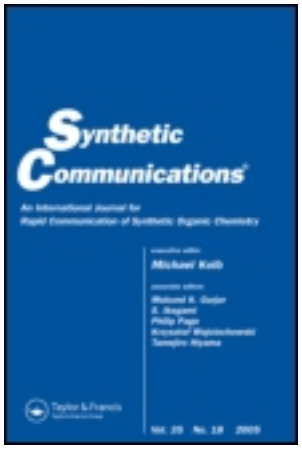

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N-Methylation of NH-Containing Heterocycles with Dimethyl Carbonate Catalyzed by TMEDA

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N-METHYLATION OF NH-CONTAINING HETEROCYCLES WITH DIMETHYL CARBONATE CATALYZED BY TMEDA

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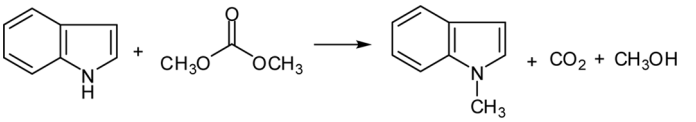
GRAPHICAL ABSTRACT



Abstract *A practical method for N-methylation of NH-containing heterocycles using an environmentally safe and less toxic methylating reagent, dimethyl carbonate, has been developed. N,N,N′,N′-tetramethylethylenediamine (TMEDA), an extremely active organocatalyst for the methylation of imides, indoles, benzimidazoles, and piperazines in conjunction with dimethyl carbonate, can lead to N-methylation products with high conversion. The reaction sequence consists of competing alkylation and acylation pathways and involves TMEDA as a nucleophilic catalyst. A possible reaction mechanism is discussed based on the reaction results.*

Keywords Dimethyl carbonate; methylation; NH-containing heterocycles; TMEDA

INTRODUCTION

Methylation, of nitrogen atoms in particular, is an important reaction in organic synthesis. It is widely used in the synthesis of natural compounds with biological activity.[1,2] Classic N-methylation reagents are methyl iodide and dimethyl sulfate, which are highly toxic and their use should be restricted.[3,4] Dimethyl carbonate (DMC) as a methylating reagent for NH-containing heterocycles is an attractive alternative.[5] In the N-methylation of NH-containing heterocycles, reactions of indoles,[6] imidazoles,[7] and pyrazoles[8] with DMC have been reported. However, the use of this "green chemical" (DMC) as a methylating reagent often requires high temperatures and long reaction times, because the reactivity of DMC at moderate temperatures can be significantly less than that of methyl iodide or dimethyl sulfate. Another problem that is associated with the use of DMC is its dual behavior as a methylating reagent and as a carbamoylating reagent can lead to poor

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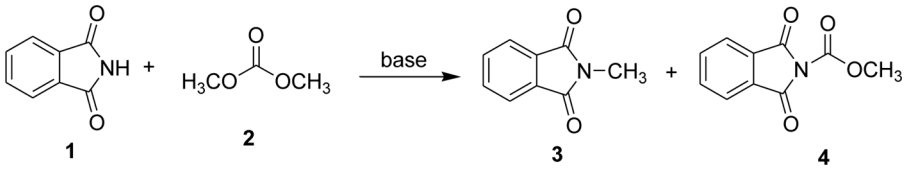
selectivity toward the desired N-methyl derivatives. In this respect, catalysis also can be a way to achieve selectivity when using DMC. Recently, the use of nucleophilic tertiary amines, such as 1,4-diazabicyclo[2.2.2]octane (DABCO)[9] and dimethylaminopyridine (DMAP),[10] as suitable organocatalysts for the N-methylation of indoles and 2,4-diaminotoluene were also reported. In some cases, a phase-transfer catalyst was also employed in these reactions.[11] However, limited substrates were used in these studies. Here we present an efficient method for N-methylation of NH-containing heterocycles with DMC using a catalytic amount of N,N,N′,N′-tetramethylethylenediamine (TMEDA) under mild conditions.

