



Iron salt-catalyzed cascade type one-pot double alkylation of indole with vinyl ketones

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ARTICLE INFO

Article history:

Received 2 March 2010

Received in revised form 24 March 2010

Accepted 24 March 2010

Available online 30 March 2010

ABSTRACT

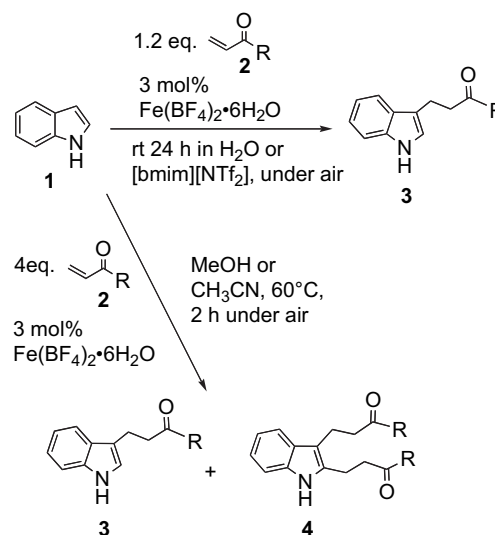
Indole was reacted with vinyl ketones in the presence of 5–8 mol% of iron (II) tetrafluoroborate or iron (III) perchlorate to give 2,3-dialkylated products; initial alkylation took place at 3-position on the indole ring and subsequent alkylation occurred at 2-position. It was found that the first alkylation proceeded very quickly, while the reaction rate of the second alkylation was very slow. Using this, cascade type synthesis of 2,3-dialkylated-indoles has been accomplished using iron (III)salt as catalyst.

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1. Introduction

Iron is well recognized as an economical and environment-friendly free metal source and iron catalysts are now extensively used in organic synthesis.¹ We have been investigating the possibility of iron-catalyzed reaction and succeeded in demonstrating many types of these reactions: the intramolecular cyclization of cyclopropanedithioacetals,² [2+2]-cyclodimerization of *trans*-anethol,³ and [2+3]-type cycloaddition of styrene derivatives with 1,4-benzoquinone; in addition, it was established that the reaction was greatly accelerated in anionic liquids solvent system.⁴ We also discovered that iron salts worked as very mild Lewis acids to catalyze efficient Michael type addition of β -ketoesters with α,β -unsaturated ketones,⁵ asymmetric Michael addition of thiols with α,β -unsaturated compounds,⁶ and Nazarov cyclization of thiophene derivatives⁷ and pyrrole derivatives.⁸ Moreover, we found that Friedel–Crafts type products were produced if indole or pyrrole was subjected to the reaction with vinyl ketones in the presence of iron salt as catalyst such as $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ under air conditions.^{9,10} Indole moiety is frequently involved in many biologically active molecules, therefore development of efficient means for preparing indole derivatives has been awaited.¹¹ Lewis acid or Brønsted acid-mediated Friedel–Crafts type alkylation of indole with unsaturated carbonyl compounds has been well accepted as such a method to prepare indole derivatives¹² and a highly enantioselective alkylation has also been reported using chiral Lewis acids and organocatalysts.¹³ Among studies of electrophilic substitution reactions of indoles, control of regioselectivity has recently attracted much attention: Leitch accomplished highly regioselective N- and C2-electrophilic substitution of 3-substituted indole using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ as Lewis acid catalyst.¹⁴ Sames reported regioselective arylation of *N*-protecting group free indoles by

palladium-catalyzed reaction in the presence of MgO .¹⁵ Azizi and co-workers also reported that 3-alkylated indole was obtained regioselectively when *N*-protected indole was reacted with vinyl ketones in the presence of iron(III) chloride in H_2O .^{12g} We found that regioselectivity of our iron salt-catalyzed alkylation of indole was controlled simply by switching the solvent system:⁹ 3-alkylated product **3** was obtained when the reaction was carried out in H_2O or ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ($[\text{bmim}][\text{NTf}_2]$) in excellent yield, while 2,3-dialkylated indole **4** was produced when indole was reacted with an excess amount of acceptor methyl vinyl ketone in the presence of iron catalyst in methanol or CH_3CN as solvent (Scheme 1).⁹



Scheme 1. Iron salt-catalyzed one-pot double alkylation of indole.

