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Artigo

A GENERAL A^3-COUPLING REACTION BASED ON FUNCTIONALIZED ALKYNES

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A range of hydroxypropargylpiperidones were efficiently obtained by a one-pot three-component coupling reaction of aldehydes, alkynols, and a primary amine equivalent (4-piperidone hydrochloride hydrate) in ethyl acetate using copper(I) chloride as a catalyst. The developed protocol proved to be equally efficient using a range of aliphatic aldehydes, including paraformaldehyde, and using protected and unprotected alkynols.

Keywords: hydroxypropargylamine; multicomponent reaction; A^3-coupling.

INTRODUCTION

Connecting organic fragments that have desired functionalities by short and inexpensive synthetic routes is one of the most exciting and challenging tasks for organic chemists, and it requires a high level of creativity and elegance.

Recently, multicomponent reactions have been receiving significant attention, because multiple carbon–carbon and carbon–heteroatom bonds can be generated in a single step, allowing for the straightforward construction of intricate organic compounds. Recent developments in this area have been very impressive, and procedures involving seven[1] and even eight[2] components have been reported.

The three-component coupling of aldehydes, amines, and alkynes (A^3-coupling) is a very efficient method for forming propargylamines by C–H activation.[3] A^3-coupling is more practical than the other methods available for preparing this class of compounds, because no moisture-sensitive stoichiometric organometallics, such as Grignard or organolithium reagents, are involved. It is also applicable to various substrates. This transformation can be catalyzed by a large number of transition-metal salts, including copper,[4] iron,[5] cobalt,[6] nickel,[7] zinc,[8] ruthenium,[9] silver,[10] cadmium,[11] indium,[12] ytterbium,[13] iridium,[14] gold,[15] mercury,[16] bimetallic salt combinations,[17] supported metals,[18] and nanostructured materials.[19] It is interesting to note that, although the use of various amines and aldehydes in this method has been described, the number of alkynes used has been limited. Non-functionalized alkynes, such as phenylacetylene and trimethylsilylacetylene, have been used most frequently, but the A^3-coupling of alkynols, to prepare functionalized allenols, has recently been described.[20]

In 2006, Gommermann and Knochel described the use of an A^3-coupling silylated adduct in the asymmetric synthesis of (*S*)-(+)-coniine.[21] We know of only a few examples of unprotected alkynols being used in the A^3-coupling reaction, and all of them, except for ones we have previously reported,[22] have been limited to aromatic aldehydes.[23,24] A general procedure for the preparation of hydroxypropargylamines would be very desirable because these chemicals are direct precursors for alkaloids. The desired carbon skeleton could be achieved in a one-pot process using an A^3-coupling-type protocol and using the correct functionalities for cyclization to form five- and six- (and higher) ring alkaloid systems.

In 2006, Carreira reported using 4-piperidone hydrochloride hydrate as a secondary amine source in an A^3-coupling reaction.[25] The authors demonstrated that using this amine source allowed the A^3-coupling adducts (tertiary amines) to be easily converted into the corresponding primary amines, in good yields, by their reaction with an amino-polystyrene resin scavenger or with a saturated ammonia–ethanolic solution. This procedure is highly compatible with chemicals containing a triple bond, and in the presence of a hydroxyl group, it permits the isolation of the corresponding hydroxypropargylamine, which can be converted into the corresponding hydroxyallylamine or the fully saturated amino alcohol, which are valuable building blocks.

Here we present a general protocol, which is complementary to the methodologies described above, for preparing hydroxypropargylamines using catalytic amounts of CuCl to promote A^3-coupling by C–H activation among aliphatic aldehydes, 4-piperidone, protected and unprotected alkynols, and non-functionalized alkynes.

RESULTS AND DISCUSSION

To test the feasibility of using alkynols in the A^3-coupling reaction, we screened a range of solvents, temperatures, and potential metal catalysts in the reaction of butyraldehyde (**1a**), 4-piperidone hydrochloride hydrate (**2**), and homopropargyl alcohol (**3a**) using 4 Å molecular sieves as a dehydrating agent (Table 1).

