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One-Pot Three-Component Synthesis of 2-Methyl-3-Aminobenzofurans Using Calcium Carbide as a Concise Solid Alkyne Source

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Keywords

CCEDI

Salicylaldehyde | Secondary amine | Calcium carbide | Alkyne source | benzofuran

Main observation and conclusion

The one-pot three-component method for the synthesis of 2-methyl-3-aminobenzofurans using calcium carbide as a concise solid alkyne source, and salicylaldehydes and secondary amines as starting materials is described. This protocol has salient feature of the use of inexpensive, abundant and easy-to-handle alkyne source, avoiding the use of inflammable and explosive acetylene gas as an original alkyne source. In addition, step economy, satisfactory yield, and simple work-up procedure are also advantages of this route.

Comprehensive Graphic Content



 R^1 = H, Me, OMe, OEt, F, Cl, Br, NO₂, etc. R^2 , R^3 = alkyl, cycloalkyl, etc.

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Background and Originality Content

Benzofuran nucleus is present in a huge number of bioactive natural and synthetic compounds. Benzofuran derivatives have attracted attention due to their broad range of biological activities, where some of them possess unique anticancer,^[1] antitubercular,^[2] anti-Alzheimer^[3] and anti-inflammatory^[4] properties. Therefore they have potent applications in pharmaceuticals, agriculture, and polymers. Although the synthesis of benzofurans have been widely documented,^[5] 2-methyl-3-aminobenzofurans are rarely reported. Chly few literatures reported the synthesis of 2-substituted 3-aminobenzofurans, which include i) copper-catalyzed annulative amintion of *o*-alkynylphenols with hydroxylamines;^[6] ii) three-component coupling reactions of alkynylsilanes, o-hydroxybenzaldehydes, and secondary amines by Cu(I)/Cu(II) cooperative catalytic sysms;^[7] iii) treatment amides bearing an α -phenoxy moiety with triflic anhydride and 2-fluoropyridine (Scheme 1).^[8] However, some ethods utilize commercially unavailable substrates as starting materials, which have to synthesize through many steps. Meanwhile stable, expensive and difficult-to-handle alkyne sources have to be applied, which generally need to synthesize using inflammable and explosive acetylene gas as an original alkyne source. Therefore is necessary to explore concise and convenient routes to synthesize these compounds by using cheap and abundant alkyne sources d easy-to-obtain starting materials.

S heme 1 Synthesis of 2-substituted 3-aminobenzofurans

previous work



Calcium carbide as a cheap and abundant solid, which is easy to store and operate, is generally used to prepare acetylene gas in chemical industry. However, in recent years, calcium carbide was und that it could be directly used as an alkyne source to synthesize important organic compounds.^[9] Our group also reported some reactions direct using calcium carbide as a concise alkyne source to construct multifunctional alkynes,^[10] alkenes,^[11] and cyclic compounds.^[12] Although calcium carbide shows attractive prospects for direct use in organic synthesis, it is far from being studied in depth and breadth.

In this work, we report a one-pot three-component method for the synthesis of 2-methyl-3-aminobenzofurans direct using calcium carbide as a concise solid alkyne source, and salicylaldehydes and secondary amines as starting materials.

Results and Discussion

Initially, the three-component reaction of calcium carbide, salicylaldehyde (1a) and piperidine (2a) was selected as a model reaction to screen the reaction conditions. The reaction was examined with respect to mediators, bases, solvents, and temperature. It was found that silver(I) and copper(II) salts (1.0 equivalent based on 2a) as mediators exhibited guite low effect on the reaction (Table 1, entries 1-5). Copper(I) salts (1.0 equivalent based on 2a), such as Cul, CuBr, CuCl, CuOTf and CuCN, as mediators had certain effect on the reaction (Table 1, entries 6-10). Among them, CuBr showed slightly higher yield for the formation of 2-methyl-3-(piperidin-1-yl)benzofuran (3a) (Table 1, entry 7). Owing to the poor solubility of calcium carbide in most organic solvents, the reaction in DCE and PhMe could not give product (Table 1, entries 11, 12). In contrast, the reaction in DMSO, DMF and MeCN could produce a certain amount of 3a (Table 1, entries 7, 13, 14). DMSO was an applicable solvent (Table 1, entry 7). Bases played an important role in the reaction. Some organic bases, such as DMAP, DBU, pyridine and Et₃N (Table 1, entries 7, 15-17), and some inorganic bases, such as NaOH, Na₂CO₃, K₂CO₃, Cs₂CO₃, NaHCO₃ and NaOAc (Table 1, entries 18–23) were tested for the reaction, and the results showed that Na₂CO₃ could afford higher yield than others (Table 1, entry 19). In the later research it was found that the increase of the amount of CuBr from 1.0 to 1.2 equivalents could improve the yield of 3a (Table 1, entries 24). In addition, 100 °C was an appropriate temperature for the reaction, the elevated and lowered temperature could not improve the yield of 3a (Table 1, entries 25, 26).

