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Short Note

2-(1-Methoxycarbonyl-2-phenyleth-1-yl)-1-benzylpyridin-1-ium Bromide

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Abstract: In this work, we report the unexpected conversion of a pyridine derivative into the corresponding *N*-benzylated pyridinium salt due to the presence of unreacted benzyl bromide in the crude product. This transformation was observed at room temperature in a solvent-free environment and without any stirring. These interesting data show how pyridinium salts can be formed in mild conditions, avoiding high temperatures that could promote the degradation of the desired product.

Keywords: quaternary ammonium salts; α-carbon benzylation; *N*-benzylation

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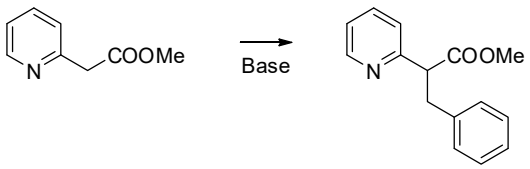
1. Introduction

Quaternary ammonium cations are known as versatile functional groups with various applications in many branches of chemistry. Within organic chemistry, ammonium cations are widely present in structures of phase-transfer compounds [1] (for instance, tetrabutylammonium bromide), drugs (neuromuscular-blocking drugs, cholinergic drugs, antimicrobials [2]), surfactants (phosphatidylcholines) and many others. In synthesis, due to their electrophilic nature, quaternary ammonium cations are also exploited as leaving groups in nucleophilic substitutions [3,4]. The most common method of synthesizing quaternary pyridinium or ammonium salts is the Menšutkin reaction, i.e., simple alkylation with alkyl halides, which often requires heat [5–7]. Pyridinium salts are often formed in toluene, acetone or acetonitrile, always at high temperatures [8,9]. While designing the synthesis of a second family of derivatives acting as disease-modifying agents in Parkinson's disease [10–12], we planned as a first step the α-benzylation of commercially available methyl 2-pyridilacetate with benzyl bromide, in basic conditions, giving compound **I** (Figure 1).

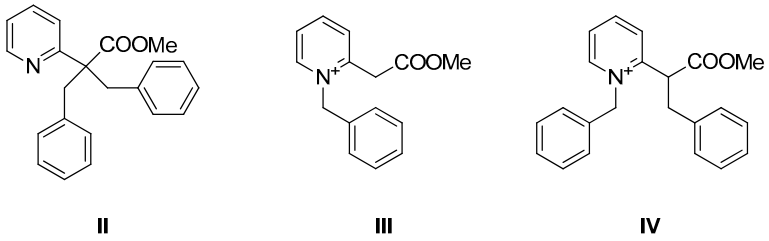


I

Figure 1. α-benzylation of methyl 2-pyridylacetate, the central reaction of the present work.

The main criticisms of this reaction, which affects both the overall yield and product purification, are twofold: the potential double alkylation of the α-carbon, yielding the undesired di-benzylated by-product **II**, and the benzylation of the pyridine nitrogen, with the resulting formation of the quaternary pyridinium salt **III**. The latter is particularly likely if the reaction is conducted at high temperatures. Moreover, another possibility is the initial obtainment of the desired compound **I**, followed by *N*-alkylation with unreacted benzyl bromide present in the reaction mixture, giving the by-product **IV** (Figure 2). Our

goals were to find acceptable conditions to achieve **I** with the highest possible yields while avoiding as much as possible the formation of any potential impurity, like **II**, **III** and/or **IV**.



II **III** **IV**

Figure 2. Structures of by-products **II**–**IV**.

While looking for the best conditions to obtain **I**, avoiding as much as possible the formation of any by-product, we noticed how the reaction's crude product, containing only **I** and unreacted benzyl bromide, spontaneously evolved to the quantitative formation of **IV**, in a complete solvent-free environment and at room temperature, upon standing.

2. Results

To obtain compound **I**, we decided to perform the reaction between methyl 2-pyridil acetate and benzyl bromide using diisopropylethyl amine (DIPEA) as a base instead of K_2CO_3, alcoholates, LDA or sodium hexamethyldisilazane, which are more commonly used as α-alkylate esters. This choice forced us to conduct the reaction at high temperatures, due to the lower basicity of DIPEA compared to the other bases, to observe reactivity. In this regard, we found that 90 °C was the temperature at which complete consumption of methyl 2-pyridilacetate could be observed in around 7 h, although we used a double amount of benzyl bromide. In these conditions, as is typical of pyridinium salt syntheses, we expected the formation of **III** and/or **IV** as by-products. Surprisingly, no traces of **III** or **IV** were found in the ^{1}H-NMR spectrum of the crude product (Figure 3), in which only **I** and an almost equimolar amount of unreacted excess of benzyl bromide were present.

