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Calcium carbide: Highly potent solid reagent for the construction of heterocycles

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ABSTRACT

An analysis of the literature over the past 10 years shows that there is a trend towards simplification of the synthetic procedures, usage of readily available and unexpensive materials, and concern for the safety of the experimental chemist. The use of calcium carbide as a solid acetylene analogue fits this trend perfectly. By replacing gaseous acetylene with calcium carbide, a complex of problems associated with working with gases can be solved at once. Due to this, the chemistry of calcium carbide is rapidly developing, opening up new possibilities of acetylene chemistry. This review highlights recent advances in carbide chemistry demonstrating its advantages in the construction of heterocycles.

1. Introduction

Heterocyclic compounds undoubtedly constitute the largest and most diverse family of organic compounds. Heterocyclic cores are found in various natural products, biologically active molecules, and medicinally relevant compounds [1–6]. Heterocyclic compounds play a key role in drug discovery and development, and therefore the development of convenient and efficient methods for their synthesis is of tremendous interest. Chemists constantly propose more and more new synthetic approaches to various classes of heterocycles [7–14]. Therefore, simple and affordable building blocks for the construction of heterocyclic compounds are currently in great demand.

Acetylene is the smallest organic molecule containing triple carbon-carbon bond that is capable to enter in a wide variety of atom-economic cyclization reactions. Due to this, acetylene can be efficiently utilized as the simplest building block for the construction of a large number of various heterocyclic cores [15–18]. However, despite the fact that highly diverse and well developed chemistry of acetylene undoubtedly favors usage of this alkyne as a universal synthetic building block, application of gaseous acetylene in regular synthetic labs encounters a number of difficulties. Flammability and explosiveness, handling difficulties and requirements for specialized high-pressure equipment impose serious limitations on the use of acetylene in synthetic procedures.

In the last two decades, the use of calcium carbide in organic synthesis as a solid, safe and easy-to-handle acetylene surrogate has gained increasing popularity [19–21]. The replacement of gaseous acetylene with calcium carbide noticeably simplified many synthetic procedures, and also significantly expanded the scope of synthetic applications of the simplest alkyne. The carbide approach has demonstrated a wide versatility towards a great variety of acyclic and cyclic products including heterocyclic compounds [19]. Four-membered lactams, wide range of five-membered heterocycles including pyrrole and indole derivatives, pyrazoles, triazoles, imidazoles, isoxazoles and benzofurans and six-membered heterocycles such as pyridines, pyridazines, pyrazines, 1,2,4-triazines, isoquinoline and pyrimidine annelated derivatives have been synthesized using CaC_2 (Scheme 1a). It should be noted that, along with the design of various heterocyclic cores, the carbide approach provides an opportunity to introduce stable ^2H and ^{13}C labels into heterocyclic molecules. The use of CaC_2/D_2O or $Ca^{13}C_2/H_2O$ mixtures allows *in situ* generation of dideuteroacetylene [22–28] or $^{13}C_2$-acetylene [29,30], a versatile D_2-or $^{13}C_2$-labeled building blocks that are suitable for the construction of stable isotope labeled heterocyclic compounds (Scheme 1b).

In the current review, we will discuss in detail briefly mentioned here syntheses of heterocyclic compounds based on calcium carbide. Taking into account the multiple important applications of stable isotope labeling [31–39], D_2-and $^{13}C_2$-labeling of heterocyclic compounds by using carbide approach will also be discussed in a special section of this review.

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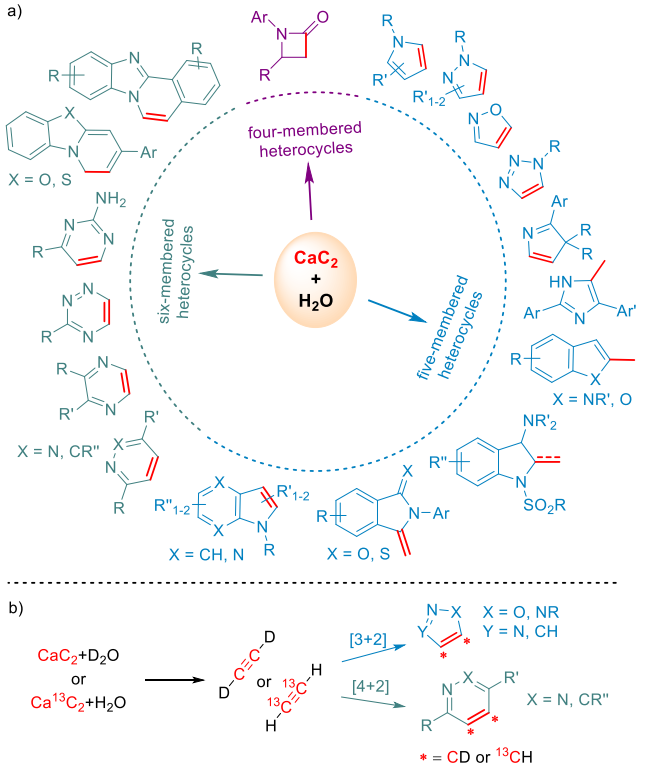


Scheme 1. Scope of heterocyclic products that are synthesized from calcium carbide (a) and D_2-and $^{13}C_2$-labeling of heterocyclic compounds by using carbide approach (b).

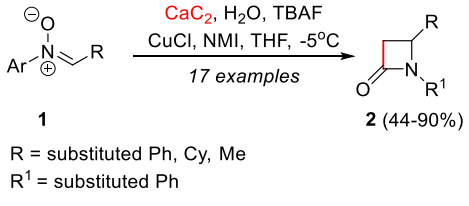
2. Small cycles construction

Calcium carbide was successfully used as a source of acetylene in Kinugasa reaction [40]. *In situ* generated acetylene reacts with nitrones **1** in the presence of copper (I) salts, tetrabutylammonium fluoride and *N*-methylimidazole, which leads to the formation of 1,4-disubstituted β-lactams **2** (Scheme 2). The unsubstituted 3rd position of the resulting cycle opens up perspectives for lactam bioconjugation and asymmetric modifications.

The proposed reaction mechanism is performed in Scheme 3 [40]. First, calcium ethynyl hydroxide is formed. Then it activates with TBAF turning to soluble complex **A**. This complex is transformed into copper acetylenide, which easily involves into cycloaddition with nitrone **1** leading to the formation of six-membered ring **B**. Intermediate **B** undergoes reductive elimination, followed by the ring opening of five-membered **C** into ketene **D**. Further intramolecular cyclization of ketene leads to enolate **E**, which turns into the product **2**.

3. The synthesis of five-membered nitrogen heterocycles

Among five-membered heterocycles which can be synthesized using calcium carbide as a solid acetylene analogue are performed the syntheses of pyrroles, pyrazoles, triazoles, indoles and isoindoles. In this



Scheme 2. Calcium carbide in the synthesis of β-lactams.

chapter we'd like to discuss new advances in carbide chemistry in this area moving from pyrroles, indole and isoindole derivatives to pyrazoles and triazoles.

The use of calcium carbide instead of gaseous acetylene in Trofimov reaction allowed to synthesize a number of 2-arylsubstituted pyrroles **4** in good yields using readily available ketoximes **3** (Scheme 4) [41]. Authors mentioned that trace amounts of *N*-vinylpyrroles **5** were observed in the reaction mixtures.

Kaewchangwat et al. proposed a three-step sequence for the synthesis of BODIPY, which is based on the construction of pyrrole **7** using Trofimov reaction (Scheme 5) [41]. On the first step, oxime **6** reacts with calcium carbide leading to **7**. Pyrrole **7** and 4-bromobenzaldehyde **8** produce indacene derivative **9**. The latter undergoes sequential oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and reacts with BF_3*Et_2O to form BODIPY derivative **10**.

Propan-2-yl/cyclohexane-1-yl aryl ketoximes **11** react with calcium carbide in the presence of inorganic bases with the formation of hydroxypyrrolines **12** and 3*H*-pyrroles **13** (Scheme 6) [42]. The reaction of **11** and CaC_2–H_2O mixture in the presence of sodium hydroxide yields products **12**, and with potassium hydroxide results in the formation of **13**.

A simple and convenient synthetic path to 1-sulfonyl-1*H*-indoles **15** by reactions of *N*-(2-iodoaryl)sulfonamides **14** with calcium carbide has been developed (Scheme 7) [43]. The special features of this methodology are the use of calcium carbide as a solid acetylene surrogate and the readily availability of the starting sulfonamide derivatives and a catalyst, $Pd_2(dba)_3$. Using the developed protocol, a wide scope of substrates was transformed to 1-sulfonyl-1*H*-indoles **15** in high yields.

An interesting method for the synthesis of 1,2,3-triarylindoles **18** through *one-pot* multicomponent procedure using calcium carbide, easily available iodoarenes **16**, and aromatic amines **17** as starting materials was described recently (Scheme 8) [44].

