poorer nucleus, whereas other diarylhydrazones, including **5**, did so towards the electron-richer nucleus. In order to explain this discrepancy we further examined the Fischer indolization of other diarylhydrazones.

Identification of the Fischer Products The structures of the Fischer products (**12**, **13**) were determined by alternative synthesis from the corresponding known NH-indoles (**14**, **15**) using the Goldberg reaction as a key step, as shown in Charts 4 and 5.

First, ethyl 7-(trifluoromethyl)indole-2-carboxylate (**14**) was treated with bromobenzene in order to obtain ethyl 7-(trifluoromethyl)-1-phenylindole-2-carboxylate (**12**).



H+ \ Products	Yield (%) 12	13
HCl / EtOH	7	74
$ZnCl_2$ / AcOH	15	82

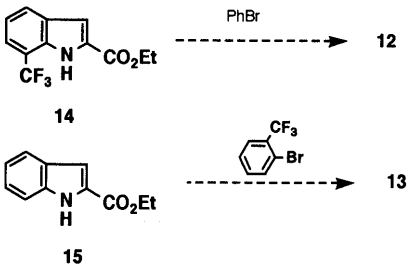


Chart 3

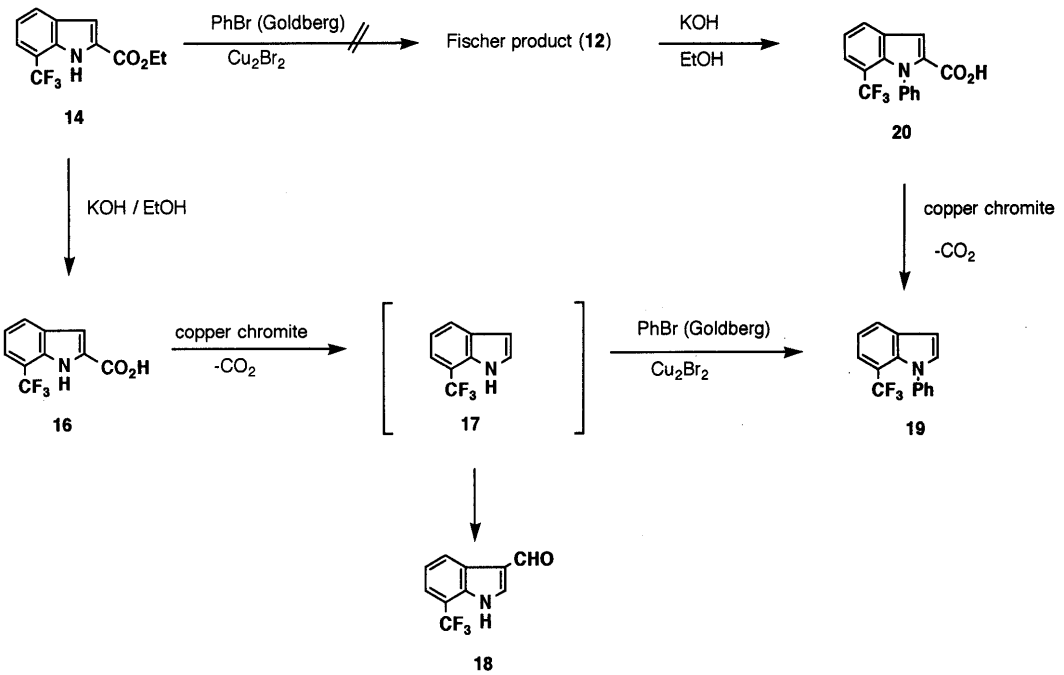


Chart 4

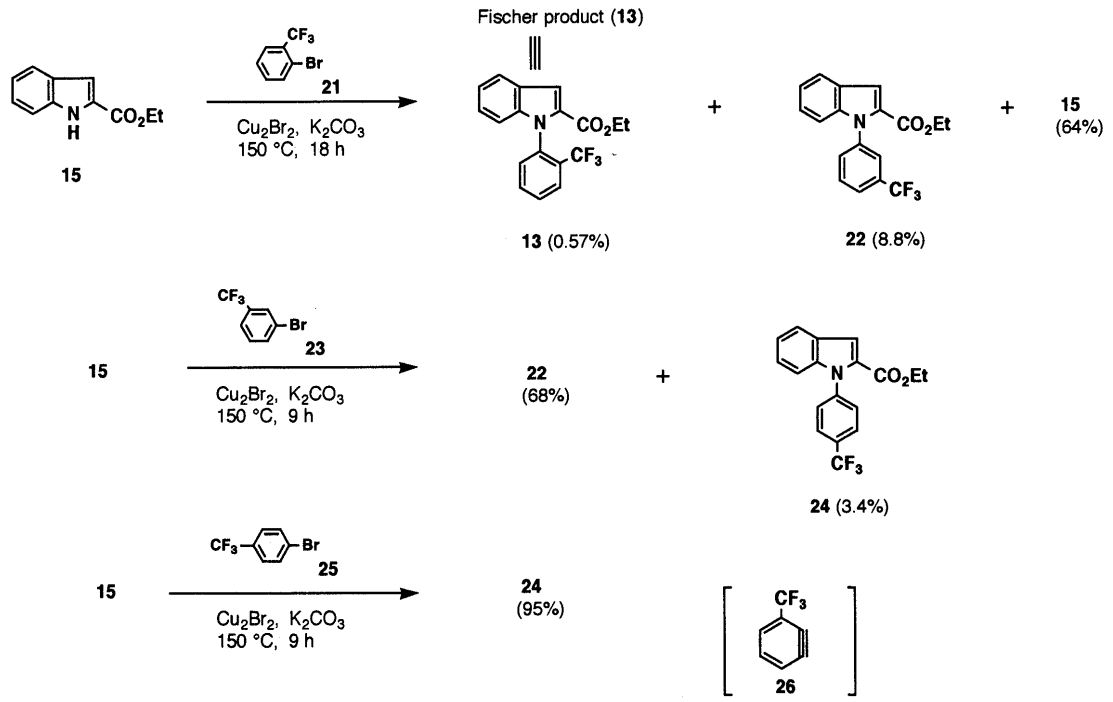


Chart 5

However, the reaction did not proceed at all. We considered that the indolic NH was sterically hindered. Thus, **14** was hydrolyzed to the carboxylic acid (**16**), followed by decarboxylation to the indole (**17**). Being labile, the indole was characterized as the 3-formyl derivative (**18**). The indole (**17**) was converted into the corresponding *N*-phenylindole (**19**). On the other hand, the Fischer product (**12**) was hydrolyzed to the carboxylic acid (**20**), which was decarboxylated to **19**. Compound **19** obtained by the two routes was identical.

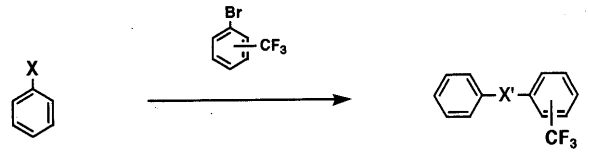
Secondly, ethyl indole-2-carboxylate (**15**) was treated with *o*-bromo-α,α,α-trifluorotoluene (**21**). The reaction proceeded very slowly and unexpectedly gave two indoles having the same molecular formula $C_{18}H_{14}F_3NO_2$ in very low yields. Their formulae corresponded with that of the desired compound formed by coupling between **15** and **21**. Their IR spectra showed no NH absorption. Thus, both compounds