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Short Note

1-{4-[(Hexyloxy)methyl]pyridin-2-yl}ethanone

Florian Charrier, Jérôme Husson * and Laurent Guyard

Institut UTINAM UMR CNRS 6213, UFR Sciences et Techniques, Université de Bourgogne-Franche-Comté, 16 route de Gray, 25030 Besançon cedex, France; florian.charrier@univ-fcomte.fr (F.C.); laurent.guyard@univ-fcomte.fr (L.G.)

* Correspondence: jerome.husson@univ-fcomte.fr; Tel.: +33-3-8166-6291

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Abstract: A new member of the 2-acetylpyridine family has been prepared and characterized. Its synthesis is a two-step process starting from a pyridyl-alcohol in which the ketone moiety is protected as a cyclic acetal. Alkylation of the alcohol followed by hydrolysis of the acetal afforded the title compound in 52% overall yield.

Keywords: 2-acetylpyridine; alkylation; acetal-deprotection

1. Introduction

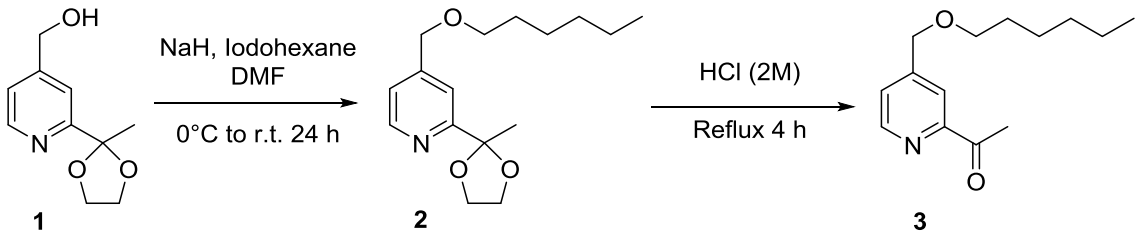
2-Acetylpyridine derivatives are interesting synthetic intermediates. For example, such compounds have been used as starting materials in the preparation of potential anti-cancer agents [1–3], of complexes with anti-microbial properties [4,5], of pyridinyl-pyrimidines [6], of catalysts [7–9], materials for water treatment [10] or molecules possessing magnetic properties [11] just to name a few.

Furthermore, 2-acetylpyridine have been widely used in Kröhnke's synthesis [12,13] of terpyridines [14–16], which are increasingly used in many applications [17]. As a consequence, the development of new 2-acetylpyridine derivatives is of great interest in view of the broad range of possible applications for these molecules.

This paper described the preparation of 1-{4-[(hexyloxy)methyl]pyridin-2-yl}ethanone, which is one member of this 2-acetylpyridine family.

2. Results and Discussion

The synthesis of 1-{4-[(hexyloxy)methyl]pyridin-2-yl}ethanone (**3**) is a two-step process, starting from alcohol derivative (**1**), which can be obtained either from methyl or ethyl 2-acetylisonicotinate [18–20] according to a procedure described in the literature [21] (Scheme 1).



Scheme 1. Synthetic route to 1-{4-[(hexyloxy)methyl]pyridin-2-yl}ethanone.

Intermediate 4-[(hexyloxy)methyl]-2-(2-methyl-1,3-dioxolan-2-yl)pyridine (**2**) (Figure 1) [22] was obtained by *O*-alkylation of **1** with iodohexane. Infrared (IR) spectra of **2** indicate the disappearance of

the O–H valence vibration band at 3607 cm^{-1}, while new C–H vibrations bands from the hexyl chain arise between 2959 and 2861 cm^{-1}, and account for ether formation.

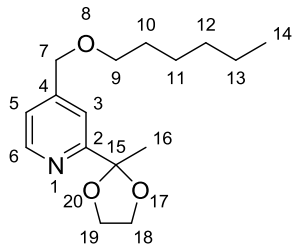


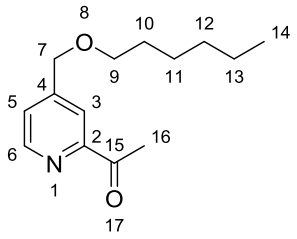
Figure 1. Structure and atom numbering of Intermediate Compound **2**.

Deprotection of the ketone function was carried out in an acidic aqueous solution under reflux. Compound **3** was obtained with an overall yield of 52% over the aforementioned two steps. Regarding the IR spectra, a new valence vibration band at 1697 cm^{-1}, corresponding to the ketone group (C=O vibration), was observed. With regard to ^{1}H-NMR spectra, an intense magnetic deshielding was detected with respect to protons of the methyl ketone group in **3** (H_{16}, δ = 2.73 ppm) compared with the same protons on Compound **2** (H_{16}, δ = 1.66 ppm). The ^{13}C-NMR spectrum confirms the presence of a new peak at 200.0 ppm, which can be attributed to the carbon of the ketone function.

