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Communications

Directed Ortho Metalation of Neopentyl Benzoates with LDA: Preparation of Arylboronic Acids

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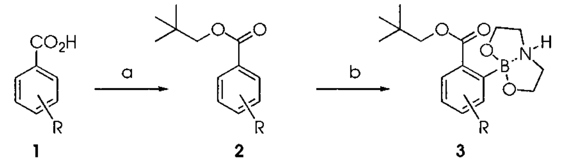
The directed ortho metalation of arenes is one of the most powerful methods for the elaboration of complex aromatic compounds.[1,2] The deprotonation of the arene usually requires a strong base, such as an alkyllithium, and a directing group such as a secondary[3] or tertiary[4] amide, an oxazoline,[5] an ether,[6] an α-amino alkoxide,[7] a carboxylic acid,[8,9] or a carbamate.[10] The resulting aryllithium can react with a variety of electrophiles including alkylating agents, aldehydes, amides, chloroformates, silylating agents, and trialkyl borates. Amides and oxazolines can serve as latent carboxylic acids in the directed metalation; however, they require harsh conditions for their hydrolysis. The use of alkyllithium bases also limits functional group compatibility, for example, by not allowing for the presence of a bromine or iodine atom on the arene due to competing halogen−metal exchange. We were recently faced with the challenge of preparing a boronic acid using a directed ortho metalation with a directing group that can be hydrolyzed to a carboxylic acid under mildly basic conditions. Herein, we report the development of the *neopentyl ester* as a directing group in the ortho metalation of arenes using lithium diisopropylamide (LDA) as the base and triisopropyl borate as the electrophile.

Esters have received comparatively little attention as directing groups, and LDA has received very little attention as a base for the directed metalation of arenes,[11] although it has been used successfully for the deprotonation of substituted pyridines.[12,13]

In 1975, Beak reported that alkyl benzoates can be deprotonated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF and that the resulting anions self-condense yielding *o*-benzoylbenzoates.[14] In 1983, Martin extended this methodology and demonstrated that the anions obtained from ethyl and isopropylbenzoate react with trimethylsilyl chloride as an in situ trap to provide the silylated products in 38% and 90% yield, respectively.[15] In both of these metalations with LTMP, LDA proved to be insufficient to affect the deprotonation. In 1989, Eaton showed that a methyl ester was a better directing group than a diethylamide in the ortho magnesiation of *p*-carbomethoxy-*N*,*N*-diethylbenzamide with bis(2,2,6,6-tetramethylpiperidino)-magnesium.[16] Surprisingly, the preparation of an alkylbenzoate ortho substituted by a boronic acid has never been described.[17]

Scheme 1[a]



[a] Key: (a) 2,2-dimethyl-1-propanol (2.0 equiv), cat. H_2SO_4, toluene; (b) (i) LDA (1.1−1.6 equiv), $B(O\text{-}i\text{-}Pr)_3$ (2.6 equiv), THF, (ii) diethanolamine (1.1 equiv).

When using esters as directing groups, we found that it was necessary to have the electrophile present in the reaction mixture as the aryllithium is generated in order to avoid condensation with another molecule of the benzoate ester, giving a benzophenone. The base must be unreactive toward the electrophile but of sufficient strength to deprotonate the arene. We found that LDA was compatible with trimethylsilyl chloride and triisopropylborate, giving *o*-(trimethylsilyl)benzoates and *o*-boronylbenzoates, respectively.[18]

After several alkylbenzoates were screened, the neopentyl ester proved to be the directing group of choice because of its ease of preparation and stability under the lithiation conditions. The neopentyl ester of the boronic acids thus prepared also showed enhanced stability toward hydrolysis in subsequent *two-phase* Suzuki couplings.[19]

The preparation and metalation of neopentyl esters is operationally simple. Esterification of benzoic acids **1** proceeds using 2,2-dimethyl-1-propanol (2 equiv) and a catalytic amount of sulfuric acid in toluene ($\sim$0.5 M) (Scheme 1). Metalation and in situ boration are accomplished by treating a THF solution (0.4−0.5 M) of neopentyl esters **2** and triisopropyl borate (2.6 equiv) with LDA (1.1−1.6 equiv of a 2.0 M solution in THF/heptane).[20] The reaction mixture is stirred under the conditions described in Table 1, quenched by pouring into 1 N HCl_{aq}, and extracted with toluene. The crude boronic acid is then treated with diethanolamine (1.1

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(1) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(2) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957−986.

(3) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653−3664.

(4) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34−46.

(5) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837−860.

(6) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.

(7) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979−3982.

(8) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265−1271.

(9) Mortier, J.; Moyround, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042−4044.

(10) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935−1937.

(11) For a demonstratin of the successful use of LDA as a base in directred metalation involving an intramolecular trap, see: Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508−6509.

(12) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773−776.

(13) Epsztajn, J.; Berski, Z.; Brzezninski, J. Z.; Zózwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739−4742.

(14) Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094−1098.

(15) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155−6157.

(16) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016−8018.

(17) The metalation of benzonitrile using LTMP as a base and trimethyl borate as the electrophile has been reported. See ref 15.

(18) The generation of benzophenones in the absence of in situ traps with LDA here, and in Beak's earlier work with LTMP (see ref 14) demonstrates that lithium amides are efficient kinetic bases for the deprotonation of alkyl benzoates. In particular, the benzophenone formation, and the in situ trapping by trimethylsilyl chloride, shows that a complex between LDA and the borate trap is not necessary for the ortho deprotonation of benzoate esters.