RESULTS AND DISCUSSION

TMEDA, a cheap and convenient reagent, is a tertiary amine base with weak basicity (pKa = 9.4).[12] The effectiveness of TMEDA as the organocatalyst for methylation of NH-containing hetercyclic compounds under mild conditions was demonstrated for the reaction of phthalimide with dimethyl carbonate. In the initial studies, we chose phthalimide as our model compound to study this reaction, because the product, N-methylphthalimide, is solid and easy to purify. As depicted in Scheme 1, the reaction between phthalimide substrate and DMC in the presence of a base was accomplished by heating the reagents in dimethylformamide at 95 °C for 8 h. In the presence of 0.1 equiv of TMEDA, the process afforded the N-methyl phthalimides in 8 h with 95% yield. In contrast, with 0.1 equiv of triethylamine, the yield of N-methylphthalimides is 69% and 28% recovered starting material. This demonstrated that TMEDA is a more effective catalyst than triethylamine. It should be noted that without any catalyst, the reaction generated no product at all. Trimethylamine hydrochloride does not play a catalytic role in this reaction (Table 1. entries 1 and 2).

With a catalytic amount of TMEDA ($\leq$10 mmol% based on phthalimide), phthalimide reacted with DMC to give N-methylphthalimide (Fig. 1). As shown in Fig. 1, increasing the amount of TMEDA led to a sharp increase of the yield first and then to a steady state. The yield approached 95% when using 10 mol% of TMEDA.

To futher illustrate the utility of this method for NH-containing heterocyclic compounds, a series of substrates were applied to this protocol, the results of which are summarized in Table 2. In some cases, isolated yields were good and ranged from 60% to 90%. Benzotriazole (**12**) affords a mixture of N-methylation product **13** as well as N-carbamoylation product **14** in a ratio of 1.5:1 (Scheme 2). A possible explanation is that a more acidic NH will lead to a high carbamoylation product, since the pKa of **12** is ~8.6[13] and the pKa of **1** is ~14.6.[14]



Scheme 1. Reaction of phthalimide and DMC.

Table 1. Effect of base on the methylation rate of phthalimide with dimethyl carbonate

Entry	Catalyst	**1** (%)	**3**[c] (%)	**4** (%)
1[a]	None	100[b]	0	0
2	Me_3N HCl	100	0	0
3	Et_3N	28	69	0
4	Bu_3N	37	60	0
5	TMEDA	0	95	0

[a]All reactions were conducted on a 1.5 g (10 mmol) scale in 5 mL of DMF and 10 mL of DMC using 0.1 equiv of base at 95 °C. The reaction time is 8 h.

[b]Yields are based on isolated products.

[c]Products were characterized by their physical constants, comparison with authentic samples, and ^{1}H NMR and MS spectroscopy.

We believe that TMEDA functions as a catalyst in our methylation protocol. A plausible mechanism for NH-containing compounds is proposed in Scheme 3, in which TMEDA performs as a nucleophilic catalyst. In the catalytic cycle, TMEDA reacts with DMC to generate a more activated methylating agent, which presumably reduces that activation energy required for methylation. A mechanistic study in our laboratory to clarify the pathways for methylation employing DMC/TMEDA is under way.

CONCLUSIONS

In summary, we have presented an efficient method for N-methylation of NH-containing hetercycles with DMC under conventional thermal conditions by employing TMEDA as an organocatalyst. TMEDA has high catalytic activities under mild reaction conditions. Although our data are preliminary, this protocol provides a practical and environmentally friendly process for an important chemical

