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Chemoselective and efficient carbomethoxylation of the alcoholic chain of phenols by dimethyl carbonate (DMC)

Roberta Bernini,[a,b,*] Enrico Mincione,[a,b] Fernanda Crisante,[a,b] Maurizio Barontini,[a,b] Giancarlo Fabrizi[c] and Patrizia Gentili[d]

[a]*Dipartimento di Agrobiologia e Agrochimica, Università degli Studi Della Tuscia, Via S. Camillo De Lellis snc, 01100 Viterbo, Italy*
[b]*Unità di Ricerca VT2, Consorzio Interuniversitario La Chimica per l'Ambiente, Via Della Libertà 5/12, 30175 Marghera, VE, Italy*
[c]*Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università Degli Studi di Roma La Sapienza, P.le A. Moro 5, 00185 Roma, Italy*
[d]*Dipartimento di Chimica, Università Degli Studi di Roma La Sapienza, P.le A. Moro 5, 00185 Roma, Italy*

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Abstract—The efficiency of dimethyl carbonate (DMC) as chemoselective carbomethoxylating agent of the alcoholic chain of phenols has been investigated. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sulfuric acid as catalysts, new carbomethoxylated phenolic compounds were obtained in quantitative yields. A new efficient derivatization of the aliphatic alcoholic chain of the precious natural hydroxytyrosol is described, which increases the lipophilicity of the hydroxytyrosol. The antioxidant activity of this new carboxymethylated hydroxytyrosol **8** has been investigated using DPPH radical scavenging test. The results showed that this new compound has an antioxidant activity similar to hydroxytyrosol.

Alkyl carbonates are an important class of compounds widely used for a variety of industrial and synthetic applications.[1] They have been used in polymer chemistry,[2] in agricultural[3] as well as in biological fields.[4] In organic and pharmaceutical synthesis, they have been used as protecting groups for the alcoholic function. In particular, the protection of amino acids and carbohydrates has been extensively studied.[5] The cleavage of the carbonate moiety can be performed under mild basic hydrolysis.

The simplest of all carbonates, namely, dimethyl carbonate (DMC), is an interesting chemical for its low toxicity and chemical versatility.[6] In fact, as extensively reported by Tundo et al., DMC possess two active centres (alkyl and carbonyl carbons) whose reactivity depends on the experimental conditions. Thus, in the presence of a nucleophile, it may react as a methylating or as a carboxymethylating agent.[7] In these reactions, DMC is an environmentally benign substitute for hazardous and toxic phosgene, methyl halides and methyl sulfate.

Recently, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been successfully utilized as a nucleophilic catalyst for the methylation of phenols, indoles, benzimidazoles and for the esterification of carboxylic acids with DMC.[8] Protonated zeolites[9] and mesoporous molecular sieves functionalized by propyl-sulfonic groups[10] show the same high activity in the selective esterification of salicylic acid with DMC.

In the presence of NaY faujasite, DMC was a highly chemoselective methylating agent of functionalized anilines such as aminophenols, aminobenzyl alcohols, aminobenzoic acids and aminobenzamides. In fact, these compounds have been converted into the corresponding *N*-methylanilines while other functional groups were fully preserved from methylation and/or carboxymethylation reactions;[11] ambident nucleophiles such as *o*- and *p*-mercaptophenols *o*- and *p*-mercaptobenzoic acids underwent only an S-methylation reaction

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* Corresponding author. Tel.: +39 761 357452; fax: +39 761 357230; e-mail: berninir@unitus.it

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without affecting OH and CO_2H groups; *o*- and *p*-hydroxybenzoic acids have been chemoselectively converted into the corresponding methyl esters.[12]

Nevertheless, to the best of our knowledge, there are no examples about the use of DMC as a reagent for the selective carbomethoxylation of the alcoholic chain in the presence of phenolic hydroxyls. On the other hand, the selective protection of the alcoholic group in phenolic compounds is an important goal in organic synthesis but only few selective procedures for acylation have been reported.[13]

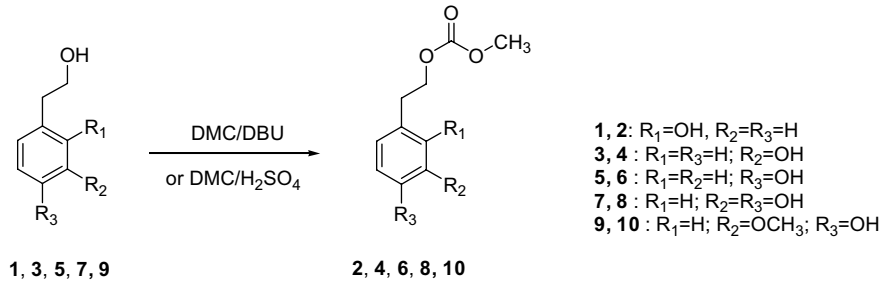
We describe here two simple and efficient procedures to obtain new methyl carbonates of aliphatic alcohols of phenolic compounds by utilizing DMC/1,8-diazabicyclo-[5.4.0]undec-7-ene or DMC/sulfuric acid (Scheme 1).

