2,4-Dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine: A Potential Synthon for 5-(1-*o*-Carboranylmethyl)pyrimidines

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The synthesis of 2,4-dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine is described. Synthetically, this novel *o*-carboranyl pyrimidine is approached from ethyl 2-acetyl-4-pentynoate through alkylation of ethyl acetoacetate with propargyl bromide and subsequent condensation with thiourea to yield 6-methyl-5-(2-propynyl)-2-thio-4(1*H*,3*H*)-pyrimidinone. Hydrolysis of the 2-thione and chlorination with $POCl_3$ gives 2,4-dichloro-6-methyl-5-(2-propynyl)pyrimidine. Gentle refluxing of this product with $B_{10}H_{14}/CH_3CN$ in toluene yields the target, 2,4-dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine, a potential synthon for a variety of 2,4-substituted 5-(1-*o*-carboranylmethyl)-6-methylpyrimidines and/or the corresponding *nido*-undecaborates.

Introduction

A number of approaches to the synthesis of 5-(1-*o*-carboranylmethyl)-substituted pyrimidines are described including the successful synthesis of 2,4-dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine. This general approach could potentially be utilized to produce a variety of boron-containing pyrimidine analogues (*o*-carboranes and/or *nido*-undecaborates). This class of compounds is of special interest because of recent advances in neutron capture therapy which have revived interest in this technique as a viable radiotherapeutic approach to the cancer problem.[1-4] This renewed interest has stimulated the synthesis of a wide variety of boronated molecules for specific testing as agents for boron neutron capture therapy (BNCT).[1-4] These synthetic efforts have predictably focused on boronation of biologically active molecules such as steroids, monoclonal antibodies, chlorpromazine, nucleosides, thiouracil, amino acids, and porphyrins which are known to concentrate in tumor tissue to varying degrees.[1,3,4]

The diverse pathways by which pyrimidines and their nucleosides are utilized in the cell make these bioactive molecules a particularly attractive target for boronation in order to concentrate ^{10}B in actively replicating tissue. While a variety of exotic boron-containing heterocycles which resemble DNA bases have been synthesized,[5] very few pyrimidine analogues have been documented.[6] The paucity of boronated analogues of the pyrimidines is due to a number of factors. Pyrimidine has very few modifiable positions if biological relevance is to be maintained. In addition, boronated heterocycles are difficult to synthesize as is evident from the work of Soloway,[7] Matteson et al.,[8] Maitra,[6c] and Schinazi and Prusoff.[5] Finally, many of these boron-containing heterocycles are hydrolytically unstable and/or possess unacceptable biological toxicity.[5]

Among the known boron-derivatized pyrimidines, 5-(dihydroxyboryl)uridine (DBDU), synthesized by Schinazi and Prusoff, stands out as an excellent BNCT candidate.[1,3,5,6b,9,10] The positive phase I results of DBDU encouraged our group to devise strategies for a general synthesis of 5-(1-*o*-carboranylmethyl)-substituted pyrimidines. This type of compound was appealing for several reasons. First, from an academic standpoint, these derivatives were a new class of carboranes and pyrimidines and they represented an superb synthetic challenge. More importantly, the *o*-carborane moiety has certain advantages over other boron-containing substituents [e.g. $B(OH)_2$] relevant to BNCT including reduced toxicity, greater stability, and higher boron content.[11] However, solubility problems are often encountered with *o*-carborane derivatives. Therefore, the more soluble corresponding *nido*-undecaborates may be prepared from the aforementioned *o*-carborane derivatives.[6g,12] Further, our successful approach, provides a strategy for synthesis of *o*-carboranyl pyrimidines and could be applicable to preparation of substrates for RNA and DNA synthesis either in a biological milieu or chemically as components of hybridizable and cross strand reactive oligonucleotides directed toward specific high expression mRNA in tumor cells. Finally, while the substitution of *o*-carborane on the 5-position of a pyrimidine causes a significant structural modification of the pyrimidine from a chemical as well as biological viewpoint, certain pyrimidine derivatives with large 5-substituents (e.g., ClUdR, BrUdR, and IUdR) can be utilized in vitro and in vivo for DNA synthesis.[13-16]

