DOI: 10.1002/ejoc.200500798

Kinetic and Theoretical Studies of a Facile, One-Pot Preparation of a Spirocyclohexylindolinone Derivative

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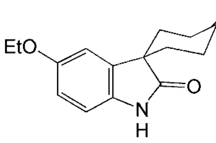
Keywords: Density functional calculations / Kinetics / Michael addition / Reaction mechanisms / Spiro compounds

Spirocyclohexylindolinone is used as a moiety in drug substances. A number of synthetic methods have been suggested to introduce the cyclohexyl ring into the C(3) position of *N*-protected indolinones, which complicates their preparation. A previously developed, consecutive, one-pot, multicomponent method is studied from a mechanistic aspect. We set out to clarify the details of this mechanism and the role of the acryl ester as a reagent and a protecting group in the same flask, by using theoretical and analytical methods, in order to optimise the preparative conditions. A mechanistic energy profile of the reaction is computed at the DFT level of theory.

Introduction

One of the most important actions of the antidiuretic hormone arginine vasopressin (AVP), a cyclic nonapeptide,[1] is the control of water homeostasis through its effect on the renal tubular V_2 receptors.[2] In recent years many effective peptides[3] and non-peptide antagonists have been developed (e.g. mozavaptan,[4] tolvaptan,[4] lixivaptan,[5] conivaptan[6] and SR121463[7]).

One of the most active and selective V_2 antagonists is SR121463.[8] Various synthetic approaches have been followed for its synthesis, their common characteristic being the use of spirocyclohexanylindolinone (**1**).[9–11]



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For the synthesis of spiro(cyclohexyl-1,3′-indoline)-4,2′-dione derivatives one of the possibilities is to start from a pre-existing 4-oxo-protected cyclohexyl compound.[9] A relevant example is the Brunner modification[12,13] of the Fischer indolisation of the cyclohexylcarbohydrazide formed from 4-ethoxyphenylhydrazine and sodium 4-(1,3-dioxolane)cyclohexanecarboxylate. Another approach is the cycloaddition[14] of 3-chloromethylene-2-indolinones and Danishefsky's diene. This multi-step synthesis can be accomplished in a "one-pot reaction" that gives spiroketone **1**. In a third method, *N*-substituted or -protected oxindoles can be used as starting material. Their condensation with protected 1,5-dihalopentan-3-one[10] or with acryl esters[15,16] results in diesters, which undergo Dieckmann condensation, hydrolysis and decarboxylation to furnish the cyclohexane ring.

As far as we are aware, a controlled one-step method for the *C*(3)-alkylation of *N*-unsubstituted oxindoles cannot be found in the literature. The reactions with alkyl halides lead to mixtures of compounds, with low yields of the *C*(3)-alkylated derivatives.[17] Michael addition to acryl esters affords mixtures of 1,3,3-tri- and 3,3-dialkylated compounds.[18–21]

A direct synthetic method has been reported for 3-mono- and 3,3-disubstituted oxindoles without competitive *N*- or *O*-alkylation.[22] Both alkyl halides and acryl esters were applied as alkylating agents, but with only a rather poor result in the case of acrylate.

The present article describes a one-pot synthesis of spiro derivative **1**, starting from 5-ethoxyindolin-2-one and an alkyl acrylate, and uses a theoretical method to clarify some of the mechanistic details of the Michael addition of the acrylate to the active methylene of indolin-2-one followed by Dieckmann condensation of the product.

Results and Discussion

Chemistry

We recently elaborated[11,16] a facile synthesis of **1** starting from **2a** (Scheme 1). We introduced the cyclohexanone moiety by Michael addition of an acryl ester to the active 3-methylene group of indolin-2-one (**2**), followed by Dieck-

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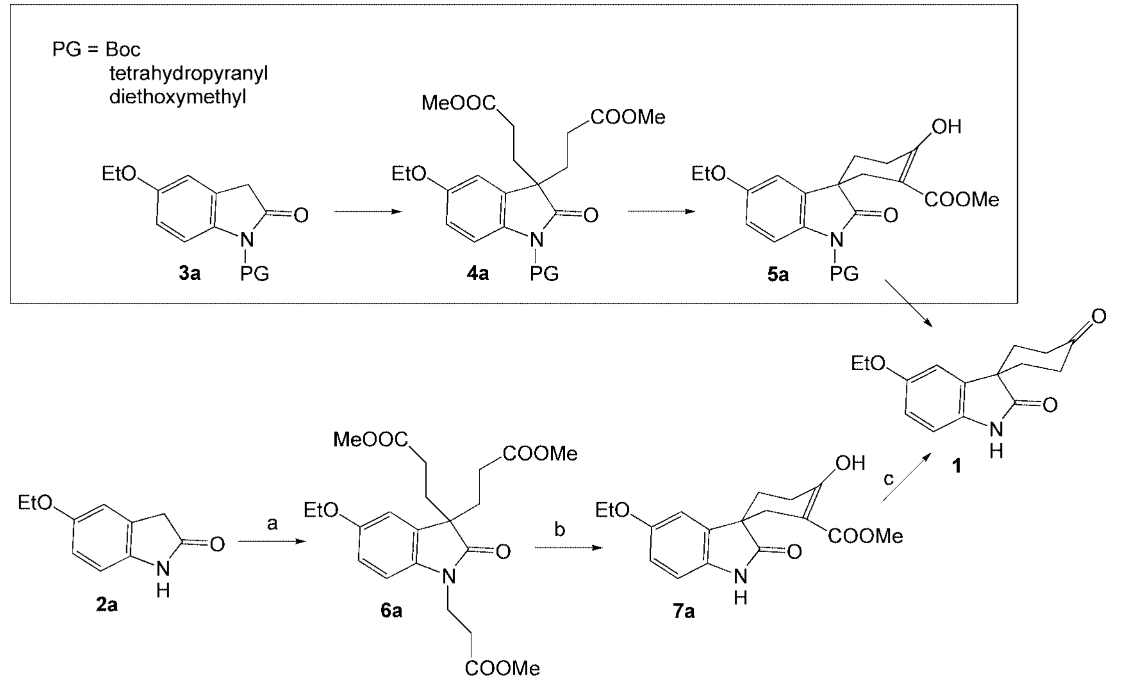


Scheme 1. (a) CH_2=CHCOOMe (3.1 equiv.), DMSO, cat. *t*BuOK, 45 °C; (b) *t*BuOK (2.25 equiv.), 60 °C (0.5 h) then 70–75 °C (3 h); (c) H_2O (PG = protective group).

mann condensation of the diester, hydrolysis and decarboxylation of β-keto ester **7**.