In a typical experiment, a mixture of 2-(2′-hydrophenyl)ethanol **1** (1.0 mmol), DBU (1.2 mmol) and DMC (8.0 mL) was heated to reflux ($T = 90$ °C). The reaction was monitored by thin layer chromatography (TLC) and by gas–mass analysis (GC–MS). After the disappearance of the substrate, the work-up of the reaction was achieved. The reaction mixture was cooled to room temperature and DMC was evaporated under vacuum as an azeotropic mixture with methanol (DMC/$CH_3OH = 1{:}3$) boiling at 64 °C.[7d] The residue was solubilized in ethyl acetate and washed with a solution of HCl 1 N. The organic extracts were treated with saturated solution and dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of crude mixture by chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent give exclusively the methyl carbonate **2**, characterized by spectroscopic analysis (Table 1, yield 98%).[14a] When the reaction was performed in the presence of sulfuric acid (20%), a similar experimental procedure was followed.

Considering the high selectivity obtained in the carbomethoxylation reaction of 2-(2′-hydrophenyl)ethanol **1**, we extended the same experimental procedures to other phenolic compounds such as 2-(3′-hydroxyphenyl)ethanol **3**, 2-(4′-hydroxyphenyl)ethanol (tyrosol) **5**, 2-(3′,4′-dihydroxyphenyl)ethanol **7** (hydroxytyrosol) and 2-(4-hydroxy-3-methoxyphenyl)ethanol (homovanillyl alcohol) **9**. Reaction conditions, conversions and yields are reported in Table 1. All reactions proceeded with complete substrate conversion and resulted in good product yield of the corresponding new methyl carbonates **4**, **6**, **8** and **10**.[14b–e] Under these controlled experimental conditions, no phenolic groups were methylated. Only by increasing reaction times (24 h), were these groups derivatized in the presence of DBU.

To increase the environmentally friendly character of this reaction, as an example, we performed the carboxymethylation reaction of tyrosol **5** using a lower amount of DBU (0.1 mmol). Also in this case, the reaction proceeded in quantitative yield even if a longer time reaction was needed (compare entry 5 with entry 11).

Of particular interest was the selective carbomethoxylation of the hydroxytyrosol **7**, one of the major phenolic compound present in olive leaves,[15] olive oil[16] and in olive mill wastewaters (OMWW).[17] Hydroxytyrosol has been reported to have a high antioxidant and radical scavenging activity for the presence of the free *o*-diOH substitution on the aromatic ring[18] and is widely used



Scheme 1. Selective carbomethoxylation of phenols **1**, **3**, **5**, **7** and **9** with DMC/DBU or DMC/H_2SO_4.

Table 1. Experimental data of the reactions depicted in Scheme 1

Entry	Substrate	Experimental conditions	Conversion (%)	Product	Yield (%)
1	**1**	DBU (1.2 mmol), 90 °C, 2 h	>98	**2**	>98
2	**1**	H_2SO_4 (20%), 90 °C, 1.5 h	>98	**2**	90
3	**3**	DBU (1.2 mmol), 90 °C, 4.5 h	>98	**4**	>98
4	**3**	H_2SO_4 (20%), 90 °C, 4.5 h	>98	**4**	>98
5	**5**	DBU (1.2 mmol), 90 °C, 7.5 h	>98	**6**	>98
6	**5**	H_2SO_4 (20%), 90 °C, 7 h	>98	**6**	>98
7	**7**	DBU (1.2 mmol), 90 °C, 1 h	>98	**8**	>98
8	**7**	H_2SO_4 (20%), 90 °C, 6.5 h	>98	**8**	>98
9	**9**	DBU (1.2 mmol), 90 °C, 7.5 h	>98	**10**	>98
10	**9**	H_2SO_4 (20%), 90 °C, 7 h	>98	**10**	>98
11	**5**	DBU (0.1 mmol), 90 °C, 12 h	>98	**6**	>98

for pharmacological, food, nutraceutical and cosmetic applications.[19]

The antioxidant activity of this new carboxymethylated hydroxytyrosol **8** has been determined by the DPPH reduction method,[20] by plotting, as indicated in note,[21] the remaining percentage of DPPH as a function of the molar ratios of **8** over DPPH. An EC_{50} (efficient concentration) of 0.11 ± 0.02 (mmol **8**/mmol DPPH) was determined, which is comparable to that of the well known hydroxytyrosol.[22] On the basis of these results, the compound **8** having an increased lipophilicity compared to hydroxytyrosol appeared as a new antioxidant useful for cosmetic and nutraceutical purposes.

In conclusion, the present Letter describes a new eco-friendly procedure for the chemoselective carbomethoxylation of the alcoholic chain in phenolic compounds using a cheap and green carboxymethylating agent such as dimethyl carbonate (DMC). The reactions proceed in good yields in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sulfuric acid as catalysts. A new antioxidant hydroxytyrosol derivative useful for industrial applications has been synthesized in quantitative yield.

