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Process Development of 5-Methoxy-1*H*-indole-2-carboxylic Acid from Ethyl 2-Methylmalonate

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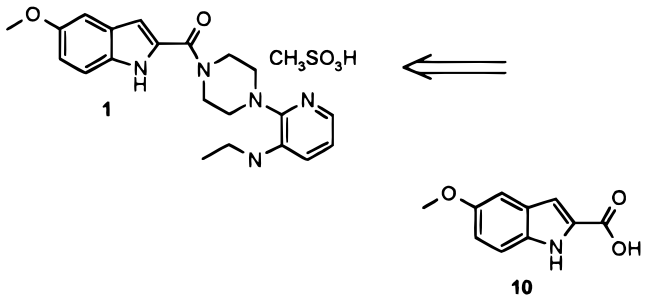
Abstract:

Development is described of a new process for the preparation from malonates of 5-methoxy-1*H*-indole-2-carboxylic acid esters, useful intermediates in the synthesis of pharmaceutical compounds. The process uses readily available starting materials, produces little waste, can be operated safely on at least 1 molar scale, and gives high yields. The main areas of optimization included the azo coupling of a diazonium salt with malonate derivatives, the Japp−Klingemann rearrangement, and the Fischer indole synthesis.

Introduction

5-Methoxy-1*H*-indole-2-carboxylic acid (**10**) has been shown to be a useful intermediate for the preparation of pharmaceutical products.[1] Moreover, **10** has been employed for the preparation of antiviral agents such as U-87201E[2] (**1,** atevirdine mesylate; (Scheme 1), a non-nucleoside, reverse transcriptase inhibitor of HIV. The increased chemical and medicinal applications of **10** and its derivatives have led to renewed interest in the synthesis and chemistry of this versatile heterocycle. As part of our program of development of synthetic methods for the construction of heterocycles, we report here a safe, economical, and reliable synthesis of 5-methoxy-1*H*-indole-2-carboxylic acid (**10**) from readily available starting materials.[3]

Scheme 1. **Atevirdine mesylate (U-87201E, 1) and its precursor (10)**



Strategy Leading to the Indole Ring. The choice of synthetic pathway is very dependent on the complexity of the indole target and on the availability of the starting material. For the preparation of 5-methoxy-1*H*-indole-2-carboxylic acid (**10**), the Fischer synthesis,[4] which is certainly the most widely used method, appears to be the most adapted for our purpose. Two classical pathways can be envisioned: reaction of a diazonium salt with a β-ketoester and cyclization of the resulting hydrazonopyruvate [Pathway (a)[5−9]] and condensation of a hydrazine with a pyruvate and cyclization of the resulting hydrazonopyruvate [Pathway (b)[10−12]] (Scheme 2). For economical reasons (availability and costs of the hydrazine) it was decided to follow the diazonium Pathway (a).

The reaction of a diazonium salt with a β-ketoester is well documented in the literature. Specifically, the 5-methoxy-1*H*-indole-2-carboxylic acid (**10**) has been prepared from the ethyl ester of 2-methylacetoacetic acid (**13**) and the diazonium salt **3** of *p*-anisidine (**2**; Scheme 3, process A). In the most detailed procedure, published by T. Kralt,[6] the 5-methoxy-1*H*-indole-2-carboxylic acid (**10**) was obtained in a 58% overall yield from *p*-anisidine. We were able to improve their procedure, and **10** was obtained in 75−80% overall yield from *p*-anisidine. Nevertheless, this process

