J. Am. Chem. Soc. **2000,** *122,* 2391−2392

Chemoselective Catalytic Side-Chain Alkylation of Aromatics by Ethylene Leading to Sterically Demanding Alkylbenzenes

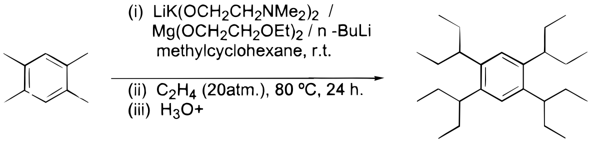
Barry R. Steele and Constantinos G. Screttas*

Institute of Organic and Pharmaceutical Chemistry
National Hellenic Research Foundation
48 Vas. Constantinou Ave., 116 35 Athens, Greece

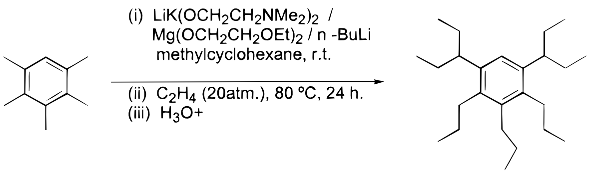
Received December 20, 1999

The preparation of sterically demanding aromatic molecules has always provided a challenge for the synthetic chemist.[1] These derivatives are important target compounds, however, since they play an important role in the organometallic chemistry of main group and transition metals,[2] as well as in the synthesis, isolation, and study of once elusive organoelement species.[3] Here we report a convenient process in which ethylene, via anionic catalysis using a higher-order LICKOR system,[4] ethylates the side chains of alkylaromatics to produce bulky arenes, many of which, despite their relatively simple structures, have not been previously reported. Although the addition of ethylene to benzylic carbanions has been known for some time, particularly from the work of Pines and co-workers,[5] it usually gives rise to mixtures of monoethylated, polyethylated, and telomeric products, and in some cases indane derivatives, and it is probably for this reason that the reaction has not found favor as a synthetic procedure. We have now found that a catalytic system comprising the very powerful metalating mixture of *n*-BuLi and $LiK(OCH_2CH_2NMe_2)_2$,[4] in combination with $Mg(OCH_2CH_2OEt)_2$, promotes the multiple and clean addition of ethylene to a series of alkylaromatics. The above metalating agent has been previously shown to combine the activating effect of a tertiary amine[6] with that of a potassium alkoxide,[7] while magnesium 2-ethoxyethoxide is known to act both as a solubilizing agent of organoalkali metals in hydrocarbons[8] as well as a modifier of their reactivity.[9] It is probable that both of these properties are responsible for its beneficial effect in the present case.

The substrates studied were a series of methylated benzenes from toluene up to hexamethylbenzene as well as *n*-butylbenzene. The results indicate that a methyl group which is flanked by two neighboring methyl groups can only add one molecule of ethylene, whereas if there is a vacant *ortho* site, it can add a second molecule at the benzylic position. Addition of a third molecule of ethylene to give a tertiary alkyl-substituted benzene was observed to only a very minor extent. Thus, toluene, the xylenes, mesitylene, and durene are ultimately converted to the corresponding 3-pentyl derivatives, while *n*-butylbenzene adds one molecule of ethylene to give 3-hexylbenzene (eq 1). Hexamethylbenzene, on the other hand, undergoes a clean conversion to hexapropylbenzene, while pentamethylbenzene gives 1,5-bis(3-pentyl)-2,3,4-tripropylbenzene [eq 2].[10]



(1)



(2)

The results are summarized in Table 1. The catalytic activity of the system decreases over a period of several hours under the conditions employed,[11] probably due to gradual quenching of the organometallic compounds by reaction with the alkoxide groups, and the amount of initial base required for the reaction to go to completion is of the order of 2.5% per ethylene added with respect to the substrate. It is of particular interest and importance to note the remarkable effect of adding magnesium 2-ethoxyethoxide. The reaction with *m*-xylene was carried out under the usual conditions both with and without addition of $Mg(OCH_2CH_2OEt)_2$. It was found that in its presence the reaction proceeded to completion (addition of 4 molecules of ethylene) and that no partially

---

(1) (a) Prinz, P.; Lansky, A.; Haumann, T.; Boese, R.; Noltemeyer, M.; Knierem, B.; de Meijere, A. *Angew. Chem.* **1997**, *109*, 1343−1346; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1289−1292. (b) Yokota, T.; Sakurai, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1997**, *38*, 3923−3926.

(2) (a) McGlinchey, M. J. *Adv. Organomet. Chem.* **1992**, *34*, 285−325. (b) Johnson, E. S.; Balaich, G. J.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 11086−11087. (c) Dilworth, J. R.; Hu, J. *Adv. Inorg. Chem.* **1994**, *40*, 411−59.