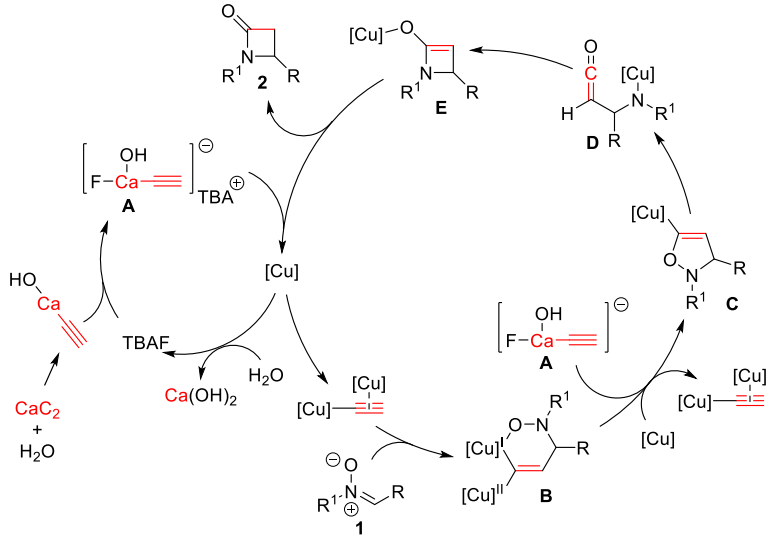
The proposed reaction mechanism for the formation of triarylindoles **18** can be described by a number of reactions (Scheme 9) [44]. First, calcium carbide reacts with water producing acetylene. The Sonogashira coupling between acetylene and aryl iodide **16** leads to arylacetylene, which reacts with **16** in the next Sonogashira reaction transforming to diarylacetylene. Meanwhile oxidative addition of aryl iodide **16** to palladium (II) produce arylpalladium iodide **A**. An interaction of **A** and diarylacetylene through migratory insertion lead to the palladium complex **B**, which lose a molecule of HI with the formation of a palladacycle **C**. A ligand (OAc) exchange of **C** with an amine **17** results in the formation of the complex **D**, which rearranges to **E**. The ellimination of AcOH accompanying the cyclization of **E** to aza-palladacycle complex **F** is followed by the final reductive elimination to yield 1,2,3-triarylindole and a Pd(0). Pd(0) can be oxidized by Cu(II) to produce Pd(II) entering the next catalytic cycle, and the resulting Cu(I) can be further converted to the required Cu(II) by aerobic oxidation.

N-(2-Iodoaryl)arylamides **19** react with calcium carbide in a similar manner producing *N*-aroyl-2-arylindoles **20** in up to 84 % yield (Scheme 10) [45]. The reactions proceed under Pd (II) catalysis, and allows to synthesize a diverse range of *N*-aroyl-2-arylindoles **20**.

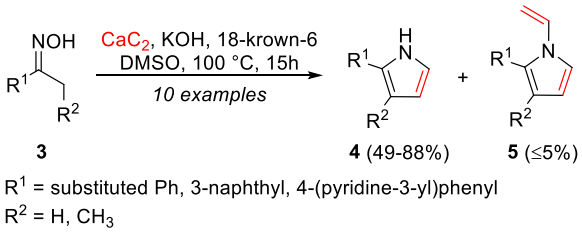
An interaction of *N*-alkyl(aryl)-3-chloroquinoxalin-2-amines **21**, calcium carbide and cyclic ketones **22** or 2-phenylpropanal **23** allowed to synthesize 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines **24** (Scheme 11) [46].

The reaction of calcium carbide, *N*-(2-formylphenyl)sulfonamides **25** and secondary amines **26** resulted in the formation of *N*-sulfonamide functionalized 2-methylene-3-aminoindolines **27** in good yields (Scheme 12, top) [47]. By adding cesium carbonate to the reaction mixture 2-methyl-3-amino-1*H*-indole derivatives **28** can be synthesized in 65–84 % yield (Scheme 12, middle line). Compounds **27** can be easily converted to indoles **28** in the presence of cesium carbonate in dimethylsulfoxide (Scheme 12, bottom) [47].

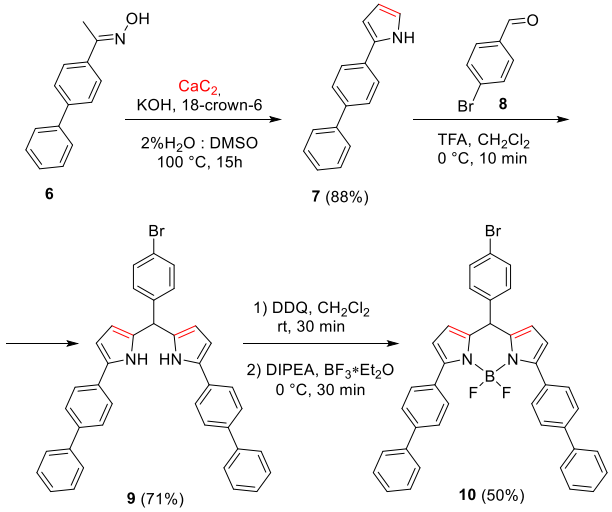
A tandem process including Sonogashira cross-coupling and nucleophilic addition between 2-bromo-*N*-arylbenzamides **29** and calcium



Scheme 3. The proposed reaction mechanism.



Scheme 4. Calcium carbide in Trofimov reaction.



Scheme 5. The synthesis of BODIPY using CaC_2.

carbide in the presence of copper (I) as a catalyst led to a variety of 3-methylene-2-arylisoindolin-1-ones **30** in 60–91 % yield (Scheme 13) [48].

In recent work copper (I) iodide – potassium *tert*-butoxide system was used in analogous reaction between **31** and calcium carbide [49]. Using the proposed procedure, a scope of the tandem process Sonogashira cross-coupling – nucleophilic addition was substantially extended and a range of 3-methylene-2-arylisoindolin-1-ones **32** was synthesized in 64–93 % yield (Scheme 14).

Replacing 2-bromo-*N*-arylbenzamides **31** to their thiobenzamide analogue **33**, 2-(2-bromophenyl)-3-methyleneisoindoline-1-thione **34** was synthesized in 68 % yield (Scheme 15) [49].

The use of calcium carbide is not limited to the synthesis of pyrrole, indole and isoindole derivatives. A number of synthetic approaches to pyrazoles have been proposed, which can be described as a (3 + 2)-cycloaddition to acetylene generated *in situ*.

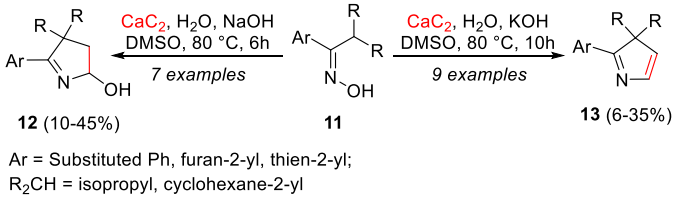
Aldehydes *p*-tosylhydrazones **35** reacted with calcium carbide in the presence of cesium carbonate to form *NH*-pyrazole derivatives **36** in moderate to good yields (Scheme 16) [50]. An interaction of ketone-derived *p*-tosylhydrazones **37** and calcium carbide resulted in 3, 4-disubstituted *NH*-pyrazoles **38** in up to 90 % yield. Authors mentioned that a regioselective migration of a substituent R^2 has occurred, and only small amounts of regioisomeric product **39** were observed in the reaction mixtures.

A replacement of **37** to their cyclic analogues **40**, **42** allowed to synthesize spiro-condensed and fused pyrazoles **41** and **43** respectively (Scheme 17) [51]. The formation of fused pyrazoles **43** can be explained with the rearrangement of the primarily formed spirocyclic pyrazoles.

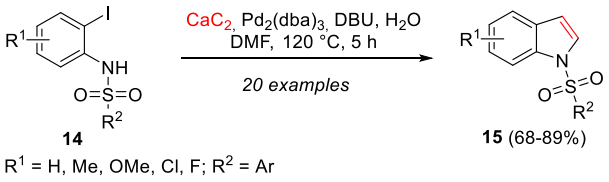
1,3-Dipolar cycloaddition of *in situ* generated nitrile imines and acetylene became a promising way to 1,3-disubstituted pyrazoles **45** (Scheme 18). As a source of a nitrile imine hydrazonoyl chloride **44** – triethylamine mixture was used. It was estimated in our group that the reaction should be performed in a two-chamber reactor to prevent side products formation [28].

The use of a two-chamber reactor allows to separate the mixture CaC_2–H_2O, which react with the formation of acetylene and an inorganic base, calcium hydroxide, from the base-sensitive substrate. It has been shown that acetylene evolving from the calcium carbide chamber readily dissolved in the reaction mixture in the other chamber [28]. During our work with hydrazonoyl chlorides **44** and CaC_2–H_2O mixture, we noted that under standard *one-pot* reaction conditions the best possible yield of pyrazoles **45** was only 79 % [28]. After conducting further investigations, it was estimated that compounds **44** decompose in the presence of $Ca(OH)_2$–H_2O mixture. The separation of a nitrile imine source from CaC_2–H_2O mixture allowed us to reach quantitative yields of pyrazoles **45**.

