Tetrahedron Letters 50 (2009) 1593–1595

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Metalations utilizing aryllithiums; *ortho*-functionalization of *p*-bromoanisole (*p*BrA)

D. W. Slocum*, Troy L. Reece, Rebecca D. Sandlin, Thomas K. Reinscheld, Paul E. Whitley

Department of Chemistry, Western Kentucky University, Bowling Green, KY 42101, United States

ARTICLE INFO

Article history:
Received 15 January 2009
Accepted 16 January 2009
Available online 23 January 2009

ABSTRACT

An *ortho*-metalation protocol has been developed, which permits the survival of a bromine substituent in *p*-bromoanisole. Eight derivatives of the generated *ortho*-lithiated intermediate have been prepared. A neglected metalation concept is being explored here; one which proposes that minimizing the pK_a difference between the aryl substrate and the conjugate acid of the metalating agent will lead to a regiospecific and selective metalation process.

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1. Introduction

Metalation reactions are rendered safer and greener by running them in hydrocarbon solvents. Initially, we had anticipated that 'activated' hydrocarbon solvents, those containing equivalents of THF or fractional equivalents of TMEDA, would support *ortho*-lithiations in yields approaching those attained in the conventional ether solvents.[1] Actually, far more efficient and atom-economical *ortho*-lithiations of several common aryl substrates can be realized utilizing this approach.[2] Also discovered was the realization that activated hydrocarbon media made possible more focused *ortho*-lithiations. These include prevention of lateral metalation in *p*-methylanisole,[3] preservation of the *p*-Cl substituent in *p*-chloro-anisole[4] and avoidance of a contaminating dimetalation in the metalation of 1,2- and 1,4-dimethoxybenzene.[5] All of the above were accomplished using the common metalating agent, *n*-BuLi.

In this Letter, we describe a strategy for preservation of an aryl-Br substituent while simultaneously maintaining our hydrocarbon media atom-economy preoccupation. Metalation of *p*-BrA in activated hydrocarbon solvent with *n*-BuLi afforded significant amounts of the undesired halogen/metal exchange. Taking a clue from the literature,[6] we metalated *p*-BrA with phenyllithium, not in ether solvent but in hydrocarbon media.[7] We eventually found conditions that allowed 50–60% yields of the *o*-TMS derivatized product to be realized as determined by uncorrected GC analysis.

What might a chemist do to expand the utility of *ortho*-lithiation reactions? One answer to this question is to devise reaction systems where substituents normally sensitive to metalation conditions can survive the process. Our approach has been to design metalating reagents that will be minimally aggressive towards such substituents while still providing the necessary hydrogen/lithium exchanges. A tightrope needs to be walked here, one that bridges the gap between the nucleophilicity and the basicity of a particular metalating agent. Additionally, we wish to design a system that will address current environmental concerns.

A successful approach to walking the tightrope was put forward at an early stage by both Gilman et al.[6a] and Wittig et al.[6b] for the *ortho*-lithiation of *p*-BrA. For this aryl substrate, the bromine substituent is readily susceptible to halogen/metal exchange and so experiences *ortho*-lithiation conditions at great risk. Their approach was to use a metalating agent, phenyllithium, somewhat weaker in basicity than alkyllithium reagents, but much less nucleophilic than these reagents (Eq. 1). As stated above, examination of this process in our laboratories but utilizing hydrocarbon media indicated that yields approaching 60% *ortho*-lithiation could be achieved. There is the caveat, of course, that metalations involving PhLi generate benzene, a listed carcinogen. It would be difficult to implement this process on a large scale by utilizing PhLi, given safety and green chemistry concerns:

(1)

If an aryl metalating agent is the key, the reason likely lies in the realm of aryllithiums being less basic and even less nucleophilic than alkyllithiums. If the production of benzene is undesirable, then let us use an aryllithium reagent of similar basicity, but one with even less nucleophilicity than PhLi. This reagent must be readily accessible. We herein propose use of *ortho*-lithiodimethylaniline (*o*-LiDMA).[8]

o-LiDMA has been difficult to prepare in the past. Recently, we have developed a reproducible preparation of this intermediate with yields $\geqslant$90%.[2] Once this intermediate has been generated in hydrocarbon media, the *o*-LiDMA evidently forms a complex, presumably an aryllithium dimer, and settles from solution. From this

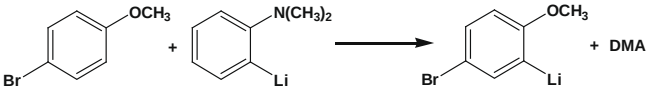
* Corresponding author. Tel.: +1 270 745 3457; fax: +1 270 745 6471.
E-mail address: donald.slocum@wku.edu (D.W. Slocum).