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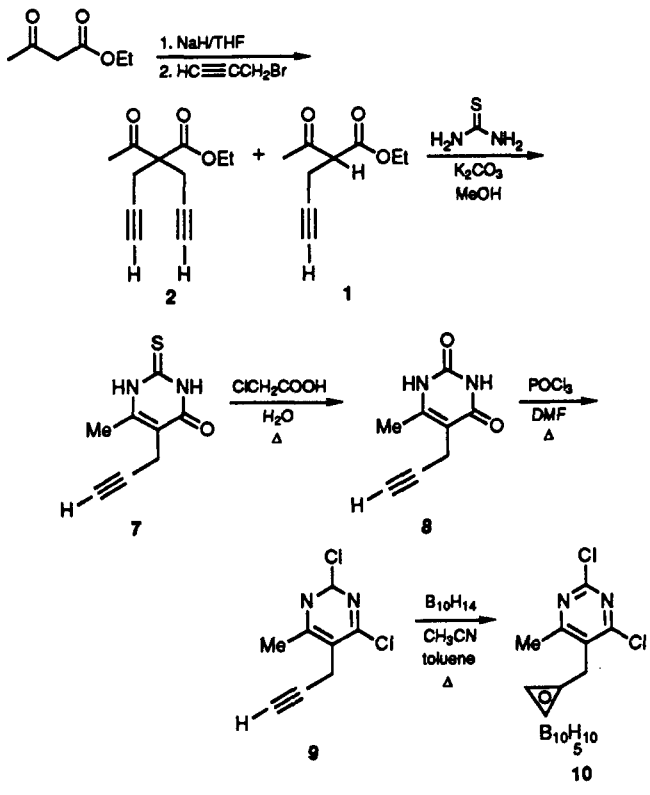
Scheme I



The actual synthesis of a carborane-substituted pyrimidine, however, presented special synthetic challenges, and a number of strategies were employed before successfully forming a carborane in the presence of a pyrimidine ring. These approaches including the productive scheme are described below.

Results

Successful Synthesis of a 5-(1-*o*-Carboranylmethyl)pyrimidine. The successful synthesis of the *o*-carborane-labeled pyrimidine is diagrammed below in Scheme I.

In this synthetic scheme the β-keto ester, ethyl 2-acetyl-4-pentynoate (1), was prepared by alkylation of ethyl acetoacetate with propargyl bromide by modification of the method of Yamamoto.[17] The β-keto ester 1 was next condensed with thiourea to give 6-methyl-5-(2-propynyl)-2-thio-4(1*H*,3*H*)-pyrimidinone (7). The thiopyrimidine was hydrolyzed with chloroacetic acid in EtOH/H_2O to give 6-methyl-5-(2-propynyl)-2,4(1*H*,3*H*)-pyrimidinedione (8) and a key intermediate was formed by reacting 8 with $POCl_3$/DMF to yield 2,4-dichloro-6-methyl-5-(2-propynyl)pyrimidine (9). The dichloro substituents replace the pyrimidine amido functions which can potentially react with decaborane and interfere with carborane formation. Furthermore, the chlorines are readily subject to displacement by a wide variety of nucleophiles allowing formation of a multitude of modified pyrimidines.

Following this strategy, *o*-carborane formation was achieved by gently refluxing $B_{10}H_{14}$/CH_3CN and 9 in toluene to yield 2,4-dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine (10).

Significantly, this synthesis is reasonably efficient using inexpensive and readily obtainable reagents. Further, compound 10 is an excellent precursor for a large variety of nucleophilic substitution reactions that could potentially be used to produce a great diversity of *o*-carboranyl or *nido*-undecaborate substituted pyrimidines for biological evaluation. In this regard, this derivative is potentially attractive and economical for introduction of a ^{10}B-enriched *o*-carborane to provide a rich assortment of boron substituted pyrimidines for use as BNCT agents.

Discussion

Elaboration of the straightforward synthetic scheme for synthesis of the 5-(1-*o*-carboranylmethyl)pyrimidine described above was only achieved after undertaking several strategies for preparation of the target compound. These are detailed below because of their relevance to the chemistry and preparation of both substituted *o*-carboranes and pyrimidines.

These are two general approaches for preparing substituted *o*-carboranes: (a) reaction of a metallo *o*-carborane with an electrophilic center and (b) reaction of an appropriately modified alkyne with decaborane and a Lewis base in either benzene or toluene.[18]

Synthesis of a molecule which contained both an *o*-carborane and a pyrimidine proved especially difficult and was highly dependent on the manner in which the carborane was introduced. The first method, reaction of a metallo *o*-carborane with an electrophilic center, had advantages in that *o*-carborane is a stable solid that can be purchased and readily reacts with alkyllithium or Grignard reagents to yield the desired metallo *o*-carborane. However, it should be noted that the *o*-carboranyl anion is a very strong, hindered base and is thus only weakly nucleophilic. This characteristic explains the observation that the *o*-carboranyl anion will attack (S_N2) primary alkyl bromides or iodides but will not couple with primary alkyl chlorides or secondary or tertiary alkyl halides.[18]

