Green chemistry metrics: a comparative evaluation of dimethyl carbonate, methyl iodide, dimethyl sulfate and methanol as methylating agents

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The methylating efficiency of dimethyl carbonate (DMC), dimethyl sulfate (DMS), methyl iodide (MeI), and methanol (MeOH) was assessed based on atom economy and mass index. These parameters were calculated for three model reactions: the O-methylation of phenol, the mono-C-methylation of phenylacetonitrile, and the mono-N-methylation of aniline. The analysis was carried out over a total of 33 different procedures selected from the literature. Methanol and, in particular, DMC yielded very favourable mass indexes (in the range 3–6) indicating a significant decrease of the overall flow of materials (reagents, catalysts, solvents, etc.), thereby providing safer greener catalytic reactions with no waste.

Introduction

Alkylation reactions are among the key industrial/organic transformations for the production of a variety of fine and bulk chemicals.[1] In this field, particularly in the past two decades, the need for more environmentally acceptable processes has fuelled a great interest towards dialkylcarbonates ($ROCO_2R$) as innovative alkylating agents.[2] These compounds, in fact, possess physico-chemical and reactivity features which make them appealing for general synthetic applications, including, for example, the selective alkylation of amines and phenols carried out by both linear and cyclic organic carbonates.[3] In addition, environmental benefits come from the (eco)toxicological profiles of dialkyl carbonates. This is especially true for the lightest term of the series, dimethyl carbonate (DMC), which is currently considered a genuine example of a green compound:[2,4] the synergy between its non-toxicity, its good biodegradability, its clean industrial methods of synthesis (Scheme 1),[5] and its versatile reactivity imparts to it a great potential as a reagent for the methylation of several O-, S-, C-, and N-nucleophiles.[2,6]
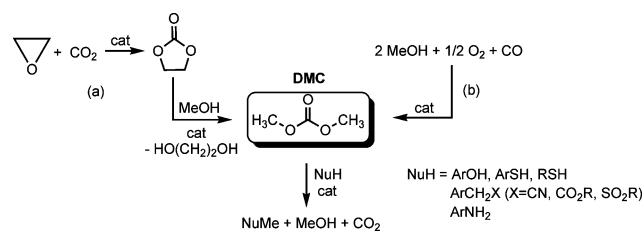
Scheme 1

DMC-mediated methylations have been extensively investigated by us:[7] the green features of these reactions have been readily recognised in the overall improvement of safety, in their true catalytic nature, in the absence of by-products, and importantly, in the lack of added solvents. Besides, a further specific added-value is the unprecedented high selectivity (over 99%) which has been attained, for example, in the reactions of dimethyl carbonate with CH_2-active compounds and with primary aromatic amines (Scheme 2).
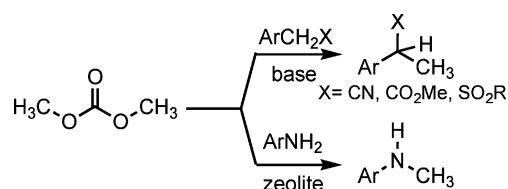
Scheme 2

Both these processes have been reported with the exclusive formation of the corresponding mono-C- and mono-N-methyl derivatives, while the use of classical reagents and methods always give mixtures of products of multiple C- and N-alkylations.[7,8]

So far however, the synthetic elegance of DMC-based procedures with respect to traditional alkylation techniques, has been mostly described through conventional criteria of selectivity and yields.

An important progress of green chemistry has been the transition from general qualitative descriptions of the greenness of a process to more quantitative comparisons based on measurable metrics able to account for several aspects of a given chemical transformation, including: (i) the economic viability; (ii) the global mass flow and the waste products; (iii) the toxicological and eco-toxicological profiles of all the chemical species involved (reagents, solvents, catalysts, products).[9–11]

In this paper, green chemistry metrics are used to compare some emblematic examples of methylation reactions carried out with four different reagents: dimethyl carbonate ($MeOCO_2Me$, DMC), methanol, dimethyl sulfate ($MeOSO_3Me$, DMS) and methyl iodide (MeI). In particular, three model transformations such as the O-methylation of phenol, the mono-C-methylation

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of phenylacetonitrile, and the mono-N-methylation of aniline, have been examined.

The atom/mass balances as well as the overall flow of materials (reagents/catalysts/solvents, *etc.*) of these processes have been compared in terms of the atom economy (AE) and the mass index (MI). The reason for choosing atom economy and mass index as indicators was due mainly to their immediate connotation of the process efficiency. Other existing metrics such as effective mass yield (EMY), environmental factor (E), reaction mass efficiency (RME), carbon efficiency (CE), cost index (CI), and energy input either lacked the parameters necessary to calculate them in the literature, or are based on figures that are to some extent subjective (*e.g.* waste, non-benign reagent), and therefore hard to define.