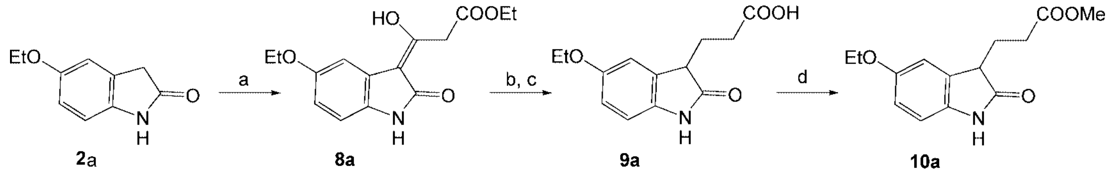
Earlier literature observations suggest that the indole NH must be substituted in order for the desired spiro derivative to be obtained. One aim of our work was to discover an appropriate protective group (some kind of acyl group) that results in good selectivity. Depending on the nature of the protecting group and the reaction conditions various amounts of side-products − *N*,*O*-diacylated compounds and *C*(3)-substituted derivatives formed through O–C(3) acyl migration − may be obtained.[23,24] The use of acid-labile protective groups (see Scheme 1) for indole NH protection does not allow convenient handling of the protection/deprotection steps and the yield is not sufficient. Thus, instead of an acid-labile protecting group we introduced a base-sensitive one that can be easily removed by utilizing the retro-Michael concept.

We decided to use an acryl ester as both the reagent for *C*(3)-alkylation and as a protecting group as it can be eliminated in a base-catalysed reaction in an E1cB mechanism.[25] In contrast with earlier observations,[21] we obtained a single product in a facile and more economical way. The treatment of **2a** with 3.1 equivalents of methyl acrylate in DMSO in the presence of a catalytic amount of *t*BuOK as base at 40–45 °C afforded 1,3,3-trisubstituted compound **6** in excellent yield. Without the isolation of **6a**, a further 2.25 equivalents of *t*BuOK was added to the mixture, while the temperature was increased up to 70–75 °C. The *N*-propionic ester moiety is unstable towards base and the higher temperature results in the elimination of methyl acrylate in a retro-Michael mechanism, the completed Dieckmann condensation furnishing **7a**. After hydrolysis and decarboxylation, the reaction led to the formation of **1**.

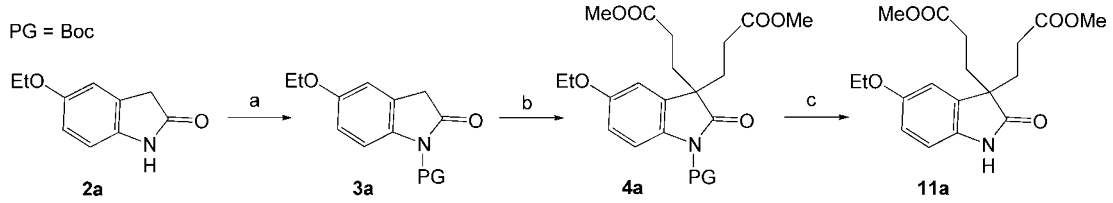
Scope

We set out to understand the nature of the sequence of the reaction steps, with a view to proposing a mechanism of formation of triester **6**. In order to facilitate the following of the reaction by analytical methods, besides triester **6a** we synthesised two other possible intermediates (**10a** and **11a**) in processes analogous to those described in the literature[19] (Schemes 2 and 3, respectively).

For modelling, molecules without an OEt group were used (Scheme 4), numbered **2b**–**23b** (see Figure 4). The reaction can be divided into a pre-equilibrium and the Michael addition. In the pre-equilibrium (Scheme 4), **2** takes part in



Scheme 2. (a) $CH_2(COOEt)_2$, Na, EtOH; (b) H_2/Pd-C, AcOH, H_2SO_4; (c) H_2O; (d) HCl gas, MeOH.



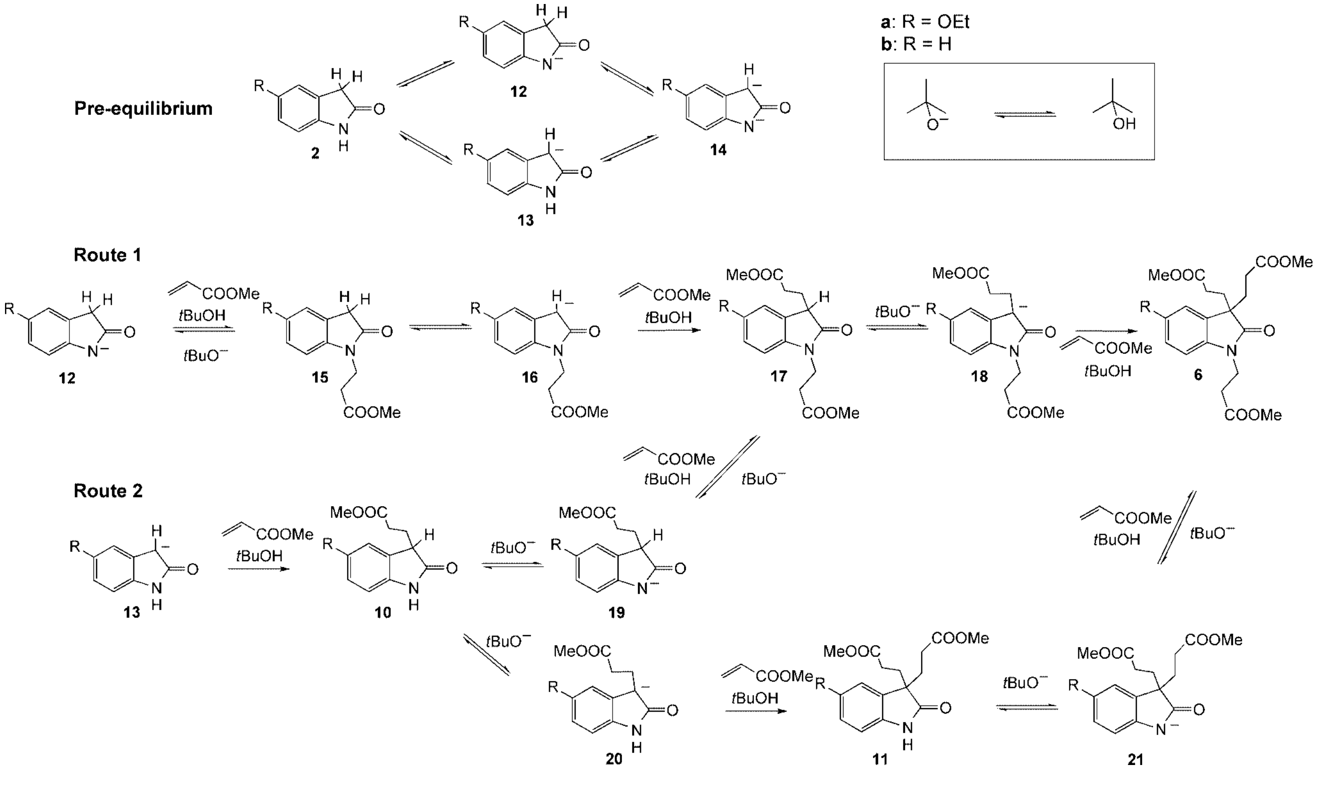
Scheme 3. (a) Boc_2O, THF, Na_2CO_3; (b) $CH_2{=}CHCOOMe$, *t*BuOK, DMF; (c) HCl, DCM.

a deprotonation equilibrium with *t*BuOK, resulting in **12**, **13** and **14**, the deprotonation occurring at $H_2C(3)$, HN(1) or both. If merely a catalytic amount of *t*BuOK is used, only **12** and **13** can form in a considerable amount. On the other hand, the poor yields of the alkylations of dianionic **14** may be due to the lower reactivity of this species,[22] therefore **14** is ignored in our discussion. Both **12** and **13** can react with methyl acrylate, the cascades starting with **12** and **13** being named routes 1 and 2, respectively (Scheme 4). As we will demonstrate below, the *N*-alkylation is reversible, while the *C*-alkylation is irreversible. In the presence of less than three equivalents of methyl acrylate, therefore, a very complex equilibrium mixture is obtained that involves practically all the species in different proportions (**2**, **10**, **11** and **6**). Because these reactions are required for the pre-equilibrium approximation, both the reaction rate and the protonation/deprotonation equilibrium constants must be considered. For this purpose, we computed the equilibrium constants and the activation energies of these reactions.

