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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 9537–9540

Synthesis and properties of 1-bromo-2,3,5,6-tetrakis(3-pentyl)benzene: a highly sterically hindered aryl bromide

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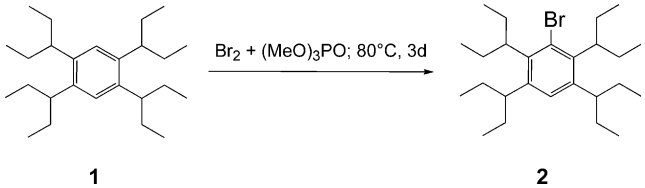
Received 28 September 2004; revised 19 October 2004; accepted 26 October 2004
Available online 11 November 2004

Abstract—The preparation of 1-bromo-2,3,5,6-tetrakis(3-pentyl)benzene is reported. The ^{1}H and ^{13}C NMR spectra indicate the presence of rotational isomers at room temperature which interconvert on heating. Coalescence of the NMR peaks for the methine and methylene aliphatic protons is observed at 100–120 °C. The conversion of this aryl bromide to the corresponding aryllithium is reported. Similar but less bulky aryl bromides have also been synthesised.

Sterically demanding aromatic molecules have found many applications, in particular for the stabilisation of organoelement compounds in low oxidation states and coordination environments and as building blocks used in the construction of ligands for transition metal catalysts. We have reported a method for the facile preparation of a series of bulky aromatic hydrocarbons containing 3-pentyl substituents,[1] and we are now studying the synthesis and properties of their functionalised derivatives.[2] In this letter we describe the bromination of these hydrocarbons and certain of their physical and chemical properties which demonstrate the high degree of steric hindrance in some of them.

The conventional procedures for the bromination of benzene derivatives are not generally applicable when bulky alkyl groups such as *tert*-butyl are present due to the susceptibility of these groups to cleavage by the HBr formed or by other acid reagents used in the reaction.[3,4] Indeed we found that bromination by Br_2 or NBS in CCl_4 invariably gave a mixture of compounds and was not a useful synthetic procedure. The method of Pearson et al.,[4] avoids this problem by using trimethyl phosphate as both solvent and HBr scavenger. We have found that this method is useful for the bromination of a number of the aforementioned 3-pentyl-substituted aromatic hydrocarbons and cleanly gives the monobrominated product in all cases. For the 1,2- and 1,3-bis(alkyl)benzenes, even after taking into account the *ortho–para* directing influence of the alkyl groups which appears to prevail over steric effects, more than one isomer could possibly be formed but only the less hindered one is actually obtained. The reaction proceeds readily in most cases although for the highly crowded 1,2,4,5-tetrakis(3-pentyl)benzene, **1**, (Eq. 1), long reaction times were required and careful monitoring of the progress of the reaction by GC was necessary, not only in order to prevent undesirable side reactions, but also to ensure that all the starting material had been consumed, since it proved virtually impossible to separate the product **2** from **1** by either recrystallisation, distillation or chromatography. The difficulty encountered for this separation is quite possibly due to the dominant effect of the very high lipophilicity of **2**.



1 **2** (1)

Keywords: Bulky aromatic; Restricted rotation; Electrophilic substitution; Bromination; Organolithium; NMR.
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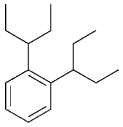
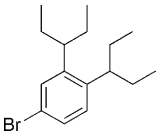
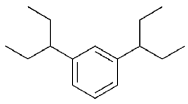
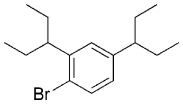
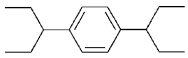
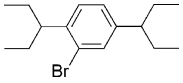
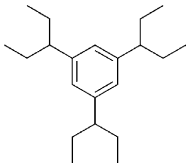
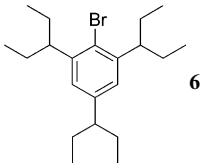
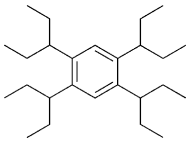
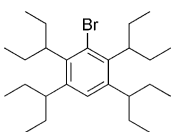
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.144

Table 1. Bromination of (3-pentyl)-substituted benzenes

Starting material	Product	Yield (isolated), %
	 **3**	60
	 **4**	73
	 **5**	62
	 **6**	83
	 **2**	29