In all cases DMC has proven to be an excellent methylating agent, often the best, among those considered.

Results and discussion

Safety and costs

A preliminary comparison of the four methylating agents was based on their chemical and toxicological properties.[12] Table 1 summarizes the figures and gives an estimation of costs of these compounds. It was readily appreciable that DMC was the only non toxic compound (it is merely classified as a flammable liquid), that could be handled without any of the precautions required for highly toxic MeI and DMS, and toxic methanol.

On the other hand, the cost of methanol was nearly 50% lower than that of DMC and DMS, and about 1/10 than that of MeI. This first set of figures indicated that methanol and DMC were both greener than MeI and DMS as far as safety and costs are concerned.

The literature sources

For the three process under investigation, the choice of bibliographic references was crucial for an objective comparison of different synthetic methods. Two major criteria were used to select examples from the literature: (i) better overall performance (yield and selectivity) of the process, and (ii) availability of the detailed description of the procedure. Nonetheless, at least

for some cited papers, authors might not have optimized experimental conditions in terms of the overall flow of materials (washing solvents, reactant's molar ratio, *etc.*).

The O-methylation reaction of phenol

The synthesis of anisole from phenol and alkylating agents such as methyl iodide and dimethyl sulfate (Williamson reaction), has been widely reported by both academic and industrial sources (Scheme 3, eqn (1), (2) and (3)).[13] These reactions were compared to processes carried out with non toxic dimethyl carbonate and with methanol (Scheme 3, eqn (4), and (5)).
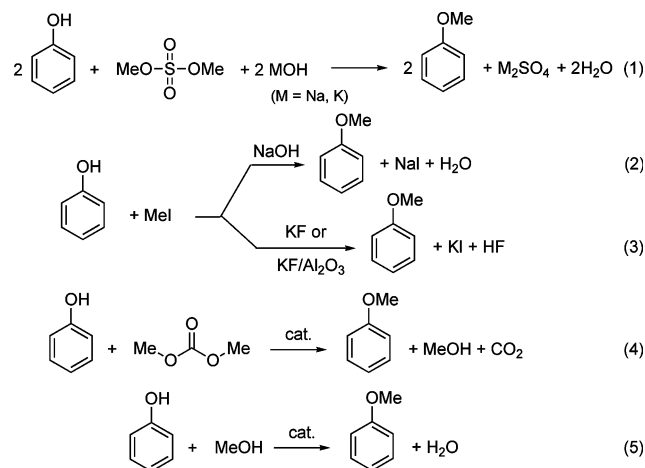
Scheme 3

Table 2 summarizes the results of thirteen different methods for the preparation of anisole.[3,13–23]

The reactions of DMS occurred in presence of over-stoichiometric amounts of alkaline hydroxides, at $T > 60$ °C (processes 1–4). Under these conditions, both methyl groups of dimethyl sulfate were incorporated in the product, according to the stoichiometry of eqn (1), Scheme 3.[14–16,23,24] In the case of MeI, basic co-reagents such as NaOH or KF were necessary (processes 5–9).[25]

DMC-mediated processes took place over catalytic beds of potassium carbonate either as pure or supported/suspended on

Table 1 General properties of DMC, DMS, MeI and methanol

	DMC	DMS	MeI	MeOH
Oral acute toxicity (LD_{50} rats/mg kg^{-1})	13800	440	76	5700
Acute toxicity per contact (LD_{50} cavy/mg kg^{-1})	>2500	na[a]	110	na
Acute toxicity per inhalation (LC_{50} rats/mg l^{-1}, 4h)	140	1.5	na	64
Mutagenic properties	None	Mutagenic	Possible teratogen	na
Irritating properties (rabbits, eyes, skin)	None	Causes burns	Irritant to skin	Irritant to skin, eyes
Hazard identification	Highly flammable	Very toxic and corrosive	Very toxic	Toxic and highly flammable
Use of solvents	No	Yes	Yes	No
Waste water treatment	No	Yes	Yes	Yes/No
NaOH consumption	No	Yes	Yes	No
By-products[b]	MeOH, CO_2	NaSO$_4$Me	NaI	H_2O
Thermodynamic	Not or slightly exothermic	Exothermic	Exothermic	
Cost/€ L^{-1}	~30	~30	≥120	15–20

[a] na: not available. [b] By-products defined for methylation processes.