The second approach to substituted *o*-carboranes, reaction of a modified alkyne with decaborane and a Lewis base, is also not straightforward in its application to the synthesis of *o*-carborane-labeled pyrimidines. Fabrication of the *o*-carborane by reaction of decaborane with an alkyne requires that particular attention be given to the design of the alkyne moiety. Decaborane is a good Lewis acid that can form irreversible adducts with a number of heteroatoms (SH, OH, NH, etc.) that act as Lewis bases.[18] Therefore, special care must be taken in designing the alkyne with which the decaborane is reacted. It is critical to leave out or protect heteroatoms which might irreversibly bind or degrade the decaborane cage. This requirement proved to be quite challenging since our goal was to synthesize *o*-carboranyl heterocycles containing a large percentage of nitrogen, a superb Lewis base. During this work, a number of *o*-carborane-forming reactions were not fruitful because of apparent degradation of the decaborane cage through interaction with other functions in the alkyne molecule besides the triple bond targeted for modification.

Furthermore, while *o*-carborane is a very stable molecule for an organoborane, it is still an electron-deficient cage and heating for extended periods is precluded in the

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presence of strong bases or nucleophiles if the carborane cage system is to be preserved.

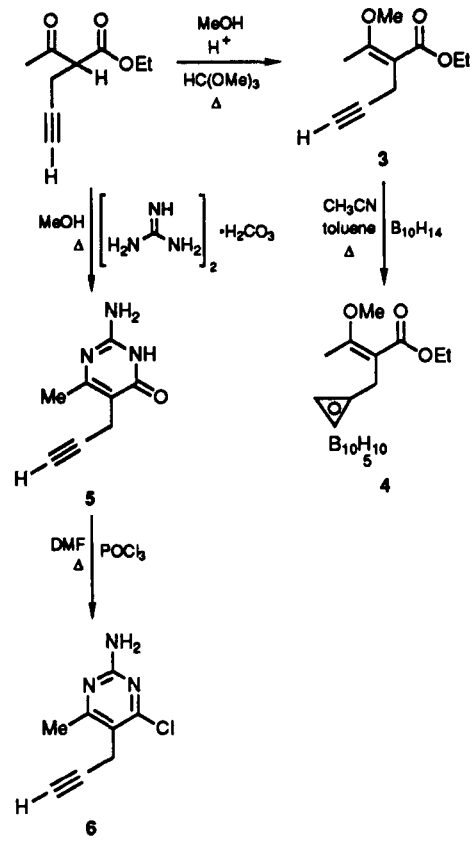
Approaches to Synthesis of 5-(1-o-Carboranylmethyl)pyrimidines. The first strategy we attempted for synthesis of 5-(1-o-carboranylmethyl)pyrimidines involved reaction of the o-carboranyl anion with several 2,4-dichloro-5-(X-methyl)-6-R-pyrimidines (X = Cl, I; R = H, Me). This approach was particularly appealing since the above pyrimidine precursors were readily attained in good yield by reacting either uracil[19] or 6-methyluracil[20] with formaldehyde in base to give the appropriate 5-(hydroxymethyl)pyrimidines. Subsequent chlorination ($POCl_3/PCl_5$ for R = H,[19] $POCl_3$ for R = Me[20]) yields the corresponding 2,4-dichloro-5-(chloromethyl)pyrimidines. It was expected that these derivatives would react readily with the o-carborane anion to give the expected 5-(1-o-carboranylmethyl) derivatives since benzyl halides react efficiently with metallo o-carboranes to give (o-carboranylmethyl)benzenes.[18] As discussed above the alkyl iodides are much more effective substrates in the displacement reaction with the o-carboranyl anion, and therefore, the 5-(iodomethyl)pyrimidine derivatives were prepared in excellent yield from the corresponding 5-(chloromethyl)pyrimidines with NaI in refluxing acetone in order to compare the final displacement reaction between these pyrimidine derivatives.[19]

For the final step, reaction of the (halomethyl)pyrimidine with the o-carboranyl anion, a number of conditions were varied (metal, leaving group, temperature, and solvent) without success. Without exception there was no reaction between the o-carboranyl anion and the (halomethyl)pyrimidine until temperatures were raised well above 0 °C, which also led to extensive degradation of the starting pyrimidines without evidence of product formation. It is probable that the large, basic o-carborane anion cannot attack the 5-halomethyl group for steric reasons, but rather, acts as a base leading to the significant decomposition evidenced in these reactions. Lithium acetylide–ethylene diamine complex was also used as a nucleophile in an attempt to circumvent any steric factors encountered because of the large bulk of the o-carborane anion. However, these reactions also produced intractable tars indicative of starting material degradation. It was concluded that the starting pyrimidines were probably sensitive to the extremely basic conditions.

