ORGANIC LETTERS

2012
Vol. 14, No. 11
2690–2693

[3 + 2]-Dipolar Cycloaddition Reactions of an N-Heterocyclic Carbene Boryl Azide

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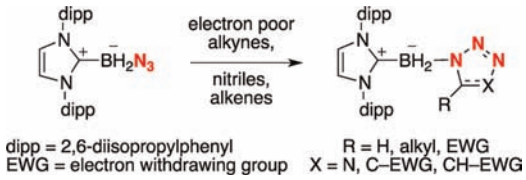
Received April 3, 2012

ABSTRACT



Thermal 1,3-dipolar cycloaddition reactions of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene dihydridoboron azide occur smoothly with alkynes, nitriles, and alkenes bearing electron-withdrawing groups. New, stable NHC-boryl-substituted triazoles, tetrazoles, and triazolidines are formed in good to excellent yields.

Recent studies of N-heterocyclic carbene-boranes (NHC-boranes) are unearthing a surprisingly rich chemistry for compounds that can be viewed as simple Lewis acid/Lewis base complexes.[1] A key feature of many classes of complexes is that they are stable to air and water and do not dissociate even under relatively forcing conditions.[2] Carbene-boranes are of interest as reagents in organic synthesis[3] and as initiators in polymer chemistry.[4] And the study of carbene-boranes as reactants has led to the synthesis of diverse stable compounds with unusual boron substituents and bonding patterns.[1,5]

Figure 1 shows a relatively general method to make heteroatom-substituted NHC-boranes starting from the

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parent complex 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene borane **1**. Treatment of **1** with triflic acid gives a solution-stable triflate **2** that can be displaced in situ to produce unusual functionalized NHC-borane compounds **3** including boryl azides, nitroboranes, boryl nitrites, boryl nitriles, and boryl isonitriles, among others.[6]

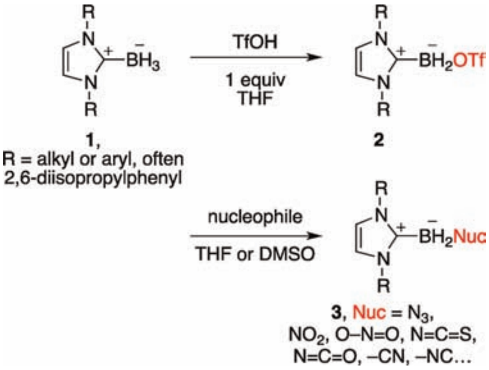


Figure 1. NHC-boranes **2** bearing good leaving groups (here, triflate) are easily made, and the leaving groups can be displaced to make unusual heteroatom-functionalized NHC-boranes **3** that are surprisingly stable.

Similar chemistry can also be done with easily generated boryl iodide and bromide analogs of triflate **2** as well. Because such functionalized boranes **3** are rare, little is known about their chemistry.

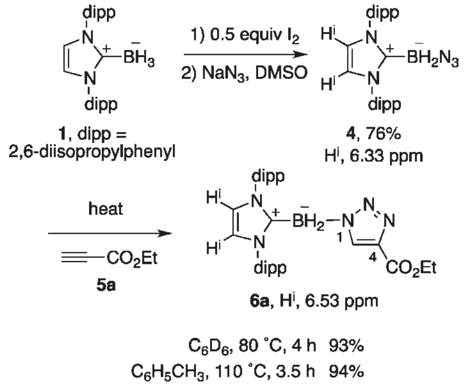
We selected boryl azides (**3**, Nuc = N_3) for initial study because the azides are easy to prepare and handle.[6] We were also intrigued because azides are commonly reduced by boranes, but NHC-boryl azides bearing adjacent B−H bonds are stable. Will this stability translate to onward reaction products derived from boryl azides?

The boron atom of an NHC-borane is often compared to a tetravalent carbon atom because the two are isoelectronic. The quintessential reaction of carbon-substituted azides[7] is a Huisgen [1,3]-dipolar cycloaddition,[8] one of the most valuable "click reactions".[9] An assortment of cycloaddition reactions of heteroatom-substituted azides, notably with tin[10a−c] and sulfonyl[10d] azides, are also well-known.

In contrast, to the best of our knowledge, there are no known cycloaddition reactions of boron-substituted azides, doubtless because such azides have been so rare.[11] Here we report that a prototypical NHC-boryl azide **4** behaves as an electron-rich [1,3]-dipole in cycloaddition reactions with electron-poor alkynes, alkenes, and nitriles to provide remarkably stable NHC-boryl triazoles, triazolidines, and tetrazoles.