The A^3-coupling of **1a**, **2**, and **3a** was tested using a number of solvents with CuCl (5 mol%) as the catalyst. 1,4-Dioxane and toluene (Table 1, entries 2 and 3, respectively) gave comparable results to ethyl acetate (entry 10), and the latter was chosen for further study because it is more environmentally benign than the other solvents. We are aware of only two reports of ethyl acetate being used as the solvent for such a reaction, but only one substrate was described in each case.[26,27] The reaction was completed in lesser time at 70 °C (entry 12) than at the other temperatures tested, and adduct **4a** was isolated in 71% yield. When the same reaction was performed at 50 or 100 mmol scales, adduct **4a** was isolated in slightly better yields (75 or 80%, respectively, entry 12). Using more CuCl did not significantly improve the yield of adduct **4a** (entries 17–20), but using less catalyst caused the yield to be significantly lower under the same reaction conditions (entries 13–16). Other catalysts that have previously been used in A^3-coupling reactions were also tested using our optimized conditions, but only CuBr (entry 21) performed comparatively well. We decided to use CuCl as the catalyst in further work, rather than CuBr, for economic reasons.[28] We reacted homopropargyl compounds **3b**–**e** under the same conditions

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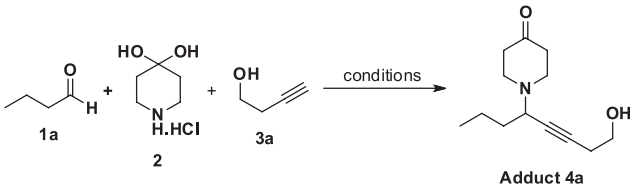
Table 1. Solvent, catalyst and temperature screening for A^3-coupling reaction



Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Yield (%)[a,b,c]	Time (h)[d]
1	Hexane	CuCl (5)	r.t.	74	15
2	1,4-Dioxane	"	"	82	15
3	Toluene	"	"	87	19
4	Et_2O	"	"	75	20
5	THF	"	"	62	20
6	CH_2Cl_2	"	"	33	24
7	MeOH	"	"	14	36
8	CH_3CN	"	"	10	24
9	H_2O[e]	"	"	22	48
10	EtOAc	"	"	81	18
11	"	"	50	76	12
12	"	"	70	71/75[f]/80[g]	4
13	"	" (0.1)	"	2	"
14	"	" (0.5)	"	13	"
15	"	" (1.0)	"	32	"
16	"	" (2.5)	"	50	"
17	"	" (7.5)	"	71	"
18	"	" (10)	"	72	"
19	"	" (25)	"	76	"
20	"	" (50)	"	80	"
21	"	CuBr (5)	"	71	"
22	"	CuI (5)	"	59	"
23	"	CuCN (5)	"	32	"
24	"	AgI (5)	"	---	"
25	"	$HgCl_2$ (5)	"	Trace	"
26	"	$Zn(OAc)_2$ (5)	"	Trace	"

[a] All reactions were conducted under an air atmosphere, and the solvents were used without special treatment. [b] Isolated yields. [c] In some cases, small amounts of alkyne homocoupling byproducts were detected, but they were easily removed by performing an acid–base liquid extraction. [d] All reactions were monitored by GC-FID. [e] 4 Å molecular sieves were not used. [f] Reaction was performed at the 50 mmol scale. [g] Reaction was performed at the 100 mmol scale.

as reported for entry 12 (3 mmol scale) to assess the influence of other functional groups on the alkyne. These substrates tolerated the reaction conditions well, allowing the corresponding adducts **4b**–**e** to be isolated in good yields, free of exogenous byproducts (Scheme 1).

Based on these results, we applied the conditions to the reactions of other alkynols (**3f**–**o**) with **1a**, and the results are summarized in Table 2.

From Table 2, it can be seen that the A^3-coupling reactions using alkynols and aliphatic aldehydes gave better results than the reactions using non-functionalized alkynes (compare entries 1–7 with 8–10). Other aldehydes (**1b**–**h**) were reacted with 4-pentyn-2-ol (**3f**) (Table 3) to assess the scope and limitations of the protocol.

