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Controlled formation of tetramethylammonium mono- and diylide

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Abstract

The reaction of tetramethylammonium bromide with *n*-butyllithium can selectively yield either trimethylammonium methylide or lithium dimethylammonium dimethylide, depending on the reaction conditions, as shown by ^{13}C-NMR analysis of the deuterium-labelled species resulting from acidic trapping with DCl. So a simple synthesis of mono- or twice-functionalised methylammonium salts is allowed from a very usual starting material. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Nitrogen ylides; Isotopic labelling; Lithiation; NMR spectroscopy

1. Introduction

In his work devoted to the ylide chemistry, Wittig was first interested in ammonium ylides [1]. One of the encountered problems was connected with the formation of the trimethylammonium methylide **2**. Wittig formed this zwitterionic species in the reaction of tetramethylammonium halide **1** with phenyllithium used in a 1:1 ratio. The identification of the ylide was based on its trapping with various electrophiles such as water, iodine, methyl iodide and mainly benzophenone, which needed a subsequent acidic work-up. In such a way, the β-hydroxyalkylammonium bromide **3** was isolated in a 42% yield (Scheme 1).

Changing to a 1:2 ratio, the authors observed that the amount of salt **3**, considered as representative of the amount of transient monoylide **2**, decreased in the course of time [1b]: 68% for a 2 days metalation, 21% after 4 days and, finally, 18% after 7 days [1c]. Meanwhile, 20% of the disubstituted ammonium salt **5** appeared and 20% of the starting material **1** was recovered (Scheme 2). Compound **5** was considered as the result of the formation of the diylide **4**. A still larger excess of phenyllithium (four equivalents) and a longer time (40 h) resulted in yields of 12 and 26% of compounds **3** and **5**, respectively.

With this background in mind, the metalation of tetramethylammonium salts could settle the initial step of a selective synthesis of either mono or difunctionalised methylammonium species, like **3** or **5**, provided the amount of basic agent and the kinetics of its reaction on tetramethylammonium bromide **1** were very carefully controlled. Herein, we report our results in this controlled formation of tetramethylammonium monoylides **2** and diylides **4**.

2. Results and discussion

For his experiments, Wittig chose benzophenone as the best electrophile to trap the ylide: at this time, the choice was judicious as it avoided any competitive transylidations, such as could happen using other electrophiles, such as methyl iodide (actually, in the same experimental conditions, methyl iodide gave only 16% of trimethyl ethylammonium salt, to be compared to the 42% of **3** resulting from the benzophenone reaction). Nevertheless, one cannot exclude that the ylide adduct with benzophenone may be partly reversible; the resulting equilibrium would pervert thus the actual results. To avoid this problem, quenching of the reaction mixture by an excess of the acidic electrophile DCl should nowadays facilitate the kinetic analysis, as a very fast and irreversible chemical trapping of carbanions to give stable salts. Moreover, deuterium could be

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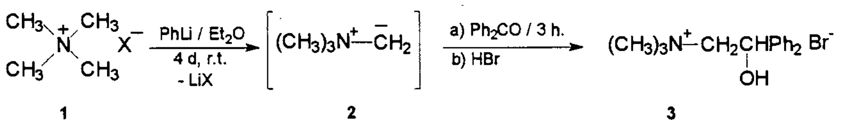
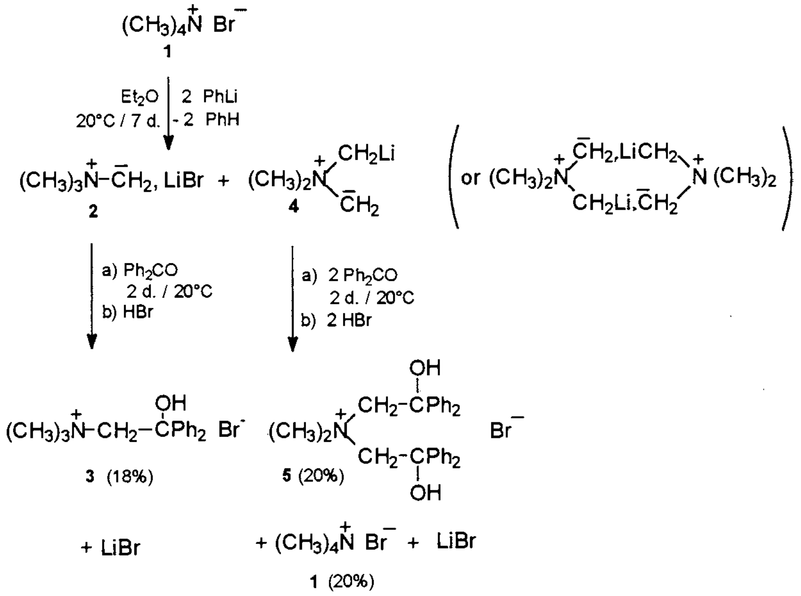
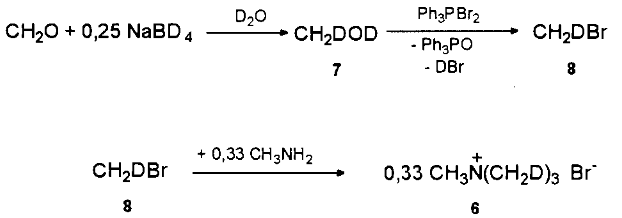


