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The Use of Calcium Carbide as Acetylene Source in a Three-component Coupling with ω -chlorinated Ketones and Primary Amines

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Abstract: Calcium carbide was used in a Cu(I)-catalyzed three component coupling with ω -chlorinated ketones and primary amines to generate terminal 2-alkynyl-N-heterocycles. The formation of an imine and subsequent intramolecular substitution results in the active electrophilic iminium species, which can be alkynylated by in situ formed copper acetylide. A number of aliphatic primary (functionalized) amines and aliphatic or aromatic alkynes together with different alkyl or aryl substituted γ - or δ -chloroketones could be used. Simple acid-base work-up instead of column chromatography can be applied to obtain the resulting 2-alkynylpyrrolidines and – piperidines.

Introduction

Calcium carbide, classically the product of the reaction of lime and coke in an electric arc furnace, is produced on megaton scale annually.^[1] However, a recent report shows that calcium carbide can also be produced via reaction of lime and biorenewable fine biochars at lowered temperatures, rendering this process more energy-efficient and sustainable.^[2] Although mass-produced, reactions in organic synthesis involving calcium carbide, apart from simple protonation by water for the generation of acetylene gas, are scarce. It is only recently that the application of calcium carbide in organic synthesis became appreciated, proven by the rising number of scientific reports using calcium carbide in organic synthesis in the last decade.

The use of calcium carbide over acetylene has an important advantage; the handling of the solid calcium carbide is easier and safer than the handling of gaseous acetylene, which is inherently a thermodynamically unstable molecule.^[3] If stored properly, calcium carbide can be kept for longer periods and it only degrades slowly by protonation in humid air. Especially in a laboratory environment, the storage of calcium carbide is a safer alternative than storage of acetylene cylinders. For industrial applications, the use of pressurized acetylene has historically been regarded as safe, since it has been used for years.^[4] Although the use of high temperatures renders the synthesis of calcium carbide energy-intensive, calcium carbide is a cheap reagent.^[5] Furthermore, the synthesis of terminal alkynylated

substrates often uses TMS-protected acetylene,^[6] as this is an easy-to-handle liquid. However, installing the TMS-protecting group and deprotection afterwards result in the generation of additional waste, which is to be avoided by the principles of green chemistry.^[7] One important disadvantage of calcium carbide, and probably the main reason why it is difficult to use in organic reactions, is its poor solubility in organic solvents. Since calcium carbide is an ionic molecule, only polar solvents will (partly) dissolve calcium carbide, as can be seen in the literature overview (*vide infra* – Scheme 1). Most commonly used solvents include MeCN, DMSO and DMF. Although calcium carbide is assumed to be the reactive species, most of published methods use a certain amount of water, for the main purpose to help dissolve calcium carbide by breaking up its polymeric structure.^[8] However, water reacts quickly with calcium carbide to form acetylene, so that not the solution of calcium carbide but the production of acetylene is important.^[9] Interestingly, calcium carbide or rather its protonated product acetylene, can be used as either dipolarophile, electrophile or nucleophile, underlining its diversity as reagent in organic synthesis. As a dipolarophile it can be used in Huisgen [3+2] cycloadditions with azides,^[10] or with 1,3-dipolar tosylhydrazones.^[11] As an electrophile, calcium carbide is coupled to ketoximes to form pyrroles in a Trofimov-like reaction.^[12] The presence of small amounts of *N*-vinylpyrrole led to further investigation of vinylation reactions on indoles and phenols,^[13] alcohols,^[14] sugars,^[15] epoxides^[16] and thiols.^[17] As a nucleophile, calcium carbide can be involved in Sonogashira cross-coupling reactions to form either internal alkynes via double cross coupling or intermediate terminal alkynes, although it is hard to control single coupling.^[18] Moreover, calcium carbide can react with various carbonyl moieties such as aldehydes/ketones or imines generating acetylenic alcohols,^[19] propargylamines,^[8, 20] enamines^[21] or (iso)quinolines^[22] by making use of its nucleophilic properties.^[23] Application of the above mentioned methods in laboratory scale organic synthesis experiments for the synthesis of internal alkynes,^[24] vinyl thioethers,^[25] or propargylamines^[26], next to the generation of acetylene on lab scale^[27] underline the usability of calcium carbide. However, for industrial applications acetylene will probably remain more favoured over calcium carbide, because industry is better adapted to working with gaseous reagents.