are *N*-(trifluoromethyl)phenyl derivatives of **15**. The minor product was found to be identical with one of the Fischer products (**13**). In the Fischer indolization, if cyclization occurred on the B ring, the product should have an *N*-(2-trifluoromethyl)phenyl group. On the other hand, if the Goldberg reaction with **21** proceeded on the NH group of **15**, the trifluoromethyl group should be located on the *N*-phenyl nucleus. Thus, the Fischer product (**13**) should be ethyl 1-[2-(trifluoromethyl)phenyl]indole-2-carboxylate. However, it seemed improbable that the minor product was identical with the Fischer product. The structure of the major product (**22**) could not be determined from the ^{1}H-NMR spectrum, which was very complicated. Thus, chemical means were adopted for that purpose.

We presumed that **22** was a positional isomer of the trifluoromethyl group on the *N*-phenyl group. Thus, the Goldberg reactions of **15** with *m*- and *p*-bromo-α,α,α-trifluorotoluenes (**23**, **25**) were carried out. The reaction of **15** with the *m*-bromide (**23**) proceeded more rapidly than that with *o*-bromo-α,α,α-trifluorotoluene (**21**) to give two compounds (**22**, **24**). The major product (**22**) was identical with the major product in the Goldberg reaction of **15** with the *o*-bromide (**21**). The reaction of **15** with *p*-bromo-α,α,α-trifluorotoluene (**25**) under the same conditions as used with the *m*-bromide (**23**) gave only a single product in very high yield (95%), which was identical with the minor product (**24**) in the reaction with the *m*-bromide (**23**). As the last reaction gave only one product in high yield, the product (**24**) should be authentic ethyl 1-[4-(trifluoromethyl)phenyl]indole-2-carboxylate. On the basis of the clear-cut structure of **24**, the structures of the other two Goldberg products (**13**, **22**) are established.