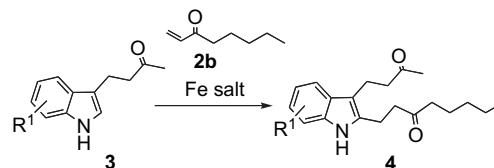
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The products of these reactions contain important structural motifs found in natural products and are essential intermediates in preparing pharmaceuticals and other chemicals. Therefore, we focused on optimization of double-point alkylation of indole using an iron salt catalyst system as an extension of our iron-catalyzed reaction work. Herein, we report the iron salt-catalyzed cascade type double-point alkylation of indole derivatives.

2. Results and discussion

It is well recognized that 3-position on the indole ring is the most reactive point.¹⁶ Our iron salt-catalyzed alkylation of indole derivatives, in fact, took place first at the 3-position of indole, then the second alkylation occurred at the 2-position. Because the second alkylation proceeded very slowly, a significant amount of polymerized by-products was produced when strong Lewis acid was used as catalyst for the second alkylation step.⁹ It was thus assumed that the key point for realization of efficient dialkylation might depend on improving the efficiency of the second step. Therefore, we first attempted to optimize the reaction conditions of alkylation at 2-position using 3-substituted indole derivative **3a** with 1-octen-3-one (**2b**) as a model reactant (Scheme 2).

The catalytic activity was significantly dependent on the anionic part of the iron (III) salts; alkylation products **3a** were obtained using $K_3Fe(CN)_6$ as catalyst, though the yield was less than 10%, and



Scheme 2. Iron salt-catalyzed alkylation of 3-substituted indole derivative.

no desired product was obtained for Fe_2O_3 or $FeO(OH)$. Among tested iron salts, the best results were obtained for $Fe(BF_4)_2 \cdot 6H_2O$, $Fe(ClO_4)_3 \cdot nH_2O$. Strong Lewis acids, $Fe(NO_3)_3$ and $FeCl_3$, afforded the desired product **4b**, but the results were inferior to those of $Fe(BF_4)_2 \cdot 6H_2O$ or $Fe(ClO_4)_3 \cdot nH_2O$ -catalyzed reaction because a significant amount of polymeric by-product was produced during the reactions.

The reaction also strongly depended on the solvent, and no desired product was obtained when the reaction was conducted in CH_2Cl_2 , $CHCl_3$, Et_2O , THF, toluene, or benzene. Alkylation of indole **3a** with ketone **2b** proceeded very slowly and desired **4b** was obtained in 31% yield after 96 h reaction with 34% of the starting compound **3a** when the reaction was carried out in the presence of 10 mol % of $Fe(BF_4)_2 \cdot 6H_2O$ in CH_3CN solvent (entry 1 of Table 1). Use of methanol as solvent afforded a slightly improved reaction rate, but the yield of **4b** produced still remained at an insufficient level (39%) (entry 2). We finally found that the desired product **4b**

Table 1
Synthesis of 2,3-dialkylated indole derivatives using iron salt as catalyst

| Entry | Indole 3 | Catalyst (mol %) | Solvent | Time (temp) | Product 4 | % Yield of 4 |
|-------|-----------------|------------------------------------|------------|----------------------------|------------------|-------------------------------------|
| 1 | | $Fe(BF_4)_2 \cdot 6H_2O$ (10) | CH_3CN | 96 h (40 °C) | | 31+34 ^a |
| 2 | 3a | $Fe(BF_4)_2 \cdot 6H_2O$ (10) | MeOH | 24 h (40 °C) | 4b | 39+33 ^a |
| 3 | 3a | $Fe(BF_4)_2 \cdot 6H_2O$ (10) | No solvent | 8 h (40 °C) | 4b | 56+25 ^a |
| 4 | 3a | $Fe(BF_4)_3^d$ (5) | No solvent | 8 h (40 °C) | 4b | 31+46 ^a |
| 5 | 3a | $Fe(ClO_4)_3 \cdot Al_2O_3$ (5) | No solvent | 144 h (rt) ^c | 4b | 42+12 ^a |
| 6 | 3a | $Fe(ClO_4)_3 \cdot nH_2O$ (6) | No solvent | 72 h (40 °C) | 4b | 63+15 ^a |
| 7 | 3a | $Fe(ClO_4)_3 \cdot nH_2O$ (10) | No solvent | 8 h (40 °C) | 4b | 54+18 ^a |
| 8 | | $Fe(BF_4)_2 \cdot 6H_2O$ (8) | No solvent | 72 h (rt) ^c | | 70+16 ^a |
| 9 | | $Fe(BF_4)_2 \cdot 6H_2O$ (5) | No solvent | 72 h (rt) ^c | | 51+23 ^a |
| 10 | | $Fe(BF_4)_2 \cdot 6H_2O$ (5) | No solvent | 24 h (60 °C) | | 17+43 ^a +12 ^b |
| 11 | | $Fe(BF_4)_2 \cdot 6H_2O$ (8) | No solvent | 5 h (40 °C) | | 86 |

^a Recovered yield of substrate **3**.

