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A Practical Method for *N*-Methylation of Indoles Using Dimethyl Carbonate

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Abstract:

A new method for *N*-methylation of indoles using environmentally safe and less toxic methylating reagent, dimethyl carbonate (DMC), has been developed. The effect of various functional groups on the indole ring has been investigated. This method provides the desired product in high yields with high purity and is suitable for large-scale production. This process was used successfully in a 300-gal reactor train for *N*-methylation of 6-nitroindole.

Introduction

N-methylation of indoles with methyl iodide[1,2] and dimethyl sulfate[3] in the presence of a variety of bases, such as $NaNH_2$,[4] NaH,[5] KOH,[6] and NaOH,[6] is a classical method to form *N*-methylated indole derivatives. However, use of this method for large-scale manufacturing has several disadvantages. Methyl iodide has a very low boiling point (40 °C), causing air emission problems, and it is a suspected carcinogen.[7] Dimethyl sulfate is also highly toxic (LD_{50} orally in rats is 440 mg/kg). In addition, the byproducts generated by these methylating agents can cause waste disposal problems. In view of these disadvantages, an alternate methylating reagent and an efficient process for large-scale manufacturing is highly desirable.

In recent years, dimethyl carbonate (DMC) has emerged as a methylating agent in organic synthesis. Although it is less reactive than methyl iodide and dimethyl sulfate, it has the advantage of being much less toxic. DMC has been successfully used to introduce a methyl group at the α-position of arylacetonitriles and methyl aryl acetates.[8] It has also been used to selectively monomethylate primary aromatic amines[9] and *N*-methylate imidazoles.[10] In addition to DMC, dimethyloxalate has also been used for *N*-methylation of indoles, carbazoles, and imidazole.[11]

During development of a process for a pharmaceutical drug candidate, we required a less toxic but economically viable substitute for methyl iodide and dimethyl sulfate for *N*-methylation of indoles. Herein we report a robust and highly scalable process for *N*-methylation of indoles using dimethyl carbonate (DMC).

Results and Discussions

As depicted in Scheme 1, the reaction between an indole substrate and DMC in the presence of a base was accomplished by heating the reagents in dimethylformamide (DMF) to reflux for 2 to 3 h. The desired *N*-methylated product was obtained either by precipitation or extraction after addition of water to the reaction mixture.

Initial attempts to *N*-methylate 6-nitroindole (R = 6-NO_2) with two types of Zeolite (13X and NaY) provided 1-methyl-6-nitroindole in high yield (93−95%) with high purity (>99.6%, area, HPLC). However, the reaction required a large amount of Zeolite (>1.2 w/w to 6-nitroindole). Other bases, such as potassium carbonate could also be used. Potassium carbonate has several advantages over Zeolite. It is needed only in a small amount and could easily be removed in the workup by dissolving in water, thus eliminating a filtration step required for the Zeolite process.

Optimization studies on the stoichiometry of DMC (Table 1) led us to conclude that 2.0−3.0 equiv of DMC with the substrate would work best for this reaction. Lower quantities of DMC results in longer reaction times and higher quantities of DMC drops the boiling point of the reaction mixture, again prolonging the reaction time.

This process of *N*-methylation using DMC and potassium carbonate proved highly scalable. It was used to conduct a very successful campaign in a 300-gal reactor train for *N*-methylation of 6-nitroindole.

Next, we focused our attention on the scope and utility of the reaction. We examined the substituent effects on indole system. As can be seen from Table 2, several electron-withdrawing functional groups were investigated. There is not much difference in reaction time and yields with functional groups on the benzene or pyrrole ring of the indole system. All substrates tested with this method afforded high yields of *N*-methylated products.

To investigate the selectivity between *N*- and *O*-methylation the reaction between 3-indolylcarboxylic acids and DMC was studied (Table 3). The selectivity between esterification and *N*-methylation was not high. However, as expected, the esterification was slightly faster than *N*-methylation.