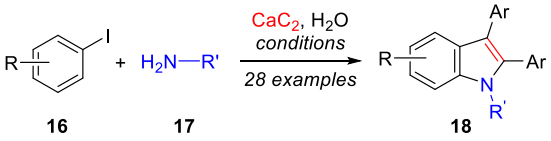
Methyl diazoacetate **46** reacted with calcium carbide in a two-chamber reactor with the formation of *NH*-pyrazole **47** in good yield (Scheme 19) [22]. The reaction should be performed in darkness to prevent the decomposition of diazoacetic ether and the use of a two-chamber reactor is nesessary to prevent side products formation. As in the previous example, the direct contact of 1,3-dipole source and



Scheme 6. Calcium carbide path to hydroxypyrrolines and 3*H*-pyrroles.



Scheme 7. CaC_2 in the construction of 1-sulfonyl-1*H*-indoles **15**.



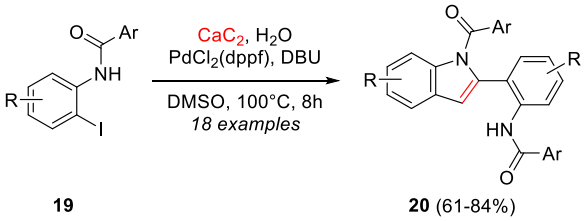
Scheme 8. The construction of 1,2,3-triarylindoles **18**.

CaC_2–H_2O mixture does not allow to synthesize pyrazole **47** in a good yield.

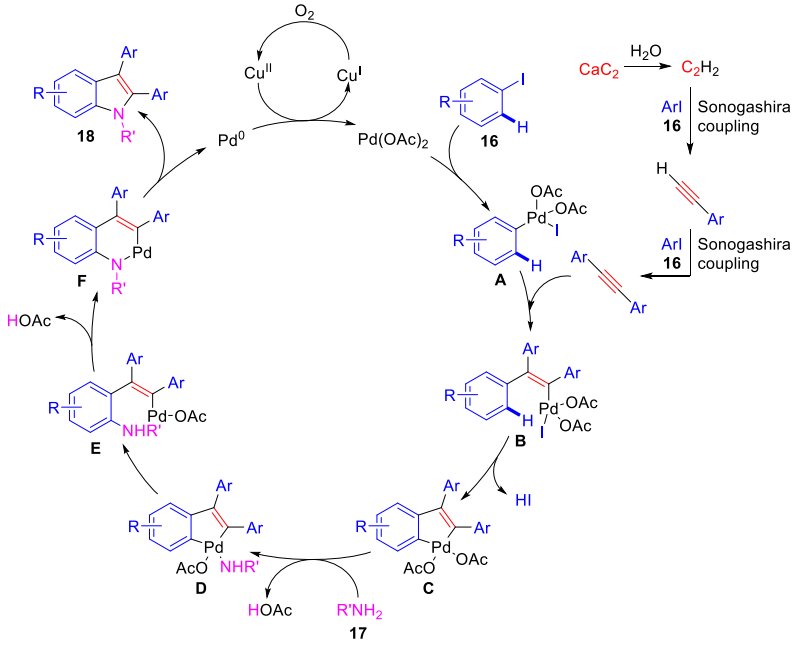
Recent research on the reactivity of calcium carbide in three-component copper (I) catalysed reactions with amidines **48** and a number of aromatic aldehydes **49** allowed to create an original highly versatile synthetic path to 2,4-diaryl-5-methylimidazoles **50** (Scheme 20) [52]. Authors proposed that the reaction includes primary transformation of aldehyde to amidine imine, which can be involved into a cross-coupling reaction with copper acetylenide resulting in acetylenic imine. The latter undergoes intramolecular cyclization transforming to imidazole **50**.

A similar reaction between 2-aminopyridines **51**, aldehydes **52** and calcium carbide in the presence of copper (I) iodide and potassium *tert*-butoxide led to a number of 3-methyl-2-arylimidazo[1,2-*a*]pyridines **53** in moderate to good yield (Scheme 21) [53].

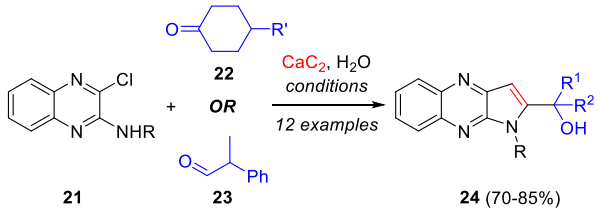
A copper-catalysed 1,3-dipolar cycloaddition of azides **54** to calcium carbide-induced acetylene in the presence of copper (I) catalyst allowed to synthesize a number of triazoles **55** in up to 90 % yield (Scheme 22, left part) [54,55]. A modification of the synthetic procedure by using Galden HT135 as a liquid membrane to gradually react calcium carbide with water allowed to synthesize *N*-benzyltriazoles **55** in 57–87 % yields [56].



Scheme 10. The synthesis *N*-aroyl-2-arylindoles using CaC_2.

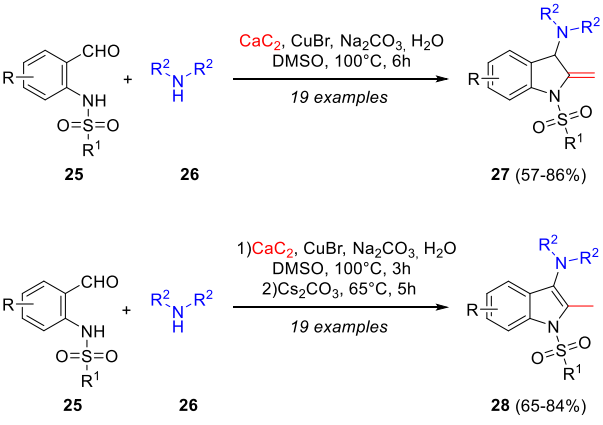


Scheme 9. The proposed reaction mechanism for the formation of triarylindoles.

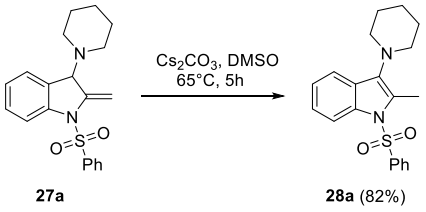


Reaction conditions: $Pd(PPh_3)_2Cl_2$, Et_3N, DMSO, 60°C, 6-8h;
R = Alk, Ph; R' = H,Me; R^1,R^2 - substituents derived from addition of **23**

Scheme 11. The synthesis of pyrrolo[2,3-*b*]quinoxalines.



R = H, Cl; R^1 = Me, substituted Ph, furan-2-yl;
R^2 = Me, Et, *n*-Bu, -$(CH_2)_5$-, -$C_2H_4OC_2H_4$-, -$C_2H_4SC_2H_4$-



Scheme 12. The synthesis of functionalized 1*H*-indole derivatives.

The use of sodium ascorbate as a base and acetonitrile-water mixture as a solvent in the presence of copper (I) catalyst allowed to synthesize aryl-substituted triazoles **55'** in up to 95 % yield (Scheme 22, right part) [57]. Aryl azides can be also generated *in situ* using aryl boronic acids and sodium azide in the presence of copper (I) catalysis [58].

Azides **56** reacted with calcium carbide in a similar way producing triazolyl-functionalized ketoximes **57** in up to quantitative yields (Scheme 23) [59].

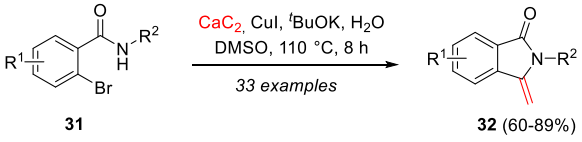
It has been demonstrated in our group that azide-alkyne cycloaddition between aromatic and selected aliphatic azides **58** and *in situ* generated acetylene can be performed in a low-polar solvent in the presence of copper (II) acetate as a catalyst [23]. By this way a number of triazoles **59** were synthesized in up to quantitative yields (Scheme 24).

4. Carbide approach to five-membered oxygen-containing heterocycles

p-Tosylhydrazone derivatives of salicylic aldehyde **60** reacted with calcium carbide in the presence of copper (I) catalyst and a strong base affording a range of 2-methylbenzofurans **61** (Scheme 25) [60].

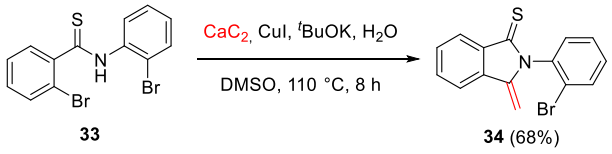
Salicylic aldehydes **62**, secondary amines **63** and calcium carbide in the presence of copper (I) bromide as a catalyst in basic media react with 3-(dialkylamino)-2-methylbenzofurans **64** in up to 81 % yield (Scheme 26) [61].

