DOI: 10.1002/cssc.201100649

Synthesis of Functional Acetylene Derivatives from Calcium Carbide

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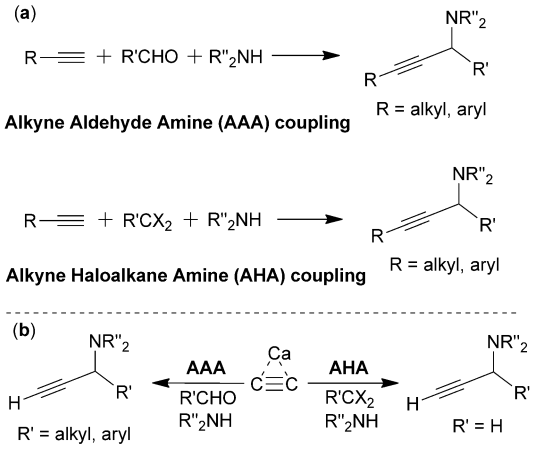
In the 1950s and 1960s, a large portion of the calcium carbide produced worldwide was transformed in industry into millions of tonnes of acetylene. Between 1960 and 1970, when the worldwide production of calcium carbide-acetylene peaked, it served as the primary feedstock for a wide variety of commodity and specialty chemicals. Since then, advances in petroleum and olefins technology have reduced and limited the importance of acetylene. However, the diminishing reserves of hydrocarbons following one century of heavy industrial petroleum use have become a major concern for future decades.[1] Hence, calcium carbide-acetylene is re-emerging as a viable feedstock for the chemical industry.

Calcium carbide is traditionally synthesized from coal. Recently, it has been demonstrated that calcium carbide can also be synthesized from lignocellulosic biomass.[2,3] The low production costs[4] of this new method have put calcium carbide in a better position to serve as a sustainable resource for the chemical industry. Due to the variety of addition reactions that the triple bond can undergo and the fact that the weakly acidic hydrogen atom of acetylene derivatives has been extensively used in organic synthesis,[5–8] it is important to develop efficient protocols for the synthesis of various functional acetylene derivatives directly from calcium carbide. This would offer the chemical industry and organic synthesis platform chemicals from a sustainable feedstock. Furthermore, the use of calcium carbide in organic synthesis is more cost-efficient and safer than the use of acetylene gas. However, its low solubility in almost all solvents and the difficulty in controlling mono-substitution reactions are major challenges in the direct synthesis of functionalized acetylene derivatives from CaC_2.[9]

Herein, we disclose efficient catalytic protocols for the synthesis of various functional acetylene derivatives from calcium carbide. The newly developed synthetic protocols are extremely useful in organic synthesis and may promote the use of calcium carbide as an alternative to petroleum.

Carbon–carbon bond formation using alkynes as a nucleophilic carbon source is a very useful method in synthetic chemistry.[10–14] However, most of the alkynes reported to be involved in nucleophilic attack are substituted terminal alkynes, not acetylene or calcium carbide. For example, the well-documented, three-component aldehyde, alkyne, and amine (AAA) coupling[15–20] is an elegant method for the synthesis and preparation of propargylamines, which are frequently used as skeletons and synthetically versatile key intermediates for nitrogen-containing biologically active compounds.[22–24] Usually, terminal alkynes are employed as nucleophilic carbon source, via C–H activation. More recently a metal-catalyzed three-component coupling of alkynes, haloalkanes, and amines (AHA) to afford propargylamines was reported.[25–27] However, the substrates used in these two reactions are limited to substituted terminal alkynes and as a result, the reactions produce internal alkynes. Although these internal alkynes, with different functional groups, are certainly important to many organic reactions, their internal structure limits many further important applications of functionalized alkynes. Hence the development of new catalytic systems for the production of mono-substituted propargylamines with a terminal alkyne function directly from calcium carbide via AAA or AHA three-component coupling reaction pathways is highly desirable. By controlling the reaction conditions, we successfully realized such mono-substituted propargylamines in high yields under mild conditions, providing a great opportunity for the application of calcium carbide in organic synthesis and the development of a versatile aminopropyne product chemistry (Scheme 1).



