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Research Article

Synthesis of [1-^{13}C]-*para*-xylene and [2-^{13}C]-*para*-xylene

Michael Mormann and Dietmar Kuck*
Fakultät für Chemie, Universität Bielefeld, Universitätsstrasse 25, D-33615 Bielefeld, Germany

Summary

An efficient synthesis of [1-^{13}C]-*para*-xylene (**1a**) and [2-^{13}C]-*para*-xylene (**1b**) is described. The incorporation of the label has been achieved by cyclocondensation of suitable 1,5-bis(bromomagnesio)alkanes with either ethyl [1-^{13}C]acetate or ethyl [^{13}C]formate which gave [*ring*-^{13}C]-labelled dimethylcyclohexanols. Dehydration of these alcohols followed by dehydrogenation of the intermediate dimethylcyclohexenes furnished the title compounds in 32 and 40% overall yield, respectively.

Key Words: carbon-13 labelled arenes; [1-^{13}C]-*para*-xylene; [2-^{13}C]-*para*-xylene; arenium ions, gaseous; carbon scrambling

Introduction

Arenium ions (protonated arenes) represent the key intermediates in electrophilic aromatic substitution, one of the most-studied and best-understood reactions in organic chemistry.[1] The structure and reactivity of these species and their derivatives in solution,[2–4] in the solid state[5–7] and in the gas phase[8–12] have been extensively studied. The investigation of the chemistry of gaseous ions has mostly been carried out by mass

*Correspondence to: Dr. D. Kuck, Fakultät für Chemie, Universität Bielefeld, Universitätsstraße 25, D-33615 Bielefeld, Germany. E-mail: dietmar.kuck@uni-bielefeld.de

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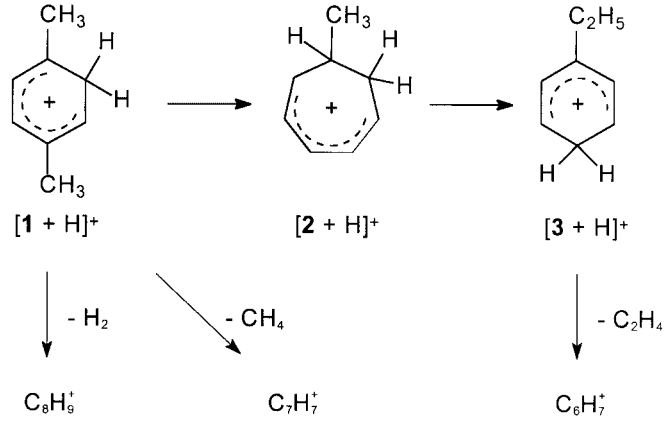
spectrometric techniques and provides deep insights into the intrinsic properties of isolated ions, i.e. cations and anions in the absence of solvent molecules and counterions.[12]

In the course of our studies on the gas-phase ion chemistry of lower protonated alkylbenzenes and their olefinic isomers, we have focused on the isomerization processes occurring prior to the fragmentation of these ions.[13–16] Long-lived xylenium ions $[\mathbf{1}+H]^+$ (i.e. protonated xylenes) fragment mainly by loss of dihydrogen and methane. However, careful examination of the mass spectra of $[\mathbf{1}+H]^+$ reveals also the loss of ethene from these ions, indicating complex skeletal rearrangement processes, such as (reversible) ring expansion to protonated methylcycloheptatrienes $[\mathbf{2}+H]^+$ and (irreversible) ring contraction of the latter isomers to ethylbenzenium ions $[\mathbf{3}+H]^+$ prior to the loss of C_2H_4 (Scheme 1).[17,18]

To investigate the complex rearrangement reactions described above with respect to carbon scrambling[19] in more detail, we have synthesized the [*ring*-^{13}C]-*para*-xylenes **1a** and **1b** bearing the label in positions C-1 and C-2, respectively. Several approaches have been reported on the incorporation of carbon isotopes into aromatic rings or into their less unsaturated, six-membered ring precursors. These have involved Diels–Alder reactions,[20,21] cyclotrimerization and co-cyclotrimerization of alkynes,[22,23] condensation reactions of C–H acidic compounds with suitable carbonyl compounds or Michael acceptors,[24–26] cyclization of hexatrienes[27–29] and cyclocondensation of bis-organometallic species with esters.[30–34] In the present contribution, we demonstrate that the latter approach can be favourably used to synthesize [*ring*-^{13}C]-labelled *para*-xylenes.