^b Yield of *N*-alkylated product.

^c A significant reduction of the desired product was recorded when the reaction was carried out at 40 °C or 60 °C.

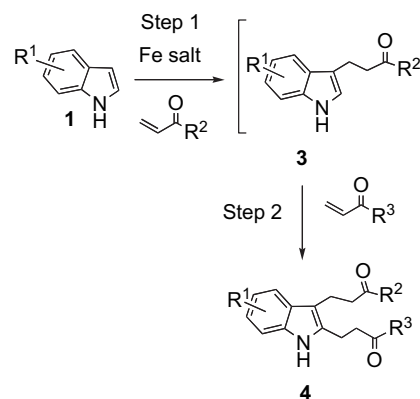
^d Prepared by the reaction of $Fe(BF_4)_2$ with 1.0 equiv of $AgBF_4$.

was obtained in moderate yield (56%) when the reaction was carried out under solvent free conditions (entry 3). Since no Lewis acidity was reported for iron(II) salt, we assume that the real catalyst of the present reaction might be ferric ion species. So, we prepared $\text{Fe}(\text{BF}_4)_3$ ⁵ and used it as catalyst, however, polymerization of vinyl ketone took place and no significant improvement of desired **4b** was recorded (entry 4). The result using 5 mol % of $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ was also insufficient and **4b** was obtained in 42% yield when the reaction was conducted at rt for 144 h (entry 5). Although it required a long reaction time, desired product **4b** was obtained in the highest yield (63%) when 6 mol % of $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ was used as catalyst (entry 6). Increasing the amount of $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ to 10 mol % decreased the chemical yield of **4b** (entry 7). Therefore, we decided to use 5 mol % of $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ or $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ as catalyst for further reaction.

Introduction of an electron-donating group at the 5 position of indole contributed to improvement of the chemical efficiency, and desired **4c** was obtained in 70% for **3c** (entry 8). On the contrary, introduction of an electron-withdrawing group such as bromide caused a slight drop of the chemical yield of **4d** (51%) (entry 9) and a poor result was obtained for cyano-substituted indole **4e** (17%) (entry 10). In this reaction, a significant yield of *N*-alkylated product was also obtained (12%) (entry 10). To our delight, the desired product **4f** was obtained in excellent yield (86%) when 7-methylindole derivative **3f** was employed as substrate (entry 11).

Based on these results, we next tried cascade type one-pot dialkylation of indole using two different acceptors in the presence of $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ or $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ as catalyst under solvent free conditions as illustrated in Scheme 3.

The reaction was carried out as follows: indole **1a** was mixed with 1-buten-3-one (**2a**) (1.1 equiv) in the presence of 3 mol % of $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ and the mixture was stirred at 60 °C for 20 min, then 2.2 equiv of 1-octen-3-one (**2b**) was added with an additional 3 mol % of $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ to the reaction mixture and the mixture was stirred for 24 h at 40 °C. Forty-seven percent of the desired product, **4b** was obtained. Since mono-alkylated compound **3b** was obtained in 12% yield, we attempted to prolong the reaction time. However, compound **3b** was not consumed but resulted only in reducing the yield of **4b** (Table 2, entry 1). It was also found that a significant polymeric product was produced when the entire course of the reaction was conducted at 60 °C. A different type of alkylation product **4g** was attained when the order of the vinyl ketones was switched. In this case, $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ worked better as



Scheme 3. Cascade type one pot 2,3-dialkylation of indole derivatives.

a catalyst than $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ and **4g** was obtained in 40% yield (entry 2). However, there was no improvement in yield of **4g** despite the testing of many reaction conditions. We assume that the poor result might have the inhibitory action of 3-substituted group to access 2-position. To our delight, 2,3-dialkylated indole **4f** was obtained in good yield when 7-methylindole **1f** was subjected to the reaction using $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ or $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ as catalyst in 62% (entry 3) and 70% (entry 4), respectively.

As we reported previously, the reaction of indole **1a** with **2a** in the presence of 1.0 equiv of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) gave interesting results.⁹ Alkylation product **3a** was obtained in 30% yield after 24 h reaction at rt in solvent free conditions in the presence of 1.0 equiv of TEMPO. On the contrary, the reaction was completely inhibited by addition of TEMPO in CH_3CN . Therefore, it was obvious that the mechanism of the present reaction depends on the reaction medium. In addition, no inhibitory action was recorded when 1.0 equiv of 2,6-di-*tert*-butylphenol was added to the reaction in any solvent system. Furthermore, it was found that no alkylation at 2-position took place when indole **3a** was reacted with vinyl ketone **2a** in H_2O as solvent using $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ or $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ as catalyst.

