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Methylation of 1,8-dihydroxy-9,10-anthraquinone with and without use of solvent-free technique☆

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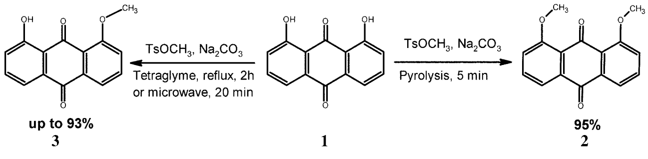
Abstract—A convenient and environmentally friendly solvent-free procedure has been developed for dimethylation of 1,8-dihydroxy-9,10-anthraquinone with excellent yield. A highly selective monomethylation of 1,8-dihydroxy-9,10-anthraquinone in refluxing tetraglyme makes monomethylated *peri*-dihydroxy-9,10-anthraquinones easily available. Alternatively, irradiation in a domestic microwave oven has been employed for the solvent-free monomethylation of 1,8-dihydroxy-9,10-anthraquinone.

In the course of our current research we encountered a necessity to synthesize 1,8-dimethoxy-9,10-anthraquinone (**2**) in large quantities. The known procedure of dimethylation[1] of 1,8-dihydroxy-9,10-anthraquinone (**1**) employs carcinogenic dimethylsulfate, dangerous sodium hydride, flammable tetrahydrofuran, takes 2–4 days for completion and provides a moderate yield of 57%.

The suggested procedure is a fast, convenient and environmentally friendly method for the complete methylation of **1** by heating of a ground mixture of **1**, methyl tosylate and sodium carbonate taken in a molar ratio of 1:2.8:1.6 at 320°C in a 6″ test tube open to air for 5 min (Scheme 1). This procedure represents solvent-free reactions that have received a great deal of attention due to their simplicity and usefulness in novel green chemistry technologies[2]

The procedure does not require chromatographic separation and provided a nearly quantitative yield (95%) of **2**.



Scheme 1.

The methylation system used (methyl tosylate with sodium carbonate) is known and was applied before to the methylation of 1,4-dihydroxy-9,10-anthraquinone and required continuous refluxing (20 h) in toxic 1,2-dichlorobenzene followed by concentration in vacuum and chromatographic separation.[3]

Refluxing of the same reactants taken at the same ratio, in tetraglyme for 2 h led to highly selective monomethylation of the starting **1** (Scheme 1) and produced 1-hydroxy-8-methoxy-9,10-anthraquinone (**3**)[4] in excellent yield (93%). The use of a high boiling solvent is essential for the reaction. Our attempt to methylate **1** by refluxing with methyl tosylate and sodium carbonate in acetone failed and only the starting material **1** was isolated.

Use of a microwave-assisted solvent-free technique for monomethylation of **1** also proved to be quite selective. Although the solvent-free procedure provided a lesser yield of monomethylation (61% versus 93%), it required less time (20 min versus 2 h) and did not require any solvents.

Although both 1,8-dimethoxy-9,10-anthraquinone **2** and 1-hydroxy-8-methoxy-9,10-anthraquinone **3** are known,[1,4] we obtained an additional proof of the structure of **2** by the single crystal X-ray analysis and a proof for the structure of **3** by a separate experiment of its methylation to **2**.

Interestingly, monomethylation of **1** in tetraglyme proved to be very selective. The methylating system taken in a two-fold excess produced exclusively the

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monomethylated product **3**. The selectivity might be attributed to a decreased stability of the intermediate anion on the second step of methylation due to the strong repulsion between the phenoxide, methoxy- and carbonyl oxygen of the species.

The developed solvent-free procedure of dimethylation provides an easy access to peri-dimethoxyanthraquinones, starting compounds for synthesis of model bicyclic systems for studies of electron transfer.[1] We have shown that the solid state procedure can be safely scaled up to at least 50 g of the starting reaction mixture without any indication of self heating or going the reaction out of control. Of special interest are derivatives of 1-hydroxy-8-methoxy-9,10-anthraquinone (**3**) that are capable of intercalating into DNA[5] and can be easily accessed via our selective protocol of monomethylation. So far, synthesis of this class compounds was carried out by complete methylation followed by partial hydrolysis.[4]

Besides the synthetic value of the suggested solvent free protocols, they are carried out within a standard laboratory period and therefore can be used for educational purposes to introduce students to environmentally safe 'green chemistry' techniques for organic synthesis.

Supplementary material

Experimental procedures and ^{1}H NMR spectra for compounds **2** and **3**, X-ray diffraction data for the compound **2**.

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