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Formation of 2-Substituted Iodobenzenes from Iodobenzene via Benzyne and Ate Complex Intermediates

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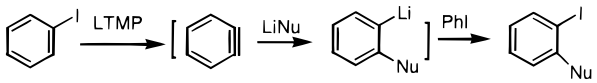
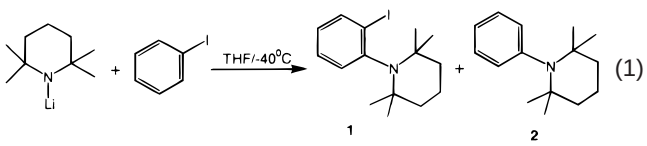
ABSTRACT



The generation of benzyne from iodobenzene with lithium tetramethylpiperidide in THF at −40 °C in the presence of lithium amides and ester enolates leads to mixtures in which 2-substituted iodobenzenes are often the major products. These products are obtained by iodine transfer from iodobenzene to the intermediate 2-lithioaromatics. The transfer of iodine occurs via a hypervalent iodine (ate) complex.

In 1973, Dougherty and Olofson reported that lithium tetramethylpiperidide (LTMP) constituted an excellent reagent for the generation of benzyne from chlorobenzene. When carried out in the presence of phenylacetilide or PhS^-Li^+, excellent yields of the trapping products diphenylacetylene and diphenyl disulfide were obtained.[1] These and further results from the Olofson laboratory were interpreted as indicating that LTMP was an extremely poor trap for benzyne.[2]

As part of a study aimed at the synthesis of benzocyclobutenones via the trapping of benzynes with ester or amide enolates,[3] we examined the generation of benzyne from iodobenzene with LTMP in THF at −40 °C. To our surprise, the major product isolated in 81% yield was *N*-(2-iodophenyl)-2,2,6,6-tetramethylpiperidine (**1**);[4] a lesser amount (9%) of *N*-phenyl-2,2,6,6-tetramethylpiperidine (**2**)[5] was also isolated (eq 1). Not only is LTMP an efficient trap for

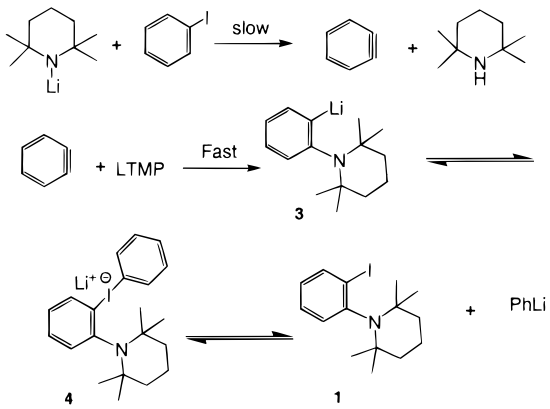


(1)

benzyne, at least in the absence of other nuceophiles, but even more surprisingly iodobenzene can function as an excellent source of electrophilic iodine and transfers its iodine to another aryllithium. Replacement of iodobenzene by bromobenzene resulted in the formation of the bromo analogue of **1** and **2** in a 1:3 ratio in 85% total yield.

The formation of **1** is rationalized in Scheme 1. The lithio derivative **3**, formed by the trapping of benzyne with LTMP,

Scheme 1



combines rapidly with unreacted iodobenzene to give the ate complex **4**. Related complexes have been shown to form quantitatively when PhI is added to PhLi in THF/HMPA at −80 °C.[6] The ate complexes are unreactive toward typical

(1) Dougherty, C. M.; Olofson, R. A. *J. Am. Chem. Soc*. **1973**, *95*, 581.
(2) Fitzgerald, J. J.; Drysdale, N. E.; Olofson. R. A. *J. Org. Chem.* **1992**, *57*, 7122.

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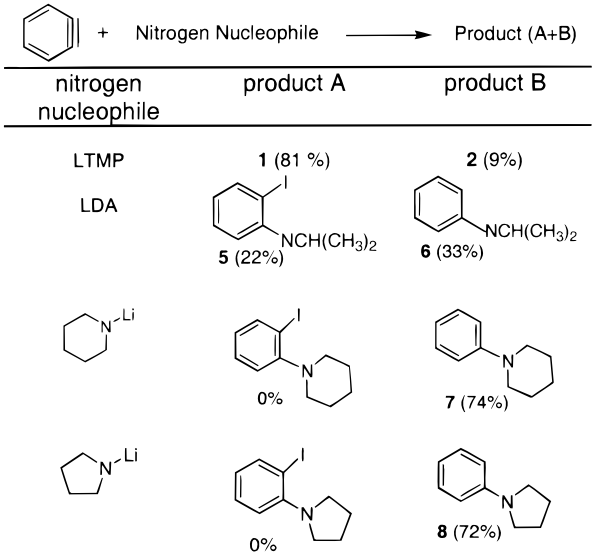
electrophiles but are in equilibrium with their components.[6] In the case of $Ph_2I^-Li^+$, reversal regenerates the starting materials.