Scheme 1. Formation and characterisation of trimethylammonium methylide **2** (taken from Wittig [1]).



Scheme 2. Formation and characterisation of lithium dimethylammonium dimethylide **4** (taken from Wittig [1]).



Scheme 3. Synthesis of tris(monodeuteromethyl)methylammonium bromide **6**.

Table 1
P_{theor} and P_{exp} vs. molecular ratio

$\frac{y}{x}$ $\frac{\text{mol.\% of } \mathbf{6}}{\text{mol.\% of } \mathbf{1}}$	$P_{theor} = \frac{4x+t}{3t}$	$P_{exp} = \frac{\%CH_3}{\%CH_2D}$
2.363	47/53	45/55
0.588	72/28	74/26
0.135	91/9	92/8

an excellent probe for the deuterated end-products analysis, through ^{13}C-NMR spectroscopy.

In order to check the validity of this titration method, we independently prepared a sample of tris(monodeuteromethyl)methylammonium bromide **6** (Scheme 3): the ^{13}C-NMR signals of CH_3 and CH_2D groups for compound **6** could be very easily differentiated through their chemical shift ($\Delta\delta \sim 0.25$ ppm) [2], multiplicity, and even integration ($P = \%CH_3/\%CH_2D$), provided that the INVGATE delay would be more than 5 s. Indeed, for the pure trideuterated compound **6**: $P_{exp} = 0.33 = P_{theor}$.

Then, known amounts of both non-deuterated **1** and deuterated **6** were mixed in such a way as to obtain samples with various P values corresponding, virtually, to the monodeuterated salt **9** ($P_{theor} = 3$) and dideuterated salt **10** ($P_{theor} = 1$). For each sample, we found that P_{theor} and P_{exp} were in very good agreement (Table 1).

n_1: mol. Number of **1**; x: mol.% of **1**;
n_2: mol. Number of **6**; y: mol.% of **6**;
$x = n_1/n_1 + n_2$; $t = n_2/n_1 + n_2$;
$P_{theor} = (4x + t)/3t$

The ^{13}C-NMR spectrum for the representative mixture of the dideuterated salt **10** ($P = 1$) is shown in Fig. 1: (B) corresponds to the third of the intensity of the CH_2D signal, whereas (A) represents the intensity of the CH_3 signal together with two thirds of the CH_2D signal.

Thus, the ^{13}C-NMR spectrometry will be fairly reliable for the intended kinetic measurements.

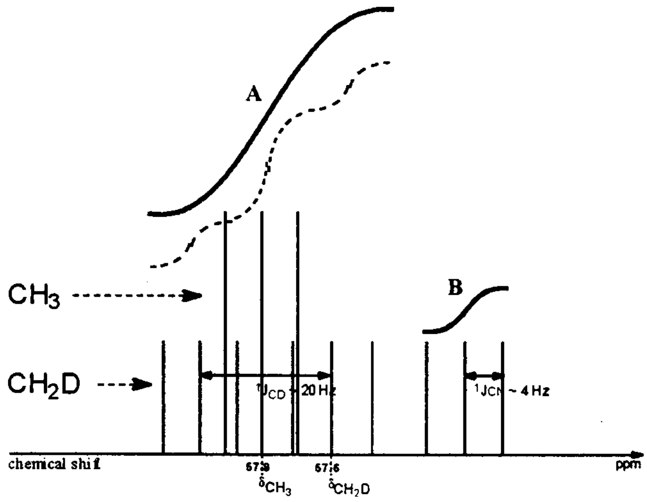


Fig. 1. ^{13}C-NMR spectrum of the mixture representative of the dideuterated salt **10**.