We previously reported that iron (III) complex works as a single electron oxidant for organic molecules to generate radical cation and subsequent radical reaction takes place.^{2,3} It is well known that TEMPO or 2,6-di-*tert*-butylphenol inhibits a radical reaction, though they work as inhibitors in a different fashion: TEMPO reacts

Table 2
Iron salt-catalyzed cascade type 2,3-dialkylation of indole with vinyl ketones

| Entry | Indole 1 | Step 1: Ketone 2 (R^2) Step 2: Ketone 2 (R^3) | Catalyst (mol %) | Time (Step 1) | Time (Step 2) | Product 4 | Yield ^b (%) |
|-------|-----------------|--|---|------------------|----------------|------------------|------------------------|
| 1 | | Step 1: $\text{R}^2 = \text{Me}$ (1.1 equiv) Step 2: $\text{R}^3 = n\text{-C}_5\text{H}_{11}$ (2.0 equiv) | $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ (3+3) ^a | 60 °C, 20 min | 40 °C, 24 h | | 47 (12) |
| 2 | | Step 1: $\text{R}^2 = n\text{-C}_5\text{H}_{11}$ (1.1 equiv) Step 2: $\text{R}^3 = \text{Me}$ (2.0 equiv) | $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (3+3) ^a | rt, 15 min. | 40 °C, 24 h | | 40 (0) |
| 3 | | Step 1: $\text{R}^2 = \text{Me}$ (1.1 equiv) Step 2: $\text{R}^3 = n\text{-C}_5\text{H}_{11}$ (2.0 equiv) | $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (3) | 60 °C, 20 min | 40 °C, 24 h | | 62 (21) |
| 4 | | Step 1: $\text{R}^2 = \text{Me}$ (1.1 equiv) Step 2: $\text{R}^3 = n\text{-C}_5\text{H}_{11}$ (2.0 equiv) | $\text{Fe}(\text{ClO}_4)_3 \cdot n\text{H}_2\text{O}$ (3+5) ^a | 60 °C, 20 min | 40 °C, 5 h | | 70 (0) |

^a Iron salt was added in two portions.

^b Isolated yield. Yield of the corresponding intermediate **3** is shown in parenthesis.

directly with carbon radical or heteroatom radical and inhibits the reaction process,¹⁷ while 2,6-di-*tert*-butylphenol captures an electron of a radical species and stops the radical chain reaction.¹⁸ Since no inhibitory action was observed by addition of 2,6-di-*tert*-butylphenol, it is clear that the present iron salt-catalyzed reaction involves no radical chain reaction pathway. We therefore assume that the origin of the present alkylation might be an appropriate Lewis acidity of iron (III) salt complex.

A plausible mechanism of iron salt-catalyzed alkylation of indole derivatives is illustrated in Figure 1. Since the reaction was carried out under air conditions, we assumed that iron (III) species might be the real catalyst even if $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ was used as catalyst. In fact, significant reduction of the reaction rate was recorded when the reaction of **1a** with **2a** was carried out under argon atmospheric conditions in the presence of $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$: indole **3a** was obtained in only 20% yield after 6 h of the reaction at 60 °C and 68% of starting indole **1a** was recovered. A polymerized product was produced when a strong Lewis acid such as FeCl_3 or $\text{Fe}(\text{BF}_4)_3$ was employed and no reaction took place when acrylonitrile or nitroethene was used as an acceptor. Therefore, we speculated that iron(III) complex **A1** might be produced by the reaction of vinyl ketone **2-1** with iron(II)bis(tetrafluoroborate) under air conditions. **A2** reacts with indole to give intermediate **B**, which then reacts with vinyl ketone **2-2** to give monoalkylated product **3** with formation of **A3**. Reaction of **A3** with indole **3** affords the final product **4** through the reaction of **2-2** and intermediate **C**. During the course of the reaction, vinyl ketone **2-1** or **2-2** seems to play both role of acceptor and ligand, which support an iron(III) species. Although this is just a working hypothesis at present, we feel that it well explains our experimental results.