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Scheme 1 Overview of reactions with calcium carbide acting as an electrophile, dipolarophile or nucleophile.

Results and Discussion

In recent research, we investigated the three-component coupling of ω -chlorinated ketones, primary amines and terminal alkynes.^[28] To obtain terminal propargylamines, we envisioned to replace terminal alkynes by calcium carbide. For the optimization of the coupling of 6-chlorohexan-2-one (**1a**), *n*-propylamine (**2a**), and calcium carbide (**3**), first a Cu(I) catalyst in MeCN was tested. Cu(I) catalyst was used successfully under similar reaction conditions for the coupling of ω -chloroketones, primary amines and terminal alkynes. It was important to use 2.5

equiv of amine **2a** in order to obtain complete conversion to product **4aa**, this can be rationalized as the amine also acts as a base to trap the formed HCl from the reaction mixture and to neutralize HI formed during the CuI mediated deprotonation of acetylene.

Table 1 Optimization of the reaction conditions

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), **3** (2.0 mmol), catalyst

Entry ^[a]	Catalyst	Solvent	Yield 4aa (%) ^[b]
1[c]	Cu ₂ O	MeCN	65
2	Fe(OTf) ₂	MeCN	0
3	AuPPh ₃ Cl	MeCN	22
4	AgOTf	MeCN	88
5	CuI	MeCN	99
6	CuI	DMSO	36
7	CuI	MeOH	64
8	CuI	DCM	63
9	CuI	Toluene	80
10	CuI	Dimethyl carbonate	76

(20 mol%), H₂O (0.5 mmol), solvent (2 mL), 60 °C, 24 h. H₂O (1.0 mmol) added after two hours. [b] NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] 10 mol% used.

Firstly, a number of transition-metal catalysts were screened for the formation of 2-ethynyl-2-methyl-1-propylpiperidine **4aa** (Table 1). In all cases **4aa** was the sole reaction product, as no bis-substituted propargylic amine, containing an internal alkyne moiety, was observed. Cu₂O gave a decent yield of 65% (Table 1 - entry 1), while other transition metals such as Fe(II) (Table 1 - entry 2), Fe(III), Sc(III), In(III), Zn(II) or Mg(II) were not able to catalyse this transformation (see SI Table S1 entries 3-9 for complete screening table). Other coinage metal salts such as AuPPh₃Cl (22%) or AgOTf (88%) were able to catalyse the reaction (Table 1 - entries 3&4), although copper, the cheapest of the three coinage metals, would be the catalyst of choice. Cu(II) salts gave a lower yield (41% - Table S1 entry 13) than Cu(I) salts (90-99% - Table S1 entries 12, 14-15) with CuI being the best (20 mol% - 99% - Table 1 entry 5), while lower catalyst loadings (10 and 5 mol% - Table S1 entries 16-17) resulted in a lowered yield, therefore 20 mol% of CuI was chosen as optimal catalytic system. Although a screening yield of 99% was obtained, we investigated the use of other solvents, since this is also a critical parameter for the solubility of calcium carbide and