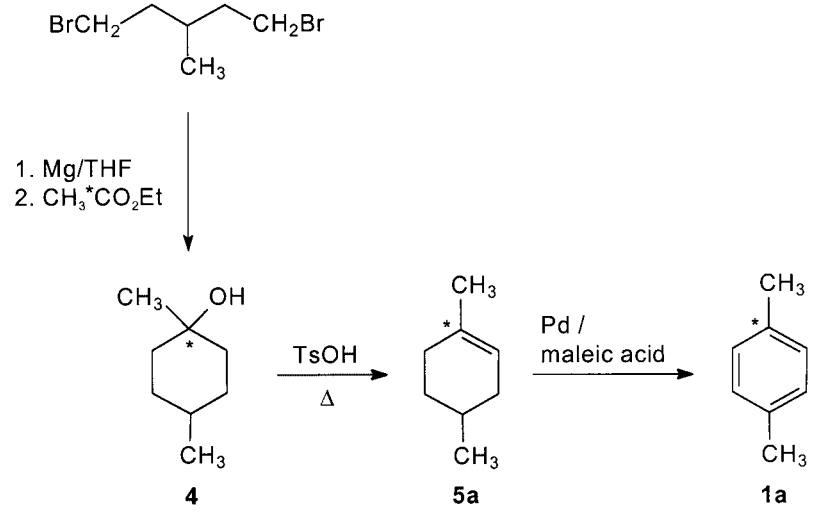
Scheme 1.

Results and discussion

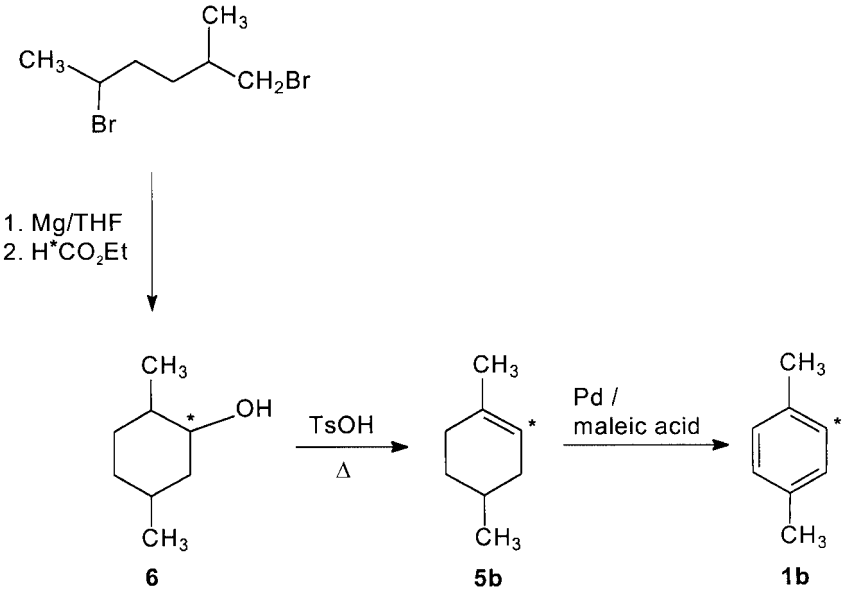
The synthesis of [1-^{13}C]-*para*-xylene was achieved by following the synthesis route outlined in Scheme 2.

Ethyl [1-^{13}C]acetate was prepared as described previously[32] and used as the carbon-13 containing building block. Application of the method described by Cannone *et al.*[35–37] involved the cyclocondensation of this ester with 3-methyl-1,5-bis(bromomagnesio)hexane in THF and produced a mixture of the diastereomeric 1,4-dimethyl-[1-^{13}C]cyclohexanols **4** in 92% yield. Elimination of water from the latter using *para*-toluenesulphonic acid furnished 1,4-dimethyl-[1-^{13}C]cyclohexene **5a**.[38] Alternatively, iodine-assisted dehydration[32] of **4** gave similar results after optimization using unlabelled reagents.

