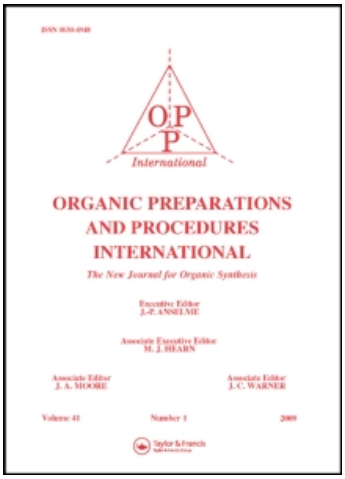

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A Practical Synthesis of 2-Bromo-6-methoxynaphthalene

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A Practical Synthesis of 2-Bromo-6-methoxynaphthalene

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2-Bromo-6-methoxynaphthalene (**2**) is an important intermediate in the preparation of non-steroidal anti-inflammatory agents,[1,2] such as 4-(6-methoxy-2-naphthyl)- 2-butanone (*nabumetone*) and 2-(6-methoxy-2-naphthyl)propionic acid (*naproxen*). A survey of the literature indicates that several synthetic procedures[1–8] already exist. Among them, methylation of 6-bromo-2-naphthol (**1**) to give 2-bromo-6-methoxynaphthalene (**2**) with dimethyl sulfate[2,3] and methyl halides[4–6] are most commonly used. Methyl chloride[5] and methyl bromide[6] are gases at room temperature and thus have a limited utility. However, other reagents (dimethyl sulfate and methyl iodide) present serious toxicological and carcinogenic risks due to their volatility and their ability to methylate nucleic acids in living organisms.

Environmental and toxicological concerns have resulted in increased interest in new methylating reagents. As a consequence, Maras *et al*.[7] developed an efficient synthesis of 2-bromo-6-methoxynaphthalene (**2**) using tetramethylammonium chloride as a methylating agent, but the reaction was carried out under microwave-assisted conditions. Alternatively, Raju *et al*.[8] reported a site-directed nuclear bromination by two-phase electrolysis of 2-methoxynaphthalene and sodium bromide to obtain **2**. The high yield accompanied with high regioselectivity of the electrochemical method might prove promising for future industrial use.

Recently, dialkyl carbonate and in particular dimethyl carbonate (DMC) was used as an environmentally benign substitute for methyl halides and dimethyl sulfate.[9] Carbon dioxide and methanol, which can be easily removed from the reaction medium, are the only by-products formed.

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As a continuation of our interest in the study of medicinal compounds,[10–11] we have developed a practical pilot-scale method for the preparation of 2-bromo- 6-methoxynaphthalene (**2**) from DMC and 6-bromo-2-naphthol (**1**) (*Scheme 1*); the latter was easily prepared by a previous reported two-step bromination of 2-naphthol.[1,3,6]

1 **2**

Scheme 1

It is noteworthy that in this process only catalytic amount of base and no additional solvent were used.

Experimental Section

Mps and bps are uncorrected. The purity of products was established on an Agilent 1100 HPLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 (400 MHz) instrument with TMS as internal standard. All chemicals were reagent grade and available commercially. The elemental analysis was performed on a Flash EA1112 instrument.

2-Bromo-6-methoxynaphthalene (2)

In a 100 mL round-bottomed flask, fitted with a mechanical stirrer, an addition funnel, and a reflux condenser fitted with a calcium chloride drying tube, was placed 22.3 g (0.10 mol) of 6-bromo-2-naphthol (**1**), 2.76 g (0.02 mol) of potassium carbonate and 2.78 g (0.01 mol) of tetrabutylammonium chloride. The temperature was raised to 135°C (oil bath) and dimethyl carbonate 9.9 g (0.11 mol) was added dropwise over 6 h while the temperature was kept between 130–135°C. Then the mixture was distilled to expel excess dimethyl carbonate and formed methanol, then cooled to room temperature. The residue was dissolved in 140 mL of ethanol and filtered. The filtrate was concentrated to 60 mL, cooled to 5°C and the precipitated crystals collected and dried *in vacuo* to afford 22.4 g (95%) of the product (**2**) as a pale-yellow solid (HPLC >98.5%). ^{1}H NMR ($CDCl_3$): δ3.89 (3 H, s), 7.07 (1 H, d, J = 2.8 Hz), 7.14 (1 H, dd, J = 2.8, 9.2 Hz), 7.48 (1 H, dd, J = 2.0, 8.8 Hz), 7.58 (1 H, d, J = 8.8 Hz), 7.62 (1 H, d, J = 8.8 Hz), 7.89 (1 H, d, J = 1.6 Hz). ^{13}C NMR ($CDCl_3$): δ 157.9, 133.0, 130.0, 129.6, 129.5, 128.5, 128.3, 119.7, 117.0, 105.7, 55.3. An analytical sample was prepared by recrystallization from ethanol, mp. 102.5–103.5°C, *lit*.[1] mp. 102.5–104°C.

Anal. Calcd. for $C_{11}H_9BrO$: C, 55.72; H, 3.83. Found: C, 55.58; H, 3.89.

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