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Dual Nucleophilic Catalysis with DABCO for the N-Methylation of Indoles

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DABCO is an extremely active catalyst for the methylation of indoles in conjunction with dimethyl carbonate (DMC). This green chemistry is highly effective and produces *N*-methylindoles in nearly quantitative yields. The reaction sequence consists of competing alkylation and acylation pathways and involves 1,4-diazabicyclo[2.2.2]octane (DABCO) dually as a nucleophilic catalyst, ultimately resulting in a single product: the N-methylated indole.

Introduction

Methylation of nitrogen atoms is a versatile biological process. For example, methylation of cytosine in CpG dinucleotide governs eukaryotic gene control.[1] Epinephrine, a catecholamine neurotransmitter, is formed by the methylation of norepinephrine catalyzed by a transmethylase that utilizes *S*-adenosylmethionine as a methyl donor.[2] Nature is sophisticated and adroit in methylation: it utilizes enzymes in a highly efficient way even if the process involves unactivated methyl donors. Despite the importance of methylation, chemists seem to lack an efficient methodology in this area. We depend largely on noncatalytic processes that employ highly reactive and toxic methylating agents. *N*-Methylindole is important within nature as the common nucleus of indole alkaloids that exhibit a wide array of biological activities. For example, affinisine has been shown to produce delayed intention tremors, marked CNS depressant activity, ataxia, hypothermia, and bradypnea,[3] and a synthetic pentacyclic indole has revealed antitumor properties.[4] Common approaches to the synthesis of *N*-methylindoles typically require a two-step protocol: (1) formation of an active indole anion by a stoichiometric amount of strong base (NaH, KHMDS, KTB, or NaOH) and (2) reaction of the resulting anion with a toxic and hazardous reagent such as methyl iodide[5] or dimethyl sulfate.[6] Improved processes have been reported recently utilizing nontoxic reagents, however, under harsh and noncatalytic conditions: (1) DMC/DMF/K_2CO_3/130 °C[7] and (2) dimethyl oxalate/DMF/*t*-BuOK/153 °C.[8] Thus, development of an efficient, safe, and environmentally friendly method of methylation constitutes an important challenge. Recently, our lab discovered that the "green" reagent dimethyl carbonate (DMC) can also function effectively for the N-methylation of indoles and benzimidazoles under milder conditions if DBU is employed as the catalyst.[9] The only drawback to this method is that it demands the use of stoichiometric amounts of DBU to achieve reasonable process efficiency. Hence, we had a need to develop a more active catalyst and thereby a more efficient process. Herein, we report a novel methodology for the methylation of the indole nitrogen in nearly quantitative yields using a *catalytic* amount of DABCO under mild conditions.

Results and Discussion

DABCO, a tertiary amine base with weak basicity (pK_a = 8.7),[10] has been used as a catalyst for the Baylis–Hillman reaction.[11] It has also been employed as a catalyst for the substitution of chloropurine with alcohols.[12] On the basis of these precedents, we considered DABCO as a potential catalyst that could react with DMC to form an activated methylating reagent. The effectiveness of DABCO serving as a catalyst for the

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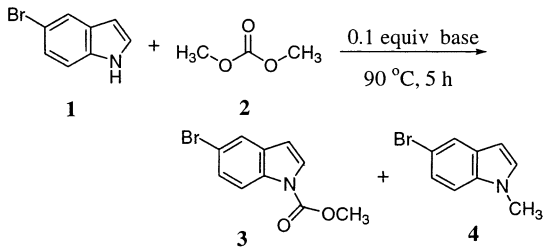
TABLE 1. Effect of Base on the Methylation Rate of 5-Bromoindole[a]



entry	base	% **1**	% **3**[b]	% **4**[b]
1	none	100	0	0
2	Bu_3N	100	0	0
3	DMAP	14	73	12
4	DBU	9	84	6
5	DABCO	0	0	>99