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14. Carboxymethylated compounds **2**, **4**, **6**, **8** and **10** are colourless oils. Spectroscopic data are given below. (a) 2-(2′-Hydrophenyl)ethyl methyl carbonate **2**. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.99 (t, 2H, $J = 7.0$ Hz, CH_2CH_2O-CO_2CH_3), 3.76 (s, 3H, OCO_2CH_3), 4.33 (t, 2H, $J = 7.0$ Hz, $CH_2CH_2OCO_2CH_3$), 6.77–6.88 (m, 2H, CH_{ar}), 7.07–7.11 (m, 2H, CH_{ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 30.1, 54.9, 67.7, 115.8, 120.7, 123.3, 128.3, 131.0, 154.3, 156.0; MS (EI) m/z 196 (M^+). Anal. Calcd for $C_{10}H_{12}O_4$ (196.20): C, 61.22; H, 6.16; O, 32.62. Found: C, 61.18; H, 6.18; O, 32.64; (b) 2-(3′-Hydrophenyl)ethyl methyl carbonate **4**. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.91 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 3.75 (s, 3H, OCO_2CH_3), 4.31 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 5.12 (1H, OH), 6.68–6.79 (m, 3H, CH_{ar}), 7.11–7.19 (m, 1H, CH_{ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 34.9, 54.7, 68.3, 113.7, 115.8, 121.3, 129.8, 139.7, 155.8, 155.9. MS (EI) m/z 196 (M^+). Anal. Calcd for $C_{10}H_{12}O_4$ (196.20): C, 61.22; H, 6.16; O, 32.62. Found: C, 61.25; H, 6.18; O, 32.57; (c) 2-(4′-Hydrophenyl)ethyl methyl carbonate **6**. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.88 (t, 2H, $J = 7.1$ Hz, CH_2CH_2O-CO_2CH_3), 3.75 (s, 3H, OCO_2CH_3), 4.28 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 5.37 (s, 1H, OH), 6.75 (d, 2H, $J = 8.6$ Hz, CH_{ar}), 7.06 (d, 2H, $J = 8.5$ Hz, CH_{ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 34.2, 54.8, 68.7, 115.4, 129.1, 130.0, 154.4, 155.8. MS (EI) m/z 196 (M^+). Anal. Calcd for $C_{10}H_{12}O_4$ (196.20): C, 61.22; H, 6.16; O, 32.62. Found: C, 61.15; H, 6.22; O, 32.63; (d) 2-(3,4-Dihydrophenyl)ethyl methyl carbonate **8**: ^{1}H NMR($CDCl_3$): δ (ppm) 2.82 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 3.75 (s, 3H, OCO_2CH_3), 4.26 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 6.60 (dd, 1H, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, CH_{ar}), 6.70 (d, 1H, $J = 2.0$ Hz, CH_{ar}), 6.76 (d, 1H, $J = 8.0$ Hz, CH_{ar}). ^{13}C NMR ($CDCl_3$): δ (ppm) 34.4, 54.8, 68.7, 115.4, 115.9, 121.3, 130.0, 142.4, 143.6, 155.9. MS (EI) m/z 212 (M^+). Anal. Calcd for $C_{10}H_{12}O_5$ (212.20): C, 56.60; H, 5.70; O, 37.70. Found: C, 56.70; H, 5.75; O, 37.55; (e) 2-(4-Hydroxy-3-methoxyphenyl)ethyl methyl carbonate **10**. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.88 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 3.74 (s, 3H, OCH_3), 3.85 (s, 3H, OCO_2CH_3), 4.28 (t, 2H, $J = 7.1$ Hz, $CH_2CH_2OCO_2CH_3$), 5.57 (s, 1H, OH), 6.67–6.71 (m, 2H, CH_{ar}), 6.82 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 34.8, 54.7, 55.8, 68.6, 111.4, 114.5, 121.6, 129.0, 144.4, 146.5, 155.7. MS (EI) m/z 226 (M^+). Anal. Calcd for $C_{11}H_{14}O_5$ (226.23): C, 58.40; H, 6.24; O, 35.36. Found: C, 58.30; H, 6.28; O, 35.42.
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21. The antioxidant activity of **8** was determined using DPPH as free radical. Aliquotes of **8** solution in methanol was added to a 2.8 mL of 6×10^{-5} M methanolic DPPH solution, to achieve different concentrations expressed as the number of moles of **8**/mole of DPPH. The decrease in absorbance was determined using a HP 8453 diode array spectrophotometer at 516 nm (ε_{516} 10357 ± 162 M^{-1} cm^{-1}) at 25 °C for different ranges of time until the reaction reached a plateau. For each antioxidant concentrations tested, the reaction kinetics were plotted. From these graphs the percentage of DPPH remaining at the steady state was determined and corrected with respect to a control DPPH solution without compound **8**. Percentage of DPPH remaining values were transferred into another graph showing the residual DPPH at the steady state as a function of molar ratio of antioxidant to DPPH and from which the antioxidant activity expressed as the amount of antioxidant necessary to decrease the initial DPPH concentration by 50% (efficient concentration, EC_{50}, mol/L antioxidant/mol/L DPPH) was extrapolated.
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