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Research Article

Synthesis of *N*-[1-^{13}C]caproyl-*N*′-phenylthiourea

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Summary

An optimal synthesis of *N*-[1-^{13}C]caproyl-*N*′-phenylthiourea with isotopic enrichment 82% is described, starting from barium [^{13}C]carbonate, using five synthetic steps. Yields were 95% relative to caproyl chloride and 46% relative to barium carbonate. Oxidation of the title compound with manganese dioxide yields the corresponding ureide. Structural similarities with anticonvulsants such as phenacemide make *N*-caproyl-*N*′-phenylthiourea an interesting model compound. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: barium [^{13}C]carbonate; 1-[^{13}C]caproic acid; 1-[^{13}C]caproyl isothiocyanate; *N*-[1-^{13}C]caproyl-*N*′-phenylthiourea; phenacemide

Introduction

Many ureides and thioureides exhibit interesting biological activity. Among them, *N*-caproyl-*N*′-phenylthiourea is closely similar to classical anticonvulsants such as phenacemide and ethylphenacemide.[1,2] Carbon-labelled analogues of *N*-caproyl-*N*′-phenylthiourea and *N*-caproyl-*N*′-phenylurea may be useful for pharmacokinetic and pharmacodynamic studies, as well as for metabolic investigations. These types of investigations have been described in detail.[3]

A five-step synthesis of *N*-[1-^{13}C]caproyl-*N*′-phenylthiourea (**7**) is described, starting from barium [^{13}C]carbonate with 82% isotopic enrichment. Manga-

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nese dioxide may be employed to convert **7** into *N*-[1-^{13}C]caproyl-*N*′-phenylurea at room temperature in chloroform solution.[4]

Results and discussion

Commercial barium [^{13}C]carbonate with 82% isotopic enrichment (**1**) was employed for carbonating (**2**) the Grignard reagent.[5] The resulting salt (**3**) was converted into 1-[^{13}C]caproic acid (**4**), which was extracted into ethyl ether. Both ^{13}C- and ^{1}H-NMR spectra were used to characterize compound **4**. The acid chloride (**5**) was then prepared with thionyl chloride, and **5** was treated with an excess of ammonium thiocyanate, whereupon caproyl isothiocyanate (**6**) was formed (an analogous reaction for α-phenylthiourea has been described[6]). The five synthetic steps are presented in Figure 1.

Since the formation of **6** is a critical step in the synthesis, the reaction conditions were optimized. We found that 25 min refluxing in anhydrous acetone was optimal for consuming all the caproyl chloride. A previous report[4] gave 5 min as sufficient for this reaction, but the presence of unreacted acid chloride leads to the formation of an anilide as a by-product, and this by-product is difficult to separate from the target compound. In order to avoid any thermal decomposition, the next step (dropwise addition of aniline to **6** under mechanical stirring) was carried out at 25°C. The formation of the target compound, *N*-[1-^{13}C]caproyl-*N*′-phenylthiourea (**7**), was monitored by TLC. The product was precipitated by addition of methanol, and purified by

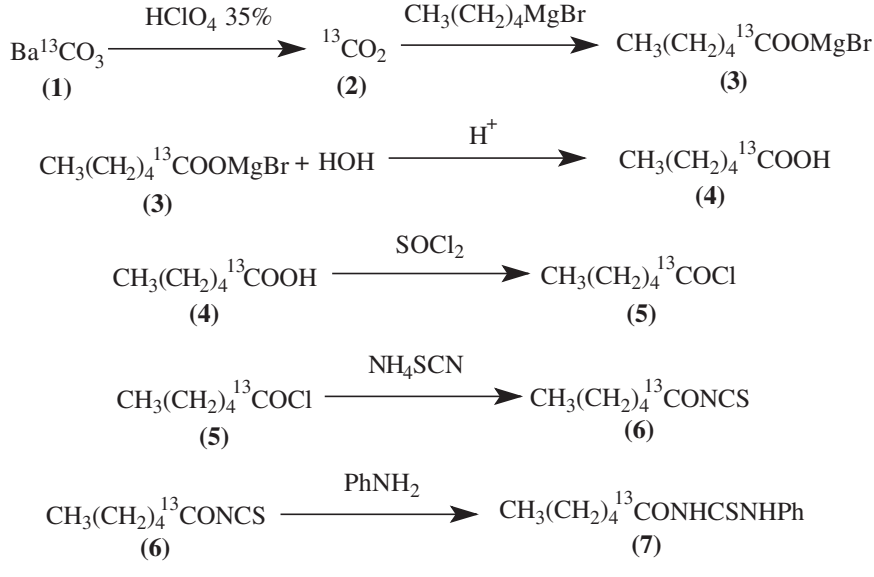

Figure 1. The five reaction steps 1 –> 3 –> 4 –> 5 –> 6 –> 7 for the synthesis of 7 from $Ba^{13}CO_3$

recrystallization from aqueous methanol. The overall yield was 46% with respect to $Ba^{13}CO_3$, and the yield relative to the acid chloride was 95%.

