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Article

A^3-Coupling Reaction as a Strategy Towards the Synthesis of Alkaloids

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Uma série de aldeídos, alquinóis e benzilaminas foram submetidos a reação, por catálise mediada por CuCl, na formação de hidróxi-benzilaminas funcionalizadas. O procedimento permite a utilização de aldeídos alquílicos e arílicos. Substratos representativos foram convertidos em alcalóides cíclicos de cinco e seis membros através da reação concomitante de *N*-debenzilação e redução total da ligação tripla promovida por Pd, seguido de ciclização tipo Mitsunobu.

A number of aldehydes, alkynols and benzylamines were submitted to A^3-coupling reaction, under CuCl catalysis, giving strategically functionalized hydroxy-propargylamines. The procedure allows the use of alkyl as well as aryl aldehydes. Representative substrates were converted into five- and six-membered cyclic alkaloids by sequential one-pot *N*-debenzylation/triple bond reduction promoted by Pd, followed by a Mitsunobu-type cyclization.

Keywords: hydroxy-propargylamines, A^3-coupling, C–H activation, cyclic alkaloids

Introduction

In the last decades, multicomponent reactions have become an important alternative to prepare highly functionalized building blocks in high yields and in a straightforward way.[1] This kind of transformation is very attractive since the whole process is intrinsically atom-, energy- and step-economical.[2,3] Many relatively old, as well as new multicomponent strategies, have been investigated and important contributions have been made in this field. Structurally complex compounds can be assembled by means of multicomponent reactions, and recently, by coupling this strategy with organocatalysis, enantioenriched products were efficiently prepared in a short and elegant way.[4-11] Propargylamines are important building blocks for the preparation of complex amino derivatives and bioactive substances.[12-16] An important strategy for the synthesis of this class of compounds consists in the addition reaction of non-functionalized terminal alkynes to C–N double bond containing-compounds, usually imines, nitrones, iminium salts, etc.[17-21] There are several reports on the preparation of propargylamines by a A^3-coupling multicomponent reaction, but most of them are restricted to non-functionalized alkynes,[22-24] which is quite unattractive from the synthetic point of view. In addition, many procedures are dependent on the aldehyde nature, presenting good performance for either alkyl or aryl ones[25] but rarely for both.

Due to the importance of nitrogen-containing compounds, development of practical strategies to construct highly functionalized nitrogen-containing skeletons is desirable.

Recently, we demonstrated that alkynols could be used as the alkyne source in an A^3-coupling reaction, by reacting them with 4-piperidone hydrochloride.[26] It was found that alkyl aldehydes and alkynols are suitable partners in the reaction with this amine source allowing the preparation of a large number of propargyl 4-piperidones in good yields.[27] Aiming to improve the methodology to a more synthetically useful tool, we decided to use benzylamines as the amine source, since concomitant Pd-catalyzed hydrogenolysis and full triple bond reduction reactions can be performed in a single operation, leading to saturated amino-alcohols, which are direct precursors of alkaloids.

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Results and Discussion

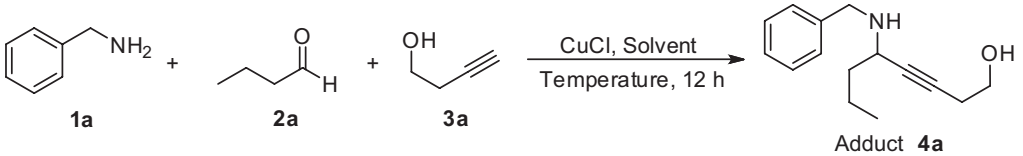
To test the feasibility of the strategy we selected benzylamine (**1a**), butyraldehyde (**2a**) and 3-butyn-1-ol (**3a**) as the starting materials for the A³-coupling reaction and CuCl (30 mol%) as the catalyst. In the first attempt to obtain the corresponding hydroxy-propargylamine, the reaction was performed in tetrahydrofuran (THF) in a sealed tube at 105 °C, and after 12 h the desired adduct **4** was obtained in only 27% yield. Aiming to improve the yield, a systematic study involving solvent, catalyst amount and temperature was undertaken and the results are presented in Table 1.

