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The Reaction of Dialkyl Carbonates with *o*-Aminophenol Catalysed by K_2CO_3: A Novel High-Yield Synthesis of *N*-Alkylbenzoxazol-2-ones

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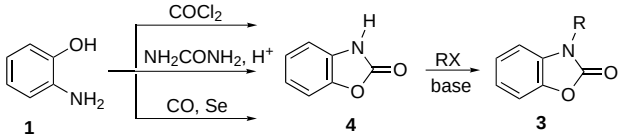
Abstract: At 130–150 °C and in the presence of catalytic K_2CO_3, *o*-aminophenol (**1**) readily reacts with dialkyl carbonates (**2**: $ROCO_2R$; **2a**: R = Me, **2b**: Et, **2c**: Allyl, **2d**: Bn) to give the corresponding *N*-alkylbenzoxazol-2-ones (**3a**–**d**) in high yields (88–98%). This reaction is a rare example where dialkyl carbonates may simultaneously act as carbonylating and alkylating agents likely through a $B_{Ac}2/B_{Al}2$ sequence. Moreover, compounds **2a**–**c** serve also as solvents. In the case of **2d**, 1,2-dimethoxyethane (DME) is the reaction medium.

Key words: alkylations, allylations, benzylations, carbonylations, catalysis

Introduction

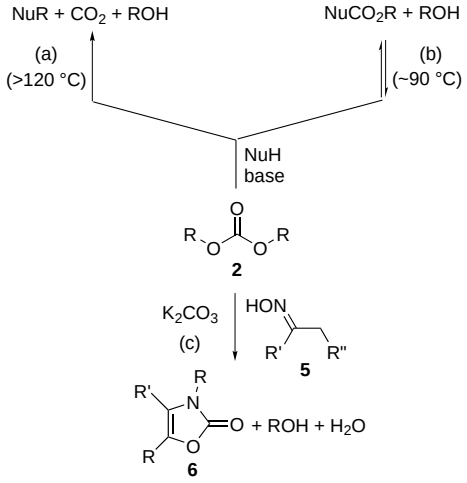
N-alkylbenzoxazol-2-ones **3** are intermediates of widespread use for the synthesis of analgesics, pesticides, herbicides, and more recently, of new classes of anticonvulsants.[1] In most cases, the preparation of compounds **3** is achieved through a two steps sequence, i.e. the carbonylation of *o*-aminophenol (**1**) with phosgene, urea or CO, followed by the *N*-alkylation of the resulting benzoxazol-2-ones **4** with an alkyl halide (RX, Scheme 1).[1,2]



Scheme 1 Conventional syntheses of *N*-alkylbenzoxazol-2-ones (**3**); R = alkyl, allyl, benzyl

These procedures, though efficient, pose environmental and operational concerns since highly harmful and/or corrosive reagents are used.[3]

A safer and eco-friendly alternative can be conceived with the use of non toxic dialkyl carbonates (**2**: $ROCO_2R$).[4] These compounds are versatile electrophiles and may serve for both alkylations and alcoxycarbonylations,[3b,5] although however, these two reactions are often discriminated by the temperature [Scheme 2 path (a) and (b): $B_{Al}2$ and $B_{Ac}2$ mechanisms, respectively].[6]

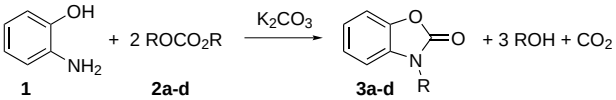


Scheme 2 Base-promoted reactions of dialkyl carbonates with a generic nucleophile [NuH: ArOH, $ArOCH_2X$, $ArCH_2X$, X = CN; CO_2R; path (a) and (b)] and with oximes [path (c)]

Dialkyl carbonates simultaneously act as alcoxycarbonylating and alkylating agents in only a few instances. Among them, the case of oximes with an α-CH_2 group [**5**: $R''CH_2C(=NOH)R'$] was reported by us for the synthesis of *N*-alkyloxazolinones (**6**) [path (c)].[7] Compounds **5** were formed via two reactions of *O*-alkoxycarbonylation and *N*-alkylation, respectively.