The unsymmetrical ate complex **4** fragments preferentially to **1** and PhLi rather than PhI and the ortho-lithiated amine **3**. The lithio derivatives formed in these fragmentations presumably react further with tetramethylpiperidine to yield benzene, **2**, and LTMP.

When iodobenzene was reacted with excess LDA in THF at −40 °C, the ratio of the products, 2-iodo-*N*,*N*-diisopropylaniline, **5**, to *N*,*N*-diisopropylaniline, **6**, was 2:3. In contrast, when benzyne was generated from iodobenzene in the presence of *N*-lithiopiperidine or *N*-lithiopyrrolidine, only *N*-phenylpiperidine, **7**, and *N*-phenylpyrrolidine, **8**, could be isolated. No evidence of the 2-iodo derivatives of these compounds could be detected (Table 1).

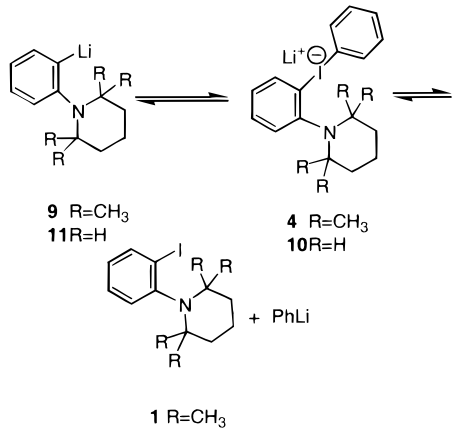
Table 1. Trapping of Benzyne with Various Nitrogen Nucleophiles[a]



[a] Yields are based on 2 mol of iodobenzene and 1 mol of product.

The preferred direction of the fragmentation of unsymmetrical ate complexes such as **4** and **10** appears to be governed by steric effects. Internal coordination of lithium to nitrogen should be less favorable in **9** than in **11**. Additionally, the sterically less hindered lithiated benzenes in each equilibrium may be favored by the formation of more stable dimers.[6] It is also possible that the highly hindered lithio derivative **9** is much less reactive toward tetramethylpiperidine than is PhLi and thus the fragmentation of **4** occurs irreversibly toward **1** (Scheme 2).

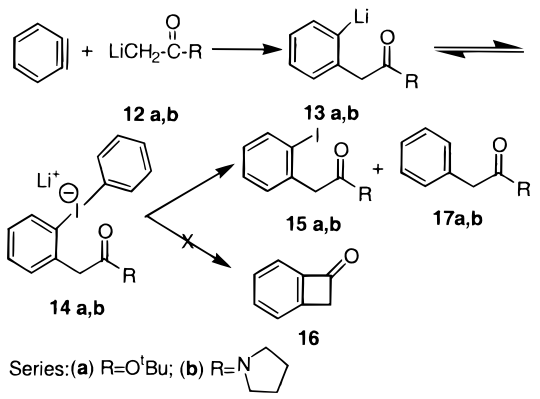
Scheme 2



When benzyne was generated in the presence of the ester and amide enolates **12a**,**b**, the 2-iododerivatives **15a**,**b** respectively were obtained in 69% and 88% isolated yields along with minor quantities of the monosubstituted ester and amide **17a**,**b**.[7]

No evidence for the formation of the desired benzocyclobutanone **16** was found. We also anticipated that the lithio derivatives **13a**,**b** might be quenched rapidly by the acidic hydrogens which are both benzylic and α to the ester carbonyl group. The results indicate that ate complex formation is very facile and faster than these processes. Once formed, the ate complexes **14a**,**b** were expected to revert preferentially to **13a**,**b** and PhI, rather than **15a**,**b** and PhLi, due to the strong internal coordination available in **13a**,**b**. Since this is not the case, an alternate explanation for the formation of the ortho iodo derivatives **15** must be sought (Scheme 3).

Scheme 3



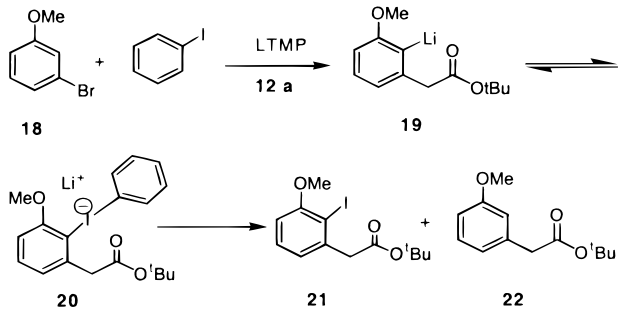
Addition of an equimolar mixture of 3-bromoanisole (**18**) and iodobenzene to a solution of THF containing the enolate

(3) LeBlanc, R. M.Sc. Thesis, University of Ottawa, 1999.