Table 2 The evaluation of atom economy (AE,%) for the *O*-methylation of phenol

Process number	Alkylating agent	Base	Operating mode	T/°C	Anisole yield (%)	AE (%)	Ref.
1	DMS	NaOH	Batch	100	55[a]	55	14
2		NaOH		100	74[a]		15
3		NaOH		100	72–75[a]		16
4		KOH		65	97[a]	51	17
5	MeI	NaOH	Batch	25	90[a]	39	18
6		NaOH		60	97[a]		19
7		KF		25	88[a]	35	20
8		KF/Al$_2$O$_3$		25	95[b]		21
9		KF/Al$_2$O$_3$		25	100[b]		22
10	DMC	K$_2$CO$_3$[c]	c.-f.[d]	180	100[a]	59	3a
11		K$_2$CO$_3$[c]		200	100[a]		3d
12		K$_2$CO$_3$	Batch	160	92[a]		23
13	MeOH/PhCO$_2$Me	NaOH	Batch	320	42[e]	86	13b

[a] Isolated yields. [b] Yield determined by GLC. [c] K$_2$CO$_3$ was coated/suspended with/in PEG 1500-6000. [d] Continuous-flow conditions. [e] The yield was evaluated at a conversion of 44%.

PEGs (polyethylene glycols). Although high temperatures (160–200 °C) were necessary, the base could be recycled indefinitely both under continuous-flow (c.-f.) and batch conditions (processes 10–12). Finally, a recent example of catalytic Williamson ether synthesis (CWES) was examined, by which anisole was prepared at a very high temperature (320 °C), from the reaction of phenol, methanol, benzoic acid, and NaOH (process 13). This environmentally benign CWES method, whose formal stoichiometry is described by eqn (5), Scheme 3, worked at a moderate conversion (44%), with an overall yield of 42% on the desired methyl ether.

The overall set of alkylation methods was initially evaluated through atom economy (AE,%: eqn (6)), which represents the mass-balance of a process related to its stoichiometric equation, *i.e.* the percentage of atoms of the reagent which end up in the product.[11]

$$AE = \frac{MW \left(g\,mol^{-1}\right)\ product}{\sum MW \left(g\,mol^{-1}\right)\ of\ all\ reagents\ used} \times 100 \quad (6)$$

According to eqn (5) of Scheme 3, procedures mediated by MeOH allowed the best AE (86%, process 13). The reactions of DMS and DMC offered comparable values of AE (55–59%, processes 1–3 and 10–12, respectively). In fact, notwithstanding the non-catalytic nature of processes 1–3 (eqn (1), Scheme 3), both methyl groups of dimethyl sulfate ended up in the final product. The consumption of bases and most of all, the release of iodide salts, accounted for the poor AE in the case of MeI (35–39%, processes 5–9). However, by its intrinsic definition, the atom economy did not suffice to identify the cleaner (greener) process.

In order to include the chemical yield and the selectivity towards the desired product, as well as the mass of all reagents, solvents, catalysts, *etc.*, used in the examined reactions, a more all-encompassing metric, the mass index (MI or S^{-1}), was considered (eqn (7)).[26]

$$MI = S^{-1}$$
$$= \frac{\sum reagents\ +\ catalysts\ +\ solvents\ +\ etc.\ (kg)}{Desired\ product\ (kg)} \quad (7)$$

The overall flows of materials necessary for the calculation of MI, were taken from ref. 7b and 8–18.

Table 3 details the weight amounts of reagents, reaction auxiliaries (catalysts, solvents, co-reagents), and the desired product involved in processes 1–13.

The MI was initially evaluated only for the actual methylation reaction step. In some cases (processes 1–4 and 6), two values (a and b) of the mass index are indicated (Table 3): the first (a) included the mass of water used as the solvent and for workup, while the second (b) did not.[27] The comparison based on this metric showed that: (i) methyl iodide was the least efficient reagent (MI of 21–88, processes 6–9). The presence of iodine in the exhausted salt reasonably accounted for this result. (ii) Dimethyl sulfate (DMS) and dimethyl carbonate (DMC) afforded similar MI values (2.5 to 3.9, processes 1–3 and 10, 12), only on the condition that water was excluded from the mass balance. Otherwise, the mass index of reactions with DMC was, on average, 4 to 8 times lower than that of DMS mediated procedures (14 to 31, processes 1–2 and 4); (iii) the use of MeOH did not significantly improve the MI (2.9, process 13).

To further refine this mass analysis the reaction work-up had to be considered as well, by including all the solvents used for washes and extractions. Due to the lack of detailed experimental descriptions, the evaluation of MI for both the reaction and purification steps was possible only in a limited number of the examined processes. In particular, ref. 14–16, 3 and 23 allowed comparison of methods 1–3 and 10–12. In the reactions carried out with DMS, the extraction of anisole required extra solvents such as diethyl ether (150 mL, proc. 1–2), and benzene (200 mL, proc. 3), and CaCl$_2$ (10 g) as the drying agent. In the case of DMC, the c.-f. methods (proc. 10–11), did not involve additional materials, while the batch reaction consumed diethyl ether (20 mL, proc. 12) for the filtration/washing of the catalyst.[28] The comparison of the corresponding MI is summarized in Table 4.