More recently, also the preparation of **3a** (R = Me) from *o*-aminophenol and dimethyl carbonate was claimed with catalytic $Pb(AcO)_2$, but this Lewis-acidic catalysis involved a completely different mechanism.[1b]

In this paper, we wish to report that in the presence of catalytic K_2CO_3, the reaction of *o*-aminophenol (**1**) with dialkyl carbonates represents a novel example in which an uncommon $B_{Ac}2/B_{Al}2$ sequence [analogous to path (c) of Scheme 2] takes place: *N*-alkylbenzoxazol-2-ones (**3**) are obtained in high yields (88–98%) (Scheme 3).



R = Me (**3a**), Et (**3b**), Allyl (**3c**), Bn (**3d**)

Scheme 3 The reaction of *o*-aminophenol with dialkylcarbonates and K_2CO_3

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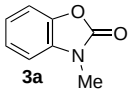
Results and Discussion

Initial experiments were carried out using the lightest compound in the carbonate series, dimethyl carbonate (DMC, **2a**: $MeOCO_2Me$). A mixture of *o*-aminophenol (0.5 g, 4.6 mmol), DMC (30 mL), and K_2CO_3 (1.27 g, 9.0 mmol) was made to react at temperatures of 90 °C, 110 °C, and 130 °C and for different time intervals. In particular, reactions run above the boiling point of DMC (90 °C), were performed in a stainless steel autoclave of 150 mL. At 130 °C, two experiments were also carried out in the presence of DME (5 mL) and *N*,*N*-dimethylformamide (DMF, 5 mL) as co-solvents. Results are reported in Table 1.

Table 1 The Reaction of *o*-Aminophenol with Dimethyl Carbonate

Entry[a]	Time (h)	Temp (°C)	Co-solvent	Product Yield[b] (%)
				 **3a**
1	9	90		11
2	18	90		48
3	28	90		63
4	48	90	None	83
5	3	110		14
6	3	130		23
7	15	130		74
8	27	130	DME	89
9	15	130	DMF	37

[a] Entries 1–4: reactions run in a glass apparatus; entries 5–9: reactions run in an autoclave; entries 8 and 9: DME (5 mL) and DMF (5 mL) were used, respectively.
[b] Isolated yield of **3a**.

At 90 °C, the effect of reaction time is evident (entries 1–4): from 9–48 h, the yield of **3a** increases progressively from 11% to 83%. The enhancement of the temperature allows faster reactions with unaltered selectivity: at 130 °C, after 15 hours, **3a** is isolated as a sole product in a 74% yield (entry 7). Under these conditions (130 °C, 15 h), a further improvement is achieved in the presence of DME as a co-solvent (entry 8: Y = 89%): this behavior is reasonable due to a moderate increase of the solubility of the base (K_2CO_3) and/or the reactant anion [(*o*-$H_2N)C_6H_4O^-K^+$] in the DMC–DME mixture with respect to DMC alone.[8] In the case of DMF co-solvent, the unsatisfactory outcome (entry 9: Y = 37%), is not attributable to a drop in the reaction conversion, but rather to the difficulty in the separation of the high-boiling co-solvent from the product.

The effect of the base was then investigated. Two sets of reactions were performed using solutions of *o*-aminophenol (0.5 g, 4.6 mmol) in DMC (30 mL), to which different amounts of K_2CO_3 – in the range of 0.1–2.0 molar equivalents with respect to the substrate – were added. Experiments were run for 18 hours and 16 hours, at 90 °C and 130 °C, respectively. At 130 °C, DME (5 mL) was always used as a co-solvent. Results are reported in Figure 1.