Results of Experiments

Reaction Followed by HPLC

We monitored the reaction of **2a** with three equivalents of methyl acrylate in the presence of a catalytic amount of *t*BuOK by HPLC. Two types of experiments were carried out. In the first, the three equivalents of methyl acrylate were added to the DMSO mixture in one portion. In this case, the reaction was completed in 10 minutes and practically only **6a** could be detected in the reaction mixture (Figure 1, A), the concentrations of other species being negligible. In the second experiment, the methyl acrylate was added in three equal portions (Figure 1, B). A mixture of four compounds (**2a**, **6a**, **10a** and **11a**) was formed during the reaction, but the total transformation of the mixture to **6a** was achieved only following the addition of the third equivalent of methyl acrylate. TLC yielded similar results. It is interesting that *N*-alkylated mono- and unsubstituted **2a** (**17a** and **15a**) were not detected in significant concentrations in the reaction mixture. These observations suggest a



Scheme 4. Competing reaction routes in the alkylation of **2**.

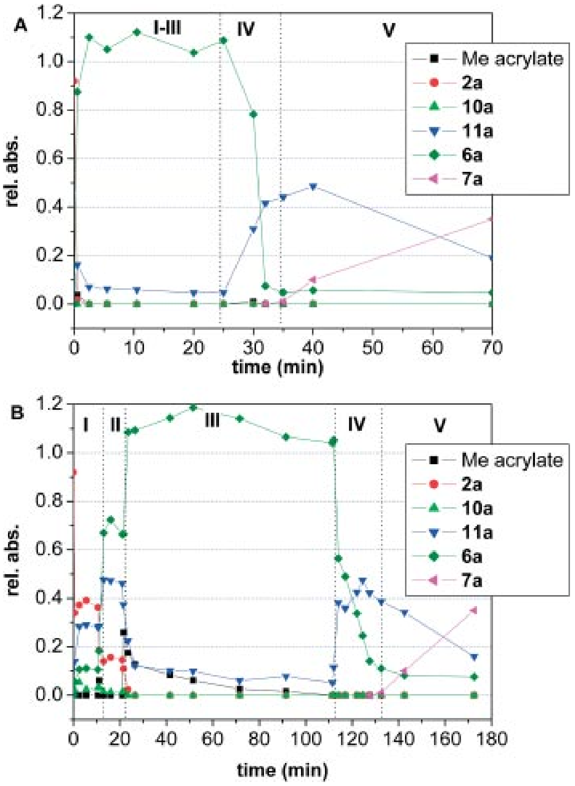


Figure 1. Reaction followed by HPLC. **A**: Methyl acrylate addition in one portion; **B**: methyl acrylate addition in three portions. **I**–**III**: Methyl acrylate addition to **2a** and cat. *t*BuOK in DMSO solution at 40 °C; **IV**: addition of 2 equiv. of *t*BuOK; **V** stirring at 70 °C and 100 mbar.

complicated equilibrium in the solution, with comparable energies of the transition states. Since the presumed mechanism is very complex and branching, the reaction can be conducted under kinetic or thermodynamic control, the acryl ester being added to the reaction mixture in one (first experiment) or more portions (second experiment). For this purpose, we decided to determine the equilibrium and reaction rate constants of this reaction by calculation.

IR Spectroscopy

IR spectroscopy (ReactIR-1000, Mettler–Toledo) was used in two cases: an attempt was made to identify the anionic form of **2** in the pre-equilibrium, and the whole reaction was followed in situ when the methyl acrylate was added in portions (as in the second experimentabove).

To confirm the formation of anion **12a**, the reaction following the addition of one equivalent of base to the solution of **2a** in DMSO was analysed. During the addition, the N–H peak (3181 cm^{-1}) progressively disappeared (Figure 2) and a new peak emerged at 3400 cm^{-1}, possibly due to the formation of *t*BuOH and/or the shift of the N–H peak on formation of anion **13a**, as indicated by the calculations (Table 1). A considerable shift of the C=O stretching vibration to lower value was observed (1706 → 1555 cm^{-1}), pointing to a weaker C=O bond, on delocalisation of the negative charge from the N in **12a** or C(3) in **13a** to the carbonyl oxygen. The calculated values for **13a** and **12a** (1531 and 1551 cm^{-1}, respectively) are sufficiently close to each other to serve as clear evidence of the anion structure. After the addition of one more equivalent of base, the O–H peak at 3400 cm^{-1} flattened out completely (caused by the rapid H exchange with the *t*BuO^{-} without any further peak shifts). The same result was observed when one equivalent of *t*BuOK was added to the DMSO solution containing one equivalent of *t*BuOH. This suggests that anion **12a** predominates in the mixture, in good agreement with the theoretical assumption. Upon increasing the *t*BuOK concentration further (up to 10 equivalents), the C=O peak shifted further (in 1476 cm^{-1}), thus indicating the predominance of **14a**, in reasonable agreement with the calculated data (1430 cm^{-1}).

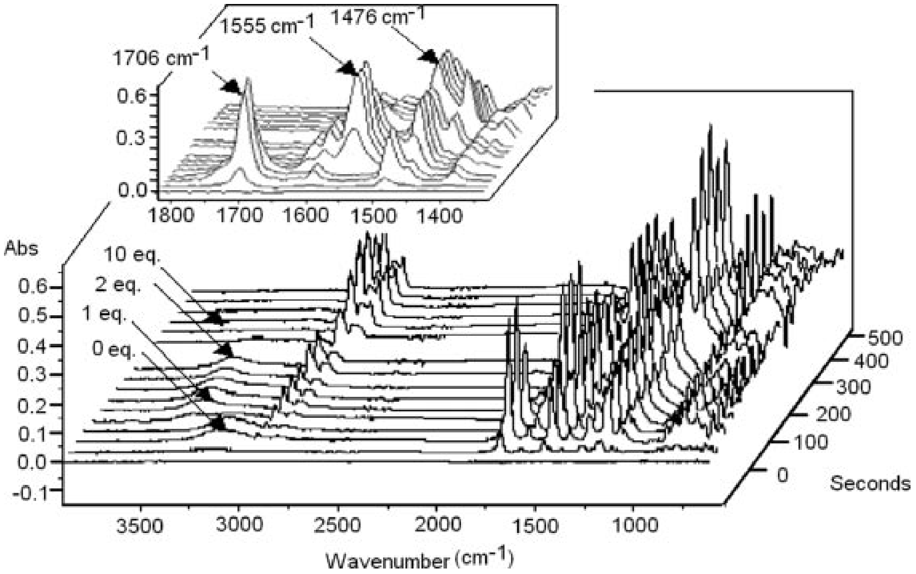


Figure 2. Effect of addition of 1–10 equivalents of base (*t*BuOK) to **2a**, monitored by IR spectroscopy (magnified range 1350–1800 cm^{-1}).