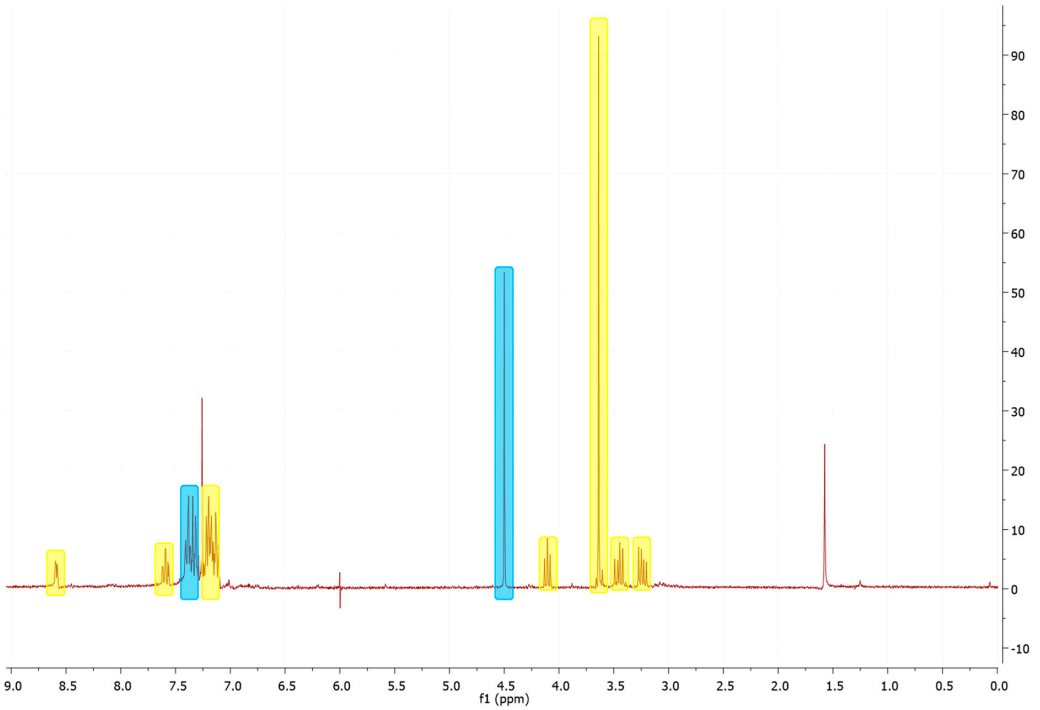


Figure 3. NMR spectrum of the crude product. NMR signals of compound **I** are highlighted in yellow, while unreacted benzyl bromide signals are marked in blue.

Thus, we decided to maintain and use these conditions to perform the reaction and, in particular, to continue along the synthetic pathway without further purification or removal of the unreacted benzyl bromide, since the following reaction should not be influenced by its presence.

Unfortunately, after 72 h, we noticed that the crude product's appearance changed from an oil to a wax and thus decided to re-check the crude product's quality via NMR. Surprisingly, we noticed how, simply upon standing at room temperature, the crude product **I** completely evolved to the formation of **IV**, which was caused by the *N*-alkylation of **I** with unreacted benzyl bromide (Figure 4).

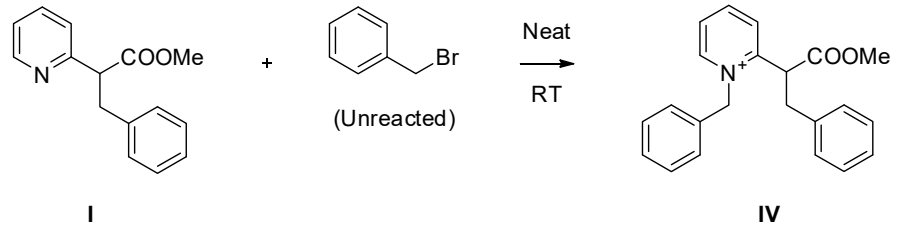


Figure 4. Conversion of **I** to **IV** in neat conditions at room temperature (RT).

The nature of the formed by-product could be easily identified by observing the number of aromatic hydrogens, the peculiar doublets of the benzyl CH_2 signal, at 6.40 and 6.17 ppm, and a shift of pyridine aromatic hydrogen signals to a higher ppm due to the EWG nature of the charged nitrogen was observed (Figure S2).