The above strategy was followed because it was straightforward and utilized readily available reagents. However, the high basicity and poor nucleophilicity of the o-carborane anion required that the target molecule be approached by first synthesizing an appropriate alkyne which could then be reacted with decaborane to give an o-carborane-substituted derivative. For this approach, ethyl 2-acetyl-4-pentynoate (1) was synthesized as the key intermediate (see Scheme I). From this point it was envisioned that 1 could be reacted first with decaborane to yield ethyl 2-acetyl-3-(1-o-carboranyl)propanoate, which could then be further elaborated to a variety of o-carborane-substituted pyrimidines depending on the urea derivative employed in the condensation reaction. Alternatively, it appeared that 1 could be first reacted with a urea derivative to form an alkyne-derived pyrimidine which could subsequently be reacted with decaborane to form the desired o-carborane pyrimidine analogue.

Initially, therefore, 1 was reacted with decaborane in an attempt to form an o-carboranyl-substituted ethyl acetoacetate because of the potential utility of this o-carborane derivative as an intermediate for synthesis of several other o-carborane-containing heterocycles in addition to the pyrimidines. Unfortunately, the reaction of 1 with decaborane resulted in the formation of a noisome tar from which no product could be isolated. However, the possibility that the enolic form of the 4-oxo group had reacted with the decaborane cage causing the observed degradation suggested that protection of the ketone before carborane formation was advisable. To this end we pursued the following sequence of reactions and obtained the protected carborane derivative 4 (see Scheme II). Unexpectedly, numerous attempts to effect pyrimidine formation by reaction of 4 with urea, thiourea, and guanidine were fruitless. The methyl enol ether could potentially be deprotected to give ethyl 2-acetyl-3-(1-o-carboranyl)-propanoate. This compound could provide an intermediate for pursuit of other o-carborane-containing heterocycles, but it was not exploited for this work because of the concern that the o-carborane cage may be sensitive to the conditions required to effect pyrimidine ring formation.

Scheme II



An attempt was then made to design a 5-(2-propynyl)-pyrimidine which would react with decaborane to yield a 5-(1-o-carboranylmethyl)pyrimidine. This strategy was conceived to circumvent problems that could occur from degradation of the o-carborane upon pyrimidine ring formation (see Scheme II).

Pyrimidine formation was carried out by reacting guanidine carbonate with 1 in ethanol containing an equivalent of potassium carbonate to yield 2-amino-6-methyl-5-(2-propynyl)-4(1*H*)-pyrimidinone (5). Chlorination in $POCl_3$/DMF yielded the 4-chloro derivative (6). It was hoped that the 4-chloro substituent would deactivate the 2-amino group sufficiently to allow carborane formation, but the reaction with decaborane again yielded an intractable brown tar, and this reaction was no longer pursued.

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These fruitless attempts finally led to the successful synthesis outlined in Scheme I and, in summary, an efficient and economical synthesis of a potential synthon for 5-(1-*o*-carboranylmethyl)pyrimidine derivatives, 2,4-dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine (**10**) was achieved. It should be pointed out that nucleophilic displacement of the chlorine atoms can be carefully controlled in order to preserve the *o*-carborane cage.[6g] However, the cage can also be selectively degraded to prepare the more water soluble *nido*-undecaborate derivatives which increases the potential utility of the target, compound **10**.[6g,12]

Experimental Section

General Procedures. Melting points were determined on a Büchi-510 and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 684 spectrometer. ^{1}H NMR spectra were recorded on an IBM NR-80 spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer. Chemical shifts are reported relative to Me_4Si for $CDCl_3$ and DMSO-d_5 for DMSO-d_6 as the solvent. GC–MS were obtained on a Hewlitt-Packard GC–MS Model 5992-A and are low resolution. TLC was performed on EM aluminum silica gel sheets (0.2 mm) with a fluorescent indicator. All glassware was carefully dried at 150 °C and cooled under dry argon immediately before use. Both toluene and THF were distilled from the sodium ketyl of benzophenone at the time of use. MeOH was distilled over $Mg(OMe)_2$ and stored over 3-Å molecular sieves. DMF was distilled from CaH under reduced vacuum and stored over 3-Å molecular sieves.

