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Synthesis of Functionalized Carboranes as Potential Anticancer and BNCT Agents

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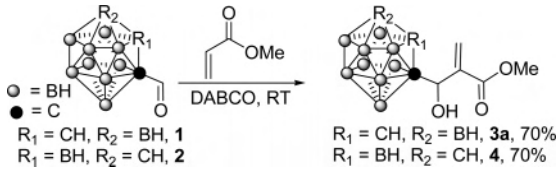
Carboranyl aldehydes react with α,β-unsaturated esters, ketones, and nitriles in the presence of DABCO to provide functionalized carboranyl alcohols in good yields. Acetates of these alcohols undergo a facile isomerization with a variety of nucleophiles and afford structurally interesting carboranes. Biological evaluation of these molecules exhibited impressive antiproliferative activity for brain and breast cancer cells.

Carboranes are a very good source of multiple boron atoms with a wide variety of potential applications in medicinal chemistry.[1] The carborane moiety could also be introduced to study the hydrophobic interactions between a drug molecule and the enzyme/receptor.[1c] Carboranes and other polyhedral boranes have also been extensively studied for Boron Neutron Capture Therapy (BNCT).[2] Functionalization of carboranes is an extremely important transformation to achieve all of these goals.[3]

The Baylis−Hillman reaction is an important C−C bond-forming reaction, and it offers densely functionalized alcohols and amines in one step.[4] The reaction is highly atom efficient, and the products undergo a facile isomerization with a variety of nucleophiles in SN_2' fashion to afford valuable synthons. We envisaged that the Baylis−Hillman reaction of carboranyl aldehyde with electron-deficient olefins in the presence of tertiary amines like 1,4-diazabicyclo[2.2.2]octane (DABCO) should provide a wide variety of functionalized carboranes very easily. We also envisioned that these products could, in turn, be converted into carboranes of structural and biological interest.

Scheme 1. Baylis−Hillman Reaction of *m*-Carboranyl Aldehyde



For the present study, we chose carboranyl aldehydes **1** and **2** as the electrophiles and several activated olefins such as acrylates, and acrylonitrile, as olefin partners. The required aldehydes **1** and **2** were prepared according to a literature procedure by treating the corresponding *o*- or *m*-carborane with ^{n}BuLi and quenching with methyl formate at −78 °C.[5] The initial reaction of **1** with 2 equiv of methyl acrylate in the presence of 10% DABCO was sluggish, and only a partial reaction took place to afford ∼20% of the alcohol **3** after 12 h. Prolonged continuation of the reaction for an additional 48 h did not improve the yield. However, usage of stoichiometric amounts of DABCO resulted in the complete consumption of aldehyde **1**, and compound **3a** was obtained in 70% yield after silica gel column chromatography. The reaction with *m*-carboranyl aldehyde **2** was also equally facile, and the alcohol **4** was obtained in 70% yield (Scheme 1).

Similarly, the reaction of *o*-carboranyl aldehyde **1** with olefins such as ethyl, benzyl, and phenyl acrylates proceeded satisfactorily to yield the corresponding alcohols **3b**−**d** in

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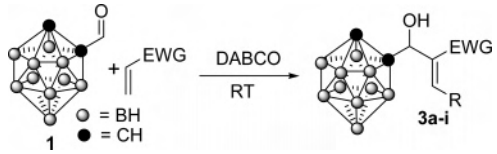
Table 1. Baylis−Hillman Reaction of *o*-Carboranyl Aldehyde



no.	EWG	R	**3**	DABCO (%)	time (h)	yield (%)
1	COOMe	H	**3a**	70	12	70
2	COOEt	H	**3b**	70	12	75
3	COOBn	H	**3c**	70	12	71
4	COOPh	H	**3d**	70	12	60
5	CHO	H	**3e**	10	1	60[a]
6	$COCH_3$	H	**3f**	10	6	63[b]
7	$COOCH_2CF_3$	H	**3g**	10	0.5[a]	81
8	CN	H	**3h**	30	2.0	90
9	COOMe	Ph	**3i**	*c*	*c*	65

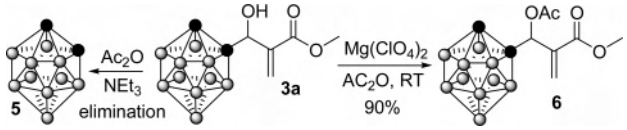
[a] The reaction was performed at 0 °C. [b] Isolated as its acetate. [c] β-Substituted acrylates fail to undergo the Baylis−Hillman reaction; hence, **3i** was synthesized via an alternate protocol involving vinylalumination.[6]