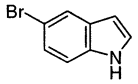
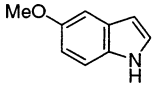
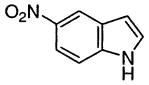
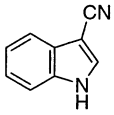
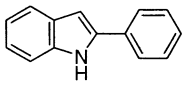
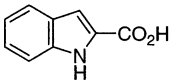
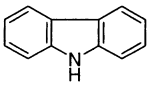
[a] All reactions were conducted on a 1 g (5 mmol) scale in 1 mL of DMF and 10 mL of DMC using 0.1 equiv of base at 90 °C. Product distributions were determined by HPLC analysis of the reaction mixture after 5 h. [b] Identity of product was confirmed by ^1H and ^{13}C NMR and MS.

methylation of indoles with DMC under mild conditions was demonstrated for the reaction of 5-bromoindole (**1**). In the presence of 0.1 equiv of DABCO, the catalytic process afforded the *N*-methyl-5-bromoindole (**4**) in nearly quantitative yield within 5 h (Table 1, entry 5). In contrast, with use of 0.1 equiv of DMAP or DBU, the same reaction affords the methylcarbamate (**3**) as the major component of the reaction mixture (Table 1, entries 3 and 4). This demonstrated that DABCO is a more effective catalyst in comparison to either DMAP or DBU. It should be noted that without any catalyst or in the presence of Bu_3N, the reaction generated no product at all (Table 1, entries 1 and 2).

We examined the structure−reactivity profile for a series of indoles, the results of which are summarized in Table 2. In all cases, isolated yields were excellent and ranged from 95 to 99%.[13] Varying the electronic properties of the substituent on the aromatic ring from electron-donating (**6**) to electron-withdrawing (**7**) enhances the methylation rate (entries 1 through 4). Increasing the steric hindrance around the nitrogen atom by introducing a phenyl group at the 2-position (**9**) slows the reaction when compared to the unsubstituted indole (entries 2 and 6). When an additional carboxylic acid functionality was present (**10**), 1.1 equiv of DABCO was employed, where the additional 1 equiv of base functioned as a proton scavenger. Under these conditions, methyl *N*-methylindole-2-carboxylate (**10b**, Chart 1) was isolated in excellent yield (entry 7). Hence, the system provided an advantage: concurrent methylation of both the indole nitrogen and a carboxylic acid group can be accomplished. This is superior to an analogous two-step process.[5a] The protocol also worked efficiently for carbazole **11**.

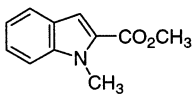
(13) All N-methylated indoles are known. For the methylated indole **1**, see: Soll, R. M.; Park, J. A.; Rimele, T. J.; Heaslip, R. J.; Wojdan, A.; Oshiro, G.; Grimes, D.; Asselin, A. *Eur. J. Med. Chem.* **1990**, *25*, 191. For methylindoles **5**, **7**, and **11**, see: ref 8. For indole **6**, see: ref 7. For indole **8**, see: Tamura, Y. Adachi, M.; Kawasaki, T.; Yasuda, H.; Kita, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1132. For indole **9**, see: ref 9. For indole **10**, see: Kitano, M.; Kojima, A.; Nakano, K.; Miyagishi, A.; Noguchi, T.; Ohashi, N. *Chem. Phar. Bull.* **1999**, *47*, 1538.

TABLE 2. DABCO-Catalyzed N-Methylation of Indoles with DMC

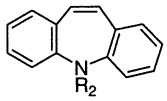
Entry	Substrate		Time(h)[a]	%Yield[b,c]
1		**1**	4	99
2		**5**	8	97
3		**6**	10	97
4		**7**	2	95
5		**8**	8	98
6		**9**	24	97
7		**10**	21[d]	95[e]
8		**11**	24	97

[a] General procedure: a reaction flask was charged with substrate (1 g), DABCO (0.1 equiv), DMF (1 mL), and DMC (10 mL). The mixture was heated to 94−95 °C, and the reaction was monitored by HPLC until trace or no starting substrate was detected (reaction time). [b] Identity of the methylated products was confirmed by ^1H and ^{13}C NMR and MS. [c] Isolated yield based on starting substrate. [d] Same as procedure in footnote a, except 1.1 equiv of DABCO was charged to the reaction mixture. [e] Isolated yield of **10b**, methyl *N*-methylindole-2-carboxylate.