greenness of the reaction.^[29] To our surprise, all of the screened solvents (see SI Table S2) gave the product **4aa**; even less polar solvents such as DCM or toluene (Table 1 - entries 8&9) were still able to catalyse this transformation in good yields. Since calcium carbide is only slightly soluble in polar solvents, it is virtually insoluble in apolar solvents, pointing towards a different reacting species other than calcium carbide. On the other hand, the solubility of acetylene is not considered problematic, since it readily dissolves in most organic solvents,^[30] and probably immediately reacts to form copper acetylide (Cu_2C_2).^[31] For safety reasons the neat reaction was not evaluated, since the presumed intermediate copper acetylide (Cu_2C_2) is highly explosive in dry form.^[32] When this species is formed in a small amount *in situ* in solution, the safety risks are reduced to a minimum. The addition of water was important, and addition of one equivalent of water at the beginning of the reaction combined with addition of another two equivalents of water after two hours gave the best result. Together with the one equivalent of water that is formed from the reaction of the ketone with the amine, 4 equivalents of water are formed, which could form 2 equivalents of acetylene together with two equivalents $\text{Ca}(\text{OH})_2$. After optimization of the reaction conditions, the scope of the reaction was evaluated by using different primary amines and ω -chlorinated ketones (Scheme 2). The reaction of 6-chlorohexan-2-one (**1a**), *n*-propylamine (**2a**) and calcium carbide (**3**) in acetonitrile for 24 hours at 60 °C gave product **4aa** in 95% yield after simple acid-base work-up, thereby avoiding the use of column chromatography. The use of the more sterically hindered *iso*-propylamine resulted in a slightly diminished yield of 86% of product **4ab**. Other amine substituents such as allyl and benzyl gave yields of 80% and 77% respectively. For high boiling amines, such as benzylamine or the chiral (*S*)-(-)-1-phenylethylamine, only one equivalent was used together with 1.5 equivalents of triethylamine as base with a low boiling point for easy removal by evaporation after work up. The use of chiral (*S*)-(-)-1-phenylethylamine resulted in the formation of a 4/1 diastereomeric mixture of **4ae** in 64% yield. The use of tertiary substituents on the primary amine such as *tert*-butyl, dimethylpropynyl or adamantyl did not lead to intended products **4af**, **4ag**, **4ah** but gave δ -aminoketones **4af'**, **4ag'**, **4ah'** in low yields. From previous work,^[28] we know that steric hindrance around the reacting electrophilic iminium species complicates the addition of nucleophilic species. Therefore, the reaction temperature was increased to 90 °C, but even then no products **4af**, **4ag**, **4ah** were obtained. Using δ -chlorovalerophenone as ketone did not result in the formation of intended products **4ai** or **4aj** either. In the case of reaction of δ -chlorovalerophenone with *n*-benzylamine, cyclic enamine **4ai''** was obtained, while combination with *n*-propylamine resulted in a mixture of δ -aminoketone **4aj'** and cyclic enamine **4aj''**. Since both cyclic enamines are formed, tautomerization to the cyclic iminium should be possible, but might be less favoured, since the enamine structure is stabilized by conjugation with the phenyl group. Again, repetition of the reaction at higher reaction temperatures (90 °C, or 130 °C in DMSO instead of acetonitrile) gave a similar outcome and no intended products **4ai** or **4aj** were obtained. Phenethylamine as coupling partner gave a high

yield of 96% of product **4ak**, while also an alcohol functionalized amine could be used to form product **4al** in 79% yield. The α -aminoester derived from glycine, gave a low yield of 26% of the intended product **4am**, while no other products were obtained after filtration over a plug of silica, in order to avoid aqueous workup. Since we were convinced that the problem lies in the hydrolytic stability of the α -aminoester in the presence of copper salts,^[33] where also $\text{Ca}(\text{OH})_2$ is formed, we investigated the reaction in an H-tube, a two-chamber glass system, previously used for the formation of acetylene is a separate but connected chamber.^[34] When the reaction was conducted in the H-tube, the isolated yield of **4am** rose to 42% with a similar workup (Figure 1). However, HPLC analysis of the crude reaction mixture confirmed ester hydrolysis. This improvement could be explained by the absence of basic Ca-salts (CaC_2 or $\text{Ca}(\text{OH})_2$) that could cause saponification of the ester function.

Figure 1 H-tube schematic overview (left), after the reaction (right).