This second approach confirmed that if water was excluded from the mass analysis, the flows of materials involved in processes mediated by DMS and DMC were comparable.

Except for process 1, mass indexes ranged from 3.0 to 6.2; in particular, for processes 3 and 10, the corresponding MI were 3 (DMS) and 3.5 (DMC). These data clearly indicated that the non toxic DMC was not only a safer replacement of DMS, but under suitable experimental conditions, the two alkylating agents were synthetically equivalent in terms of amounts of reactants and reaction auxiliaries involved.

Table 3 Overall flow of materials involved in processes of Scheme 3. The evaluation of mass index

Process	Phenol/g	Alkylating agent (g used)	Base (g used)	Solvents[a] (g used)	Anisole (g used)	Others[b] (g used)	MI[c]	Ref.
1	18.8	DMS (12.6)	NaOH (15)	H_2O (328.8)	11.9	—	(a) 31.5; (b) 3.9	14
2	47.0	DMS (63.0)	NaOH (21)	H_2O (400)	40	—	(a) 13.2; (b) 3.3	15
3	470.0	DMS (315.0)	NaOH (200)	H_2O (1000)	388	—	(a) 5.1; (b) 2.5	16
4	6.6	DMS (8.8)	KOH (14)	H_2O (2) Dioxane (72)	7.4	—	(a) 14.0; (b) 13.7	17
5	0.94	MeI (2.5)	NaOH (1.6)	DMSO (20)	0.98	—	25.6	18
6	9.4	MeI (15.1)	NaOH (200)	H_2O (1000)	10.5	CTMAB (3.2)	(a) 117; (b) 21.4	19
7	0.94	MeI (1.26)	KF (1.74)	MeCN (20)	0.95	—	25.2	20
8	0.41	MeI (0.68)	KF/Al_2O_3 (3.3)	MeCN (5.1)	0.45	—	21.0	21
9	0.05	MeI (0.2)	KF/Al_2O_3 (0.4)	MeCN (4.4)	0.057	—	88.6	22
10	94	DMC (180)	K_2CO_3 (95)	—	108.0	PEG 6000 (5)	3.5	3a
11	73.5	DMC (76.5)	K_2CO_3 (6)	—	84.5	PEG 1000 (300)	5.4	3d
12	10	DMC (25)	K_2CO_3 (4)	—	10.6	—	3.7	23
13	213.4	MeOH (70.4)	NaOH (3.2)	—	102.9	$PhCO_2H$ (8.5)	2.9	13b

[a] Overall amounts of solvents used as reaction media. [b] Additional reagents/catalysts. [c] (a) including water, (b) not including water.

Table 4 The mass index evaluated for both reaction and work-up steps of the synthesis of anisole

| Process	Alkylating Agent	MI[a] Reaction	MI[a] Reaction and workup	Ref.
1	DMS	3.9	13.5	14
2		3.3	6.2	15
3		2.5	3.0	16
10	DMC	3.5	3.5	3a
11		5.4	5.4	3d
12		3.7	5.0	23

[a] Water was always excluded from the mass-flow calculation.

The selective mono-C-methylation reaction of phenylacetonitrile

In the past thirty years, the selective mono-C-methylation of arylacetic acid derivatives (arylacetonitriles and arylacetoesters) has been used for the synthesis of non steroidal analgesics belonging to the class of 2-arylpropionic (hydratropic) acids.[2b,29] Ibuprofen, Ketoprofen, and Naproxen are well-known commercial examples (Scheme 4).

Scheme 4
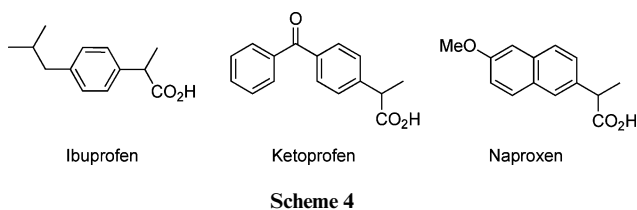
However, in the case of methylene active compounds, conventional methylation procedures with methyl halides or dimethyl sulfate, were often not satisfactory since competitive bis-C-alkylation reactions took over even at moderate conversions. The mono-methyl selectivity could be improved using phase-transfer (PT) catalysis. However, costly and not readily available PT-agents were necessary, and sizeable amounts of highly polluted water streams were generated. Scheme 5 (eqn (8) and (9))[30] and Table 5 (processes 14–18) report specific examples of the mono-methylation of phenylacetonitrile with MeI and DMS, to prepare 2-phenylpropionitrile (**1**).[31–35]

