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Note

Optimised synthesis of the ^{15}N-labelled insecticide phosmet (1)

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Summary

A simple strategy for the small-scale synthesis of the ^{15}N-labelled insecticide phosmet has been developed, starting from ^{15}N-phthalimide-K. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: phosmet; stable isotope; ^{15}N

Introduction

Through the use of pesticides in agriculture crops can be effectively protected, but this brings with it problems such as the production of pesticide residues. Whilst extractable pesticide residues and metabolites can readily be analysed by residue analysis techniques, bound residues can not be analysed so simply. One approach to analyse bound residues is by means of immunochemical methods.[1,2] To study the tendency of pesticides to form bound residues, stable isotope compounds can be used in field trials and the amount of bound residues determined through an increased ratio of the stable isotope compared to the untreated samples. By comparison with radio-active labelled compounds, no special radiochemical facilities are required.

The organophosphorous insecticide phosmet, belonging to the group of dithiophosphates, is used in plant protection as well as against parasites on animals in commercially available formulations such as Imidan®, Prolate® or GX-118®.

Results and discussion

In this study, we developed a simple and effective strategy for the small-scale synthesis of the ^{15}N-labelled insecticide phosmet. Previously

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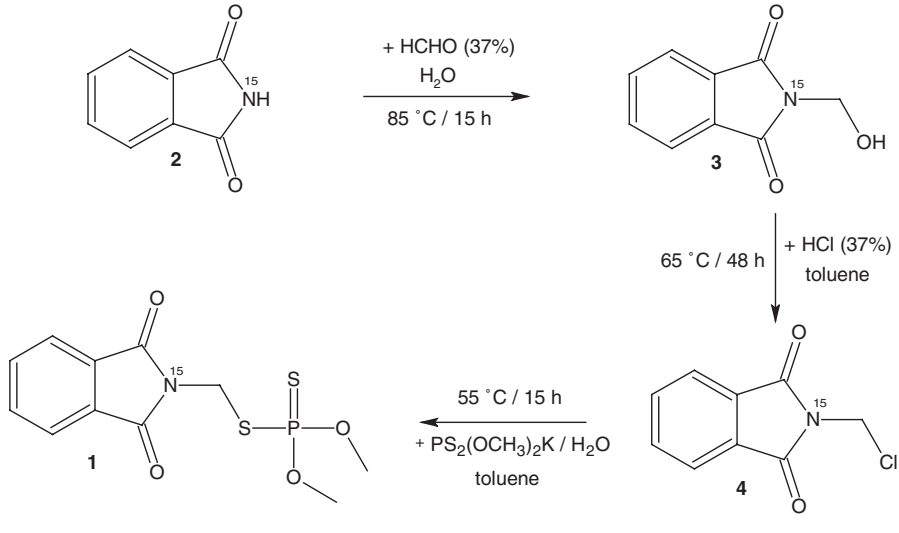
mentionend literature methods[3,4] use different intermediates, such as *N*-chloromethylphthalimide and *N*-hydroxymethylphthalimide. Moreover, different types of catalysis (acid,[4,5] base[6]) are proposed for the reaction of *N*-hydroxymethylphthalimide and *O*,*O*-dimethyldithiophosphate to phosmet. All these methods are geared to synthesize large quantities.

Therefore, the current methods[3] were optimized in order to obtain high yields and to carry out the syntheses on a small scale bearing in mind the high cost of the stable isotope labelled educt. During our first experiments, employing the direct reaction between *N*-hydroxymethylphthalimide and *O*,*O*-dimethyldithiophosphate in concentrated sulfuric acid,[4] we only obtained small yields and numerous unwanted by-products, thereby complicating the isolation of the pure product. For this reason, we chose an alternative strategy of using the intermediates *N*-hydroxymethylphthalimide and *N*-chloromethylphthalimide.

Furthermore, we used 10 ml pressure stable centrifuge tubes which could be easily sealed as reaction vessels. This made the introduction of additional HCl gas unnecessary.