The final step, the dehydrogenation of the cycloalkene, appeared to be critical within the synthesis of carbon-13 ring-labelled lower alkylbenzenes. Oxidation reagents such as DDQ or tetrachloro-*para*-benzoquinone are not suitable for such conversions due to the low electron density present in the alkene.[34,39,40] Dehydrogenation using an industrial catalyst (Pt or Pd on asbestos) at 450°C was reported to lead to partial disproportionation.[31,32] Therefore, we decided to use palladium on charcoal as the catalyst in the presence of maleic acid as a hydrogen acceptor, analogous to a procedure described by Robertson and Djerassi.[33] However, GC–MS analysis of the product indicated the



Scheme 2.



Scheme 3.

formation of minor amounts (ca 6%) of 1,4-dimethylhexanes as disproportionation products.

The synthesis of the isomeric *para*-xylene **1b** bearing the carbon-13 label in ring position C-2 was achieved in a similarly straightforward manner (Scheme 3). Cyclocondensation of 1,5-bis(bromomagnesio)-2-methylhexane and ethyl [^{13}C]formate[41,42] as the carbon-13 containing synthone led to incorporation of the label at the desired position of the cyclohexanol **6**, which was obtained as a mixture of four diastereomeric species (GC–MS). It is noted that the yield of cyclohexanol **6** was similar (85%) to that of isomer **4**; thus, the secondary/primary 1,5-dibromide proved to react as efficiently as did the bis(primary) 1,5-dibromide. Dehydration of the cyclohexanol **6** to cyclohexene **5b** and subsequent dehydrogenation led to xylene **1b** in 40% overall yield.

Experimental

General

^{1}H nuclear magnetic resonance (NMR) spectra were measured on a Bruker DRX 500 (500 MHz) instrument. Electron ionization (EI) mass spectra were recorded on a double-focusing sector-field instrument with

EBE geometry (VG Autospec, Fisons, Manchester/UK), ionization energy 70 eV, accelerating voltage 8 kV. Samples were introduced via a heated septum inlet. GC–MS analysis was performed on a Shimadzu QP 5050 instrument equipped with a GC17 (version 3), HP-5 MS column (25 m, ID 0.2 mm, film thickness 0.33 μm, He carrier gas, optimized temperature programme), ionization mode EI (70 eV), quadrupole mass filter at full scan from m/z 50–500, cycle time 0.6 s. Melting points (uncorrected) were determined using an electrothermal melting point apparatus. All reactions were carried out under dry argon in flame-dried glassware. All reactants used were purified by standard procedures; solvents were dried immediately before use.[43]

Barium [^{13}C]carbonate was obtained from Deutero GmbH, Kastellaun, Germany (carbon-13 contents 92%). 1,5-Dibromo-3-methylpentane was obtained from 1,5-dihydroxy-3-methylpentane (Fluka) by treatment with concentrated hydrobromic acid.[44] 1,5-Dibromo-2-methylhexane was prepared by condensation of ethyl acetoacetate and methyl methacrylate to give diethyl 2-acetyl-4-methylglutarate, which was converted into 2-methyl-5-ketohexanoic acid by hydrolysis in concentrated hydrochloric acid.[45,46] The keto acid was reduced to a mixture of diastereomeric 2-methyl-1,5-hexanediols using lithium aluminium hydride in THF. The diol was esterified with *para*-toluenesulphonyl chloride in pyridine giving the corresponding bis(tosylate) as a crude product,[47] followed by conversion into 1,5-dibromo-2-methylhexane using lithium bromide in acetone.[48]

Synthesis of [1-^{13}C]-para-xylene ***1a***

Sodium [1-^{13}C]acetate. This compound was prepared by reacting [^{13}C]carbon dioxide, which was generated from barium [^{13}C]carbonate and degassed concentrated sulphuric acid, with methylmagnesium iodide in diethyl ether, as described previously[32] using a modified apparatus.[49]

Ethyl [1-^{13}C]acetate. This compound was prepared from sodium [1-^{13}C]acetate and triethyl phosphate.[50]

