10th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-10). 1-30 November 2006. http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm & http://www.mdpi.org/ecsoc-10/

[e006]

Zagreb, Croatia

Microwave assisted carboxymethylation of anilines and phenols

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Abstract. Carboxymethylation reactions of aromatic amines and phenols with dimethyl carbonate were studied using microwave irradiation.

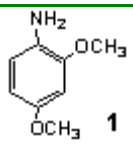
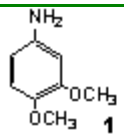
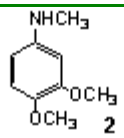
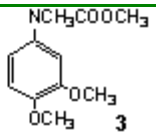
Introduction. Environmental concerns have put great pressure on chemical industry to develop green reagents for organic synthesis. Dimethylcarbonate (DMC) was found to be very suitable reagent as substitute for phosgene, alkyl halides and dimethyl sulfate.[1] DMC readily reacts with primary amines to form carbamates at room temperatures, however at elevated temperatures (over 130 ^{o}C) DMC reacts as N-methylating agent and often mixtures of several products are obtained.[2] In order to increase selectivity, reactions at low temperatures using various catalysts were explored.[3] High pressure carboxymethylations of primary amines were also examined.[4] On the other hand, microwave irradiation (MW) has not been employed for carboxymethylations with DMC and there is single report on MW use for methylations with DMC.[5] All these methods were employed in order to prepare carbamates, which are widely used in plastics industry, they are common components of pesticides[6] or drugs used for treatment of Alzheimer's disease.[7]

Our objective in this work was to investigate reaction of DMC with aromatic amines and phenols under microwave irradiation[8] with the aim of increasing the yields of carboxymethylation reactions and preparation of novel products. In this study, carboxymethylations of various aromatic amines and phenols have been conducted and results are collected in Tables 1-6. In all experiments, 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD) was used as a base catalyst, unless otherwise stated.

Results and discussion. Firstly, reaction of DMC with 2,4-dimethoxyaniline **1** was investigated in detail, in order to optimize reaction conditions. These results are summarized in Table 1. Under MW irradiation catalyzed by TBD two products were detected: N-methyl-3,4-dimethoxyaniline **2** and N-carbmethoxy-N-methyl-3,4-dimethoxyaniline **3**.

Influence of reaction temperature, time, ratio of reagents, amount of catalyst, solvent and change of catalyst was analyzed. Elongation of reaction time from 5, 10, 15 to 20 minutes (Entries 3-6) leads to the increased formation of product **3**, while the yield of N-methylated product **2** decreases. Similar conclusion can be drawn from the results of reactions with 1:1 ratio of DMC:amine (Entries 10-12). Ratio of reactants: DMC:amine 10:1, 5:1, 1:1, 1:5 (Entries 13, 4, 10 and 14) shows that by increasing the ratio, more product **2** is formed. Amount of catalyst (1:0.05, 1:0.5 and 1:1, Entries 4, 13, and 14), the best conversion was obtained for 1:0.5 ratio. The replacement of TBD catalyst by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Entries 7-9) does not lead to significant change in reaction outcomes. However, addition of one equivalent of Al_2O_3 to reaction mixture causes a sharp drop in yield of products (Entry 1).

Table 1. Reaction of DMC with 2,4-dimethoxyaniline under MW irradiation[f]

Entry	Substrate	Conditions	Ratio DMC:amine	Products		
	 **1**			 **1**	 **2**	 **3**
1		150 °C 10 min[c]	1:1	95	5	
2		155 °C 10 min	5:1	95	5	
3		170 °C 5 min	5:1	37	2	41
4		170 °C 10 min	5:1	24	22	54
5		170 °C 15 min	5:1	9	15	76
6		170 °C 20 min	5:1	3	1	96
7		170 °C 5 min[a]	5:1	67	17	16
8		170 °C 10 min[a]	5:1	18	29	52
9		170 °C 20 min[a]	5:1	10	19	70
10		170 °C 10 min	1:1	24	37	37
11		170 °C 20 min	1:1	29	29	40
12		170 °C 30 min	1:1	14	19	66
13		170 °C 10 min	10:1	29	18	53
14		170 °C 10 min	1:5	100	-	-
15		170 °C 10 min	5:1	10	22	62
16		170 °C 5 min[d]	5:1	18	26	39[b]
17		170 °C 5 min[e]	5:1	-	8	57[b]
		170 °C 20 min[ad]				