A three-component reaction of aldoxime derivatives **65**, *N*-chlorosuccinimide and CaC_2 resulted in the formation of 3-substituted isoxazoles **66** in up to quantitative yields (Scheme 27) [27]. The mechanism of the process can be considered as a typical 1,3-dipolar cycloaddition. Oxime **65** and NCS react with chloroaldoxime **67** formation. Calcium carbide and water transform to acetylene and a base, calcium hydroxide. In the presence of this base, **67** lose HCl with the

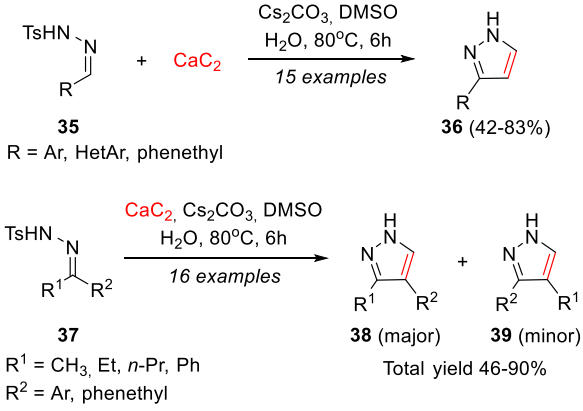


R^1 = H, Me, MeO, F, Cl, CF_3
R_2 = Ph, C_6H_4Hal, C_6H_4Alk, C_6H_4OAlk, 2-Naphth, 3-Py, $Et_2NC_2H_4$, $(MeO)_2C_2H_3$

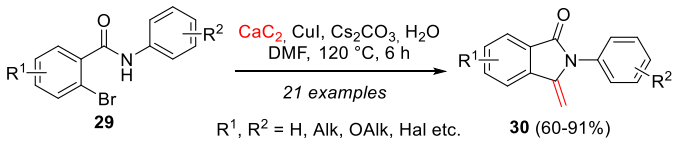
Scheme 14. The synthesis of 3-methylene-2-arylisoindolin-1-ones in the presence of CuI-KO^{t}Bu.



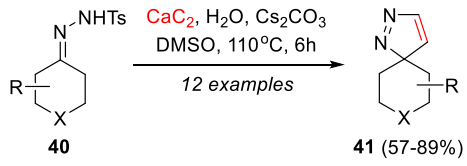
Scheme 15. The synthesis of 2-(2-bromophenyl)-3-methyleneisoindoline-1-thione using CaC_2.

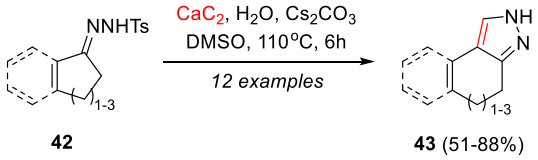


Scheme 16. Calcium carbide in the reaction with *p*-tosylhydrazones.

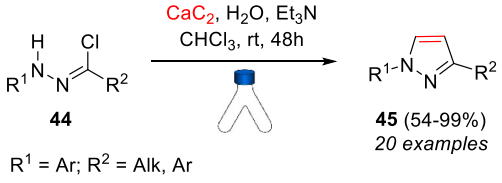


Scheme 13. Copper (I) catalysed reaction between **29** and CaC_2.

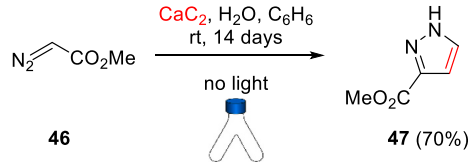




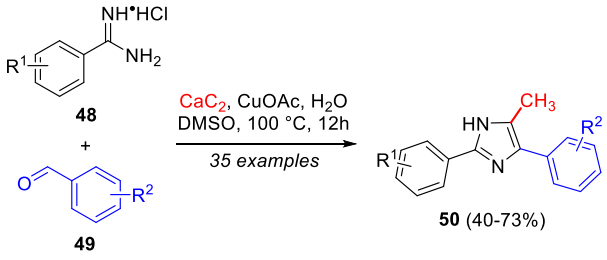
Scheme 17. The reaction of CaC_2 and cyclic *p*-tosylhydrazones.



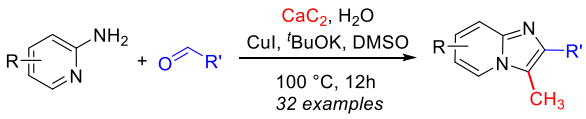
Scheme 18. Hydrazonoyl chloride path to pyrazoles.



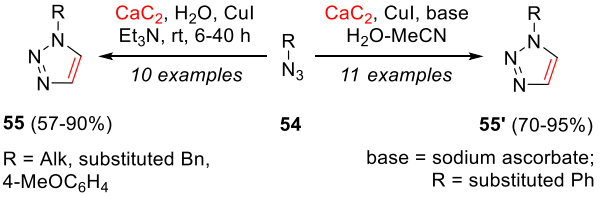
Scheme 19. The synthesis of NH-pyrazole using methyl diazoacetate and CaC_2.



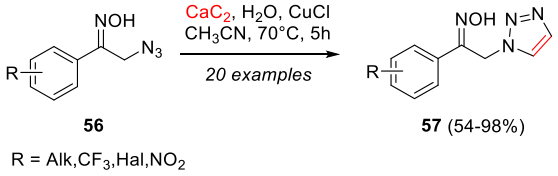
Scheme 20. CaC_2 in the construction of imidazoles.



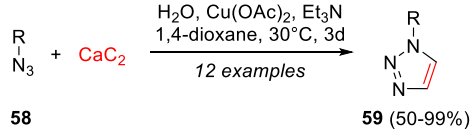
Scheme 21. The synthesis of 3-Methyl-2-arylimidazo[1,2-*a*]pyridines using CaC_2.



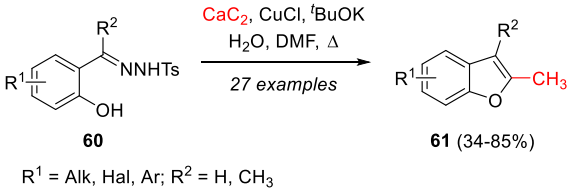
Scheme 22. *One-pot* synthesis of 1,2,3-triazoles.



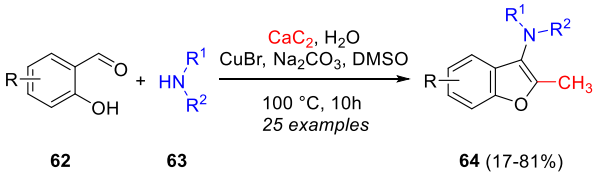
Scheme 23. The synthesis of functionalized triazoles **57**.



Scheme 24. The synthesis of 1,2,3-triazoles in 1,4-dioxane.



Scheme 25. CaC_2 in the construction of 2-methylbenzofurans.



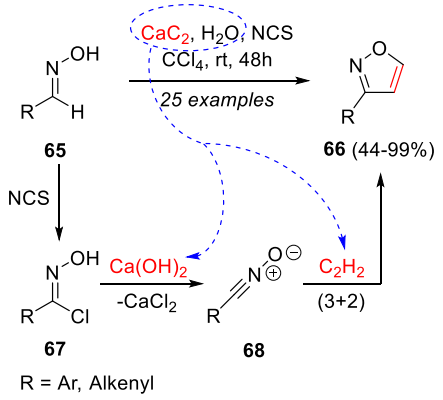
Scheme 26. The synthesis of 3-amino-2-methylbenzofurans **64**.

formation of a highly reactive nitrile oxide **68**. The dipole **68** reacts with acetylene producing isoxazole **66**.

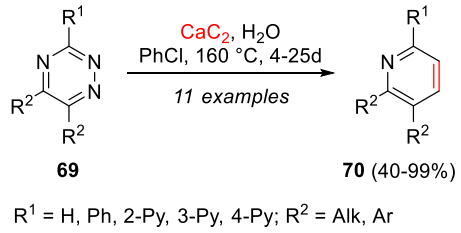
5. Six-membered nitrogen heterocycles synthesis

The reaction of 1,2,4-triazines **69** and calcium carbide was successfully used for the synthesis of 2,3,6-trisubstituted pyridines **70** (Scheme 28) [62]. The reactions were performed at heating to 160 °C in chlorobenzene.

A number of pyridazines **72** were synthesized using 1,2,4,5-tetrazines **71** and CaC_2-derived acetylene in a two-chamber reactor (Scheme 29, top) [63]. As a solvent 1,4-dioxane, $CHCl_3$ or benzene was



Scheme 27. The construction of isoxazole ring using CaC_2.

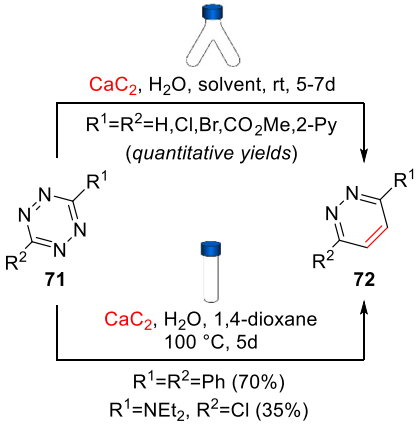


Scheme 28. 1,2,4-Triazines and calcium carbide in the synthesis of pyridines **70**.

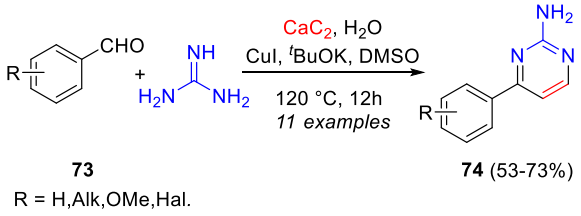
used. The use of a two-chamber reactor, which allows to separate CaC_2–H_2O mixture from 1,2,4,5-tetrazine, is necessary for some 1,2,4,5-tetrazines **71** to avoid undesired substitution reactions (in which R^1 or R^2 can be replaced with OH from water in basic media) or the opening of the tetrazine ring [64–69]. 3,6-Diphenyl-1,2,4,5-tetrazine and 3-chloro-6-(diethylamino)-1,2,4,5-tetrazine reacted with CaC_2 in a *one-pot* manner at heating in 1,4-dioxane (Scheme 29, bottom).