Scheme 1. a) Traditional AAA and AHA coupling reactions, and b) AAA and AHA coupling reactions with calcium carbide.

Currently, the most useful methods for the synthesis of aminopropynes include the use of the very sensitive Grignard reagent HCCMgBr[28] and metal-catalyzed propargylic substitution reactions with propargylic acetates, propargylic alcohols, and propargylic halides.[29–34] Here, we modified the AAA and AHA reaction conditions and achieved versatile, simple, and direct synthetic protocols for aminopropynes with calcium carbide as alkyne feedstock. Initial tests for the AHA reaction with calcium carbide were carried out under the following conditions: calcium carbide (1.0 mmol), dichloromethane (1.5 mmol),

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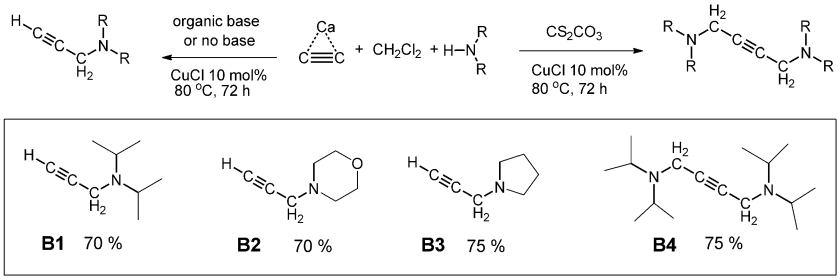
Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201100649.

and diisopropylamine (1.5 mmol) were mixed with CuCl (10 mol%) as catalyst at 80 °C in CH_3CN. This afforded the mono-substituted acetylene product diisopropylaminopropyne (**B1**) in good yield (70%; Scheme 2; see Supporting Information, Table S1, entry 1). Inspired by this result, reaction conditions were further optimized (Table S1). Notably, organic bases such as triethylamine (TEA) or N-ethyl-*N*-isopropylpropan-2-amine (DIEA) also delivered the mono-substituted aminopropyne product in reasonably good yield (Scheme 2). Generally, acyclic aliphatic (**B1**), heterocyclic (**B2**), and cyclic (**B3**) secondary amines gave good product yields (Scheme 2). However, under the same conditions reactions with inorganic base, (i.e., K_2CO_3 or Cs_2CO_3) produced the corresponding symmetric *bis*-substituted propargylic amines with an internal alkyne structure (**B4**) in yields of 70% and 75% respectively (Scheme 2; Table S1, entries 9 and 10,). The reactions generally took a long time probably due to the poor solubility of calcium carbide in the reaction system.[9]