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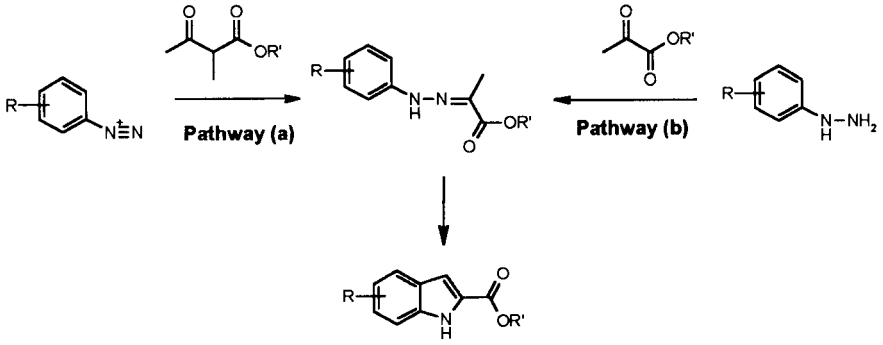
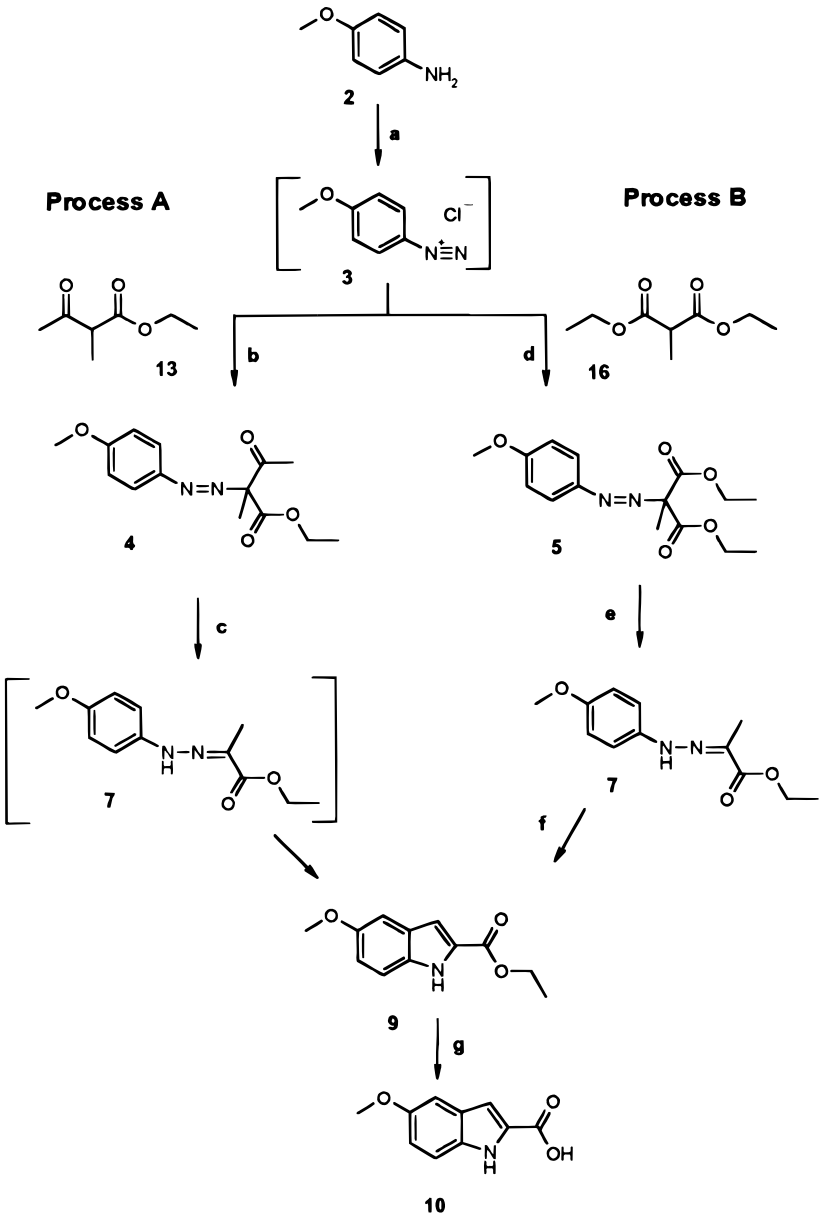
Scheme 2. **Pathway (a) from a diazonium derivative and Pathway (b) from a hydrazine derivative**



Scheme 3. **General reaction scheme: Process A from a β-ketoester and Process B from a malonate**[a]



[a] Process A. (a) $NaNO_2$/HCl, (b) CH_3COONa (10 equiv) in C_2H_5OH/H_2O, (c) HCl in C_2H_5OH, (g) KOH in H_2O; overall yield, 80% (lit.[6] 58%). Process B. (a) $NaNO_2$/HCl, (d) Na_2CO_3 (1 equiv)/Et_3N (1 equiv) in CH_3OH/H_2O, (e) C_2H_5ONa (0.2 equiv) in C_2H_5OH, (f) HCl (gas), (g) KOH in H_2O; overall yield, 64%.

suffers two major drawbacks: ethyl 2-methylacetoacetate (**13**) is not available in large quantities and the ring formation is extremely exothermic, limiting the possibility of safe scale-up. To overcome these drawbacks, we considered the use of the readily available diethyl 2-methylmalonate (**16**) for the coupling reaction with the diazonium salt **3**. Surprisingly, very little is known in the literature of the reaction of diethyl 2-methylmalonate and *p*-anisidine (Scheme 3, Process B).

Scheme 4. **Coupling reaction: Process A from a β-ketoester, Process B from a malonate, and process C from methyl-Meldrum's acid**

