The Potential Utility of Homoacylation through the Pummerer Rearrangement-intermediates. A Direct Approach to the 1-Benzenesulfonyl-4-keto-8-methoxy-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole *via* intra-Homoacylation

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A convenient synthesis of tricyclic ketone **7** is described based on an intra-homoacylation *via* a Pummerer intermediate. The indole **3**, was both annelated and functionalized for the next step through its protected indoline **4** using the single reagent dimsyllithium. The produced sulfoxide **5** generated the thionium ion intermediate upon treatment with trifluoroacetic anhydride, which subsequently underwent intramolecular cyclization to ketone **6** in the presence of a Lewis acid.

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The physiological properties of ergot alkaloids have stimulated considerable research activity in the area of these striking compounds. Thereby various routes towards their total synthesis have been envisioned and a number of protocols exist [1]. However, in this research area, activity towards the oxygenated ergots in the benzenoid ring is scarce [2], despite the reported discovery concerning the significant physiological activity of some hydroxy ergoline metabolites [3].

Since the original synthetic work of Kornfeld-Woodward on lysergic acid, the 4-keto-tricyclic ketone **8**, has been used as an invaluable building block in some routes of the total synthesis of ergolines [1,4,5]. Therefore, advantage can be taken of the analogous substituted key intermediate **7** towards the construction of the ergoline ring skeleton carrying substituents in a specific position of the aromatic ring. However, the existing protocol for the preparation of the unsubstituted 4-keto-derivative **8** describes a sequence of reactions which pass through the 5-keto-isomer [5,6]. Consequently, by analogy the 5-keto-isomers of **7**, substituted in the benzene moiety [7] would be logical precursors of the corresponding substituted 4-keto-isomers, and subsequently of the corresponding ergolines which would carry now the substituents in a specific position of the benzenoid ring.

Herewith, we describe the development of an alternative pathway for the preparation of the 4-keto-isomers **7**, obviating the lengthy intermediacy of 5-keto-isomers [8], as outlined in the Scheme.

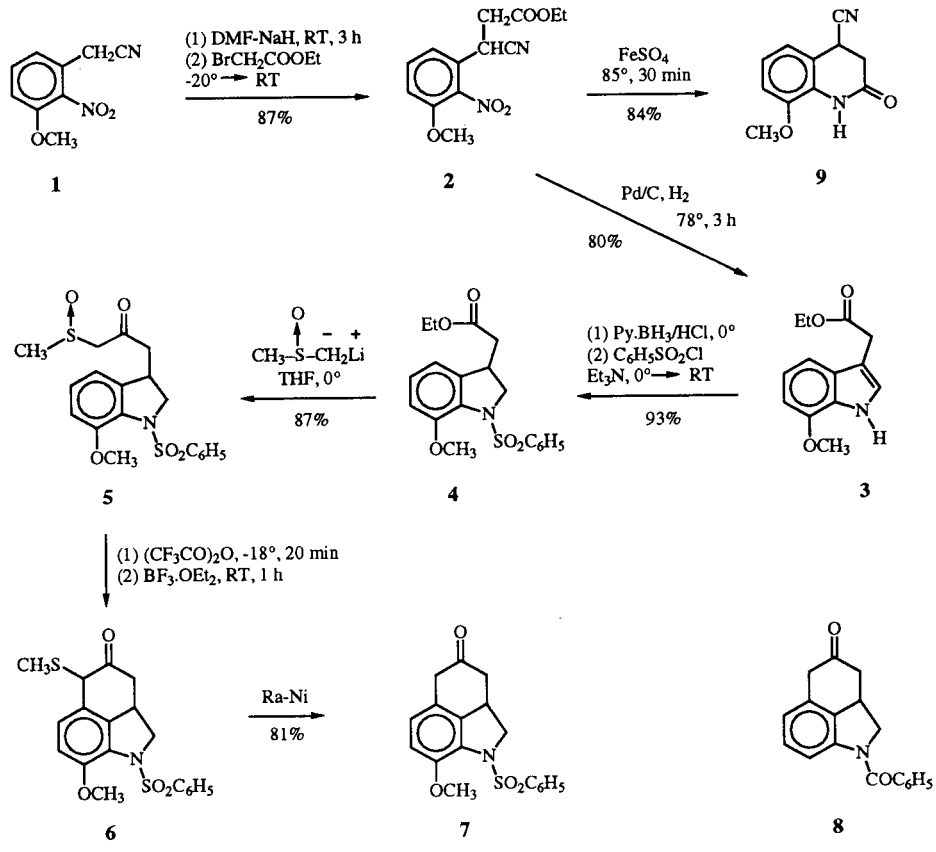
We have commenced with the 3-methoxy-2-nitrophenylacetonitrile **1** (mp 117-119°) which was readily obtained from the 3-methoxy-2-nitrophenylpyruvic acid [9] through decarboxylation of its oxime (mp 170°) with acetic anhydride. This nitrile was also prepared by an alternative pathway, *via* decarboxylation of the morpholine enamine of the above pyruvic acid to produce the corresponding aldehyde [10], followed by dehydration of oxime [11] with acetic anhydride. The transformation of **1** to the required 7-methoxyindole **3** was carried out *via* the ester **2**. Thus, the blue-purple colored carbanion generated by treatment of **1** with sodium hydride in DMF, was subsequently reacted with ethyl bromoacetate to furnish the ester **2** in 87% yield. This procedure gave the product accompanied with a small amount of disubstituted by-product, as indicated by its nmr spectrum, which is separated with difficulty by liquid chromatography.