The experiments were conducted for 12 h in a sealed tube to achieve temperatures higher than the boiling points of the solvents. In hexane and benzene (entries 1 and 2), using 30 mol% of CuCl, the A³-coupling product was isolated in 60 and 76% yield, respectively. In 1,4-dioxane, THF and ethanol the product was formed in lower yields (entries 3-5). In ethyl acetate the product was isolated in the same average yield as in benzene (entries 2 and 6). As ethyl acetate is an environmentally benign solvent, it was chosen for the next experiments. No product was detected when the reaction was performed at room temperature (entry 7), the starting materials remaining unchanged. Increase in the product yields were observed when the reactions were performed at higher temperatures (entries 8-10), and a maximum of 75% yield was achieved at 105 °C (entry 6). This temperature was considered as limit for security reasons, as the sealed tubes were designed to operate at this temperature or below.[28] After setting this temperature, the quantity of the catalyst was screened. By using 5 and 15 mol% of CuCl, the product was obtained in 22 and 51% isolated yield respectively (entries 11 and 12). Use of 30 as well as 50 mol% of the catalyst led to the product in the same average yield (entries 6 and 13). In this way, 30 mol% was chosen as the ideal amount of the catalyst.

In order to define the scope and limitations of the protocol, other alkynes, aldehydes and benzylamines were submitted to the A³-coupling reaction under the conditions of choice, and the results are presented in Table 2.

As can be observed in Table 2, the methodology is quite general tolerating structurally diverse alkynols, alkyl and aryl aldehydes with equally good performance. Ethynylcyclohexanol and propargyl alcohol gave the desired adducts in reasonable yields (entries 1 and 8). Good yields were achieved using high-weight alkynols and alkyl aldehydes (entries 3 and 9). *p*-Formaldehyde presented good reactivity allowing the isolation of the corresponding A³-coupling product in 61% yield (entry 4). Benzaldehyde

Table 1. Solvent, catalyst amount and temperature screening for A³-coupling reaction

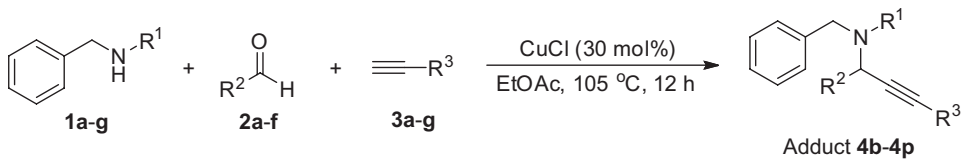


1a **2a** **3a** Adduct **4a**

entry	Solvent	CuCl[a] / mol%	Temperature / °C	Yield[b,c,d] / %
1	Hexane	30	105	60
2	Benzene	30	105	76
3	1,4-Dioxane	30	105	48
4	THF	30	105	27
5	EtOH	30	105	17
6	EtOAc	30	105	75
7	EtOAc	30	27	–[e]
8	EtOAc	30	40	11
9	EtOAc	30	65	30
10	EtOAc	30	80	63
11	EtOAc	5	105	22
12	EtOAc	15	105	51
13	EtOAc	50	105	73

[a]Based on the alkyne amount; [b]all reactions were conducted under air atmosphere and the solvents were used as received; [c]isolated yields; [d]all reactions were monitored by gas chromatography-flame ionization detector (GC-FID); [e]the starting materials were not consumed.

Table 2. A^3-coupling reaction of benzylamines using different alkynols and aldehydes



1a-g + **2a-f** + **3a-g** → Adduct **4b-4p**

entry	R^1	R^2	R^3	Adduct	Yield[a,b] / %
1	H, **1a**	, **2a**	, **3b**	, **4b**	56
2	**1a**	**2a**	, **3c**	, **4c**	71
3	**1a**	**2a**	, **3d**	, **4d**	87
4[c]	**1a**	H, **2b**	, **3a**	, **4e**	61
5	**1a**	, **2c**	**3a**	, **4f**	60
6	**1a**	Ph, **2d**	**3a**	, **4g**	64
7	**1a**	Ph, **2e**	**3a**	, **4h**	54
8	**1a**	, **2f**	, **3e**	, **4i**	63
9	**1a**	**2f**	, **3f**	, **4j**	80
10	Ph, **1b**	**2a**	**3a**	, **4k**	83/88[d]
11	Ph, **1c**	**2a**	**3a**	, **4l**	68