Next to the formation of piperidines via 6-chlorohexan-2-one as ketone equivalent, also pyrrolidines can be formed via 5-chloropentan-2-one as ketone equivalent. Product **4ba** was formed in 90% yield, due to its volatility the product is isolated as its hydrochloric acid salt **4ba'**. Reaction of 5-chloropentan-2-one with benzylamine gave a similar yield of 71%, while reaction with chiral (*S*)-(-)-1-phenylethylamine only gave a sluggish 31% yield, and here a diastereomeric mixture (75/25) was formed. Again, tertiary substituted amines did not give the intended products **4bf** or **4bg**, but no γ -aminoketones were observed in this case, as they are not stable.

When the more sterically hindered γ -chlorobutyrophenone was used, product **4bj** was formed in 49% yield. The reason why 2-phenylpyrrolidine **4bj** is formed and 2-phenylpiperidine **4aj** not, might be explained by the increased ring strain of dihydropyrroles compared to tetrahydropyridines, rendering the first to be more reactive than the latter. Various substituted γ -chlorobutyrophenones could be used to obtain different pyrrolidines **4bac**, **4bad**, **4bae** and **4baf**, albeit in low yields.

Scheme 2 Scope of the reaction.

Examples of amines, bearing pyridinyl moieties, could also be used and gave pyrrolidines **4bz** and **4baa** in 35% and 37% respectively. Different substituted benzylamines could also be used to generate pyrrolidines **4bv**, **4bw** and **4bx** in good yields.

Product **4bx** was also prepared on gram scale with a comparable yield, proving the scalability of this reaction. Interestingly, pyrrolidine **4bag**, an intermediate of a poly ADP Ribose Polymerase (PARP) inhibitor, previously prepared in a three-step synthesis,^[6a] could be prepared in one step via this synthesis, albeit in a low 21% yield. Overall, yields of pyrrolidines **4b** are lower than yields of piperidines **4a**, which can be explained by side reaction of γ -chloroketone (see Scheme 3 and SI – Table S3). α -Deprotonation of γ -chloroketone due to

the presence of basic calcium salts such as calcium carbide or hydroxide, followed by substitution of the chlorine atom leads to methyl cyclopropyl ketone as side product. Only cyclopropanation occurs, since no cyclopentanone (via α -deprotonation on the other side of the carbonyl moiety) is formed in the case of 5-chloropentan-2-one. For piperidines **4a**, no side products containing cyclobutyl or cyclohexane rings, formed in a similar way via α -deprotonation, were observed.

Scheme 3 Side reaction via α -deprotonation of γ -chloroketones.

To show the possibilities of the terminal alkyne, product **4bj** was synthesized and in one pot sequential KA²-Sonogashira cross-coupling reacted with Pd(OAc)₂, triphenylphosphine and iodobenzene to obtain the substituted alkyne **4bah** (Scheme 4).

Scheme 4 One-pot sequential three-component coupling with calcium carbide, and Sonogashira cross-coupling.

From a mechanistic point of view, firstly calcium carbide is thought to be protonated to form acetylene (Scheme 5). This assumption is underlined by the fact that the reaction can be conducted in an H-tube, where acetylene is formed in a separate vessel. Also, many different (apolar) solvents can be used for this coupling, proving that the solubility of calcium carbide is of no importance. Furthermore, during the reaction a bright red colour appeared, which could indicate the presence of Cu₂C₂, a species that is known to form under similar reaction conditions.^[35] Then, ω -chlorinated ketone **1** and primary amine **2** react to form ketimine **5**, thereby releasing a molecule of water, which is directly consumed to protonate the calcium carbide. Hence, the role of calcium carbide in this is double; in the first

place it forms the reagent acetylene, but it also acts as a drying agent, thereby promoting the formation of ketimine **5**. Ketimine **5** then undergoes an intramolecular substitution reaction forming ketiminium species **6**. Addition of Cu₂C₂ to this species and protonation leads to the formation of terminal propargylamine **4**, and regeneration of the catalyst. Ketiminium **6** is in tautomeric equilibrium with enamine **7**, and depending on the stability of enamine **7** this tautomer can become a resting state for the reaction. Especially when the R group of the ketone is an aryl group, extra stabilization by conjugation, pushes the equilibrium towards enamine **7**. The only by-products of this transformation are HCl and Ca(OH)₂ (slaked lime) and slaked lime can be recovered and re-used in the sustainable production of calcium carbide from biochars.^[2]

Scheme 5 Proposed reaction mechanism.