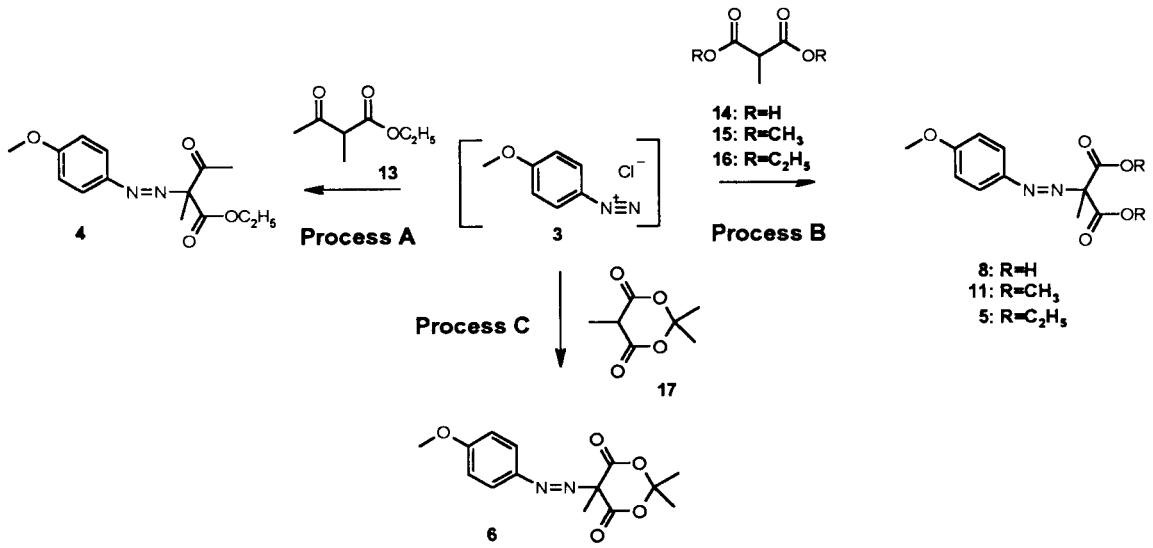


Table 1. **Comparison of reaction conditions for the coupling reaction**

entry no.	reactants	base/solvent systems	reaction time	conversion[a] to
1	ethyl 2-methylacetoacetate (**13**)	CH_3COONa (10 equiv)/H_2O/EtOH	2 h	>90% (**4**)
2	diethyl 2-methylmalonate (**16**)	CH_3COONa (10 equiv)/H_2O/EtOH	22 h	10−15% (**5**)
3	diethyl 2-methylmalonate (**16**)	pyridine/H_2O	24 h	60−65% (**5**)
4	diethyl 2-methylmalonate (**16**)	Na_2CO_3(1.5 equiv)/pyridine/H_2O	24 h	85−90% (**5**)
5	diethyl 2-methylmalonate (**16**)	Na_2CO_3 (2.5 equiv)/pyridine/H_2O/DMF	20 h	90−95% (**5**)
6	diethyl 2-methylmalonate (**16**)	Na_2CO_3 (2 equiv)/H_2O/MeOH	20 h	85−90% (**5**)
7	diethyl 2-methylmalonate (**16**)	Na_2CO_3 (1 equiv)/Et_3N (1 equiv)/H_2O/MeOH	3 h	85−90% (**5**)
8	dimethyl 2-methylmalonate (**15**)	Na_2CO_3 (1 equiv)/Et_3N (1 equiv)/H_2O/MeOH	1 h	>90% (**11**)
9	dimethyl 2-methylmalonate (**15**)	Na_2CO_3 (2 equiv)/H_2O/MeOH	4 h	>90% (**11**)
10	2-methylmalonic acid (**14**)	CH_3COONa (10 equiv)/H_2O/EtOH	4 h	*b*
11	methyl-Meldrum's acid (**17**)	CH_3COONa (10 equiv)/H_2O/EtOH	<2 h	>90% (**6**)

[a] The conversion of the reactant to the azo-intermediate was measured by ^1H NMR. [b] Decomposition of 2-methylmalonic acid (**14**).

To our knowledge, 5-methoxy-1*H*-indole-2-carboxylic acid (**10**) has never been prepared starting from a malonic acid derivative, though some malonic acid derivatives have been used for the preparation of azo- and hydrazono-intermediates via coupling reactions with diazonium salts.[13]

Even though the reaction of the diazonium salt of *p*-anisidine[14,15] with diethyl 2-methylmalonate and the reaction between the diazonium salt of benzidine and toluidine with the ethyl ester of 2-methyl(and 2-ethyl)malonic acid[16] were reported more than 60 years ago, this concept has never been utilized for indole formation. The low yields obtained for these reactions can explain why the use of malonic derivatives has never been attractive in indole chemistry.

Results and Discussion

The two processes (Process A and Process B) were studied in order to identify their scope and limitations for large scale manufacture.

1. Formation of the Diazonium Salt 3. The diazonium salt was prepared under classical conditions by the reaction of *p*-anisidine (**2**) with sodium nitrite in aqueous acid (0 °C/1 h). The reaction mixture was then used directly for the next step (coupling reaction).

2. Coupling Reaction (Scheme 4). The coupling reaction was first studied following the β-ketoester route (Process A). This reaction is almost always carried out under basic conditions. Although potassium hydroxide[5] was sometimes used, sodium acetate[6,9] was preferred, due to the milder conditions, providing a cleaner reaction. Using the reaction conditions described in the literature[6] (Table 1, entry 1), ethyl 2-methylacetoacetate (**13**) was rapidly converted to the corresponding azo-intermediate[17] **4** (>90% conversion/2 h/0 °C). Nevertheless, such a good conversion could only be obtained by using a very large excess of sodium acetate (up to 10 equiv), which would drastically increase the costs of the waste treatment. As mentioned, another major drawback was that 2-methyl derivatives of β-ketoesters are not available in bulk quantities.[18,19]