Interestingly, this quantitative conversion happened in a completely solvent-free environment and at room temperature, in reaction conditions that significantly differ from the "standard" ones employed to obtain quaternary ammonium and pyridinium salts. Then, we further confirmed compound **IV**'s nature using High-Resolution Mass Spectrometry (HRMS) analysis, which identified the expected exact mass as well as the elemental composition (Figure S4), and ^{13}C-NMR (Figure S3).

3. Material and Methods

All the reagents and solvents were acquired from commercial suppliers (Merck, Darmstadt, DE, Fluorochem, Hadfield, UK, and TCI Europe N.V., Zwijndrecht, BE) and used without further purifications. Silica gel matrix, with a fluorescent indicator of 254 nm, was used in analytical thin-layer chromatography (TLC on aluminum foils), and silica gel (particle size 40–63 µm, Merck) was used in flash chromatography with a Puriflash XS 420 (Sepachrom, Rho (Milan), Italy). Visualizations were accomplished with UV light (λ 254 or 280 nm).

The ^{1}H-NMR spectra were measured with a Varian Mercury 300 NMR spectrometer/Oxford Narrow Bore superconducting magnet operating at 300 MHz. The ^{13}C-NMR spectra were acquired at 75 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent as an internal standard. Signal multiplicity is described according to the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, t = triplet and m = multiplet.

HRMS spectra were acquired with a Q-tof SYNAPT G2-Si HDMS 8K (Waters) coupled with an electrospray ionization (ESI) source in positive (ES+) ion mode.

Methyl 3-phenyl-2-(pyridin-2-yl)propanoate (I): DIPEA (1.38 mL, 7.94 mmol) and benzyl bromide (1.57 mL, 13.24 mmol) were added to a solution of methyl 2-pyridilacetate (0.89 mL, 6.62 mmol) in toluene (10 mL). The reaction mixture was heated at 90 °C and stirred for 7 h. Then, the reaction was diluted with ethyl acetate (10 mL), washed once with 10 % aqueous NaCl (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give 1.40 g of an orange oil corresponding to a mixture of **I** and an almost equimolar amount of unreacted benzyl bromide. ^{1}H-NMR ($CDCl_3$): δ 8.59 (ddd, *J* = 4.9, 1.8, 0.9 Hz,

1H), 7.61 (dt, *J* = 7.7, 1.8 Hz, 1H), 7.25–7.08 (m, 7H), 4.12 (t, *J* = 7.8 Hz, 1H), 3.64 (s, 3H), 3.46 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.24 (dd, *J* = 13.8, 7.8 Hz, 1H) ppm.

2-(1-methoxycarbonyl-2-phenyleth-1-yl)-1-benzylpyridin-1-ium bromide (IV): 1.40 g of compound **IV** was obtained from the crude derivative **I**, obtained as mentioned above, upon standing in neat conditions as a yellowish oil. ^{1}H-NMR ($CDCl_3$): δ 10.20 (dd, *J* = 6.2, 1.1 Hz, 1H), 8.54 (dt, *J* = 7.9, 1.4 Hz, 1H), 8.19–8.09 (m, 2H), 7.42–7.34 (m, 3H), 7.20 (m, 3H), 7.15–7.09 (m, 2H), 6.85–6.78 (m, 2H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.17 (d, *J* = 15.6 Hz, 1H), 4.60 (dd, *J* = 8.1, 6.9 Hz, 1H), 3.58 (s, 3H), 3.49–3.39 (m, 1H), 3.09 (dd, *J* = 13.7, 6.7 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$): 168.8, 153.9, 148.5, 146.5, 135.4, 132.3, 129.7, 129.4, 129.1, 128.9, 128.8, 128.7, 127.6, 127.5, 127.2 ppm. HRMS (TOF ES+, Na+-adduct): m/z 332.1650, 333.1682. Calculated mass 332.1645, evaluated mass 332.1650.

4. Conclusions

Within this work, we report the complete and unexpected conversion of a pyridine nitrogen to a quaternary pyridinium salt at room temperature and in neat conditions, without stirring. These interesting results could be further exploited for the obtainment of this important class of compounds, avoiding elevated-temperature conditions that could promote product degradation phenomena.

Supplementary Materials: The following are available online: Figure S1: ^{1}H-NMR spectrum of **I**. Figure S2: ^{1}H-NMR spectrum of **IV**. Figure S3: ^{13}C-NMR spectrum of **IV**. Figure S4: HRMS and elemental composition report of **IV**.

Author Contributions: L.S.: investigation, data curation, writing—original draft preparation, V.S.: supervision, project administration, writing—review and editing, resources. E.V.: conceptualization, supervision, project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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

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