0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.01.104

Table 1
ortho-Substituted *p*-bromoanisoles

Reactant	*o*-Derivative	% Isolated Yield	Mp (°C) (uncorrected)	
			Lit.	Observed
Benzaldehyde	–CHPhOH	58		76.4–78.4[12]
Benzophenone	$-CPh_2OH$	65	127–128	98.6–99[12]
Cyclopentanone		69		67.5–69.1[12]
Cyclohexanone		74		93.9–97.6[12]
$CH_2=N^+Me_2I^-$	$-CH_2NMe_2$	28		oil
TMS-Cl	–TMS	60	58–58.5[10]	56.7–57.7
Hexachloroethane	–Cl	67	65.8–67	66.5–68.2[12]
Diphenyl diselenide	–SePh	73	92–93[13]	59.7–61.1

two-phase system the supernate is syringed off and replaced with an equal volume of hexanes. In this manner, most unreacted *n*-BuLi and DMA are removed. The remaining suspension, considered as being 75% of the original DMA molarity,[9] is then used as the metalating agent for *p*-BrA (Eq. 2):



(2)

A sustainability component of this approach is that DMA is recoverable and potentially recyclable from this process by acid extraction of the product solution.

Treatment of *p*-BrA in cyclohexane with a slurry of *o*-LiDMA in cyclohexane afforded a reaction solution from which small aliquots were taken over various periods. Each sample was quenched with chlorotrimethylsilane (CITMS) and analyzed by GC. These studies revealed that maximum extents of *ortho*-lithiation of *p*-BrA were realized by allowing the metalation to run overnight. Using purified *o*-LiDMA solutions (96 ± 2%),[9] an equal quantity of *p*-BrA could be from 85% to 90% *ortho*-lithiated.

The literature reveals that our methodology has synthetic advantage over the use of PhLi in ether. Wittig et al.[6b] reported a 70% yield of the benzophenone addition product, but this was contaminated with a 10% yield of Ph_3COH, that is, the product of the reaction of PhLi with benzophenone. Little (<2%) to no metalating reagent derived products were noted in our product mixtures. Eaborn and Walton[10] prepared the trimethylsilyl derivative in 44% yield using the procedure reported by Wittig et al.[6b]

The use of *o*-LiDMA, prepared in hydrocarbon solvents, in conjunction with addition of the derivatizing agent to the generated *o*-Li-p-BrA without dissolution, fulfills our preoccupation with making DoM a greener and safer protocol. The use of ethers is thereby minimalized. Synthetic results from this protocol are summarized in Table 1.

2. Experimental

2.1. Preparation of *o*-lithio-*p*-bromoanisole and subsequent derivatization

To a clean, dry round-bottomed flask under nitrogen atmosphere were added 1.0 equiv of *N*,*N*-dimethylaniline (DMA), 0.15 equiv of TMEDA, 1.0 equiv of *n*-butyllithium (10 M in hexanes) and sufficient anhydrous cyclohexane to bring the reaction concentration to 2 M. The solution was allowed to stir at 60 °C for 18–22 h, where upon cooling, a copious precipitate of the *o*-LiDMA formed. At this point, the *o*-LiDMA was 85–91% pure by TMSCl derivatization and GC analysis. The suspension was transferred via a syringe equipped with a 14 gauge needle to graduated centrifuge tubes and was centrifuged for ca. 2 m. The supernate was removed and replaced with an equal volume of cold anhydrous hexanes. Following centrifugation, removal of the hexane supernate and repetition of the hexane washing process, the now 96 ±% pure *o*-LiDMA[9,11] was diluted to 0.65 M with anhydrous cyclohexane and was placed in a clean, dry round-bottomed flask under nitrogen atmosphere. To increase homogeneity and to speed up the reaction,[2] 1.0 equiv of anhydrous methyl *tert*-butyl ether (based on the 0.75 equiv DMA being carried forward primarily as *o*-LiDMA) and 0.75 equiv of *p*-bromoanisole were added, and the reaction mixture was allowed to stir at 55–60 °C for 24 h. The resulting 85–90% *o*-lithio-*p*-bromoanisole solution was treated with the various electrophiles (0.95 equiv with respect to *p*-BrA) without dissolution. *Use of THF to dissolve the various carbonyl compounds led to products resulting from benzyne formation.* The yields were calculated based on the amount of electrophile.

