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Selective monomethylation reactions of methylene-active compounds with dimethylcarbonate. An example of clean synthesis*

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Abstract: Dimethylcarbonate (DMC), an environmentally friendly substitute for dimethylsulfate and methyl halides in methylation reactions, is also a very selective reagent. Under batch conditions, with potassium carbonate as the catalyst, the reactions of DMC, used as the solvent of the reactions, with methylene-active compounds (arylacetonitriles and arylacetoesters, aroxyacetonitriles and methyl aroxyacetates, benzylaryl- and alkylaryl-sulfones) produce monomethylated derivatives, with a selectivity not previously observed (i. e., >99%). These are examples of "green chemistry".

Dimethylcarbonate (DMC) is a nontoxic building block, used in organic syntheses as a "green" substitute for toxic and corrosive reagents such as phosgene, dimethylsulfate, and methyl iodide [1,2]. Depending on the experimental conditions, it may act as a methylating agent (Eq. 1), in the place of dimethylsulfate (Eq. 2) and methyl iodide (Eq. 3), or a carboxymethylating agent (Eq. 4), as a substitute of phosgene (Eq. 5).

$$PhOH + CH_3OCOOCH_3 \longrightarrow PhOCH_3 + CO_2 + CH_3OH \quad (1)$$

$$PhOH + (CH_3O)_2SO_2 + NaOH \longrightarrow PhOCH_3 + CH_3OSO_2Na + H_2O \quad (2)$$

$$PhOH + CH_3I + NaOH \longrightarrow PhOCH_3 + NaI + H_2O \quad (3)$$

$$ROH + CH_3OCOOCH_3 \rightleftharpoons ROCOOCH_3 + CH_3OH \quad (4)$$

$$2\,ROH + COCl_2 + 2\,NaOH \longrightarrow ROCOOR + 2\,NaCl + 2H_2O \quad (5)$$

Both reactions (methylation and carboxymethylation) occur in the presence of a weak base (usually an alkaline carbonate) that provides nucleophile activation. The nucleophilic anion may react at one of the two carbon centers of DMC, the carbonyl group or the methyl group.

In particular, when the reaction is performed under refluxing conditions (T = 90 °C), the nucleophilic anion attacks the acyl carbon, giving the carboxymethylation product and the methoxide anion as the leaving group ($B_{Ac}2$ mechanism). The latter provides further substrate activation, so that only catalytic amounts of the base are required.

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When operating at high temperatures (T ≥ 160 °C), the nucleophilic anion attacks the methyl group of the organic carbonate ($B_{Al}2$ mechanism). In such conditions, the leaving group (methoxycarbonate anion, CH_3OCOO^-) is not stable; it rapidly decomposes into methoxide anion and CO_2. Also in this case, the base is used in catalytic amounts.

While carboxymethylation is an equilibrium reaction, the methylation is not. Both carboxylation with phosgene and methylation with dimethylsulfate or methyl iodide generate stoichiometric quantities of the inorganic salt as byproducts, a base being used as a reagent. Instead, the corresponding processes of DMC do not involve disposal problems since no salts are produced and the only byproduct, methanol, can be easily recycled in the DMC production plant [3].

Methylation reactions with DMC can be profitably carried out both under gas–liquid phase-transfer catalysis (GL-PTC) conditions [4,5] and batchwise [6].

As DMC boils at 90 °C and acts as a methylating agent only when operating at high temperature, the batch reactions are performed in a stainless steel autoclave heated by an electrical oven. The base (K_2CO_3) can be used in catalytic amounts (0.05 molar equiv.). DMC can be used in large excess (10–30 molar excess), acting at the same time as the solvent and the reagent.

Monomethylation reactions of methylene-active compounds are not a one-step process in the industry because of the relevant quantity of dimethyl derivatives obtained with the usual methylating agents [7]. However, under batch conditions, the reactions of DMC with methylene-active compounds produce monomethylated derivatives, with a selectivity not previously observed.

The mono-methylation reactions of arylacetonitriles and arylacetoesters are noteworthy for the production of 2-arylpropionic acid, a class of intermediates for the production of anti-inflamatory drugs, such as ketoprofen, naproxen, etc.