Table 1. The effect of reaction conditions on the yield of 3a^a

C 1a	HO H H 2a	Ca Ce Solvent,	ator, base	3a
Entry	Mediator (eq)	Base (1 eq)	Solvent	Yield (%) ^b
1	AgCl (1)	DMAP	DMSO	0
2	AgOAc (1)	DMAP	DMSO	34
3	CuCl ₂ (1)	DMAP	DMSO	11
4	CuBr ₂ (1)	DMAP	DMSO	12
5	Cu(OAc) ₂ (1)	DMAP	DMSO	Trace
6	Cul (1)	DMAP	DMSO	38
7	CuBr (1)	DMAP	DMSO	44
8	CuCl (1)	DMAP	DMSO	40
9	CuOTf (1)	DMAP	DMSO	41
10	CuCN (1)	DMAP	DMSO	13
11	CuBr (1)	DMAP	DCE	0
12	CuBr (1)	DMAP	PhMe	0
13	CuBr (1)	DMAP	DMF	33
14	CuBr (1)	DMAP	MeCN	23
15	CuBr (1)	DBU	DMSO	Trace
16	CuBr (1)	Pyridine	DMSO	31
17	CuBr (1)	Et₃N	DMSO	35
18	CuBr (1)	NaOH	DMSO	41
19	CuBr (1)	Na ₂ CO ₃	DMSO	53
20	CuBr (1)	K_2CO_3	DMSO	43
21	CuBr (1)	CS ₂ CO ₃	DMSO	46

22	CuBr (1)	NaHCO ₃	DMSO	42
23	CuBr (1)	NaOAc	DMSO	12
24	CuBr (1.2)	Na ₂ CO ₃	DMSO	70
25 ^c	CuBr (1.2)	Na_2CO_3	DMSO	58
26 ^d	CuBr (1.2)	Na ₂ CO ₃	DMSO	62

^{*a*} Reaction conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), CaC₂ (3.0 mmol), mediator (appropriate amount), base (1.0 mmol) and H₂O (6.0 mmol) in solvent (3 mL) at 100 °C for 10 h under N₂ atmosphere. ^{*b*} The isolated yield. ^{*c*} 80 °C. ^{*d*} 20 °C

Scheme 2. Synthesis of 2-methyl-3-aminobenzofurans^a



 a Reaction conditions: 1 (1.5 mmol), 2 (1.0 mmol), CaC₂ (3.0 mmol), CuBr (1.2 mmol), Na₂CO₃ (1.0 mmol) and H₂O (6.0 mmol) in DMSO (3 mL) at 100 °C for 10 h under N₂ atmosphere.

Based on the above findings, the scope of the one-pot three-

component reactions of calcium carbide, salicylaldehydes and secondary amines to synthesize a series of 2-methyl-3-aminobenzofurans were examined by using CuBr as a mediator, Na₂CO₃ as a base, and water as a promoter in DMSO at 100 °C. It was found that the reactions of calcium carbide, salicylaldehyde (1a) with different secondary amines including cyclic amines, such as piperidine, morpholine, 1,2,3,4-tetrahydroisoquinoline and pyrrolidine, and acyclic amines, such as diethylamine and dibenzylamine, could give the corresponding products in good yield (Scheme 2, 3a-3e, 3g). However, diallylamine as a secondary amine only gave the product in 26% yield (Scheme 2, 3f). The reactions of calcium carbide, piperidine (2a) with different salicylaldehydes showed that salicylaldehydes substituted by electron-withdrawing groups (NO₂, F, Cl, Br) afforded higher yield (Scheme 2, 3h-3k) possibly because electron-withdrawing effect could cause the nucleophilicity increase of salicylaldehydes, and favor to subsequent reactions. In contrast, salicylaldehydes substituted by electron-donating groups (Me, MeO) afforded slightly lower yield (Scheme 2, 3m-3q). In addition, salicylaldehydes bearing meta- and para-substituents to OH gave the corresponding products in good yield (Scheme 2, 3h-3n). In contrast, salicylaldehydes bearing ortho-substituents to OH afford products in moderate yield because of the large steric hindrance (Scheme 2, 30-3q). In addition, the reactions of calcium carbide, various salicylaldehydes with other secondary amines demonstrated that cyclic amines (Scheme 2, 3r, 3s, 3w-3y) could give much higher yield than acyclic amines (Scheme 2, 3t, 3v), except diethylamine (Scheme 2, 3u).