Ethyl 2-Acetyl-4-pentynoate (1). NaH (12.6 g of a 50% oil dispersion, 0.26 mol) was washed twice with *n*-pentane (2 × 200 mL) and suspended in 250 mL of freshly distilled THF. All of the above manipulations as well as the subsequent reactions were carried out under a dry argon atmosphere. Next ethyl acetoacetate (50 mL, excess) was dripped in carefully while the receiving flask was cooled in an ice/*i*-PrOH mixture (−10 °C). After the addition was completed, the mixture was removed from the cooling bath and left stirring at room temperature overnight. The next day, propargyl bromide (29 mL of a solution 80% wt/wt in toluene, 0.26 mol) was syringed into the flask. The reaction spontaneously warmed, and a precipitate formed after 1 h. Again, the reaction was left overnight. The reaction was terminated the next day by pouring into 100 mL of ice-cold 10% HCl and extracting with ether (3 × 300 mL). The combined ether washings were rinsed with brine (2 × 200 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent and careful distillation (0.15 mmHg) gave three fractions: 29–34 °C, 50–55 °C (41.19 g), and 65–68 °C (2.13 g). GC–MS of the second fraction showed mild contamination by the material of the third fraction. Redistillation of this fraction (0.15 mmHg) from 50 to 52 °C gave 38.4 g (88%) of the monopropargylated derivative. The third fraction was presumed to be the dialkylated product as evidenced by the proton NMR below: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3, CH_3CH_2O), 2.07 (t, J_{3-5} = 2.5 Hz, 1, $CH_2C{\equiv}CH$), 2.30 (s, 3, CH_3CO), 2.70 (dd, J_{3-5} = 2.5 Hz, J_{2-3} = 7.1 Hz, 2, $CH_2C{\equiv}CH$), 3.72 (t, J_{2-3} = 7.1 Hz, 1, $COCH(COOEt)CH_2$), 4.21 (q, J = 7.0 Hz, 2, CH_3CH_2O). Anal. Calcd for $C_9H_{12}O_3$: C, 64.28; H, 7.19; O, 28.54. Found: C, 64.12; H, 7.25; O, 28.67. GC–MS: The GC was run on a 6-ft OV-101 column with temperature programming from 150 to 265 °C (16 °C/min). One peak was observed with a retention time of 2.4 min. MS: m/e 168.0 (M^+), 139.0 (168.0 − Et), 125.0 (168.0 − Ac).

The proton NMR of the dialkylated product (**2**) is given below: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 7.0 Hz, 3, CH_3CH_2O), 2.07 (t, $J_{1'-3'}$ = 2.7 Hz, 2, 2 $-CH_2C{\equiv}CH$), 2.21 (s, 3, CH_3CO), 2.94 (d, $J_{1'-3'}$ = 2.7 Hz, 4, 2 $CH_2C{\equiv}CH$), 4.24 (q, J = 7.0 Hz, 2, CH_3CH_2O).

Ethyl 2-(1-Methoxyethylidene)-4-pentynoate (3). Compound **1** (48.94 g, 0.29 mol) was dissolved in a solution of trimethyl orthoformate (50 mL) and dry MeOH (100 mL) containing a small spatula measure of *d,l*-10-camphorsulfonic acid. After 15 h under reflux, TLC (30% ether–petroleum ether) showed complete conversion to a product which was slightly more polar than the starting material (R_f = 0.35). The spot was visualized by short UV and was developed by spraying with $KMnO_4$ and warming. The deep purple solution was cooled, and the trimethyl orthoformate and MeOH were removed on the rotary evaporator. Distillation of the remaining liquid under high vacuum (0.15 mmHg) gave three fractions: 28–40 °C (2.12 g), 40–52 °C (5.63 g), 52–53 °C (47.81 g). The second fraction was a 50:50 mixture (by GC) of a lower boiling material contaminated with the product of fraction 3. The mass spectrum of this material indicated that it was simply the transesterification product of **1** with MeOH. Fraction 3 was also contaminated with this byproduct and was redistilled to high purity to give a final yield of 37.92 g (72%) with a boiling point from 53 to 55 °C: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3, CH_3CH_2O), 1.85 (t, J_{3-5} = 2.6 Hz, 1, $CH_2C{\equiv}CH$), 2.40 (s, 3, CH_3CO), 3.20 (d, J_{3-5} = 2.6 Hz, 2, $CH_2C{\equiv}CH$), 3.80 (s, 3, CH_3O), 4.20 (q, J = 7.2 Hz, 2, CH_3CH_2O); ^{13}C NMR ($CDCl_3$) δ 14.21, 14.45, 15.43, 54.96, 59.84, 65.89, 83.58, 105.63, 166.32, and 167.69. GC–MS: The gas chromatogram was run on a 6-ft OV-101 column with temperature programming from 150 to 270 °C at 16 °C/min. Compound **4** had a retention time of 3.3 min under these conditions. MS: m/e 182.1 (M^+), 153.0 (182.1 − Et), 139.0 (182.1 − Ac), 137.1 (182.1 − OAc), 109.0 (182.1 − COOEt).