The reaction of 3-indolylpropionic acid with dimethyl carbonate in the presence of potassium carbonate in DMF afforded 65% *N*-,*O*-dimethylated product after 4 h at reflux temperature, together with 30% of only *O*-methylated

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Scheme 1. ***N*-Methylation of indoles using DMC**

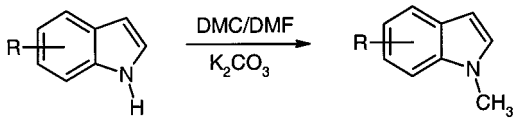
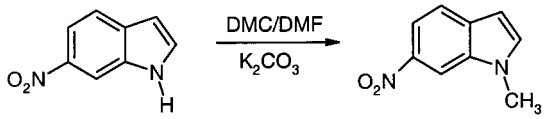
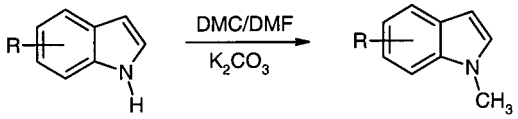


Table 1. **Optimization of DMC stoichiometry**



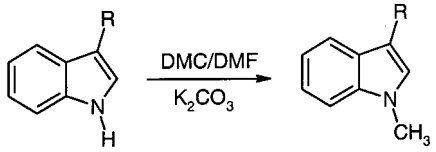
ratio (mol) DMC/6-nitroindole	reaction time (h)	yield (%)
0.8	8	50.0
1.1	3	96.5
1.6	2.5	96.7
2.0	2.0	95.8
2.2	1.5	96.4

Table 2. **Electron-withdrawing effects on indole system**



substituent (R)	reaction time (h)	*N*-methylated product yield (%)
3-CN	3.5	97
4-NO_2	2.0	96
5- NO_2	3.0	97
6- NO_2	2.0	97
5-Br	3.5	95
6-Cl	3.5	96
3-CHO	3.5	85
3-CO_2CH_3	3.5	96

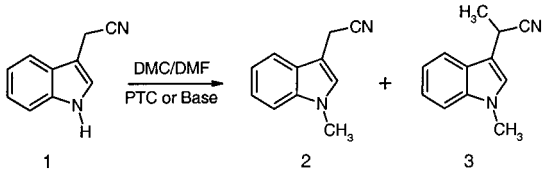
Table 3. **Selectivity between *N*- and *O*-methylation**



substituent (R)	reaction time (h)	product yield (%)
3-COOH	5	*N*-,*O*-dimethylation (50%) *N*-methylindole (45%)
3-CH_2COOH	6	*N*-,*O*-dimethylation (89%) *O*-methylation (8%)
	8	*N*-,*O*-dimethylation (95%)
3-CH_2CH_2COOH	4	*N*-,*O*-dimethylation (65%) *O*-methylation (30%)
	8	*N*-,*O*-dimethylation (93%)

product. After the reaction mixture was heated at reflux for another 4 h, only dimethylated product was obtained in 93% yield. As demonstrated in Table 3, similar results were observed with 3-indolylacetic acid. With 3-indolylcarboxylic acid, however, along with 50% of the dimethylated product, 45% of *N*-methylindole was isolated, probably due to the decarboxylation of 3-indolylcarboxylic acid at high temperature (128 °C).

Table 4. **Selectivity between *N*- and *C*-methylation**



1 2 3

base	catalyst	reaction time (h)	*N*-methyl[a] % (**2**)	*N*-,*C*-dimethyl[a] % (**3**)
K_2CO_3	none	30	89	8
none	TBAB	2.5	93	2.5
KOH	TBAB	3	90	3
NaOH	TBAB	2.5	92	3
NaOH	18-crown-6	6	79	3.5

[a] Results reported are based on HPLC area %.

With DMC as a methylating agent, the *N*-methylation of indole systems containing electron-donating groups was also studied. For example, *N*-methylation of 5-methoxyindole with DMC at reflux temperature for 5 h gave 1-methyl-5-methoxyindole in 97% isolated yield. However, other substrates, such as gramine, 3-indolylmethanol, 3-indolylethanol and tryptamine gave complex mixtures.

To further illustrate the utility of this method, 3-indolylacetonitrile was chosen to examine the selectivity between *N*-methylation and *C*-methylation of activated methylene group. Faul and co-workers have reported quantitative *N*-methylation of 3-indolylacetonitrile using methyl iodide.[12] We wanted to see if similar selectivity can be obtained with DMC as methylating agent. The results of our experiments are listed in Table 4. The reaction of 3-indolylacetonitrile with DMC in the presence of a base in DMF gave a mixture of *N*-methylated and *N*-,*C*-dimethylated product. However the amount of α-methylation can be altered by changing the reagents and reaction conditions. In the presence of DMC and potassium carbonate, along with 89% of 1-methyl-3-indolylacetonitrile (**2**), dimethylated byproduct (**3**) was also produced in 8% yield. However, the reaction was sluggish, and it took 30 h to convert 3-indolylacetonitrile to the desired products. This difficulty was overcome by using a phase transfer catalyst (PTC).