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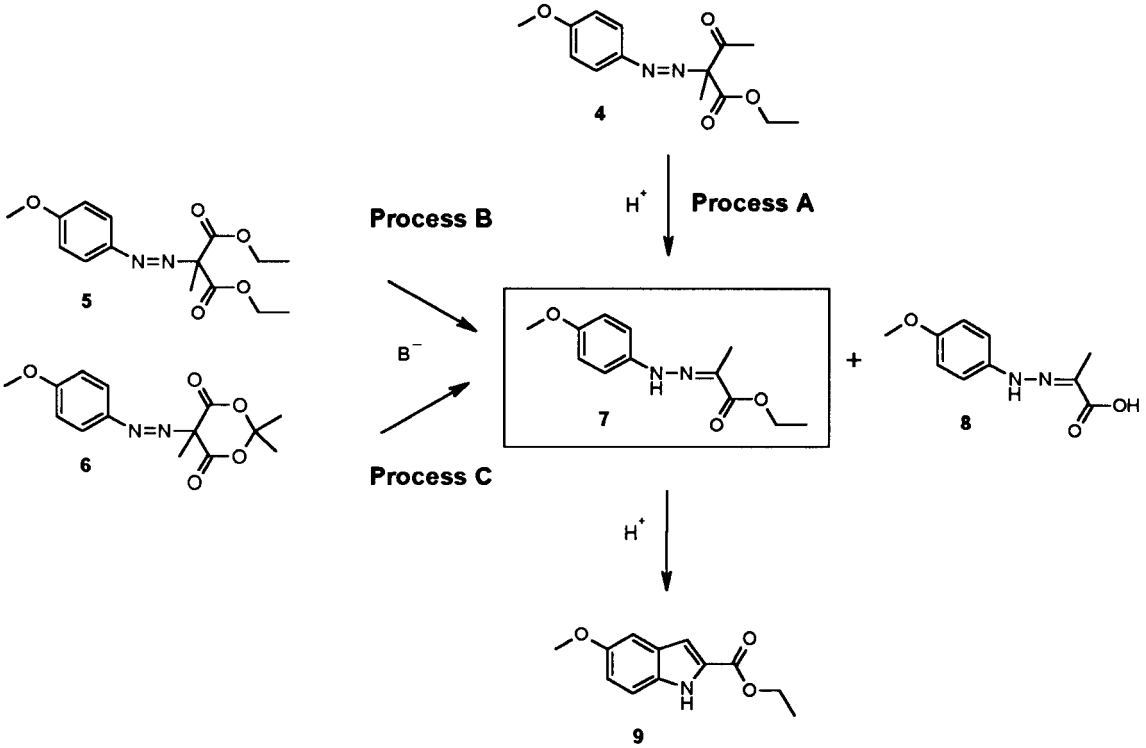
(17) For simplificity, the intermediate formed during the coupling reaction, is called the *azo-intermediate* (using the Heath-Brown and Philpott[7] terminology).

Scheme 5. **Japp−Klingemann rearrangement**



When we tried to couple diethyl 2-methylmalonate (**16**) (Process B) with the diazonium salt under the same conditions (entry 2), very disappointing results were obtained. The conversion to the azo intermediate **5** was only 10−15% complete after 2 h. Due to the relatively weak acidity of the activated methylene group of the malonate **16** compared to that of the β-ketoester **13**, more strongly basic conditions were required. However, the use of strong bases (sodium and potassium hydroxide) led to an increasing formation of side-products. Since the pH and also the polarity of the reaction mixture were very important, a number of combinations of solvent systems (water, methanol, ethanol, pyridine dimethylformamide) and bases (sodium acetate and carbonate, potassium acetate and carbonate, sodium and potassium hydrogen carbonate, sodium and potassium hydroxide, trimethylamine, triethylamine, triisopropylamine) were then studied. A selection of the results are reported in Table 1. The optimum pH was found to be in the region of 9.5 ± 0.5. The best result was obtained when the reaction was carried out in a methanol/water mixture with 1 equiv of sodium carbonate and 1 equiv of triethylamine. Under these conditions 85−90% conversion was achieved within 3 h at 0 °C (entry 7). Under the same conditions, the reaction with the corresponding dimethyl ester **15** is notably faster (entry 8). Even under relatively mild conditions (sodium acetate), the free acid **14** decomposes before undergoing any reactions (entry 10).

As expected, the methyl-Meldrum's acid (**17**) (Process C) reacts very quickly with the diazonium salt to give the corresponding azo-intermediate **6** (entry 11). However, this alternative route was, unfortunately, economically not competitive.

3. Japp−Klingemann Rearrangement (Scheme 5). Under the acidic conditions in Process A, the azo-intermediate **4** rearranges with cleavage of the acetyl group to give the hydrazono-intermediate[20] **7** which immediately undergoes Fischer cyclization to the indole ester **9**. This "one-step" reaction sequence is extremely fast and exothermic. In the original preparation,[6] a solution of HCl gas in ethanol was added in one portion at 0 °C to **4** and the temperature rose to reflux within a few seconds. On the other hand, no reaction occurred if the temperature was maintained under 40 °C but as soon as the temperature reached 50 °C it was almost impossible to keep the reaction under control. A slow adddition of HCl was not helpful because there was an induction period with almost no reaction, and then the temperature suddenly rose to the boiling point. The same problems are encountered with the reverse addition. The best way was to introduce HCl to a refluxing solution of **4** in ethanol, but even under these conditions, the reaction was hardly controllable, even at 100 mmol scale. Scale-up was thus almost impossible.