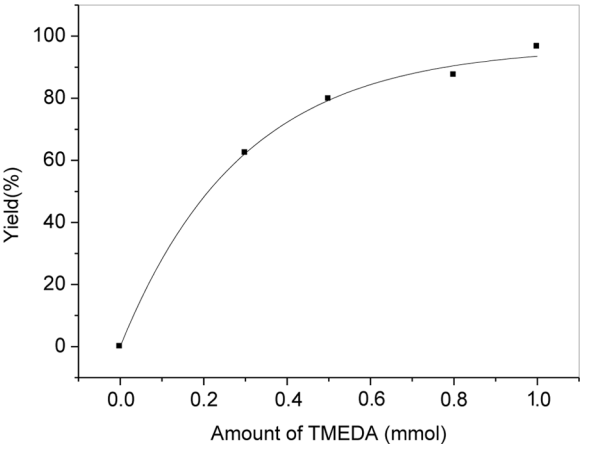
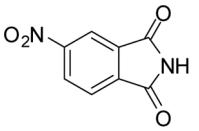
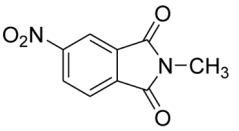
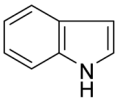
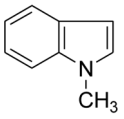
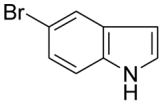
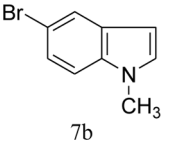
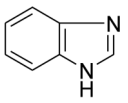
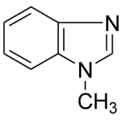
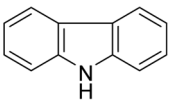
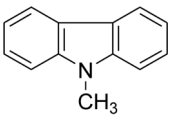
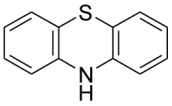
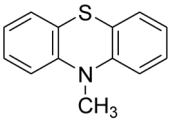
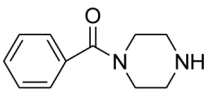
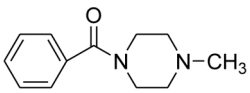
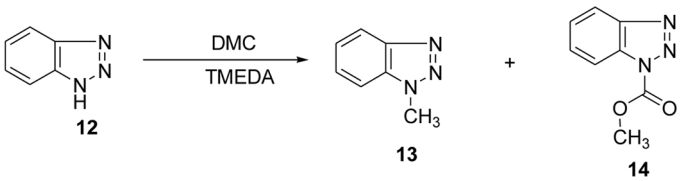


Figure 1. Effect of catalyst amount. Reaction conditions: Phthalimide, 10 mmol; DMF, 5 mL; DMC, 10 mL; reaction time, 8 h; temperature, 95 °C.

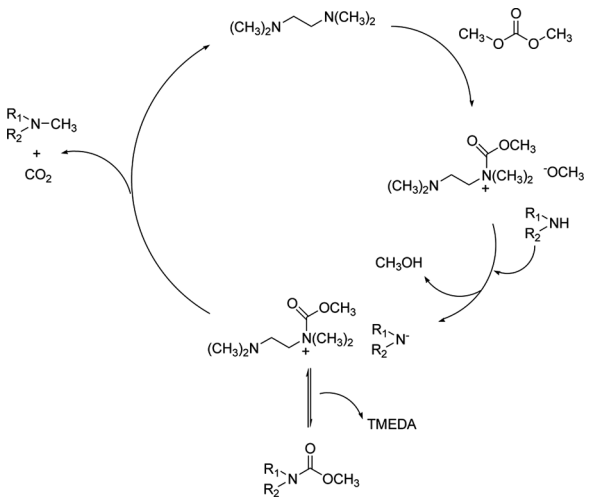
Table 2. N-Methylation of NH-containing heterocyclic compounds with dimethyl carbonate catalyzed by TMEDA[a]

Entry	N-Heterocycles	Product	Time (h)	Yield (%)[b]
1	 5a	 5b	12	86
2	 6a	 6b	8	89
3	 7a	 7b	9	87
4	 8a	 8b	9	90
5	 9a	 9b	8	86
6	 10a	 10b	12	72
7	 11a	 11b	8	60

[a]Reaction conditions: N-heterocycles, 10 mmol; DMC, 10 mL; DMF, 5 mL; TMEDA, 1 mmol; 95 °C.
[b]Isolated yield.



Scheme 2. Reaction of benzotriazole and DMC in the presence of TMEDA.



Scheme 3. Plausible catalytic cycle for NH methylation catalyzed by TMEDA.

transformation. Futher mechanistic studies are required to elucidate the details and mechanistic pathways leading to the methylation product.

EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Products were characterized by their physical constants, comparison with authentic samples, and ^{1}H NMR and mass (MS) spectroscopy. Melting points were determined with a RY-1 apparatus and were uncorrected. ^{1}H NMR spectra were recorded using a Bruker AV 400-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Electron impact (EI) mass spectra were obtained on a HP 5973 MS instrument. The purity determination of substrates and reaction monitoring were accompanied by thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates and high-performance liquid chromatography (HPLC) analysis. All the products were known compounds, and the data of mp and ^{1}H NMR accord with those reported in the literature.