The bromides prepared by this route are listed in Table 1. For all compounds except **2**, the NMR data were as expected and there was no evidence for restricted rotation of the 3-pentyl groups at room temperature. In the case of **2**, however, although the analytical GC and GC–MS data indicated that the expected product had been formed, the room temperature NMR spectra were rather complicated and the presence of three signals for the single aromatic proton suggested that three isomers were present. From the integration for this proton, two isomers were present in approximately equal proportions with the third constituting about 10% of the mixture. In order to determine whether the data were consistent with the presence of rotational conformers, ^{1}H and ^{13}C NMR spectra were measured at temperatures up to 148 °C (Figs. 1 and 2).[5] For ^{1}H NMR spectra, DMSO-d_6 or chlorobenzene solutions were studied and for ^{13}C NMR spectra, we used $CDCl_3$ solutions up to 60 °C and neat samples referenced to an external sealed D_2O capillary for temperatures above the melting point (74 °C) of **2**. Coalescence of signals occurred at ca. 110–125 °C and eventually a more simple pattern corresponding to that anticipated for the symmetrical molecule was observed. The high coalescence temperatures are indicative of the severe steric crowding in this molecule. It should be mentioned here also that the spectra of the samples which were used for the high temperature NMR measurements were also measured again on recooling to room temperature. Although some slight yellowing of the sample had occurred, the spectra obtained were identical to the initial room temperature spectra.

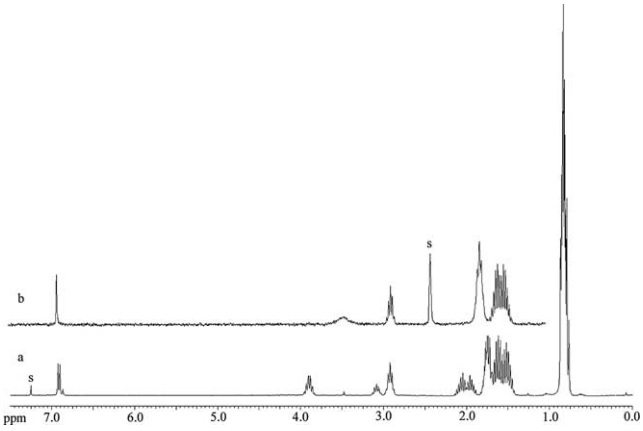


Figure 1. ^{1}H NMR spectra of **2**: (a) 24 °C in $CDCl_3$, (b) 148 °C in DMSO-d_6 [s = solvent].

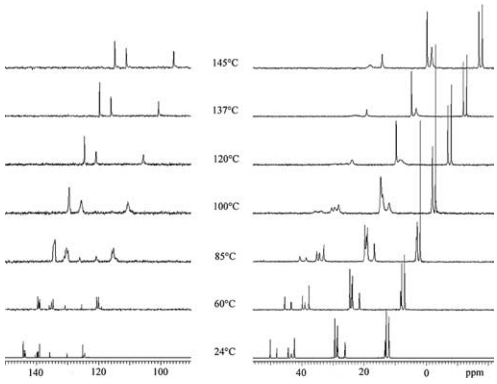
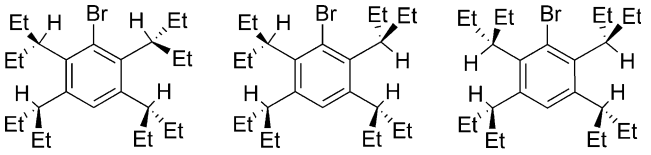


Figure 2. ^{13}C NMR spectra of **2** in $CDCl_3$ (24 °C and 60 °C) and as neat liquid (85–145 °C).

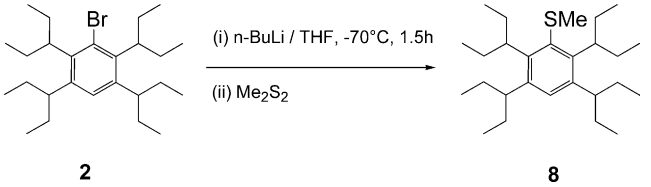
Based largely on an analysis of the 1 D and 2 D (COSY, NOESY, HOESY) NMR spectra and particularly taking into account the low field shifted aliphatic CH signals (ca. 3.8 ppm) which we assigned to conformations in which these protons are directed towards the bromine atom, we assigned the two major isomers to the conformations **A** and **B** shown below. The third minor isomer is most likely **C** in which both the methine protons on the 2,6-alkyl groups are pointed away from the bromine. Restricted rotation of the groups *meta* to the bromine is not expected since it should otherwise also be apparent in the spectra of the other bromides in Table 1. Also no evidence of restricted rotation is evident in the room temperature NMR spectra of the parent hydrocarbon, **1**. Since the spectra for **4**, **5** and **6** also indicate free rotation of the alkyl groups *ortho* to the bromine, we conclude that the restricted rotation of the *ortho*-3-pentyl groups in **2** is due to a combined effect of the adjacent bromine and 3-pentyl groups.