(3) For recent examples and reviews, see: (a) Loss, S.; Widauer, C.; Grützmacher, H. *Angew. Chem.*, **1999**, *111*, 3546−3548; *Angew. Chem., Int. Ed.* **1999**, *38*, 3329−3331. (b) Suzuki, H.; Tokitoh, N.; Okazaki, R.; Nagase, S.; Goto, M. *J. Am. Chem. Soc.* **1998**, *120*, 11096−11105. (c) Stürmann, M.; Weidenbruch, M.; Klinkhammer, K. W.; Lissner, F.; Marsmann, H. *Organometallics* **1998**, *17*, 4425−4428. (d) Su, J.; Li, X.-W.; Robinson, G. H. *Chem. Commun.* **1998**, 2015−2016. (e) Rabe, G. W.; Heise, H.; Yap, G. P. A.; Liable-Sands, L. M.; Guzei, I. A.; Rheingold, A. L. *Inorg. Chem.* **1998**, *37*, 4235−4245. (f) Cardin, C. J.; Cardin, D. J.; Constantine, S. P.; Drew, M. G. B.; Rashid, H.; Convery, M. A.; Fenske, D. *J. Chem. Soc., Dalton Trans.* **1998**, 2749−2756. (g) Beck, A. K.; Dobler, M.; Plattner, D. A. *Helv. Chim. Acta* **1997**, *80*, 2073−2083. (h) Trommer, M.; Miracle, G. E.; Eichler, B. E.; Powell, D. R.; West, R. *Organometallics* **1997**, *16*, 5737−5747. (i) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585−1592. (j) Reddy, S. S.; Shashidhar, G.; *Eur. Polym. J.* **1997**, *33*, 583−585. (k) Tokitoh, N.; Matsumoto, T.; Okazaki, R. *J. Am. Chem. Soc.* **1997**, *119*, 2337−2338. (l) Rappoport, Z.; Frey, J.; Sigalov, M.; Rochlin, E. *Pure Appl. Chem.* **1997**, *69*, 1933−1940. (m) Takeda, N.; Suzuki, H.; Tokitoh, N.; Okazaki, R.; Nagase, S. *J. Am. Chem. Soc*. **1997**, *119*, 1456−1457. (n) Weidenbruch, M.; Wilms, S.; Saak, W.; Henkel, G. *Angew. Chem.* **1997**, *109*, 2612; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2503−2504.

(4) Screttas, C. G.; Steele, B. R. *J. Organomet. Chem.* **1993**, *453*, 163−170.

(5) (a) Pines, H.; Vesely, J. A.; Ipatieff, V. N. *J. Am. Chem. Soc.* **1955**, *77*, 554−559. (b) Pines, H.; Mark, V. *ibid.* **1956**, *78*, 4316−4322. (c) Schaap, L.; Pines, H. *ibid.* **1957**, *79*, 4967−4970. (d) Pines, H. *Acc. Chem. Res.* **1974**, *7*, 155−162. (e) Pines, H.; Stalick, W. M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*; Academic Press: New York, 1977; pp 240−308.

(6) Screttas, C. G.; Eastham, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 3276−3277.

(7) (a) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9−16. (b) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257−262.

(8) Screttas, C. G.; Micha-Screttas, M. *J. Organomet. Chem.* **1985**, *290*, 1−13.

(9) (a) Screttas, C. G.; Steele, B. R. *J. Org. Chem.* **1989**, *54*, 1013−1017. (b) Kostas, I. D.; Screttas, C. G. *ibid.* **1997**, *62*, 5575−5577. (c) Kostas, I. D.; Screttas, C. G. *Main Group Met. Chem.* **1997**, *20*, 787−790.

(10) The products from mesitylene, durene, and pentamethylbenzene have not been previously reported. Hexapropylbenzene has been obtained previously by Friedel−Crafts reaction of benzene with chloropropane or by trimerization of oct-4-yne; Hopff, H.; Gati, A. *Helv. Chim. Acta* **1965**, *48*, 509−517.

(11) Full experimental details for all the products listed in Table 1 are provided in the Supporting Information. In a typical procedure, a stirred pressure reactor was charged with durene (13.4 g; 100 mmol), $LiK(OCH_2CH_2NMe_2)_2$ (30 mL of a 0.67 M solution in methylcyclohexane [MCH]; 20 mmol), $Mg(OCH_2CH_2OEt)_2$ (2.8 mL of a 1.8 M solution in MCH.; 5 mmol), *n*-BuLi (14 mL of a 1.6 M solution in MCH.; 20 mmol), and 10 mL MCH. After stirring for 30 min, the reactor was filled with ethylene to 20 atm and stirred with heating at 80 °C. The pressure was maintained at 20 ± 2 atm. The reaction was stopped when no further gas consumption was evident (∼24−36 h). The mixture was hydrolyzed and acidified, and the product was extracted with hexane. Removal of solvents, fractional distillation under reduced pressure, and recrystallisation from ethanol gave 1,2,4,5-tetrakis(1-ethylpropyl)benzene as a white crystalline solid, yield: 21.5 g (60%), mp 79−80 °C. Analogous stoichiometric ratios of the reactants were employed for entries 6, 8, and 9 (Table 1), while for entries 1−5 the ratio for substrate/*n*-BuLi/$LiK(OCH_2CH_2NMe_2)_2$/$Mg(OCH_2CH_2OEt)_2$ was 100/10/10/2.5.