The methylation process with DMC (Eq. 6) affords the corresponding mono-C-methylderivatives with unprecedented selectivity [6]. A few examples are reported in Table 1.

$$ArCH_2X + CH_3OCOOCH_3 \xrightarrow[X = CN,\ COOCH_3]{K_2CO_3} ArCH(CH_3)X + CH_3OH + CO_2 \quad (6)$$

Table 1 Reaction of arylacetonitriles and methyl arylacetates with DMC[a].

	Substrate ***ArCH$_2$X***		*T (°C)*	*Reaction time (h)*	*Conv. (%)*[b]	*Product Yield(%)*[c]
1	Ar = Ph	X = CN	180	3.75	100	90
2	Ar = *o*-MeOC$_6$H$_5$	X = CN	180	14.5	100	85
3	Ar = *m*-MeO C$_6$H$_5$	X = CN	180		100	80
4	Ar = *p*-MeOC C$_6$H$_5$	X = CN	180	4.75	99	88
5	Ar = *o*-MeC C$_6$H$_5$	X = CN	180	7.5	99	82
6	Ar = *p*-MeC C$_6$H$_5$	X = CN	180	7.5	98	80
7	Ar = *p*-Cl C$_6$H$_5$	X = CN	180	2.25	100	89
8	Ar = *p*-F C$_6$H$_5$	X = CN	180	2.75	100	81
9	Ar = *m*-MeO$_2$C C$_6$H$_5$	X = CN	180	8.00	100	91
10	Ar = Ph	X = COOMe	220	8.00	99	80
11	Ar = 2-(6-MeOC$_{10}$H$_6$)	X = COOMe	220	6.00	100	90

[a] Substrate, DMC and K_2CO_3 = 1:18:2 molar ratio.
[b] Conversions determined by GC
[c] Yields based on distilled (entries 1-10) or recrystallized (entry 11) products.

Also, the methylation of aroxyacetonitriles and methyl aroxyacetates proceeds with a selectivity up to 99% in the mono-methyl derivatives (examples are given in Table 2): 2-aroxypropionitriles and methyl 2-aroxypropionates are the corresponding products (Eq. 7) [7].

$$ArOCH_2X + CH_3OCOOCH_3 \xrightarrow[X = CN,\ COOCH_3]{base} ArOCH(CH_3)X + CH_3OH + CO_2 \qquad (7)$$

Table 2 Reactions of aryloxyacetates and aryloxyacetonitriles with DMC[a].

Substrate ***ArOCH$_2$X***			*T (°C)*	*Reaction time (h)*	*Conv. (%)*[b]	*Product Yield(%)*[c]
1	ArO = PhO	X = $COOCH_3$	190	40	99	94
2	ArO = *p*-$CH_3C_6H_4O$	X = $COOCH_3$	190	70	100	92
3	ArO = *m*-ClC_6H_4O	X = $COOCH_3$	190	26	100	91
4	ArO = PhO	X = CN	190	32	100	69
5	ArO = *p*-$CH_3C_6H_4O$	X = CN	180	40	100	51
6	ArO = *m*-ClC_6H_4O	X = CN	180	24	100	79
7	ArO = PhO	X = COOH	200	48	100	96

[a] Substrate, DMC and K_2CO_3 = 1:30:2 molar ratio.
[b] Conversions determined by GC analyses.
[c] Yields based on distilled products.

Sulfones bearing α-methylene groups (benzylaryl- and alkylaryl-sulfones: $ArCH_2SO_2Ar'$ and RCH_2SO_2Ar') can be effectively mono-C-methylated (selectivity > 99%) by DMC (Eq. 8) [8]. A few examples are reported in Table 3.

$$RCH_2SO_2R' + CH_3OCOOCH_3 \xrightarrow{K_2CO_3} RCH(CH_3)SO_2R' + CH_3OH + CO_2 \qquad (8)$$

Table 3 Reactions of benzylaryl- and alkylarylsulfones with DMC.

Substrate ***RCH$_2$SO$_2$R'***			*T (°C)*	*Product Yield (%)*[a]
1	R = Ph	R'= Ph	180	78
2	R = *p*-ClC_6H_5	R' = Ph	"	76
3	R = *p*-$CH_3C_6H_5$	R' = Ph	"	92
4	R = Ph	R' = *p*-ClC_6H_5	"	80
5	R = *p*-ClC_6H_5	R' = *p*-ClC_6H_5	"	81
6	R = Ph	R' = CH_3	200	85
7	R = *p*-ClC_6H_5	R' = CH_3	"	77
8	R = *p*-$CH_3C_6H_5$	R' = CH_3	210	76

[a] Yields based on distilled products.