Typical Procedure for the Reaction of NH-Containing Heterocycles with Dimethyl Carbonate Catalyzed by TMEDA

In a typical procedure, a mixture of the NH-containing heterocycles (10 mmol), TMEDA (1 mmol), DMC (10 mL), and DMF (5 mL) was stirred and heated to 95 °C for the specified time. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the mixture was cooled to room temperature, and water (8 mL) was added. After extraction with EtOAc (15 mL × 2), the organic phase was washed with water (10 mL × 2) and dried over $NaSO_4$. The solvent was removed, and the residue was recrystallized from ethanol to yield the specified

product. All the products were known compounds, and the data of mp and ^{1}H NMR accord with those reported in the literature.

Selected Data

N-Methylphthalimide (3)[15]. Mp: 130–132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.22 (s, 3H, CH_3), 7.73–7.76 (m, 2H, Ar-H), 7.86–7.89 (m, 2H, Ar-H). MS (EI, m/z): 161 $[M]^+$.

4-Nitro-N-methylphthalimide (5b)[16]. Mp: 178–180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H, CH_3), 7.96 (d, $J = 8.1$ Hz, 1H, Ar-H), 8.52 (d, $J = 8.1$ Hz, 1H, Ar-H), 8.60 (s, 1H, Ar-H). MS (EI, m/z): 206 $[M]^+$.

1-Methyl-1H-indole (6b)[17]. Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75 (s, 3H, CH_3), 6.46 (d, $J = 3.8$ Hz, 1H, Ar-H), 7.01 (d, $J = 3.8$ Hz, 1H, Ar-H), 7.08–7.11 (m, 1H, Ar-H), 7.20–7.22 (m, 1H, Ar-H), 7.28 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.61 (d, $J = 8.1$ Hz, 1H, Ar-H). MS (EI, m/z): 131 $[M]^+$.

1-Methyl-5-bromo-1H-lindole (7b)[18]. Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H, CH_3), 6.43 (d, $J = 3.4$ Hz, 1H, Ar-H), 7.03 (d, $J = 3.4$ Hz, 1H, Ar-H), 7.16 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.28 (dd, $J = 8.8$ Hz, $J = 1.8$ Hz, 1H, Ar-H), 7.76 (d, $J = 1.8$ Hz, 1H, Ar-H). MS (EI, m/z): 210 $[M]^+$.

1-Methyl-1H-benzimidazole (8b)[19]. Mp: 60–61 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 3H, CH_3), 7.29–7.35 (m, 2H, Ar-H), 7.41–7.43 (m, 1H, Ar-H), 7.83 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.90 (s, 1H, Ar-H). MS (EI, m/z): 132 $[M]^+$.

9-Methyl-9H-carbazole (9b)[20]. Mp: 80–82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H, CH_3), 7.18 (t, $J = 8.6$ Hz, 2H, Ar-H), 7.33 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.40 (t, $J = 8.6$ Hz, 2H, Ar-H), 8.03 (d, $J = 7.8$ Hz, 2H, Ar-H). MS (EI, m/z): 181 $[M]^+$.

10-Methyl-10H-phenothiazine (10b)[21]. Mp: 97–99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39 (s, 3H, CH_3), 6.74–7.21 (m, 8H, Ar-H). MS (EI, m/z): 213 $[M]^+$.

1-Benzoyl-4-methylpiperazine (11b)[22]. Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H, CH_3), 2.38 (brs, 4H, CH_2), 3.39 (brs, 2H, CH_2), 3.72 (brs, 2H, CH_2), 7.28–7.34 (m, 5H, Ar-H). MS (EI, m/z): 204 $[M]^+$.

1-Methyl-1H-benzotrazole (13)[23]. Mp: 60–62 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 4.29 (s, 3H, CH_3), 7.35–7.40 (m, 1H, Ar-H), 7.48–7.53 (m, 2H, Ar-H), 8.02–8.08 (m, 1H, Ar-H). MS (EI, m/z): 133 $[M]^+$.

1H-Benzotriazole-1-carboxylic acid methyl ester (14)[24]. Mp: 78–80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 4.45 (s, 3H, CH_3), 7.19–7.33 (m, 2H, Ar-H), 7.77–7.82 (m, 2H, Ar-H). MS (EI, m/z): 177 $[M]^+$.

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