The results for **2** are reminiscent of those observed for the likewise highly sterically hindered 1-bromo-2,4,6-tris[bis(trimethylsilyl)methyl]benzene which at −40 °C in solution exists as one conformer with the *ortho*-methine hydrogens coplanar with the ring and directed towards the bromine.[6] The 1,3,5-tris[bis(trimethylsil-

yl)methyl]phenyl group has been used extensively by Okazaki and co-workers as a protective group for the kinetic stabilisation of highly reactive species,[7] and so, on the basis of the present observations, it is expected that the 1,2,4,5-tetra(3-pentyl)phenyl group should also find similar applicability.



The bromo-derivatives reported here may be readily converted into the corresponding organolithium reagents by reaction with *n*-butyllithium. We were particularly interested in examining the behaviour of the lithium reagent, **7**, prepared from **2** in view of its seemingly high steric demands and we found that it appears to exhibit normal reactivity with electrophiles. This aryllithium is a potentially very useful reagent and its reactions are now being actively explored and will be reported separately. A ^{6}Li NMR spectrum of the C_6D_6 solution was recorded for this reagent. Only one resonance was observed at 0.9 ppm (ext. $LiCl/D_2O$) so it is not clear whether there is also restricted movement in this case. Lithium is smaller than bromine and so it is possible that there is more freedom for the alkyl groups to rotate. This could also be dependent on the state of aggregation of the aryllithium. This is not known for **7** but other sterically hindered aryllithiums have been shown to exist as monomers, dimers or tetramers in the solid state[8] or in solution,[9] the state of aggregation depending not only on the steric demands of the aryl group but also on the nature of the solvent. Restricted rotation is not confined to the bromo-derivative, **2**, but is also observed in the methylthio-derivative, **8**, prepared by reaction of the organolithium with dimethyldisulfide. The ^{1}H NMR spectrum for **8** has the same general characteristics as that for **2**, indicating the presence of similar conformers and a similar degree of crowding.



(2)

Further work is planned on the reactions of these compounds in view of the possibility offered by bulky groups for the stabilisation of low oxidation states and unsaturated compounds,[7,10] and on the preparation of sterically demanding ligands, which in recent years play a prominent role in transition metal coordination chemistry and homogenous catalysis.[11]

Typical experimental procedure: 1,2-bis(3-pentyl)benzene (10.9 g, 50 mmol) and distilled trimethylphosphate (TMPO) (25 mL) were heated with stirring to 70 °C on an oil-bath. The reaction mixture was protected from moisture with a drying tube containing molecular sieves. A solution of Br_2 (2.7 mL, 53 mmol) in TMPO (25 mL) was added over 20 min and the reaction mixture stirred with heating for 16 h after which time it had almost completely discolored. After cooling, water (100 mL) was added and the crude product extracted with dichloromethane (3 × 50 mL). The combined extracts were dried over anh. Na_2SO_4, filtered, concentrated on a rotary evaporator and distilled in vacuo. Yield of 1-bromo-3,4-bis(3-pentyl)benzene, **3**, 8.9 g (60%, bp 101–104 °C/0.2 mbar). 1-Bromo-2,4-bis(3-pentyl)benzene, **4**, (73%, bp 99–102 °C/0.2 mbar), 1-bromo-2,5-bis(3-pentyl)benzene, **5**, (62%, bp 100–103 °C/0.2 mbar) and 1-bromo-2,4,6-tris(3-pentyl)benzene, **6**, (83%, bp 125–128 °C/0.1 mbar), were prepared in a similar way. For 1-bromo-2,3,5,6-tetrakis(3-pentyl)benzene, **2**, a temperature of 85–90 °C was required with a reaction time of 60–72 h (for disappearance of the starting material as determined by GC) and the solid product was purified by recrystallisation from methanol (29%, mp 74 °C). All compounds gave satisfactory elemental analyses and were judged to be at least 97% pure by GC and NMR.

NMR data (^{1}H 300 MHz, ^{13}C 75 MHz, $CDCl_3$ unless otherwise stated). *1-Bromo-3,4-bis(3-pentyl)benzene,* **3**: ^{1}H NMR: δ 0.81 (tr, 6H, J = 7.3 Hz, CH_3), 0.82 (tr, 6H, J = 7.3 Hz, CH_3), 1.54 (m, 4H, CH_2), 1.67 (m, 4H, CH_2), 2.80 (m, 2H, CH), 7.03 (d, J = 9.2 Hz, 1H, CH), 7.26 (d, J = 9.2 Hz, 1H, CH), 7.28 (s, 1H, CH); ^{13}C NMR: δ 12.2, 29.0, 41.9, 42.1, 119.6, 127.8, 128.6, 128.9, 143.1, 146.8.