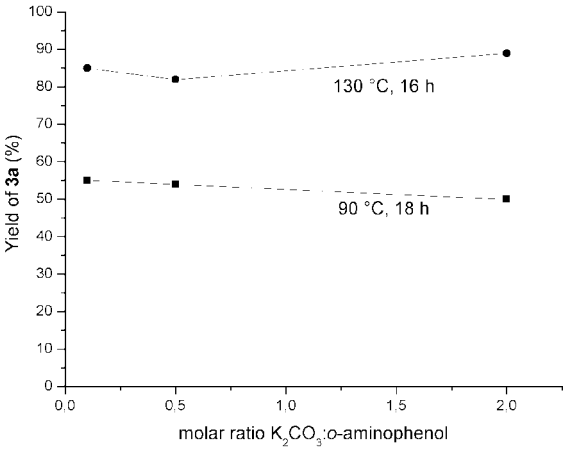


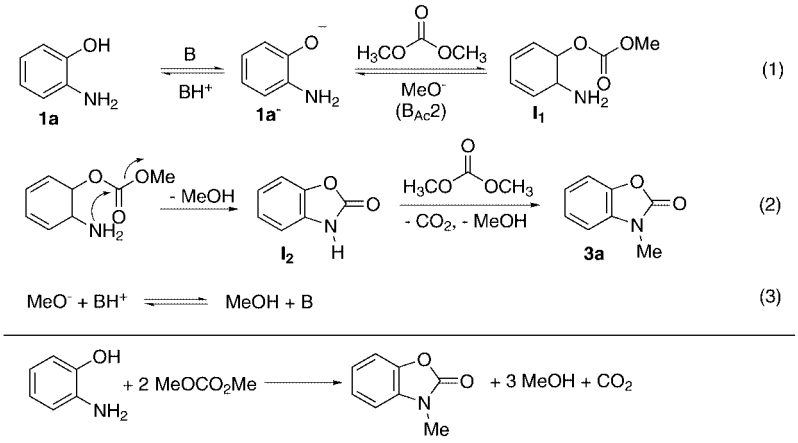
Figure 1 Isolated yield of **3a** in the reaction of *o*-aminophenol and DMC with different amounts of K_2CO_3

Under both conditions (90 °C and 130 °C), data clearly show that the base can be used catalytically: when the molar ratio K_2CO_3/**1** changes from 0.1 to 2, the yield of isolated product **3a** is in the range of 82–89% at 130 °C, and of 48–55% at 90 °C. This behavior appears in line with the modest solubility of K_2CO_3 in DMC.[5a]

Based on the parallel with the reaction of oximes of Scheme 2, a preliminary mechanistic hypothesis was formulated as follows (Scheme 4).

The reagent **1** undergoes a transesterification reaction with DMC to yield the intermediate $\mathbf{I_1}$ ($B_{Ac}2$ reaction), which in turn, gives the ring closure to the benzoxazol-2-one ($\mathbf{I_2}$). The $B_{Al}2$ *N*-methylation of $\mathbf{I_2}$ yields the final product **3a** through a reaction analogous to the known DMC-mediated methylation of amides.[9] The scheme indicates the catalytic role of the base B (K_2CO_3). Still, the sequence $B_{Ac}2/B_{Al}2$ of *O*-methoxycarbonylation and *N*-methylation, needs to be demonstrated. Presently, the proposed intermediates $\mathbf{I_1}$ and $\mathbf{I_2}$ have not been isolated nor observed.

o-Aminophenol was then made to react with higher homologues of DMC, such as diethyl-, diallyl-, and dibenzyl-carbonates (**2b**, **2c**, and **2d**, respectively). Previous experiments indicated that the electrophilic reactivity of compounds **2** followed the trend: **2a** ≥ **2d** ca. = **2c** > **2b**.[10] Reaction conditions were chosen accordingly. In the case of **2c** and **2d**, experiments were carried out at 130 °C, while diethyl carbonate **2b** was used at 150 °C. Liquid carbonates **2b**,**c** were used as solvents, while DME was the reaction medium in the case of the solid **2d**: solutions of **1** (0.5 g, 4.6 mmol) in **2b** or **2c** (38 mL or 45 mL, re-



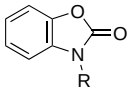
Scheme 4 Mechanistic hypothesis for the reaction of *o*-aminophenol and DMC. B: a base

spectively; molar ratio **2**/**1** = 70), and solutions of **1** (0.5 g, 4.6 mmol) and **2d** (2.8 g, 11. 6 mmol; molar ratio **2d**/**1** = 2.5) in DME (25 mL) were used. The catalyst K_2CO_3 was added in different amounts in the range of 0.1–2 molar equivalents with respect to **1**. Reactions were always run in a stainless steel autoclave of 150 mL. Results are reported in Table 2.

Table 2 shows that *N*-alkylbenzoxazol-2-ones (**3b**–**d**) are obtained in good yields. As for DMC, the base can be used in a catalytic amount: in the case of **2b** and **2c**, at comparable reaction times, a very limited variation of the final yield is observed when the molar ratio K_2CO_3/**1** changes from 0.1 to 2.