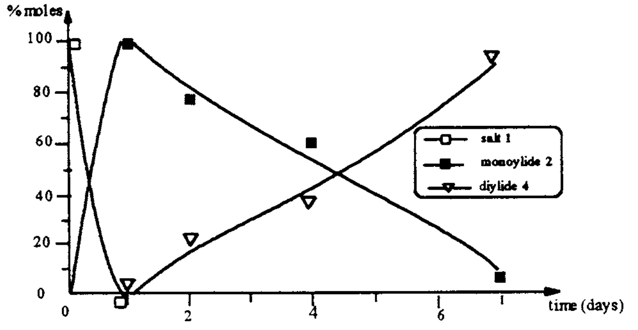


Fig. 2. Kinetic of the ylide formation from **1**.

Taking into consideration the expected acidity of the starting compound **1** ($41 < pK_a < 43$) [1a,3], *n*-BuLi was chosen as the basic reagent (*n*-butane: $pK_a = 50$). Reasonably, depending on the duration of the reaction and on the stoichiometry of the reagents (**1**–*n*-BuLi, 1:1 or 1:2), mixtures of at most two consecutive ylides either **2** and **4** or **4** and **11** (Scheme 4) could result from the reaction upon salt **1**, since the electron-withdrawing effect of the positively charged nitrogen, and therefore the α-hydrogen acidity, will be gradually minimised as more negative charges appear on the vicinal carbon atoms.

Thus, after DCl quenching, if not a pure salt, either a **1**–**9**, **9**–**10**, or even **10**–**6** binary salt mixture could be formed, which will be easily distinguished, as already shown, through ^{13}C-NMR analysis.

At this time, it can be stated that:

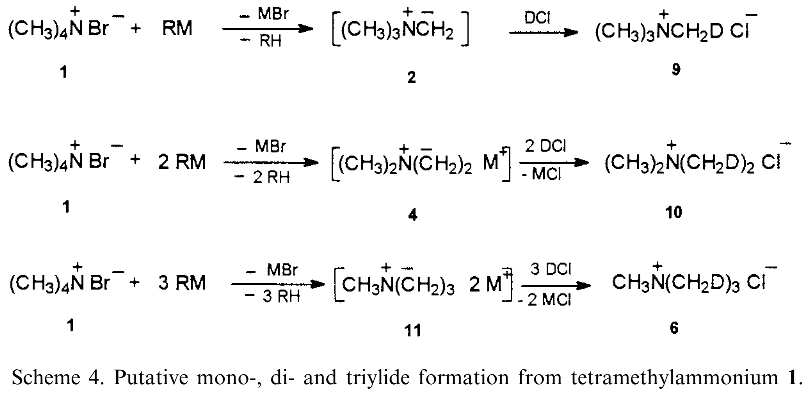
- the reaction of one equivalent of *n*-BuLi upon the salt **1**, for 2 days at 20°C in ether, quantitatively leads to the monoylide **2** (using phenyllithium, this reaction proceeded only at 50%).
- the reaction of two equivalents of *n*-BuLi upon the salt **1**, after only 24 h, quantitatively leads to the monoylide **2**, which was progressively wholly transformed into the diylide **4** after 6 additional days (Fig. 2, Scheme 5).

3. Conclusions

Using *n*-BuLi, instead of PhLi, we achieved for the first time selective formation of either the monoylide **2** or diylide **4**. Interestingly, this result affords a new and simple route for the synthesis of mono or doubly functionalised methylammonium salts, starting from the very common tetramethylammonium bromide **1**.

Actually, when the lithium and dimethylammonium dimethylide **4**, generated as described here, was reacted for 2 days with two equivalents of benzophenone, then acidified, the bis(2,2-diphenyl-2-hydroxyethyl)dimethylammonium salt **5** was obtained in 65% yield. Only traces of the (2,2-diphenyl-2-hydroxyethyl)trimethylammonium salt **3** are perceptible. In the same experimental conditions, but using phenyllithium instead of *n*-BuLi, Wittig obtained only a 20% yield [1b].