Cycloaddition reactions were conducted with 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene borane azide **4** because simple safety guidelines project that it will not be explosive.[12] On a gram scale, **4** was conveniently prepared by reaction of **1** with iodine (0.5 equiv, makes NHC-BH_2I in quantitative yield) and then addition of sodium azide in DMSO. After purification by flash chromatography, **4** was isolated in 76% yield (Scheme 1).

Scheme 1. Gram-Scale Synthesis of **4** and Preliminary Cycloaddition Reactions with Ethyl Propiolate



Azide **4** melts to a clear liquid at 180−183 °C.[6] It bubbles (N_2 release?) at ~270 °C and then turns from yellow to brown above 300 °C. It is also stable to heating alone in toluene at 110 °C overnight. Even so, all reactions were conducted behind safety shields as a standard precaution. In a preliminary experiment, **4** (30 mg, 0.07 mmol) and ethyl propiolate **5a** (2 equiv) were dissolved in C_6D_6 and reaction progress was followed by ^{1}H NMR spectroscopy. A new singlet at 6.53 ppm (imidazolyl protons H^i) of **5a** grew in as the starting singlet of **4** (6.33 ppm) decreased, but the conversion reached only about 50% after 1.5 days at rt. A similar reaction at 80 °C was complete after 4 h. Simple solvent evaporation and flash chromatography provide the stable NHC-boryl triazole **6a** as the only apparent regioisomer in 93% yield. A larger scale experiment (100 mg, 0.23 mmol) was conducted in the more practical solvent toluene at 110 °C, giving **6a** in 94% isolated yield.

Boryl triazole **6a** is a robust, stable compound that is convenient to handle. The crystal structure, shown in

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(11) The closest relative of **4** is $Me_3N-BH_2N_3$, which has been reported to explode at 200 °C. (a) Miller, N. E.; Chamberland, B. L.; Muetterties, E. L. *Inorg. Chem.* **1964**, *3*, 1064–1065. (b) Skillern, K. R.; Kelly, H. C. *Inorg. Chem.* **1977**, *16*, 3000–3005. Trivalent azido boranes are more common. See for example: (c) Bettinger, H. F.; Filthaus, M.; Neuhaus, P. *Chem. Commun.* **2009**, 2186–2188. (d) Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4744–4747.

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Figure 2, demonstrates that **6a** is the 1,4-regioisomer resulting from addition of the azide nitrogen bearing the boron atom to the β-carbon of ethyl propiolate. At 1.567(5) Å, the N–B bond of **6a** is longer than comparable bonds in carbon-substituted triazoles. For example, the corresponding N–C bond in an analogous *N*-benzyl-substituted triazole is 1.471(2) Å.[13]

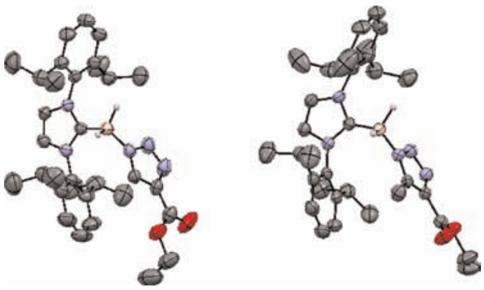


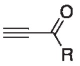
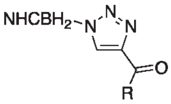
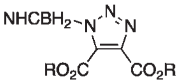
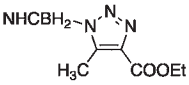
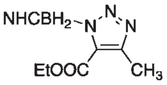
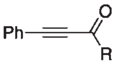
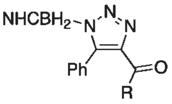
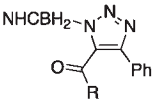
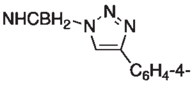
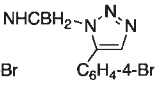
Figure 2. X-ray crystal structures of cycloadducts **6a** and **6f**.

Table 1 summarizes the results of cycloaddition reactions of **4** with other electron-poor alkynes **5b–i** bearing carbonyl or phenyl substituents. (Formal changes are omitted on these and the subsequent structures.) Similar results were observed in reactions of **4** with methyl propiolate **5b**, 3-butyn-2-one **5c**, and dimethyl- and diethylacetylene dicarboxylate **5d**,**e**. Single products—1,4-disubstituted (**6b**,**6c**) or 1,4,5-trisubstituted tetrazoles (**6d**,**6e**)—were isolated in yields ranging from 84% to 94% (entries 1–5).

