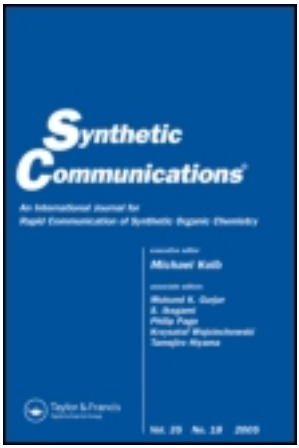

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N-Methylation of Nitrogen-Containing Heterocycles with Dimethyl Carbonate

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Abstract: Reactivity of dimethyl carbonate, the environmentally friendly reagent, as methylating agent for nitrogen-containing heterocyclic compounds has been studied. Reactions of imidazole, pyrazole, pyrrole, morpholine, and piperazine with dimethyl carbonate to afford N-methylated products were reported. The reactions were carried out with neither catalyst nor solvent at a temperature range of 110–170°C under atmospheric pressure.

Keywords: Dimethyl carbonate, imidazole, methylation, morpholine, NH-containing heterocycles, piperazine, pyrazole, pyrrole

N-Methylation of NH-containing heterocyclic compounds is an important reaction in organic synthesis. Conventionally, methyl halides[1,2] or dimethyl sulfate[3,4] were used as methylating agents. Those processes involve not only the use of highly toxic reagents but also generate a stoichiometric amount of salt to be disposed of. In view of these disadvantages, an environmentally benign reagent with an efficient process that is easy to scale up is very desirable.

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Address correspondence to Sophie Thiébaud, Laboratoire de Chimie Agro-industrielle, UMR 31010 INRA/INP-ENSIACET 118 route de Narbonne, 31077, Toulouse cedex 4, France. Tel.: +33-5-62-88-57-20; Fax: +33-5-62-88-57-30. E-mail: Sophie.ThiebaudRoux@ensiacet.fr

Recently, dimethyl carbonate (DMC) was reported to be a potential harmless and versatile methylating reagent.[5–7] In the N-methylation of NH-containing heterocycles, the reaction of indoles,[8,9] xanthine,[10] uracils,[11] thiamine,[11] and imidazoles[12] with DMC have been reported. All those reactions were carried out in the presence of a catalyst, which is an organic or inorganic base. In some cases a phase-transfer catalyst was employed.[10–12]

We report herein a simple process for N-methylation of various aromatic and nonaromatic NH-containing heterocyclic compounds with DMC in the absence of either a catalyst or a solvent, except for the N-methylation of pyrrole.

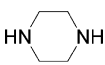
RESULTS AND DISCUSSION

The reactions were carried out under atmospheric pressure at a temperature ranging from 110°C to 170°C depending upon nature of substrate. DMC, a low-boiling-point reagent (bp = 90°C) was loaded progressively into the preheated reactor containing another substrate. During the reaction, a low-boiling-point by-product, methanol, and the excess of DMC were immediately distilled from the reaction medium. The reactor was therefore equipped with a suitable distillation column enabling a good separation of methanol from dimethyl carbonate.[13]

Table 1 shows that the N-methylation of imidazole at 170°C leads to quantitative yield of N-methylimidazole. For the N-methylation of pyrazole, a better yield of N-methylpyrazole was obtained at 140°C because on one hand, when this reaction was operated at a higher temperature, the DMC concentration in the liquid phase is nearly null as a result of operation at atmospheric pressure. On the other hand, at lower temperature, the rate of N-methylation is too slow and the formation of by-products increases. At the same time, the N-methylation of nonaromatic NH-containing heterocyclic morpholine and piperazine with DMC takes place in the absence of catalyst even at 110°C to yield 67% and 29% of N-methylmorpholine and 1-methylpiperazine respectively. In the case of morpholine, the selectivity toward N-methylation was 81% and the main by-product was N,N-carbonyl-dimorpholine whereas in the case of piperazine selectivity was only 60% and the main by-product was 1,4-dimethylpiperazine.

However, no reaction takes place when pyrrole was allowed to react with DMC at 120°C in the absence of a catalyst. The low basicity of pyrrole would certainly explain its nonreactivity. When a catalytic amount of tetrabutyl-ammonium bromide (TBAB) was added, the reaction occurred and led mainly to methyl-1-pyrrolecaboxylate and 1-methylpyrrole. After 24 h of reaction at 120°C total conversion of pyrrole was attained and the reaction yielded 36% and 51% of 1-methylpyrrole and methyl-1-pyrrolecaboxylate respectively. This poor selectivity toward N-methylation is probably due to low reaction temperature.[14] We also observed that when this reaction was carried out at 110°C, the selectivity of N-methylation drops from 36% to

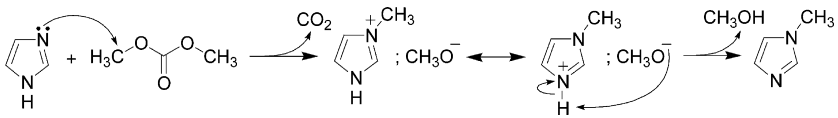
Table 1. Effect of reaction conditions on yield and on MHSVb of the reaction of heterocycles *N*-methylation with dimethyl carbonate

	Physical properties		Reaction conditions and results				
Substrates	bp (°C)	pK_a[a]	T (°C)	MHSV[b] (h^{-1})	Time (h)	Conversion (%)	Yield (%)
	255	7.0	170	0.2	9	100	98
	186	2.5	140	0.2	8	74	69
	204		140	0.2	8	85	43/39[c]
	218		140	0.2	8	60	57
	131	−4.0	120	0.1	24[d]	100	36
	129	5.7	110	0.4	10	82	67
	146	4.2	110	0.2	10	48	29