An alternative way for the preparation of **2** was developed using solid potassium carbonate in DMF as the base, for the generation of the required anion. This procedure delivered a purer product but in a lower yield (83%).

Hydrogenation-hydrogenolysis of the ester under pressure and heating in a Parr-apparatus in the presence of Pd/C catalyst formed the indole moiety, pressumably by nucleophilic attack of the produced aniline functional group on the nitrile. However, using ferrous sulfate as the reducing agent the nucleophilic attack was directed toward the ester group resulting in the formation of the lactam ring instead [12]. Selective reduction of the indole was achieved with a borane-pyridine complex in acidic environment [7], to yield the indoline, which was protected as the benzenesulfonyl derivative.

The cyclization process to the fused six membered ring requires a one-carbon annelation and dimsyllithium-THF complex was chosen to introduce, in addition, the proper functionality necessary to complete the skeletal construction to the tricyclic ketone.

The dimsyllithium-THF complex prepared was added dropwise into the solution of the ester **4** until the pink



color of the triphenylmethane anion persisted. This mode of addition produced the sulfoxide **5** in a very good yield (87%) as a glassy gum consisting of a mixture of two diastereomers. The sulfoxide fulfills the requirements for the generation of the carbonium ion, under Pummerer reaction conditions, necessary to accomplish the intramolecular homoacylation [8]. Treatment with trifluoroacetic anhydride in the presence of a Lewis acid such as boron trifluoride etherate produced ketone **6**, which was desulfurized with Raney nickel without isolation, to yield the target ketone **7**. The final ketone **7**, as well as the precursor ketone **6**, were found to undergo aerial oxidation, especially in dichloromethane solution. The ketone **6** was fully characterized as its oxime.

EXPERIMENTAL

α-(Hydroxyimino)-3-methoxy-2-nitrobenzeneacetic Acid.

To a solution of 23.9 g (0.1 mole) of 2-nitro-3-methoxy-α-(oxo)benzeneacetic acid dissolved in 200 ml of ethanol and diluted with 100 ml of water was added three equivalents of hydroxylamine hydrochloride (20.85 g, 0.3 mole). Into this mixture was added portionwise with stirring, sodium bicarbonate until the solution was weakly basic. The reaction mixture was stirred overnight (20 hours), some of the alcohol was evaporated under vacuum at ambient temperature [13], diluted with water (precipitate formed), made weakly acidic, and extracted with ethyl acetate-toluene.

The combined extracts were dried, filtered through a bed of silica gel, concentrated and the product was crystallized from toluene-ethyl acetate as a white solid, which melts at 170° with evolution of carbon dioxide, yield 23 g (91%); ir (potassium bromide): 3260 (br), 3100 (br), 2900 (br), 1710, 1615, 1590 cm^{-1}; ^{1}H-nmr (80 MHz, DMSO-d_6): δ 4.38 (2H, s, CH_2), 4.5 (3H, s, CH_3O), 7.34 (1H, d, J = 8 Hz, Ar, H-4/H-6), 7.75 (1H, d, J = 8 Hz, Ar, H-4/H-6), 8.05 (1H, t, J = 8 Hz, Ar, H-5), 11.94 (br, OH).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.24; H, 3.94. Found: C, 46.77; H, 3.42.