It is clear that the present series of Goldberg reactions gave abnormal results, as the Goldberg reaction is expected to proceed at the halogenated position of aromatic halides. The abnormal product is not due to contamination[9] with the starting bromides. Rather, the abnormality should be attributed to the "benzyne" (**26**) (formed from **21**) intermediate, which would be slowly formed during the Goldberg reaction. Although amination of aryl halides by the use of strong bases proceeds *via* the benzyne mechanism,[7a] it is considered[7b] that the Goldberg reaction proceeds *via* *S*$_N$Ar (or *S*$_N$1) substitution. Our present results demonstrate that the Goldberg reaction actually proceeds *via* the benzyne mechanism, at least in part or in some cases. Lower reactivity of the bromides **21** and **23** than **25** in the reaction of **15**, due to steric hindrance, would allow the formation of the benzyne.

Examination of Abnormal Goldberg Reaction In order to examine whether or not the benzyne mechanism often occurs in the Goldberg reaction, the Goldberg reaction of acetanilide (**27**) and phenol (**28**) with *o*- and *m*-bromo-α,α,α-trifluorotoluenes (**21**, **23**) was carried out. The reaction of acetanilide (**27**) with **21** proceeded more

Table 1. Goldberg Reaction of Acetanilide (**27**) and Phenol (**28**) with *o*- and *m*-Bromo-α,α,α-trifluorotoluenes (**21**, **23**)



27: X=NHAc
28: X=OH

29: X'=–NAc–(*o*-: **29a**=**8**, *m*-: **29b**)
30: X'=–O–(*o*-: **30a**, *m*-: **30b**)

Substrate	Reagent (molar eq with respect to substrate)	Reaction conditions		Products		Starting material recovered
		Temperature (°C)	Time (h)			
Acetanilide	**21** (6 eq)	150—160	55	**29a** (35%),	**29b** (0.40%)	**27** (45%)
(**27**)	**23** (2 eq)	150	20	**29a** (0%),	**29b** (75%)	**27** (14%)
Phenol	**21** (2 eq)	150—160	20	**30a** (71%),	**30b** (0%)	Not tried
(**28**)	**23** (2 eq)	150	20	**30a** (0%),	**30b** (67%)	Not tried

slowly than with **23**, and thus, much more of the reagent (**21**) was used. The reaction of acetanilide (**27**) with the *o*-bromide (**21**) gave a small amount of the *m*-product (**29b**) with a large amount of the normal *o*-product (**29a**), whereas the reaction with the *m*-bromide (**23**) gave only the normal *m*-product (**29b**). The reactions of phenol (**28**) with *o*- and *m*-bromide (**21**, **23**) gave only normal products (**30a**, **30b**), respectively. From the steric environments of the substituting atom (N and O) of the indole (**15**), acetanilide (**27**), and phenol (**28**), the order of steric crowdedness should be **15**≫**27**>**28**. This implies that steric crowdedness favors the benzyne mechanism in diphenylamine synthesis *via* the Goldberg reaction.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. For spectral data, the following instruments were used: IR; Hitachi EPI-G3. ^{1}H-NMR; JEOL JMN-4H-100 (100 MHz). MS; Hitachi RMU-6E spectrometer. 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 disappearance of the signals after addition of D_2O. Mass spectra were measured with a direct inlet system. For column chromatography, silica gel (Kiesel gel 60, 70—230 mesh, Merck) and for preparative TLC, Kiesel gel GF_{254}, Merck, were used. Identification of the products was done by IR spectroscopy, mixed melting point determination, and TLC. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; dif, diffused; br, broad. Distillation for elemental analysis was performed with a Micro Distillation & Sublimation apparatus, Miyamoto Riken Ind. Co., Ltd. Japan.

α,α,α-Trifluoro-*o*-acetotoluidide (7a) Commercial α,α,α-trifluoro-*o*-toluidine (**6**) (5.00 g) was dissolved in Ac_2O (20 ml) and stirred at room temperature for 1 h. Then the reaction mixture was poured into H_2O, the whole was extracted with Et_2O, and the organic layer was washed with 5% $NaHCO_3$, and dried over anhydrous K_2CO_3. Removal of the solvent *in vacuo* gave a solid (4.68 g). Recrystallizations from hexane gave colorless needles (4.50 g, 71%), mp 99—100 °C (lit.[6] mp 94—95 °C). *Anal.* Calcd for $C_9H_8F_3NO$: C, 53.20; H, 3.97; F, 28.06; N, 6.89. Found: C, 53.50; H, 4.25; F, 28.21; N, 6.70. IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH), 1660 (C=O). ^{1}H-NMR (CCl_4) δ: 2.40 (3H, dif s, $COCH_3$), 7.12 (1H, t, J=8.0 Hz, C_4-H), 7.34 (1H, br s, NH), 7.50 (1H, t, J=7.0 Hz, C_5-H), 7.54 (1H, d, J=7.0 Hz, C_6-H), 8.28 (1H, d, J=8.0 Hz, C_3-H).