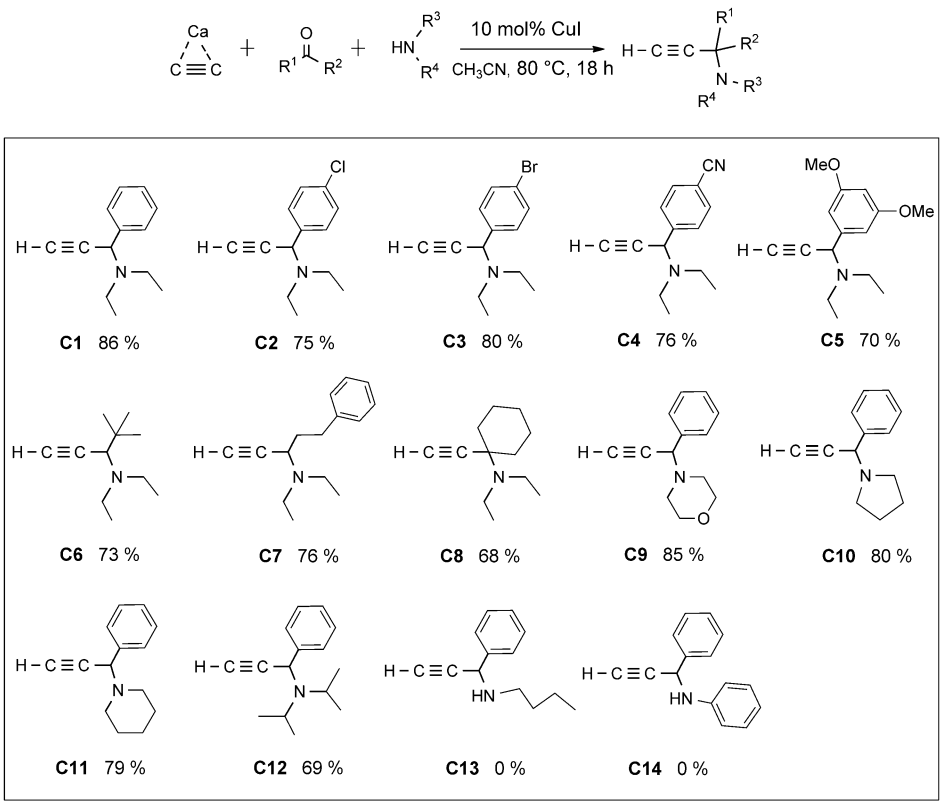
Scheme 2. AHA coupling with calcium carbide.

Following the successful synthesis of mono-substituted aminopropynes from calcium carbide via AHA coupling, the (more versatile) three-component AAA coupling with calcium carbide as the alkyne source was attempted. To our delight, with the initial conditions of calcium carbide (1.2 mmol), benzaldehyde (1.0 mmol), diisopropylamine (1.5 mmol), and CuCl (10 mol%) at 80 °C in CH_3CN, a moderate yield of mono-substituted AAA product (*N*,*N*-diisopropyl-1-phenylprop-2-yn-1-amine) was obtained in 72 h (Table S2, entry 1). No *bis*-substituted product was observed. The optimum ratio of calcium carbide to aldehyde to and amine was found to be 1.2:1.0:1.5. Among the copper catalysts screened, CuCl, CuBr, $Cu(OAc)_2$, $Cu(acac)_2$, and $CuCl_2$ gave moderate to low conversions, while CuI gave the best isolated yield of 72% (Table S2, entries 1–6). No reaction took place at room temperature and higher reaction temperatures did not improve the product yield. Interestingly, no *bis*-substituted propargylic amine product was observed even with inorganic base present in the reaction system. Similar to the AHA reaction protocol, the AAA-type coupling reaction involving calcium carbide also required a long time (72 h) to reach high yields, again due to poor solubility in the reaction system. However, the reaction time could be drastically shortened (to 18 h) while retaining a similar yield when using undried acetonitrile (containing 0.02 vol% of water) was used (Table S2, entry 14). The trace amount of water (2 mol% of substrates) may help to break down the calcium carbide's polymeric structure, thereby promoting the reaction. Further reactions were carried out in undried solvent. Due to the greater structural variety, further studies were focused on AAA-type coupling reactions with calcium carbide.