Experimental

The synthesis was carried out as follows (Scheme 1). ^{15}N-Phosmet (phosphorodithioic acid, *S*-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl] *O*,*O*-dimethyl ester, ^{15}N, **1** Scheme 1) was synthesized starting from ^{15}N-phthalimide-K (obtained from Euroisotop, Saarbrücken, Germany; ^{15}N, 98 at%). 4.1 mmol (0.7633 g) of ^{15}N-phthalimide-K were dissolved in deionized water (2 ml) and the solution was neutralized with hydrochloric acid



Scheme 1. Synthesis of ^{15}N-labelled phosmet

(37%, 300 µl) to allow ^{15}N-phthalimide (**2**) to precipitate. The crystallized **2** was spun down in a centrifuge and 5 mg of $NaHCO_3$ and 0.7 ml of formalin solution (37%) were added to the reaction assay.[3] The reaction was carried out for 15 h at 85°C in the closed vessel. The obtained ^{15}N-hydroxymethylphthalimide (**3**) crystallized in the vessel and was isolated from the mother liquor after completed crystallization at 4°C by filtration (0.58 g, yield = 77% of theory).

After addition of 2.5 ml of toluene and 1.8 ml of hydrochloric acid (37%) to **3**, the reaction was performed in the closed vessel at 65°C with agitation over a period of 48 h. The organic layer was separated, and the water phase was extracted with diethyl ether (2 ml) twice. The resulting organic layers (toluene and diethyl ether) were combined and evaporated to dryness. ^{15}N-chloromethylphthalimide (**4**) was obtained as colourless crystals (0.56 g, yield = 86% of theory).

For the synthesis of ^{15}N-phosmet (**1**), 1.0 g of potassium *O*,*O*-dimethyldithiophosphate (synthesized[7] from phosphorous(V)sulphide and absoluted methanol in toluene) was suspended in 2 ml of deionized water. The suspension was added to a toluene solution of the dried **4** (6 ml) and the reaction mixture was shaken vigorously in the closed vessel for 15 h at 55°C. The organic layer was separated and the water phase extracted twice with 2 ml of diethyl ether. The resulting organic layers (toluene and diethyl ether) were combined and evaporated yielding 0.84 g of crude ^{15}N-phosmet (**1**) (93% of theoretical value). The obtained residue was dissolved in methanol and subjected to preparative HPLC.[†] Fractions were collected, the methanol evaporated off and the residual water phase lyophilized (yield after purification = 52% of theory). The overall yield, based on the amount of employed ^{15}N-phthalimide-K resulted in 35% of the theoretical value.

Spectroscopic properties: MS (ESI+) *m/z* 319 ($[M+H]^+$), 336 ($[M+NH_4]^+$), 357 ($[M+K]^+$); MS (EI+) *m/z* 318 (9%, M^+), 161 (100%, M^+-$PS_2(OCH_3)_2$), 133 (6%), 105 (3%), 104 (4%), 93 (8%), 77 (8%), 76 (5%), 63 (2%); ^{1}H NMR, δ (ppm) ($CDCl_3$) 3.83 (6H, d, CH_3), 5.08 (2H, d, CH_2), 7.96-7.80 (4H, m, Ar-H); ^{13}C NMR, δ (ppm) ($CDCl_3$) 54.21 (d, CH_3), 39.19 (dd, CH_2), 123.74, 131.81, 134.5 (s, Ar-C), 166.36 (d, C=O); ^{15}N NMR, δ (ppm) ($CDCl_3$) −221.2; IR (ATR) (cm^{-1}) 3482 (w), 2995 (w), 2950 (w), 2849 (w), 1779 (m), 1718 (s), (C=O), 1607 (w), 1463 (m), 1452 (m), 1404 (s), 1359 (s), 1335 (m), 1294 (m), 1277 (s), 1183 (m), 1066 (s), 998 (s), 914 (s), 830 (s), 816 (s), 796 (s), 722 (s), 691 (w), 675 (w); Accurate mass: $[M+H^+]$ calcd for $C_{11}H_{13}NO_4PS_2$, 318.9994, found, 318.9998 ± 0.0005 (mean of 6 measure-

[†]Preparative HPLC conditions: C18 column (250 × 20 mm 7 µm); mobile phase methanol and 10 mM ammonium formate buffer, (pH 4.0); gradient 0/50, 1/80, 12/100, 20/100, 28/50, 31/50 (min/% of methanol). UV detection 220 nm.

ments ± SD), melting point: 74°C, UV(methanol): λ_{max}(nm): 222 ($\log \varepsilon = 4.6$); 294 ($\log \varepsilon = 3.2$). The data corresponded to the respective data for unlabelled phosmet.[4,8]

Conclusions

A simple and successful strategy for the synthesis of the activated (chlorinated) ^{15}N-labelled *N*-phthalimidomethyl-group cannot only be used as valuable tool for the synthesis of labelled pesticides but also for the production of a variety of cosmetic and pharmaceutical products.[9–11]

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