A three-component reaction of benzaldehydes **73**, guanidine and calcium carbide was successfully used for the synthesis of 4-arylpyrimidin-2-amines **74** (Scheme 30) [70]. As a catalyst, copper (I) iodide was applied.

Benzo[4,5]imidazo[2,1-*a*]isoquinolines **76** were successfully synthesized via copper-catalysed Sonogashira cross-coupling of 2-(2-bromophenyl)benzimidazoles **75** and *in situ* generated acetylene (Scheme 31, top) [71]. Two-step process including sequential interaction of *o*-phenylenediamine **77** with *o*-bromobenzaldehyde **78** and calcium carbide in Sonogashira coupling conditions allowed to synthesize benzo



Scheme 29. 1,2,4,5-Tetrazines in the reaction with CaC_2.



Scheme 30. The synthesis of 4-arylpyrimidin-2-amines.

[4,5]imidazo[2,1-*a*]isoquinoline **76a** in 71 % yield (Scheme 31, bottom) [71].

A convenient method for the synthesis of 2-aryl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidines **81** using calcium carbide as a solid acetylene surrogate, 2-aminobenzothiazoles **79** and aromatic aldehydes **80** in a *one-pot* three-component cascade process was proposed recently (Scheme 32) [72].

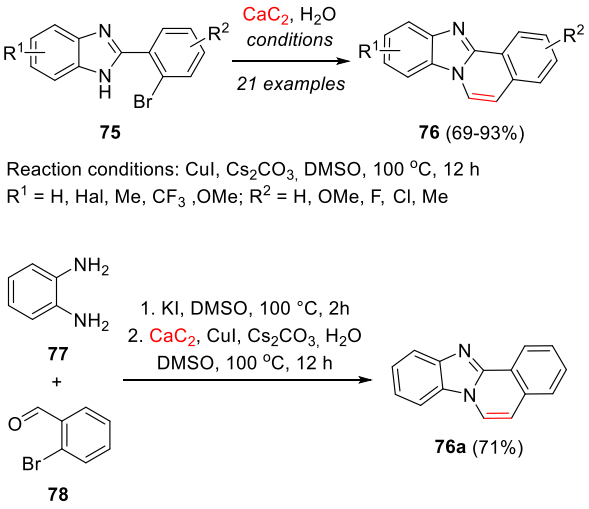
A replacement of 2-aminobenzothiazoles **79** with 2-aminobenzoisoxazole **82** in the reaction with benzaldehyde **80a** and calcium carbide allowed to synthesize 2-phenyl-4*H*-benzo[4,5]isoxazolo[3,2-*a*]pyrimidine **83** (Scheme 33) [72].

6. Carbide approach to synthetic intermediates for the construction of heterocyclic compounds

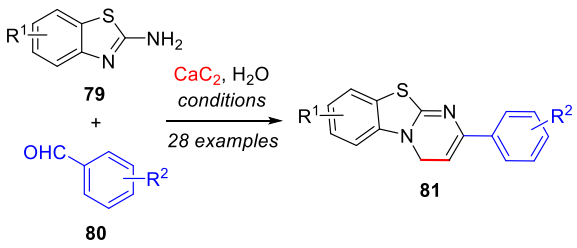
Calcium carbide-derived acetylene in a two-chamber reactor can be easily transformed to glyoxal **84** in the presence of 2,3-dichloropyridine *N*-oxide and gold (I) catalyst [73]. Using *in situ* generated glyoxal quinoxaline **86** and 3-(4-methoxyphenyl)-1,2,4-triazine **88** were synthesized from nitrogen substrates **85** and **87** correspondingly (Scheme 34).

Calcium carbide has been succesfully applied in the synthesis of vinyl ethers and their sulfur and nitrogen analogues [17,25,74–85]. For example, the synthesis of vinyl ethers **89** can be performed in the presence of potassium *tert*-butoxide and potassium fluoride at heating in dimethylsulfoxide (Scheme 35, top) [26]. Vinyl derivatives seem convenient analogues of acetylene which can be used as a sourse of C_2-fragment in a *one-pot* manner even in the reactions with base-sensitive substrates.

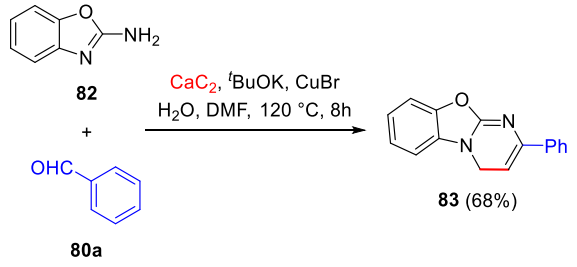
Benzyl vinyl ether **89a** was used as a sourse of acetylene in the reactions with hydrazonoyl chlorides **90** (Scheme 35, left reaction) [24]. By this way, pyrazoles **91**were synthesized in 77–99 % yield. The procedures with using vinyl ethers as acetylene surrogate seem convenient



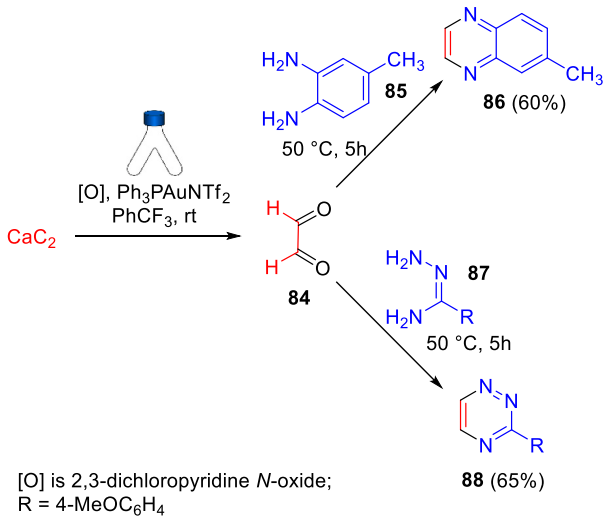
Scheme 31. CaC_2 in the construction of benzo[4,5]imidazo[2,1-*a*]isoquinoline moiety.



Scheme 32. The synthesis of tricyclic products **81**.



Scheme 33. The synthesis of 2-phenyl-4*H*-benzo[4,5]isoxazolo[3,2-*a*]pyrimidine **83**.



Scheme 34. CaC_2-derived glyoxal in heterocycles construction.

because a reaction of vinyl ethers (as acetylene sourse) can be checked by NMR at any moment, as acetylene leakage is impossible in this case.

Chloroaldoximes **92** reacted with vinyl ethers **89a**,**b** with the formation of 5-alkoxy-substituted 2-isoxazolines **93** (Scheme 35, right reaction) [86]. Isoxazolines **93** in the acidic media are able to lose a molecule of an alcohol with the formation of isoxazoles **94** (Scheme 35, bottom).

The mechanism of the reaction between hydrazonoyl chlorides **90** and benzyl vinyl ether **89a** seem interesting. Mechanistic investigations allowed to estimate that the reaction mechanism includes the primary formation of nitrile imines **95** followed by 1,3-dipolar cycloaddition of **95** to benzyl vinyl ether **89a** with the formation of 5-benzyloxypyrazoline **96**. Further aromatizarion of **96** with a cleavage of benzyl alcohol molecule leads to pyrazoles **91** (Scheme 36) [24].

Benzyl vinyl ether **89a** reacted with 1,2,4,5-tetrazines **97** leading to the formation of 3,6-disubstituted pyridazines **98** (Scheme 37) [63]. The reaction includes a hetero-Diels-alder [4 + 2] cycloaddition between **89a** and **97** resulting in the bicyclic intermediate **99**. The latter lose a molecule of nitrogen and benzyl alcohol with the formation of an aromatic pyridazine ring.

7. Calcium carbide strategy in D- and ^{13}C-labeling of heterocycles

By replacing water in the reaction with calcium carbide with deuterium oxide, 1,2-dideuteroactylene can be generated *in situ*. The use of dideuteroacetylene in cycloaddition reactions allows to synthesize dideuterated heterocycles. The first example of CaC_2-D_2O mixture use is the preparative synthesis of D_2-labeled triazoles, which was performed in the paper of Novák et al. [54] The reactions of azides **100** and calcium carbide were performed in 1:1 mixture of deuterium oxide and triethylamine (Scheme 38). As a result, the number of dideuterated triazoles **101** was synthesized with 90–94 % deuteration degree.

In our group the synthesis of D_2-triazoles was performed using a two-chamber reactor technique [23]. By separating a mixture of an azide **102**, triethylamine and copper (II) catalyst from calcium carbide – heavy water mixture, triazoles **103** were synthesized in good yields and 96–98 % of deuteration value (Scheme 39).