Scheme 5
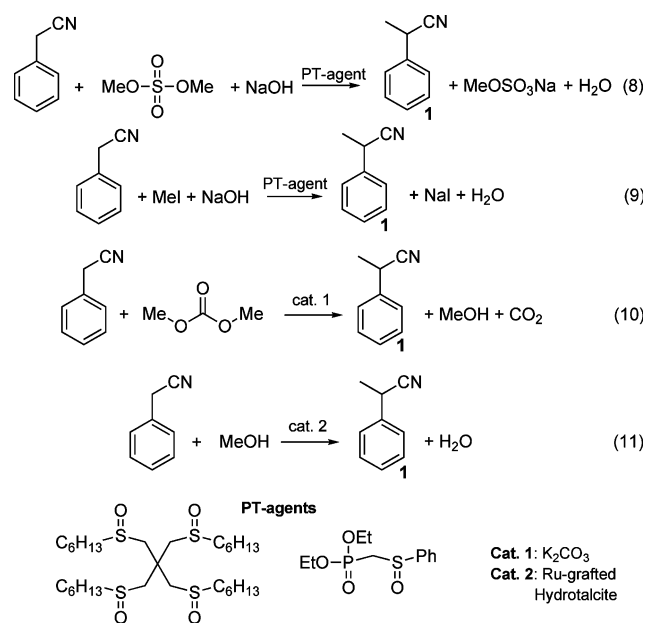
The use of dimethylcarbonate procured a major enhancement of both selectivity and process safety. In fact, in the presence of solid green catalysts (*e.g.* alkaline carbonates and zeolites), the reactions of a number of arylaceto-esters and -nitriles with DMC, gave the corresponding mono-C-methyl derivatives in up to 99% yield and selectivity.[2b,7,36]. Moreover, neither additional solvents nor treatment of waste effluents were required. Scheme 5 (eqn (10)) and Table 5 detail the case of phenylacetonitrile by considering both continuous-flow and batch operating modes (processes 20 and 21, respectively).[7a,e,37]

Finally, Table 5 also includes a recent report on the use of methanol for the methylation of phenylacetonitrile carried out over a Ru-grafted hydrotalcite catalyst (process 22, eqn (11)).[38]

Methylations with DMC and MeOH were highly atom economic (63–88%, processes 20–21 and 22) with respect to those mediated by MeI and DMS (44–46%, processes 14–18). In fact, the latter required one equivalent of base, thereby forming

Table 5 The evaluation of atom economy (AE,%) and mass index for the mono-*C*-methylation of phenylacetontrile

Process number	Alkylating agent	Base	O. M.[a]	T/°C	Prod. 1 yield (%)	AE (%)	MI	Ref.
14	MeI	$NaNH_2$	Batch	80	74[b]	44	5.8	31
15		NaOH	Batch	rt	92[b]	44	4.1	32
16		NaOH	Batch	rt	66[b]	44	9.7	33
17		NaOH	Batch	rt	83[b]	44	6.4	34
18	DMS	K_2CO_3	Batch	rt	82[b]	46	21.6	35
20	DMC	K_2CO_3[d]	c.-f.[e]	180	98[c]	63	3.7	36
21		K_2CO_3	Batch	180	98[c]	63	8.2–11.9	7a,37[f]
22	MeOH	none	Batch	180	65[b]	88	21.5	38

[a] O. M.: operating mode. [b] Yield determined by GLC. [c] Isolated yields. [d] K_2CO_3 was coated/suspended with/in PEG 6000. [e] Continuous-flow conditions. [f] The range of mass index depends on the DMC:substrate molar ratio (from 18:1 to 10:1) reported in ref. 7a and 37.

one equivalent of an inorganic salt as by-product (eqn (8) and (9), Scheme 5).

Experimental details of ref. 31–35 were not sufficient to estimate the mass flow of both reaction and work-up steps of processes 14–18. Therefore, the evaluation of MI was limited only to the methylation step of Scheme 5. Comparable mass indexes were calculated for MeI and DMC (4.1–9.7: processes 14–17; 3.7–11.9: processes 20–22). However, for MeI: (i) water had to be carefully excluded from the mass balance, and (ii) all PT-agents (processes 15–17) had to be considered as genuine catalysts, for which a quantitative recovery and reuse was possible.[39]

In the case of process 22, despite the high atom economy, the MI was penalized by the excess of MeOH with respect to the substrate (a molar ratio $MeOH/PhCH_2CN$ of ~50 was used).[38]

Table 5 leads to conclusions similar to those mentioned above for the synthesis of anisole. In the methylation of phenylacetonitrile and of related CH_2-active compounds, the non toxic DMC allowed a higher mono-C-methyl selectivity, and proved to be equivalent to or better than DMS and MeI, in terms of both AE and MI.

