Convenient Syntheses of Nabumetone

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Dedicated to Professor W. Hilger on the occasion of his 60th birthday.

Two novel and convergent one- and two-step syntheses of 4-(6′-methoxy-2′-naphthyl)-2-butanone (nabumetone, **6**) via palladium-catalyzed coupling of 2-halo-6-methoxynaphthalene (**1**) with 3-buten-2-ol (**2**) and 3-buten-2-one (**3**) are described. The product is obtained in 60–92% yield.

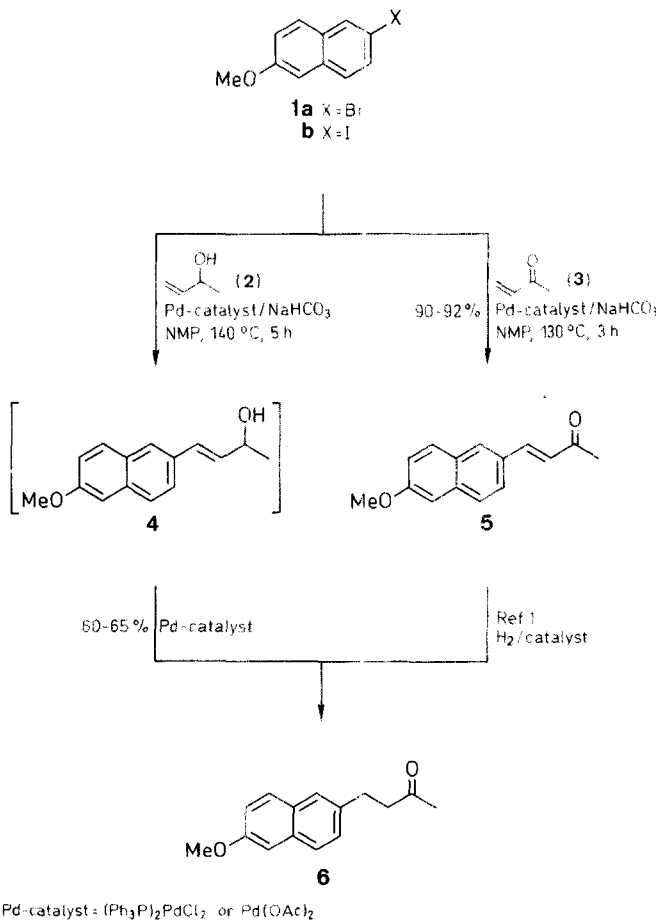
Nabumetone, 4-(6′-methoxy-2′-naphthyl)-2-butanone (**6**), like α-arylpropionic acids ibuprofen and naproxen, has been shown to possess good non-steroidal anti-inflammatory (NSAI) activity. However, unlike α-arylpropionic acids, gastro-intestinal irritation is often reduced or eliminated as a result of **6** being devoid of a carboxyl moiety.[1]

Currently, **6** is synthesized in several steps from 2-bromo-6-methoxynaphthalene (**1a**) via 6-methoxy-2-naphthalenecarbaldehyde.[1,2] Other synthetic approaches to **6** via 6′-methoxy-2′-acetonaphthone[3] and 2-methoxynaphthalene[4] are also reported in the literature. More economical synthetic routes, with fewer reaction steps would be desirable. Consequently, we have used palladium-catalyzed coupling methodology in developing both a one- and two-step synthesis of **6** by treating **1** with 3-buten-2-ol (**2**) and 3-buten-2-one (**3**), respectively.

Palladium-catalyzed coupling of aryl and vinyl halides with vinylic compounds has been described both by Heck[5] and Mizoroki et al.[6] Palladium-catalyzed coupling of aryl halides with allylic alcohols for the synthesis of aldehydes and ketones is also well documented in the literature.[7,8] Aryl iodides, which are relatively inaccessible, are most commonly used as substrates in these coupling reactions. We therefore sought to develop palladium-catalyzed coupling reactions of allylic alcohols and α,β-unsaturated ketones using bromonaphthalenes as substrates.

Palladium-catalyzed coupling of **1a** with **2** to afford **6** was studied using two different catalysts. Using palladium acetate, triphenylphosphine, and sodium bicarbonate in 1-methyl-2-pyrrolidone at 140 °C for 5 hours, the reaction proceeded with complete conversion of **1a**, and **6** was formed in 60% yield. With bis(triphenylphosphine)palladium(II)chloride as the catalyst, we again observed complete conversion of **1a**, and **6** was isolated in 65% yield. The product also contained 4-(6′-methoxy-2′-naphthyl)-3-buten-2-ol (**4**) (9%) as the major impurity. The unsaturated alcohol **4** is probably formed as an intermediate by the initial palladium-catalyzed coupling of **1a** with **2**. Palladium-catalyzed isomerization of allylic alcohol function in **4** affords **6**. Similar observations have been reported in the palladium-catalyzed coupling of 3-bromopyridine with allylic alcohols.[9]

We have also studied the synthesis of 4-(6′-methoxy-2′-naphthyl)-3-buten-2-one (**5**), an intermediate in the commercial production of **6**, by reacting **1a** with **3** in the presence of a palladium catalyst. The reaction was carried out using 1.2 equivalents of **3**, sodium bicarbonate, bis(triphenylphosphine) palladium(II) chloride in 1-methyl-2-pyrrolidone at 130 °C for 3 h in an autoclave under nitrogen pressure. The reaction



proceeded with complete conversion of **1a** and **5** was isolated in 90% yield. Catalytic hydrogenation of the double bond, as described in the literature[1] would afford **6**.