(19) We have found that the hydrolyses of neopentyl esters proceed at comparable rates as ethyl esters under single-phase conditions. The results of our study of the use of neopentyl benzoates in Suzuki couplings will be reported in due course.

(20) LDA was purchased from ACROS. We found no difference in yield between the commercial solution and the material freshly prepared from diisopropylamine and *n*-butyllithium.

Table 1. Formation and Metalation of Arylneopentyl Esters

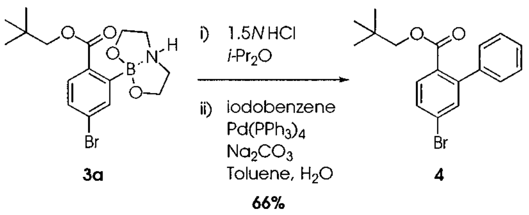
R	ester	% yield	product	conditions (T (°C), time)	equiv of LDA	% yield
4-Br	**2a**	100	**3a**	−78, 5 min	1.1	84
4-CF_3	**2b**	99	**3b**	0, 30 min	1.1	74
4-OMe	**2c**	100	**3c**	0, 3 h	1.6	70
4-F	**2d**	99	**3d**	−78, 15 min	1.1	52[a]
4-Cl	**2e**	93	**3e**	−78, 10 min	1.2	90
2-Br	**2f**	91	**3f**	−78, 10 min	1.2	88
2-CF_3	**2g**	77	**3g**	−78, 1 h	1.2	93
3-F	**2h**	82	**3h**	−78 to −40, 3 h	1.2	90

[a] This represents an isolated yield of pure **3d** after trituration from *i*-PrOH. Analysis of the HPLC indicated that the reaction was in near-quantitative yield but provided a 2:1 ratio of lithiation ortho to the ester over the fluorine.

equiv) and concentrated to a solid. The advantage of generating diethanolamine complexes **3** is that they provide very stable high melting solids.[21,22] Moreover, the diethanolamine adducts can be hydrolyzed back to boronic acids with mild aqueous acids.[23]

As shown in Table 1, the lithiation of neopentyl benzoates esters was successful with a variety of substrates. In most cases, the reaction is rapid at −78 °C, although the 4-methoxy-substituted ester required reaction at 0 °C.[24] The lithiation of the 4-fluoro-substituted substrate **2d** proved to be problematic because of the directing capability of fluorine.[25] It is the only substrate where the boron was not introduced regioselectively ortho to the ester group. Although the reaction proceeded very smoothly at −78 °C, a 2:1 mixture of products favoring the product metalated ortho to the ester was obtained. Fortunately, trituration of the crude mixture with 2-propanol provided the desired product **3d** in pure form. Interestingly, while the addition of TMEDA had very little effect on the regioselectivity,[26] the presence of DMPU (2.0 equiv) led to selective deprotonation ortho to the fluorine (17:1 HPLC ratio). In the case of the 3-fluoro-substituted ester **2h**, preferential deprotonation was observed between the two directing groups in 90% yield. Although excess LDA and triisopropyl borate is used in these reactions, only one boron is introduced onto the arene. In general, the reaction proceeds best when the arene is substituted with an electron-withdrawing group. Unactivated arenes such as neopentyl benzoate and 4-*tert*-butylneopentyl benzoate were converted to the corresponding diisopropylamides, and no directed metalation was observed.

Scheme 2



A major advantage of employing LDA rather than an alkyllithium for the deprotonation is that it allows for the presence of a bromide in the substrate (e.g., **2a** and **2f**). Furthermore, the resulting boronic acid obtained from the directed metalation can be used in subsequent reactions, such as the Suzuki coupling with iodobenzene illustrated in Scheme 2.[27] Diethanolamine complex **3a** was hydrolyzed under biphasic conditions, and the crude boronic acid was coupled with iodobenzene under standard conditions using only 0.25 mol % of Pd(PPh_3)$_4$ to provide biphenyl **4** in 66% yield.

In summary, the neopentyl ester is an efficient directing group for the ortho metalation of arenes using LDA as the base and triisopropyl borate as an in situ trap. This methodology allows for the preparation of a new class of boronic acids with *o*-carbonyl substituents, which are useful in Suzuki couplings. The mild reaction conditions required for the metalation could potentially be extended to other electrophiles and prove to be useful for multiple applications.

Acknowledgment. We would like to thank Dr. Jon Bordner and Debra DeCosta of Pfizer Central Research for the determination of the single-crystal X-ray structure of **3c**.

Supporting Information Available: Experimental procedures and spectral data, including ORTEP representation of compound **3c**, for all compounds (6 pages). The author has deposited atomic coordinates for structure **3c** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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(21) Smith, K.; Leach, J. B. *Organometallic Compounds of Boron*; Chapman and Hall: New York, 1985.

(22) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093−5096.

(23) Van Veen, R.; Bichelhaupt, F. *J. Organomet. Chem.* **1973**, *47*, 33−38.

(24) The single-crystal X-ray crystal structure of compound **3c** was solved and is depicted in the Supporting Information.

(25) Gilman, H.; Soddy, T. S. *J. Org. Chem.* **1957**, *22*, 1715−1716.

(26) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

(27) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.