The selective mono-*N*-methylation reaction of aniline

The methylation of primary aromatic amines with methyl halides and dimethyl sulfate is even less selective than that of CH_2-active compounds. These reactions lead to mixtures of mono- and bis-*N*-methyl amines along with the corresponding trimethylanilinium salts.[8]

Therefore, the selective syntheses of mono-*N*-methyl anilines are mostly indirect multi-step procedures[8,40] that are inherently inefficient, especially from a green chemistry perspective.[9]

These drawbacks can be overcome by using green alkylating agents such as dialkyl carbonates, in the presence of zeolites. Such methods not only make use of safer reagents and catalysts, but are also experimentally straightforward.

For example, in presence of alkali metal exchanged faujasites, a variety of anilines, even deactivated by both steric or electronic effects, reacted with dimethyl carbonate or methyl alkyl carbonates ($ROCO_2Me$, R = $MeO(CH_2CH_2O)_n$, $n \geq 2$) to produce the corresponding mono-*N*-methyl anilines with up to 98% selectivity (Scheme 2) at quantitative conversions.[7,41] Likewise, the use of methanol with different heterogeneous catalysts (V-, Cs–P-oxides, and Mg-phosphates) was reported to induce the selective formation of *N*-methyl aromatic amines;[42] though,

under such conditions, the high reaction temperature (up to 500 °C) demanded gas-phase operations in continuous-flow. A modest conversion (not over 15–25% per pass) was compulsory to control the final selectivity.

In Table 6, the model mono-N-methylation of aniline is compared using the title methylating agents under different conditions (Scheme 6).[20,40,43–50]
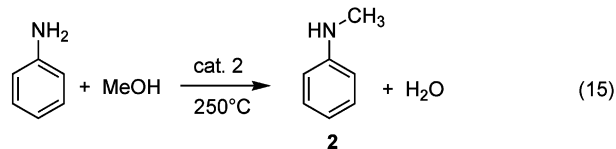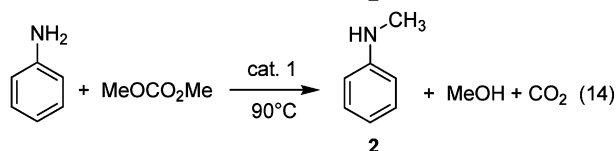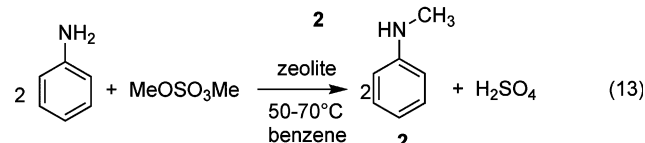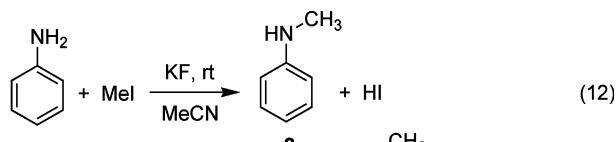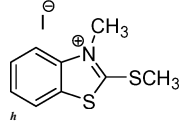

cat. 1: zeolites, V-AlPO$_4$, K$_2$CO$_3$
cat. 2: V-AlPO$_4$, Cs-P-Si oxide, Mg$_3$(PO$_4$)$_2$

Scheme 6

The choice of the reactions, and of the related references, was dictated by the possibility of calculating the mass index with sufficient uniformity.

The reaction of methanol showed the best atom economy, as almost 50% of the mass of the alcohol ended up in the product. For the other methylating agents, the trend of AE was different with respect to O- and C-alkylations (Tables 2 and 5): in particular, DMS afforded higher AE than DMC, followed by methyl iodide. The catalytic nature of processes 23–25, which represented rare examples where both DMS and MeI were used for a direct synthesis of mono-N-methyl aniline, accounted for this result.[51] Notwithstanding the reasonably good AE, procedures based on methyl iodide (eqn (12), Scheme 6), and more so on DMS (eqn (13), Scheme 6), offered moderate

Table 6 The evaluation of atom economy (AE) and mass index (MI) for the mono-*N*-methylation of aniline