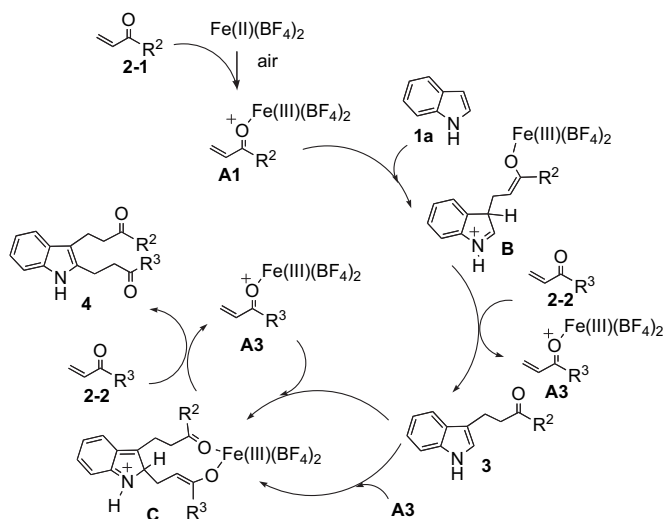


Figure 1. Plausible catalytic cycle of $\text{Fe}(\text{BF}_4)_2$ -catalyzed one-pot double alkylation of indole.

3. Conclusion

In summary, we have established a very simple protocol for the synthesis of 2,3-dialkylated indol derivatives using economical iron salts as catalyst. To the best of our knowledge, this is the first example of the cascade type one-pot double alkylation of *N*-protecting group free indole with vinyl ketones. Although the chemical yields still remain at a moderate level, the reaction requires no tedious argon atmospheric conditions and two types of 2,3-dialkylated indole could be obtained by simply switching the order of the vinyl ketones. It should be emphasized that the reaction was realized under very mild conditions. We hope that the present iron salt-catalyzed reaction might become a useful means in the stage of natural product syntheses.

4. Experimental section

4.1. General procedures

Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Wako gel C-300 and Wako gel B5F were used for flash column chromatography and thin-layer chromatography (TLC), respectively. NMR spectra were recorded on JEOL MH-500 (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometers, and chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) in CDCl_3 as an internal reference. IR spectra were obtained on a SHIMADZ FTIR-8000 spectrometer.

4.1.1. 4-(1*H*-Indol-3-yl)butan-2-one (3a)^{9,12g,12i}. To a solution of indol (**1a**) (117 mg, 1.0 mmol) and 1-buten-3-one (**2a**) (140 mg, 2.0 mmol) in water (1.0 ml) was added $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (10 mg, 0.03 equiv) in one portion, and the mixture was stirred at 60 °C for 5 h under air conditions. After removing water by evaporation, the residue was diluted with ether and the organic layer was filtered through a florisil short column, evaporated to dryness and purified by silica gel flash column chromatography to give **3a** (165 mg, 0.88 mmol) in 88% yield: mp 115–117 °C (recrystallized from hexane/dichloromethane); R_f 0.52 (ether/hexane=3/1); IR (KBr, cm^{-1}) 3319, 1701, 1458, 1350, 1273, 1165, 1099, 785, 739; ^1H NMR (500 MHz, δ , CDCl_3 , J =Hz) 2.13 (3H, s), 2.84 (2H, t, J =7.6), 3.04 (2H, t, J =7.4), 6.95 (1H, s), 7.11 (1H, t, J =7.6), 7.19 (1H, t, J =7.6), 7.33 (1H, d, J =7.8), 7.58 (1H, d, J =7.8), 8.00 (1H, br s); ^{13}C NMR (125 MHz, δ , CDCl_3) 19.29, 30.01, 44.04, 111.14, 115.08, 118.61, 119.24, 121.44, 121.98, 127.11, 136.25, 208.83. Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.91; H, 7.02; N, 7.49.

Using the similar reaction conditions, substrates **3c**, **3d**, **3e**, and **3f** were prepared in >70% yield.

4.1.2. 4-(5-Methyl-1*H*-indol-3-yl)butan-2-one (3c)¹²ⁱ. Mp 113–115 °C (recrystallized from hexane/dichloromethane); R_f 0.75 (ether/hexane=6/1); IR (KBr, cm^{-1}) 3327, 1701, 1340, 1161, 802, 783, 605; ^1H NMR (500 MHz, δ , CDCl_3 , J =Hz) 2.14 (3H, s), 2.46 (3H, s), 2.83 (2H, t, J =7.4), 3.01 (2H, t, J =7.3), 6.93 (1H, d, J =0.9), 7.00 (1H, d, J =0.7), 7.02–7.23 (2H, m), 7.91 (1H, br s); ^{13}C NMR (125 MHz, δ , CDCl_3) 19.37, 21.47, 30.01, 44.13, 110.80, 114.65, 118.28, 121.57, 123.62, 127.38, 128.51, 134.62, 208.82. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.34; H, 7.45; N, 6.98.