1,4-Dimethyl-[1-^{13}C]cyclohexanol ***4***. A solution of the bis(Grignard) reagent prepared from 1,5-dibromo-3-methylpentane (19.9 g, 81.6 mmol) and magnesium turnings (4.66 g, 192 mmol) in 100 ml THF was stirred at 0 °C, while a solution of ethyl [1-^{13}C]acetate (2.2 g, 24.7 mmol) in 20 ml of THF was added dropwise. Stirring of the reaction mixture was continued for 48 h at ambient temperature. After

hydrolysis by careful addition of saturated aqueous ammonium chloride at 0 °C, the mixture was extracted several times with diethyl ether. In addition, the aqueous layer was extracted with the same solvent for 24 h by use of a Kutscher–Steudel extractor. The combined organic layers were washed with saturated sodium chloride solution and dried over sodium sulphate. The solvents were carefully removed by distillation through a 30-cm-Vigreux column. The crude residue obtained was sublimed at 65 °C (25 mbar) yielding cyclohexanol **4** (2.93 g, 92%) as a mixture of diastereomers (GC–MS) and as a colourless solid; mp.: 64°C; ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 1.60$–1.69 (m, 2 H), 1.48–1.51 (m, 2 H), 1.35–1.38 (m, 3 H), 1.22–1.33 (m, 3 H), 1.21 (d, $J(^1H,^{13}C) = 4.1$ Hz, 3 H), 0.91 (d, $J = 5.9$ Hz, 3 H); MS (EI, 70 eV): $m/z = 129$ (4, $M^{\bullet+}$), 114 (17), 112 (4), 111 (3), 100 (2), 96 (18), 85 (7), 72 (100), 71 (38), 59 (23), 44 (33), 41 (28).

1,4-Dimethyl-[1-^{13}C]cyclohexene ***5a***. A mixture of cyclohexanol **4** (2.8 g, 21.7 mmol) and *para*-toluenesulphonic acid (200 mg, 1.1 mmol) was heated to 160 °C in a microdistillation apparatus equipped with a 20-cm electrically heated Vigreux column. The azeotropic alkene/water mixture (bp.: 81–87 °C) distilling off was collected at a column temperature of 90 °C. The organic layer was separated and dried carefully by addition of sodium pieces (200 mg). Subsequent distillation afforded cyclohexene **5a** (1.78 g, 78%) as a colourless liquid; bp.: 121°C; ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 5.34$ (br s, 1 H), 1.91–2.03 (m, 2 H), 1.66–1.70 (m, 2 H), 1.64 (d, $J(^1H,^{13}C) = 5.9$ Hz, 3 H), 1.55–1.60 (m, 2 H), 1.18–1.25 (m, 1 H), 0.93 (d, $J = 6.2$ Hz, 3 H); MS (EI, 70 eV): $m/z = 111$ (40, $M^{\bullet+}$), 96 (77), 82 (19), 78 (10), 69 (91), 68 (1 0 0), 59 (13), 55 (24), 41 (27).

[1-^{13}C]para-xylene ***1a***. A mixture of cyclohexene **5a** (250 mg, 2.3 mmol) and Pd/C catalyst (100 mg, 10% Pd) was shaken for 15 min. The alkene was then separated from the catalyst by centrifugation and added to an intimately mixed, dried and powdered mixture of maleic acid (800 mg, 6.9 mmol) and Pd/C catalyst (280 mg, 10% Pd). This mixture was heated to reflux (130 °C) for 48 h. The product was collected by condensing it into a cooling trap (liquid nitrogen) to give *para*-xylene **1a** (105 mg, 44%). GC–MS analysis of the product indicated contamination with the corresponding cyclohexanes (ca 6%). ^{1}H-NMR of **1a** (500 MHz, $CDCl_3$): $\delta = 7.06$ (br s, 4 H), 2.31 (d, $J(^1H,^{13}C) = 5.5$ Hz, 3 H), 2.31 (s, 3 H); MS (EI, 70 eV): $m/z = 107$ (59, $M^{\bullet+}$), 106 (36), 92 (100), 91 (16), 79 (7), 78 (12), 77 (5), 66 (5), 65 (4), 52 (7), 51 (9).