3-Methoxy-2-nitrobenzeneacetonitrile, **1**.

Method A.

The above prepared oxime, 5.08 g (0.02 mole) was gently warmed with 5 ml of acetic anhydride. Suddenly a violent exothermic reaction occurred. When the evolution of carbon dioxide ceased, the reaction mixture was poured into ice-water. The solid product which formed was collected by filtration, dissolved in ethyl acetate, washed exhaustively with aqueous sodium bicarbonate, dried, and evaporated to dryness. The solid residue was dissolved in toluene and filtered through silica gel. The filtrate was evaporated to dryness to give the product as a white fluffy solid, yield 100%, mp 118-120°; ir (potassium bromide): 3100, 2980, 2950, 2860, 2250, 1610, 1590 cm^{-1}; ^{1}H-nmr (300 MHz, deuteriochloroform): δ 3.75 (2H, s,

CH_2CN), 3.91 (3H, s, OCH_3), 7.05 (1H, d, J = 8.3 Hz, Ar, H-4/H-6), 7.18 (1H, d, J = 7.5 Hz, Ar, H-4/H-6), 7.48 (1H, t, J = 8.2 Hz, Ar, H-5).

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.16. Found: C, 56.70; H, 4.31.

Method B.

3-Methoxy-2-nitrobenzeneacetaldoxime was dehydrated according to the described procedure in the literature [11].

The oxime had ^{1}H-nmr (300 MHz, deuteriochloroform): two isomers in a ratio 1:1.2, δ 3.46 (2H, d, J = 6.0 Hz, one isomer), 3.65 (2H, d, J = 5.2 Hz, the other isomer), 3.864 (3H, s, OCH_3 of one isomer), 3.868 (3H, s, OCH_3 of the other isomer), 6.80-6.95 (6H, aromatic, multiplet of two isomers), 7.47 (1H, vinal, t, J = 6.0 Hz, of one isomer), 7.36 (1H, vinal, t, J = 8.0 Hz, the other isomer).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.76. Found: C, 51.65; H, 4.95.

Ethyl 3-Cyano-3-(3-methoxy-2-nitrobenzene)propionate, **2**.

Method A.

2-Nitro-3-methoxyphenylacetonitrile 5.76 g (30 mmoles) was added portionwise with stirring under an argon atmosphere into a suspension of sodium hydride (0.84 g, 35 mmoles from 1.5 g of 56-57% sodium hydride in oil dispersion washed with petroleum ether) in 100 ml of dry dimethylformamide. The deep blue-purple colored solution was stirred at rt for 3 hours and then cooled below 0° with an ice-salt bath (-15° to -20°). Ethyl bromoacetate 6.7 g (40 mmoles) was added rapidly and the reaction mixture was stirred for 2 hours at 0° and for one hour at room temperature. It was then poured into ice-water (300 ml) and extracted with toluene-ethyl acetate. The combined extracts were washed well with water, dried (sodium sulfate), filtered through silica gel and solvent evaporated.

Chromatography on silica gel (toluene-petroleum ether and toluene) gave 7.6 g (87%) of colorless syrup accompanied by traces of unreacted starting material, according to tlc, and some disubstituted by-product, as shown by the ^{1}H-nmr spectrum and tlc (Rf smaller but very close to the main product).

Method B.

Into a red solution of 5.76 g (30 mmoles) of 2-nitro-3-methoxyphenylacetonitrile in 60 ml of dry DMF under argon, was added with stirring 5.52 g (45 mmoles) of ethyl chloroacetate and then anhydrous potassium carbonate (6.22 g, 45 mmoles) in small portions over a period of several hours. The progress of the reaction was followed by tlc. After completion of the reaction (3 days), it was worked up as above, yield 6.92 g (83%). This reaction gave only traces of the disubstituted by-product; ir (chloroform): 3030, 3000, 2950, 2850, 2250, 1730, 1600 cm^{-1}; ^{1}H-nmr (80 MHz, deuteriochloroform): δ 1.25 (3H, t, J = 7 Hz, CH_2CH_3), 2.94 (2H, d, J = 8 Hz, CH_2CO), 3.87 (3H, s, OCH_3), 4.12 (3H, m, CH_2CH_3 and CHCN), 7.12 (two doublets coalesced into a triplet, 2H, aromatic, H-4 and H-6), 7.50 (1H, t, J = 8 Hz, aromatic H-5).

Ethyl (7-Methoxy-3-indolyl)acetate, **3**.