Table 1. Comparison of the measured and calculated IR stretching frequencies [cm^{-1}] of the C=O group.

Compound	Measured	Computed
2a	1706	1711
12a or **13a**	1555	1551 1531
14a	1476	1430

In the second case, the IR analysis was performed under the original reaction conditions (with a catalytic amount of base) with stepwise addition of the three equivalents of methyl acrylate (Figure 3). After the addition of the first equivalent of reactant, the N–H bond peak remained at 3181 cm^{-1}, and the monosubstituted product **10a** could hardly be detected (both by HPLC and TLC): only the disubstituted and trisubstituted products **11a** (with an N–H bond) and **6a** could be identified in considerable amounts in the mixture, in good agreement with the HPLC findings. The situation was very similar after the addition of the second equivalent of methyl acrylate. The N–H bond peak totally disappeared only after the addition of the third equivalent of methyl acrylate.

Discussion

Below, we discuss the suggested mechanism of the Michael addition of **2** to furnish **6**, based on ab initio and DFT theoretical calculations (see Experimental Section). The formation of **7** is also explained. The Michael addition can be divided into two steps (see Scheme 5): the deprotonation of the indolinone derivative (**2b**, **15b**, **17b**, **10b** and **11b**), involving the pre-equilibrium, and the addition of methyl acrylate to the anions (**12b**, **13b**, **16b**, **18b**, **19b**, **20b** and **21b**; Schemes 4 and 5).

In the first step, the deprotonation of the NH hydrogen of **2b**, leading to **12b**, was predicted to be the favourable process ($\Delta E_{\mathbf{12b-13b}}$ = –3.3 kJ mol^{-1} at the B3LYP/6-311++(2d,2p)[DMSO] level of theory), which is in good agreement with the measured value obtained from the pK_a determination[26] (ref.[32] $\Delta E_{\mathbf{12b-13b}}$ = –2.3 kJ mol^{-1}; Figure 4). As shown in Table 3 (see Exp. Sect.), $relK_{eq}$ depends strongly on the alkyl substituents at different positions. Above all the $relK_{eq}$ values of N(1)H deprotonation are lower when C(3) is mono- or disubstituted, while C(3)H deprotonation is easier or much easier when N(1) or C(3) are substituted ($relK_{eq\mathbf{11b}\rightarrow\mathbf{21b}} < relK_{eq\mathbf{10b}\rightarrow\mathbf{19b}} < relK_{eq\mathbf{2b}\rightarrow\mathbf{14b}} < relK_{eq\mathbf{2b}\rightarrow\mathbf{13b}} < relK_{eq\mathbf{2b}\rightarrow\mathbf{12b}} < relK_{eq\mathbf{15b}\rightarrow\mathbf{16b}} < relK_{eq\mathbf{10b}\rightarrow\mathbf{20b}} < relK_{eq\mathbf{17b}\rightarrow\mathbf{18b}}$), thus increasing the reaction rate of the following steps.

In the second step, the nucleophilic attack of **12b** on methyl acrylate (Figure 4) is associated with a slightly lower energy gap ($\Delta E_N^{\ddagger}$ = 56.0 kJ mol^{-1}) than that for **13b** ($\Delta E_C^{\ddagger}$ = 57.6 kJ mol^{-1}). Applying the Curtin–Hammet principle,[27–29] the final difference between the two activation energies ($\Delta E_{\mathbf{13bTS-12bTS}}$) is roughly 4.9 kJ mol^{-1} in favour of the *N*-alkylation (**12b** → **15b**), meaning that the *N*-alkylation is roughly seven times faster than *C*-alkylation. Nevertheless, the *C*-alkylated product (**10b**) has a lower energy than the *N*-alkylated product (**15b**; $\Delta E_{\mathbf{10b-15b}}$ = –15.2 kJ mol^{-1}). Moreover, in the presence of *t*BuOK as base, the anion **23b** is more stable than **15b** ($\Delta E_{\mathbf{23b-15b}}$ = –7.0 kJ mol^{-1}). In other words, the *C*-alkylation is irreversible whereas the *N*-alkylation is reversible process (Scheme 5).

An NICS calculation[30] (Nuclear Independent Chemical Shift), which indicates the aromatic ring current of the examined ring structures,[31] suggests a strongly aromatic system for dianionic **13** and **14** (Table 2), which can be explained by its resonance structures as well (Scheme 6). These computed values are very near to the values calculated for benzene.

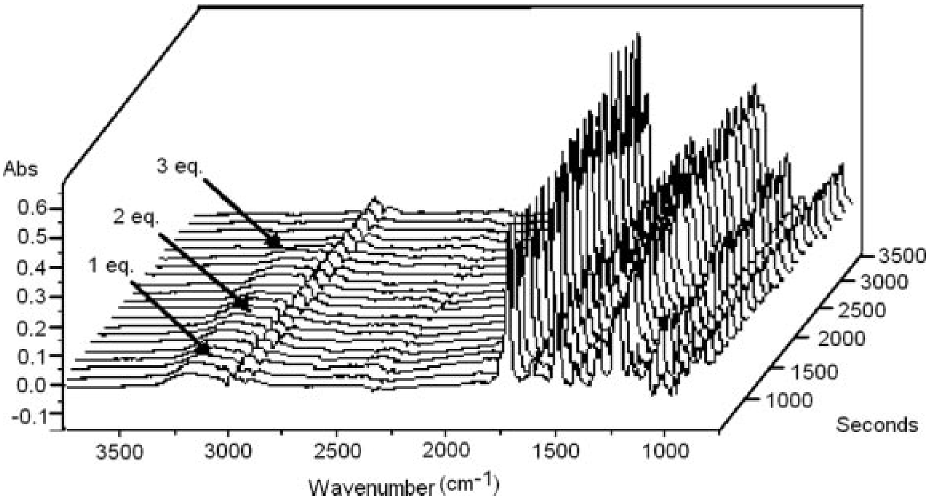
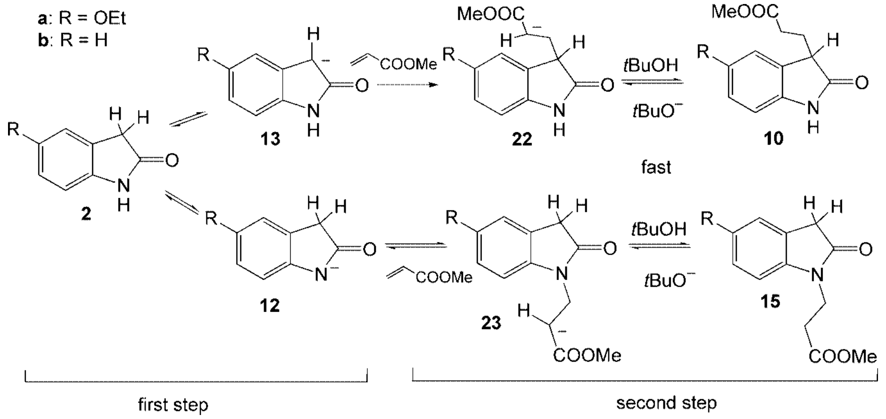


Figure 3. Reaction of **2** with one, two and three equivalents of methyl acrylate in the presence of a catalytic amount of *t*BuOK, monitored by IR spectroscopy.



