Pergamon

Tetrahedron Letters 41 (2000) 667–670

TETRAHEDRON
LETTERS

The rate retarding effect of alkyl groups on arene metalation quantified

Eckhard Baston, Qian Wang and Manfred Schlosser *

Section de Chimie (BCh), Université, CH-1015 Lausanne, Switzerland

Received 21 October 1999; accepted 12 November 1999

Abstract

Metalation/trapping sequences applied to relatively inert, *tert*-alkyl substituted arenes tend to give poor yields unless the reagent is used in high concentrations. Under optimized conditions, even 1,4-bis(*tert*-butyl)benzene, 1,1,3,3-tetramethylindane and 1,1,2,2,3,3-hexamethylindane can be smoothly converted into derivatives. Competition experiments enable the quantitative assessment of *tert*-alkyl substituent effects on the metalation rates at aromatic *ortho, meta* and *para* positions. Unlike alkyl groups, hetero elements generally accelerate metalation reactions. 1,1,3,3-Tetramethyl-1,3-dihydroisobenzofuran undergoes the hydrogen/metal exchange 3–6 times faster than the indanes mentioned above, the reaction occurring at both the 5- and at the 4-position. © 2000 Published by Elsevier Science Ltd. All rights reserved.

One decade ago, we reported the metalation and subsequent transformation of *tert*-butylbenzene and related 'spiny' hydrocarbons.[1] However, yields exceeding 50%, as reported,[1] proved to be difficultly reproducible. As it turned out, satisfactory yields can be achieved only when the substrate and the superbasic mixed-metal reagent (LIC–KOR)[2,3] are employed in the 1.5–2.0 M range (see Fig. 1).

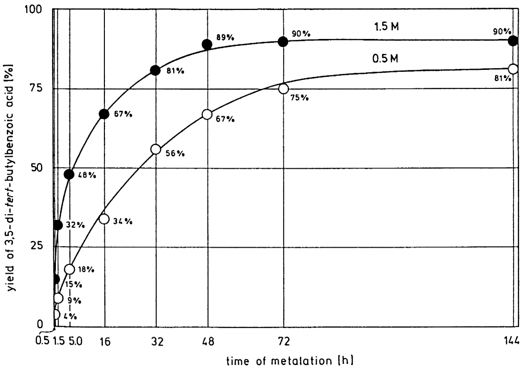


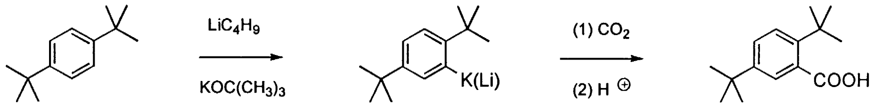
Fig. 1. Consecutive reaction of 1,3-bis(*tert*-butyl)benzene with butyllithium potassium *tert*-butoxide (suspension in hexanes) and dry ice: yields of isolated 3,5-bis(*tert*-butyl)benzoic acid as a function of the metalation time (t) and concentration

---

[*] Corresponding author. Fax: ++41-21-692-39-65.

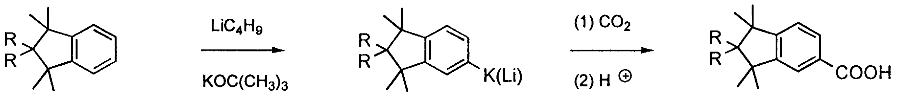
PII: S0040-4039(99)02160-7

Employing a high-concentration (1.5 M) protocol, it was possible for the first time to attack a position *ortho* to a bulky *tert*-butyl group. When a suspension of potassium *tert*-butoxide in cyclohexane containing equivalent amounts of butyllithium and 1,4-di(*tert*-butyl)benzene was stirred for 25 h at 25°C before being poured on dry ice and neutralized, 10% of 2,5-di(*tert*-butyl)benzoic acid (**1**) were formed. The yield raised to 24% when the reaction was conducted at 75°C under otherwise identical conditions.