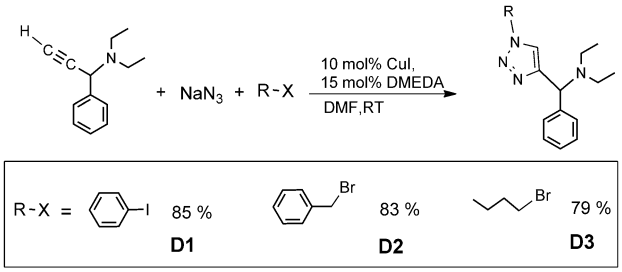
The substrate scope for the AAA-type coupling reaction was then investigated by using the optimized conditions: calcium carbide (1.2 mmol), aldehyde or ketone (1.0 mmol), amine (1.5 mmol) and CuI (10 mol%) in CH_3CN at 80 °C (Scheme 3). Aromatic aldehydes, either with electron-donating or electron-withdrawing groups, smoothly underwent AAA-type coupling with calcium carbide to give the corresponding mono-substituted aminopropynes in good yields (Scheme 3, **C1**–**5**). The catalytic system was not sensitive to various functional groups, such as –CN, –Cl, –Br, or –OR. In addition, aliphatic aldehydes (**C6**–**7**) or ketone (**C8**, with longer reaction times) also gave the corresponding aminopropynes in good yields. When varying the amine substrates, it was found that cyclic, heterocyclic, and acyclic aliphatic secondary amines gave very good yields of products under the standard reaction conditions (**C9**–**12**). However, no reaction was observed for primary amines (**C13**–**14**). This may due to the lower activity of imine intermediates for primary amines compared to iminium intermediates for secondary amines.

The mono-substituted acetylene products synthesized from AAA- and AHA-type three-component coupling reactions with calcium carbide could have various applications in organic synthesis.[35–36] Herein, several reactions were realized to demonstrate the versatility of mono-substituted acetylene aminopropynes in synthesis and to show the untapped potential of calcium carbide in synthesis and the chemical industry.

The copper-catalyzed alkyne–azide cycloaddition ("click") reaction is well-known and widely used in different fields.[37–38] Here, a multiple-component reaction using the aminopropyne that was synthesized from calcium carbide AAA-type coupling reaction, sodium azide, and aryl/alkyl halide to afford 1,2,3-triazole was demonstrated. A mixture of *N*,*N*-diethyl-1-phenylprop-2-yn-1-amine, sodium azide, iodobenzene, CuI (10 mol%), and *N*,*N*-dimethylethylenediamine (15 mol%) were mixed in DMF. The functionalized triazole product, *N*-ethyl-*N*-(phenyl(1-phenyl-1H-1,2,3-triazol-4-yl)methyl) ethanamine **D1**, was obtained in 85% isolated yield. Interestingly, the click reaction did not proceed with phenylazide and the aminopropyne using the same catalytic system. Other than iodobenzene, benzylic bromide (**D2**) and alkyl bromide (**D3**) also gave good triazole yields (Scheme 4). The use of sodium azide and aryl/alkyl halide instead of aryl/alkyl azide not only provides an easily accessible and versatile substrate scope, but also a safer procedure for the click reaction.

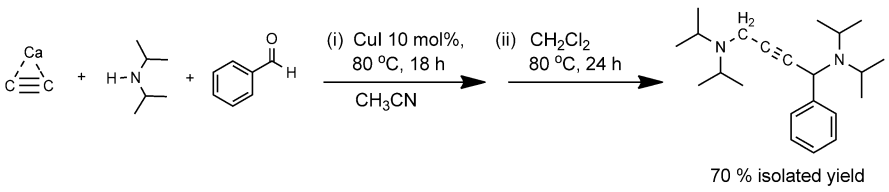


Scheme 3. AAA coupling reactions with calcium carbide.

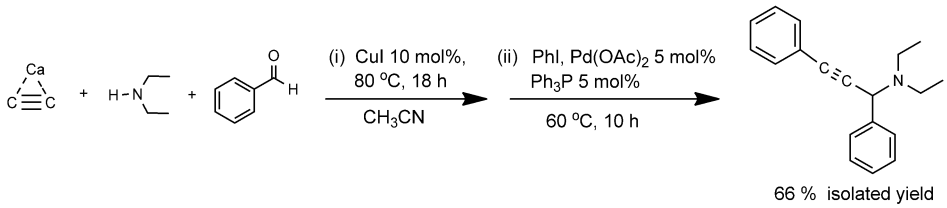


Scheme 4. Three-component coupling cyclization reactions.