It is worth noting that adduct **4p** was isolated in reasonable yield (59%) from the reaction using the equivalent of formaldehyde (paraformaldehyde, **1b**) (Table 3, entry 1). Even volatile aldehydes, such as *n*-propanaldehyde (**1c**) and *iso*butyraldehyde (**1d**), were successfully converted into the corresponding A^3-coupling adducts in good yields (entries 2 and 3, respectively). The yields were equally good when medium-chain **1f** and long-chain **1g** aldehydes were used (entries 5 and 6, respectively). Aromatic aldehydes did not give the corresponding adducts in acceptable yields, but the benzylic aldehyde **1h** gave the desired adduct **4v** in good yield (entry 7).

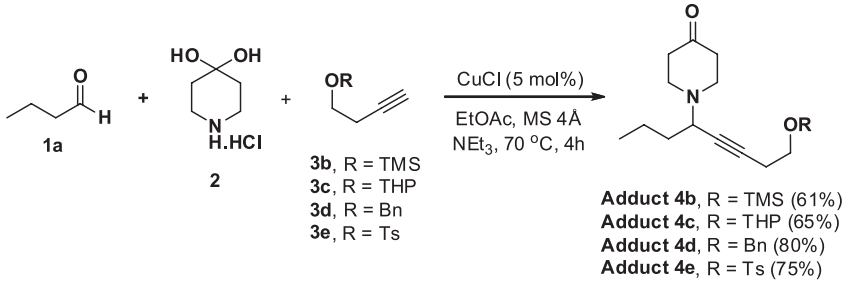
In general, aliphatic and cyclic primary, secondary, and tertiary alkynols gave the desired A^3-coupling adducts in good yields without the detection of any dehydration products or other byproducts (see Tables 1-3).

As described by Carreira et al.,[25] 4-piperidones can be converted into the corresponding primary propargylamines by refluxing in an NH_4Cl/ammonia-saturated ethanolic solution or by heating in the presence of an amine-polystyrene resin in an NH_4Cl/ethanolic solution. Using this approach, hydroxypropargyl-4-piperidones produced in our study were eventually converted into the corresponding amino alcohols.

To the best of our knowledge, there has been only one report of the synthesis of a piperidine alkaloid, (*S*)-(+)-coniine, from an A^3-coupling adduct.[21] The three-component reaction strategy using trimethylsilylacetylene as the alkyne component was used to produce that chemical; hence, a -CH_2CH_2OH unit had to be introduced by the methylene oxide alkylation reaction after deprotonation using *n*-BuLi. The strategy we have demonstrated here, i.e., using alkynols as the alkyne component, is complementary to the approach employed by Gommermann and Knochel, because no additional chain homologation is required to prepare the amino-alcohol skeleton needed for preparing cyclic alkaloids.

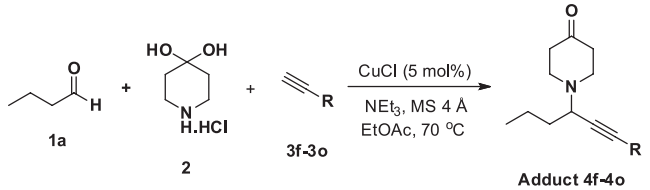
A tentative mechanism for the A^3-coupling reaction is presented in Scheme 2, and it agrees with mechanisms proposed by other authors.[29]

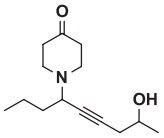
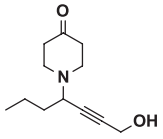
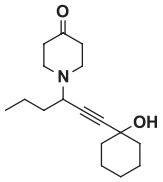
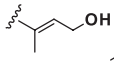
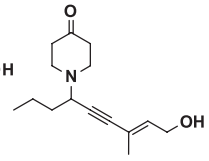
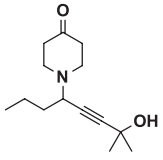
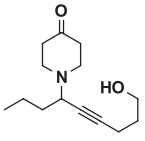
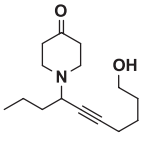
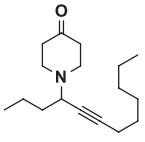
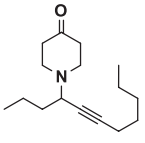
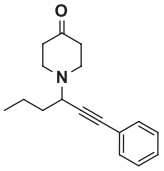
As is already known, the amines present in the reaction media are weak bases and are not sufficiently strong to deprotonate a terminal alkyne without other stimuli.[30] We speculate that a ϖ-copper–alkyne complex could be generated, leading to a more acidic terminal alkyne, which would be able to be removed by a weak base, such as an amine. The iminium chloride would be concurrently produced from the aldehyde and amine. The addition of the resulting acetylide to the iminium salt would result in the formation of propargylamine, regenerating the copper ion for another cycle.