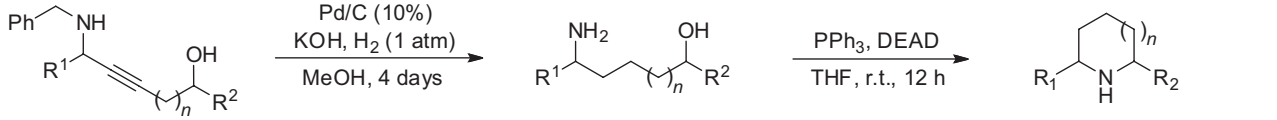
Table 2. A^3-coupling reaction of benzylamines using different alkynols and aldehydes

entry	R^1	R^2	R^3	Adduct	Yield[a,b] / %
12	Ph, **1d**	**2a**	**3a**	, **4m**	60
13	OH, Ph, **1e**	**2a**	Ph, **3g**	, **4n**	63
14[e]	OTBDMS, Ph, **1f**	**2a**	**3a**	, **4o**	60 (30% d.e.)
15[e]	OTIPS, Ph, **1g**	**2a**	**3a**	, **4p**	30 (24% d.e.)

[a]All reactions were performed with a benzylamine (1 mmol), aldehyde (1.3 mmol) and alkynol (2 mmol) in a pressure tube with CuCl (30 mol%), EtOAc at 105 °C; [b]isolated yields; [c]reaction was performed using paraformaldehyde; [d]reaction performed using 1 mol% of the catalyst for 2 h; [e]reaction was performed at 80 °C for 24 h. d.e.: diastereoisomeric excess.

and *p*-tolualdehyde also reacted as expected leading to the corresponding propargylamines in reasonable yields (entries 6 and 7). By monitoring the reactions by gas or thin layer chromatography a much faster conversion of the starting materials was observed when dibenzylamine (**1b**) was used as the amine source on reaction with butyraldehyde and 3-butyn-1-ol (entry 10). Aiming to optimize the reaction conditions for dibenzylamine (**1b**), it was found that the use of only 1 mol% of the catalyst resulted in the corresponding product in 88% yield after 2 h reaction time (entry 10). On the other hand, higher reaction times and catalyst amounts were necessary when the racemic as well as the optically active methyl-substituted benzylamines (**1c** and **1d**) were reacted with the same alkyne and aldehyde (entries 11 and 12). No diastereoisomeric excess (d.e.) was observed for the optically active amine (entry 12). Phenylglycinol was used in the coupling reaction in order to verify if diastereoselection could be achieved; however, instead of the A^3-coupling product, the corresponding *N*,*O*-ketal was isolated in 63% yield, resulting from the intramolecular attack of the hydroxyl group to the intermediate iminium carbon (entry 13). To circumvent this side reaction, the corresponding silyl ethers were used. The *tert*-butyl dimethylsilyl (TBDMS) derivative led to the A^3-coupling product in 60% yield and 30% d.e., and the tri-isopropylsilyl (TIPS) analogue led to the product in only 30 and 24% d.e. (entries 14 and 15).

Hydroxy-propargylamine adducts **4a**, **4c** and **4i** were converted into the corresponding cyclic alkaloids by concomitant hydrogenation/hydrogenolysis, followed by a Mitsunobu-type[29,30] cyclization reaction, as presented in Scheme 1.