For example, when using 18-crown-6 and a base (NaOH) the amount of dimethylated byproduct (**3**) was reduced to about 3%. Under these reaction conditions, 75−80% of the desired product, 1-methyl-3-indolylacetonitrile, was obtained within 5−6 h. With tetrabutylammonium bromide (TBAB) and a base (NaOH or KOH) the reaction time dropped to 2.5−3 h, and the level of dimethylated byproduct remained around 3%. However, to our surprise, TBAB alone was just as effective in achieving selective *N*-methylation without the presence of any base.

For comparison purposes, indoline and aniline were methylated with DMC. As depicted in reaction Scheme 2, both indoline and aniline were converted to the desired

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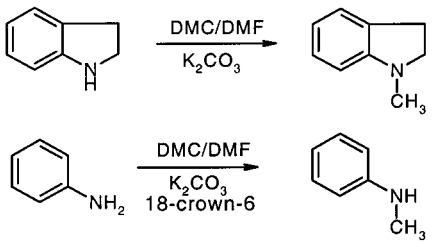
Scheme 2. ***N*-Methylation of indoline and aniline using DMC**



products in high yields(>90%). However, a longer reaction time was required for indoline (9 h). For aniline, 20 h was required even in the presence of PTC (18-crown-6).

Mechanistic studies for this methylation with dimethyl carbonate is under way, and the results will be reported in due course.

Conclusions

Methylation with dimethyl carbonate (DMC) has been found to be a practical method to prepare *N*-methylated indole analogues in high yields and purity. By changing the reaction conditions, this method provides a high selectivity of *N*-methylation over *C*-methylation in activated methylene compounds. This method also provides an efficient way to synthesize *N*-methylindole carboxylic acid methyl ester (*N*- and *O*-dimethylation) from indole carboxylic acid in one pot.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. NMR was performed on a Varian 400 MHz spectrometer. HPLC was performed on a Hewlett-Packard 1100 system with UV detection at 254 nm. Separation was accomplished using a Zorbax SB-CN column (L = 250 mm, i.d. = 4.6 nm) and mobile phase (with gradient) consisting of 25% acetonitrile: 75% potassium phosphate buffer (pH 2.5).

***N*-Methylation of 6-Nitroindole.** Sixty grams (370 mmol) of 6-nitroindole, 12 g of K_2CO_3, 240 mL of DMF, and 66 mL (790 mmol) of DMC were mixed together and heated to reflux (around 126 °C). The reaction was (monitored by HPLC) complete within 2 h. After the completion of the reaction, the mixture was cooled to about 5 °C, and 480 mL of ice cold water was added slowly. The product precipitated as a bright yellow solid during the addition. The product, *N*-methyl-6-nitroindole, was washed with 250 mL of water and dried under vacuum at 60 °C for 24 h to give a 96% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.56 (d, 1H), 7.33 (d, 1H), 7.61 (d, 1H), 7.97(d, 1H), 8.27 (d, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 33.14, 102.03, 106.24, 114.68, 120.58, 133.16, 134.54, 135.14, 142.78.

***N*-Methylation of Indole.** Ten grams (85 mmol) of indole, 5 g of K_2CO_3, 70 mL of DMF, and 11 mL (130 mmol) of dimethyl carbonate were mixed together and refluxed (around 130 °C) for 2 h. At this point TLC (silica gel; hexane:ethyl acetate 7:3, R_f^1 0.46, R_f^2 0.55) showed starting material largely unchanged. The reaction mixture was cooled to about 50 °C, and another 5.5 mL (65 mmol) dimethyl carbonate was added in one portion. The mixture was again refluxed for another 7 h when TLC indicated complete disappearance of the starting material. The reaction mixture was cooled to room temperature, and 150 mL of water was slowly added. The resulting mixture was extracted with 150 mL of TBME. The organic layer was washed with 2 × 100 mL of water and evaporated under vacuum to isolate the product, 1-methylindole, as light-yellow oil in 96.5% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.842 (s, 3H), 6.556−6.536 (d, 1H), 7.088−7.096 (d, 1H), 7.191−7.212 (m, 1H), 7.281−7.319 (m, 1H), 7.374−7.394 (m, 1H), 7.703−7.723 (d, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 32.688, 100.798, 109.121, 119.188, 120.789, 121.403, 128.405, 128.716, 136.614.