Ethyl 2-(1-Methoxyethylidene)-3-(1-*o*-carboranyl)-propanoate (4). Compound **3** (1.07 g, 5.9 mmol) was added to 1.25 g (1.06 equiv) of the $B_{10}H_{12}$–CH_3CN complex in 25 mL of freshly distilled toluene. After 1 h of refluxing, the reaction was complete and TLC (30% ether–petroleum ether) showed a new spot slightly more polar than the starting material (R_f = 0.27). The black reaction was rinsed through a short column of silica gel (220–400 mesh), and the column was rinsed thoroughly with toluene. The solvent was evaporated, and the remaining light yellow oil was dissolved in hot hexane and crystallized with cooling in the freezer to yield 0.146 g (26%) of small white cubes. These crystals still retained a strong odor of $B_{10}H_{14}$ and were recrystallized from MeOH–H_2O to obtain short thick needles which melted from 72 to 74 °C: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3, CH_3CH_2O), 3.32 (s, 2, $CH_2C_2B_{10}H_{11}$), 3.70 (bs, 1, H-C2 of carborane cage), 3.80 (s, 3, CH_3O), 4.20 (q, J = 7.0 Hz, 2, CH_3CH_2O); ^{13}C NMR ($CDCl_3$) δ 14.25, 14.55, 33.95, 55.01, 60.18, 60.33, 75.88, 105.92, 167.79, and 169.39. GC–MS: The gas chromatogram was run on a 6-ft OV-101 column with temperature programming from 260 to 270 °C at 5 °C/min. One broad peak was observed with a retention time of 3.3 min. MS: m/e 301.3 (M^+), 286.3 (301.3 − Me), 272.2 (301.3 − Et), 256.2 (301.3 − OEt), 228.3 (301.3 − COOEt); IR (KBr, cm^{-1}) 3070 m (C–H stretch carborane), 2600 vs (B–H). Anal. Calcd for $B_{10}C_{10}H_{24}O_3$: C, 39.98; H, 8.05. Found: C, 39.72; H, 7.97.

2-Amino-6-methyl-5-(2-propynyl)-4(1*H*)-pyrimidinone (5). Compound **1** (10.26 g, 0.061 mol) was mixed with guanidine-carbonate (12.61 g, 0.07 mol) in 150 mL of MeOH and refluxed for 15 h. The majority of the MeOH was distilled off, yielding a thick beige slurry which was carefully neutralized with concentrated HCl and cooled in the freezer to give 8.18 g (82%) of a fine white solid. The crystals dissolved in hot *i*-PrOH and recrystallized on cooling to yield small plates with a melting range of 250–251 °C dec: ^{1}H NMR (Me_2SO-d_6) δ 2.05 (s, 3, $CH_3C(6)$), 2.55 (t, J = 2.5 Hz, 1, $CH_2C{\equiv}CH$), 3.10 (d, J = 2.5 Hz, 2, $CH_2C{\equiv}CH$), 6.53 (bs, 2–3, NH_2 and N*H*); ^{13}C NMR (Me_2SO-d_6) δ 13.56, 20.34, 69.63, 82.80, 106.69, 153.98, 159.73, and 164.03. Anal. Calcd for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 59.05; H, 5.69; N, 26.01.

2-Amino-4-chloro-6-methyl-5-(2-propynyl)pyrimidine (6). Compound **5** (6.60 g, 0.04 mol) was added to 50 mL of $POCl_3$ and 0.5 mL of DMF. The reaction was refluxed for 7 h and was left stirring at room temperature overnight. The excess $POCl_3$ was distilled off under house vacuum (65–67 °C), and the remaining viscous brown oil was poured into 250 mL ice-cold 10% HCl. After sitting on ice the oily brown mixture precipitated long, mild brown needles (2.09 g). The brown needles were dissolved in warm ethyl acetate and filtered through a pad of silica gel (220–400 mesh) in order to remove color. Next, *n*-hexane was dripped into the filtrate with warming until the solution became turbid. Slow cooling on the benchtop and then the freezer yielded 1.68 g (23%) of the analytically pure sample with a melting range of 168.5–169.5 °C: ^{1}H NMR ($CDCl_3$) δ 2.05 (t, J = 2.7 Hz, 1, $CH_2C{\equiv}CH$), 2.50 (s, 3, CH_3-C(6)), 2.53 (d, J = 2.7 Hz, 2, $CH_2C{\equiv}CH$), 5.60 (bs, 2, NH_2); ^{13}C NMR ($CDCl_3$) δ 18.48, 22.34, 70.32, 80.80, 115.56, 160.66, 162.47, and 169.34. Anal. Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14; Cl, 19.52. Found: C, 53.11; H, 4.50; N, 23.42; Cl, 19.47.

