Research Article

Synthesis of $^{13}C_3$-hydroxyacetone

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Summary

$^{13}C_3$-Hydroxyacetone is prepared in three steps from $^{13}C_2$-2-bromoacetic acid. Bromide displacement by sodium *p*-methoxybenzyl alkoxide followed by treatment of the carboxylic acid with ^{13}C-methyl lithium furnishes PMB-protected hydroxyacetone. Deprotection using DDQ delivers the title compound. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: acetol; acyloin; methyl ketone; carbon-13

Introduction

Low-molecular-weight carbonyls such as methylglyoxal, hydroxyacetone and glycolaldehyde (**1–3**, Figure 1) have attracted the attention of researchers for a variety of biological[1] and toxicological studies.[2] Recent work showed that protein conjugates of these materials accumulate in tissues during aging and often lead to aging and diabetes pathologies.[3] Photooxidation of anthropogenic and biogenic emissions, such as alkylbenzenes and isoprene, are proposed as an environmental source of hydroxy carbonyls.[4] However, the identification of these oxygenated

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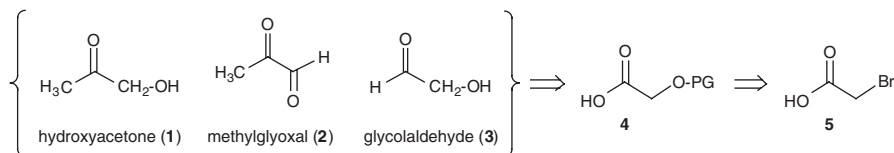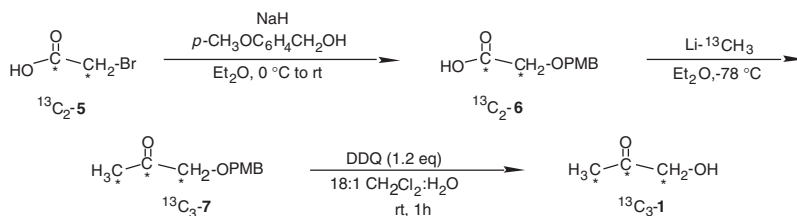
Figure 1. Volatile oxygenated compounds and retrosynthetic analysis.

volatile organic compounds (VOCs) remains tentative due to the lack of commercially available standards, and accurate quantification is hindered by the absence of isotopically labeled standards. Moreover, few ambient air measurements of hydroxy carbonyls exist. Work by Spaulding *et al.*[5] suggests that the lifetime of hydroxyacetone is sufficiently long to provide insight into sources and transport of VOCs, most notably the biogenic hydrocarbon isoprene.[6] Greater information regarding the distribution and concentration of hydroxyacetone in air is thus urgently needed to improve our understanding of the role that oxygenated VOCs play in tropospheric ozone (O_3) formation, and the distribution of other greenhouse gases that effect global climate change; and to address uncertainties in regional and global photochemical models formulated to devise strategies to reduce tropospheric ozone.

    Isotope dilution mass spectrometry is well recognized as the most accurate approach for quantification of low-molecular-weight, water-soluble, oxygenated VOCs.[7] To improve the accuracy of methods for quantification of hydroxyacetone and other hydroxy carbonyls, herein, we report the synthesis of $^{13}C_3$-hydroxyacetone.

Results and discussion

Our retrosynthetic strategy (Figure 1) identifies *O*-protected acetic acid derivative **4** as the proximal target. We envisioned that $^{13}C_2$-**4** would be accessible from commercially available $^{13}C_2$-α-bromoacetic acid (**5**) by displacement approaches,[8] and subsequent conversion to $^{13}C_3$-**1** would proceed via the well-established carboxylic acid-to-methyl ketone transformation[9] using ^{13}C-iodomethane as a source of labeled methyl. Initially we examined the use of acyl and benzyl groups as the protection groups in **4**. In the course of developing the synthesis as outlined using - α-OPv and α-OBn analogs of **4**, we encountered impassable problems arising from inefficient methyl ketone formation and protection group removal. We were gratified, however, to find that the *p*-methoxybenzyl

^{13}C$_2$-**5** + *p*-CH$_3$OC$_6$H$_4$CH$_2$OH, NaH, Et$_2$O, 0 °C to rt → ^{13}C$_2$-**6** + Li-^{13}CH$_3$, Et$_2$O, -78 °C →

^{13}C$_3$-**7** + DDQ (1.2 eq), 18:1 CH$_2$Cl$_2$:H$_2$O, rt, 1h → ^{13}C$_3$-**1**

Scheme 1. Synthesis of ^{13}C$_3$-1.