Synthesis of [2-^{13}C]-para-xylene ***1b***

Potassium [^{13}C]formate. This compound was prepared as described previously[41,42] starting from [^{13}C]carbon dioxide, which was produced from barium [^{13}C]carbonate (10 g, 50 mmol) by treatment with degassed concentrated sulphuric acid. [^{13}C]Carbon dioxide was absorbed in a solution of potassium hydroxide (3.36 g, 60 mmol) in decarbonated water (80 ml) at 0 °C during a period of 48 h. To the resulting solution of potassium hydrogen [^{13}C]carbonate was added Pd/C catalyst (10% Pd) (7.0 g) and the mixture was reacted in an autoclave under hydrogen at 88 °C (initial pressure before heating: 140 bar) for 24 h. Workup of the reaction mixture by careful removal of the catalyst by filtration and removal of the water in vacuo gave crude potassium [^{13}C]formate (4.38 g, > 100%), which was directly used in the following conversion.

Ethyl [^{13}C]formate. This compound was prepared from potassium [^{13}C]formate by reaction with triethylphosphate, as described above for the synthesis of ethyl [1-^{13}C]acetate; yield 3.48 g (93% based on barium [^{13}C]carbonate).

2,5-Dimethyl-[1-^{13}C]cyclohexanol ***6***. A solution of the bis(Grignard) reagent prepared from 1,5-dibromo-2-methylhexane (37.1 g, 144 mmol) and magnesium turnings (7.69 g, 317 mmol) in 350 ml of THF was stirred at 0 °C, while a solution of ethyl [1-^{13}C]formiate (3.0 g, 40.0 mmol) in 60 ml of THF was added dropwise. Stirring of the reaction mixture was continued for 48 h at ambient temperature. After hydrolysis by careful addition of saturated aqueous ammonium chloride, the mixture was extracted five times with diethyl ether. In addition, the aqueous layer was extracted with the same solvent for 20 h in a Kutscher–Steudel extractor. The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous sodium sulphate. The solvents were carefully removed by distillation through a 30-cm-Vigreux column and the residue was distilled under reduced pressure to give cyclohexanol **6** as a mixture of four diastereomers (GC–MS) (4.38 g, 85%), bp: 77 °C/17 mbar; ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 3.68$ (m_c, $J(^1H,^{13}C) = 147.0$ Hz, $\frac{1}{4}$ H, C^{1}H), 3.61 (m_c, $J(^1H,^{13}C) = 139.9$ Hz, $\frac{1}{4}$ H, C^{1}H), 3.47 (m_c, $J(^1H,^{13}C) = 141.4$ Hz, $\frac{1}{4}$ H, C^{1}H), 3.07 (m_c, $J(^1H,^{13}C) = 138.7$ Hz, $\frac{1}{4}$ H, C^{1}H), 1.85–1.92 (m, 1 H), 1.60–1.66 (m, 1 H), 1.52–1.57 (m, 1 H), 1.39–1.48 (m, 2 H), 0.92–0.97 (m, 2 H), 0.81–0.89 (m, 6 H); MS (EI, 70 eV): $m/z = 129$ (3, $M^{\bullet+}$), 111 (38), 96 (65), 82 (48), 72 (100), 69 (65), 68 (47), 56 (54), 55 (53), 43 (50), 41 (60).

1,4-Dimethyl-[2-^{13}C]cyclohexene ***5b***. Reaction of cyclohexanol **6** (3.90 g, 28.0 mmol) with *para*-toluenesulphonic acid (210 mg, 1.40 mmol) as described above afforded cyclohexene **5b** (2.34 g, 76%) as a colourless oil; bp: 126–128°C; ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 5.40$ (d, $J(^1H, ^{13}C) = 77.0$ Hz, 1 H), 1.88–2.01 (m, 2 H), 1.64–1.67 (m, 2 H), 1.61 (br s, 3 H), 1.52–1.58 (m, 2 H), 1.19–1.26 (m, 1 H), 0.91 (d, $J = 6.5$ Hz, 3 H); MS (EI, 70 eV): $m/z = 111$ (45, $M^{\bullet +}$), 110 (7), 96 (87), 95 (13), 92 (13), 82 (42), 81 (10), 69 (100), 68 (85), 67 (21), 56 (34), 55 (32), 54 (16), 42 (19), 41 (32), 40 (17) 39 (21).