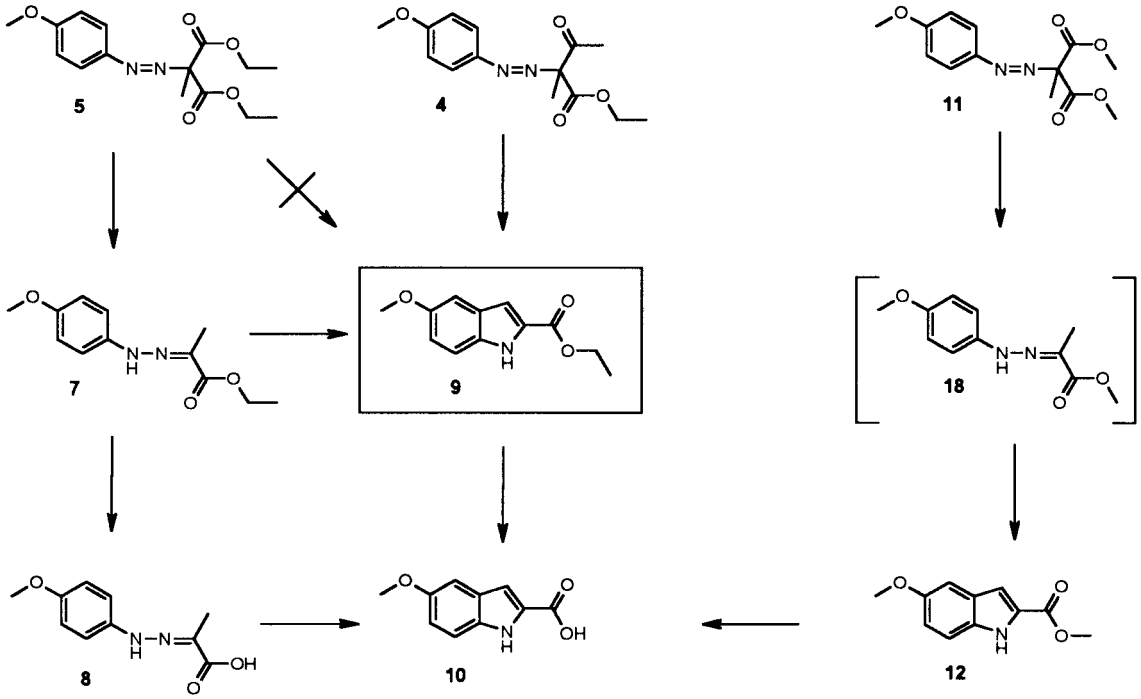
In Process B, the azo-intermediate **5** did not rearrange under acidic conditions to give the hydrazono-intermediate **7**. The rearrangement, with cleavage of an ester group, occurred only under basic conditions. At this stage, the key point was to obtain the hydrazono-intermediate **7** selectively. With mild bases ($NaHCO_3$, Na_2CO_3, K_2CO_3) no reaction occurred, and under relatively strong basic conditions (NaOH/water, NaOH/ethanol, or NaOH/water/ethanol), the

(18) This was the situation when the project was initiated.

(19) Ethyl 2-methylacetoacetate (**13**) is most often prepared by alkylation of ethyl acetoacetate. The use of cheap alkylating agents (such as dimethyl sulfate) often requires a large excess of reagent, leading to a greater amount of undesired bis-alkylated by-product and an expensive separation. On the other hand, selective akylation methods use expensive alkylating agents.

(20) For simplificity, the intermediate formed during the Japp−Klingemann reaction, is called the *hydrazono-intermediate* (using the Heath-Brown and Philpott[7] terminology).

Scheme 6. **Fischer indole synthesis**



hydrazono acid **8** was already present with the expected hydrazono ester **7** before all of the azo ester **5** had reacted, the ratio between the three compounds depending on the excess of the base. Eventually, selective and fast reaction conditions were found by using alcoholates (*t*-BuOK, *t*-BuONa, CH_3OK, CH_3ONa, EtONa). During optimization, the amount of base was progressively reduced from 2 to 0.2 equiv. Thus, the NaOEt (0.2 equiv)/ethanol system gave selectively the desired hydrazono-intermediate **7** in 15 min at room temperature. In this process, the hydrazono-intermediate **7** did not have to be isolated, and the reaction mixture was used directly for the next step (the Fischer cyclization). However, for analytical purposes, a reaction was worked up and the hydrazono-intermediate **7** was isolated in 90% yield from *p*-anisidine.

The azo-intermediate **6** of the methyl-Meldrum's acid (**17**), Process C, behaved similarly compared to the azo-intermediate **5**. Thus, under conditions developed for the Process B, the hydrazono-intermediate **7** was also obtained selectively.

4. Fischer Indole Synthesis (Scheme 6). For the Fischer cyclization, generally an ethanolic solution of HCl gas[21] has been used.[5−7] The use of *p*-toluenesulfonic acid[9] as well as sulfuric acid[10] has also been reported (many other conditions such us Lewis acids in acetic acid have also been used, but for differently substituted indoles). As already mentioned, the azo-intermediate **4** (Process A) can be directly converted, under acidic conditions, to the indole ester **9** without isolation of the hydrazono-intermediate **7**.