1-Bromo-2,4-bis(3-pentyl)benzene, **4**: ^{1}H NMR: δ 0.77 (tr, J = 7.3 Hz, 6H, CH_3), 0.81 (tr, 6H, J = 7.3 Hz, CH_3), 1.54 (m, 4H, CH_2), 1.69 (m, 4H, CH_2), 2.28 (m, 1H, CH), 3.08 (m, 1H, CH), 6.82 (dd, J = 2.4,7.9 Hz, 1H, CH), 6.93 (d, J = 2.4 Hz, 1H, CH), 7.46 (d, J = 7.9 Hz, 1H, CH); ^{13}C NMR: δ 11.6, 12.1, 28.5, 29.2, 46.5, 49.4, 123.0, 126.4, 127.4, 132.3, 143.9, 145.0.

1-Bromo-2,5-bis(3-pentyl)benzene, **5**: ^{1}H NMR: δ 0.78 (tr, J = 7.3 Hz, 6H, CH_3), 0.81 (tr, J = 7.3 Hz, 6H, CH_3), 1.55 (m, 4H, CH_2), 1.68 (m, 4H, CH_2), 2.26 (m, 1H, CH), 3.04 (m, 1H, CH), 7.05 (AB q, J = 7.9 Hz, 2H, CH), 7.32 (br m, 1H, CH); ^{13}C NMR: δ 11.8, 12.2, 28.7, 29.2, 46.4, 49.0, 125.9, 127.0, 127.2, 131.7, 141.8, 145.0.

1-Bromo-2,4,6-tris(3-pentyl)benzene, **6**: ^{1}H NMR: δ 0.76 (tr, J = 7.3 Hz, 6H, CH_3), 0.78 (tr, J = 7.3 Hz, 12H, CH_3), 1.5 (m, 4H, CH_2), 1.7 (m, 8H, CH_2), 2.25 (m, 1H, CH), 3.23 (m, 2H, CH), 6.73 (s, 2H, CH); ^{13}C NMR: δ 11.6, 12.0, 28.8, 29.2, 47.1, 49.3, 124.6, 127.2, 143.8, 144.2.

1-Bromo-2,3,4,5-tetrakis(3-pentyl)benzene, **2**: (assignments to the conformers **A**, **B** and **C**, based on comparison with spectra for related structures and on analysis of 2 D spectra, are given where possible but should be regarded as tentative.): ^{1}H NMR (rt; the relative proportions of the conformers were estimated from the relative intensities given in square brackets for the alkyl

methylene and methine protons and for the aromatic protons): δ 0.8 (m, 24H, CH_3, **A**, **B**, **C**), 1.52 (m, ca. 4H, CH_2 [*meta*], **A**, **B**, **C**), 1.62 (m, ca. 4H, CH_2 [*meta*], **A**, **B**, **C**), 1.75 (m, ca. 4.6H, CH_2 [*ortho*], **A**, **B**, **C**), 1.96 (m, ca. 1.7H, CH_2 [*ortho*], **B**, **C**), 2.05 (m, ca. 1.7H, CH_2 [*ortho*], **B**, **C**), 2.92 (m, 2.1H, CH, **A**, **B**, **C**), 3.09 (m, 0.5H, CH, **B**), 3.90 (m, 1.4H, CH, **A**, **B**), 6.87 (s, 0.1H, CH, **C**), 6.90 (s, 0.45H, CH, **A** or **B**), 6.93 (s, 0.45H, CH, **A** or **B**); ^{1}H NMR (148 °C, DMSO-d_6): δ (rel. to aromatic proton = 6.90 ppm) 0.78 (m, 24H, CH_3), 1.5–1.7 (m, 8H, CH_2), 1.8 (m, 8H, CH_2), 2.9 (m, 2H, CH), 3.4 (br, 2H, CH), 6.90 (s, 1H, CH); ^{13}C NMR (rt) δ [CH_3 carbons] 11.8, 12.0 (*ortho*), 12.8, 13.1, 13.3 (*meta*); [CH_2 carbons] 26.0 (*ortho*, **B**), 26.2 (*ortho*, **C**), 28.4 (*ortho*, **A** or **B**), 28.7 (*ortho*, **A** or **B**), 28.8 (*ortho*, **A** or **B**), 29.3 (*meta*, **A**, **B** and/or **C**); [aliphatic CH carbons] 42.3 (**A**, **B**, **C**), 43.3 (**C**), 44.3 (**B**), 48.0 (**B**), 50.1 (**A**); [aromatic carbons] 124.4 (CH, **C**), 125.1 (CH, **A**, **B**), 130.2 (CBr, **A** or **B**), 135.7(CBr, **A** or **B**), 139.0, 139.5, 139.7, 140.4, 143.5, 143.6, 143.9, 144.3 (*C*–$CHEt_2$); ^{13}C NMR (145 °C, neat, ext. ref D_2O): 11.7, 12.8, 27.9, 29.4, 43.8, 46.7 125.5, 140.8, 143.4.

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