Scheme 5. Modelling of the formation of *C*(3)- and *N*-monosubstituted indolinone derivatives (**10**, **15**).

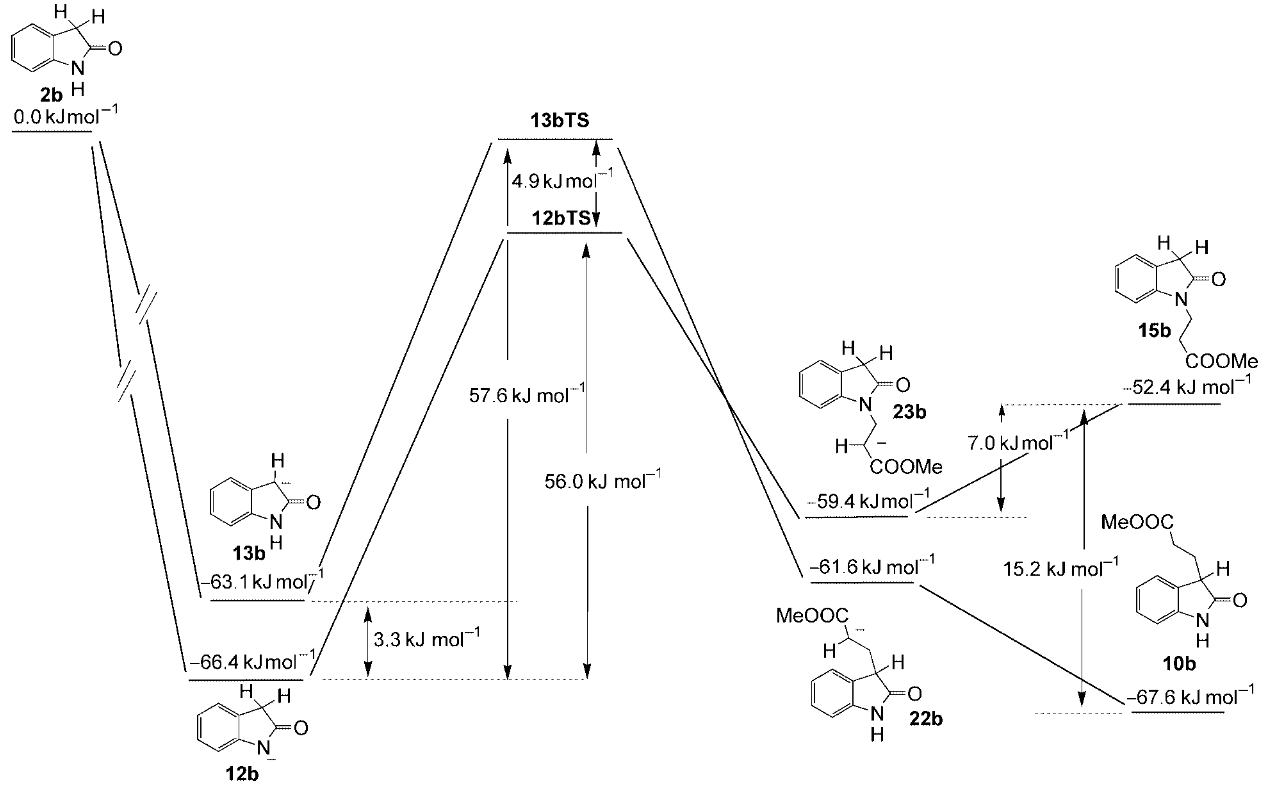


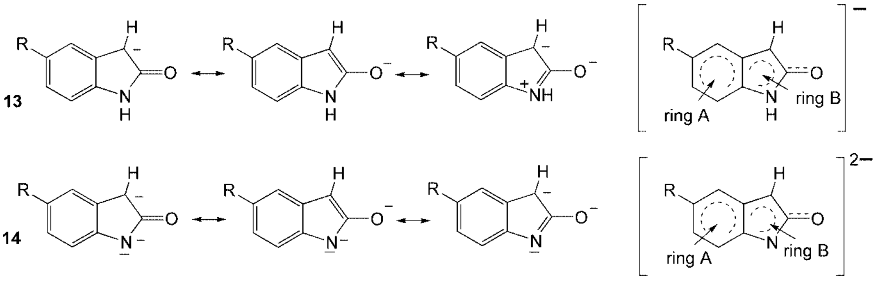
Figure 4. Energy profile of the competing reactions based on ab initio calculations.

Table 2. NICS values for **2b**, **12b**, **13b** and **14b**. Rings A and B refer to the six- and five-membered rings, respectively (Scheme 6).

	Ring A		Ring B	
	NICS(0.0)	NICS(2.0)	NICS(0.0)	NICS(2.0)
2b	–8.0	–4.8	–0.3	–0.5
12b	–6.1	–3.6	+3.5	–0.9
13b	–8.1	–3.3	–10.0	–2.9
14b	–7.0	–3.6	–10.0	–4.1
Benzene	–8.7	–4.2	–	–

The deprotonation of C(3) allows an aromatisation of the indolinone rings, which explain the strong acidity of these hydrogens. In fact, C(3)H is almost as acidic as N(1) H, which was experimentally measured earlier.

As indicated previously, **6** can be synthesised under kinetic and thermodynamic control, both procedures finally yielding **6** with good conversions. In the experiment in which the three equivalents of methyl acrylate were added to the reaction mixture in one portion, the reaction takes place via route 1 and there is practically no chance for branching to route 2 (see Scheme 4). The reaction sequence is as follows: **2** → **12** → **15** → **16** → **17** → **18** → **6**, because *N*-alkylation is roughly seven times faster than *C*-alkylation. However, the following reaction rates are so high that only **6** is detected during the reaction and the reversible *N*-alkylation has no time to reach its equilibrated state; this type is therefore referred to as a "reaction under kinetic control" (Figure 5, A). Since $relK_{\mathrm{eq}\mathbf{17}\rightarrow\mathbf{18}}$ is larger than



Scheme 6. Resonance structures of **13** anion and **14** dianion.

$relK_{\mathrm{eq}\mathbf{2}\rightarrow\mathbf{13}}$ and $relK_{\mathrm{eq}\mathbf{15}\rightarrow\mathbf{16}}$ (Table 3), this cascade accelerates and, accordingly, the concentrations of the intermediates are negligible. During the fast reactions, large amounts of heat are liberated in a very short time, and the necessary intensive cooling may therefore cause many problems on scaling-up.