During the development of the Process B, considerable effort was expended to transform the azo-intermediate **5** to the indole ester **9** in one step. However, all of the conditions tested (longer reaction time, up to 16 h, or use of stronger acids such as $HClO_4$) were unsuccessful (recovery of the starting material or unidentified material). Therefore, the azo-intermediate **5** was transformed to the hydrazono-intermediate **7** under basic conditions (NaOEt (0.2 equiv)/ethanol) and, without any work-up, the reaction mixture heated to reflux while adding gaseous HCl. The excess of HCl was progressively reduced from 7[6] to 3 equiv. Before we were able to develop a selective method for the transformation of the azo-intermediate **5** to the hydrazono-intermediate **7**, the only clean reaction achievable was the transformation of the azo-intermediate **5** to the hydrazono acid **8**. Unfortunately, this could be converted to the indole acid **10** in only moderate yield (∼50%).

5. Hydrolysis of the Indole Ester (Scheme 6). The literature procedure[6] was modified in order to increase the throughput of this step. A suspension of the indole ester **9** in water was heated to reflux in the presence of potassium hydroxide (∼1.2 equiv). In less than 1 h, a clear solution was obtained. After acidification, the indole acid **10** precipitated and could then be isolated by filtration. The yield of this step was practically quantitative (>98%).

6. "Methyl Ester" Pathway (Scheme 6). The azo intermediate **11** obtained from the dimethyl 2-methyl-malonate (**15**) was also transformed (after the Japp−Klingemann rearrangement to **18**) to the indole ester **12** and then to the indole acid **10** with 65% overall yield from *p*-anisidine, following Process B.

Conclusions

Even with the improvements made (especially the increase in yield from 58 to 80%), the original procedure (Process A) presents too many drawbacks: the excessive amount of salts generated by the process (needed for good conversion in the coupling reaction); the highly exothermic reaction leading to the indole ester **9** (reaction technically not

(21) In presence of water, the reaction is inhibited.

controllable in large scale); and the availablity of the expensive ethyl 2-methylacetoacetate in bulk quantities. With Process B, the indole acid **10** is isolated in 65% overall yield from *p*-anisidine, with an average purity normally >99%. Compared to Process A, there is a significant reduction of the amount of salts; the exothermicity of the cyclization step can be safely controlled, and readily available starting materials can be used. Even with a lower overall yield, this process is economically more competitive than the Process A. Process B was successfully scaled up from 100 mmol (routine laboratory experiments) to 1000 mmol without encountering any difficulties, yield drop, or loss of product purity. The alternative route (Process C) using the methyl-Meldrum's acid for the coupling reaction is chemically interesting but, owing to the cost of Meldrum's acid, too expensive.

Experimental Section

General Procedures. Reagents and solvents were reagent grade and used as received. All reactions were conducted under nitrogen. Melting points were determined on a Büchi 535 apparatus and have not been corrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded on a Varian spectrometer. Chemical shifts are reported as parts per million. Tetramethylsilane was used as internal standard. Coupling constants *J* are given in hertz.

Process B. From 2-Methylmalonic Acid Diethyl Ester[22] (16). *Diazonium Salt Solution **3**.* The reaction is conducted in a 2.5 L reactor with mechanical stirring and external cooling. A solution of sodium nitrite (73.2 g, 1060 mmol) in water (200 mL) is slowly added to a solution of *p*-anisidine (125.7 g, 1000 mmol) in concentrated HCl (220 mL, 2100 mmol) and ice (1000 g). The temperature is kept at 0 °C during the course of the addition (40 min) and then for an additional 30 min.

*Diethyl 2-(4-Methoxyphenylazo)-2-methylmalonate (**5**).* The reaction is conducted in a 10 L reactor with mechanical stirring and external cooling. The diazonium salt solution **3** is added in portions (in 40 min) to a 0 °C stirred suspension of diethyl 2-methylmalonate (**16**) (174.9 g, 1000 mmol), sodium carbonate (106.5 g, 1000 mmol), and triethylamine (100.2 g, 985 mmol) in water (500 mL) and methanol (1000 mL). After 2.5 h at 0 °C, water (2000 mL) is added to the brown suspension (pH 10.1). The resulting solution is concentrated (750 mL distillate) under vacuum (30 °C/50 mmHg). The reaction mixture is then extracted with toluene (3 × 1000 mL), and the solvent evaporated under vacuum (30 °C/50 mmHg), leaving the crude azo diester **5** as a red oil (~325 g). A sample was purified by chromatography (silica gel, 2:1 ethyl acetate/hexane) for analytical purposes. The red oil decomposes upon heating. ^{1}H NMR ($CDCl_3$): δ 7.75 (d fine structure, 2H), 6.95 (d fine structure, 2H), 4.30 (q, 4H), 3.85 (s, 3H), 1.78 (s, 3H), 1.30 (t, 6H).

*Ethyl 2-[(4-Methoxyphenyl)hydrazono]propionate (**7**).* The reaction is conducted in a 2.5 L reactor with mechanical stirring and external cooling and heating. To the crude azo diester (**5**, 325 g) in ethanol (400 mL) a 21% solution of sodium ethanolate (65.0 g, 200 mmol) is added dropwise (in 20 min) at 25−30 °C. After 15 min, the conversion is checked by TLC (2:1 hexane/ethyl acetate). A sample was taken and worked up for analytical purposes. Beige solid, mp 96−98 °C (lit.[7] mp 94 °C; lit.[23] mp 97 °C). ^{1}H NMR ($CDCl_3$): δ 7.6 (br s, 1H), 7.15 (d fine structure, 2H), 6.87 (d fine structure, 2H), 4.32 (q, 2H), 3.80 (s, 3H), 2.10 (s, 3H), 1.38 (t, 3H).