Disubstituted alkynes with only one carbonyl group (ethyl but-2-ynoate **5f**, methyl 3-phenylpropiolate **5g**, and 4-phenylbut-3-yn-2-one **5h**) were less reactive and gave two regioisomers **6f–h** and **7f–h**. These reactions took about 7 days at 110 °C in toluene but still gave good total yields. The regioisomeric triazoles **6f**/**7f** from the butynoate reaction were formed with high selectivity (96/4) and were partially separated. We obtained 19% of pure **6f** and 67% of a mixture of **6f** and **7f** in a 95/5 ratio (entry 6). The corresponding triazoles **6g** and **7g** from methyl 3-phenylpropiolate were formed with lower selectivity but were well separated. We isolated 54% of **6g** and 27% of **7g** (entry 8). Likewise the products **6h** and **7h** from 4-phenylbut-3-yn-2-one were separable and were isolated in 61% and 28% yields (entry 9; the crystal structure of **6h** is shown in the Supporting Information (SI)).

The major regioisomer **6f–h** in each case has the carbonyl directing group on C4 of the triazole. The positions of the substituents were initially assigned by a shielding trend in the ^{1}H NMR spectra, and both the structure of **6f** and the origin of the trend (protons on the C5 substituent are shielded by one of the dipp rings[14]) were confirmed by X-ray crystallography (see Figure 2).

Table 1. Dipolar Cycloaddition Reactions of Boryl Azide **4** with Substituted Alkynes **5b–5i**

entry	alkyne, conditions^a	product(s)^{b,c}	
			
1	**5b**, R = OMe, 80 °C, 4 h	**6b**, 91%	
2	**5c**, R = Me, 80 °C, 3.5 h	**6c**, 94%	
	RO_2C—≡—CO_2R		
3	**5d**, R = Me, 80 °C, 5 h	**6d**, 96%^{d}	
4	**5d**, R = Me, 110 °C, 3 h	**6d**, 84%	
5	**5e**, R = Et, 110 °C, 3 h	**6e**, 92%	
	H_3C—≡—COOEt		
6	**5f**,110 °C, 7 d	**6f** 96/4 **7f** 19% **6f**; 67% **6f/7f**, 95/5	
7	**5f**, 180 °C, 3 h	**6f** 90/10 **7f** 55% **6f**; 23% **6f/7f**, 80/20	
			
8	**5g**, R = OMe, 110 °C, 7 d	**6g**, 54%	**7g**, 27%
9	**5h**, R = Me, 110 °C, 7 d	**6h**, 61%	**7h**, 28%
10	**5h**, R = Me, 180 °C, 2 h	**6h**, 47%	**7h**, 39%
	≡—C_6H_4-4-Br		
11	**5i**, 110 °C, 3 d	**6i**, 50%	**7i**, 8%

^{a} 80 °C in C_6D_6, followed by ^{1}H NMR spectroscopy; 110 °C in toluene; 180 °C, microwave in benzotrifluoride. ^{b} NHC = 1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene. ^{c} Isolated yields after flash chromatography unless otherwise indicated. ^{d} NMR yield in C_6D_6.

Control experiments (see SI) provided no evidence for thermal cycloreversion or 1,3-boryl shift. So we believe that the isomer ratios are kinetically controlled.

When the carbonyl group was removed, we still observed reasonable reactivity for phenyl-substituted alkynes like (4-bromophenyl)ethyne **5i** (entry 11). However, unlike the other monosubstituted alkynes **5a–c**, the reaction now produced a small amount of the 1,5-regioisomer **7i** (8%) along with the major 1,4-regioisomer **6i** (50%). Results from a few alkyl-substituted alkynes were much less encouraging (see SI). Reactions were dramatically slower and sometimes not clean. Attempts at copper catalysis with several of the poorly reactive substrates did not give significantly improved results.

In contrast, microwave reactions can reduce reaction times dramatically for less reactive alkynes. Again due to

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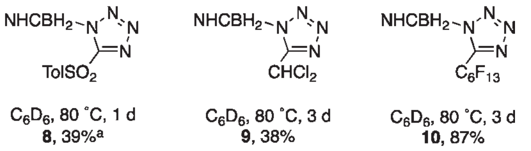
(13) Huang, C.-C.; Wu, F.-L.; Lo, Y. H.; Lai, W.-R.; Lin, C.-H. *Acta Crystallogr., Sect. E* **2010**, *66*, o1690.

(14) For example, the imidazole CH_3 group resonates at 2.27 ppm when it is on C4 (**7f**) and 1.78 ppm when it is on C5 (**6f**).