CHART 1



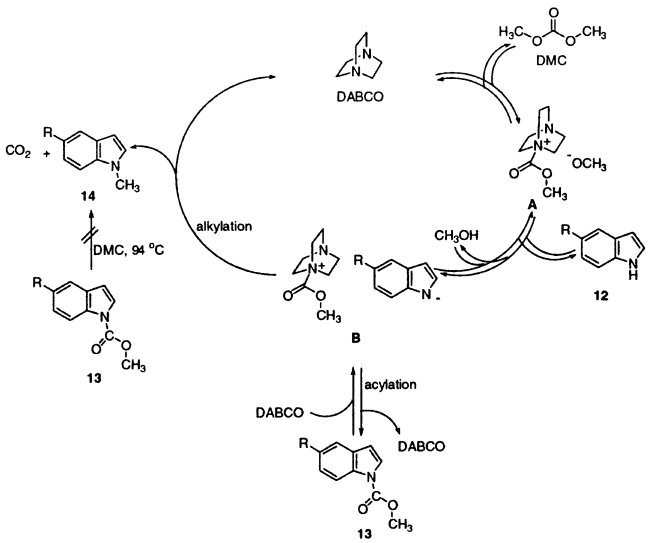
10b



15, R_2 = H
15b, R_2 = $COOCH_3$

A plausible mechanism consisting of two competing pathways, acylation and alkylation, in the catalytic cycle (Scheme 1) is proposed for the methylation of indoles. As mentioned before, a combination of indole and DMC is initially inert. However, methylation of indole with DMC was highly efficient in the presence of DABCO (Table 1, entries 1 and 5). This implied that DMC must be transformed by DABCO to an activated species that can react with indole. It is reasonable to assume that in the catalytic cycle, DABCO functions as a nucleophilic catalyst reacting with DMC to generate an ion pair **A**.[14] Deprotonation of indole **12** with the methoxide ion of **A** could lead to an indole-containing ion pair **B**. We ob-

SCHEME 1. Plausible Catalytic Cycle for Indole Methylation



served that the relative rates of methylation for 5-substituted indoles correlated to the electronegativity of the substituents and were determined in the order of: NO_2 > Br > H > OCH_3 (Table 2). In each individual methylation reaction, formation of significant amounts of a stable intermediate was observed, as indicated by HPLC analyses. These intermediates were isolated and determined to be the corresponding indole carbamates (**13**, R = Br, H, OCH_3, or NO_2) as supported by ^{1}H and ^{13}C NMR, MS, and elemental analyses. The relative rates of carbamate **13** formation were also dependent on the electronegativity of the substituents and were determined to be in the order of OCH_3 > H > Br > NO_2. It was experimentally verified that these carbamate intermediates were transformed into the methylated products **14** during the course of the reaction.

It is noteworthy that when the individual indole carbamates (**13**, R = Br, H, OCH_3, or NO_2) were heated to 94−95 °C in DMC in the absence of DABCO, no corresponding N-methylated indole **14** was produced (Scheme 1). This eliminates the possibility that a thermally induced rearrangement of carbamates **13** was responsible for the formation of *N*-methylindole **14**. However, when a catalytic amount of DABCO (0.1 equiv) was added to the same system, complete conversion to the methylated indole **14** occurred with the observed relative rate R = NO_2 > Br > H > OCH_3. Observation of small amounts (<10%) of "free" indole in the reaction mixture by HPLC during the course of conversion provided qualitative evidence for the existence of ion pair **B**, which could generate indole and DABCO when it is quenched with HPLC mobile phase. These results suggested that ion pair **B** could be involved in the indole methylation reaction. One can envision the existence of two competing pathways: an acylation step leading to the indole carbamate and an alkylation step that is responsible for the methylindole formation (Scheme 1). The acylation step may be reversible wherein DABCO functions as a nucleophilic catalyst to regenerate ion pair **B** and eventually afford methylated indole **14**. The relative rates of acylation and alkylation for the substituent series (**B**, R = Br, H, OCH_3, or NO_2) are consistent with the hardness of the nucleophiles. The preference of acylation over alkylation for 5-methoxyindolyl anions (**B**, R = OCH_3) during the reaction may result from a relatively faster reaction of the 5-methoxyindolyl anion (a hard nucleophile) with the polarized sp^2 carbonyl carbon of the carbamate (a hard electrophile) than with the sp^3 methyl carbon of the carbamate (a relatively softer electrophile).[15] On the other hand, the electron-deficient 5-nitroindolyl anion behaves as relatively a softer nucleophile due to the stabilization of its negative charge by delocalization of the charge density around nitrogen through the π system, facilitating alkylation leading to the formation of *N*-methylindole **14**.