α,α,α-Trifluoro-*o*-diacetotoluidide (7b) Ac_2O (2 ml) was added to a solution of α,α,α-trifluoro-*o*-toluidine (**6**) in pyridine (2 ml) and the whole was stirred with heating at 100 °C (bath temperature) for 4 h. Work-up as described for the mono acetyl compound (**7a**) gave a solid (643 mg). Recrystallization from hexane gave colorless needles (347 mg, 46%), mp 96—97 °C. *Anal.* Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; F, 23.25; N, 5.71. Found: C, 53.69; H, 4.17; F, 23.54; N, 5.75. IR ν_{max}^{Nujol} cm^{-1}: no NH, 1700 (C=O). ^{1}H-NMR (CCl_4) δ: 2.18 (6H, s, 2×$COCH_3$), 7.18 (1H, dd, J=7.0, 2.0 Hz, C_6-H), 7.60 (2H, m, C_4, C_5-H), 7.74 (1H, dd, J=8.0, 2.0 Hz, C_3-H).

α,α,α-Trifluoro-*N*-phenyl-*o*-acetotoluidide (8) a) From α,α,α-Trifluoroacetotoluidide (**7a**): A mixture of the acetotoluidide (**7a**) (15.00 g), anhydrous K_2CO_3 (10.20 g), Cu_2Br_2 (0.75 g) and bromobenzene (40 ml) was heated at 170—180 °C (bath temperature) under an Ar atmosphere for 26 h. Then the reaction mixture was poured into ice-H_2O, the whole was extracted with Et_2O, and the organic layer was dried over anhydrous K_2CO_3. Removal of the solvent and excess bromobenzene gave a dark red oil, which was distilled at 110—120 °C under reduced pressure (0.5 mmHg) [lit.,[5] bp 180 °C (10 mmHg)] to give a colorless crystalline (18.1 g). Recrystallization from hexane–Et_2O gave colorless prisms (16.36 g, 79%), mp 70—72 °C. *Anal.* Calcd for $C_{15}H_{12}F_3NO$: C, 64.51; H, 4.33; F, 20.41; N, 5.02. Found: C, 64.70; H, 4.04; F, 20.71; N, 5.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1672 (C=O). ^{1}H-NMR (CCl_4) δ: 1.91 (3H, s, $COCH_3$), 7.05—7.74 (9H, m, arom. H). MS *m/z*: 279 (M^+).

b) From α,α,α-Trifluoro-*o*-diacetotoluidide (**7b**): A mixture of the diacetotoluidide (**7b**) (500 mg), anhydrous K_2CO_3 (0.34 g), Cu_2Br_2 (0.025 g), and bromobenzene (0.5 ml) in nitrobenzene (5.0 ml) was heated at 210 °C (bath temperature) under an Ar atmosphere for 25 h. The reaction mixture was worked-up as above. Yield 77 mg (14%).

α,α,α-Trifluoro-*N*-phenyl-*o*-toluidine (9) A solution of the *N*-phenylacetotoluidide (**8**) (3.48 g) in 10% KOH/EtOH (20 ml) was refluxed for 6 h, then poured into H_2O. The mixture was extracted with Et_2O, and the organic layer was dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (3.05 g) was chromatographed over silica gel using hexane–benzene as an eluent to give two products. The first eluate afforded the desired toluidine (**9**) (2.45 g, 83%). Distillation at 100—110 °C (2 mmHg) [lit.,[10] bp 116 °C (0.7 mmHg)] gave the pure compound as colorless oil. IR ν_{max}^{neat} cm^{-1}: 3410 (NH).

The product from the second eluate (301 mg) was distilled at 145—148 °C (2 mmHg) to give a pale yellow oil (294 mg, 9.6%). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.83; H, 6.26; N, 5.78. IR ν_{max}^{neat} cm^{-1}: 3340 (NH), 1670 (C=O).

This compound, ethyl *N*-phenylanthranilate, was identical with a sample prepared by esterification (with HCl/EtOH) of *N*-phenylanthranilic acid.

α,α,α-Trifluoro-*N*-nitroso-*N*-phenyl-*o*-toluidine (10) A solution of $NaNO_2$ (1.00 g) in H_2O (6 ml) was added dropwise to a solution of the diphenylamine (**9**) (2.50 g) in EtOH (30 ml) and concentrated HCl (2 ml) at 0—4 °C. The reaction mixture was stirred for 2 h, then poured into H_2O, and the whole was extracted with Et_2O. The organic layer was dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (2.43 g) was recrystallized from hexane to give pale brown prisms (2.20 g, 81%), mp 56—57.5 °C. *Anal.* Calcd for $C_{13}H_9F_3N_2O$: C, 58.65; H, 3.41; N, 10.52. Found: C, 58.91; H, 3.71; N, 10.48. IR ν_{max}^{Nujol} cm^{-1}: 1470 (NO).

