

## COMPARISON OF THREE METHODS FOR THE SYNTHESIS OF CARBORANE CARBOXYLIC ACID ESTERS

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### SUMMARY

Three procedures for the esterification of polyhedral carborane carboxylic acids with long chain unsaturated fatty alcohols are compared with regard to rate of reaction, ease of isolation and over-all yield. The optimum procedure is based on room temperature reaction of the acid chloride and alcohol in the presence of 4-dimethylaminopyridine in  $\text{CH}_2\text{Cl}_2$ .

Unsaturated fatty alcohol esters of polyhedral carborane carboxylic acids were required for a study involving replacement of the natural cholesterol ester core of LDL with hydrophobic boranes, and their subsequent use as selective boron delivery agents for neutron capture therapy. Although several methods have been utilized for synthesis of simple alkyl esters of carboranyl acids, none of these met our requirements since they either gave low yields, required forcing conditions or both. For example, the most frequently used method has been the condensation of  $\text{B}_{10}\text{H}_{14}$  with an ester of propynoic acid under reflux in benzene or toluene for 24 hours or longer (1). Typical yields for this process are only in the 35-50% range, and prolonged heating at such temperatures is not suitable for multiply unsaturated alcohols such as arachidonyl alcohol. Other procedures have used prolonged reflux of the free carborane acid with alcohol in the presence of conc. sulfuric acid (2). Methods which involve strong bases, such as triethylamine, are also unsuitable due to the base-sensitivity of the carborane cage. The ideal method would involve rapid room temperature reaction, high yield such that the method could be applied to the preparation of  $^{10}\text{B}$ -enriched esters, and facile isolation for the pure product. We compare here three methods for the preparation of such esters using palmitoleyl alcohol as the example.

### Method A

A solution of carborane carboxylic acid (3) (0.500g, 2.66 mmol), *N,N*-dicyclohexylcarbodiimide (0.602g, 2.92 mmol), palmitoleyl alcohol (0.700g, 2.92 mmol) and 4-dimethylaminopyridine (0.323g, 2.66 mmol) in dry dichloromethane (25 ml) was stirred at room temperature under argon for 56 hrs. The *N,N*-dicyclohexyl urea was filtered and the filtrate washed with 0.1N HCl (2x30 ml), 5%  $\text{NaHCO}_3$  (2x30 ml) and brine (1x30 ml). Following drying with  $\text{MgSO}_4$  and filtration, the solvent was evaporated *in vacuo* to give an oil which was purified by flash chromatography on silica gel with 10%  $\text{CH}_2\text{Cl}_2$ /hexane to elute the hydrophobic product.

Rotary evaporation of the  $\text{CH}_2\text{Cl}_2$ -hexane yielded 0.714g (65.4%) chromatographically pure product.

#### Method B

To a solution of carborane carboxylic acid chloride (0.500g, 2.42 mmol) prepared from the acid using  $\text{PCl}_5$ , the alcohol (0.639g, 2.66 mmol) and 4-dimethylaminopyridine in dry dichloromethane (25 ml) was stirred at room temperature under argon for 1 hr. The reaction mixture was poured into a separatory funnel containing 30 ml of 0.1N HCl and extracted. This procedure was repeated once again with 0.1N HCl, twice with 0.5%  $\text{NaHCO}_3$  (30 ml) and once with brine (30 ml). After drying over  $\text{MgSO}_4$  and filtration, removal of volatiles *in vacuo* gave an oil which was purified as in Method A to yield 0.826g (83.2%) ester product.

#### Method C

A solution of carborane carboxylic acid chloride (0.500g, 2.42 mmol), palmitoleyl alcohol (0.639g, 2.66 mmol) and dry pyridine (1 ml) in dry dichloromethane was stirred for 24 hrs at room temperature under argon. The reaction mixture was extracted three times with 30 ml portions of 0.1N HCl, twice with 30 ml portions of 5%  $\text{NaHCO}_3$  and finally with a single 30 ml portion of brine. After drying over  $\text{MgSO}_4$  and removal of volatiles *in vacuo*, the remaining oil was purified by flash chromatography as previously described to yield 0.452g (45.5%) product.