Process number	Methylating agent	Catalyst	O.M.[a]	$T/°C$	Prod. 2 Yield (%)	AE (%)	MI	Ref.
23	MeI	KF	Batch	25	67[b]	46	27.9[f]	20
24	DMS	Zeolite K-X	Batch	79	55[c]	69	126[a]	43
25	DMS	Zeolite K-Y	Batch	50	58[c]	69	480[f]	44
26	DMC	Zeolite Na-Y	Batch	90	93[b]	59	6.3	45
27	DMC	V–AlPO$_4$	c.-f.[e]	250	39[c]	59	5.3[f g]	46
28	DMC	K$_2$CO$_3$[d]	c.-f.[e]	180	41[c]	59	51.2[g]	47
29	MeOH	V–AlPO$_4$	c.-f.[e]	250	32[c]	86	3.4[f g]	46
30	MeOH	Mg$_3$(PO$_4$)$_2$	c.-f.[e]	500	24[c]	86	10.2[f g]	48
31	MeOH	Cs–P–Si oxide	c.-f.[e]	300	14[c]	86	58.2[f g]	49
32	TosCH$_3$		batch (3 steps)	25–100	88[b]	14	774	40
33	(CH$_3$O)$_3$CH	H$_2$SO$_4$	Batch (2 steps)	180	44[b]	54	15.9	50

[a] O.M.: operating mode. [b] Isolated yields. [c] Yield determined by GLC. [d] K$_2$CO$_3$ was coated with PEG 6000. [e] Continuous-flow conditions. [f] Does not include workup. [g] For convenience of comparison, the MI was normalized for 1h of c.-f. operation. [h] 3-methyl-2-methylthiobenzothiazolium iodide was used as a stoichiometric reagent.

yields (58–67%) and required large amounts of added materials (excess of reagents and solvents), that raised significantly the corresponding MI (27.9, 126, and 480). Plus, they suffered from laborious workup procedures, whose overall mass flow was not exactly quantifiable, that would have multiplied MI by a factor of at least 3. Not to mention the toxicity of both the methylating reagents.

The methylations using DMC were effective both in batch and in c.-f. conditions, in the presence of zeolites and V–AlPO$_4$ catalysts (processes 26 and 27). These procedures showed extremely good MIs of 6.3 and 5.3, respectively. In particular, a good example was process 26, reported here for the first time as an optimization of a previous procedure:[45] it worked at 90 °C, and gave the product (**2**) in a 93% isolated yield. At 250 °C, instead, in the c.-f. system 27, a high mono-N-methyl selectivity was possible only by operating with low conversions which resulted in low yields per pass (39%). The MI would improve by recycling the feed.[52] Process 28 was also considered among c.-f. methods mediated by DMC. In this case, the use of K$_2$CO$_3$ as catalyst allowed only a 41% yield of mono-*N*-methyl aniline even in the presence of a relatively large molar excess of dimethyl carbonate (4 with respect to aniline), that resulted in a poor MI of 51.2.

The methylation of aniline with MeOH was highly efficient in the gas phase (250–500 °C) under c.-f. conditions.[53] An excellent MI of 3.4 was calculated with V–AlPO$_4$ as the catalyst (process 29). The overall reaction effectiveness decreased considerably with other catalytic systems: in fact, the mono-N-methyl selectivity was of only 78% over Mg-phosphates (process 30), while the reaction catalysed by mixed oxides required large volumes of methanol (PhNH$_2$: MeOH in a 1 : 20 molar ratio; process 31). The corresponding MIs were of 10.2 and 58.2, respectively.

In Table 6, two more examples were considered in which batch multistep methods and different methylating agents were involved. Process 32 was based on toluene *p*-sulfonate and it represented a very elegant and high yielding procedure for the mono-N-methylation of a number of amines. The large number

of steps and of reagents, along with the fact that the reaction was stoichiometric rather than catalytic, provided for the low atom economy (14%) and the staggering mass index (774). This represents a perfect example of a high yielding laboratory method (overall yield = 88%) that will hardly be used on large scale, and was inserted mainly for comparison.

The second method, process 33, used trimethylorthoformate in presence of catalytic amounts of H$_2$SO$_4$. This was a procedure published in *Organic Syntheses*, whose values of AE (54%) and MI (15.9, including workup) could be calculated reliably and were competitive. However, it required two steps, and the isolation of *N*-methylformanilide as an intermediate.

Conclusions

The synthesis of anisole, of 2-phenylpropionitrile, and of mono-*N*-methyl aniline, representative of industrial processes for the production of pharmaceuticals, fragrances, dyestuffs, and cosmetics, were used to compare the methylating efficiency of dimethyl carbonate, dimethyl sulfate, methyl iodide and methanol.

Atom economy and mass index were calculated for 33 different procedures. The results are summarized in Fig. 1, where the best values of AE and MI are plotted for each methylating agent and for each of the tested reactions.