The reactions of CaC_2-D_2O mixture with other 1,3-dipoles, namely, nitrile imines **105** and nitrile oxides **108**, resulted in 4,5-dideuterated pyrazoles **106** and isoxazoles **109** correspondingly (Scheme 40) [27,28]. To achieve high deuteration degrees in the resulting pyrazoles **106** and isoxazoles **109**, various approaches have been applied. In the synthesis of D_2-pyrazoles **106**, a deuterated solvent was used to prevent undesired H-D exchange, and the resulting deuteration degrees were pretty good, ≥95 % [28]. To reach high deuteration values (94–98 %) in the synthesis of isoxazoles **109**, a pre-deuterated substrate **107** was used [27]. The use of anhydrous carbon tetrachloride in the synthesis of **109** allowed to avoid the use of a D-labeled solvent.

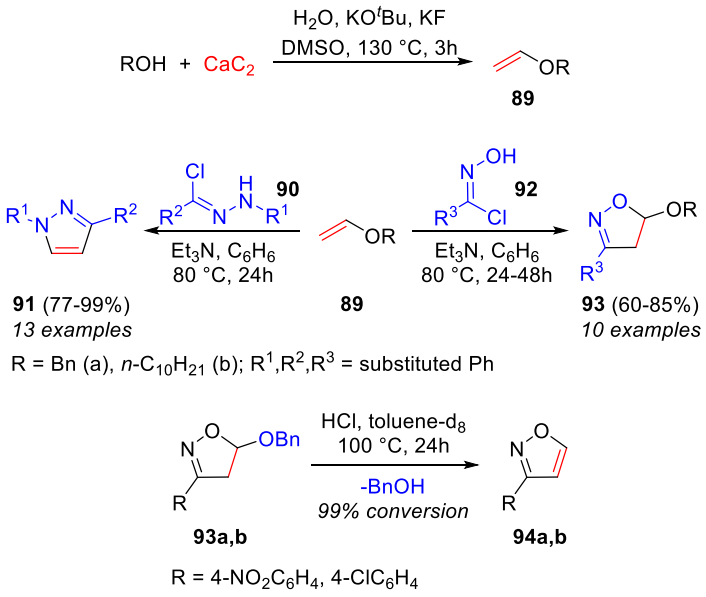
In recent work it has been demonstrated that 1,4-dioxane can be used as a solvent to prevent undesired hydrogen-deuterium exchange. The use of 1,4-dioxane allows to achieve >98 % values of deuteration in the synthesis of D_2-labeled pyrazoles and isoxazoles (Scheme 41) [23]. Performing the reactions of 1,3-dipole sources **110** and CaC_2-D_2O mixture in a two-chamber vessel (reversed Y-type or COware/H-tube) allows to prevent side products formation and avoid the contact of 1, 3-dipole source and inorganic base, calcium D-hydroxide, providing the best yields of 4,5-dideuterated isoxazoles and pyrazoles **111** with excellent deuteration degrees.

In similar reaction conditions using 1,4-dioxane as a solvent for the reaction of 1,2,4,5-tetrazines **112** and CaC_2-D_2O mixture as dideuteroacetylene source in a two-chamber reactor [23,63], a number of 4, 5-dideuteropyridazines **113** was synthesized in quantitavive yields and ≥98 % deuteration degree (Scheme 42).

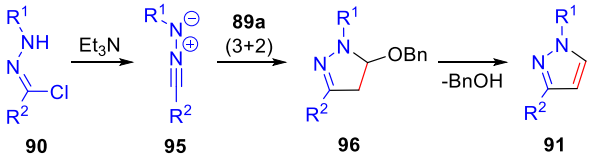
The use of deuterium oxide in the reaction with calcium carbide and 1,2,4-triazines **114** for the generation of D_2-labeled acetylene allowed to synthesize 2,3,6-trisubstituted 4,5-dideuteropyridines **115** in up to quantitative yield and ≥94 % deuteration degree (Scheme 43) [62].

Direct usage of CaC_2-D_2O mixture is not a single option for the introducing C_2D_2 fragment into organic molecules. The use of CaC_2-D_2O for the synthesis of trideuterovinyl ethers which are used as a surrogate of labeled acetylene makes it possible to achieve the good isotope-economy in cycloaddition reactions [24,63].

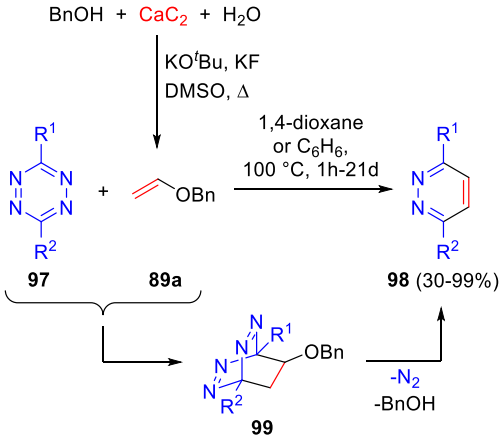
Benzyl trideuterovinyl ether **116** can be easily synthesized using readily available benzyl alcohol, calcium carbide and deuterium oxide (Scheme 44, top line). Using 1,4-dioxane with an admixture of DMSO-d_6 as a solvent trideuterated derivative **116** was synthesized in 94 % yield and high deuteration degree (96 %) [24]. Trideuterovinyl ether **116** can be used as a surrogate of dideuteroacetylene in the reactions with hydrazonoyl chlorides **117** [24] and 1,2,4,5-tetrazines **119** (Scheme 44, bottom lines) [63]. 1,3-Dipole source **117** reacts with **116** producing 4,



Scheme 35. Vinyl ether route to pyrazoles and isoxazoles.



Scheme 36. The mechanism of pyrazoles **91** formation.

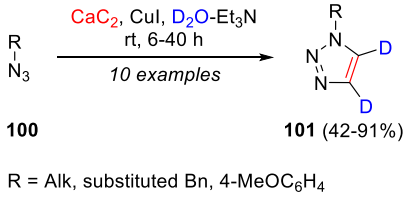


Scheme 37. Benzyl vinyl ether in the synthesis of pyridazines.

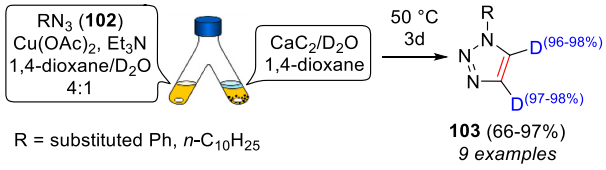
5-dideuteropyrazoles **118**, and tetrazine **119** transforms to 4,5-dideuteropyridazine moiety **120**. The value of deuteration in resulting products corresponds to the starting trideuterovinyl derivative.

An aromatic chloroaldoxime **121** reacts with *n*-decyl trideuterovinyl ether with the formation of 3-(4-chlorophenyl)-5-(*n*-decyloxy)-4,4,5-trideutero-4,5-dihydroisoxazole **122** in good yield (Scheme 45) [86].

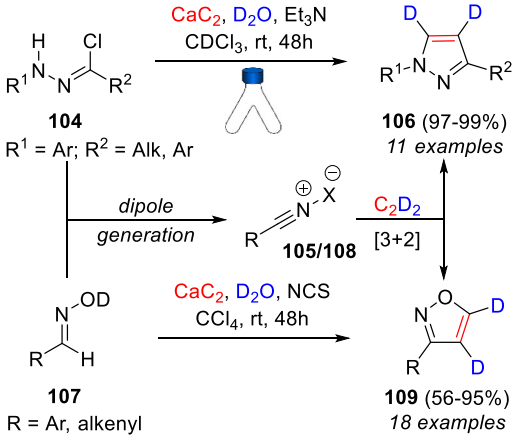
A three-step sequence based on calcium carbide was performed for the synthesis of 5-deuteropyrazoles **126** (Scheme 46) [24]. On the first



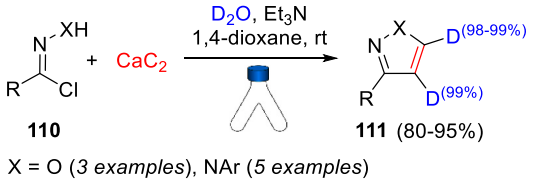
Scheme 38. The synthesis of D_2-triazoles performed by Novák et al.



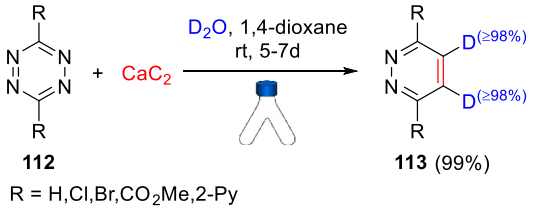
Scheme 39. The synthesis of D_2-triazoles performed in our group.



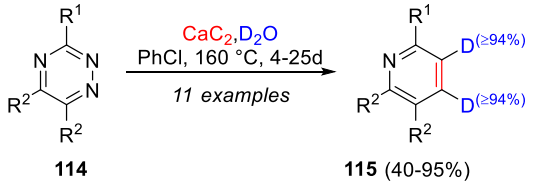
Scheme 40. CaC_2-D_2O mixture in the synthesis of D_2-pyrazoles and isoxazoles.