*Ethyl 5-Methoxy-1H-indole-2-carboxylate (**9**).* The reaction mixture of **7** is heated to reflux, and, simultaneously, gaseous HCl (120 g, 3290 mmol) is added over 2h. Reflux is maintained for 15 min after the end of addition of HCl. The reaction mixture is cooled to room temperature, and water (100 mL) is added. The reaction mixture is then cooled to 0 °C for 2.5 h. The suspension is filtered and washed first with precooled (0 °C) ethanol (4 × 100 mL) and then with water (2 × 250 mL). The cake is pressed as dry as possible, leaving the crude indole ester as a yellow powder (**9**, ~146 g). A sample was taken for analytical purposes. Yellow solid, mp 159−161 °C (lit.[7] mp 154−157 °C; lit.[9] mp 158−160 °C). ^{1}H NMR ($CDCl_3$): δ 9.1 (br s, 1H), 7.31 (d, 1H, J = 8.9 Hz), 7.15 (d, 1H, J = 0.9 Hz), 7.08 (d, 1H, J = 2.4 Hz), 7.00 (dd, 1H, J = 6.5, 2.5 Hz), 4.41 (q, 2H, J = 7.2 Hz), 3.84 (s, 3H), 1.41 (t, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6): δ 162.1, 154.8, 132.4, 128.0, 127.9, 117.0, 112.8, 108.2, 102.7, 61.0, 55.7, 14.4.

*5-Methoxy-1H-indole-2-carboxylic Acid (**10**).* The reaction is conducted in a 2.5 L reactor with mechanical stirring and external cooling and heating. To a suspension of the crude indole ester (**9**, ~146 g) in water (1300 mL) is added potassium hydroxide (56 g, 850 mmol). The suspension is heated to reflux for 1 h. The resulting clear solution is then cooled to 0 °C, and concentrated aqueous HCl (150 mL) is added (during the addition of HCl a heavy white precipitate is formed). After 1.5 h at 0 °C, the precipitate is filtered, washed with water (2 × 500 mL), and dried (vacuum, 20 °C, 16 h) to give 123.6 g (64%; overall yield from *p*-anisidine) of white solid (99.2% assay by titration), mp 197.0−198.3 °C (lit.[6] mp 196 °C; lit.[10] mp 192−193 °C/196 °C recrystallized from water). ^{1}H NMR (DMSO-d_6): δ 12.8 (br s, 1H), 11.6 (br s, 1H), 7.35 (d, 1H, J = 8.9 Hz), 7.10 (s, 1H), 7.02 (d, 1H, J = 0.5 Hz), 6.91 (dd, 1H, J = 6.6, 2.3 Hz), 3.71 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 162.7, 153.8, 132.6, 128.6, 127.1, 115.7, 113.3, 106.9, 102.0, 55.2.

Process A. From Ethyl 2-Methylacetoacetate[22] (13). Optimization is based on the literature procedure.[6]

*Diazonium Salt Solution **3**.* The reaction is conducted in a 0.5 L reactor with mechanical stirring and external cooling. A solution of sodium nitrite (7.5 g, 108 mmol) in water (20 mL) is added slowly to a solution of *p*-anisidine (12.6 g, 100 mmol) in 15% HCl (65 mL, 260 mmol) and ice (100 g). The resulting solution is kept at 0 °C during the course of the addition (40 min) and then for an additional 30 min before being used in the next step.

(22) The process can be followed by TLC (ethyl acetate/hexane); the order of increasing polarity is as follows: indole acid > hydrazono ester > indole ester > azo diester.

(23) Rydon, H. N.; Siddappa, S. *J. Chem. Soc*. **1951**, 2462.

Ethyl 2-(4-Methoxyphenylazo)-2-methyl-3-oxobutanoate[24] ***(4)***. The reaction is conducted in a 1 L reactor with mechanical stirring and external cooling. The diazonium salt solution **3** is added in portions (in 10 min) to a 0 °C stirred suspension of ethyl 2-methylacetoacetate (**13**) (17.6 g [91% assay], 111 mmol), sodium acetate (82 g, 1000 mmol) in water (100 mL), and ethanol (100 mL). After 2 h at 0 °C, the reaction mixture is slowly warmed to room temperature and then extracted with toluene (5 × 80 mL). The toluene extracts are dried with anhydrous sodium sulfate, and the solvent is evaporated under vacuum (30 °C/50 mmHg), leaving the crude azo diester (**7**) as a red oil (∼30 g). A sample was taken for analytical purposes. The red oil decomposes upon heating. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 2H), 6.98 (d, 2H), 4.27 (m, 2H), 3.88 (s, 3H), 2.34 (s, 3H), 1.64 (s, 3H), 1.28 (t, 3H).