***N*-Methylation of 3-Cyanoindole.** One gram (7.03 mmol) of 3- cyanoindole, 0.5 g of K_2CO_3, 10 mL of DMF, and 1.8 mL (21.4 mmol) of dimethyl carbonate were mixed together and heated to reflux (around 130 °C). The reaction was complete in 3.5 h. The reaction mixture was cooled to 3 °C, and 25 mL of ice cold water was slowly added. The product precipitated as oily suspension. The mixture was extracted with 40 mL of *tert*-butyl methyl ether (TBME) and washed with 3 × 25 mL of water. The organic layer was evaporated under vacuum to obtain the product, 3-cyano-1-methylindole, as dark oil in 97.4% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.805 (s, 3H), 7.275 (m, 3H), 7.499 (s, 1H), 7.712 (d, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 33.625, 85.331, 110.413, 116.012, 119.738, 122.127, 123.857, 127.772, 135.625, 136.012.

***N*-Methylation of 5-Bromoindole.** Three grams (15 mmol) of 5-bromoindole, 1.5 g of K_2CO_3, 20 mL of DMF, and 3.9 mL (46 mmol) of dimethyl carbonate were mixed together and heated to reflux (around 130 °C) for 3.5 h. After the completion of the reaction, the mixture was cooled to about 3 °C, and 50 mL of ice cold water was slowly added. The product appeared as light-brown oily suspension. The product, 5-bromo-1-methylindole, was extracted with 60 mL of TBME and washed with 3 × 50 mL of water. The solvent was evaporated under vacuum to isolate the product as light brown oil in 94.8% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.678 (s, 3H), 6.372−6.381 (d, 1H), 6.976−6.984 (d, 1H), 7.098−7.120 (d, 1H), 7.237−7.263 (m, 1H), 7.709−7.714 (d, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 32.862, 100.419, 110.600, 112.542, 123.163, 124.165, 129.907, 130.029, 135.256.

***N*-Methylation of 6-Chloroindole.** One gram (6.59 mmol) of 6-chloroindole, 0.5 g of K_2CO_3, 10 mL of DMF, and 1.7 mL (20 mmol) of DMC were mixed together and heated to reflux (around 130 °C). The reaction was complete in 3.5 h. The reaction mixture was cooled to 3 °C, and 25 mL of ice cold water was slowly added. The product, 6-chloro-1-methylindole, precipitated as oily suspension. The mixture was extracted with 30 mL of TBME, which was washed with 3 × 25 mL of water and evaporated under

vacuum to isolate the product as light-yellow oil in 96.1% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.714 (s, 3H), 6.435−6.445 (m, 1H), 7.002−7.009 (d, 1H), 7.047−7.073 (m, 1H), 7.291−7.296 (m, 1H), 7.493−7.514 (d, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 32.809, 101.110, 109.189, 119.901, 121.623, 126.941, 127.472 129.475, 137.054.

***N*-Methylation of Indole-3-carboxaldehyde.** Three grams (20 mmol) of indole-3-carboxaldehyde, 1.5 g of K_2CO_3, 20 mL of DMF, and 5.2 mL (61 mmol) of dimethyl carbonate were mixed together and heated to reflux (around 130 °C). The reaction was complete within 3.5 h. The reaction mixture was cooled to about 3 °C, and 60 mL of ice cold water was slowly added. The product precipitated as dark oily suspension. The product was extracted with 60 mL of TBME, which was washed with 2 × 50 mL of water and evaporated under vacuum to isolate the product, indole-(1-methyl)-3-carboxalehyde, as dark-brown oil in 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.812 (s, 3H), 7.324−7.327 (m, 3H), 7.605 (s, 1H), 8.3 (d, 1H), 9.938 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 33.678, 109.906, 118.023, 121.999, 122.924,124.024, 125.246, 137.884, 139.356, 184.442.