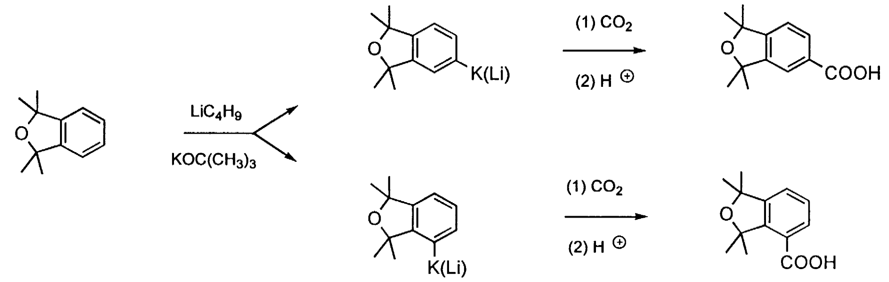
1

In view of the difficulties to prepare 1,2-di(*tert*-butyl)benzene,[4] the readily accessible 1,1,3,3-tetramethylindane[5] and 1,1,2,2,3,3-hexamethylindane[6] were selected as surrogates. Superbase promoted metalation proceeded smoothly (24 h at 25°C in hexanes) and, after carboxylation, the 5-(1,1,3,3-tetramethyl)indanecarboxylic acid (**2**) and the 5-(1,1,2,2,3,3)-hexamethylindane carboxylic acid (**3**), were isolated in 51 and 55% yield, respectively.



2 : R = H
3 : R = H_3C

The oxa-analogous 1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran[7] afforded two regioisomers side by side.[8] The main product (23%) was the already described 5-(1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran)carboxylic acid (**4a**).[9] The minor isomer 4-(1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran)carboxylic acid (**4b**; 12%) appears to have been previously overlooked.



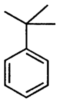
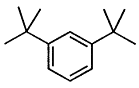
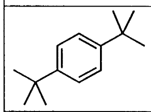
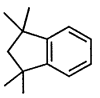
4a

4b

Competition experiments[1,10] were carried out to quantify the substituent effects on the metalation rates (see Tables 1 and 2).[11] All 'spiny' hydrocarbons were found to react more slowly than benzene itself, the sterically shielded 1,4-di(*tert*-butyl)benzene being clearly the most inert substrate. As the partial rate factors of simple substrates (e.g., *tert*-butylbenzene, see Table 1, or 1-methyl-1-phenylcyclopropane[1]) reveal, alkyl substituents seem to exert a slightly stronger rate retarding effect when located at the *meta* rather than the *para* position relative to the deprotonation site.

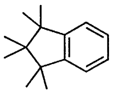
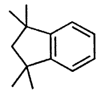
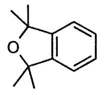
In comparison with the 1,1,3,3-tetramethylindane case, the additional pair of geminal methyl groups present in 1,1,2,2,3,3-hexamethylindane impedes the metalation of the latter substrate by a factor of two (see Table 2). In contrast, 1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran reacts with the superbase three times faster than the oxygen-free reference compound (Table 2). If one breaks down this overall effect according to the competing regioisomeric channels, metalation at the positions 5 and 4 proves to be accelerated twofold and at least 20-fold, respectively. At present, it is not clear whether the inductive electron-withdrawing effect of the heteroatom is transmitted through the σ-bonded skeleton or by polarization of the π-cloud of the aromatic electron sextet. As molecular models show, a direct coordination of the oxygen atom to the proton abstracting reagent can be ruled out for reasons of congestion. Therefore, no analogy should be drawn to the *ortho*-lithiation of methyl triphenylmethyl ether[12] which in a sequence of subsequent steps is converted into 9-phenyl-9-fluorenyllithium while 1,1,1-triphenylethane is totally unreactive under identical conditions.

Table 1
Metalation of *tert*-alkyl substituted benzenes by means of the LIC–KOR superbase in hexanes (HEX) or tetrahydrofuran (THF): relative rates and partial rate factors[a] as assessed by competition experiments

substrate	in HEX (at +25 °C)				in THF (at -75 °C)			
	k_{rel}	k^{f}_{o}	k^{f}_{m}	k^{f}_{p}	k_{rel}	k^{f}_{o}	k^{f}_{m}	k^{f}_{p}
	≡ 6.00	≡ 1.00	≡ 1.00	≡ 1.00	≡ 6.00	≡ 1.00	≡ 1.00	≡ 1.00
	0.28	< 0.005 [b]	0.063 [c]	0.15 [c]	0.24	< 0.005 [b]	0.006 [c]	0.11 [c]
	0.081	-	1.3 [d]	-	[e]	-	-	-
	0.011	0.044 [d]	-	-	[e]	-	-	-
	0.078	-	-	0.62 [d]	0.15	-	-	1.1 [d]