In summary, this study allows the following conclusions: i) the reaction of *o*-aminophenol with compounds **2a**–**d** represents a unusual example where dialkylcarbonates act at the same time as alkylating and carbonylating agents through $B_{Al}2/B_{Ac}2$ mechanisms; ii) the base K_2CO_3 is truly catalytic and yields of *N*-alkylbenzoxazol-2-ones **3a**–**d** are satisfactory in all cases; iii) in the range of 90–150 °C, the increase of temperature allows for a faster reaction while it does not affect the selectivity towards final compounds **3** (reaction intermediates are not observed); iv) although the method is rather energy-intensive because of the relatively high reaction temperature, valuable environmental and synthetic advantages are the use of non toxic compounds and catalyst, and the fact that neither organic nor inorganic by-products are formed.[3]

Table 2 Reactions of *o*-Aminophenol (**1**) with Dialkyl Carbonates **2b**–**d**

Entry	$ROCO_2R$/**1**[a] (mol/mol)	K_2CO_3/**1**[b] (mol/mol)	Temp (°C)	Time (h)	Product, Yield (%)[c] 
1	**2b** (70)	2	150	28	**3b**: R = Et, 81
3	**2b** (70)	0.5	150	26	**3b**: R = Et, 98
4	**2b** (70)	0.1	150	26	**3b**: R = Et, 86
5	**2c** (70)	2	130	16	**3c**: R = Allyl, 98
6	**2b** (70)	0.5	130	16	**3c**: R = Allyl, 93
7	**2b** (70)	0.1	130	16	**3c**: R = Allyl, 89
8[d]	**2d** (2.5)	2	130	16	**3d**: R = Bn, 69
9[d]	**2d** (2.5)	2	130	26	**3d**: R = Bn, 88

[a] Molar ratio $ROCO_2R$/**1**.
[b] Molar ratio K_2CO_3/**1**.
[c] Isolated Yield of compounds **3**.
[d] Entries 8 and 9: Reactions in DME as a solvent (25 mL).

All compounds used were ACS grade and were employed without further purification. ^{1}H NMR spectra were recorded on 300 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. GLC and GC–MS (70 eV) analyses were run using CPSil24CB and HP5 capillary columns (30 m), respectively. Melting points are uncorrected.

Reaction of *o*-Aminophenol with DMC (2a); General Procedure
According to the reaction temperature, two different procedures **A** and **B** were used.

Procedure A: At 90 °C, experiments were run at atmospheric pressure. A two-necked, jacketed, 50 mL round-bottomed flask fitted with a reflux condenser connected to a N_2 reservoir (ca 1 L), a stopcock and a magnetic bar, was loaded with *o*-aminophenol (0.5 g, 4.6 mmol), DMC (30 mL), and K_2CO_3 (the molar ratio K_2CO_3/**1** was made to vary in the range of 0.1–2.0, see Table 1 and Figure 1). Four cycles of vacuum/N_2 were carried out. Then, the mixture was kept under N_2, heated at the reflux temperature of DMC (90 °C), and vigorously stirred. After a particular time interval (9 h, 18 h, 28 h, and 48 h), the flask was cooled to r.t., K_2CO_3 was filtered and washed with EtOAc (8–10 mL), and finally, solvents were removed by rotary-evaporation. To the solid residue was added a mixture (35 mL) of petroleum ether–EtOAc (35:1) and heated at the reflux temperature for 30 min. The light suspension was allowed to settle and at 50 °C the upper clear solution (containing the product) was decanted. After removal of solvents, *N*-methyl benzoxazol-2-one (**3a**) was isolated and characterized as such (yields given in Table 1 and Figure 1).

Procedure B: At 110 °C and 130 °C (above the bp of DMC), reactions were run in an autoclave. A stainless steel autoclave (150 mL) fitted with a thermostatic jacket, a manometer, and a thermocouple, was loaded with a mixture of *o*-aminophenol (0.5 g, 4.6 mmol), DMC (30 mL), and K_2CO_3 (the molar ratio K_2CO_3/**1** was made to vary in the range of 0.1–2.0; see Table 1 and Figure 1). Before heating, the autoclave was purged with a N_2 stream using two on/off valves (fixed on the autoclave head). The mixture was kept under magnetic stirring and made to react for time intervals in the range of 3–18 h. Then, the apparatus was cooled to r.t. and K_2CO_3 filtered. The product **3a** was isolated as described above for the procedure **A**.