Ethyl 2-cyano-3-(2-nitro-3-methoxybenzene)propionate 11.12 g (40 mmoles) and 6 g of 5% Pd/C in 200 ml of reagent grade ethyl acetate were hydrogenated for 3 hours at 78° and 45 psi, as described in the literature [12], yield 7.46 g (80%), after chromatography on silica gel (toluene-petroleum ether and then toluene), mp 68-70° from ether-hexane; ^{1}H-nmr (80 MHz, deuteriochloroform): δ 1.25 (3H, t, J = 7 Hz, $OCHCH_3$), 3.69 (2H, s, CH_2CO), 3.87 (3H, s, OCH_3), 4.12 (4H, q, J = 7 Hz, CH_2CH_3), 6.56 (1H, d, J = 9 Hz, H-2), 7.06 (3H, m, aromatic), 8.31 (1H, br, NH); ir (potassium bromide): 3340, 1690 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.00. Found: C, 67.24; H, 6.56; N, 5.86.

Ethyl (1-Benzenesulfonyl-7-methoxy-3-indolinyl)acetate, **4**.

To a solution of ethyl (7-methoxy-3-indolyl)acetate, 9.32 g (40 mmoles) dissolved in 150 ml of ethanol, cooled with an ice-water bath was added 30 ml of borane-pyridine complex and then dropwise with stirring 60 ml ~18% hydrochloric acid (made from 30 ml of ethanol and 30 ml of 36-37% hydrochloric acid) over a period of several hours. The mixture was stirred overnight at ice-water temperature. The progress of the reaction was monitored by the disapperance of the starting material (tlc, van Urk's reagent).

Some of the ethanol was rotary evaporated at ambient temperature, and then the reaction mixture was diluted with ice-water-dichloromethane and basified under stirring and cooling with solid potassium carbonate. It was extracted exhaustively with dichloromethane, dried (sodium sulfate), concentrated to about 200 ml, cooled with an ice-water bath and added with stirring 12.36 g (70 mmoles) of benzenesulfonyl chloride and then 7.5 g (75 mmoles) of triethylamine. It was stirred overnight at room temperature, diluted with dichloromethane, washed twice with cold dilute hydrochloric acid, then with cold dilute sodium bicarbonate, dried (sodium sulfate), the solvent rotary evaporated, and the remaining syrup was chromatographed on silica gel (petroleum ether, toluene, toluene containing ethyl acetate). Evaporation of the solvent gave 13.95 g (93%) of a colorless syrup, which was slowly solidified. An analytical sample was recrystallized from ether-hexane to give white crystals of mp 77-79°; ir (chloroform): 3020, 2940, 2840, 1720, 1600 cm^{-1}; ^{1}H-nmr (80 MHz, deuteriochloroform): δ 1.25 (3H, t, CH_2CH_3), 2.19-2.80 (2H, two dd, J = 5 Hz, J = 9 Hz, CH_2CO), 3.31 (1H, pentaplet, H-3), 3.68 (3H, s, OCH_3), 3.75-4.5 (4H, m, OCH_2, NCH_2), 6.60-7.35 (3H, m, Ar, H-4, H-5, H-6), 7.44 (3H, m, $ArSO_2$, H-3, H-4, H-5), 7.75 (2H, m, $ArSO_2$, H-2, H-6).

Anal. Calcd. for $C_{19}H_{21}NO_5S$: C, 60.80; H, 5.60; N, 3.73. Found: C, 61.56; H, 5.83; N, 3.83.

(1-Benzenesulfonyl-7-methoxy-3-indolinyl)methyl Methylsulfinylmethyl Ketone, **5**.

To a mixture of 20 ml of dry DMSO and 70 ml of dry THF under argon, at 0° was added dropwise with stirring 35 ml of *n*-BuLi (1.36 *M* in benzene). After 30 minutes stirring, the milky suspension of the lithium salt of dimethyl sulfoxide was added dropwise *via* a syringe over a period of more than an hour, into a vigorously stirring solution of **4** in 70 ml of dry THF cooled to 0° with an ice-water bath, under argon containing triphenylmethane as an indicator. When the triphenylmethane sodium red color persisted, the reaction mixture was poured into ice-water-dichloromethane and neutralized to *p*H 6-7 with dilute hydrochloric acid. It was extracted with dichloromethane, dried (sodium sulfate), evaporated and the residual viscous product was chromatographed on silica gel (ethyl acetate, and then ethyl

