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# THE IN SITU GENERATION AND USE OF IODOMETHYLLITHIUM FOR THE ONE-CARBON HOMOLOGATION OF BORONIC ESTERS AND EPOXIDE FORMATION FROM CARBONYL COMPOUNDS

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**Abstract**: Iodomethyllithium is shown to be an effective reagent for the onecarbon homologation of oxygenated boronic esters. The use of iodomethyllithium for the preparation of pinacol iodomethaneboronate and for the synthesis of epoxides from carbonyl compounds is also discussed.

During the course of investigating the use of vinylboronic esters as dipolarophiles in 1,3-dipolar cycloadditions, we attempted the one-carbon homologation<sup>1-3</sup> of boronic ester substituted  $\Delta^2$ -isoxazoline 1.<sup>4</sup> After attempts to homologate 1 employing chloromethyllithium<sup>2</sup> and bromomethyllithium,<sup>3</sup> both of which have been used successfully on numerous other boronic esters, were met with failure we investigated the use of iodomethyllithium<sup>5,6</sup> in this reaction. This provided the homologated boronic ester in 69% yield. (eq 1) To the best of our knowledge this was the first reported homologation of a boronic ester with iodomethyllithium.



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Matteson has shown that the one-carbon homologation of oxygen containing boronic esters is slow and can be problematic.<sup>7</sup> Based upon the results obtained with boronic ester substituted  $\Delta^2$ -isoxazolines, we questioned if iodomethyllithium might prove to be generally applicable for the homologation of oxygen-containing boronic esters. Boronic ester 2 was chosen as a model system for these studies. Matteson and coworkers have reported the homologation of this compound previously with both chloromethyllithium<sup>2</sup> and bromomethyllithium.<sup>3</sup> In Matteson's work it was found that chloromethyllithium afforded the homologated product in 90% yield and bromomethyllithium afforded a 40-50% yield. We repeated the experiments with chloro- and bromomethyllithium and the yields obtained in our hands for chloro-, bromo- and iodomethyllithium are shown in equation 2. Chloromethyl- and bromomethyllithium were generated in situ as described by Matteson and coworkers.<sup>2,3</sup> The reaction employing iodomethyllithium was carried out by the slow addition of *n*-BuLi to a solution of **2** and CH<sub>2</sub>I<sub>2</sub> in THF at -78°C.



Pinacol iodomethaneboronate (4) has been shown to be a very reactive electrophile and provides a convenient means for the introduction of the boronic ester functionality into a molecule. Compound 4 and the di-*n*-butyl ester have been prepared previously by a variety of methods.<sup>8</sup> Matteson and others have shown that 4 (and the di-*n*-butyl ester) react readily with a variety of nucleophiles including amines,<sup>8a</sup> enamines,<sup>8b</sup> amides,<sup>8c</sup> enolates,<sup>8h</sup> and others.<sup>8b</sup> During the course of this work we explored a new method for the preparation of 4 based on the route shown

#### IODOMETHYLLITHIUM

below. This procedure involves the reaction of borate **3**<sup>9</sup> with *in situ* generated iodomethyllithium. This procedure afforded **4** in 73% isolated yield after work-up and Kugelrohr distillation.



Cainelli,<sup>11</sup> Matteson,<sup>4,10</sup> and Villieras<sup>12</sup> have shown halomethyllithiums to be efficient reagents for the conversion of carbonyl compounds to epoxides. During our studies, we have also explored the use of iodomethyllithium for the conversion of ketones and aldehydes to the corresponding epoxide.<sup>13</sup> The procedure for the epoxidation reactions employed the slow addition of MeLi to a -78°C solution of carbonyl compound and CH<sub>2</sub>I<sub>2</sub> in THF. Although the reaction could be effectively carried out employing n-BuLi in place of MeLi, removal of n-BuI (produced in the halogen-metal exchange) from the epoxides proved to be difficult, a problem Matteson and Sadhu had encountered previously.<sup>10</sup> The isolated yields obtained from various ketones and aldehydes are shown in Scheme 1.

SCHEME 1



As can be seen from the results presented above, iodomethyllithium is an effective reagent for the one-carbon homologation of boronic esters and for the conversion of carbonyl compounds to epoxides. It is important to note that in some cases iodomethyllithium is the only reagent to provide the homologated boronic ester in good yield, and it may prove to be the reagent of choice for oxygenated boronic esters.

#### Experimental

Reagents were purchased from Aldrich and used as received. Alkyllithiums were standardized prior to use by titration with 1,3diphenyl-2-propanone tosylhydrazone.<sup>14</sup> CH<sub>2</sub>I<sub>2</sub> was purified immediately before use by passage (neat) through a plug of Brockmann I activated, basic, alumina. THF was distilled from sodium-benzophenone ketyl. All reactions were carried out under an atmosphere of argon.

#### General procedure for the homologation of boronic ester 2 with "ICH2Li".

A solution of the boronic ester (1.5 mmol) and  $CH_2I_2$  (3.0 mmol) in THF (30 ml) were stirred at -78°C. A solution of *n*-BuLi (1.6M in hexanes, 3.0 mmol) was added dropwise and the reaction was warmed to room temperature. The reaction was stirred at room temperature for 24 hours. The solvent was evaporated under aspirator vacuum and the residue dissolved in Et<sub>2</sub>O (50 ml). The ether solution was washed with saturated aqueous NH<sub>4</sub>Cl (2 x 30ml) and the combined aqueous phases extracted with Et<sub>2</sub>O (2 x 30ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed on a rotary evaporator. The residue was purified by flash chromatography (SiO<sub>2</sub>, hexane:EtOAc, 15:1), to afford the purified product.<sup>2</sup>

## Procedure for the preparation of pinacol iodomethylboronate (4).

A solution of borate  $3^9$  (2.19 g, 11.8 mmol) and CH<sub>2</sub>I<sub>2</sub> (1.43 ml, 17.7 mmol) in THF (30 ml) was stirred at -78°C under argon. MeLi (as complex with LiBr in Et<sub>2</sub>O) (13.93 ml, 17.7 mmol) was added dropwise. The reaction was warmed to room temperature and allowed to stir until clear. The solvent was removed on a rotary evaporator and the viscous residue was taken up in Et<sub>2</sub>O (100 ml). The Et<sub>2</sub>O was washed with saturated aqueous NH<sub>4</sub>Cl (3 x 30ml) and the combined aqueous layers were extracted with Et<sub>2</sub>O (50 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to yield the crude product. The crude material was purified by Kugelrohr distillation, (65°C, 0.5 mm Hg), to afford pure **4**. The spectral data obtained for **4** were in complete agreement with those previously reported.<sup>8f</sup>

### General procedure for the preparation of epoxides.

A solution of carbonyl compound (10 mmol) and CH<sub>2</sub>I<sub>2</sub> (11 mmol) in THF (30 ml) was stirred at -78°C. MeLi (as complex with LiBr in Et<sub>2</sub>O) (12 mmol) was added dropwise after which the reaction was warmed to room temperature. The reaction was washed with saturated aqueous NH<sub>4</sub>Cl (2 x 20ml) and the combined aqueous phases were extracted with Et<sub>2</sub>O (3 x 20ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated, and the epoxides isolated by Kugelrohr distillation. All of the epoxides shown in Scheme 1 are known compounds<sup>10-12</sup> and displayed spectral and physical properties in agreement with those previously reported. <u>Acknowledgments</u>: We thank the Research Grants Committee of The University of Alabama for financial support of this work.

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