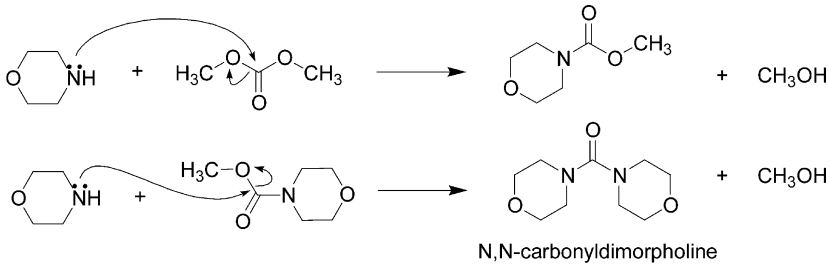
[a] pK_a of protonated form.
[b] Molar hourly space velocity per mole of NH-containing substrate.
[c] Molar ratio 1,3-dimethylpyrazole/1,5-dimethylpyrazole.
[d] Reaction was carried out in the presence of a catalytic amount of tetrabutylammonium bromide (8% molar).

only 4% whereas that of N-methoxycarbonylation increases from 51% to 92%. However, at 110°C the conversion rate of pyrrole is divided by two.

As the reactions of imidazole, pyrazole, morpholine, and piperazine with DMC take place without a catalyst, we suggest that the electronic loan pair on nitrogen would be basic enough to react directly with DMC through B_{Al}-2 mechanism resulting N-methylated product (Scheme 1) or through B_{Ac}-2, resulting in a N-methoxycarbonylated product (Scheme 2). Also, reaction



Scheme 1. Plausible mechanism of methylation of imidazole with DMC (B_{Al}-2 mechanism).



Scheme 2. Formation of by-product, N,N-carbonyldimorpholine, via B_{Ac}-2 mechanism.

temperature plays an important role in the orientation toward one of these mechanisms. Methylation is favored while temperature rises.

CONCLUSION

DMC is a convenient reagent for N-methylation of basic NH-containing heterocycles. The absence of catalyst and high selectivity toward methylation at high temperatures enables DMC to replace toxic dimethyl sulfate or methyl halides. For high-boiling-point starting material, the reaction can even be carried out at atmospheric pressure by progressively loading and withdrawing DMC and methanol respectively. However, reaction in a sealed tube or in a high-boiling-point solvent would be the solution to raise temperature for the methylation of a low-boiling-point compound. Therefore, DMC provides an alternative clean and easy route to N-methylated nitrogen-containing heterocyclic.

EXPERIMENTAL

Methods

N-methylation of imidazole: A 100-ml reactor equipped with a mechanical stirrer and a distillation column ($l = 200$ mm, $\phi = 15$ mm) was loaded with 34.02 g (0.5 mol) of imidazole. The reactor was heated to 170°C. Once it attained 170°C, DMC was progressively fed into the reactor with a velocity of $9\,g \cdot h^{-1}$ ($0.1\,mol \cdot h^{-1}$) during 9 h. Methanol and the excess of DMC were withdrawn at the end of the distillation column to maintain the reaction temperature constant at 170°C. After reaction, 1-methylimidazole was purified by distillation.

The other syntheses were carried out according to this experimental procedure.

Data

1-Methylimidazole: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.24 (s, 3H), 6.48 (s, 1H), 6.61 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 32.8, 119.9, 128.6, 137.4.

1-Methylpyrazole: ^{1}H NMR (200 MHz, DMSO, d_6) δ (ppm): 3.73 (s, 3H), 6.16 (t, $J = 2.0$ Hz, 1H), 7.36 (d, $J = 1.6$, 1H), 7.57 (d, $J = 2.2$, 1H); ^{13}C NMR (50 MHz, DMSO, d_6) δ (ppm): 47.9, 104.8, 130.0, 138.3.

1,3-Dimethylpyrazole: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.86 (s, 3H), 3.34 (s, 3H), 5.57 (d, $J = 1.9$ Hz, 1H), 6.78 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.2, 38.0, 104.8, 130.4, 147.9.

1,5-Dimethylpyrazole: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.80 (s, 3H), 3.24 (s, 3H), 5.57 (d, $J = 1.9$ Hz, 1H), 6.92 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 10.6, 35.5, 104.7, 137.5, 137.8.

1,3,5-Trimethylpyrazole: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.79 (s, 6H), 3.80 (s, 3H), 5.84 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 7.5, 14.1, 34.4, 106.3, 143.9, 150.0.

1-Methylpyrrole: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.03 (s, 3H), 6.73 (t, $J = 2.0$ Hz, 2H), 7.09 (t, $J = 2.0$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 36.1, 108.7, 122.0.

4-Methylmorpholine: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H), 2.40 (t, $J = 4.6$ Hz, 4H), 3.71 (t, $J = 4.8$ Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 45.8, 54.9, 66.2.

1-Methylpiperazine: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.46 (s, 1H), 2.26 (s, 3H), 2.37 (s, 4H), 2.88 (t, $J = 2.4$ Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 46.1, 46.7, 56.5.

1,4-Dimethylpiperazine: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 6H), 2.44 (s, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 46.1, 55.0.

Methyl 1-pyrrole carboxylate: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.95 (s, 3H), 6.36 (t, $J = 2.4$ Hz, 2H), 7.40 (t, $J = 2.4$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 53.8, 112.5, 120.0, 150.9.

N,N-Carbonyldimorpholine: ^{1}H NMR (200 MHz, D_2O) δ (ppm): 3.02 (s, 8H), 3.30 (s, 8H); ^{13}C NMR (50 MHz, D_2O) δ (ppm): 64.5, 68.8, 165.1.

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