(4) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (dd, 1 H, J = 7.9, 1.5 Hz), 7.41 (dd, 1 H, J = 7.9, 1.6 Hz), 7.27 (dt, 1 H, J = 7.8, 1.5 Hz), 6.87 (dt, 1 H, J = 7.9, 1.6 Hz), 1.89 (m, 1 H), 1.80 (broad dt, 2 H, J = 12.1, 2.5 Hz), 1.63 (m, 1 H), 1.56 (m, 2 H), 1.28 (s, 6 H), 0.91 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.9, 139.7, 131.8, 127.9, 127.2, 114.3, 56.1, 41.3, 31.6, 25.6, 18.5. HRMS: calcd for $C_{15}H_{22}N$ 343.0798, found 343.0788. The observation that the methyl groups in **1** occur as two singlets (1:1 ratio) indicates a significant barrier to rotations around the *N*-aryl bond. Molecular mechanics calculations show that the barrier to ring flipping/nitrogen inversion is approximately 41 kcal/mol. In compound **2**, a single peak is observed for the four methyl groups.

12a and LTMP yielded the iodoester **21** as the major product (36%) along with minor amounts of monosubstituted **22**. This further substantiates that the product **21**[8] is formed by addition of ester enolate **12a** to 3-methoxybenzyne with iodine being transferred to the lithio derivative **19** via the ate complex **20** (Scheme 4).

Scheme 4

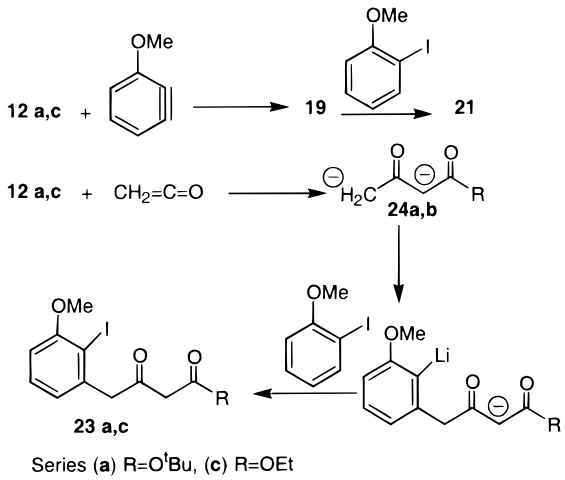


The iodo derivative **21** was also formed in 15% yield when 2-iodoanisole was added to a solution of LTMP containing **12a**. A 30% yield of the β-ketoester **23a** was also obtained. We have observed that benzyne formation from 2-iodoanisole is relatively slow and requires somewhat higher tempertures than −40 °C. Thus some of the enolate **12a** can generate ketene and combine with remaining **12a** to give the dianion **24a**. This species reacts with 3-methoxybenzyne and iodobenzene to give **23a** via an ate complex analogous to **20** (Scheme 5). A similar reaction was found when 2-iodoanisole was added to a mixture of the enolate of ethyl acetate and LTMP in THF at −40 to 0 °C. The 2-iodoester **21c** (R = OEt) and the iodo β-ketoester **23c** were obtained in 18% and 28% isolated yields, respectively.[9]

To the best of our knowledge, these results, especially the formation of the iodo derivatives **15**, **21**, and **23** represent

(5) ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25 (m, 5 H), 1.62−1.59 (m, 6 H), 1.05 (s, 12 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 147.3, 134.8, 128.2, 126.1, 54.6, 42.9, 30.4, 19.1. HRMS: calcd for $C_{15}H_{23}N$ 217.1831, found 217.1816.

Scheme 5



the first examples of iodobenzene serving as a source of positive iodine in a synthetically useful manner. The transfer of bromine from bromobenzene to an aryllithium via an ate complex has also been observed.

Acknowledgment. The support of NSERC (Canada) is gratefully acknowledged.

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(6) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444. Reich, H. J.; Reich, I. L.; Phillips, N. H. *J. Am, Chem. Soc.* **1985**, *107*, 4101.

(7) The structures of all the compounds are characterized by the combination of HRMS and ^{1}H and ^{13}C NMR data.

(8) For compound **21**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 (t, 1 H, J = 7.6 Hz), 6.85 (d, 1 H, J = 7.6 Hz), 6.68 (d, 1 H, J = 7.6 Hz), 3.89 (s, 1 H, OMe), 3.76 (s, 2 H), 1.45 (s, 9 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.5, 158.9, 140.9, 129.6, 123.8, 109.9, 94.1, 81.7, 57.1, 48.5, 28.7. HRMS: calcd for $C_{13}H_{17}OI$ 348.0226, found 348.0223.

(9) For compound **23c**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (t, 1 H, J = 8.6 Hz), 6.82 (d, 1 H, J = 8.6 Hz), 4.18 (q, 2 H), 4.05 (s, 2 H), 3.85 (s, 3 H, OMe), 3.51 (s, 2 H), 1.25 (t, 3 H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.2, 166.9, 158.5, 139.4, 129.2, 123.4, 109.6, 90.6, 61.3, 56.4, 54.8, 46.2, 14.1. HRMS: calcd for $C_{13}H_{15}O_4I$ 362.0015, found 362.0027.