

Dimethyl Carbonate as a Methylating Agent. The Selective Mono-C-methylation of Alkyl Aryl Sulfones

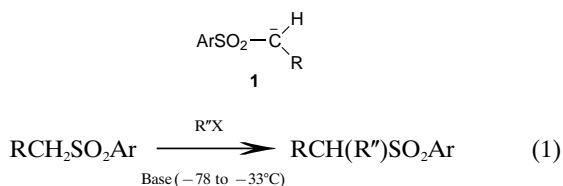
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At 180–210 °C, α -methylene sulfones (both benzyl aryl and alkyl aryl sulfones, $\text{RCH}_2\text{SO}_2\text{Ar}$: $\text{R} = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$, $\text{Ar} = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$, $p\text{-MeC}_6\text{H}_4$, and $\text{R} = \text{Me}$, $\text{Ar} = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$, $p\text{-MeC}_6\text{H}_4$) react with dimethyl carbonate to yield the corresponding mono-C-methyl derivatives $[\text{RCH}(\text{CH}_3)\text{SO}_2\text{Ar}]$ in a selectivity >99%, at conversions of 76–99% (isolated yields: 97–92%).

α -Sulfonyl carbanions, e.g. **1**, may react with a number of different electrophiles yielding, for example, condensation with esters, aldehydes and isocyanates, though their most widely used reaction is by far nucleophilic displacement with alkyl halides [eqn. (1)].



$\text{R} = \text{aryl, alkyl}$; base = BuLi; MNH₂ (M = Li, Na, K)

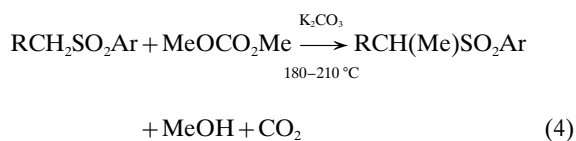
However, the generation of carbanions **1** necessitates very strong bases.^{1,3–5} Only in the case of triflones ($\text{RCH}_2\text{SO}_2\text{CF}_3$)⁷ may mild bases act efficiently to promote alkylations; however, triflones themselves are not always accessible.¹

An alternative route for alkylation processes can be conceived with the use of dialkyl carbonates (DAICs) as alkylating agents. In particular, dimethyl carbonate (DMC) is an excellent methylating agent which allows unprecedented high mono-C- and mono-N-methyl selectivities: derivatives of both aryl- and aryloxy-acetic acid derivatives and primary aromatic amines [$\text{XCH}(\text{CH}_3)\text{W}$: $\text{X} = \text{Ar}$ and ArO , $\text{W} = \text{CN}$ and CO_2Me , and ArNHCH_3 , respectively] have been obtained in 90–99% selectivity at substantially quantitative conversions (up to 99%).^{12–16,17}

This paper reports that also sulfones bearing α -methylene groups (benzyl aryl and alkyl aryl sulfones: $\text{ArCH}_2\text{SO}_2\text{Ar}'$ and $\text{RCH}_2\text{SO}_2\text{Ar}'$) can be effectively mono-C-methylated (selectivity >99%) by DMC, even when a mild base (K_2CO_3) is used.

Batchwise reactions are performed in an autoclave by loading a mixture of the substrate, K_2CO_3 and DMC in a 1:2:130–210 molar ratio, respectively, DMC acting both as the methylating agent and the solvent.

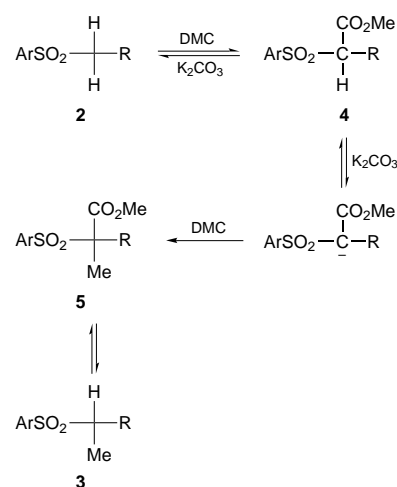
At 180–210 °C, mono-C-methylations of benzyl aryl and alkyl aryl sulfones [$\text{ArCH}_2\text{SO}_2\text{Ar}'$, **2a–c** and **2g–h**: $\text{Ar} = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$; $\text{Ar}' = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$, $p\text{-MeC}_6\text{H}_4$, and $\text{RCH}_2\text{SO}_2\text{Ar}'$, **2d–f**: $\text{R} = \text{Me}$; $\text{Ar}' = \text{Ph}$, $p\text{-ClC}_6\text{H}_4$, $p\text{-MeC}_6\text{H}_4$) proceed with a selectivity >99% (at conversions of 95–99%), and afford good to high yields (77–92%) of isolated products [**3a–h**; eqn. (4)].