(a) Cycloadducts with nitriles



(b) Cycloadducts with alkenes

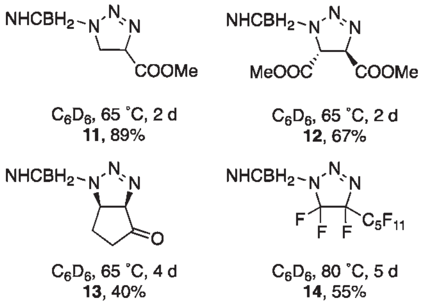


Figure 3. Reaction conditions, product structures, and yields for cycloadditions of **4** with nitriles (top) and alkenes (bottom). NHC is 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [a]5% of the 1,4-regioisomer was also isolated.

safety concerns, we limited these reactions to a small scale. First, a 10 mg sample of **4** was heated alone in a microwave in benzotrifluoride[15] ($C_6H_5CF_3$) for 1 h at 180 °C. No unusual pressure or temperature increase was observed. After cooling, the solvent was removed and the sample **4** was recovered intact as assessed by a ^{1}H NMR spectrum.

Microwave reactions in benzotrifluoride with **4** (30 mg) and either **5f** (entry 7) or **5h** (entry 10) provided the expected regioisomeric adducts in comparable yields to the standard heating reactions. There was small erosion in regioselectivity at 180 °C compared to the conductive heating experiments at 110 °C (compare entries 6 and 7), but reaction times were much shorter, decreasing from 1 week to 2 and 3.5 h (compare entries 6/7 and 9/10).

Observations during cycloaddition experiments of **4** with nitriles as dipolarophiles were qualitatively similar to those with alkynes. Azide **4** did not react rapidly in thermal reactions with acetonitrile and benzonitrile. However, nitriles substituted with electron-withdrawing groups gave 1,5-disubstituted tetrazoles upon heating. Products and yields from cycloadditions with tosyl cyanide (**8**, 39%), dichloroacetonitrile (**9**, 38%[16]), and perfluoroheptanenitrile (**10**, 87%) are shown in the top part of Figure 3. All these products were isolated by chromatography and are stable white solids. The crystal structure of **10** is shown in the SI. The cycloaddition with tosyl cyanide also gave a small amount (5%) of the 1,4-regioisomer.

A few alkenes with electron-withdrawing groups were also surveyed, and the products from reactions with methyl acrylate, dimethyl fumarate, cyclopent-2-en-1-one, and perfluoro-1-heptene are shown in the lower part of Figure 3. Reactions with methyl acrylate and perfluoroheptene gave single regioisomers **11** (89%), and **14** (55%) with the electron-withdrawing group at position 4 of the triazolidene ring. Reactions with dimethyl fumarate and 2-cyclopenten-1-one gave single stereoisomers, *trans* (**12**, 67%) and *cis* (**13**, 40%), respectively. The crystal structure of **13** was solved and is shown in the SI. A cycloaddition reaction with dimethyl maleate gave the same product **12** as from dimethyl fumarate, but the reaction was much slower and less clean. From this result, it is clear that the *cis* maleate is less reactive than *trans* fumarate, but it is not clear whether the isomerization that ultimately produces **12** occurs before or after cycloaddition of the maleate. Again, standard alkenes (including norborene) were not very reactive toward **4**.

In summary, prototypical NHC-boryl azide **4** undergoes dipolar cycloaddition reactions with an assortment of alkyne, nitrile, and alkene dipolarophiles, provided that the dipolarophiles are substituted with at least one electron-withdrawing group. It thus seems likely that NHC-boryl azides are Type III dipoles according to the Sustman classification,[17] with the important frontier orbital interaction occurring between the HOMO of the dipole and the LUMO of the dipolarophile. This picture of NHC-boryl as a good inductive electron-donating group is consistent with the radical chemistry, ionic chemistry, and electrochemistry of NHC-boranes.[1]

The boryl azide is different in cycloaddition behavior from azides bearing electron-withdrawing groups (sulfonyl azides, for example) and also different from typical carbon-substituted azides. Phenyl azide (PhN_3), for example, is a classic Type II dipole whose cycloaddition reactions are accelerated by both an electron-donating and -withdrawing substituent on alkenes and alkynes.[17] Tin azides[10a−c] might be more comparable to boryl azides because tin is also an electron donor. Even so, cycloadducts of tin azides often experience a thermal 1,2- or 1,3-tin shift, and such adducts are readily destannylated. But the products of cycloaddition of **4** are very stable; no evidence of a boryl shift has yet been obtained, and deborylation does not occur under typical ambient and chromatographic conditions.

Acknowledgment. We thank the U.S. National Science Foundation, the French Agence Nationale de la Recherche (grant ANR-11-BS07-008, NHCX), and CNRS for funding this work. We thank Prof. Louis Fensterbank (UPMC) for helpful discussions.

Supporting Information Available. Contains complete experimental details and copies of NMR spectra of all cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.