Conclusions

In summary, we developed an eco-friendly three-component coupling of commercially available ω -chloroketones, primary amines and calcium carbide, which has a dual role of drying agent and production of acetylene. The reaction can be catalysed by a number of Cu(I) salts, while also Ag(I) or Au(I) salts are able to catalyse this transformation, albeit in lower yields. Since many solvents give high yields of the intended products, the solvent of choice can be chosen depending on the application. A number of primary amines were evaluated, with primary or secondary substituted amines the reaction works well, but for tertiary substituents no reaction products **4** could be obtained. This transformation allows for the synthesis of 2-alkynylpiperidines **4aa-m** and -pyrrolidines **4ba-ag**, which could serve as viable intermediates, in good yields.

Experimental Section

General information

All reactions were carried out in oven dried 10 mL microwave vials. Other glassware (roundbottomed flasks) can be used but must be sealed tightly as gaseous products arise. All ketones and amines were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa-Aesar, Fluorochem, TCI and J&K). Calcium carbide was obtained from Sigma-Aldrich in granulated form (pieces) and technical quality ($\geq 75\%$ gas-volumetric). Calcium carbide is further ground in a mortar with a pestle until a fine powder is obtained and used immediately. ^1H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Bruker Avance III HD spectrometer using CDCl_3 as solvent and TMS as the internal standard. Assignments were determined using 2D (HSQC, HMBC and DEPT or APT) spectra. Chemical shifts are given in parts per million (ppm), J -values are given in hertz (Hz), and number of protons for each signal are also indicated. For high resolution mass spectrometric analysis (HRMS), samples were dissolved in methanol/water (1/1), containing 0.1% formic acid and diluted to a concentration of approximately 10–6 mol/L. 10 μL of this solution was injected using a CapLC system (Waters) and electrosprayed using a standard electrospray source, positive ion mode accurate mass spectra were acquired using a Q-TOF II instrument (Waters). The parent ions $[\text{M}+\text{H}]^+$ are quoted.

General experimental procedure

In an oven-dried 10 mL microwave vessel were introduced CaC_2 (128 mg, 2 mmol), ω -chlorinated ketones (1) (0.5 mmol), primary amine (2) (1.25 mmol – in case of low boiling point) or primary amine (2) (0.5 mmol) and triethylamine (0.75 mmol) in case of high boiling point of primary amine, CuI (19.05 mg, 0.1 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol). The vessel was quickly capped and placed in a preheated oil bath at 60°C for 24 h. After 2 h, H_2O (18 mg, 1 mmol) was added. The reaction mixture turns red after a while, probably due to the formation of copper acetylide (Cu_2C_2). Afterwards, the reaction mixture was quenched by addition of 2 mL water and subjected to acid-base work-up; addition of MTBE (15 mL) and extraction of the organic phase phase with 3 M HCl solution (2 x 10 mL). The aqueous phase was then basified with 10 M NaOH, forming insoluble Ca^{2+} -salts and extracted with MTBE (2 x 15 mL). The organic phases were combined and dried over $\text{MgSO}_4 \cdot 3\text{H}_2\text{O}$, and concentrated in vacuo to yield propargylamines (4) as orange oils.

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Keywords: calcium carbide • alkynylation • ketones • amines • copper

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Layout 2:

FULL PAPER

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The Use of Calcium Carbide as
Acetylene Source in a Three-
component Coupling with α -
chlorinated Ketones and Primary
Amines

Calcium carbide can be used as an acetylene source, via *in situ* hydrolysis, and used in a three-component coupling with α -chlorinated ketones and primary amines, rendering terminal cyclic propargylamines.