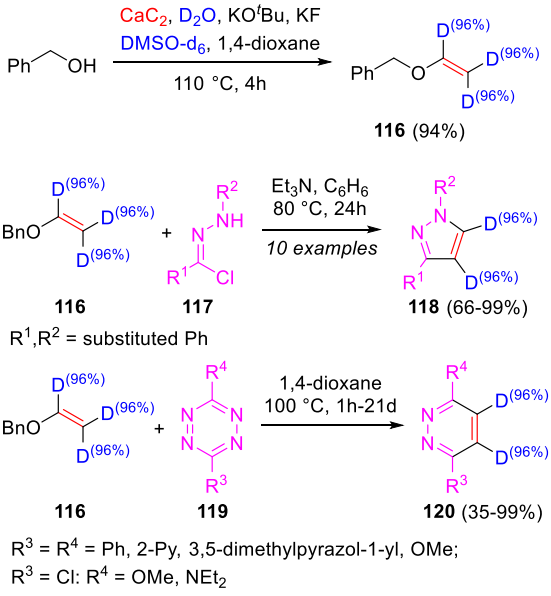
Scheme 41. 1,4-Dioxane as a reaction media for highly efficient D-labeling of isoxazoles and pyrazoles.



Scheme 42. The synthesis of 4,5-dideuteropyridazines.

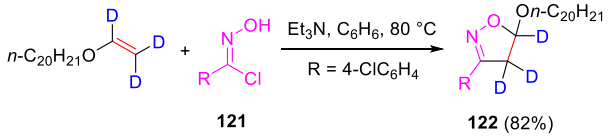


Scheme 43. Calcium carbide in the construction of 4,5-dideuteropyridines.

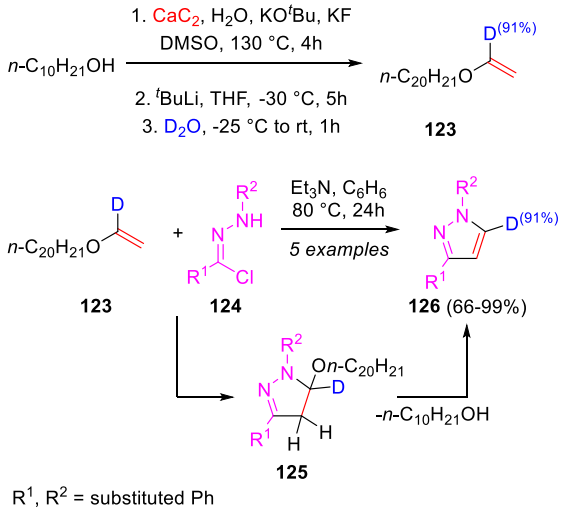


Scheme 44. D-economic synthesis of D_3-benzyl vinyl ether and its usage for D-labeling of pyrazoles and pyridazines.

step 1-decanol was transformed to vinyl ether via the reaction with calcium carbide. A sequential treatment of *n*-decyl vinyl ether with *tert*-butyl lithium and deuterium oxide allowed to synthesize *n*-decyl 1-deuterovinyl ether **123**. The latter reacted with hydrazonoyl chlorides **124** in the presence of triethylamine regioselectively producing



Scheme 45. *N*-Decyl trideuterovinyl ether in the reaction with a nitrile oxide source.

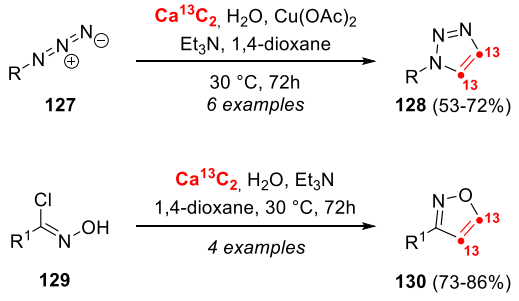


Scheme 46. Three-step synthesis of 5-deuteropyrazoles.

pyrazoline **125**. Pyrazoline **125** is unstable under heating and decomposed with the formation of aromatic 5-deuteropyrazoles **126** and 1-decanol. The value of deuteration of **126** corresponds to the starting D-vinyl ether **123**.

By a replacement of calcium carbide with its labeled analogue, calcium carbide-$^{13}C_2$, a number of $^{13}C_2$-labeled heterocycles was synthesized. An isotope-economic reaction of $Ca^{13}C_2$ and 1,3-dipoles, organic azides **127** and nitrile oxides, was performed recently [29]. To achieve high levels of isotope-economy, an excess of a dipole was used in the reactions with $Ca^{13}C_2$. As a source of nitrile oxide the mixture of a corresponding chloroaldoxime **129** and triethylamine was used. It was demonstrated that calcium carbide-$^{13}C_2$ reacts with azides **127** in the presence of copper (II) acetate as a catalyst and triethylamine as a base with the formation of 4,5–$^{13}C_2$-labeled triazoles **128** (Scheme 47, top). Chloroaldoximes **129** and triethylamine in the reaction with $Ca^{13}C_2$-induced labeled acetylene transform to 4,5–$^{13}C_2$-isoxazoles **130** in good yields (Scheme 47, bottom).

Calcium carbide-$^{13}C_2$ was successfully used for $^{13}C_2$- and double



Scheme 47. $Ca^{13}C_2$ in 1,3-dipolar cycloaddition.

D_2-$^{13}C_2$-labeling of the pyridine moiety [62]. The reaction of 1,2,4-triazines **131** with $Ca^{13}C_2$ and water or deuterium oxide resulted in the formation of 4,5–$^{13}C_2$-pyridines **132** and double D_2-$^{13}C_2$-labeled pyridines **133** respectively (Scheme 48).

A total synthesis of $^{13}C_2$-labeled Azintamide **137** was performed using the carbide strategy (Scheme 49) [30]. On the first step a key transformation of 3,6-dichloro-1,2,4,5-tetrazine **134** and $Ca^{13}C_2$ to $^{13}C_2$-labeled pyridazine **135** was performed in a two-chamber vessel. The treatment of **135** with sodium hydrosulfide led to the product **136**. The latter reacted with 2-chloro-*N*,*N*-diethylacetamide in the presence of a base producing $^{13}C_2$-Azintamide **137**.

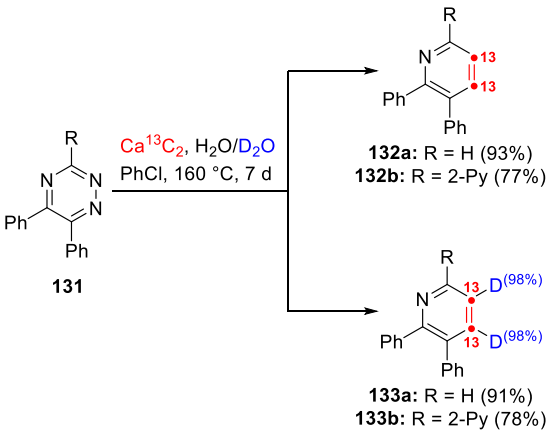
Another example of the synthesis of $^{13}C_2$-labeled pyridazine using calcium carbide-$^{13}C_2$ was performed in recent paper (Scheme 50) [29]. A two-step procedure includes the direct transformation of readily available dodecan-1-thiol or 9*H*-carbazol to the corresponding $^{13}C_2$-vinyl derivatives **138** and a sequential reaction of **138** and 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **139** resulting in 3,6-di(pyridin-2-yl) pyridazine-4,5–$^{13}C_2$ **140** in almost quantitative yield in both cases.

8. Comparative analysis of calcium carbide and acetylene gas in the synthesis of heterocyclic compounds

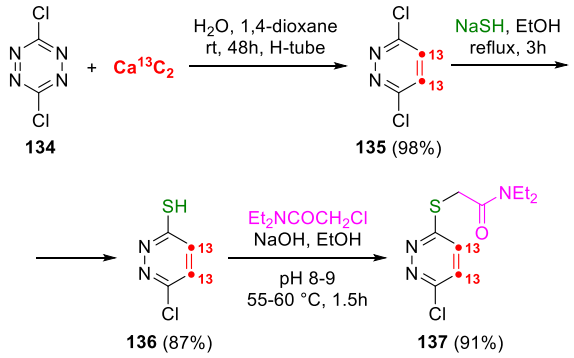
Considering the active use of calcium carbide as a replacement for acetylene gas in recent years, it would be interesting to compare these building blocks. In this section, we will evaluate the use of calcium carbide and acetylene gas in the synthesis of heterocyclic compounds.

Overall, the range of heterocycles obtained from gaseous acetylene is quite limited. The above described carbide approaches for the synthesis of pyrazoles, indole, benzofurane, imidazole, pyrimidine and isoquinoline derivatives have no analogues based on acetylene gas. The synthesis of pyridines **142** through cyclocotrimerization reaction between acetylene and nitriles **141** can be mentioned as an interesting example of the use of acetylene gas for the preparation of heterocycles, which has not yet been implemented by using calcium carbide (Scheme 51) [87–91].