[a] Partial rates factors ($k^{\mathrm{f}}_{\mathrm{pos.}}$) were determined by multiplying relative rates (k_{rel}) with the percentage of reaction occurring at the site under inspection and by dividing this value by the number of equivalent exchange-active positions. [b] Limit of detection. [c] The partial rate factors of *tert*-butylbenzene were calculated taking into account a 45 : 55 (HEX) and 55 : 45 (THF) *m*-/*p*-isomer distribution. [1] [d] In the last three substrates, two positions are occupied by *tert*-alkyl substituents. Inevitably one of them is located in a *meta* position with respect to the metalation site. Therefore, to obtain the partial rate factors listed in Table 1, the global relative rates were first statistically corrected and then divided by 0.063 (HEX) or 0.066 (THF), the k^{f}_{m} of *tert*-butyl benzene, assuming first-order additivity of group effects. [e] No product (≤ 0.3%) found.

Table 2
Metalation and subsequent carboxylation of 1,1,3,3-tetramethylindane, 1,1,2,2,3,3-hexamethylindane and 1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran by means of the LIC–KOR superbase: relative rates and partial rate factors[a] as assessed by competition experiments

substrate	in HEX (at +25 °C)			in THF (at -75 °C)		
	k_{rel}	$k^{5\text{-pos.}}_{\mathrm{rel}}$	$k^{4\text{-pos.}}_{\mathrm{rel}}$	k_{rel}	$k^{5\text{-pos.}}_{\mathrm{rel}}$	$k^{4\text{-pos.}}_{\mathrm{rel}}$
	0.47	0.47	< 0.01 [b]	0.46	0.46	< 0.01 [b]
	≡ 1.0	≡ 1.0	< 0.01	≡ 1.0	≡ 1.0	< 0.01
	2.9 [c]	1.9	1.0	2.8 [c]	2.2	0.34

[a] As in Table 1. [b] Limit of detection. [c] The 5- and 4-(1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran)carboxylic acids (**4a** and **4b**) were obtained in ratios of 66 : 34 (HEX) and 78 : 12 (THF).

Acknowledgements

This work was supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant nos. 20-49’307-96 and 20-55’303-98).

References

1. Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633–5648.
2. Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9–16; Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741–744.
3. Schlosser, M. *Modern Synthetic Methods* **1992**, *6*, 227–271.
4. Hoogzand, C.; Hübel, W. *Angew. Chem.* **1961**, *73*, 680; Barclay, L. R. C.; Milligan, C. E.; Hall, N. D. *Can. J. Chem.* **1962**, *40*, 1664–1671; Burgstahler, A. W.; Chien, P.-L.; Abdel Rahman, M. O. *J. Am. Chem. Soc.* **1964**, *86*, 5281–5290; Nakayama, J.; Yamaoka, S.; Nakanishi, T.; Hoshino, M. *J. Am. Chem. Soc.* **1988**, *110*, 6598–6599; Nakayama, J.; Hirashima, A. *J. Am. Chem. Soc.* **1990**, *112*, 7648–7653.
5. Bogert, M. T.; Davidson, D. *J. Am. Chem. Soc.* **1934**, *56*, 185–190; Sikkar, R.; Martinson, P.; Nilsson, B. *Acta Chem. Scand. Ser. B* **1978**, *32*, 257–263.
6. Baran, J.; Mayr, H. *J. Org. Chem.* **1988**, *53*, 4626–4628.
7. Bennett, G. M.; Wain, R. L. *J. Chem. Soc.* **1936**, 1114–1120.
8. As expected (see: Schlosser, M.; Geneste, H. *Chem. Eur. J.* **1998**, *4*, 1969–1973), the superbasic mixture of *tert*-butyllithium and potassium *tert*-butoxide deprotonates the ‘spiny’ isobenzofuran exclusively at the 5-position.
9. Shi, G.-Q.; Cottens, S.; Shiba, S. A.; Schlosser, M. *Tetrahedron* **1992**, *48*, 10560–10574.
10. Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927**, 2918–2929; Schlosser, M.; Ladenberger, V. *Chem. Ber.* **1967**, *100*, 3901–3915.
11. The consumption of starting materials as the formation of derivatives thereof was monitored by gas chromatography (30 m, silicon rubber SE-30, 120°C; 30 m, silicon rubber DB-1701, 130°C), the corresponding peak areas being integrated relative to those of reference compounds (‘internal standards’) and being corrected by calibration factors. New products were characterized by their NMR and mass spectral data and by correct elementary analyses.
12. Gilman, H.; Meikle, W. J.; Morton, J.W. *J. Am. Chem. Soc.* **1952**, *74*, 6282–6284.