Anion stability appears qualitatively to control the rate of the alkylation step. This accounts for the formation of iminostilbene carbamate (**15b**,[16] Chart 1) as the dominant product (90% isolated yield, 8% SM) from the carbazole analogue iminostilbene (**15**), under the same conditions: 0.1 equiv DABCO/DMC/94−95 °C. Apparently, the nonplanar butterfly form of **15**[17] inhibits delocalization of the negative charge on nitrogen into the aromatic rings.

Conclusion

In summary, we developed the first catalytic process for the N-methylation of the indole family. This protocol is efficient and affords excellent yields under mild conditions for a variety of indoles. A plausible multistep mechanism is proposed in which an alkylation pathway competes with a reversible acylation pathway and DABCO serves twice as a nucleophilic catalyst in the catalytic cycle. Mechanistic data that are available at this point do not permit quantitative verification of this hypothesis. Further mechanistic studies are required to elucidate the details of the mechanistic pathway(s) leading to the methylation product.

Experimental Section

All reagents and solvents were purchased from commercial suppliers and used without further purification. All *N*-methylindoles **1** and **5**−**11** are known compounds.[13] The identity of the methylated products was confirmed by ^{1}H and ^{13}C NMR and MS spectra. Solvents used were of technical grade. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. DCI used a robotic probe (Scientific Instrument Services) with reagent-grade ammonia gas. HPLC analyses were performed on a Waters HPLC system with a 996 PDA detector and Waters Symmetry Shield RP_8 column (5 μm, 3.9 × 150 mm) at 40 °C.

General Procedure for the Methylation of Indoles with DMC. A reaction flask was charged with an indole

(14) A nucleophilic catalysis mechanism involving DBU was proposed for the esterification of carboxylic acid with DMC. Shieh, W.; Dell, S.; Repič, O. *J. Org. Chem.* **2002**, *67*, 2188.

(15) For the hard−soft acid−base concept and definition, see: (a) Carey, F. A.; Sundberg, R. J. Nucleophilic Substitution. In *Advanced Organic Chemistry*, 2nd ed.; Plenum Press: New York, 1984; Part A, Chapter 5. (b) Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.

(16) Compound **15b**: IR (KBr) 1711 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30−7.41 (m, 8H), 6.92 (s, 2H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.5, 134.2, 132.1, 130.6, 130.2, 129.1, 128.5, 127.4, 53.1; EIMS *m*/*z* 251 (M^+). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 77.00; H, 5.14; N, 5.55.

(17) Reetz, M. T.; Hutte, S.; Goddard, R.; Minet, U. *J. Chem. Soc., Chem. Commun.* **1995**, 275.

substrate (1 g), 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.1 equiv), DMF (1 mL), and dimethyl carbonate (10 mL). The mixture was heated to 94−95 °C, and the reaction was monitored by HPLC until a total conversion to the respective methylindole was detected. The reaction was cooled to room temperature and diluted with EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated and washed in sequence with H_2O (50 mL), 10% aqueous citric acid (2 × 50 mL), and H_2O (4 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to give the corresponding *N*-methylindole.