The aminopropynes synthesized through AAA coupling could also further undergo AHA-type coupling to form asymmetric *bis*-substituted propargylic amines. Interestingly, this two-step reaction could be conducted in one pot as a sequential AAA–AHA reaction (Scheme 5). For example, an asymmetric *bis*-substituted product, N^1,N^1,N^4,N^4-tetraisopropyl-1-phenylbut-2-yne-1,4-diamine, was obtained in 70% overall isolated yield (Scheme 5). It should be noted that a reversed sequential AHA–AAA reaction did not occur.



Scheme 5. One-pot AAA–AHA coupling reaction.



Scheme 6. One-pot AAA–Sonogashira coupling reaction.

The Sonagashira reaction is among the most useful and important coupling reactions in organic synthesis.[39–40] The Sonogashira reaction of calcium carbide and iodobenzene has been reported, producing *bis*-substituted diphenylacetylene.[9] Herein, a sequential AAA-Sonagashira coupling reaction was successfully developed. As shown in Scheme 6, *N*,*N*-diethyl-1,3-diphenylprop-2-yn-1-amine was obtained in 66% overall isolated yield. The reaction described here provides an efficient, simple, and fast method to construct complex alkynyl compounds from calcium carbide.

In conclusion, a novel catalytic system for the production of propargylamines from calcium carbide via AAA or AHA three-component coupling reaction pathways is described. Monosubstituted aminopropyne products with a terminal alkyne function can be produced in high yields, under mild conditions. Furthermore, a series of novel synthesis protocols were demonstrated based on calcium carbide and aminopropyne. A click reaction between aminopropyne and azide, a one pot sequential AAA–AHA coupling, and a AAA–Sonogashira coupling reaction with calcium carbide demonstrate the versatile applications of this novel methodology in organic synthesis. Calcium carbide directly undergoes different types of reactions and complex structures are formed using provides versatile and fast synthetic protocols. The direct usage of calcium carbide

also avoids many protection and de-protection steps that greatly reduce the number of synthetic steps, resulting in more efficient and greener organic synthesis. The new synthetic methods presented here demonstrate that calcium carbide could play a major role as a sustainable and cost efficient carbon source in modern organic synthesis.

Experimental Section

All solvents were purchased from Aldrich or Fluka. All starting materials were commercially available and used as-received unless indicated otherwise. Calcium carbide was purchased from Aldrich (purity 80%). Reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel coated glass plates (60F-254) with UV light. Chemical yields refer to pure, isolated substances. Gas chromatography–mass spectrometry (GC–MS) was performed with Shimadzu GC-2010 instrument coupled to a GCMS–QP2010. ^{1}H and ^{13}C NMR spectra were obtained by using a Bruker AV-400 (400 MHz) spectrometer. In the Supporting Information, chemical shifts are reported in ppm relative to tetramethylsilane, with the solvent resonance as internal standard. Data are reported in the following order: chemical shift (δ, in ppm), multiplicity [indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), m_c (centered multiplet)]; coupling constants (J, in Hz); integration; assignment.

General Procedure for AAA coupling: A mixture of calcium carbide (1.2 mmol, 77 mg), benzaldehyde (1.0 mmol, 106 mg), diisopropylamine (1.5 mmol, 151.5 mg), and CuI catalyst (0.1 mmol, 20.0 mg) was added to a reaction tube (10 mL) with 2 mL CH_3CN. After stirring at 80 °C for 18 h, the mixture was diluted with H_2O (10 mL) and the aqueous layer was extracted with diethyl ether (2×10 mL), dried over Na_2SO_4, and concentrated under vacuum to give the crude product. This crude was further purified by column chromatography on silica gel (ethyl acetate/hexane 1:4) to afford the corresponding pure aminopropyne. All products gave satisfactory spectroscopic data.

Acknowledgements

This work was funded by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council), Agency for Science, Technology and Research, Singapore).

Keywords: amines · calcium · carbides · renewable resources · synthetic methods

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Received: October 18, 2011
Revised: November 24, 2011
Published online on February 29, 2012