(PMB) analog was conveniently transformed into the title compound (Scheme 1).

Reaction of ^{13}C$_2$-2-bromoacetic acid (**5**) with an excess of the alkoxide derived from *p*-methoxybenzyl alcohol furnished the displacement product ^{13}C$_2$-**6**. Transformation to the methyl ketone was accomplished following the method of Jorgenson.[9] The ^{13}C-MeLi required for this step was prepared according to an established procedure.[10] We found that cannulation of a 0.3 M solution of ^{13}C-MeLi in ether-pentane into an ethereal solution of ^{13}C$_2$-**6** delivered methyl ketone ^{13}C$_3$-**7** (A synthesis of unlabeled **7** has been disclosed; see Wallace *et al*)[11] in 63% yield (2 steps). This optimized product yield was achieved only when a small quantity of ethyl acetate was introduced to the reaction mixture immediately prior to its slow addition into a rapidly stirring solution of aqueous. NH$_4$Cl – other modes of quenching gave inferior results. The PMB group was cleaved without incident using Yonemitsu's conditions,[12] and ^{13}C$_3$-**1** was isolated in pure form by Kugelrohr distillation (Figure 2).

In summary, ^{13}C$_3$-hydroxyacetone was prepared in three steps. ^{13}C$_3$-**1** may be useful for the preparation of ^{13}C$_3$-methylglyoxal based on the established oxidation of **1** to **2**,[13] and for syntheses of isotopically labeled 1-deoxyxyluloses, intermediates in the much investigated biosynthesis of thiamine and pyridoxal.[14]

Experimental

Ether was distilled from CaH$_2$ and THF was distilled from sodium-benzophenone ketyl. Carboxylic acids were dried prior to reaction by azeotropic distillation with toluene. All chemicals were obtained from the Aldrich Chemical Company and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ using a Varian Inova
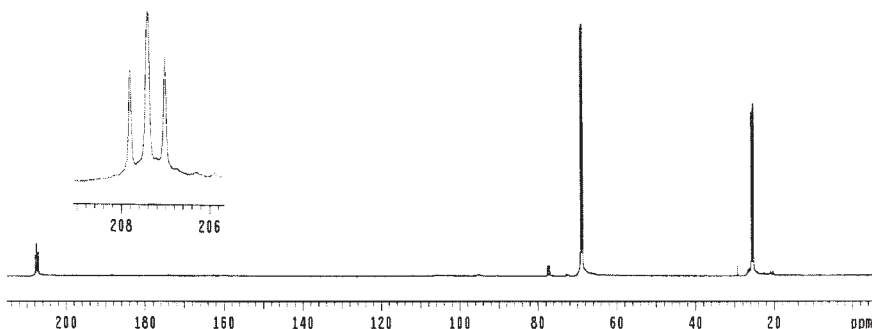
Figure 2. ^{13}C NMR (CDCl$_3$) of ^{13}C$_3$-hydroxyacetone.

400 spectrometer with ^{1}H and ^{13}C signals referenced to TMS and residual CHCl$_3$.

$^{13}C_2$-2-(4′-Methoxy-benzyloxy)-acetic acid (**6**)

To a suspension of NaH (0.68 g, 28 mmol) in freshly distilled THF (25 ml) at 0°C was added dropwise a solution of *p*-methoxybenzyl alcohol (1.80 ml, 14.2 mmol). To the reaction mixture was added a solution of ^{13}C$_2$-α-bromoacetic acid (1.00 g, 7.10 mmol) in THF (15 ml) at 0°C via a cannula. The reaction mixture was heated to reflux for 2 h and then stirred at room temperature for 18 h. The reaction was quenched by pouring over 5% aqueous. NaHCO$_3$ and excess PMB-OH was extracted with ether (2 × 50 ml). The aqueous fraction was acidified to pH 3.5 with 10% HCl and extracted with EtOAc (3 × 100 ml). The combined EtOAc fraction was dried (Na$_2$SO$_4$) and concentrated *in vacuo* to afford the crude acid as a white solid (1.31 g) which was used without further purification; TLC, R_f = 0.10 (5% MeOH, CH$_2$Cl$_2$); IR 3400, 2864, 1675 cm^{-1}; ^{1}H NMR δ 8.59 (br, 1 H), 7.29 (m, 2 H), 6.90 (m, 2 H), 4.58 (d, $^3J_{C,H}$ = 4.5 Hz, 2 H), 4.11 (dd, $^1J_{C,H}$ = 144 Hz, $^2J_{C,H}$ = 4.8 Hz, 2 H), 3.81 (s, 3 H); ^{13}C NMR δ 175.4 (d, $^1J_{C,C}$ = 60.2 Hz), 159.7, 130.1, 128.8, 114.2, 73.3, 66.5 (d, $^1J_{C,C}$ = 60.2 Hz), 55.6.