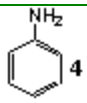
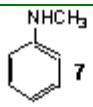
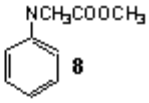
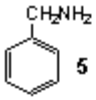
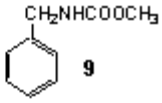
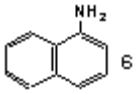
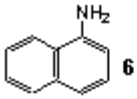
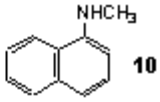
[a] DBU; [b] sideproducts detected; [c] Al_2O_3; [d] 50 % catalyst; [e] 100 % catalyst; [f] 5 % TBD catalyst, unless otherwise stated

The effect of solvent was investigated in the reactions summarized in Tables 2-6. In general, addition of acetonitrile as solvent does not significantly change reaction outcome.

MW assisted reactions of DMC with aromatic amines such as aniline **4**, benzylamine **5** and naphthylamine **6** are depicted in Table 2. In the case of aniline (Entries 18-20), two products were obtained: N-methylaniline **7** and N-

carbmethoxy-N-methylaniline **8**. At higher reaction temperature (170 C), significantly more products were obtained. The use of acetonitrile as solvent increases the formation of product **8**. On the other hand, reaction of DMC with benzylamine gave in all cases (Entries 21-23) single product **9** in high yield. Finally, reactions of 1-naphthylamine (Entries 24-26) gave N-methylated product **10** exclusively.

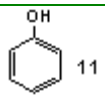
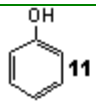
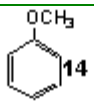
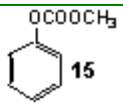
Table 2. Reactions of DMC with aromatic amines under MW irradiation[a]

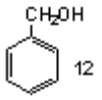
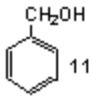
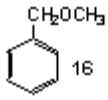
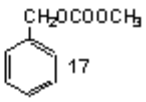
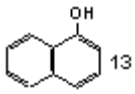
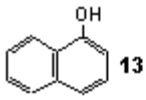
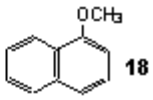
Entry	Substrate	Conditions	Products		
					
18		150 ^{o}C 10 min	90	10	-
19		170 ^{o}C 10 min	20	10	70
20		160 ^{o}C 10 min CH_3CN	10	-	90
					
21		150 ^{o}C 10 min	-	100	
22		170 ^{o}C 10 min	-	100	
23		160 ^{o}C 10 min CH_3CN	5	95	
		a			
24		150 ^{o}C 10 min[b]	32	68	
25		170 ^{o}C 10 min	20	80	
26		160 ^{o}C 10 min CH_3CN	16	84	

[a] presence of non-identified side-product in quantity 5 %; [b] 9 % product

Results of reactions of DMC with aromatic alcohols are depicted in Table 3. Reactivities of phenol **11**, benzylalcohol **12** and 1-naphthol **13** were investigated. The examination of results shows that phenol reaction conditions gave O-alkylated product, anisol **14** exclusively, while carboxymethylation product **15** was not detected (Entries 27-29). On the other hand, benzyl alcohol produces both products, O-alkylated benzylmethylether **16** and carbomethylated product **17** in approximately equal amounts (Entries 30 and 31). Reaction with 1-naphthol gave only O-alkylated product, 1-methoxynapthalene **18** (Entries 32-34), which is the outcome similar to results obtained for phenol.

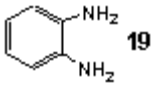
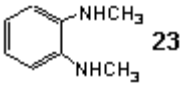
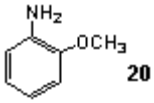
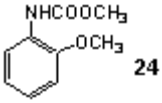
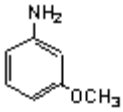
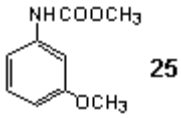
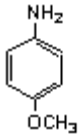
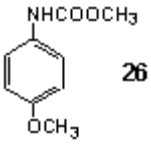
Table 3. Reactions of DMC with aromatic alcohols under MW irradiation