Ethyl Pyruvate 2-[2-(Trifluoromethyl)phenyl]phenylhydrazone (5) Zn powder (2 g) was added dropwise to a solution of the *N*-nitroso compound (**10**) (2.2 g) in a mixture of AcOH (16 ml), H_2O (6 ml), and EtOH (10 ml) at 0 °C. The reaction mixture was stirred for 5 h, then poured into H_2O,

and unreacted Zn powder was filtered off. The filtrate was made alkaline with 10% NaOH, and extracted with Et_2O. The organic layer was washed with H_2O, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave crude 1-[2-(trifluoromethyl)phenyl]-1-phenylhydrazine (2.00 g), which was dissolved in EtOH (16 ml) and allowed to react with ethyl pyruvate (921 mg) under reflux for 30 min. The residue (1.61 g) obtained by evaporation of the solvent *in vacuo* was chromatographed over silica gel using benzene as an eluent to give a product (1.52 g). Recrystallizations from hexane gave colorless prisms (1.49 g, 52%), mp 52.5—55 °C. *Anal.* Calcd for $C_{18}H_{17}F_3N_2O_2$: C, 61.71; H, 4.89; N, 8.00. Found: C, 61.78; H, 4.99; N, 8.10. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.5 Hz, $CH_2\underline{CH_3}$), 1.52 (3H, s, CH_3), 4.30 (2H, q, J=7.5 Hz, $OC\underline{H_2}CH_3$), 6.90—7.85 (9H, m, arom. H). MS m/z: 350 (M^+).

Fischer Indolization of Ethyl Pyruvate 2-[2-(Trifluoromethyl)phenyl]-phenylhydrazone (5) with HCl/EtOH The hydrazone (**5**) (1.503 g) was dissolved in EtOH (30 ml) saturated with dry HCl gas and the solution was stirred at room temperature for 7.5 h, then poured into ice-H_2O. The whole was extracted with Et_2O. The organic layer was washed with 5% $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (1.387 g) was chromatographed over silica gel using hexane–Et_2O (10 : 1) as an eluent to give two products.

a) Ethyl 7-(Trifluoromethyl)-1-phenylindole-2-carboxylate (**12**): The product from the first eluate (0.100 g, 7%) was recrystallized from pentane to give colorless needles, mp 54—55 °C. *Anal.* Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; N, 4.20. Found: C, 65.15; H, 3.95; N, 4.44. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). ^{1}H-NMR (CCl_4) δ: 1.14 (3H, t, J=8.0 Hz, $CH_2\underline{CH_3}$), 4.07 (2H, q, J=8.0 Hz, $OC\underline{H_2}CH_3$), 7.05—7.50 (7H, m, arom. H), 7.58 (1H, dd, J=8.0, 1.0 Hz, $\underline{C_4}$-H), 7.83 (1H, dd, J=8.0, 1.0 Hz, $C_{6'}$-H). MS m/z: 333 (M^+).

b) Ethyl 1-[2-(Trifluoromethyl)phenyl]indole-2-carboxylate (**13**): The product from the second eluate (1.055 g, 74%) was recrystallized from hexane to give colorless prisms, mp 58—60 °C. *Anal.* Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; F, 17.10; N, 4.20. Found: C, 64.99; H, 4.32; F, 17.06; N, 4.36. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). ^{1}H-NMR (CCl_4) δ: 1.18 (3H, t, J=7.0 Hz, CH_2CH_3), 4.11 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.71 (1H, dd, J=8.0, 1.0 Hz, C_7-H), 6.96—7.72 (7H, m, arom. H), 7.80 (1H, dd, J=7.0, 3.0 Hz, $C_{3'}$-H). MS m/z: 333 (M^+).

This compound was identical with an authentic sample whose preparation will be described later.

Fischer Indolization of Ethyl Pyruvate 2-[2-(Trifluoromethyl)phenyl]-phenylhydrazone (5) with $ZnCl_2$/AcOH Anhydrous $ZnCl_2$ (2.0 g) was added to a solution of the hydrazone (**5**) (1.00 g) in AcOH (20 ml). The reaction mixture was gently refluxed for 20 min, then poured into H_2O and the whole was extracted with Et_2O. The organic layer was washed with diluted $NaHCO_3$, dried over $MgSO_4$, and evaporated *in vacuo* to give an oily residue (962 mg). The residue was chromatographed in a same manner as that obtained in the reaction with HCl/EtOH, to afford ethyl 7-(trifluoromethyl)-1-phenylindole-2-carboxylate (**12**) (141 mg, 15%), and ethyl 1-[2-(trifluoromethyl)phenyl]indole-2-carboxylate (**13**) (782 mg, 82%).

Trial for Independent Synthesis of Ethyl 7-(Trifluoromethyl)-1-phenylindole-2-carboxylate (12) A mixture of ethyl 7-(trifluoromethyl)-indole-2-carboxylate[10] (**14**) (80 mg), Cu_2Br_2 (10 mg), and anhydrous K_2CO_3 (86 mg) in a mixture of bromobenzene (2 ml) and pyridine (1 ml) was heated at 150—160 °C for 8 h under an Ar atmosphere. However, no reaction occurred as judged by TLC. Work-up resulted in recovery of the starting indole (**14**) (71 mg).