10.1021/ja994432p CCC: $19.00

Table 1. Products and Yields of Catalyzed Addition of Ethylene to Methylbenzenes

entry	substrate	product	yield (%)[a]
1	toluene	3-pentylbenzene	68
2	*n*-butylbenzene	3-hexylbenzene	66
3	*o*-xylene	1,2-bis(3-pentyl)benzene	61
4	*m*-xylene	1,3-bis(3-pentyl)benzene	79
5	*p*-xylene	1,4-bis(3-pentyl)benzene	75
6	mesitylene	1,3,5-tris(3-pentyl)benzene	72
7	durene	1,2,4,5-tetrakis(3-pentyl)benzene	60
8	pentamethylbenzene	1,5 bis(3-pentyl)−2,3,4-tripropylbenzene	75
9	hexamethylbenzene	hexapropylbenzene	68

[a] Iisolated yields.

ethylated products were observable by GC. The only side products observed were higher molecular weight products, presumably telomers, which could be separated by distillation. In the absence of $Mg(OCH_2CH_2OEt)_2$ the reaction did not proceed to completion, and a mixture of partially ethylated products were obtained, mainly 1-methyl, 3-(3-pentyl)benzene (44%), and 1-methyl,3-propylbenzene (20%), as well as unreacted *m*-xylene (25%). The tetra-ethylated product constituted only 4.6% of the mixture.

The reaction is believed to take the following course. After the initial metalation of substrate to give a benzylic carbanion, addition of a molecule of ethylene gives rise to a very reactive 3-arylpropylcarbanion. This will provide a metalating agent as strong as that originally applied and will metalate available benzylic sites. Normally a methyl group will be metalated more easily than a secondary benzylic site, but it was observed that there is a strong preference for ethylation at the latter. To illustrate this point, the course of the reaction with *m*-xylene as substrate was investigated, and it was found that the formation of 1-methyl,3-(3-pentyl)benzene,**1**, was greatly favored over that of 1,3-dipropylbenzene, **2**, (ratios of **1**/**2** of 4:1 to 20:1 were found depending on the time of reaction; shorter reaction times gave the higher ratios). Previous detailed studies have been made by Maercker et al. on systems of this type in ethereal solvents and support an intermolecular process.[12] The observed results indicate, therefore, that, although the metalation of the benzylic position of the propyl side chain is less favorable than that of the methyl group, the resulting secondary carbanion is sufficiently more reactive toward ethylene,[13] that products such as **1** are formed preferentially, and that the reaction is driven by the effectively irreversible protonation of the addition product.[14] Metalation of **1** would produce a tertiary 3-arylpentyl carbanion which would be expected to be even more reactive than the secondary 1-arylpropyl carbanion, but we found no evidence for the production of triethylated compounds, except in trace amounts from the reaction with toluene. We infer from this that the benzylic site of a 3-arylpentane is either not susceptible to metalation under the conditions used or that steric factors prevent addition of ethylene. That there do indeed appear to be appreciable steric constraints to the addition of ethylene is indicated by the lack of diethylation of methyl groups flanked by neighboring methyl groups.

The preparation of these new sterically demanding arenes can be now readily carried out in substantial quantities using inexpensive starting materials.[15] Alternative procedures might be envisaged but suffer from various drawbacks. The Friedel−Crafts reaction is rarely a satisfactory method for the introduction of alkyl groups into specific positions and without isomerization, while other more selective procedures such as the transition metal catalyzed trimerization of alkynes or the alkylation of transition metal complexed arenes require more expensive starting materials and are not readily applicable to large-scale preparations.[1,16,17] One of the subsequent objectives will be to explore their applications to organometallic synthesis and catalysis while an investigation into the extension of the process described here to the preparation of heteroatom analogues is now underway.

Supporting Information Available: Full experimental procedures for all alkylations, analytical data, ^1H and ^{13}C NMR spectral data, and mass spectral data for the products for entries 3−9 of Table 1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA994432P

---

[12] Maercker, A.; Stötzel, R. *J. Organomet. Chem.* **1983**, *254*, 1−12.

[13] Assadourian, L.; Gau, G. *New J. Chem.* **1990**, *14*, 57−62.

[14] Maercker, A.; Passlack, M. *Chem. Ber.* **1982**, *115*, 540−577.

[15] Using a 250 mL pressure reactor it is quite straightforward to use up to 250 mmol of substrate and to isolate 35−40 g of pure product. No problems are envisaged in scaling up the process for the production of larger quantities.

[16] (a) Maitlis, P. M. *J. Organomet. Chem.* **1980**, *200*, 161−176. (b) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1−8. (c) Yur'eva, L. P. *Russ. Chem. Rev.* **1974**, *43*, 48−68.

[17] (a) Moulines, F.; Gloaquen, B.; Astruc, D. *Angew. Chem.* **1992**, *104*, 452−454; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 458−460. (b) Astruc, D.; Hamon, J. R.; Mandon, D.; Moulines, F. *Pure Appl. Chem.* **1990**, *62*, 1165−1168.