Scheme 1. *A^3-coupling using different homopropargyl derivatives*

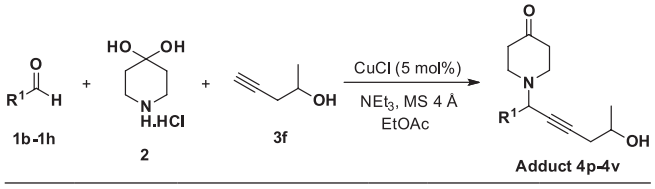
Table 2. A^3-coupling reaction of butyraldehyde and different alkynols

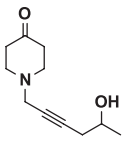
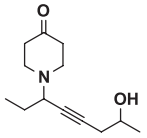
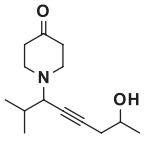
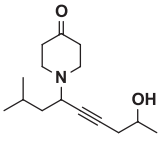
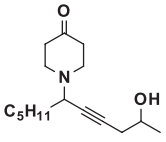
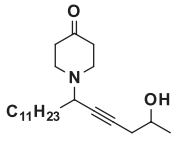
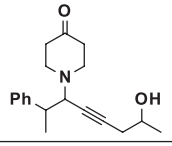


Entry	R	Adduct / number	Yield (%)[a]	Time (h)[b]
1		 **4f**	72	4.5
2		 **4g**	75	4
3		 **4h**	73	6
4		 **4i**	76	5.5
5		 **4j**	85	5.5
6		 **4k**	80	6.5
7		 **4l**	77	4
8		 **4m**	69	4
9		 **4n**	66	4
10		 **4o**	62	6

[a] Isolated yields. [b]All reactions were monitored by GC-FID.

Table 3. A^3-coupling reaction using different aliphatic aldehydes



Entry	R^1	Adduct / number	Yield (%)[a]	Time (h)[b]
1[c]	H	 **4p**	59[d]	24
2		 **4q**	65[d]	4.5
3		 **4r**	99[e]	5
4		 **4s**	97[f]	5
5		 **4t**	78[f]	4.5
6		 **4u**	75[f]	6
7		 **4v**	72[f]	5

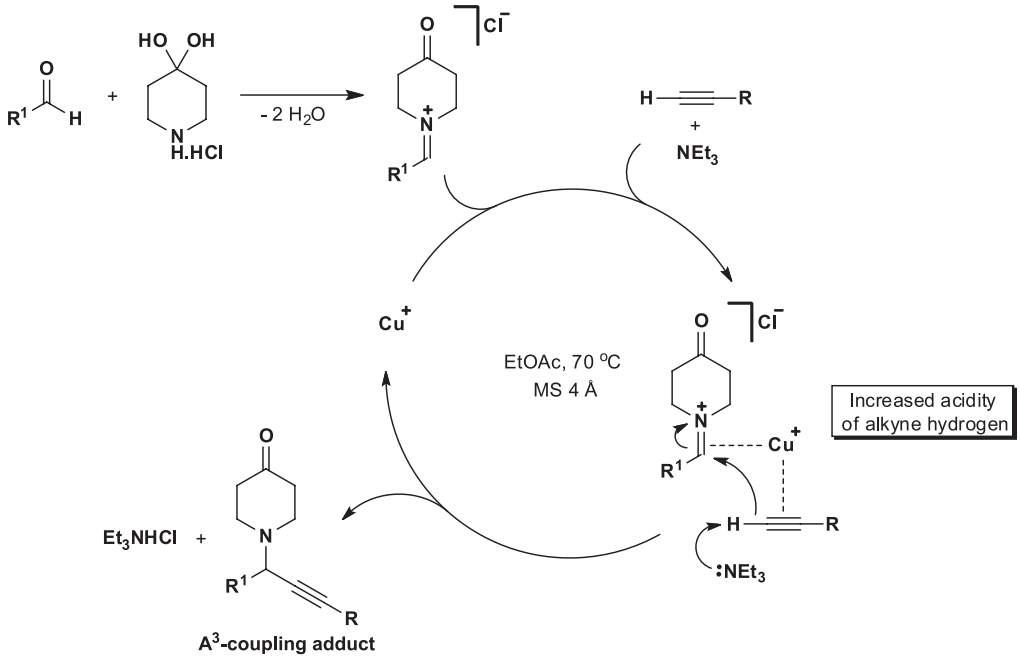
[a] Isolated yields. [b] All reactions were monitored by GC-FID. [c] Reaction was performed using paraformaldehyde (equivalent to formaldehyde). [d] Reaction was performed at room temperature (27 °C). [e] Reaction was performed at 50 °C. [f] Reaction was performed at 70 °C.