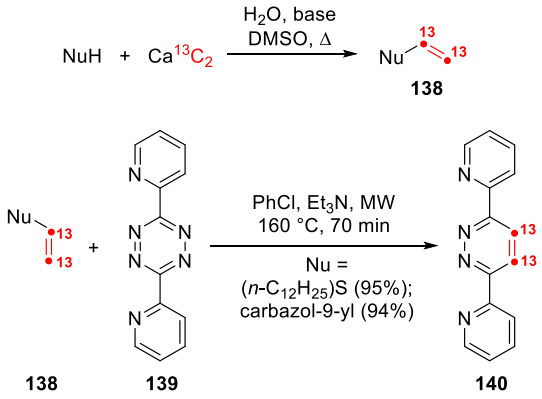
Examples of reactions that have been carried out with both calcium carbide and acetylene gas are shown on Scheme 52. As can be seen from Scheme 52, the yields of most reactions with acetylene do not exceed the yields of previously described similar reactions with calcium carbide. Reactions described here require special gas handling equipment and/or the use of very large excesses of acetylene gas. For example, the reaction of acetylene with diazocompounds **143** was carried out in an autoclave under a pressure of 12–15 atm [92] or in a sealed tube using vacuum-transfer technique for loading the starting materials (Scheme 52a) [93]. The average yields of pyrazoles **144** obtained from diazocompounds **143** and acetylene gas were similar to the yield of pyrazole **47** obtained from methyl diazoacetate **46** and calcium carbide (Scheme 19) [22].



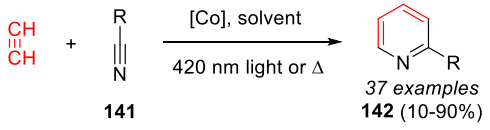
Scheme 48. Carbide approach in $^{13}C_2$- and double D_2-$^{13}C_2$-labeling of pyridines.



Scheme 49. The synthesis of $^{13}C_2$-labeled Azintamide.



Scheme 50. Two-step synthesis of 3,6-di(pyridin-2-yl)pyridazine-4,5–$^{13}C_2$.



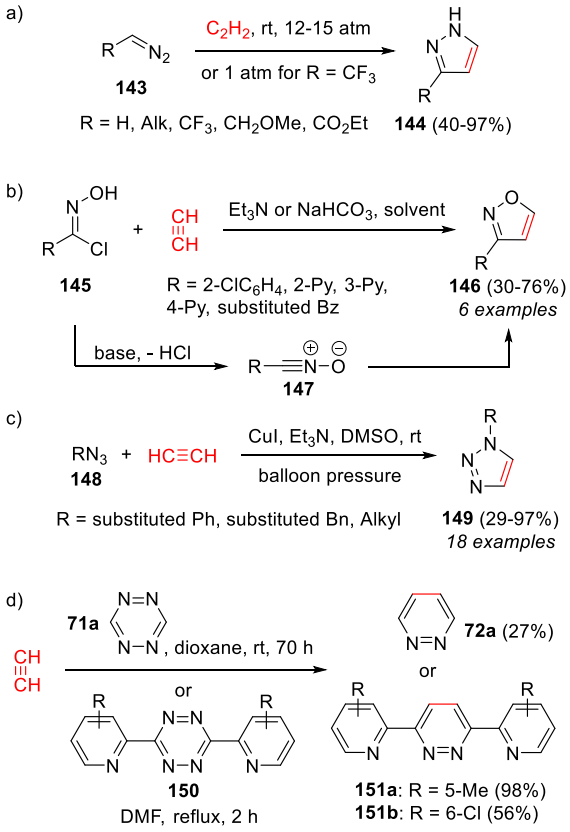
[Co] = CpCo(cod), $(Cp)_2Co$, $CpCo(BC_5H_5)$
R = H, NH_2, SMe, Alk, functionalized Alk, OAlk, $NAlk_2$, Ar, HetAr, (substituted)vinyl

Scheme 51. The synthesis of pyridines via [2 + 2+2] cyclocotrimerization of acetylene and nitriles.

In the next example, isoxazoles **146** were synthesized through the cycloaddition reaction between acetylene gas and nitrile oxides **147** generated from chloraldoximes **145** (Scheme 52b) [94–96]. The yields of isoxazoles **146** were lower compared to the similar synthesis from calcium carbide described above (Scheme 27) [27]. Reactions were carried out in a saturated solutions of acetylene, which implies passing excess of acetylene gas through the solutions [96].

Click reaction of azides **148** and acetylene afforded triazoles **149** in 29–97 % yields (Scheme 52c) [97–99]. Sterically hindered azides such as *o*-substituted phenylazides and 1-substituted benzylazides gave the corresponding triazoles in moderate yields. The yields for other aryl- and alkyl-substituted azides were high and comparable with the yields of aryl- and alkyltriazoles obtained from calcium carbide (Schemes 22–24) [23,54–59]. These reactions typically do not require very large excess of acetylene gas and can be performed under a balloon pressure of acetylene [97,98].

Acetylene gas reacted with 1,2,4,5-tetrazines **71a,150** yielding pyridazines **72a,151** (Scheme 52d) [100–102]. Unsubstituted 1,2,4,



Scheme 52. Representative examples of the heterocycles synthesis from acetylene gas for comparison with carbide approach.

5-tetrazine (**71a**) reacted with acetylene itself to give pyridazine (**72a**) in 27 % yield (Scheme 52d, top) [100], whereas the same reaction with calcium carbide afforded pyridazine (**72a**) in quantitative yield (Scheme 29) [63]. The reaction of 5-methyl-2-pyridyl-substituted tetrazine **151a** with acetylene gas (Scheme 52d, bottom) [101], as well as the reaction of similar 2-pyridyl-substituted tetrazine with calcium carbide (Scheme 29) [63] gave the corresponding pyridazines in quantitative yield. It should be noted, that these reactions were carried out bubbling acetylene gas into the reaction solution during the whole reaction period. Therefore, enormous excesses of acetylene gas were consumed.

While the yields of the above discussed reactions with acetylene gas and calcium carbide were on average comparable, synthetic procedures involving calcium carbide are undoubtedly much more convenient and safer in comparison with acetylene itself, because they do not involve the transfer of flammable gas into the reaction vessel and do not require any complex equipment such as autoclaves or gas supply system. The sensitivity of certain substrates or reagents to water and aqueous bases can be considered as a limitation of calcium carbide usage in organic synthesis. However, this limitation can easily be circumvented by using a two-chamber reactor, as shown in the previous sections. The use of the two-chamber reactor enables the efficient synthesis of pyrazoles (Schemes 18 and 19) [22,23] and pyridazines (Scheme 29) [63] and their labeled derivatives (Schemes 40–42) [23,28,63], as well as the synthesis of six-membered heterocycles from the carbide-derived glyoxal (Scheme 34) [73]. Also, the two-chamber reactor technique allows to achieve a high deuteration degree in the synthesis of D_2-labeled heterocycles (Schemes 39 and 41) [23]. The two-chamber reactor is not required for for all other syntheses described in current review, and the reactions can be easily carried out in usual reaction vessels.

To summarize, we can state that the greater availability, safety and unsurpassed handling ease provides significant competitive advantages of calcium carbide against acetylene in cylinders. These advantages have led to the rapid development of carbide chemistry in recent years and the discovery of new carbide-based synthetic approaches to a diverse range of heterocycles.

9. Conclusion

The chemistry of alkynes holds significant importance in the chemical science, constituting an essential tool for organic synthesis. In contrast to functionalized alkynes, the application of acetylene among synthetic chemists remains rather restricted, mostly due to the intricate challenges associated with the laboratory use of acetylene gas as well as safety concerns. By substituting gaseous acetylene with its solid equivalent, calcium carbide, a notable surge in the utilization of acetylene within the domain of organic synthesis was observed in past decades. The use of calcium carbide instead of acetylene gas allowed to propose a range of novel synthetic approaches to a great number of powerful building blocks with double or triple carbon-carbon bonds and to a huge variety of heterocyclic molecules.

An overview is provided of the recent advances in the synthesis of heterocycles using carbide approach. By direct transformations of calcium carbide a range of β-lactams, pyrroles, indole and isoindole derivatives, pyrazoles, imidazoles, triazoles, isoxazoles, 2-methylbenzofurans, pyridines, pyridazines and a number of isoquinoline and pyrimidine annelated derivatives were synthesized. The use of CaC_2 as a starting material for the construction of C_2-functional allowed to propose synthetic approaches to quinoxaline and 1,2,4-triazine derivatives, pyrazoles, 2-isoxazolines, isoxazoles and a wide range of pyridazines.

A replacement of water in the reactions with calcium carbide to deuterium oxide was used for *in situ* generation of 1,2-dideuteroacetylene. The use of CaC_2-D_2O mixture gave a promising synthetic approach to 4,5-dideuterated pyrazoles, triazoles, isoxazoles, pyridines and pyridazines. Using calcium carbide-$^{13}C_2$ instead of CaC_2 in cycloaddition reactions a number of $^{13}C_2$-labeled triazoles, isoxazoles, pyridines and pyridazines were synthesized for the first time. CaC_2–D_2O and $Ca^{13}C_2$–H_2O-based building blocks also seem very promising for the construction of D_2-and $^{13}C_2$-labeled heterocyclic cores.

Looking forward, we expect the advancement of carbide chemistry is poised to revolutionize organic chemistry, fostering advancements in both fundamental and applied chemistry. The development of carbide chemistry holds the potential to introduce novel synthetic methodologies and techniques and can stimulate the development of the entire chemical science and related fields of science and life.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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