$^{13}C_3$-1-(4′-Methoxy-benzyloxy)-propan-2-one (**7**)

To a solution of ^{13}C-iodomethane (1.16 ml, 18.6 mmol) in ether (40 ml) at −78°C was added *t*-BuLi (24 ml of a 1.7 M in pentane, 41 mmol). The solution was maintained at −78°C for an additional 15 min and then warmed to room temperature and stirred 1 h to destroy excess *t*-BuLi. In

a separate flask, ^{13}C$_2$-acid **6** (1.15 g, 5.80 mmol) was dissolved in ether (100 ml) and cooled to –78°C. The newly prepared solution of ^{13}C-MeLi was cooled to –78°C and added dropwise via a cannula to the ethereal solution of acid **6**. The reaction mixture was stirred at –78°C for 30 min, warmed to room temperature and stirred for 4 h, and then cooled to 0°C. EtOAc (1 ml) was added to the reaction mixture to destroy excess ^{13}C-MeLi. The reaction mixture was then slowly added via a cannula into a rapidly stirred solution of saturated aqueous. NH$_4$Cl at 0°C and followed by extraction with EtOAc (3 × 100 ml). The combined organic extract was washed with water, brine, and then dried (Na$_2$SO$_4$). The solvent was removed *in vacuo* and the residue was chromatographed (SiO$_2$), eluting with 5% MeOH in CH$_2$Cl$_2$, to afford ^{13}C$_3$-ketone **7** as a colorless oil (0.71 g, 66%, two steps); TLC, R_f = 0.22 (hexane : EtOAc, 4:1); IR 2920, 2864, 2842, 1685 cm^{-1}; ^{1}H NMR δ 7.28 (m, 2 H), 6.89 (m, 2 H), 4.53 (d, $^3J_{C,H}$ = 4.4 *Hz*, 2 H), 4.03 (dd, $^1J_{C,H}$ = 140 Hz, $^2J_{C,H}$ = 3.6 Hz, 2 H), 3.81 (s, 3 H), 2.15 (ddd, $^1J_{C,H}$ = 128.0 Hz, $^2J_{C,H}$ = 6.4 Hz, $^3J_{C,H}$ = 1.6 Hz, 3 H); ^{13}C NMR δ 206.6 (dd, $^1J_{C,C}$ = 43.0 Hz, $^1J_{C,C}$ = 40.6 Hz), 159.3, 129.5, 129.0, 113.8, 74.9 (dd, $^1J_{C,C}$ = 43.0 Hz, $^2J_{C,C}$ = 15.4 Hz), 72.9, 55.3, 26.5 (dd, $^1J_{C,C}$ = 40.6 Hz, $^2J_{C,C}$ = 15.4 Hz).

^{13}C$_3$-1-Hydroxypropan-2-one (**1**)

To a solution of ketone **7** (0.19 g, 0.95 mmol) in an 18 : 1 mixture of CH$_2$Cl$_2$: H$_2$O (6.35 ml) at room temperature was added DDQ (258 mg, 1.14 mmol) in one portion. The reaction solution was stirred for 1.5 h before addition of solid Na$_2$SO$_4$. The solution was then filtered through a short pad of celite, and the filtrate was concentrated by distillation. The orange oily residue was distilled (Kugelrohr bulb-to-bulb distillation at 60°C, 48 mm Hg) to afford **1** as a colorless oil (28 mg, 38%); TLC, R_f = 0.30 (5% MeOH in CH$_2$Cl$_2$); IR 3453, 2981, 1686 cm^{-1}; 1 H NMR δ 4.27 (dd, $^1J_{C,H}$ = 143 Hz, $^2J_{C,H}$ = 3.3 Hz, 2 H), 3.147 (b, 1 H), 2.19 (ddd, $^1J_{C,H}$ = 128 Hz, $^2J_{C,H}$ = 6.2 Hz, $^3J_{C,H}$ = 2.1 Hz, 3 H); ^{13}C NMR δ 207.2 (dd, $^1J_{C,C}$ = 41.8 Hz, $^1J_{C,C}$ = 36.8 Hz), 69.0 (dd, $^1J_{C,C}$ = 36.8 Hz, $^2J_{C,C}$ = 16.5 Hz), 25.7 (dd, $^1J_{C,C}$ = 41.8 Hz, $^2J_{C,C}$ = 16.5 Hz).

Acknowledgements

03137). The 400 MHz NMR spectrometer was partially funded by NSF (CHE-9808183).

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