6-Methyl-5-(2-propynyl)-2-thio-4(1*H*,3*H*)-pyrimidinone (7). Compound 1 (25.10 g, 0.15 mol) was dissolved in 150 mL of MeOH with thiourea (11.64 g, excess) and K_2CO_3 (19.72 g, excess). The reaction was stirred under reflux for 24 h and neutralized with concentrated HCl followed by cooling in the freezer. The solid was filtered and rinsed with 250-mL ice-cold 25% H_2O–MeOH. The fine white powder was dissolved in hot *i*-PrOH and precipitated small thin needles on cooling (15.69 g, 58%). The crystals melted from 258 to 260 °C, and TLC showed one spot at R_f = 0.77 in 10% MeOH–ether: ^{1}H NMR (Me_2SO-d_6) δ 2.10 ()s, 3, CH_3-C(6)), 2.63 (t, J = 2.4 Hz, 1, $CH_2C{\equiv}CH$), 3.11 (d, J = 2.4 Hz, 2, $CH_2C{\equiv}CH$), 12.25 (bs, 2, NHCSNH). ^{13}C NMR (Me_2SO-d_6) δ 13.27, 15.90, 70.51, 80.99, 110.25, 149.93, 160.51, and 174.31. Anal. Calcd for $C_8H_8N_2OS$: C, 53.32; H, 4.47; N, 15.54. Found: C, 53.30; H, 4.60; N, 15.74.

6-Methyl-5-(2-propynyl)-2,4(1*H*,3*H*)-pyrimidinedione (8). The thiopyrimidine 7 (15.69 g, 87 mmol) was added to a solution of $ClCH_2COOH$ (26.5 g, excess) in 50 mL of EtOH and 250 mL of H_2O, and the suspension was refluxed for 7 h at which time the clear, light yellow solution showed no starting material and only one UV (254 nm) active component by TLC (10% MeOH–ether) at R_f = 0.52. The reaction was cooled slowly, and filtration and thorough rinsing with ice-cold EtOH to remove the mephitic odor of thioacetic acid yielded a good crop of small, colorless needles. The crystals were dissolved in hot *i*-PrOH and recrystallized with slow cooling to give 11.85 g (83%) of fine, white needles which melted from 268 to 270 °C dec: ^{1}H NMR (Me_2SO-d_6) δ 2.05 (s, 3, CH_3-C(6)), 2.60 (t, J = 2.4 Hz, 1, $CH_2C{\equiv}CH$), 3.10 (d, J = 2.4 Hz, 2, $CH_2C{\equiv}CH$), 10.62 (s, 1, NH), 10.97 (s, 2, NH); ^{13}C NMR (Me_2SO-d_6) δ 13.22, 16.14, 70.17, 82.01, 104.74, 149.79, 150.76, and 163.63. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.28; H, 5.05; N, 17.05.

2,4-Dichloro-6-methyl-5-(2-propynyl)pyrimidine (9). The dioxopyrimidine 8 (12.07 g, 74 mmol) was stirred into a solution of 100 mL of $POCl_3$ and 0.5 mL of DMF. The mixture was refluxed for 5 h and turned dark black by this time. All excess $POCl_3$ was distilled off, and the thick, black tar was dissolved in ether and poured into 100 mL of ice water. Next, the mixture was separated, the aqueous layer was extracted with ether (2 × 200 mL), and the organic phases were combined, extracted with brine (100 mL), and dried over anhydrous Na_2SO_4. The ether was removed, and the black tar was dissolved in hot *n*-hexane and rinsed over a small column of silica gel (220–400 mesh) to remove color and polar impurities. The eluant was concentrated, and cooling yielded 12.38 g (84%) of broad, white plates which melted from 71.5 to 72.5 °C: ^{1}H NMR ($CDCl_3$) δ 2.11 (t, J = 2.7 Hz, 1, $CH_2C{\equiv}CH$), 2.74 (s, 3, CH_3-C(6)), 3.72 (d, J = 2.7 Hz, 2, $CH_2C{\equiv}CH$); ^{13}C NMR ($CDCl_3$) δ 18.74, 22.49, 75.69, 77.25, 125.90, 157.84, 161.35, 170.66. GC–MS: The gas chromatogram was run on a 6-ft OV-17 column with temperature programming from 150 to 250 °C at 16 °C/min. One peak was observed with a retention time of 5.2 min. MS: m/e 204.1 (M + 4, 11.5), 202.2 (M + 2, 64.5), 200.2 (M^+, 100), 165.1 (M - Cl). Anal. Calcd for $C_8H_6N_2Cl_2$: C, 47.49; H, 3.01; N, 13.93; Cl, 35.27. Found: C, 47.61; H, 3.00; N, 13.97; Cl, 34.96.