Independent Synthesis of Ethyl 1-[2-(Trifluoromethyl)phenyl]indole-2-carboxylate (13). Goldberg Reaction of Ethyl Indole-2-carboxylate (15) with *o*-Bromo-α,α,α-trifluorotoluene (21). General Method for Goldberg Reaction A mixture of ethyl indole-2-carboxylate (**15**) (400 mg), Cu_2Br_2 (40 mg), anhydrous K_2CO_3 (312 mg), *o*-bromo-α,α,α-trifluorotoluene (**21**) (3 ml), and pyridine (1.6 ml) was heated at 150 °C with stirring under an Ar atmosphere for 18 h. The reaction mixture was poured into H_2O and the whole was extracted with Et_2O. The organic layer was washed with diluted HCl and H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (452 mg) was chromatographed over silica gel using benzene–hexane (1 : 1) as an eluent to give three products.

a) Ethyl 1-[3-(Trifluoromethyl)phenyl]indole-2-carboxylate (**22**): The product from the first eluate (62 mg, 8.8%) was recrystallized from pentane to give colorless columns, mp 66.5—67.5 °C. *Anal.* Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; F, 17.10; N, 4.20. Found: C, 64.78; H, 4.37; F, 17.09; N, 4.38. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). ^{1}H-NMR (CCl_4) δ: 1.24 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 4.19 (2H, q, J=7.0 Hz, $OC\underline{H_2}CH_3$), 6.90—7.94 (9H, m, arom. H). MS m/z: 333 (M^+).

This compound was identical with an authentic sample prepared by the Goldberg reaction of ethyl indole-2-carboxylate (**15**) with *m*-bromo-α,α,α-trifluorotoluene (**23**) as described later.

b) Ethyl 1-[2-(Trifluoromethyl)phenyl]indole-2-carboxylate (**13**): The product from the second eluate (4 mg, 0.57%) was recrystallized from pentane to give colorless fine prisms, mp 58.5—60 °C. *Anal.* Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; N, 4.20. Found: C, 64.73; H, 4.13; N, 4.15.

c) Recovered Ethyl Indole-2-carboxylate (**15**): The product from the third eluate (255 mg, 64%) was recrystallized from EtOH to give the starting material, mp 125—126.5 °C.

7-(Trifluoromethyl)indole-2-carboxylic Acid (16) A solution of KOH (50 mg) in EtOH (1 ml) was added to a solution of ethyl 7-(trifluoromethyl)indole-2-carboxylate[10] (**14**) (50 mg) in EtOH (1 ml) and the whole was refluxed for 30 min. The reaction mixture was concentrated *in vacuo* to about half the initial volume, poured into H_2O, acidified with 2 N HCl, and extracted with Et_2O. The organic layer was washed, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (37 mg, 83%) was recrystallized from benzene to give colorless needles, mp 195 °C (sublimed at 180—195 °C). *Anal.* Calcd for $C_{10}H_6F_3NO_2$: C, 52.41; H, 2.64; N, 6.11. Found: C, 52.67; H, 2.67; N, 6.20. IR ν_{max}^{Nujol} cm^{-1}: 3475 (NH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 7.22 (1H, m, C_5-H), 7.28 (1H, dif s, C_3-H), 7.60 (1H, dif d, J=8.0 Hz, C_4-H), 7.95 (1H, dif d, J=8.0 Hz, C_6-H), 11.64 (1H, dif s, NH). MS m/z: 229 (M^+).

7-(Trifluoromethyl)indole (17) A mixture of the carboxylic acid (**16**) (80 mg) and copper chromite[11] (19 mg) in quinoline (1.5 ml) was heated at 200—210 °C with stirring for 45 min under an Ar atmosphere. The mixture was poured into diluted HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give an oily residue. The residue was chromatographed over silica gel using benzene as eluent to give a pure sample as an oil (64 mg, 99%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: no C=O. MS m/z: 185 (M^+).

This oily compound was converted into a crystalline compound, 7-(trifluoromethyl)indole-3-carboxaldehyde (**18**), for characterization as follows.

A solution of 7-(trifluoromethyl)indole (**17**) (180 mg) in *N,N*-dimethylformamide (DMF) (1 ml) was added to a solution of $POCl_3$ (298 mg) in DMF (2 ml) under ice-cooling. The resulting mixture was heated at 80 °C with stirring for 30 min, then poured into H_2O, basified with diluted KOH, and extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (172 mg, 83%) was recrystallized from benzene to give pure **18**, mp 127—128 °C, colorless leaflets. *Anal.* Calcd for $C_{10}H_6F_3NO$: C, 56.34; H, 2.84; N, 6.57. Found: C, 56.56; H, 2.92; N, 6.80. IR ν_{max}^{Nujol} cm^{-1}: 3240 (NH), 1662 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.22—7.64 (2H, m, arom. H), 7.92 (1H, d, J=3.0 Hz, C_2-H), 8.50 (1H, dif d, J=8.0 Hz, C_4-H), 9.28 (1H, br s, NH), 10.06 (1H, s, CHO). MS m/z: 213 (M^+).