acetate spiked with methanol) to give a colorless gum 6.11 g (87%) which foams under high vacuum; ^{1}H-nmr (300 MHz, deuteriochloroform): two diastereoisomers, δ 2.64 (3H, s, S(O)CH_3), 2.76 (0.5H, dd, J = 14.9, 9.2 Hz, C(H)*H*CO of one diastereoisomer), 2.82 (0.5H, dd, J = 14.9, 9.2 Hz, C(H)*H*CO of the other diastereoisomer), 2.94 (0.5H, dd, J = 16.2, 4.8 Hz, C(*H*)HCO of the other diastereoisomer), 3.03 (0.5H, dd, J = 16.0, 4.6 Hz, C(*H*)HCO of one diastereoisomer), 3.37 (1H, m), 3.58 (0.5H, B part of ABq, J = 13.6 Hz, CO(H)*H*S(O) of one diastereoisomer), 3.63 (3H, s, OCH_3), 3.65 (0.5H, B part of ABq, J = 13.6 Hz, CO(H)*H*S(O) of the other diastereoisomer), 3.80 (0.5H, A part of ABq, J = 13.6 Hz, CO(*H*)HS(O) of one diastereoisomer), 3.82 (0.5H, A part of ABq, J = 13.6 Hz, CO(*H*)HS(O) of the other diastereoisomer), 3.87 (1H, dd, J = 12.2, 5.4 Hz), 4.31 (1H, dd, J = 12.8, 8.2 Hz), 6.69 (1H, dd, J = 7.3, 4.9 Hz), 6.74 (1H, d, J = 8.1 Hz), 7.01 (1H, t, J = 7.8 Hz), 7.43 (2H, t, J = 7.8 Hz), 7.53 (1H, tt, J = 7.3, 1.5 Hz), 7.81 (2H, d, J = 7.8 Hz).

1-Benzenesulfonyl-4-keto-8-methoxy-1,2,2α,3,4,5-hexahydrobenz[*cd*]indole, **7**.

To a solution of the sulfoxide [15] **5** (1.221 g, 3 mmoles) in 60 ml of dry dichloromethane cooled with an ice-salt bath at -18° under an argon atmosphere, was added dropwise *via* a syringe trifluoroacetic anhydride (0.48 ml, 3.4 mmoles) with stirring. After about 20 minutes stirring boron trifluoride etherate (0.40 ml, 3.3 mmoles) was added dropwise. The reaction solution turned immediately deep red. The ice-salt bath was removed and the reaction mixture was stirred at room temperature for about an hour. Both steps were monitored by tlc. The reaction mixture was quenched with ice-water-dichloromethane, neutralized with sodium bicarbonate solution to about *p*H 6, and extracted with dichloromethane. The combined orange-colored extracts were dried (sodium sulfate), concentrated to about 40 ml under vacuum at ambient temperature and treated with Raney nickel with vigorous stirring. When tlc indicated completion of the desulfurization, the reaction solution was filtered through Celite under vacuum, and the Celite washed with dichloromethane, avoiding prolonged exposure to air [15]. The combined filtrates were concentrated under vacuum at ambient temperature and flash chromatographed under argon on a silica pad (dichloromethane containing a few drops of methanol). Crystallization of the product from dichloromethane-hexane under argon gave off-white crystals, mp 138-140°, 0.83 g (81%); ir (potassium bromide): 1695 cm^{-1}; ms: m/z, 343 (M^+), 202, 174, 159, 146, 131, 115, 84 and 77; ^{1}H-nmr (300 MHz, deuteriochloroform): δ 1.95 (1H, dd, J = 15.9, 12.4 Hz, H-4), 2.71 (1H, dd, J = 15.9, 5.5 Hz, H-4), 3.11 (1H, m, H-3), 3.30 (2H, d, J = 8.5 Hz, H-6), 3.54 (1H, t, J = 11.4 Hz, H-2), 3.73 (1H, s, OCH_3), 4.60 (1H, dd, J = 12.0, 7.5 Hz, H-2), 6.76 (1H, d, J = 8.3 Hz, H-8/H-9), 6.84 (1H, d, J = 8.3 Hz, H-8/H-9), 7.39 (2H, t, J = 7.6 Hz), 7.52 (1H, t, J = 6.8 Hz), 7.73 (2H, d, J = 7.7 Hz); ^{13}C-nmr (300 MHz, deuteriochloroform): δ 208.1, 150.0, 139.2, 136.9, 132.8, 128.6 and 127.3 (AA'BB'), 125.9, 122.7, 113.7, 60.7 (NCH_2), 56.1 (OCH_3), 43.9, 40.9, 35.9.