Continuing our attempts to provide synthetic methods useful to the industrial community, we made effort to isolate the compounds with convenient and potentially scalable procedures. Thus, most derivatives were isolated by crystallization and/or trituration from hexanes. The exceptions were the benzophenone derivative that was isolated by crystallization from MTBE/hexanes, the phenylselenide derivative that was isolated by column chromatography (hexanes/ethyl acetate) and the dimethylaminomethyl derivative that was isolated by a novel extraction method. This extraction method employed 0.24 M acetic acid which selectively protonates the more basic tertiary aliphatic amine but not the tertiary arylamine.

Acknowledgements

Support of this research by both PRF, 42090-B1 and NSF 0710021 is greatly appreciated. We thank Mr. Greg Hayes and Mr. Phillip Shelton for performing the preliminary metalation of *p*-BrA with PhLi.

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7. 1.0 M *p*-BrA, 1.8 M PhLi diluted with hexanes to 1.0 M (commercial grade, that is, dissolved in *n*-Bu_2O) in *n*-hexane with no catalyst, heated at 60 °C for 4–6 h.
8. *o*-LiDMA is less basic than PhLi. The pK_a of the *o*-hydrogen of DMA has been estimated as $\geqslant$40.3 (Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.*, **1983**, *105*, 7790) Most textbooks assign a pK_a value of 43 to benzene.
9. A reproducible 25% loss of DMA accrues from the combined effects of incomplete metalation, *o*-LiDMA solubility in hydrocarbon solvent and the two transfers necessary for the two washings with cold hexanes.
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11. If the washing purification procedure is omitted, biphenyl formation via benzyne intermediate production is increased. Even with these washings about 2% of biphenyl contaminants can be detected. This is likely due to the lingering amounts of TMEDA bringing about an increase in the basicity of the remaining *o*-LiDMA.
12. The benzophenone and chloro derivatives are commercially available (Sigma–Aldrich and Capot Chemical Co., respectively). NMR's for the benzaldehyde, the cyclopentanone and the cyclohexanone derivatives are shown below in respective order: ^{1}H NMR ($CDCl_3$) δ 2.69 (br s, OH), 3.77 (s, 3H), 6.01 (s, 1H), 6.72–6.74 (d, 1H), 7.25–7.29 (t, 1H), 7.31–7.37 (m, 5H), 7.44–7.45 (d, 1H). ^{13}C NMR δ 55.8, 71.5, 112.5, 113.4, 126.6, 127.6, 128.5, 130.4, 131.4, 142.7, 155.7.^{1}H NMR ($CDCl_3$) δ 1.65–1.74 (m, 2H), 1.93-2.02 (m, 6H), 3.32 (s, OH), 3.88 (s, 3H), 6.76–6.79 (m, 1H), 7.31–7.35 (m, 1H), 7.43–7.46 (m, 1H). ^{13}C NMR δ 23.5, 39.2, 55.7, 82.4, 112.9, 113.4, 129.0, 130.7, 136.6, 156.5.^{1}H NMR ($CDCl_3$) δ 1.22–1.97 (m, 10H), 3.67 (s, OH), 3.87 (s, 3H), 6.77–6.79 (d,1H), 7.31–7.33 (d, 1H), 7.43–7.44 (d, 1H). ^{13}C NMR δ 21.9, 25.8, 36.5, 55.7, 73.0, 113.2, 113.8, 129.1, 130.5, 138.8, 156.4..
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