4.1.3. 4-(5-Bromo-1*H*-indol-3-yl)butan-2-one (3d)¹²ⁱ. Mp 99–101 °C (recrystallized from hexane/dichloromethane); R_f 0.53 (ether/hexane=4/1); IR (KBr, cm^{-1}) 3355, 2932, 2854, 1701, 1458, 1163, 1049, 794, 590; ^1H NMR (500 MHz, δ , CDCl_3 , J =Hz) 2.14 (3H, s), 2.81 (2H, t, J =7.4), 2.99 (2H, t, J =6.8), 6.99 (1H, t, J =0.9), 7.20–7.27 (2H, m), 7.70 (1H, s), 8.01 (1H, br s); ^{13}C NMR (125 MHz, δ , CDCl_3) 19.04, 30.02, 43.83, 112.50, 112.89, 114.78, 121.20, 122.81, 124.75, 128.91, 134.84, 208.54. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{BrNO}$: C, 54.16; H, 5.54; N, 5.26. Found: C, 54.05; H, 4.53; N, 5.31.

4.1.4. 3-(3-Oxobutyl)-1*H*-indole-5-carbonitrile (3e). Mp 140–141 °C (recrystallized from hexane/dichloromethane); R_f 0.56 (ether only); IR (neat, cm^{-1}) 3393, 2218, 1714, 1612, 1577, 1473, 1155, 804, 628; ^1H NMR (500 MHz, δ , CDCl_3 , J =Hz) 2.16 (3H, s), 2.85 (2H, t, J =7.39), 3.03 (2H, t, J =6.9), 7.11 (1H, d, J =1.1), 7.39–7.42 (2H, m), 7.93 (1H, s), 8.77 (1H, br s); ^{13}C NMR (125 MHz, δ , CDCl_3) 18.75, 30.01, 43.68, 102.04, 112.06, 115.98, 120.82, 123.83, 124.30, 124.73, 127.00, 137.91, 208.20.

Anal. Calcd for C₁₃H₁₂N₂O: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.38; H, 5.67; N, 13.19.

4.1.5. 4-(7-Methyl-1H-indol-3-yl)butan-2-one (3f). Mp 140–141 °C (recrystallized from hexane/dichloromethane); *R_f* 0.52 (ether/hexane=6/1); IR (neat, cm⁻¹) 3336, 1710, 1409, 1382, 1163, 792, 742, 597; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 2.14 (3H, s), 2.47 (3H, s), 2.84 (2H, t, *J*=7.6), 3.04 (2H, t, 7.6), 6.98–7.00 (2H, m), 7.05 (1H, t, *J*=7.4), 7.44 (1H, d, *J*=7.7), 7.91 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 16.53, 19.47, 30.01, 44.10, 115.66, 116.35, 119.52, 120.33, 121.17, 122.55, 125.67, 135.86, 208.77. Anal. Calcd for C₁₃H₁₅NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.23; H, 7.50; N, 7.00.

4.1.6. 1-(3-(3-Oxobutyl)-1H-indol-2-yl)octan-3-one (4b) (Scheme 2). To a mixture of **3a** (187 mg, 1.0 mmol) and 1-buten-3-one (**2a**) (140 mg, 2.0 mmol) was added Fe(ClO₄)₃·nH₂O (21 mg, 0.06 equiv) in one portion, and the mixture was stirred at 40 °C for 72 h. The residue was diluted with ether and the organic layer was filtered through a florisil short column, evaporated to dryness and purified by silica gel flash column chromatography to give **4b** (197 mg, 0.63 mmol) in 63% yield and **3a** (28 mg, 0.15 mmol) was recovered in 15% yield. Compound **4b**: bp 132–135 °C (3 Torr, Kugelrohr); *R_f* 0.82 (ether/hexane=6/1); IR (neat, cm⁻¹) 3386, 2929, 2860, 1713, 1710, 1461, 1406, 1363, 1161, 740, 551; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 0.78–0.82 (3H, m), 1.14–1.26 (4H, m), 1.47–1.53 (2H, m), 2.01 (3H, s), 2.30–2.35 (2H, m), 2.69–2.73 (4H, m), 2.88 (2H, t, *J*=7.4), 2.93 (2H, t, *J*=6.6), 6.98 (1H, t, *J*=8.2), 7.04 (1H, t, *J*=7.8), 7.20 (1H, d, *J*=7.8), 7.38 (1H, d, *J*=7.8), 8.43 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 13.79, 18.17, 19.13, 22.33, 23.17, 23.45, 30.20, 31.24, 42.80, 44.25, 109.87, 110.61, 117.82, 118.86, 121.10, 127.66, 134.98, 135.24, 208.76, 209.44; HRMS (MALDI-TOF MS, matrix: SA) found 313.2045 (C₂₀H₂₇NO₂, Calcd: 313.20418).