***N*-Methylation of Methyl Indolyl-3-carboxylate.** Five grams (29 mmol) of methyl indolyl-3-carboxylate, 2.5 g of K_2CO_3, 35 mL of DMF and 7.2 mL (85 mmol) of dimethyl carbonate were mixed together and heated to reflux (around 130 °C) for 3.5 h. After the completion of the reaction, the mixture was cooled to about 3 °C, and 100 mL of ice cold water was slowly added. The product precipitated as pale-white solid. The product, *N*-methyl-indolyl-3-carboxylate, was filtered and washed with 2 × 50 mL of water and dried in a vacuum at 45 °C for 24 h. No further purification was performed. The isolated yield was 96.3%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.830 (s, 3H), 3.908 (s, 3H), 7.256−7.361 (m, 3H), 7.777 (s, 1H), 8.160−8.185 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 33.416, 50.948, 106.890, 109.728, 121.631, 121.851, 122.753, 126.569,135.127, 137.152, 165.450.

***N*-Methylation of 5-Methoxyindole.** One gram (6.79 mmol) of 5-methoxyindole, 0.5 g of K_2CO_3, 10 mL of DMF, and 1.7 mL (20 mmol) of dimethyl carbonate were mixed together and refluxed (around 130 °C) for 5 h. The reaction was monitored by HPLC. After the completion of the reaction, the mixture was cooled to about 3 °C, and 30 mL of ice cold water was slowly added. The product, 1-methyl-5-methoxyindole, precipitated as white solid. The product was filtered and washed with 2 × 30 mL of water, followed by 30 mL of hexane and dried under vacuum at 25 °C for 48 h. The isolated yield was 97.4%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.765 (s, 3H), 3.854 (s, 3H), 6.396−6.406 (m, 1H), 6.877−6.905 (m, 1H), 7.015−7.023 (d, 1H), 7.092−7.098 (d, 1H), 7.202−7.224 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 32.981, 55.916, 100.376, 102.515, 109.905, 111.870, 128.774, 129.305, 132.135, 153.985.

Methylation of 3-Indolylacetonitrile. Five grams of 3-indolylacetonitrile, 2.5 g of base (K_2CO_3/KOH/NaOH), 10 mL of dimethyl carbonate, 40 mL of dimethylformamide (DMF), and 1 g of catalyst (TBAB/18-crown-6) were mixed together and heated to reflux. The reaction was monitored, and the products were identified by HPLC. The products (a mixture of *N*-methylated and *N*-,*C*-dimethylated 3-indolylacetonitrile) were isolated by cooling the reaction mixture to room temperature and adding 80 mL of water. Then an extraction was carried out with 100 mL of TBME which was washed twice with 100 mL of water. TBME was distilled under vacuum to about 20 mL. The resulting mixture was cooled in ice-bath, and 100 mL of heptane was added dropwise with vigorous agitation. The product precipitated on cooling to −15 °C. It was filtered, washed with 50 mL of heptane, and dried under vacuum at 25 °C. No further purification was performed.

Methylation of Indole-3-carboxylic Acid. Indole-3-carboxylate (2.5 g), 1.25 g of potassium carbonate, 20 mL of DMF, and 3.9 mL of dimethyl carbonate (DMC) were mixed and heated to reflux (about 130 °C) for 5 h. The reaction was monitored, and the products were identified by HPLC. After the reaction was complete, the reaction mixture was cooled to room temperature, and then 50 mL of water and 100 mL of TBME were added. Two layers were separated, and the organic layer was washed twice with 50 mL of water. The solvent was evaporated under reduced pressure. The crude was identified (by HPLC) as 50% *N*-methylindole (decarboxylated byproduct) and 50% methyl-(*N*-methyl)-indole-3-carboxylate. The crude mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate, 70:30) to isolate the pure products.

***N*-Methylindole:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.842 (s, 3H), 6.556−6.536 (d, 1H), 7.088−7.096 (d, 1H), 7.191−7.212 (m, 1H), 7.281−7.319 (m, 1H), 7.374−7.394 (m, 1H), 7.703−7.723 (d, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 32.688, 100.798, 109.121, 119.188, 120.789, 121.403, 128.405, 128.716, 136.614.

Methyl-indole-(*N*-methyl)-3-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.830 (s, 3H), 3.903 (s, 3H), 7.276−7.342 (m, 3H), 7.777(s, 1H), 8.160−8.185 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 33.416, 50.948, 106.89, 109.728, 121.621, 121.851, 122.753, 126.569, 135.127, 137.152, 165.450.