Further reactions of the lithium and dimethylammonium dimethylide **4** with various carbon or heteroatomic electrophiles are currently in progress.



Scheme 4. Putative mono-, di- and triylide formation from tetramethylammonium **1**.

4. Experimental

All reactions were run under dry nitrogen in flame-dried glassware unless otherwise noted. Ether was freshly distilled from sodium–benzophenone. ^{1}H-NMR and ^{13}C-NMR spectra, recorded at room temperature on a Bruker AC200 spectrometer, were referenced to TMS (δ in ppm, J in Herz). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; INVGATE sequence (D1 = 5 s) was used for ^{13}C NMR. Mass spectra (MS) were obtained on a Jeol JMS-DX 300 instrument (positive FAB) using *m*-nitrobenzyl alcohol as matrix.

*4.1. Tris(monodeuteromethyl)methylammonium bromide (**6**)*

*4.1.1. Methanol-d_1-OD (**7**)*

A mixture of paraformaldehyde (1.68 g, 19 mmol) in 15 ml dry *m*-xylene and sodium borohydride-d_4 (0.59 g, 14 mmol) in 5 ml D_2O, was stirred for 15 min at 20°C. From the mixture were distilled 2.5 ml of a liquid ($Eb_{760} = 65°C$) containing CH_2DOD–*m*-xylene–CH_3-OD, respectively, in a 38:4:1 molar ratio: CH_2DOD **7**: ^{1}H-NMR: $\delta = 3.2$ (t, $^{2}J_{HD} = 1.6$) [4]; ^{13}C-NMR: $\delta = 49.9$ (t, $^{1}J_{CD} = 21.6$).

*4.1.2. Tris(monodeuteromethyl)methylammonium bromide (**6**)*

This mixture, containing 88% of methanol-d_1-OD, is added to the dibromotriphenylphosphorane (^{31}P-NMR ($CDCl_3$) $\delta = 40$), prepared at 10°C from dry triphenylphosphine (11.8 g, 45 mmol) and bromine (2.32 ml, 45 mmol) in DMF (200 ml). The evolved monodeuteromethylbromide **8** is bubbled, at −50°C, into DMF simultaneously to a counter-current of gaseous anhydrous trimethylamine. After 2 h, the filtrated solid (0.45 g) is a mixture of methyldeuteromethylammonium bromides $[MeNH_n(CH_2D)_{3-n}]^+X^-$ ($n = 0$–3). Addition of an aqueous solution of potassium hydroxide transforms most of the salts ($n \neq 0$) into volatile amines. The expected salt **6** is isolated from the remaining solution. 5% yield. ^{1}H-NMR (D_2O): $\delta = 3.2$ (t, $^{2}J_{HD} = 1.6$, 6H; CH_2D), 3.2 (s, 3H, CH_3); ^{13}C-NMR (D_2O): $\delta = 57.6$ (tt, $^{1}J_{CN} = 4$, $^{1}J_{CD} = 22.1$, 3C; CH_2D), 57.9 (t, $^{1}J_{CN} = 4$, 1C; CH_3); MS (FAB/NBA): 77 [M$^+$].

*4.2. Trimethylammonium methylide (**2**) and monodeuteromethyltrimethylammonium chloride (**9**)*