The synthesis of product **3a** through the reaction of salicylaldehyde (**1a**), piperidine (**2a**) and calcium carbide was also carried out on a gram scale. The reaction of 1.46 g of **1a**, 0.68 g of **2a** with 1.53 g of calcium carbide in 40 mL of DMSO under standard conditions gave 1.15 g of **3a** in 67% yield. The success of this gram scale reaction further demonstrated the effectiveness of optimized conditions for the bulk process (Scheme 3).

Scheme 3. Gram-scale Synthesis of 3a^a



^{*a*} Reaction conditions: **1a** (12 mmol), **2a** (8 mmol), CaC_2 (24 mmol), CuBr (9.6 mmol), Na_2CO_3 (8 mmol), H_2O (48 mmol) in DMSO (24 mL) was heated at 100 °C for 10 h under N_2 atmosphere.

The obtained product could also be found applications in the organic synthesis. For example, product **3y** could be easily reacted with phenol to synthesize 2-methyl-3-(morpholin-4yl)-5-phenoxybenzofuran (**4**) in good yield (Scheme 4).

Scheme 4. Application of 3y



^{*a*}Reaction conditions: **3y** (1 mmol), phenol (1.2 mmol), CsOH (2.5 mmol) in DMSO (1 mL) under air was heated at 150 $^{\circ}$ C for 12 h.

A plausible mechanism for the synthesis of **3a** was proposed (Scheme 5). Salicylaldehyde (**1a**) first reacts with piperidine (**2a**) through nucleophilic addition to give adduct **A**, which loses hydroxyl to form **B**. **B** easily tautomerizes into quaternary ammonium hydroxide **C**.^[13,14] Meanwhile calcium carbide is hydrolyzed to yield acetylene calcium hydroxide (**D**),^[9f, 9g] which can be further transformed into cuprous acetylide **E** in the presence of cuprous bromide. **C** is attacked by **E** to give intermediate **F**. **F** is further hydrolyzed to afford intermediate **G**.^[15] The hydroxyl in **G** attacks intramolecular triple bond to produce intermediate **H**,^[16, 17] followed by isomerizing into the more stable **3a** as a final product.

Scheme 5. Proposed Mechanism for the Synthesis of 3a



Conclusions

In conclusion, a concise method for the synthesis of 2-methyl-3-amnobenzofurans through one-pot three-component reactions of calcium carbide, salicylaldehydes and secondary amines has deloped. The salient features of this protocol are the use of inexpensive and easy-to-handle alkyne source, broad substrate scope, satisfactory yield, and simple work-up procedure. This method may good alternative to the synthesis of biologically active substances bearing benzofuran moiety through further structural modif cation.

cperimental

General procedure for the synthesis of 2-methyl-3-aminobenzofurans: Salicylaldehyde (1.5 mmol), calcium carbide (3 mmol, 98 % purity), secondary amine (1.0 mmol), cuprous bromide (1.2 mmol), sodium carbonate (1.0 mmol) and water (6 mmol) in DMSO (dry) (3 mL) were stirred at 100 °C for 10 h. The reaction was monitored by TLC. After the reaction was complete, the resulting mixture was filtered to remove the solid, and the liquor was extracted with ethyl acctate (3×10 mL), and washed with saturated brine (3×10 mL). The resulting organic phase was dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was isolated by aluminum oxide column chromatography by using petroleum ether and ethyl acetate as eluent to give the pure products.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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One-Pot Three-Component Synthesis of 2-Methyl-3-Aminobenzofurans Using Calcium Carbide as a Concise Solid Alkyne Source Xiaolong Ma, Zhiqiang Wang, Zhenrong Liu and Zheng Li*

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In this protocol, calcium carbide was used as a concise solid alkyne source to react with salicylaldehydes and secondary amines through one-pot three-component procedure, and a series of 2methyl-3-aminobenzofurans were synthesized in satisfactory yield.

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