CONCLUSIONS

We have demonstrated, for the first time, a general and selective CuCl-catalyzed A^3-coupling reaction for preparing hydroxypropargyl-4-piperidones, which are valuable precursors for cyclic alkaloids. The procedure gives good yields and has short reaction times, and hydroxypropargylamines can be prepared using functionalized alkyne sources (free alcohols, silyl ethers, ethers, ketals, and tosylates). Even volatile aliphatic aldehydes were well tolerated in the procedure, and the corresponding adducts were isolated in good yields.

EXPERIMENTAL

All reagents were purchased from Aldrich. Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated plates,



Scheme 2. *Proposed catalytic cycle in the A³-coupling reaction*

and the chemicals were made visible using vanillin as a coloring reagent (using 1.0 g vanillin in a 99:1 CH_3CO_2H / H_2SO_4 solution). Gas chromatography (GC) was performed using a Shimadzu® GC2014 instrument equipped with a DB-5 column (30 m length, 0.25 mm id, 0.25 μm film) and a flame ionization detector (FID). All new compounds were characterized by NMR, IR, EI-MS, and ESI-HRMS spectroscopy. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker® DRX 400 spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million (ppm, δ) downfield of TMS. The IR spectra were recorded using a Bomen Hartmann & Braun® MB-Series Model Arid-Zone® instrument. Low-resolution mass spectra were recorded using a Shimadzu® QP 5000 mass spectrometer after gas chromatographic separation using an HP-5MS GC column (30 m length, 0.25 mm id, 0.25 μm film). High-resolution mass spectra were recorded using a Bruker® Daltonics MicroTOF Ic LC/MS instrument from direct injections of the pure samples.

General procedure for the synthesis of hydroxypropargylamine derivatives

CuCl (0.009 g, 0.1 mmol), 4 Å molecular sieves (0.300 g), 4-piperidone hydrochloride monohydrate (0.169 g, 1.1 mmol), and EtOAc (2 mL) were added, in that order, to a 10-mL round-bottomed flask. The mixture was stirred at 70 °C and then triethylamine (0.110 g, 0.15 mL, 1.1 mmol), alkynol (2.0 mmol), and the appropriate freshly distilled aldehyde (1.0 mmol) were added. The reaction mixture was stirred, and the progress of the reaction was monitored by GC-FID or TLC. The reaction mixture was passed through a short pad of Celite® in a column and eluted with EtOAc (3 × 5 mL). A saturated NH_4Cl solution (10 mL) was added to the organic phase, and the mixture was stirred vigorously for 20 min, separated, and the organic phase was treated with HCl (15 mL, 10% v/v) in a separatory funnel. The aqueous phase was washed with EtOAc (10 mL) to remove any homocoupling products, neutralized with a saturated $NaHCO_3$ solution (3 × 10 mL) and extracted again with EtOAc (4 × 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using the appropriate eluent.

SUPPLEMENTARY MATERIAL

The ^{1}H NMR, ^{13}C NMR, IR, EI-MS, and EI-HRMS spectra, and the corresponding spectral data, for all of the newly synthesized compounds are available as supplementary material.

ACKNOWLEDGMENTS

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