4i, R^1 = *i*-Prop, R^2 = H, *n* = 0
4a, R^1 = *n*-Prop, R^2 = H, *n* = 1
4c, R^1 = *n*-Prop, R^2 = Me, *n* = 1

5a, R^1 = *i*-Prop, R^2 = H, *n* = 0
5b, R^1 = *n*-Prop, R^2 = H, *n* = 1
5c, R^1 = *n*-Prop, R^2 = Me, *n* = 1

6a, R^1 = *i*-Prop, R^2 = H, *n* = 0; (55% two steps)
6b, R^1 = *n*-Prop, R^2 = H, *n* = 1; (62% two steps)
6c, R^1 = *n*-Prop, R^2 = Me, *n* = 1; (60% two steps)

Scheme 1. Synthesis of cyclic alkaloids from the A^3-coupling adducts.

The pyrrolidine alkaloid **6a** is used in the food industry as flavoring[31] and its structure is found as a substituent group in several bioactive compounds.[32] Coniine (**6b**) is a highly toxic alkaloid extracted from mushrooms and is able to induce muscular paralysis.[33-36] Dihydropinidine (**6c**) was isolated from young seedlings of *Pinus ponderosa* presenting activity against Alzheimer's diseases[37] and displays a high antifeedant activity for the pine weevil *Hylobius abietis*.[38]

The presented synthetic strategy allowed the synthesis of the alkaloids 2-isopropylpyrrolidine (**6a**), coniine (**6b**) and dihydropinidine (**6c**) in three synthetic steps in an overall yield of 35, 46 and 42%, respectively. The A^3-coupling reaction can be considered as the key step of the synthetic sequence, and consequently as an alternative route to the synthesis of bioactive alkaloids.

Conclusions

In summary, we demonstrated the easy preparation protocol to access hydroxy-propargylamines, by a catalyzed A^3-coupling reaction. Alkynols and benzylamines were directly reacted with aromatic and aliphatic aldehydes presenting good reactivity. Alkyl and aryl aldehydes, as well as functionalized alkynes, were tolerated. The use of benzylamines is synthetically strategic since concomitant hydrogenonlysis of the benzyl nitrogen and triple bond reduction can be performed in good yields, resulting in the corresponding saturated amino-alcohols. Cyclic alkaloids can be easily obtained by sequential A^3-coupling, hydrogenation/hydrogenolysis sequence followed by a Mitsunobu-type cyclization reaction. As a proof of concept this procedure was applied to the synthesis of three cyclic bioactive alkaloids.

Experimental

General information

All reagents were purchased from Aldrich. The reactions was performed using an Ace® pressure tube bushing type, back seal, volume ca. 35 mL, 17.8 cm × 25.4 mm (L × o.d.) from Sigma-Aldrich (product code Z181072). Analytical thin layer chromatography (TLC) was carried out by using silica gel 60 F_{254} pre-coated plates. Visualization was accomplished with vanillin [0.01 g mL^{-1} vanillin in $AcOH/H_2SO_4$ (99:1) solution] or ninhydrin as color reagent [0.005 g mL^{-1} ninhydrin in EtOH (96%) solution]. The gas chromatography (GC) analyses were performed on a Shimadzu® GC2014 equipment, with flame ionization detection (FID), N_2 as carrier gas and equipped with a DB-5 column (30 m × 0.25 mm × 0.25 mm) or DB-5-HT (30 m × 0.32 mm × 0.10 mm). All new products were characterized by their nuclear magnetic resonance (NMR), infrared (IR), mass spectrometry (MS) and high-resolution MS (HRMS) spectra. The ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) were recorded on a Bruker® AC 200 spectrometer and the ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker® DRX 400 spectrometer, in both cases using tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in parts *per* million (ppm, δ) downfield from the TMS. The infrared analyses were recorded on a Shimadzu® equipment, model IRPrestige-21, and Bomen Hartmann & Braun® MB-Series equipment, model Arid-Zone®. Low-resolution mass spectra were recorded on a Shimadzu® GC-17A coupled with QP5050A MS, using HP-5MS column (30 m × 0.25 mm × 0.25 mm). High-resolution mass analyses were recorded on a LC/MS Bruker® Daltonics MicroTOFIc equipment by direct injection of pure samples. High performance liquid chromatography (HPLC) analyses were performed on Shimadzu® LC-10AD and LC-30AD devices equipped with a UV-Vis SPD-M20A detector, using a Daicel Chiralpak® OD-H and Daicel Chiralpak® OD columns and hexane:isopropanol (99:1) as mobile phase with 0.8 mL min^{-1} flow.