Methylation of Indole-3-acetic Acid. Three grams of indole-3-acetic acid, 1.5 g of potassium carbonate (powder), 20 mL of DMF, and 4.3 mL of dimethyl carbonate (DMC) were mixed together and heated to reflux (about 130 °C) for 6 h. The reaction was monitored by HPLC. After the reaction was complete, the reaction mixture was cooled to room temperature and 50 mL of water and 60 mL of TBME were added. Two layers were separated, and the organic layer was washed with 50 mL of water. The solvent was evaporated under reduced pressure. The crude was identified (by HPLC) as 89% *N*-,*O*-dimethylated product (methyl-indole-(*N*-methyl)-3-acetate) and 8% *O*-methylated product (methyl-indole-3-acetate). The crude mixture was subjected

to column chromatography on silica gel (hexane/ethyl acetate, 70:30) to isolate the pure products.

Methyl-indole-3-acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.657 (s, 3H), 3.746 (s, 2H), 6.898−7.591 (m, 5 h). ^{13}C NMR (400 MHz, $CDCl_3$): δ 30.973, 51.813, 107.702, 111.230, 118.528, 119.378, 121.858, 123.239, 126.979, 136.007,172.763

Methyl-indole-(*N*-methyl)-3-acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.662 (s, 3H), 3.679 (s, 3H), 3.742 (s, 2 H), 6.980−7.569 (m, 5 h). ^{13}C NMR (400 MHz, $CDCl_3$): δ 31.147, 32.717, 52.026, 106.850, 109.339, 119.042, 119.285, 121.864, 127.774, 127.850, 137.000, 172.682.

Methylation of Indole-3-propionic Acid. One gram of indole-3-propionic acid, 0.5 g of potassium carbonate, 10 mL of DMF, and 1.33 mL of dimethyl carbonate (DMC) were mixed, and the resulting mixture was heated to reflux (about 130 °C) for 5 h. The reaction was monitored by HPLC. After the reaction was complete, the reaction mixture was cooled to room temperature and 25 mL of water and 40 mL of TBME were added. Two layers were separated, and the organic layer was washed twice with 5 mL of water. The solvent was evaporated under reduced pressure. The crude was identified (by HPLC) as 65% *N*-,*O*-dimethylated product (methyl-indole-(*N*-methyl)-3-propionate) and 30% *O*-methylated product (methyl-indole-3-propionate). The crude mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate, 70:30) to isolate the pure products.

Methyl-indole-(*N*-methyl)-3-propionate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.662−2.701 (m, 2 H), 3.069−3.072 (m, 2 H) 3.643 (s, 3H), 3.662 (s, 3H),), 6.809−7.290 (m, 5 h). ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.389, 32.362, 34.820, 51.373, 109.052, 113.225, 118.604, 118.605, 121.433, 126.122, 127.404, 136.849, 173.658.

Methyl-indole-3-propionate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.649−2.687 (m, 2 H), 3.035−3.073 (m, 2 H), 3.585 (s, 3H), 6.783−7.553 (m, 5 h). ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.603, 34.751, 51.548, 111.260, 114.371, 118.528, 119.127, 121.616, 121.828, 127.040, 136.280, 174.106.

***N*-Methylation of Indoline.** Three grams (25 mmol) of indoline, 1.5 g of K_2CO_3, 20 mL of DMF, and 6.4 mL (76 mmol) of DMC were mixed together and heated to reflux (around 130 °C) for 14 h. The reaction was monitored by TLC (silica gel, hexane: ethyl acetate; 8:2, R_f indoline = 0.22, R_f^1 (component 1) = 0.48, R_f^2 (component 2) = 0.36) and HPLC. After 14 h, the percent composition of the reaction mixture was as follows: indoline, 0.3%; *N*-methylindoline, 98.8% (area % HPLC). The reaction mixture was cooled to room temperature, and 50 mL of water was slowly added. The product was extracted with 60 mL of TBME, washed with 3 × 50 mL of H_2O. The product, *N*-methylindoline, was isolated as light-yellow oil by evaporating the solvent under vacuum, in 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.726 (s, 3H), 2.892−2.2.912 (m, 2 H), 3.233−3.274 (m, 2 H), 3.662 (s, 3H),), 6.454−7.606 (m, 4 h).

^{13}C NMR (400 MHz, $CDCl_3$): δ 28.652, 36.147, 56.046, 107.103, 117.655, 124.149, 127.214, 130.165, 153.304.

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