good yield (entries 2−4). Acrolein is an extremely sensitive monomer, polymerizes instantaneously in the presence of amines, and generally is not a good substrate for unreactive Baylis−Hillman electrophiles. Fortunately, aldehyde **1** is sufficiently reactive so as to afford the corresponding hydroxyl aldehyde **3e** in good yield (entry 5). The reaction was done in THF as the solvent at 0 °C to minimize the polymerization of acrolein. The reaction of **1** with methyl vinyl ketone took place smoothly, but the product alcohol **3f** could not be obtained in very pure form. Accordingly, we characterized **3f** via conversion to its acetate (entry 6). In the cases of 2,2,2-trifluoroethylacrylate and acrylonitrile (entries 7 and 8), the reaction went to completion within half an hour using 30% DABCO, affording the alcohols **3g** and **3h** in 81% and 90% yield, respectively. β-Phenyl-substituted alcohol **3i** was prepared via the reaction of methyl 3-phenyl-2-propynoate with DIBAL-H/NMO followed by treatment with carboranyl aldehyde **1** (entry 9, Table 1).[6]

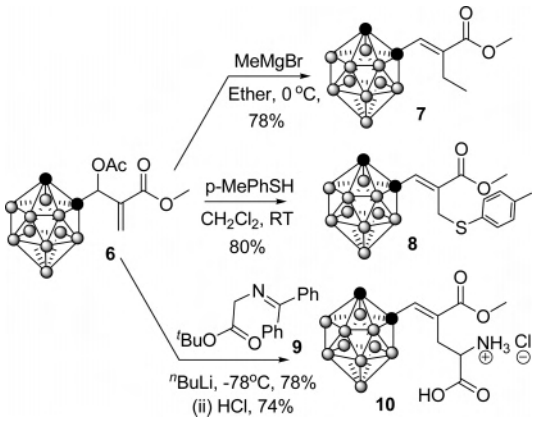
After successfully synthesizing the functionalized carboranyl alcohols, we carried out further studies to synthesize some useful and structurally interesting functionalized carboranyl intermediates via nucleophilic allylic substitution. As a representative example, we took the acetate **6** derived from alcohol **3a**. The acetate formation under standard basic conditions resulted in the formation of *o*-carborane via elimination. Similar observations were made by Yamamoto et al., wherein *o*-carborane was used as a protecting group for the hydroxyl moiety and was subsequently deprotected under basic conditions.[7] Fortunately, acetate formation under Lewis acidic conditions took place very smoothly. Treatment of **3a** with Ac_2O in the presence of a catalytic amount of $Mg(ClO_4)_2$[8] furnished acetate **6** in 90% yield (Scheme 2).

After obtaining the acetate, we carried out the isomerization with several nucleophiles. The reaction of **6** with

Scheme 2. Acetylation of Baylis−Hillman Alcohols



Scheme 3. Nucleophilic Allylic Rearrangement of Baylis−Hillman Acetates



MeMgBr was very facile, and α,β-unsaturated ester **7** was formed in 78% yield. Treatment with 4-methylbenzenethiol was also very smooth, and the thioether **8** was obtained in 80% yield. We have also performed the isomerization with lithiated benzophenone glycinimine **9**. This afforded the α-diphenylimino ester that upon acidic hydrolysis afforded the amino acid **10** in very good yield (Scheme 3). This particular reaction could be useful because of the easy access of carborane containing functionalized amino acids.[2c]

Owing to the importance of carboranes in medicinal chemistry, some of these compounds have been evaluated as potential anticancer agents, and preliminary results are highly encouraging for brain and breast cancer cells. The antiproliferative activity of these compounds was tested in human LN229 gliomablastoma cells, MCF-7 (estrogen receptor-positive), and MDA-MB-231 (estrogen receptor-negative) breast carcinoma cells. The cells were incubated at 37 °C in 96-well plates for 3 days in the presence or absence of the compounds. The cell numbers were quantified by a crystal violet assay[9] and normalized to the untreated cells. At 25 μM, both **3a** and **3h** exhibited over 95% inhibition of cell proliferation in all three cell lines. Compounds **3a** and **3h** were also active at lower concentrations (5−15 μM), whereas the corresponding Baylis−Hillman product obtained from benzaldehyde and methyl acrylate was totally inactive.

In conclusion, we have carried out a systematic study of the Baylis−Hillman reaction on carboranyl aldehydes with electron-deficient olefins and obtained functionalized carboranyl alcohols in a single step. The acetate of hydroxy ester has been successfully isomerized with a variety of nucleophiles in SN_2' fashion, and several functionalized carboranes of structural and biological interest were obtained in good yields. Preliminary biological evaluation showed

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impressive antiproliferative activity for the brain and breast cancer cells. A detailed biological evaluation of these compounds is in progress and will be reported in due course. Owing to the significance of the Baylis−Hillman reaction, the ease of functionalization, and the importance of carboranes in various fields, we believe that the present study would be of interest to inorganic, organic, and medicinal chemists.

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Supporting Information Available: Experimental and spectral data along with ^{1}H and ^{13}C NMR spectra for various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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