Method A is essentially that described by Hassner (4) and has been widely applied to the one pot synthesis of many esters (5). Hindered carboxylic acids like pivalic or mesitoic generally work well with alcohols, but apparently the polyhedral carborane cage presents a more sterically constrained situation as judged by the yields obtained with this method. Yields using the DCC-DMAP procedure are generally in the 65%-90% region whereas in our cases they generally were 55%-65%. Increasing reaction times up to 24 hrs did not appear to increase the yields substantially. Moreover the presence of unreacted DCC in the reaction mixture presented additional problems in the flash chromatographic isolation as compared with Method B. One advantage to this method over Method B is the use of the free carboxylic acid rather than the acyl chloride. However, the conversion of carborane carboxylic acid to its acid chloride using  $\text{PCl}_5$  proceeds with 90-95% isolated yields. The lower overall yields and more complicated workup procedures of Method A make it less attractive than Method B.

Similarly there is no advantage to simply reacting the acid chloride and alcohol in the presence of pyridine (Method C). Pyridine is not basic enough to open the carborane cage, and is easily removed from the reaction mixture by acid-wash. However, the lower yields resulting from even prolonged reaction times make this method unsuitable for the preparation of  $^{10}\text{B}$ -enriched carborane esters.

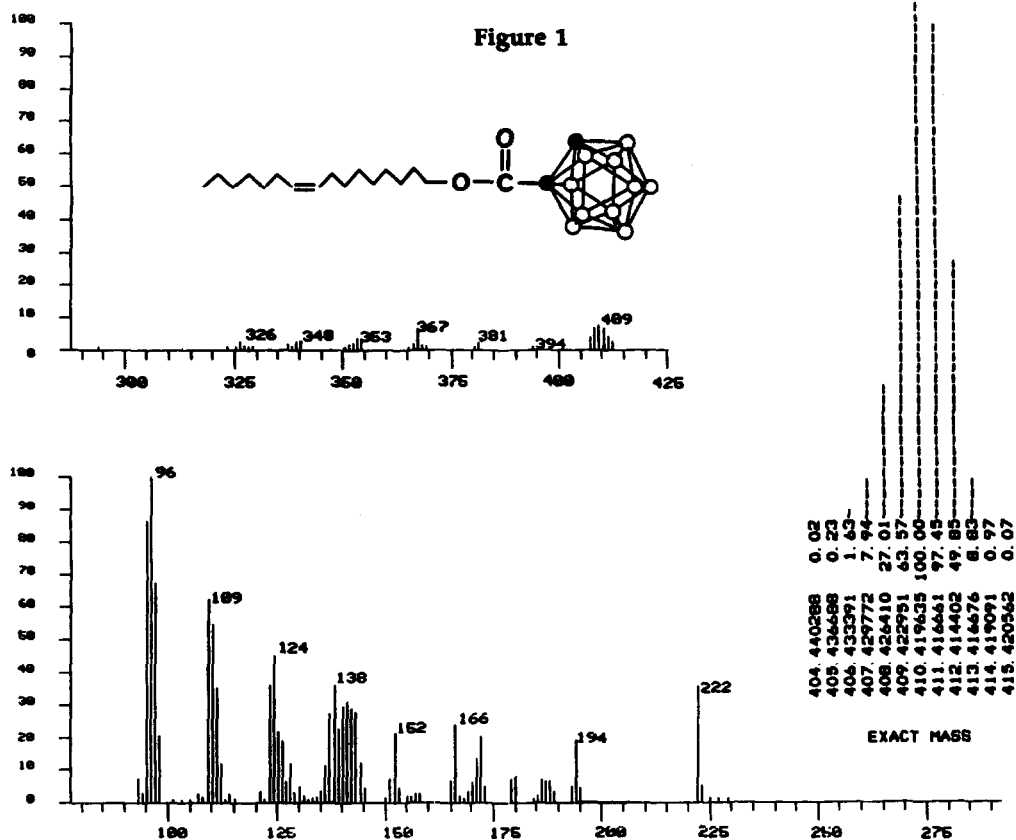
The DMAP-assisted reaction of carborane carboxylic acid chloride with fatty alcohols (Method B) is clearly the method of choice. The reaction is complete within ~1/2 hr as observed by TLC. Unreacted acid chloride and DMAP are conveniently removed by  $\text{NaHCO}_3$  and HCl