General procedure for the synthesis of benzylamines **1b** and **1c**

To a 10 mL round-bottomed flask containing benzaldehyde (0.233 g, 0.202 mL, 2.2 mmol) was added dropwise the amine (2.0 mmol). The mixture was stirred at room temperature and the progress of amine consuption was monitored by GC-FID or TLC chromatography. To the reaction mixture, at 0 °C, EtOH (2.0 mL) and sodium borohydride (0.076 g, 2.0 mmol) were added sequentially. The reaction was warmed to room temperature, stirred for 2 h and quenched with water (5 mL) and HCl (10 mL, 10% v/v). After separantion, the aqueous phase was treated using $NaHCO_3$ solution (until pH 8) and then extracted with EtOAc (4 × 10 mL). After combination, the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure giving the corresponding amine in high purity grade.

General procedure for the synthesis of benzylamines **1f** and **1g**

To a 10 mL round-bottomed flask, under nitrogen atmosphere, containing (*R*)-2-(benzylamino)-2-phenylethanol (0.500 g, 2.0 mmol), imidazol (0.204 g,

1.5 mmol) and *N*,*N*-dimethylformamide (1 mL) at 0 °C, was added, in two portions, the trialkylsilane (2.0 mmol). The reaction was warmed to room temperature and, after 18 h, quenched with water (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined and washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure giving the corresponding amine in high purity grade.

General procedure for the synthesis of hydroxypropargyl benzylamines

To a 35 mL pressure tube were sequentially added copper(I) chloride (0.060 g, 0.6 mmol), benzylamine (0.107 g, 0.14 mL, 1.0 mmol), aldehyde (1.3 mmol), alkynol (2.0 mmol) and EtOAc (2 mL). The mixture was stirred at 105 °C and the progress of the reaction was monitored by GC-FID or TLC. The reaction mixture was filtered in a short pad Celite® column. The Celite® residue was washed with EtOAc (2 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was directly purified by silica gel column chromatography using the appropriate eluent.

General procedure for the synthesis of amino alcohols **5a**, **5b** and **5c**

To a 10 mL round-bottomed flask containing Pd/C 10% (0.070 g), previously activated with hydrogen gas, were sequentially added MeOH (15 mL), hydroxypropargylamine (2.0 mmol) and KOH (two drops, 1.0 mol L^{-1} solution). The mixture was stirred at room temperature, in H_2 atmosphere (1 atm) and the progress of the reaction (4 days) was monitored by GC-FID. The reaction mixture was filtered in a short pad Celite® column. The Celite® residue was washed with CH_2Cl_2 (4 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was directly purified by silica gel column chromatography using the appropriate eluent.

General procedure for the synthesis of cyclic alkaloids **6a**, **6b** and **6c**

To a 25 mL round-bottomed flask were added triphenylphosphine (0.619 g, 2.36 mmol) and THF (8 mL). The mixture was refrigerated in an ice/acetone/NaCl bath (–10 °C) followed by dropwise addition of diethyl azodicarbolylate (0.411 g, 0.37 mL, 2.36 mmol). After 30 min a white solid was formed and a solution of amino alcohol (2.0 mmol) in THF (7 mL) was added. The mixture was stirred for 12 h and the progress of the reaction was monitored by GC-FID or TLC. At the end of this time, the reaction mixture was concentrated under reduced pressure and the crude product was purified by Kugelrohr distillation apparatus.

Typical procedure for A^3-coupling

To a 35 mL pressure tube were sequentially added copper(I) chloride (0.060 g, 0.6 mmol), benzylamine (1.0 mmol), aldehyde (1.3 mmol), alkynol (2.0 mmol) and EtOAc (2 mL). The mixture was stirred at 105 °C and the progress of the reaction was monitored by GC-FID or TLC. The reaction mixture was filtered in a short pad Celite® column. The Celite® residue was washed with EtOAc (2 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was directly purified by silica gel column chromatography using the appropriate eluent.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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