2,3-Dialkylated-indoles, **4c**, **4d**, and **4e** were prepared by the same method in the yields described in Table 1. Compound **4a**⁹ was also obtained in 70% yield from **3a**⁹.

4.1.7. 1-(5-Methyl-3-(3-oxobutyl)-1H-indol-2-yl)octan-3-one (4c). Bp 115 °C (1 Torr, Kugelrohr); *R_f* 0.69 (ether/hexane=17/5); IR (neat, cm⁻¹) 3368, 3013, 2957, 2930, 2860, 1717, 1699, 1449, 1364, 1163, 910, 797, 735; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 0.86 (3H, t, *J*=7.1), 1.20–1.30 (4H, m), 1.55 (2H, quin, *J*=7.5), 2.09 (3H, s), 2.37 (2H, t, *J*=7.6), 2.43 (3H, s), 2.74–2.77 (4H, m), 2.92 (2H, t, *J*=7.4), 2.96 (2H, t, *J*=6.2), 6.92 (1H, d, *J*=8.3), 7.14 (1H, d, *J*=8.3), 7.23 (1H, s), 8.41 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 13.78, 18.17, 19.17, 21.42, 22.31, 23.43, 30.18, 31.22, 42.80, 42.82, 44.30, 109.38, 110.27, 117.56, 122.56, 127.90, 128.01, 133.55, 135.07, 208.84, 212.18; HRMS (MALDI-TOF MS, matrix: SA) found 327.2198 (C₂₁H₂₉NO₂, Calcd: 327.2198).

4.1.8. 1-(5-Bromo-3-(3-oxobutyl)-1H-indol-2-yl)octan-3-one (4d). *R_f* 0.67 (ether/hexane=6/1); IR (neat, cm⁻¹) 3340, 3057, 2957, 2928, 1719, 1638, 1400, 1309, 1076, 1049, 796; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 0.86 (3H, t, *J*=7.1), 1.19–1.31 (4H, m), 1.57 (2H, quin, *J*=7.5), 2.09 (3H, s), 2.41 (2H, t, *J*=7.6), 2.75 (2H, t, *J*=7.4), 2.80 (2H, t, *J*=5.9), 2.90 (2H, t, *J*=7.1), 2.99 (2H, t, *J*=6.0), 7.13 (1H, d, *J*=8.7), 1.17–7.19 (1H, m), 7.56 (1H, s), 8.65 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 13.83, 17.95, 19.09, 22.36, 23.50, 30.28, 31.26, 42.64, 42.87, 44.04, 109.76, 112.08, 112.15, 120.42, 123.85, 129.54, 133.87, 136.59, 208.42, 212.61; HRMS (MALDI-TOF MS, matrix: SA) found 391.1141 (C₂₀H₂₆BrNO₂, Calcd: 391.1147).

4.1.9. 3-(3-Oxobutyl)-2-(3-oxooctyl)-1H-indole-5-carbonitrile (4e). Mp 108–110 °C (recrystallized from hexane/ethyl acetate); *R_f* 0.41 (ether/hexane=6/1); IR (neat, cm⁻¹) 3337, 2957, 2930, 2862, 2218(CN), 1709, 1476, 1364, 1267, 1163, 737; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 0.86 (3H, t, *J*=7.2), 1.24–1.29 (4H, m), 1.59 (2H, quin, *J*=7.6), 2.10 (3H, s), 2.44 (2H, t, *J*=7.1), 2.85 (2H, t, *J*=5.7), 2.95 (2H, t,

J=7.1), 3.03 (2H, t, *J*=5.8), 7.29–7.34 (2H, m), 7.80 (1H, s), 9.05 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 13.82, 17.73, 19.06, 22.35, 23.50, 30.27, 31.25, 42.47, 42.85, 43.89, 101.81, 110.96, 111.41, 121.03, 123.41, 124.25, 127.61, 136.98, 137.72, 207.99, 212.95. Anal. Calcd for C₂₁H₂₆N₂O₂: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.39; H, 7.77; N, 8.29.