Entry	Substrate	Conditions	Products		
					
27		150 ^{o}C 10 min	85	15	-
28		170 ^{o}C 10 min	-	100	-
29		160 ^{o}C 10 min CH_3CN	-	100	-

					
30		170 °C 10 min	10	45	35
31		160 °C 10 min CH_3CN	5	45	40
					
32		150 °C 10 min	89	11	
33		170 °C 10 min	16	84	
34		160 °C 10 min CH_3CN	-	100	

Influence of substitution of aromatic amines was studied in reactions of *o*-phenylenediamine **19**, *o*-anisidine **20**, *m*-anisidine **21** and *p*-anisidine **20** (Table 4). Substitution with additional amino group in **19** leads to the formation of bis-N-alkylated product **23** in high yield (Entries 35-37). On the other hand, substitution of aromatic ring with methoxy group, either in *ortho*-, *meta*- or *para*- position leads to exclusive formation of N-carbomethylated products **24-26** (Entries 38-40). Furthermore, substitution of aromatic ring by two methoxy groups in **1**, leads to formation of several products, as described previously in Table 1.

Table 4. Reactions of DMC with substituted aromatic amines under MW irradiation[a]

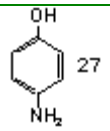
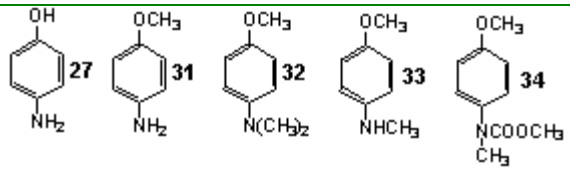
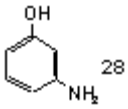
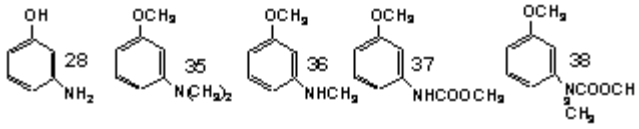
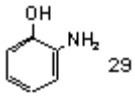
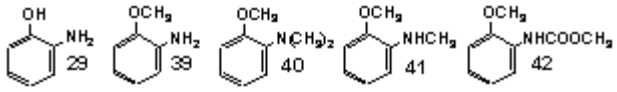
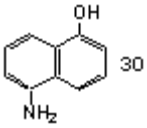
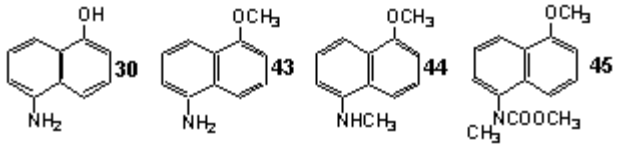
Entry	Substrate	Product	Temp	Time	Yield %
35			150 °C	10 min	55
36			170 °C	10 min	100
37			160 °C MeCN	10 min	100
38			175 °C	10 min	50 [a]
39			175 °C	10 min	63 [a]
40			170 °C	10 min	100

DMC:bis-amine ratio 10:1 (5:1 for each amino group), [a]after chromatography starting amine was isolated, [b]yields estimated by ^{1}H-NMR spectroscopy, [c]GC analysis

Mixed aminophenols **27-30** were investigated in order to establish relative reactivity of amino and phenol group towards DMC reactions (Table 5). For all investigated substrates, mixture of several products was obtained, which are the result of N- alkylation, O-alkylation or N-carboxymethylation. For instance, depending on reaction conditions, *p*-aminophenol **27** gave products od O-alkylation (**31**), or combined O- and N-alkylation (**32** and **33**) and finally combined O- alkylation and N-carboxymethylation-N-alkylation (**34**), (Entries 41-43). It may be concluded that

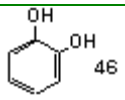
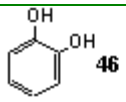
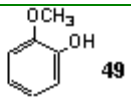
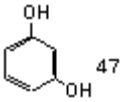
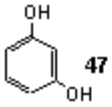
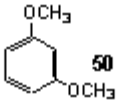
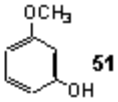
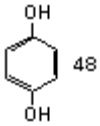
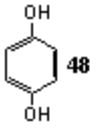
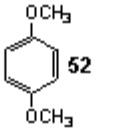
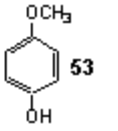
oxygen atom is more reactive towards alkylation than nitrogen atom.