wash, respectively, and the very hydrophobic product is easily separated from unreacted alcohol by flash chromatography over a short column of silica. Products isolated in this manner are chromatographically pure by TLC, GC and mass spectrometry. Yields are excellent, averaging 80-90% in all cases tried so far. A list of esters prepared by this technique appears in Table 1.

Table 1  
Accurate Mass Data for Fatty Alcohol Esters of Carborane Carboxylic Acid

Name	formula	calculated mass	measured mass	mmu	deviation ppm
myristoleyl	C <sub>17</sub> H <sub>38</sub> O <sub>2</sub> B <sub>10</sub>	382.3882	382.3891	0.9	2.4
palmitoleyl	C <sub>19</sub> H <sub>42</sub> O <sub>2</sub> B <sub>10</sub>	410.4196	410.4178	-1.8	-4.3
γ-linolenyl	C <sub>21</sub> H <sub>42</sub> O <sub>2</sub> B <sub>10</sub>	434.4197	434.4204	0.7	1.6
linolenyl	C <sub>21</sub> H <sub>42</sub> O <sub>2</sub> B <sub>10</sub>	434.4197	434.4176	-2.1	-4.8
linoleyl	C <sub>21</sub> H <sub>44</sub> O <sub>2</sub> B <sub>10</sub>	436.4356	436.4344	-1.2	-2.8
oleyl	C <sub>21</sub> H <sub>46</sub> O <sub>2</sub> B <sub>10</sub>	438.4501	438.4511	1.0	2.3
elaidyl	C <sub>21</sub> H <sub>46</sub> O <sub>2</sub> B <sub>10</sub>	438.4501	438.4509	0.8	1.8
arachidonyl	C <sub>23</sub> H <sub>44</sub> O <sub>2</sub> B <sub>10</sub>	460.4356	460.4347	-0.9	-1.9
homo-γ-linolenyl	C <sub>23</sub> H <sub>46</sub> O <sub>2</sub> B <sub>10</sub>	462.4501	463.4501	0.0	0.0
11-eicosenyl	C <sub>23</sub> H <sub>50</sub> O <sub>2</sub> B <sub>10</sub>	466.4821	466.4823	0.2	0.4

The palmitoleyl ester prepared by Method B is typical of fatty alcohol esters of carborane carboxylic acid. It is a clear, colorless oil at room temperature having no detectable odor. Intense characteristic infrared stretching bands were present at 2990 cm<sup>-1</sup> (νBH) and 1750 cm<sup>-1</sup> (νCO). This compound, like the other esters, may be vacuum distilled only at high temperature, and the purity of chromatographically isolated products makes such procedures unnecessary. Instead the esters have been characterized by both low and high resolution electron impact mass spectrometry. Figure 1 shows the low resolution mass spectrum and structure of the palmitoleyl ester. Superimposed are theoretical masses and intensities for the molecular ion cluster. The deviation between calculated and measured mass is only -1.8 mmu (4.3 ppm). Table 1 shows the calculated and measured masses for the series of esters prepared, as well as the differences for each. In all cases the deviations are less than 5.0 ppm and support the structure claimed. The fragmentation pattern is typical for esters of this type with some cleavage at the alcohol C-O bond (m/e=222). The base peak at nominal mass m/e=96 is observed in all mass spectra of these esters, and arises from fragmentation of the fatty alcohol side chain rather than the carborane. Exact mass analysis of peak envelopes centered at 96, 109, 124 best match fragments of C<sub>7</sub>H<sub>12</sub>, C<sub>8</sub>H<sub>14</sub> and C<sub>9</sub>H<sub>16</sub>, respectively.



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