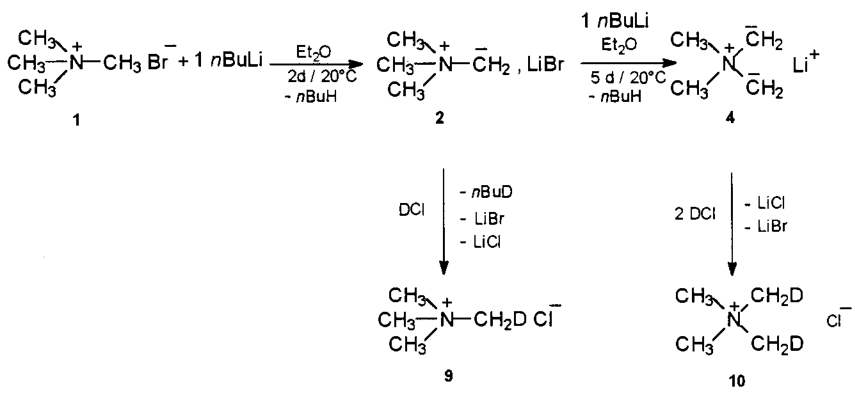
To 2 g (13 mmol) of dried tetramethylammonium bromide **1** in 50 ml dry ether are dropped 11 ml (13 mmol) of *n*-BuLi in hexane (1.44 M). After 2 days at 20°C, the mixture gave a negative Gilman test [5]; 1.2 ml of 37% DCl–D_2O is added to give a quantitative yield of **9**. ^{1}H-NMR (D_2O): $\delta = 3.2$ (t, $^{2}J_{HD} = 1.6$, 2H; CH_2D), 3.2 (s, 9H; CH_3); ^{13}C-NMR (D_2O): $\delta = 57.6$ (tt, $^{1}J_{CN} = 4$, $^{1}J_{CD} = 22.1$, 1C; CH_2D), 57.9 (t, $^{1}J_{CN} = 4$, 3C; CH_3); MS (FAB/NBA): 75 [M$^+$].

*4.3. Dimethylammonium dimethylide (**4**) and bis(monodeuteromethyl)dimethylammonium chloride (**10**)*

To 2 g (13 mmol) of dried **1** in 50 ml dry ether are dropped 22 ml (26 mmol) of *n*-BuLi in hexane (1.44 M). After stirring for 7 days at 20°C, the Gilman test became negative. The heterogeneous white mixture is quenched with 2.4 ml (26 mmol) of 37% DCl–D_2O. ^{1}H-NMR (D_2O): $\delta = 3.2$ (t, $^{2}J_{HD} = 1.6$, 4H; CH_2D), 3.2 (s, 6H; CH_3); ^{13}C-NMR (D_2O): $\delta = 57.6$ (tt, $^{1}J_{CN} = 4$, $^{1}J_{CD} = 22.1$, 2C; CH_2D), 57.9 (t, $^{1}J_{CN} = 4$, 2C; CH_3); MS (FAB/NBA): 76 [M$^+$].

*4.4. Bis(2,2-diphenyl-2-hydroxyethyl)-dimethylammonium bromide (**5**)*

To the heterogeneous white mixture of **4**, 4.74 g (26 mmol) benzophenone are added (slightly exothermic). After a further 2 days at 20°C, the addition of 3 ml of 47% aqueous HBr (26 mmol), gives a suspension. The yellow solid is dissolved in chloroform and precipitated into 200 ml of ether. After filtration, the combined



Scheme 5. Deuteration of the tetramethylammonium monoylide **2** and diylide **4**.

organic fractions are evaporated; the residue (1.3 g) is identical with benzophenone (yield: 30%). The white solid **5** is dried; m = 5.3 g (65%), and recrystallised from *n*-pentanol. M.p. 140°C (Lit. 145°C) [1b]. ^{1}H-NMR ($CDCl_3$): $\delta = 7.3$ (m, 20H; H_{Ar}), 5.7 (s, 2H; C^3OH), 4.5 (s, 4H; NC^2H_2), 3.5 (t, $^3J_{HH} = 6.7$, 2H; $C^{12}H_2O$), 2.9 (s, 6H; NCH_3), 1.8 (s, 1H; $C^{12}H_2OH$), 1.5 (m, 2H; $C^{11}H_2$), 1.3 (m, 4H; $C^{10}H_2C^9H_2CH_3$), 0.9 (t, $^3J_{HH} = 6.7$; CH_3). ^{13}C-NMR ($CDCl_3$): $\delta = 55.7$ (CH_3), 76.3 (CH_2), 73.6 (COH), 125.7 (C_p), 127.5 (C_m), 128.6 (C_o), 144.7 (C_i). MS (FAB/NBA): 438 [M^+].

Traces of (2,2-diphenyl-2-hydroxyethyl)trimethylammonium bromide (**3**) are perceptible in the ^{1}H-NMR spectrum (D_2O): $\delta = 7.3$ (m, 10H; H_{Ar}), 5.3 (s, 1H; OH), 4.8 (s, 2H; CH_2N), 3 (s, 9H; CH_3N). MS (FAB/NBA): 256 [M^+].

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