The atom economy generally follows the trend: MeOH >> DMC ≥ DMS > MeI (Fig. 1, left). Two factors account for this behaviour: (i) for methanol, 47% of its mass is incorporated in the final products, more than twice as much as the other reagents (DMC 16%, DMS 12%, or 24% when both methyl groups are incorporated, MeI 11%); (ii) methanol and DMC require catalytic base or zeolites, as opposed to DMS and MeI.

MeOH and DMC offer similar low values of MI (on average, in the range of 3–5.5), better than those achievable with DMS and MeI (Fig. 1, right).

This analysis is, of course, far from being exhaustive. For example, the energy input and the cost index of each process
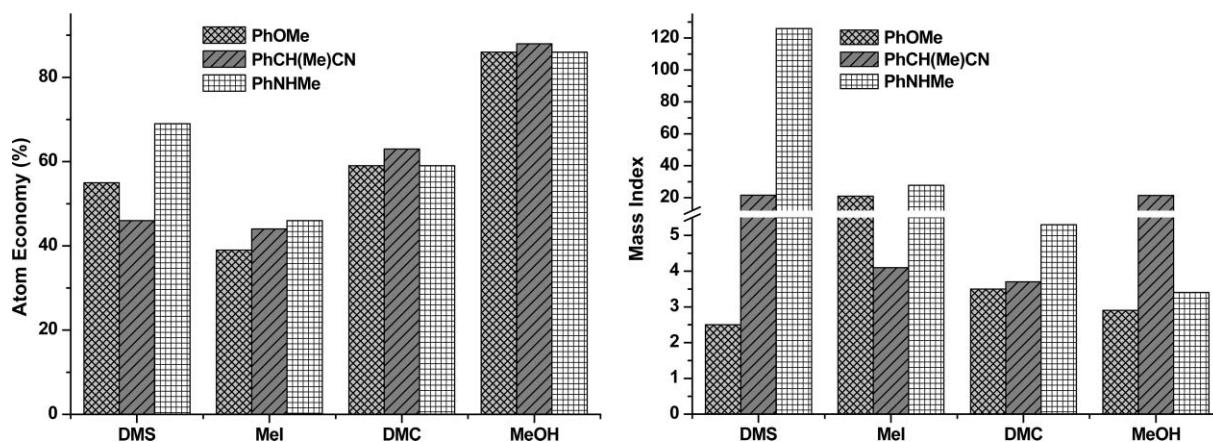
Fig. 1 The atom economy (right) and the mass index (left) for the reaction of phenol, phenylacetonitrile, and aniline with different methylating agents.

as well as eco-toxicological metrics[3d] were not examined. This, however, is beyond the scope of this work.

The conclusion is that the favourable AE and MI of methylation processes mediated by dimethyl carbonate and methyl alcohol, inherently reflect the greenness of these reactions, attained by avoiding wastes and by-products, by avoiding additional solvents and derivatization sequences, by the catalytic use of base or solid catalysts, and thanks to the ease of workup (if any). Additional factors make the use of DMC favourable with respect to MeOH: (i) DMC is non toxic; (ii) it is active at lower temperatures than methanol; (iii) usually, DMC operates with simple catalytic systems that can be recycled indefinitely.[54] MeOH, on the other hand, often requires catalysts prepared *ad hoc*, the synthesis of which should perhaps be included in the calculations of the mass balance, along with an evaluation of their lifetime.

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26 As reported in ref. 3, the MI is expressed as the ratio of all raw materials [kg] to the product [kg]. From both environmental and synthetic standpoints, the lower the MI, the better the process is. In the ideal situation, MI would approach 1.

27 Stemming from the fact that water is an intrinsically safe solvent and it is often used in large amounts, some authors tend to exclude it from mass calculations to not skew mass data (see ref. 3). However, in the present study, water streams are highly polluted by toxic alkylating agents (DMS and MeI).

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52 Recycling of the feed was not mentioned by the authors of ref. 44 (process 27).

53 At high temperatures, batch reactions with MeOH proceed under high autogenous pressures. For instance, at 320 bar, a volume of 90 mL of methyl alcohol generates 60 bar of pressure (see ref. 9b). Therefore, c.-f. methods are always recommended with volatile alcohols, to avoid hazardous conditions.

54 The formation of the toxic methanol as a co-product of DMC-mediated methylations (Scheme 3, 4 and 6), might somewhat mitigate the environmental benefits of DMC. Methanol is usually isolated (and disposed) by filtration/distillation, under conditions which are more controlled (and safer) than those used for the reactions. A thorough assessment of this problem should however, be carried out by toxicological metrics, not pertinent to this work.