Table 5. Reactions of DMC with aminophenols under MW irradiation[a]

Entry	Substrate	Conditions	Products				
							
41		155 ^{o}C 10 min	36.7	33.8	9.0	9.6	-
42		170 ^{o}C 10 min	-	26.1	31.2	24.3	11.7
43		160 ^{o}C 10 min CH_3CN	-	25.1	-	-	22.7
							
44		155 ^{o}C 10 min	-	72.4	16.8	-	-
45		170 ^{o}C 10 min	-	45.6	24.3	-	26.8
46		160 ^{o}C 10 min CH_3CN	-	41.3	44.2	-	-
							
47		155 ^{o}C 10 min	-	-	13.4	3.2	75.4
48		170 ^{o}C 10 min	-	7.3	22.2	9.6	57.8
49		160 ^{o}C 10 min CH_3CN	-	27.3	-	-	59.4
							
50		155 ^{o}C 10 min	30.5	50.0	7.2	-	
51		170 ^{o}C 10 min	1.8	53.8	18.9	24.0	
52		160 ^{o}C 10 min CH_3CN	50.3	49.7	-	-	

Reactions of dihydroxybenzenes with DMC (Table 6) were studied on three derivatives: pyrocatechol **46**, resorcinol **47** and hydroquinone **48**. Two products (O-alkylated and O,O-bisalkylated) were obtained for **47** and **48**, while **46** gives only monoalkylated product, 2-methoxyphenol **49**. This result could be explained by steric reasons. In reactions conducted at lower temperature (155 ^{o}C) monoalkylated product dominate (Entries 56 and 59), while in reactions conducted at elevated temperature (170 ^{o}C) dominate bis-alkylated products **50** and **52**, (Entries 56 and 58). Reactions conducted in acetonitrile lead to preferential or exclusive formation of monoalkylated products **49**, **51** and **53** (Entries 55, 58 and 61).

Table 6. Reactions of DMC with dihydroxybenzenes under MW irradiation[a]

Entry	Substrate	Conditions	Products %		
					
53		155 ^{o}C 10 min	76.5	19.2	
54		170 ^{o}C 10 min	13.5	77.3	
55		160 ^{o}C 10 min CH_3CN	80.6	12.4	
					
56		155 ^{o}C 10 min	63.4	-	20.7
57		170 ^{o}C 10 min	-	63.2	35.9
58		160 ^{o}C 10 min CH_3CN	66.0	2.8	31.2
					
59		155 ^{o}C 10 min	65.0	3.1	32.6
60		170 ^{o}C 10 min	-	94.0	-
61		160 ^{o}C 10 min CH_3CN	63.2	-	35.1

These results indicate that MW reactions gave high yields of products in significantly shorter reaction times than reactions conducted in classical conditions. For, instance, there is a report in literature for the reaction of DMC with aromatic amines, catalyzed by $Yb(OTf)_3$. Aniline, *p*-anisidine and *p*-nitroaniline gave corresponding carbamates in 96, 88 and 61 %, yields, respectively (by heating at 80 ^{o}C, for 8 hours).[9] On the other hand, experiments conducted in MW conditions in this study usually take place within 10-20 minutes. In most of the studied reactions, depending on reaction conditions, several products were obtained.

General procedure. Mixtures of DMC (5 mmol), substrate (1 mmol) and TBD (0.05 mmol) were subjected to MW reaction. Reactions were conducted in CEM Discover®LabmateTH/ExplorerPLS® single mode microwave reactor using closed reaction vessel technique (power = 125 W). Excess of DCM was removed in vacuo and products analysed by either GC or ^{1}H-NMR spectroscopy. Varian 3300 gas chromatograph, on DB1701 capillary column (15 m). Injector temperature = 250 °C, detector temperature = 300 °C, starting temperature = 100 °C (for 2 min), final temperature = 220 °C (for 2 min), with temperature gradient of = 40 °C/min. N_2 flow = 30 mL/min, O_2/H_2 flow ratio = 10/1. Radial chromatography was used to isolate pure products and all new compounds gave satisfactory spectroscopic data.

Acknowledgements. The authors acknowledge the Croatian Ministry of Science, Education and Sport for financial support (grants 0098056 and 0098147).

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