General Procedure for the Preparation of Indole Carbamates. A solution of indole or 5-substituted indoles (1 g) and 10 mL of dimethyl carbonate at 94 °C was instantaneously charged with a solution of of 1,4-diazabicyclo[2.2.2]-octane (DABCO, 0.1 equiv) in 1 mL of DMF. The reaction was stirred at 94 °C for a specified period of time as follows: **1** (10 min), **5** (10 min), **6** (10 min), and **7** (5 min). The reaction mixture was rapidly cooled to 23 °C and concentrated under vacuum. The resulting crude product was purified by flash chromatography (silica gel, 9:1 hexanes/EtOAc).

Indole-1-carboxylic Acid Methyl Ester (13a, R = H). Colorless oil: IR (KBr) 1741 (s) cm^{-1}; ^1H NMR[18a] ($CDCl_3$) δ 8.18 (d, J = 7.9 Hz, 1H), 7.53−7.58 (m, 2H), 7.32 (ddd, J = 7.2, 7.2, 1.1 Hz, 1H), 7.23 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 6.57 (dd, J = 3.8, 0.8 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR[18b] ($CDCl_3$) δ 151.5, 135.2, 130.4, 125.5, 124.5, 123.0, 121.0, 115.1, 108.1, 53.7; (DCI−NH_3) m/z 176 $(M + H)^+$. Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.83; H, 5.17; N, 8.06.

5-Nitroindole-1-carboxylic Acid Methyl Ester (13b, R = NO_2). Off-white solid: mp 162−165 °C; IR (KBr) 1734 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.64 (d, J = 2.2 Hz, 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.30 (dd, J = 9.2, 2.3 Hz, 1H), 7.97 (d, J = 3.8 Hz, 1H), 7.02 (d, J = 3.9 Hz, 1H), 4.18 (s, 3H); ^{13}C NMR (acetone-d_6) δ 151.0, 144.2, 138.5, 130.8, 129.2, 119.6, 117.5, 115.4, 108.8, 54.3; (DCI−NH_3) m/z 220 (M^+). Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.40; H, 3.65; N, 12.64.

5-Bromoindole-1-carboxylic Acid Methyl Ester (13c, R = Br). White solid: mp 63−65 °C; IR (KBr) 1741 cm^{-1}; ^1H NMR (CD_3CN) δ 8.23 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 3.8 Hz, 1H), 7.61 (dd, J = 8.8, 2.0 Hz, 1H), 6.80 (d, J = 3.6 Hz, 1H), 4.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.7, 133.6, 132.0, 126.8, 126.6, 123.2, 116.1, 115.2, 106.6, 53.4; (DCI−NH_3) m/z 253 (M^+). Anal. Calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51; Br, 31.45. Found: C, 47.29; H, 3.16; N, 5.41; Br, 31.43.

5-Methoxyindole-1-carboxylic Acid Methyl Ester (13d, R = OCH_3). White solid: mp 82−85 °C; IR (KBr) 1729 (s) cm^{-1}; ^1H NMR (CD_3CN) δ 8.02 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 3.7 Hz, 1H), 7.11 (d, J = 2.6 Hz, 1H), 6.93 (dd, J = 9.0, 2.6 Hz, 1H), 6.58 (dd, J = 3.7, 0.4 Hz, 1H), 3.98 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (CD_3CN) δ 155.8, 151.0, 131.1, 129.4, 126.0, 115.2, 112.7, 107.3, 103.1, 54.8, 53.2; (DCI−NH_3) m/z 206 $(M + H)^+$. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.56; H, 5.18; N, 8.00. Found: C, 64.37; H, 5.27; N, 6.80.

General Procedure for the Conversion of Indole Carbamates into *N*-Methylindoles. A solution of indole carbamate or 5-substituted indole carbamate (100 mg) and 1 mL of dimethyl carbonate at 94 °C was instantaneously charged with a solution of of 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.1 equiv) in 100 μL of DMF. The reaction mixture was stirred at 94 °C and analyzed by HPLC periodically until the conversion to the corresponding *N*-methylindole was complete.

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