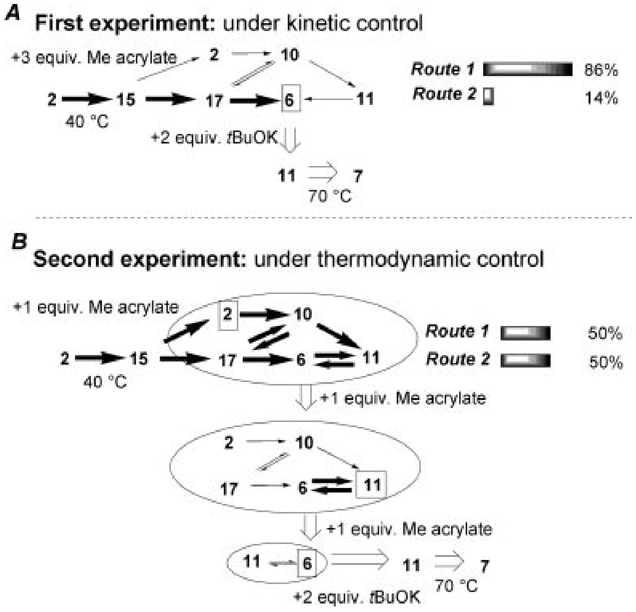


Figure 5. Schematic representation of the pathways of the first (A) and the second (B) experiments (see text for details). Numbers in boxes indicate the main component in the reaction mixture. Empty arrows denote further addition of different reagents or an increase of the reaction temperature. The diagrams on the right-hand side illustrate the approximate proportions of the two routes.

Table 3. Calculated energy differences and relative equilibrium constants obtained with the explicit-implicit solvent model at 313 K.

	ΔE [kJ mol^{-1}]	$relK_{\mathrm{eq}}$
2b → **13b**	–63.1	0.280
2b → **12b**	–66.4	1.000
2b → **14b**	–57.9	0.038
15b → **16b**	–55.2	6.300
17b → **18b**	–82.2	430
10b → **19b**	–55.9	0.018
10b → **20b**	–81.0	270
11b → **21b**	–50.2	0.002
13b → **14b**	+5.2	–
12b → **14b**	+8.5	–

In the second version, when the three equivalents of methyl acrylate are added in three portions, the reaction can branch and take place by both routes (Figure 5, B). After the addition of each portion of methyl acrylate, the reaction reaches its thermodynamically equilibrated state and, except for the final addition, practically all the *C*-alkylated species (**2**, **10**, **11** and **6**) are to be found in different concentrations in the reaction mixture. Compound **11** only disappears after the addition of the third equivalent of methyl acrylate and only **6** then remains in this reaction mixture. As slow addition allows the reaction of the *N*-alkylated species to reach equilibrium, this type is referred to as a "reaction under thermodynamic control". These experimental results are in good agreement with the theoretical expectations, and the processes taking place in the reaction mixture can be understood. The first step in this latter type is similar to that in the first experiment: mainly **12** reacts with methyl acrylate (route 1) and the **15** formed immediately undergoes deprotonation and reacts with another molecule of methyl acrylate, leading to **17** and then to **6**, thereby using up the equivalent of methyl acrylate. However, the following steps differ from the first case. In the absence of methyl acrylate, **15**, **17** and **6** are transformed into **2**, **10** and **11**, respectively, and the reaction branches into route 2. This is possible because the *N*-alkylation of indolinone is reversible and the reaction mixture attains a thermodynamically stable state within a few minutes, the predominant species being **2**, **10**, **11** and **6**. After the addition of the second equivalent of methyl acrylate, the thermodynamic equilibrium mixture contains the same species (**2**, **10**, **11** and **6**), but in different concentrations, the amount of **11** decreasing and that of **6** increasing.

Finally, the transformations are completed when the third equivalent of methyl acrylate is added (Figure 5, B). When the methyl acrylate is added in portions or drop by drop, the liberation of heat is slower and can be controlled much more easily, but the conversion of **6** does not change significantly.

The addition of the third equivalent of methyl acrylate was followed by the addition of two equivalents of *t*BuOK to the reaction mixture, causing the *N*-dealkylation of **6** and leading to **11**. Finally, the temperature was increased to 70 °C, where **11** undergoes a Dieckmann condensation to yield **7**.

Conclusions

We have elaborated an efficient, extendible, one-pot synthesis[16] for the production of spiroindolinone **1**, starting from indolinone **2**. The cyclohexanone moiety is built up in a consecutive, one-pot, multicomponent reaction[32,33] from methyl acrylate without any other protecting group. This reaction can be carried out on a very large scale (60 kg), with excellent yield and purity, without any difficulties. The first step in the reaction proved to be *N*-deprotonation (**12**), with subsequent acryl ester addition (route 1). The low activation energy for **12** → **23** → **15** indicates that the process is reversible under the reaction conditions applied. Although the formation of the C(3) anion **13** (route 2) is unfavourable in comparison with **12**, **10** is in a deep energy gap. The rate of the second deprotonation and acryl ester addition is 10^5 times higher for **10** → **20** than for **15** → **16**, therefore this route cannot be negligible. The result of the energy calculations and the kinetic data obtained are in agreement with the results of IR and HPLC measurements. In this way, a good explanation is given why a complex mixture of compounds (**2**, **10**, **11** and **16**) is obtained during the reaction. However, from the aspect of the acryl ester addition, two possibilities exist: a faster addition (kinetic control) and a slower one (thermodynamic control). Under kinetic control, when the three equivalent of acryl ester are added simultaneously the reaction proceeds mainly via the much faster route 1. Under thermodynamic control, with the acryl ester added in portions, both routes 1 and 2 occur, resulting in a complex intermediate distribution during the reaction, as observed by HPLC and IR spectroscopy. Finally, both controls lead to the same state, yielding the same product with similar quality. On the other hand, the temperature must be kept at a constant level (40 °C); in practice, therefore, it is advisable to add the acryl ester over a longer period in order to achieve a safer situation on a large scale because of the strongly exothermic reaction.

Experimental Section

General: All reagents and solvents used were obtained from commercial sources and were not subjected to any further purification. All melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. Elemental analyses were performed with a Carlo Erba Mod 1106 Analyser. IR spectra were obtained on a Bruker IFS-28 spectrometer or ReactIR-1000 (Mettler–Toledo) with a diamond probe in the range 4000–400 cm^{-1}. ^1H NMR spectra were recorded in $[D_6]DMSO$ or $CDCl_3$ with a Bruker DRX-400 spectrometer using TMS as internal standard; chemical shifts (δ) are given in ppm. UV spectra were recorded in 96% EtOH with a Perkin–Elmer Lambda 14 spectrophotometer. The reactions followed by HPLC were carried out with a Hitachi LaChrom instrument (Merck) with a Chromolith C18 column (Merck, 100 $\times$4.6 mm^2) with a solvent gradient. Eluent **A** contained 10 mM NaH_2PO_4 and 5% MeCN; eluent **B** was MeOH. The flow rate was 1 mL min^{-1}. Chromatographic measurements were made at 206 nm.