3. Materials and Methods

All reagents were purchased from commercial suppliers and used as received. Flash chromatography was carried out on a Combiflash Rf^{+} Lumen (Teledyne ISCO, Lincoln, NE, USA) using 80 g silica column from Macherey-Nagel. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AC 400 (Bruker, Wissembourg, France) at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. IR spectra were recorded as dichloromethane solutions (C = 0.055 mol·L^{-1}) on an IR Affinity spectrometer (Shimadzu, Kyoto, Japan). Elemental analyses were performed at Service d'Analyses Elementaires, UMR 7565 CNRS, Vandoeuvre-les-Nancy, France.

1-{4-[(Hexyloxy)methyl]pyridin-2-yl}ethan-1-one (**3**)



4-(hydroxymethyl)-2-(2-methyl-1,3-dioxolan-2-yl)pyridine (**1**) [21] (1.38 g, 7.07 mmol, 1 equiv) was dissolved in 20 mL of DMF. The mixture was cooled at 0 °C, NaH (60%) (7.78 mmol, 1.1 equiv) was added, and the mixture was stirred for 30 min. Iodohexane was added (1.15 mL, 7.78 mmol, 1.1 equiv), and the mixture was stirred at room temperature for 24 h. One hundred fifty milliliters of water was added, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (2 × 40 mL), brine (40 mL), dried over Na_2SO_4, and filtered, and the solvent was evaporated. Purification by flash chromatography (eluent: hexane/ethyl acetate: 75/25) yielded **2** as a colorless oil (1.34 g, 68%).

Compound **2** (4.16 g, 14.9 mmol, 1 equiv) was added with aqueous HCl (2M, 30 mL). The mixture was stirred at reflux for 4 h. After cooling occurred, a saturated solution of Na_2CO_3 (30 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and filtered, and the solvent was evaporated.

Purification by flash chromatography (eluent: hexane/ethyl acetate: 90/10 to 70/30) yielded **3** as a colorless oil (2.65 g, 76%). ^{1}H-NMR ($CDCl_3$, 400 MHz), δ (ppm) = 8.65 (d, $1H_6$, J = 4.9 Hz), 7.98 (s, $1H_3$), 7.49 (d, $1H_5$, J = 4.9 Hz), 4.57 (s, $2H_7$), 3.52 (t, $2H_9$, J = 6.6 Hz), 2.73 (s, $3H_{16}$), 1.65 (quint, $2H_{10}$, J = 7.0 Hz), 1.31–1.04 (m, $6H_{11–13}$), 0.89 (t, $3H_{14}$, J = 6.6 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz), δ (ppm) = 200.0, 153.5; 149.5; 149.0; 125.1; 119.8; 71.4; 70.9; 31.6; 29.6; 25.9; 25.8; 22.6; 14.0. IR 3052, 3007, 2961, 2932, 2861, 1697, 1603 cm^{-1}. Elemental analysis for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found C, 71.46; H, 8.99; N, 5.89.

Supplementary Materials: The following are available online: ^{1}H-NMR, ^{13}C-NMR, IR spectra, elemental analyses reports and FIDs for Compounds (**2**) and (**3**).

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Author Contributions: Florian Charrier, Jérôme Husson, and Laurent Guyard conceived and designed the experiments. Florian Charrier performed the experiments. All authors contributed to data analysis and contributed to the preparation of this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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22. Characterisation data for (**2**): ^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm) = 8.52 (d, $1H_6$, J = 5.0 Hz), 7.43 (s, $1H_3$), 7.14 (dd, $1H_5$, J = 5.0 Hz, 0.8 Hz), 4.45 (s, $2H_7$), 4.04–4.00 (m, $2H_{18}$), 3.82–3.79 (m, $2H_{19}$), 3.44 (t, $2H_9$, J = 6.6 Hz), 1.66 (s, $3H_{16}$), 1.57 (quint, $2H_{10}$, J = 7.0 Hz), 1.34–1.23 (m, $6H_{11–13}$), 0.82 (t, $3H_{14}$, J = 6.9 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz), δ(ppm) = 161.0; 149.4; 148.8; 121.0; 117.5; 108.6; 71.3; 71.3; 64.9; 31.6; 25.8; 25.4; 22.6. IR 3068, *3042*, 2959, 2934, *2861*, 1605 cm^{-1}. Elemental Analysis for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found C, 68.30; H, 8.91; N, 5.07.