The reaction mechanism has been studied in detail for the reaction of arylacetonitriles and arylacetoesters with DMC. Experimental evidences (detection and behavior of $ArCH(COOCH_3)X$ and $ArC(CH_3)(COOCH_3)X$ as reaction intermediates) support the hypothesis that the high monomethyl selectivity is not due to the S_N2 displacement of the nucleophile $ArCH(^-)X$ on DMC [9]. Instead, DMC acts first as a carboxymethylating agent ($B_{Ac}2$ mechanism) which allows the protection of the methylene-active derivatives and permits nucleophilic displacement ($B_{Al}2$) to occur with another molecule of DMC. This pattern shows the very peculiar action of the methoxycarbonyl group, that plays a two-fold role: i) the increased acidity of $ArCH(COOCH_3)X$ favors the formation of the corresponding anion and ii) the methoxycorbonyl group acts as a protecting group which prevents further methylation. The key step is the attack of the anion $ArC(^-)(COOCH_3)X$ to the DMC molecule.

As evidence, the reaction of the potassium salt of 2-carboxymethylphenylacetonitrile [K^+ $PhC(^-)(COOCH_3)CN$] with DMC affords $PhC(CH_3)(COOCH_3)CN$ as the sole product. For this reaction, the activation energy was found to be 23.4 kcal mol^{-1}, higher than as observed with usual displacements [10]. The same mechanism, in all likelihood, operates in the reactions of aroxyacetonitriles and methyl aroxyacetates and sulfones.

As a general feature, the reaction occurs faster on nitriles than on esters (Tables 1 and 2), that require higher temperatures and longer reaction times for the conversion to be completed. The higher reactivity of the nitriles may be explained with the easier formation of the corresponding carbanions $ArCH(^-)CN$ and $ArOCH(^-)CN$.

CONCLUSIONS

One of the primary objectives for pollution prevention is the adoption of processes that reduce or eliminate the use and generation of hazardous substances. This is the challenge for the future of chemical industry, its development being mostly linked to how closely environmental needs will be coupled with new ideas in fundamental research.

In this context, substitution of usual methylating agents (dimethylsulfate, methyl halides) with DMC has the following noteworthy advantages:

- a nontoxic reagent (DMC) and catalysts (K_2CO_3-PEGs) are used;
- no byproducts (inorganic salts) to be disposed of are formed;
- a very high selectivity in mono-methylation (of methylene active compounds) is obtained.

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REFERENCES

1. P. Tundo.*Continuous Flow Methods in Organic Synthesis*. Horwood, E. Pub., Chichester, UK (1991).
2. M. Lissel, A. R. Rohani-Dezfull, G. Vogt. *J. Chem. Res. (M)*, 2434 (1989).
3. D. Delledonne, F. Rivetti, U. Romano. *J. Organomet. Chem.* **448**, C15–C19 (1995).
4. P. Tundo. *J. Org. Chem.* **44**, 2048–2049 (1979).
5. P. Tundo, G. Moraglio, F. Trotta. *Ind. Eng. Chem. Res.* **28**, 881–890 (1989).
6. M. Selva, C. A. Marques, P. Tundo. *J. Chem. Soc. Perkin Trans. 1*, 1323 (1994).
7. A. Bomben, C. A. Marques, M. Selva, P. Tundo. *Tetrahedron*, **51**, 11573 (1995).
8. A. Bomben, M. Selva, P, Tundo. *J. Chem. Res. (S)* 448 (1997).

9. P. Tundo, M. Selva, S. Memoli. "Dimethylcarbonate as a Green Reagent". In *Green Chemistry: Advances in Synthesis and Chemical Processing*, ACS Symposium Series No. 767, P. Anastas, L. Bartlett, T. Williams (Eds.), American Chemical Society, Washington, DC (2000).
10. A. K. Axelson, A. Nordahl, R. Carlson. *J. Chemom.* **9**(6), 441–449 (1995).