7-(Trifluoromethyl)-1-phenylindole (19) from 7-(Trifluoromethyl)indole (17) A mixture of 7-(trifluoromethyl)indole (**17**) (181 mg), Cu_2Br_2 (42 mg), and anhydrous K_2CO_3 (243 mg) in a mixture of bromobenzene (3 ml) and pyridine (1.5 ml) was heated at 150—160 °C with stirring under an Ar atmosphere for 8 h. The reaction mixture was then poured into H_2O, and extracted with Et_2O. The organic layer was washed with diluted HCl and H_2O, and dried over anhydrous K_2CO_3. The residue obtained by evaporation of the solvent was chromatographed on silica gel with hexane followed by benzene as eluents to give two compounds. The product from the first eluate (8 mg, 3.1%) was recrystallized from hexane to give colorless prisms, mp 98—98.5 °C. *Anal.* Calcd for $C_{15}H_{10}F_3N$: C, 68.96; H, 3.86; N, 5.36. Found: C, 69.23; H, 3.83; N, 5.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: no characteristic band. MS m/z: 261 (M^+).

The product from the second eluate (101 mg, 56%) was the starting 7-(trifluoromethyl)indole (**17**).

7-(Trifluoromethyl)-1-phenylindole-2-carboxylic Acid (20) A solution of KOH (95 mg) in EtOH (2 ml) was added to a solution of ethyl 7-(trifluoromethyl)-1-phenylindole-2-carboxylate (**12**) (113 mg) in EtOH (2 ml). The resulting solution was refluxed for 30 min and the solvent was removed *in vacuo*. The residue was dissolved in H_2O, and this solution was acidified with diluted HCl, and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give a crystalline mass (100 mg, 97%). This was recrystallized from benzene to give colorless columns, mp 222—224 °C. *Anal.* Calcd for $C_{16}H_{10}F_3NO_2$: C, 62.95; H, 3.30; N, 4.59. Found: C,

62.65; H, 3.56; N, 4.79. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 7.20—7.76 (8H, m, arom. H), 8.07 (1H, d, J=8.0 Hz, C_6-H). MS m/z: 305 (M^+).

7-(Trifluoromethyl)-1-phenylindole (19) from the Carboxylic Acid (20) A mixture of the carboxylic acid (**20**) (60 mg) and Cu_2Br_2 (11 mg) in quinoline (1.3 ml) was heated at 200—210 °C with stirring under an Ar atmosphere for 45 min. The reaction mixture was poured into H_2O, and extracted with Et_2O. The organic layer was washed with 2 N HCl and H_2O, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo* to give an oil (72 mg). The oil was chromatographed on silica gel with benzene as an eluent to give a solid (49 mg, 95%). Recrystallization from hexane gave colorless prisms, mp 98—99 °C. This compound was identical with a sample prepared from 7-(trifluoromethyl)indole (**17**).

Goldberg Reaction of Ethyl Indole-2-carboxylate (15) with *m*-Bromo-α,α,α-trifluorotoluene (23) A mixture of ethyl indole-2-carboxylate (**15**) (200 mg), Cu_2Br_2 (20 mg), anhydrous K_2CO_3 (155 mg), *m*-bromo-α,α,α-trifluorotoluene (**23**) (1.5 ml), and pyridine (0.8 ml) was heated at 150 °C with stirring under an Ar atmosphere for 9 h. The reaction mixture was worked-up according to the general method for the Goldberg reaction to give three compounds.

The first compound (12 mg, 3.4%) was recrystallized from hexane to give colorless fine plates, mp 80—82 °C and was identical with a sample of ethyl 1-[4-(trifluoromethyl)phenyl]indole-2-carboxylate (**24**) prepared by the Goldberg reaction of ethyl indole-2-carboxylate (**15**) with *p*-bromo-α,α,α-trifluorotoluene (**25**).

The second compound (239 mg, 68%) was recrystallized from pentane to give colorless columns, mp 68—69 °C, and was identical with a sample of ethyl 1-[3-(trifluoromethyl)phenyl]indole-2-carboxylate (**22**) prepared by the Goldberg reaction of ethyl indole-2-carboxylate (**15**) with *o*-bromo-α,α,α-trifluorotoluene (**21**).

The third compound (32 mg, 16%) was identical with the starting ethyl indole-2-carboxylate (**15**).