[2-^{13}C]para-xylene ***1b***. Dehydrogenation of cyclohexene **5b** (800 mg, 7.20 mmol) was carried out as described for isomer **1a** (see above). The product was collected in a cold trap, yielding 470 mg (61%) as a colourless liquid. Again, GC–MS analysis revealed the formation of minor amounts of dimethylcyclohexanes (4%); ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 7.04$ (s, 3 H), 7.04 (dd, $J(^1H,^{13}C) = 155.8$ Hz, $J(^1H,^1H) = 8.2$ Hz, 1 H), 2.29 (s, 6 H); MS (EI, 70 eV): $m/z = 107$ (56, $M^{\bullet +}$), 106 (33), 92 (100), 91 (14), 80 (6), 79 (7), 78 (11), 77 (5), 66 (5), 65 (3), 52 (6), 51 (6), 40 (8) 39 (10).

Conclusion

In the course of our investigations on the skeletal rearrangement processes of protonated *para*-xylenes in the gas phase, we have synthesized [1-^{13}C]-*para*-xylene **1a** and [2-^{13}C]-*para*-xylene **1b** bearing the carbon-13 label specifically in the ring positions C-1 and C-2, respectively. The six-membered rings were constructed by cyclocondensation of either ethyl [^{13}C]formate or ethyl [1-^{13}C]acetate with the suitable 1,5-bis(bromomagnesio)alkanes. The dimethylcyclohexanols obtained were converted to the xylenes by dehydration giving the ring-labelled dimethylcyclohexenes, followed by catalytic dehydrogenation. The method described for the synthesis of **1a** and **1b** may also be applicable to the synthesis of other lower alkylbenzenes by using [1-^{13}C]esters bearing larger acyl groupings and/or suitably substituted higher dihaloalkanes precursors for the construction of the labeled six-membered ring.

The carbon-13 labelled *para*-xylenes have been studied by chemical ionization in the ion source of a double-focusing mass spectrometer and the mechanism of the unimolecular fragmentation of protonated *para*-

xylene has been elucidated by metastable ion kinetic energy (MIKE) spectrometry.[18]

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References

1. Taylor R. *Electrophilic Aromatic Substitution*. Wiley: Chichester, 1990.
2. Olah GA. *Angew Chem* 1995; **107**: 1519–1532, *Angew Chem Int Ed Engl* 1995; **34**: 1393–1406.
3. Vogel P. *Carbocation Chemistry*. Elsevier: Oxford, 1985.
4. Fărcasiu D. *Acc Chem Res* 1982; **15**: 46–51.
5. Baenziger NC, Nelson AD. *J Am Chem Soc* 1968; **90**: 6602–6607.
6. Rathore R, Hecht J, Kochi JK. *J Am Chem Soc* 1998; **120**: 13278–13279.
7. Reed CA, Fackler NLP, Kim KC, *et al*. *J Am Chem Soc* 1999; **121**: 6314–6315.
8. Kuck D. *Mass Spectrom Rev* 1990; **9**: 583–630.
9. Kuck D. *Mass Spectrom Rev* 1990; **9**: 187–233.
10. Fornarini S. *Mass Spectrom Rev* 1996; **15**: 365–389.
11. Fornarini S, Crestoni ME. *Acc Chem Res* 1998; **31**: 827–834.
12. Kuck D. *Angew Chem* 2000; **112**: 129–134; *Angew Chem Int Ed* 2000; **39**: 125–130.
13. Kuck D, Schneider J, Grützmacher HF. *J Chem Soc, Perkin Trans* 1985; **2**: 689–696.
14. Mormann M, Kuck D. *J Mass Spectrom* 1999; **34**: 384–394.
15. Mormann M, Kuck D. *Int J Mass Spectrom* 2001; **210/211**: 531–544.
16. Kuck D, Mormann M. In *The Chemistry of Dienes and Polyenes*, vol. 2, Rappoport Z (ed.), Wiley: Chichester, 2000; 1–57 (Chapter 1).
17. Kuck D, Prior G, Grützmacher HF, Müller DR, Richter WJ. *Adv Mass Spectrom* 1989; **11A**: 750–751.
18. Mormann M, Kuck D. *Int J Mass Spectrom*, 2002, in press.
19. Kuck D. Review on scrambling in gaseous ions. *Int J Mass Spectrom* 2002; **213**: 101–144.
20. Nystrom RF, Loo YH, Mann KM, Allen JR. *Nucleonics* 1950; **7**: 46.
21. Renaud RN, Leitch LC. *J Label Compd* 1973; **9**: 145–148.
22. Pichat L, Baret C. *Tetrahedron* 1957; **1**: 269.