Ethyl 5-Methoxy-1H-indole-2-carboxylate ***(9)***. The reaction is conducted in a 1 L reactor with mechanical stirring and external cooling. The crude product from the previous step (**7**, ∼30 g) is dissolved in 0 °C ethanol (20 mL). To this solution is added cold ethanol satured with dry hydrogen chloride gas (50 mL, ∼500 mmol of HCl) in one portion, while stirring. Upon the addition, the temperature rises quickly to the boiling point and violent reflux continues for 3−5 min. The reaction mixture is stirred for another hour at reflux. The reaction mixture is then cooled to 0 °C, and water (100 mL) is added. The cold suspension is filtered and washed with precooled ethanol (10 mL), then with water (2 × 20 mL), and again with ethanol (10 mL).

5-Methoxy-1H-indole-2-carboxylic Acid ***(10)***. The reaction is conducted in a 1 L reactor with mechanical stirring and external cooling and heating. To a suspension of the crude indole ester (**9**, ∼20 g) in ethanol (120 mL) is added potassium hydroxide (5.9 g, 90 mmol). The suspension is heated to reflux for 0.5 h and then poured into ice−water (250 mL) and acidified with concentrated HCl (25 mL) to pH 1 (a heavy white precipitate is formed). The precipitate is filtered, washed with water (2 × 25 mL) and dried (vacuum, 20 °C, 16 h) to give 15.9 g (81% overall yield from *p*-anisidine [58% overall yield lit.[6]]) of white solid (97.4% assay by titration).

Process C. From Methyl-Meldrum's Acid[22] **(17).** *Diazonium Salt Solution* ***3***. The reaction is conducted in a 0.5 L reactor with mechanical stirring and external cooling. A solution of sodium nitrite (3.5 g, 50 mmol) in water (10 mL) is added slowly to a solution of *p*-anisidine (6.3 g, 50 mmol) in 15% HCl (22 mL, 130 mmol) and ice (50 g). The resulting solution is kept at 0 °C during the course of the addition (10 min) and then for an additional 30 min before being used in the next step.

5-[(4-Methoxyphenyl)azo]-2,2,5-trimethyl-1,3-dioxane-4,6-dione ***(6)***. The reaction is conducted in a 1 L reactor with mechanical stirring and external cooling. The diazonium salt solution **3** is added in portions (in 10 min) to a 0 °C stirred suspension of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (methyl-Meldrum's acid, **17**) (8.0 g, 50 mmol) and sodium acetate (41 g, 500 mmol) in water (50 mL) and ethanol (50 mL). After 2 h at 0 °C, water (200 mL) is added to the reaction mixture and the yellow suspension is filtered, washed with water (2 × 50 mL), and dried (vacuum, 20 °C, 16 h) to give 12.3 g (84%) of **6**, mp 80−81 °C. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 2H), 6.97 (d, 2H), 3.89 (s, 3H), 1.95 (s, 3H), 1.82 (s, 3H), 1.78 (s, 3H).

Ethyl 2-[(4-Methoxyphenyl)hydrazono]propionate ***(7)***. The reaction is conducted in a 0.5 L reactor with mechanical stirring and external cooling and heating. To a solution of 5-[(4-methoxyphenyl)azo]-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**6**) (1.50 g, 5.1 mmol) in ethanol (10 mL) is added dropwise a 21% solution of sodium ethanolate (1.92 g, 6.0 mmol) in ethanol (during 5 min) at room temperature. The solution is then stirred for 60 min. Water (30 mL) is added, and the reaction mixture extracted with ethyl acetate (3 × 15 mL). The combined organic phases are dried (magnesium sulfate), and the solvent is evaporated to leave 1.15 g (95%) of ethyl 2-[(4-methoxyphenyl)hydrazono]propionate (**7**).

Data of Other Isolated Intermediates. *Dimethyl 2-(4-Methoxyphenylazo)-2-methylmalonate* ***(11)***. Prepared following Process B, from methyl 2-methylacetoacetate (**15**). A sample was taken for analytical purposes. The red oil decomposes upon heating. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 2H), 6.95 (d, 2H), 3.88 (s, 3H), 3.83 (s, 6H), 1.70 (s, 3H).

Methyl 5-Methoxy-1H-indole-2-carboxylate ***(12)***. Prepared following Process B, from dimethyl 2-(4-methoxyphenylazo)-2-methylmalonate (**11**). Grey solid, mp 178−180 °C. ^{1}H NMR ($CDCl_3$): δ 9.2−9.0 (br s, 1H), 7.32 (d, 1H), 7.15 (d, 1H), 7.08 (d, 1H), 7.00 (dd, 1H), 3.95 (s, 3H), 3.86 (s, 3H).

2-[(4-Methoxyphenyl)hydrazono]propionic Acid ***(8)***. Byproduct formed during Process B (Scheme 4). A sample was isolated for analytical purposes. White solid, mp 130−132 °C. ^{1}H NMR ($CDCl_3$): δ 7.8−7.7 (br s, 1H), 7.12 (d, 2H), 6.91 (d, 2H), 3.82 (s, 3H), 2.13 (s, 3H).

(24) An extended study has been carried out by Heath-Brown and Philpott[7] and confirms that the intermediate isolated after the coupling reaction is the azo-intermediate **4** and not the hydrazono-intermediate **7**. The latter is formed in acidic conditions and is usually not isolated but is directly transformed to the indole ester **9**.

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