Two experiments were also run with procedure **B** (130 °C, autoclave), in the presence of DME (5 mL) or DMF (5 mL) as co-solvents.

3a
Yellow solid; mp 79.1–80.3 °C (Lit.[2b] 83.0–83.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–6.92 (m, 4 H, Ar), 3.40 (s, 3 H).

GC–MS (70 eV): *m*/*z* = 149 (100) [M^+], 134 (4) [$M^+ - CH_3$], 120 (40) [$M^+ - NH{=}CH_2$], 106 (9) [$M^+ - CH_3 - CO$], 93 (20) [$M^+ - N{=}CH_2 - CO$], 92 (12), 78 (14), 51 (16).

Reaction of *o*-Aminophenol with Diethyl- and Diallyl Carbonates 2b,c; General Procedure
Procedure **B** was used. Accordingly, solutions of **1** (0.5 g, 4.6 mmol) in **2b** or **2c** (38 mL or 45 mL, respectively; molar ratio **2**:**1** = 70), were loaded in a stainless steel autoclave of 150 mL, along with the catalyst (K_2CO_3) added in the range of 0.1–2 molar equiv with respect to **1**. The reaction temperature was 150 °C and 130 °C, with **2b** and **2c**, respectively. Products **3b**,**c** were isolated as described above in procedure **A** (yields given in Table 2). *N*-Ethyl- and *N*-allyl benzoxazol-2-ones were liquids at r.t.; mp ≤ 4 °C.

3b
Liquid (Lit.[11] brown oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–6.95 (m, 4 H, Ar), 3.89 (q, *J* = 7.2 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

GC–MS (70 eV): *m*/*z* = 163 (100) [M^+], 148 (61) [$M^+ - CH_3$], 135 (62) [$M^+ - CO$], 106 (10) [$M^+ - CO - CH_2CH_3$], 91 (15), 79 (23), 78 (10), 77 (18), 51 (9).

3c
Liquid (bp Lit[12] 75–76 °C/0.07 mmHg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–6.94 (m, 4 H, Ar), 5.91 (ddt, J_{trans} = 17.3 Hz, J_{cis} = 10.2 Hz, J_a = 5.5 Hz, 1 H), 5.31 (dd, J_{trans} = 17.3 Hz, J_{gem} = 1.2 Hz, 1 H), 5.30 (dd, J_{cis} = 10.2 Hz, J_{gem} = 1.2 Hz, 1 H), 4.45 (d, J_a = 5.5 Hz, 2 H).

GC–MS (70 eV): *m*/*z* = 175 (100) [M^+], 146 (9), 134 (57) [$M^+ - CH_2CHCH_2$], 130 (9), 120 (7), 106 (34) [$M^+ - CH_2CHCH_2 - CO$], 78 (16), 77 (10), 41 (36) [$M^+ - C_7H_4NO_2$], 39 (14).

Reaction of *o*-Aminophenol with Dibenzyl Carbonate 2d; Typical Procedure
Procedure **B** was used. At 130 °C, solutions of **1** (0.5 g, 4.6 mmol) and **2d** (2.8 g, 11. 6 mmol; molar ratio **2d**:**1** = 2.5) in DME (25 mL) were made to react in the presence of K_2CO_3 (1.3 g, 9.2 mmol; K_2CO_3/**1** in a 2:1 molar ratio) for time intervals in the range of 16–26 h. Then, the autoclave was cooled to r.t. and K_2CO_3 was filtered. The solution was distilled under reduced pressure to remove the co-product benzyl alcohol (bp 40 °C/10 mm) and the unreacted DBnC (**2d**: bp 90 °C/10 mm). The solid residue was treated as described above (see procedure **A**) to isolate *N*-benzyl benzoxazol-2-one (**3d**: yields given in Table 2), which was characterized as such.

3d:
Recrystallized (EtOH); mp 102–4 °C (Lit.[1c] mp 123–124).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–6.80 (m, 9 H, Ar), 5.01 (s, 2 H).

GC–MS (70 eV): *m*/*z* = 225 (44) [M^+], 91 (100) [$M^+ - C_7H_4NO_2$].

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(6) The alkylation reaction with **2** takes place only at a high temperature [≥ 120 °C; Scheme 2, path (a)]. Under these conditions, the alkylation is the sole possible process because of the reversibility of path (b).
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