4.1.10. 2,3-Bis(3-oxobutyl)-1H-indol (4a)⁹. Bp 145 °C, 6 Torr/Kugelrohr; *R_f* 0.2 (ether/hexane: ether=2/1); ¹H NMR (400 MHz, δ, CDCl₃, *J*=Hz) 2.09 (3H, s), 2.16 (3H, s), 2.76–2.83 (4H, m), 2.93–3.00 (4H, m) 7.03–7.13 (2H, m), 7.26 (1H, d, *J*=8.1), 7.45 (1H, d, *J*=7.7), 8.48 (1H, br s, NH); ¹³C NMR (125 MHz, δ, CDCl₃, *J*=Hz) 18.16, 19.10, 30.04, 30.25, 43.85, 44.24, 109.96, 110.64, 117.88, 118.94, 121.20, 127.66, 134.90, 135.25, 208.80, 209.76; IR (neat, cm⁻¹) 3398, 2924, 1715, 1701, 1365, 1159, 808. Anal. Calcd for C₁₆H₁₉NO₂: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.34; H, 7.42; N, 5.49.

4.1.11. 1-(7-Methyl-3-(3-oxobutyl)-1H-indol-2-yl)octan-3-one (4f) (Scheme 3). To a mixture of indol **1f** (131 mg, 1.0 mmol) and 1-buten-3-one (**2a**) (77 mg, 1.1 mmol) was added Fe(ClO₄)₃·nH₂O (11 mg, 0.03 equiv) in one portion, and the mixture was stirred at 60 °C for 20 min. Then the reaction flask was moved to an oil bath at 40 °C, a mixture of 1-octene-3-one (**2b**) (252 mg, 2.0 equiv) and Fe(ClO₄)₃·nH₂O (17 mg, 0.05 equiv) was added to the reaction mixture and stirred at 40 °C for 5 h. The residue was diluted with ether and the organic layer was filtered through a florisil short column, evaporated to dryness and purified by silica gel flash column chromatography to give **4f** (229 mg, 0.70 mmol) in 70% yield: 123–125 °C (1 Torr, Kugelrohr); *R_f* 0.67 (ether/hexane: ether=6/1); IR (neat, cm⁻¹) 3377, 3117, 3053, 2957, 2861, 1717, 1701, 1541, 1448, 1364, 1080, 1061, 779, 746; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 0.86 (3H, t, *J*=7.4), 1.20–1.33 (4H, m), 1.56 (2H, quin, *J*=7.4), 2.08 (3H, s), 2.39 (2H, t, *J*=7.6), 2.44 (3H, s), 2.75–2.80 (4H, m), 2.94 (2H, t, *J*=7.3), 3.01 (2H, t, *J*=6.2), 6.91 (1H, d, *J*=7.3), 6.97 (1H, t, *J*=7.3), 7.31 (1H, d, *J*=7.8), 8.50 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 13.78, 16.44, 18.28, 19.20, 22.31, 23.48, 30.16, 31.23, 42.84, 42.88, 44.26, 110.33, 115.55, 119.13, 119.82, 121.72, 127.15, 134.68, 134.73, 208.84, 212.42; HRMS (MALDI-TOF MS, matrix: SA) found 327.2198 (C₂₁H₂₉NO₂, Calcd: 327.2198).

4.1.12. 1-(2-(3-Oxobutyl)-1H-indol-3-yl)octan-3-one (4g). Bp 138–140 °C (0.5 Torr, Kugelrohr); IR (neat, cm⁻¹) 0.53 (Et₂O/H=6/1); 3398, 2956, 292, 2860, 1709, 1460, 1364, 1242, 1163, 910, 739; ¹H NMR (500 MHz, δ, CDCl₃, *J*=Hz) 0.85 (3H, *J*=7.3), 1.16–1.27 (4H, m), 1.51 (2H, quin, *J*=7.8), 2.16 (3H, s), 2.31 (2H, t, 7.8), 2.74 (2H, t, *J*=7.3), 2.94–3.00 (4H, m), 7.05 (1H, t, *J*=6.9), 8.46 (1H, br s); ¹³C NMR (125 MHz, δ, CDCl₃) 13.83, 18.26, 19.12, 22.36, 23.44, 30.03, 31.31, 43.21, 43.23, 43.88, 110.15, 110.63, 117.92, 118.93, 121.19, 127.71, 134.85, 135.28, 209.75, 211.29; HRMS (MALDI-TOF MS, matrix: SA) found 313.2042 (C₂₀H₂₇NO₂, Calcd: 313.20418).

Acknowledgements

The work was partly supported by a Grant-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.03.094.

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