| | R | Ar | T/°C | Yield (%) |
|-----------|---|---|------|-----------|
| 3a | Ph | Ph | 180 | 78 |
| 3b | <i>p</i> -ClC ₆ H ₄ | Ph | 180 | 76 |
| 3c | <i>p</i> -MeC ₆ H ₄ | Ph | 180 | 92 |
| 3g | Ph | <i>p</i> -ClC ₆ H ₄ | 180 | 80 |
| 3h | <i>p</i> -ClC ₆ H ₄ | <i>p</i> -ClC ₆ H ₄ | 180 | 81 |
| 3d | Ph | Me | 200 | 85 |
| 3e | <i>p</i> -ClC ₆ H ₄ | Me | 200 | 77 |
| 3f | <i>p</i> -MeC ₆ H ₄ | Me | 210 | 76 |

A major influence on reactivity arises from the different aryl and alkyl groups directly bound to the methylene reacting group: thus benzyl aryl sulfones ($\text{ArCH}_2\text{SO}_2\text{Ar}'$: **2a–c, g–h**) are efficiently mono-methylated at 180 °C while alkyl aryl sulfones ($\text{MeCH}_2\text{SO}_2\text{Ar}$: **2d–f**) do not, and actually require a more elevated reaction temperature of 200–210 °C for the reaction to go to completion. Such a behaviour seems to be clearly related to the stabilization of aryl sulfonyl carbanions [$\text{ArSO}_2\text{CHAr}'$ formed during the reactions] induced by the resonance with the adjacent Ar' group.

The methylation of the sulfones **2a–h** follows, in all likelihood, the mechanistic pattern reported for aryl- and aryloxy-acetic acid derivatives.^{14–16} Accordingly, the monomethyl selectivity is explicable through the occurrence of two consecutive nucleophilic displacements (Scheme 1): (i) a methoxycarbonylation of the initially formed sulfonyl carbanion [$\text{ArSO}_2\text{CH}^-\text{R}$] ($B_{\text{Ac}}2$ mechanism) followed by (ii) a methylation of the resulting intermediate [$\text{ArSO}_2\text{CH}(\text{CO}_2\text{Me})\text{R}$ (**4**)] yielding the methyl derivative [$\text{ArSO}_2\text{C}(\text{Me})(\text{CO}_2\text{Me})\text{R}$, (**5**); $B_{\text{Al}}2$ mechanism]. Finally, compound **5** undergoes a de-methoxycarbonylation reaction to the final product [$\text{ArSO}_2\text{CH}(\text{Me})\text{R}$].



Scheme 1 Suggested mechanism for the mono-C-methylation of alkyl aryl sulfones with dimethyl carbonate

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Both intermediates **4** and **5** are detected during the reaction of DMC with sulfones **3a–h** (maximum amount of 10–30%, by GC; structures assigned by GC–MS).

Also, methyl aryl sulfones (ArSO_2CH_3) react with DMC as in Scheme 1: the formation of methoxycarbonylated compounds ($\text{ArSO}_2\text{CH}_2\text{CO}_2\text{Me}$) as intermediates, allows the homologation of the methyl group to a isopropyl one. Thus, PhSO_2Me yields $\text{PhSO}_2\text{CHMe}_2$ and $\text{PhSO}_2\text{C}(\text{CO}_2\text{Me})\text{Me}_2$ (**6**) (12 and 81%, respectively; 14 h at 180 °C; conversion 93%). Likewise, $\text{PhCH}_2\text{SO}_2\text{Me}$ affords $\text{PhCH}(\text{Me})\text{SO}_2\text{CHMe}_2$ and $\text{PhCH}(\text{Me})\text{SO}_2\text{C}(\text{CO}_2\text{Me})(\text{Me})_2$ (**7**) (14 and 50%, respectively; 21.5 h at 180 °C; conversion 98%). Compounds **6** and **7** have been isolated in 63 and 34% yields, respectively (characterized by ^1H and ^{13}C NMR spectra).

^1H NMR and GC–MS spectra are given in the full text for all products.

The synthesis here discussed has both synthetic advantages and remarkable environmental benefits: (i) it affords selectively only mono-methyl derivatives; (ii) it uses an intrinsically safe methylating agent (DMC) in place of the toxic methyl chloride (or dimethyl sulfate); (iii) it gives neither organic nor inorganic by-products (alkylation procedures using alkyl halides cannot avoid the formation of stoichiometric amounts of inorganic salts to be disposed of); (iv) it does not require additional solvents. Moreover, the procedure discloses intriguing perspectives of the chemistry of sulfonyl carbanions since it shows that these anionic moieties can actually be generated also in the presence of very mild bases.

Techniques used: ^1H and ^{13}C NMR, GC and GC–MS

References: 24

Table 1: Yields, reaction temperature and times, purification for products **3a–h**

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