In an effort to determine the relative reactivity of naphthyl bromide, the reaction of 2-iodo-6-methoxynaphthalene **(1b)** with **3** was carried out using bis(triphenylphosphine)palladium(II) chloride as a catalyst at 130 °C for 2 hours. The reaction proceeded with complete conversion of **1b** and **5** was isolated in 92% yield. As expected, **1b** reacts at a faster rate in comparison to **1a**. However, commercial availability of **1a** makes it more attractive starting material for the synthesis of **6**.

2-Bromo-6-methoxynaphthalene **(1a)**, 3-buten-2-ol **(2)**, 3-buten-2-one **(3)**, 1-methyl-2-pyrrolidone, $(Ph_3P)_2PdCl_2$ and $Pd(OAc)_2$ were purchased and used without further purification. ^1H- and ^{13}C-NMR spectra were obtained on Varian EM-360 and IBM AF-200 Spectrometers. GLC analysis was performed on a Hewlett Packard 5890 gas chromatograph using a 30 meter DB-1, 1.0 micron column with 0.32 I.D.

4-(6′-Methoxy-2′-naphthyl)-2-butanone [6-Methoxy-2-(3-oxobutyl)-naphthalene, 6]:

A mixture of 2-bromo-6-methoxynaphthalene (**1a**; 2.37 g, 10 mmol), 3-buten-2-ol (**2**; 1.08 g, 15 mmol), $(Ph_3P)_2PdCl_2$ (0.13 g, 0.18 mmol) and $NaHCO_3$ (1.0 g, 12 mmol) in 1-methyl-2-pyrrolidone (10 mL) is heated at 140 °C under a N_2 atmosphere for 5 h. After cooling to r.t., addition of the mixture to water causes a solid to precipitate. The mixture is filtered and the solid is dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 solution is dried ($MgSO_4$) and filtered through a celite pad. Concentration of the filtrate affords a solid (1.9 g). GC analysis of the crude product shows that **6** is present in 76% purity (65% yield). A small sample of the crude product is purified by crystallization using hexane/Et_2O (95:5); mp 76–79 °C (Lit.[1] mp 80–81 °C).

IR (KBr): ν = 1708 (C=O), 1607 cm^{-1}.

^1H-NMR ($CDCl_3$): δ = 2.16 (s, 3H); 2.79–2.87 (m, 2H); 2.99–3.08 (m, 2H); 3.91 (s, 3H, OCH_3); 7.11–7.70 (m, 6 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 29.7, 30.1, 45.1, 55.2, 105.6, 118.8, 126.2, 126.9, 127.5, 128.9, 129.0, 133.1, 136.1, 157.3, 207.9 (C=O).

MS (70 eV): m/z (%) = 228 (M^+, 40); 185 (15); 171 (100); 43 (51).

4-(6′-Methoxy-2′-naphthyl)-3-buten-2-one [6-Methoxy-2-(3-oxobutenyl) naphthalene, 5]:

From **1a**: A mixture of 2-bromo-6-methoxynaphthalene (**1a**; 5.92 g, 25 mmol), 3-buten-2-one (**3**; 2.1 g, 30 mmol), $(Ph_3P)_2PdCl_2$ (0.32 g, 0.45 mmol), and $NaHCO_3$ (2.5 g, 30 mmol) in 1-methyl-2-pyrrolidone (NMP, 60 mL) is sealed in an autoclave. The autoclave is purged with N_2 and the mixture is placed under a N_2 atmosphere (1.7 bar) and heated at 130 °C for 3 h. The autoclave is cooled, depressurized and the contents are added to water (500 mL). The ensuing solid is collected by filtration and dissolved in CH_2Cl_2 (150 mL). The CH_2Cl_2 solution is dried ($MgSO_4$) and filtered through a celite pad. Concentration of the filtrate affords **5** as a solid; yield: 5.3 g (90%); purity 96%. A small portion of the product is purified by recrystallization from EtOH to afford white crystals; mp 120–121 °C (Lit.[1] mp 120 °C).

^1H-NMR ($CDCl_3$/TMS): δ = 2.37 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 6.74 (d, 1H, J = 16 Hz, =CH); 7.07–7.17 (m, 2H, 1 H_{arom} + =CH), 7.55–7.79 (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 27.3, 55.2, 105.9, 119.3, 124.0, 126.1, 127.4, 128.5, 129.6, 129.9 (2 C), 135.7, 143.5, 158.8, 198.0 (C=O).

MS (70 eV): m/z (%) = 226 (M^+, 78); 211 (100); 183 (46); 139 (46).

From **1b**: The reaction with 2-iodo-6-methoxynaphthalene[10] (**1b**; 7.1 g, 25 mmol) with **3** (2.1 g, 30 mmol) is carried out as above for 2 h. The reaction mixture is worked up as above to afford **5**; yield: 5.6 g (92%); purity 93% (GC).

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