The ^{13}C labeling at the carbonyl group was confirmed by both NMR analysis and EI-MS study. The ^{13}C-NMR spectrum contains the enriched peak at 174.22 ppm. The mass spectrum contains the molecular peaks M at $m/z = 250$ and 251, indicating an 82% enrichment. As expected, the fragmentation pattern preserves the same enrichment ratio for the ions with $m/z = 193$ and 194 ($M - C_3H_7$), and 207 and 208 ($M - C_4H_9$).

Experimental

Chemicals were obtained from commercial sources: Monsanto Research Corporation for $Ba^{13}CO_3$, and Merck for other chemicals. The NMR spectra were recorded at 20°C in $CDCl_3$, using a Bruker Avance 400 DRX at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C analyses. Chemical shifts (δ, ppm) are reported relative to internal tetramethylsilane. The electron-impact mass spectra were recorded with a double-focusing MAT mass spectrometer at an ionization energy of 70 eV. The samples were introduced directly into the ion source and heated gradually in vacuum from 20 to 250°C.

N-[1-^{13}C]caproyl-N′-phenylthiourea (7)

[1-^{13}C]caproic acid (**4**) was prepared from 1.1 mmol of *n*-pentylmagnesium bromide (obtained by adding 1-bromopentane to magnesium turnings in diethyl ether and refluxed until completion of the reaction) and [^{13}C]carbon dioxide was generated from 200 mg (1 mmol) of barium [^{13}C]carbonate and 35% perchloric acid (4.0 ml, 5 mmol). The resulting salt (**3**) was quenched with dilute sulfuric acid, the acid **4** was extracted into 20% aqueous sodium hydroxide (10 ml). After extraction with diethyl ether the aqueous layer was acidified, the acid was extracted in diethyl ether, and the solvent was evaporated under vacuum. Refluxing of **4** with excess thionyl chloride and fractionation under vacuum afforded [1-^{13}C]caproyl chloride (**5**) in 50% yield relative to $Ba^{13}CO_3$.

Ammonium thiocyanate (114 mg, 1.5 mmol) in anhydrous acetone (10 ml) was stirred magnetically until dissolution was complete. A solution of [1-^{13}C]caproyl chloride (68 mg, 0.5 mmol) in anhydrous acetone (10 ml) was then added from a dropping funnel, and the solution was refluxed for 25 min. After cooling to 0°C, a solution of aniline (140 mg, 1.5 mmol) in anhydrous acetone (10 ml) was added, and the mixture was left at 0–5°C overnight. Cold methanol (5 ml) was added to complete the precipitation of the reaction product (**7**), which was isolated by filtration, washed on the filter with cold methanol, and recrystallized from aqueous methanol 1:3 (v/v). Compound **7** (112 mg, 95% yield relative to **5**) was obtained as fluffy white crystals with m.p. 77–78°C, in agreement with the reported data.[7,8]

^{1}H-NMR (δ, ppm): 0.92 (t, J_{HH} = 7.2 Hz, 3H), 1.35 (m, 2H), 1.36 (m, 2H), 1.71 (m, 2H), 2.39 (dd, J_{HH} = 7.3 Hz, J_{CH} = 10.4 Hz, 2H), 7.28 (d, J_{HH} = 8 Hz, 2H), 7.40 (t, J_{HH} = 8 Hz, 1H), 7.64 (d, J_{HH} = 8 Hz, 2H), 8.75 (s, 1H), 12.48 (s, 1H) (400 MHz, $CDCl_3$).

^{13}C-NMR (δ, ppm): 13.85, 22.31, 24.43, 31.15, 37.39 (d, $^{1}J_{CC}$ = 50.0 Hz, α-CH_2), 124.18, 126.91, 128.89, 137.51, 174.22 (C = O), 178.05 (C = S) (100 MHz, $CDCl_3$).

Conclusions

Optimal reaction conditions for preparing *N*-[1-^{13}C]caproyl-*N*′-phenylthiourea (**7**) in 5 steps were determined, starting from barium [^{13}C]carbonate and *n*-pentylmagnesium bromide, followed by reaction with ammonium thiocyanate, and then with aniline.

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