

The Willgerodt-Kindler reaction: direct ^{13}C NMR evidence in support of carbon skeleton integrity

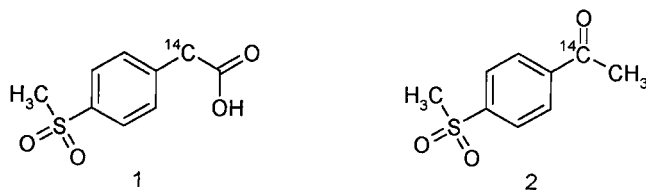
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Discussion

During the course of a lengthy multi-step synthesis of a ^{14}C labelled target compound we were required to prepare [methylene- ^{14}C]4-methylsulfonylphenylacetic acid **1** as an intermediate. The most expedient preparation of **1** appeared to be the Willgerodt-Kindler reaction¹ on acetophenone **2** for if **2** were labelled in the carbonyl position with ^{14}C , earlier studies² had indicated that there should be no carbon skeleton rearrangement. However, because of the importance of the target compound's final application we were still compelled to unequivocally document the position of ^{14}C labelling. We reasoned that a comparison of the ^{13}C NMR of **1** with that of unlabelled standard would be convenient and conclusive.

Therefore, acetophenone **2** was prepared in good overall yield by a two-step process. First, thioanisole was acylated with [carbonyl- ^{14}C]



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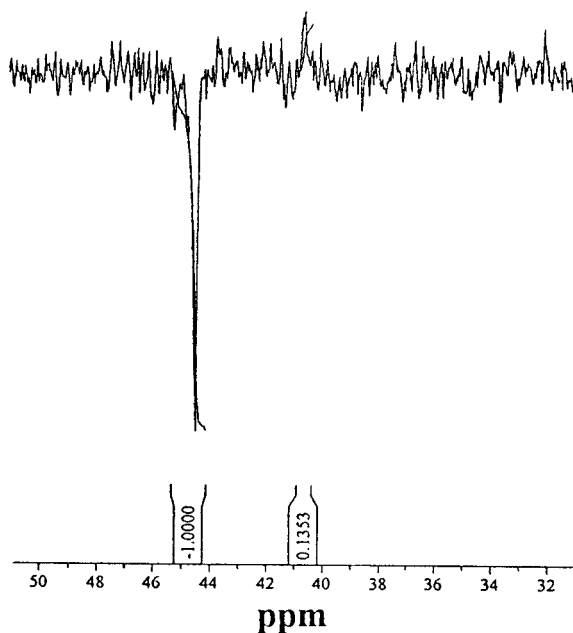


Figure 1. Partial ^{13}C NMR of **1**

acetyl chloride (55 mCi/mmol) using a literature procedure³ to afford [carbonyl- ^{14}C] 4-thiomethylacetophenone which was then oxidized with MCPBA⁴ to obtain **2**. Intermediate **2** co-chromatographed on TLC and provided a proton NMR (CDCl_3) identical with authentic unlabelled standard.[†] Its ^{13}C NMR (CDCl_3) corroborated the carbonyl- ^{14}C labelling position: both methyl resonances were clearly observed at 27 and 44 ppm, but there was no downfield carbonyl resonance.[‡] Acetophenone **2** was then subjected to classic Willgerodt-Kindler reaction conditions using a literature procedure⁵ for the exact unlabelled compound to afford key intermediate **1**. Intermediate **1** co-chromatographed on TLC, provided a convincing mass spectrum and proton NMR (CDCl_3) identical with authentic unlabelled standard,[§] but a different and informative ^{13}C NMR (CDCl_3) (Figure 1) when compared to that of authentic unlabelled standard (Figure 2). As seen above, the ^{13}C NMR of **1** was in large part clearly missing the benzylic methylene resonance at 40.6 ppm due to the major presence of ^{14}C at this position.

[†] Available from Acros Organics, Cat. #42491-0025.

[‡] All ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument using J modulated spin echo with reference on a ghost TMS peak.

[§] Available from Acros Organics, Cat. #42494-0025.

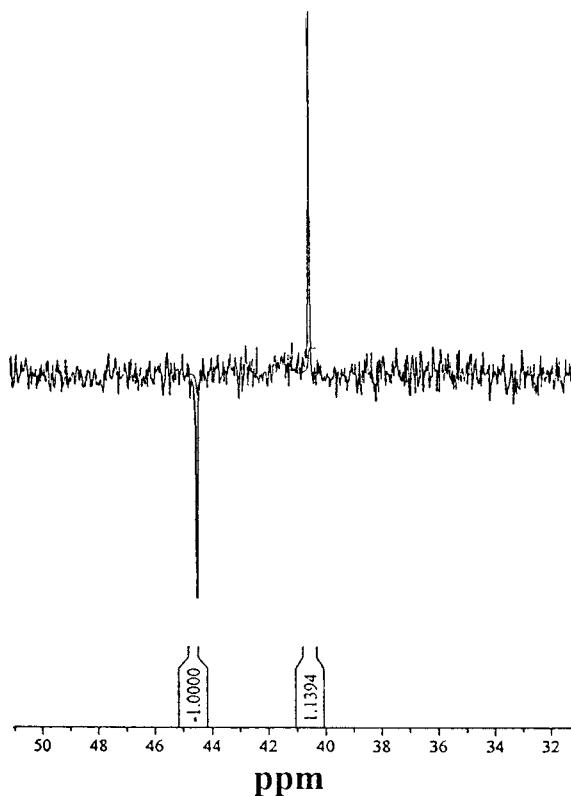


Figure 2. Partial ^{13}C NMR of unlabelled **1**

Our observation directly documents retention of the ^{14}C label at the benzylic position of **1**, thereby supporting the conclusion of earlier investigators² on a key mechanistic aspect of the Willgerodt–Kindler reaction.[†] It also showcases the use of ^{13}C NMR to conveniently elucidate ^{14}C labelling positions, a powerful technique that has only too infrequently been cited in the literature.⁷

References

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[†]We are aware of at least one unsubstantiated report in the literature where the author claims the migration of a methylene- ^{14}C label to the carboxyl group in a Willgerodt–Kindler reaction.⁶

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