Anal. Calcd. for $C_{18}H_{17}NO_4S$: C, 62.97; H, 4.96; N, 4.08. Found: C, 62.68; H, 4.90; N, 3.90.

1-Benzenesulfonyl-4-keto-5-methylthio-8-methoxy-1,2,2α,3,4,5-hexahydrobenz[*cd*]indole Oxime.

An aliquot of dichloromethane solution of ketone **6** was treated with hydroxylamine hydrochloride and sodium acetate to produce the corresponding oxime, mp 198-200°, from toluene-ethyl acetate; ms: m/z, 404 (M^+), 388, 357, 264, 245, 215, 201, 185, 158, 142, 109, 94, 77 and 51; ^{1}H-nmr (300 MHz, deuteriochloroform): δ 1.98 (3H, s, SCH_3), 2.03 (1H, dd, J = 18.6, 12.0 Hz, H-4), 3.09 (2H, d, J = 13.2 Hz, H-4), 3.08 (1H, m, H-3), 3.53 (1H, t, J = 11.9 Hz, H-2), 3.82 (H, s, OCH_3), 4.33 (1H, s, H-6), 4.60 (1H, dd, J = 12.2, 7.3 Hz, H-2), 6.79 (1H, d, J = 8.3 Hz, H-8/H-9), 6.98 (1H, d, J = 8.3 Hz, H-8/H-9), 7.40 (2H, t, J = 7.6 Hz), 7.54 (1H, t, J = 7.5 Hz), 7.71 (2H, d, J = 7.8 Hz), 7.78 (1H, br s).

Anal. Calcd. for $C_{19}H_{20}N_2O_4S_2$: C, 56.43; H, 4.95; N, 6.93; S, 15.84. Found: C, 56.36; H, 4.97; N, 6.64; S, 15.76.

4-Cyano-8-methoxy-2-oxo-1,2,3,4-tetrahydroquinoline, **9**.

To iron(II) sulfate heptahydrate (3.4 g, 12.2 mmoles) was added 10% aqueous ammonium hydroxide solution (25 ml) and then a warm ethanolic solution of **2** (0.556 g, 2 mmoles). The mixture was immediately heated under reflux in a water bath (~85°) for 30 minutes with vigorous magnetic stirring. It was then filtered with suction through Celite, and the brown solid was washed with dilute ammonium hydroxide (water/ethanol 1:1). The combined filtrate and washings were acidified with dilute hydrochloric acid, diluted further with ice-water, extracted with dichloromethane, dried (sodium sulfate), and the solvent evaporated. The residue was chromatographed on neutral alumina (ethyl acetate-toluene 8:2). The combined colorless fractions containing the pure product were concentrated under vacuum at 40° and diluted with petroleum ether to give **9**, as white crystals, mp 180-181°, 0.34 g (84%); ir (potassium bromide): 3020, 2240, 1680, 1630, 1600 cm^{-1}; ^{1}H-nmr (300 MHz, deuteriochloroform): δ 2.91 (1H, d, J = 7.3 Hz, H-3), 2.93 (1H, d, J = 3.8 Hz, H-3), 3.87 (3H, s, OCH_3), 4.21 (1H, dd, J = 9.9 and 6.5 Hz, CHCN), 6.88 (1H, dd, J = 6.5 and 3.1 Hz, H-6), 7.05 (1H, d, J = 6.4 Hz, H-5/H-7), 7.06 (1H, d, J = 3.3 Hz, H-5/H-7), 7.90 (1H, NH, br s).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.95; N, 13.86. Found: C, 65.04; H, 5.01; N, 13.52.

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[14] Care should be taken that this viscous sulfoxide be dry. In the case moisture has been absorbed, it would require an excess of trifluoroacetic anhydride to complete the reaction and then an even larger excess of boron trifluoride etherate for the following step. The excess of these two reagents would be determined after monitoring the progress of both steps with tlc. The use of excess of stannic chloride at ice-water temperature instead of boron trifluoride etherate worked better most of the time.

[15] During this experiment, prolonged exposure to air of the dichloromethane solutions should be avoided, because the products undergo air oxidation. The solutions turn deep red and then purple. When the final product appears to be pure enough on tlc, flash chromatography could be omitted.