Goldberg Reaction of Ethyl Indole-2-carboxylate (15) with *p*-Bromo-α,α,α-trifluorotoluene (25) A mixture of ethyl indole-2-carboxylate (**15**) (200 mg), Cu_2Br_2 (20 mg), anhydrous K_2CO_3 (155 mg), *p*-bromo-α,α,α-trifluorotoluene (**25**) (1.5 ml), and pyridine (0.8 ml) was heated at 150 °C with stirring under an Ar atmosphere for 9 h. The reaction mixture was worked-up according to the general method for the Goldberg reaction. The product (333 mg, 95%) was recrystallized from hexane to give colorless fine plates, mp 81.5—83 °C. *Anal.* Calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.23; N, 4.20. Found: C, 64.79; H, 4.17; N, 4.22. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1717 (C=O). ^{1}H-NMR (CCl_4) δ: 1.26 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 4.17 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.88—7.86 (9H, m, arom. H). MS m/z: 333 (M^+).

Goldberg Reaction of Acetanilide (27) a) With *o*-Bromo-α,α,α-trifluorotoluene (**21**): A mixture of acetanilide (**27**) (900 mg), Cu_2Br_2 (150 mg), anhydrous K_2CO_3 (1.845 g, 2 molar eq) and *o*-bromo-α,α,α-trifluorotoluene (**21**) (6.0 g, 6 molar eq) in pyridine (6 ml) was heated at 150—160 °C (bath temperature) for 55 h under an Ar atmosphere. The reaction mixture was worked-up according to the general method for the Goldberg reaction to give three compounds.

The first compound (8 mg, 0.40%) was oily and was identical with a sample of α,α,α-trifluoro-*N*-phenyl-*m*-acetotoluidide (**29b**) described in b).

The second compound (646 mg, 35%) was recrystallized from hexane to give colorless prisms, mp 69.5—72 °C, and was identical with a sample of α,α,α-trifluoro-*N*-phenyl-*o*-acetotoluidide[5] (**8**) described earlier.

The third product (405 mg, 45%) was the starting acetanilide (**27**).

b) With *m*-Bromo-α,α,α-trifluorotoluene (**23**): A mixture of acetanilide (**27**) (300 mg), Cu_2Br_2 (50 mg), anhydrous K_2CO_3 (615 mg, 2 molar eq), and *m*-bromo-α,α,α-trifluorotoluene (**23**) (1.00 g, 2 molar eq) in pyridine (2 ml) was heated at 150 °C for 20 h under an Ar atmosphere. The reaction mixture was worked-up as above to give two compounds.

The first compound (465 mg, 75%) was oily, bp 105—115 °C (1 mmHg), and was characterized as α,α,α-trifluoro-*N*-phenyl-*m*-acetotoluidide (**29b**) on the basis of the following data. *Anal.* Calcd for $C_{15}H_{12}F_3NO$: C, 64.51; H, 4.33; N, 5.02. Found: C, 64.60; H, 4.37; N, 5.00. IR ν_{max}^{Nujol} cm^{-1}: 1674 (C=O). ^{1}H-NMR (CCl_4) δ: 1.91 (3H, s, $COCH_3$), 7.00—7.60 (9H, m, arom. H). MS m/z: 279 (M^+).

The second compound (42 mg, 14%) was the starting acetanilide (**27**).

Goldberg Reaction of Phenol a) With *o*-Bromo-α,α,α-trifluorotoluene (**21**): A mixture of phenol (**28**) (300 mg), *o*-bromo-α,α,α-trifluorotoluene (**21**) (1.44 g, 2 molar eq), anhydrous K_2CO_3 (880 mg, 2 molar eq), Cu (41 mg), and KI (41 mg) in pyridine (2 ml) was heated at 150—160 °C (bath temperature) for 20 h under an Ar atmosphere. The reaction mixture was worked-up according to the general method for the Goldberg reaction. The product (535 mg, 71%) was oily, bp 75 °C (1 mmHg), and was characterized as phenyl *o*-α,α,α-trifluorotolyl ether (**30a**) on the basis of the following data. *Anal.* Calcd for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 64.97; H, 3.74. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1243 (–O–). ^{1}H-NMR (CCl_4) δ: 6.90—7.60 (9H, m, arom. H). MS m/z: 238 (M^+).

b) With *m*-Bromo-α,α,α-trifluorotoluene (**23**): A mixture of phenol (**28**) (300 mg), *m*-bromo-α,α,α-trifluorotoluene (**23**) (1.44 g, 2 molar eq), anhydrous K_2CO_3 (880 mg, 2 molar eq), Cu (41 mg), and KI (41 mg) in pyridine (2 ml) was heated at 150 °C for 20 h under an Ar atmosphere. The reaction mixture was worked-up as above. The product (503 mg, 67%) was oily, bp 75 °C (1 mmHg) [lit.[12] bp 81 °C (1 mmHg)], and was characterized as phenyl *m*-α,α,α-trifluorotolyl ether (**30b**) on the basis of the following data. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1243 (–O–). ^{1}H-NMR (CCl_4) δ: 6.90—7.60 (9H, m, arom. H). MS m/z: 238 (M^+).

References and Notes

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