2,4-Dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine (10). The 2,4-dichloropyrimidine 9 (3.70 g, 18 mmol) was dissolved in a solution of $B_{10}H_{14}$ (2.51 g, 21 mmol), dry CH_3CN (2.0 mL), and 150 mL of dry toluene, and the reaction was gently refluxed for 20 h at which time TLC (20% ether–petroleum ether) showed no more starting material. The reaction was cooled and rinsed over a small column of silica gel (220–400 mesh) to remove polar, colored impurities. The eluant was concentrated and redissolved in a minimum of hot *n*-hexane by dripping in ethyl acetate until all oil had dispersed. Cooling gave light yellow needles which were recrystallized from the same solvent system to yield 4.28 g (74.5%) of white, threadlike needles which melted from 152 to 154 °C: ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3, CH_3-C(6)), 3.74 (bm, 3, $C_2B_{10}H_{11}CH_2$-C(5) and H-C(2) of carborane). The peak at 3.74 δ had a slightly downfield shoulder which was attributed to the proton on the 2-carbon of the *o*-carborane ring system: ^{13}C NMR ($CDCl_3$) δ 23.47, 36.14, 61.11, 71.69, 125.42, 159.06, 163.11, and 171.98. GC–MS: The gas chromatogram was run on a 6-ft OV-17 column with temperature programming from 200 to 260 °C at 16 °C/min. One broad peak was observed at 11.8 min. MS: $B_{10}C_8H_{16}Cl_2N_2$ m/e 318.3 (M^+), 283.3 (318.3 = Cl), 175.1 (318.3 - $C_2B_{10}H_{11}$). Anal. Calcd for $B_{10}C_8H_{16}Cl_2N_2$: C, 30.10; H, 5.06; N, 8.78; Cl, 22.21; B, 33.86. Found: C, 29.85; H, 5.08; N, 8.61; Cl, 22.43; B, 33.64. IR (KBr, cm^{-1}) 3060 m (C–H stretch of *o*-carborane), 2610 vs (B–H).

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Three Synthetic Routes to a Sterically Hindered Tetrazole. A New One-Step Mild Conversion of an Amide into a Tetrazole

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5-[4′-Methyl-1,1′-biphenyl-2-yl]-1*H*-tetrazole (6), which contains a sterically hindered *o*-tetrazole group, was synthesized by three different routes, one of them employing a new tetrazole synthesis. The first involved the reaction of trialkyltin azides with 4′-methyl-1,1′-biphenyl-2-carbonitrile (3). The resultant trimethyltin–tetrazole adduct could be hydrolyzed with acid to yield biphenylyltetrazole 6. The tri-*n*-butyltin–tetrazole adduct, however, was transformed into the corresponding *N*-trityl-protected tetrazole 5 to permit removal of the organic soluble tri-*n*-butyltin byproducts. The trityl group also permits 5 to be brominated at the benzylic position and then alkylated by imidazole derivatives. Subsequent acid hydrolysis of the trityl protecting group of 5 yielded biphenylyltetrazole 6. The second synthesis involved the nitrosation of an *N*-(2-cyanoethyl)-protected biphenylamidrazone 10 using N_2O_4 (g) to yield *N*-(2-cyanoethyl)-protected tetrazole 12. Aqueous base removes the cyanoethyl protecting group to yield biphenylyltetrazole 6. The third method involves the novel transformation of an *N*-(2-cyanoethyl)-substituted amide into the corresponding *N*-(2-cyanoethyl)-protected tetrazole *in one step* using triphenylphosphine, diethyl azodicarboxylate (DEAD), and azidotrimethylsilane. Subsequent base hydrolysis of the cyanoethyl group yielded 6 as before. Examples are also provided of the application of this new reaction to other *N*-(2-cyanoethyl)-protected carboxamides.

DuP 753 (1) is the first nonpeptide angiotensin II receptor antagonist currently in clinical trials for the treatment of hypertension.[2] This molecule is one example of an increasing number of drugs containing a tetrazole

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