5′-Ethoxyspiro[cyclohexane-1,3′-indoline]-4,2′-dione (1): Potassium *tert*-butoxide (0.38 g, 3.4 mmol) was added to a magnetically stirred solution of 5-ethoxyindolin-2-one[34] (**2a**; 11.27 g, 63.6 mmol) in DMSO (32 mL). After stirring for 10 min, methyl acrylate (17.21 g, 200 mmol) was added dropwise over 30 min to this suspension, the temperature being kept at 40–45 °C. After stirring at this temperature for another 65 min, more potassium *tert*-butoxide (16.1 g, 143 mmol) was added to the mixture over 30 min, the temperature being kept below 60 °C. The mixture was then stirred for 3 h at 70–75 °C under reduced pressure in order to remove the *t*BuOH formed and to allow the methyl acrylate to complete the reaction. The residue was poured into water (180 mL), and the solution was clarified with charcoal and filtered. The filtrate was heated to 85 °C for 3 h, and then cooled to room temperature. The precipitated product was filtered off, washed thoroughly with water and dried (11.07 g, 67%). M.p. 184–186 °C. IR: (DMSO) $\tilde{\nu}$ = 1702, 1602 cm^{-1}. UV: log ε (206 nm) = 4.41. ^1H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 1.29 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 1.96, 2.13, 2.39, 2.87 (m, 8 H, CH_2-CH_2), 3.96 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.74 [dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(6)-H], 6.77 [d, $^3J_{H,H}$ = 8.4 Hz, 1 H, C(7)-H], 7.10 [d, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(4)-H], 10.31 (br. s, 1 H, N-H) ppm. $C_{15}H_{17}NO_3$ (259.31): calcd. C 69.48, H 6.61, N 5.40; found C 69.85, H 6.92, N 5.33.

Ethyl 5-Ethoxy-β-hydroxy-β-isatylidenepropionate (8a): Na (4.5 g, 187 mmol) was stirred in EtOH (100 mL) then diethyl malonate (30.03 g, 187 mmol) was added to the stirred solution. After stirring for 10 min, **2a** (7.86 g, 50 mmol) in EtOH (250 mL) was added dropwise. The mixture was refluxed for 12 h, and the EtOH was then removed by distillation. The residue was dissolved in water (200 mL) and extracted with diethyl ether (3 $\times$ 100 mL). The layers were separated and the aqueous layer was acidified with 37% HCl. The yellow product that precipitated out was filtered off, washed with water and dried, to give **8a** (10.04 g, 69%). M.p. 148–152 °C. ^1H NMR (400 MHz, $[D_6]$DMSO, 80 °C): δ = 1.23 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, COO-CH_2-CH_3), 1.33 8t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 4.02 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 4.04 (br. s, 2 H, CH_2), 4.16 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, COO-CH_2-CH_3), 5.35 (br., 1 H, O-H), 6.71 [dd, $^3J_{H,H}$ = 8.3, $^4J_{H,H}$ = 2.3 Hz, 1 H, C(6)-H], 6.83 [d, $^3J_{H,H}$ = 8.3 Hz, 1 H, C(7)-H], 7.18 [br., 1 H, C(4)-H], 10.33 (br. s, 1 H, N-H) ppm. $C_{15}H_{17}NO_5$ (291.35): calcd. C 61.85, H 5.88, N 4.81; found C 61.42, H 5.22, N 4.93.

Methyl 5-Ethoxy-2-oxoindoline-3-propionate (10a): A stirred solution of **8a** (10 g, 34 mmol) in glacial AcOH (300 mL) containing 98% H_2SO_4 (3.5 mL) was hydrogenated at atmospheric pressure in the presence of 5% Pd on charcoal. After the completion of hydrogen uptake, the catalyst was removed by filtration, and the filtrate was evaporated. The oily residue was boiled with water (50 mL) for 1 h. On cooling, 5-ethoxyindolin-2-one-3-propionic acid (**9a**) was obtained as an amorphous solid (5.26 g, 62%), and was used in the next step without purification. A stirred solution of **9a** (5.26 g, 21 mmol) in MeOH (250 mL) was saturated with HCl gas. The stirring was continued for 4 h at room temperature, and the mixture was then clarified with charcoal and filtered. After evaporation of the filtrate, the residue was solidified under *n*-hexane. Recrystallisation from toluene gave **10a** as a beige powder (3.29 g, 60%). M.p. 112–113 °C. IR: (DMSO) $\tilde{\nu}$ = 1733, 1706, 1602 cm^{-1}. UV: log ε (206 nm) = 4.35. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 2.19–2.55 (m, 8 H, CH_2-CH_2-$COOCH_3$), 3.52 [t, $^3J_{H,H}$ = 5.6 Hz, 1 H, C(3)-H] 3.64 (s, 3 H, CO-OCH_3), 3.99 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.74 [dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(6)-H], 6.81 [d, $^3J_{H,H}$ = 8.4 Hz, 1 H, C(7)-H], 6.84 [d, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(4)-H], 8.98 (br. s, 1 H, N-H) ppm. $C_{14}H_{17}NO_4$ (263.30): calcd. C 63.87, H 6.51, N 5.32; found C 64.12, H 6.37, N 5.01.

***N*-(*tert*-Butoxycarbonyl)-5-ethoxyindolin-2-one (3a):** Di-*tert*-butyl dicarbonate (54 g, 24.8 mmol) in THF (250 mL) was added to a stirred solution of **2a** (17.72 g, 10 mmol) and Na_2CO_3 (75 g, 700 mmol) in THF (750 mL). After stirring for 48 h, the inorganic residue was removed by filtration and the filtrate was evaporated. The residue was treated with *n*-hexane (100 mL). After partial dissolution, the insoluble side-product was filtered off. The filtrate was stirred for a few hours, during which time the product precipitated as a white powder (10.71 g, 38.6%). M.p. 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 1.64 [s, 9 H, $C(CH_3)_3$], 3.62 (s, 2 H, CH_2), 4.02 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.81 [m, 2 H, C(4)-H, C(6)-H], 7.69 [m, 1 H, C(7)-H] ppm. $C_{15}H_{19}NO_4$ (277.32): calcd. C 64.97, H 6.91, N 5.05; found C 64.32, H 6.54, 5.28.

Dimethyl *N*-(*tert*-Butoxycarbonyl)-5-ethoxy-2-oxoindoline-3,3-dipropionate (4a): Potassium *tert*-butoxide (0.15 g, 1.3 mmol) was added to a magnetically stirred suspension of **3a** (10.71 g, 39 mmol) in DMF (10 mL). Methyl acrylate (6.65 g, 78 mmol) was added dropwise over 20 min, while the temperature rose to 57 °C in the exothermic reaction. The solid dissolved to give a brown solution. When the temperature of the reaction mixture had decreased to 30 °C, 96% AcOH (0.07 mL) was added. After stirring for 10 min, the reaction was quenched with ice (30 g). A yellow oil precipitated out, and slowly solidified. The yellow product was filtered off and washed thoroughly with water (15.64 g, 68%). M.p. 73–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.42 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 1.64 [s, 9 H, $C(CH_3)_3$], 1.85–2.34 (m, 8 H, CH_2-CH_2-$COOCH_3$), 3.57 (s, 6 H, $COOCH_3$), 4.02 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.71 [d, $^4J_{H,H}$ = 2.6 Hz, 1 H, C(4)-H], 6.82 [dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.6 Hz, 1 H, C(6)-H], 7.75 [d, $^3J_{H,H}$ = 8.8 Hz, 1 H, C(7)-H] ppm. $C_{23}H_{31}NO_8$ (449.51): calcd. C 61.46, H 6.95, N 3.12; found C 61.93, H 6.45, N 2.98.