23. De Suzzoni S, Noel JP. *J Label Compd Radiopharm* 1994; **34**: 1202–1206.
24. Hughes DM, Reid JC. *J Org Chem* 1949; **14**: 516–524.
25. Scott FE, Simpson TJ, Trimble LA, Vederas JC. *J Chem Soc, Chem Commun* 1986; 214–215.
26. Lang M, Lang-Fugmann S, Steglich W. *Org Synthesis* 2000; **78**: 113–122.
27. Steinbach J, Mäding P, Füchtner F, Johannsen B. *J Label Compd Radiopharm* 1995; **36**: 33–41.
28. Mäding P, Steinbach J, Johannsen B. *J Label Compd Radiopharm* 1997; **39**: 585–599.
29. Mäding P, Steinbach J, *J Label Compd Radiopharm* 1998; **41**: 647–656.
30. Fields M, Leaffer MA, Rohan J. *Science* 1949; **109**: 35.
31. Fields M, Leaffer MA, Rothchild S, Rohan J. *J Am Chem Soc* 1952; **74**: 5498–5499.
32. Rieker A, Scheffler K, Müller E. *Liebigs Ann Chem* 1963; **670**: 23–30.
33. Robertson AV, Djerassi C. *J Am Chem Soc* 1968; **90**: 6992–6996.
34. Necula A, Racoveanu-Schiketanz A, Gheorghiu MD, Scott LT. *J Org Chem* 1995; **60**: 3448–3451.
35. Canonne P, Foscolos GB, Bélanger D. *J Org Chem* 1980; **45**: 1828–1835.
36. Canonne P, Bernatchez M. *J Org Chem* 1986; **51**: 2147–2148.
37. Canonne P, Bernatchez M. *J Org Chem* 1987; **52**: 4025–4031.
38. Slomp Jr. G, Inatome M, Bowers CE, Derfer JM, Greenlee KW, Board CE. *J Org Chem* 1960; **25**: 514–518.
39. Becker HD. In *The Chemistry of Quinoid Compounds*, vol. 2, Patai S, Rappoport Z (ed.). Wiley: Chichester, 1988; 1351–1384.
40. Fu PP, Harvey RG. *Chem Rev* 1978; **78**: 317–361.
41. Melville DB, Rachele JR, Keller EB. *J Biol Chem* 1947; **169**: 419–426.
42. Weygand F, Großkinsky OA. *Chem Ber* 1951; **84**: 839–843.
43. Perrin DD, Armarego WLF, Perrin DR. *Purification of Laboratory Chemicals* (2nd edn). Pergamon Press: Oxford, 1980.
44. Johnson CR, McCants, Jr D. *J Am Chem Soc* 1965; **87**: 1109–1114.
45. Kappeler H, Stauffacher D, Eschenmoser A, Schinz H. *Helv Chim Acta* 1951; **37**: 957–964.
46. Ruzicka L. *Helv Chim Acta* 1919; **2**: 144–161.
47. Raederstorff D, Shu AYL, Thompson JE, Djerassi C. *J Org Chem* 1987; **57**: 2337–2347.
48. Willer RL, Eliel EL. *J Am Chem Soc* 1977; **99**: 1925–1936.
49. Bubner M, Schmitz C. *Die Synthese von Kohlenstoff-14-markierten Verbindungen*. VEB Thieme: Leipzig, 1966.
50. Ropp GA. *J Am Chem Soc* 1950; **72**: 2299.