Dimethyl 5-Ethoxy-2-oxoindoline-3,3-dipropionate (11a): HCl gas was bubbled through a magnetically stirred solution of **4a** (10 g, 22 mmol) in CH_2Cl_2 (50 mL) until the solution turned green. After stirring for 3 h at room temperature, the HCl addition was repeated. After stirring for 16 h the reaction was still not complete, and HCl was therefore bubbled through the solution again. After stirring for 1 h the starting material disappeared totally, as checked by TLC. The solution was clarified with charcoal and filtered, and the solvent was evaporated to obtain the product as a greenish oil that slowly crystallised on standing under hexane (6.78 g, 87%). M.p. 72–74 °C. IR: (DMSO) $\tilde{\nu}$ = 1733, 1716, 1664 cm^{-1}. UV: log ε (206 nm) = 4.38. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 1.87–2.31 (m, 8 H, CH_2-CH_2-$COOCH_3$), 3.56 (s, 6 H, CH_2-CH_2-$COOCH_3$), 3.99 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.74 [br., 1 H, C(4)-H], 6.75 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 2.3 Hz, 1 H, C(6)-H], 6.83 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(7)-H], 8.67 (br. s, 1 H, N–H) ppm. $C_{18}H_{23}NO_6$ (349.39): calcd. C 61.88, H 6.64, N 4.01; found C. 62.11, H 6.34, N 3.87.

Trimethyl 5-Ethoxy-2-oxoindoline-1,3,3-tripropionate (6a): Potassium *tert*-butoxide (0.01 g, 0.09 mmol) was added to a magnetically stirred suspension of **2a** (0.4 g, 3 mmol) in DMSO (1 mL). Methyl acrylate (0.85 g, 9.9 mmol) was next added dropwise over 3 min, while the temperature rose to 40 °C and a reddish-brown solution was formed. After stirring for 10 min, 0.1 mg (1 drop) of AcOH was added to the mixture and the crude product was precipitated with water (10 mL). The pale-pink crystals were filtered off and recrystallised from 96% EtOH (0.84 g, 64%). M.p. 83–84 °C. IR: (DMSO) $\tilde{\nu}$ = 1737, 1702, 1602 cm^{-1}. UV: log ε (206 nm) = 4.44. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.30 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 1.64–2.13 (m, 8 H, C-CH_2-CH_2-$COOCH_3$), 2.64 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, N-CH_2-CH_2-$COOCH_3$), 3.46 (s, 6 H, C-CH_2-CH_2-$COOCH_3$), 3.53 (s, 3 H, N-CH_2-CH_2-$COOCH_3$), 3.90 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, N-CH_2-CH_2-$COOCH_3$), 3.98 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.84 [dd, $^3J_{H,H}$ = 8.6, $^4J_{H,H}$ = 2.5 Hz, 1 H, C(6)-H], 6.97 [d, $^4J_{H,H}$ = 2.5 Hz, 1 H, C(4)-H], 6.99 [d, $^3J_{H,H}$ = 8.6 Hz, 1 H, C(7)-H] ppm. $C_{22}H_{29}NO_8$ (435.48): calcd. C 60.68, H 6.71, N 3.22; found C 60.97, H 6.52, N 3.08.

Spiro Compound 7a (Enol Form): Potassium *tert*-butoxide (0.01 g, 0.09 mmol) was added to a magnetically stirred solution of triester **6a** (1.72 g, 4 mmol) in DMSO (6 mL) at 40 °C. After dissolution, the temperature was raised to 70 °C and the mixture stirred under reduced pressure for another 2.5 h to remove the formed *t*BuOH and methyl acrylate. The residue was then treated with 2 N HCl (40 mL). After stirring for 1 h, the precipitated product was filtered off and washed with water. After recrystallisation from abs. EtOH (3 mL) a white product was obtained (0.36 g, 29%). M.p. 148–150 °C. IR: (DMSO) $\tilde{\nu}$ = 1710, 1666, 1617 cm^{-1}. UV: log ε (206 nm) = 4.43. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.28 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-CH_2-O), 1.73 (m, 1 H, C–CH_a-CH_2-C-OH), 1.88 (m, 1 H, C-CH_b-CH_2-C-OH), 2.30 (d, $^2J_{H,H}$ = 15.8 Hz, 1 H, C-CH_a-C-$COOCH_3$), 2.45 (m, 1 H, C-CH_2-CH_a-C-OH), 2.47 (d, $^2J_{H,H}$ = 15.8 Hz, 1 H, C-CH_b-C-$COOCH_3$), 2.62 (m, 1 H, C-CH_2-CH_b-C-OH), 3.68 (s, 3 H, $COOCH_3$), 3.91 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_3-CH_2-O), 6.69 [d, $^3J_{H,H}$ = 1.9 Hz, 1 H, C(4)-H], 6.75, 6.78 [m, 2 H, C(6)-H, C(7)-H], 10.28 (br. s, 1 H, N-H), 12.18 (br. s, 1 H, O-H) ppm.

Calculation of Pre-Equilibrium Data: As indicated in the relevant section, the constants K_{eq} of the protonation/deprotonation reactions between the indolinone derivative and *t*BuO$^–$ play a significant role in the rate of Michael addition. Accordingly, all of them were calculated from Equation (1) (see Table 3).

$$K_{eq}=\frac{[A^-][tBuOH]}{[AH][tBuO^-]}= \exp\left(\frac{E_{A^-}+E_{tBuOH}-E_{AH^-}-E_{tBuO^-}}{RT}\right)= \exp\left(\frac{\Delta E}{RT}\right) \qquad (1)$$

AH + *t*BuO$^–$ ⇋ A$^–$ + *t*BuOH

where AH = **2**, **6**, **10**, **11**, **15** or **17**, K_{eq} is the pre-equilibrium constant, *R* is the universal constant and *T* is the temperature (313 K). The energies of the different species were calculated at the B3LYP/6311++(2d,2p) level of theory, using the explicit-implicit solvent model.[35] Thus, one molecule of DMSO was considered to be hydrogen-bonded to the N(1)H of **2b** or **13b** and the OH of *t*BuOH, and these molecules or DMSO complexes were embedded in a solvent cavity modelled by the IEF-PCM[DMSO] method.

Calculation of Activation Energy ($\Delta E^{\ddagger}$) of Michael Addition: The Michael addition was modelled at the B3LYP/6311++(2d,2p)[DMSO] level of theory and with the solvent model described in the previous part. The reaction can be divided into two steps. The first is the deprotonation of the indolinone derivative (**2b**, **15b**, **17b**, **10b** or **11b**), involving the pre-equilibrium, while the second step is the addition of methyl acrylate to the anions (**12b**, **13b**, **16b**, **18b**, **19b**, **20b** or **21b**). The latter step was modelled by the reaction of different anionic forms of indolinone (**12b** or **13b**) with methyl acrylate assuming that the alkyl substituents do not influence the activation energies significantly. Finally, the alkylated anions formed (**22b** and **23b**) are protonated by the *t*BuOH formed to regenerate the catalyst. Only the energies of the final products (**10b** and **15b**) were considered, assuming fast protonation-deprotonation steps with *t*BuOK. Figure 4 depicts the results.

Acknowledgments

We thank Dr. David Durham for linguistic improvement of the manuscript.

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Received: October 13, 2005