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Proceeding Paper

[CuI–TIBAL]—Effective Catalytic System for KA² Reaction to Prepare Tetrasubstituted Propargylamine at Room Temperature †

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Abstract: We have discovered for the first time that the CuI-TIBAL catalytic system (20 mol. %) makes it possible to carry out three-component couplings of ketones, alkynes, and amines (KA² reaction) in dichloromethane or dichloroethane in quantitative yield even at room temperature. Alkyl- and aryl-substituted terminal acetylenes (including diacetylenes), a number of secondary amines (piperidine, pyrrolidine, dibutylamine) and a number of ketones (cyclohexanone, cyclopentanone, acetone, 2-octanone, 3-nonanone) were involved in KA² reaction. A solvent is an important factor in the reaction. The use of toluene and hexane leads to a negligible yield of tetrasubstituted propargylamines at room temperature. Thus, we found an activating effect of the TIBAL additive and dichloromethane on the KA² reaction.

Keywords: catalysis; KA² reaction; tetrasubstituted propargylamine

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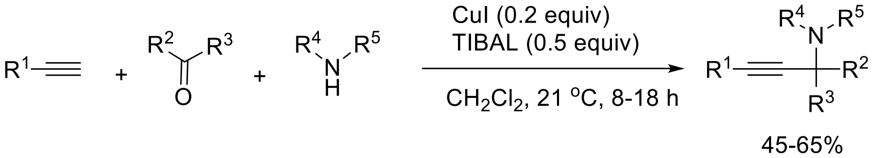
1. Introduction

Three-component couplings of ketones, alkynes, and amines (KA² reaction) are the most efficient method of forming tetrasubstituted propargylamine building blocks for rapid access to biologically active targets. Typically, the reaction is carried out at temperatures above 100 °C (or under microwave irradiation conditions) in the presence of copper catalysts in toluene or without solvent [1–4]. The use of $AuBr_3$ instead of copper salts allows the reaction temperature to be reduced to 60 °C [5]. Recently we discovered an activating effect of trialkylaluminums on the catalytic activity of copper salts [6]. In this regard, we studied the reaction of Cu-catalyzed three-component couplings of ketones, alkynes, and amines in the presence of i-Bu_3Al (TIBAL).

2. Results and Discussion

We found that the reaction of 1-octyne with 1 equivalent of cyclohexanone and 1 equivalent of piperidine in the presence of 0.2 equivalent of CuI and 0.5 equivalent of TIBAL in a dichloromethane at room temperature for 8 h led to the formation of 1-(1-(oct-1-yn-1-yl)cyclohexyl)piperidine in 62% yield (Scheme 1). After 18 h the content of tetrasubstituted propargylamine was not changed significantly. The reaction mixture was completely free of terminal acetylene dimerization products. The reaction with CuCl as a catalyst proceeded in a similar way. Similar results were obtained using dichloroethane instead of dichloromethane as a solvent. When hexane or toluene was used instead of dichloromethane, tetrasubstituted propargylamine was formed in trace amounts after 18

h. In ethereal solvents (diethyl ether, THF, 1,4-dioxane) the reaction does not take place as well.

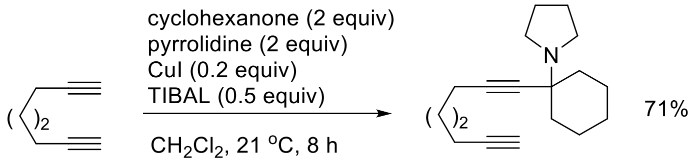


R^1 = n-C_4H_9, n-C_6H_{13}, Ph
R^2,R^3 = $(CH_2)_4$; $(CH_2)_3$; Me, Me; Me, n-Hex; Et, n-Am
R^4,R^5 = $(CH_2)_4$; $(CH_2)_3$; n-Bu, n-Bu;

Scheme 1. Three-component couplings of ketones, alkynes, and amines under the action of [CuI–TIBAL] catalytic system.

Alkyl- and aryl-substituted terminal acetylenes, a number of secondary amines (piperidine, pyrrolidine, dibutylamine) and a number of ketones (cyclohexanone, cyclopentanone, acetone, 2-octanone, 3-nonanone) were involved in KA^2 reaction to give tetrasubstituted propargylamines in moderate yield (45–65%). In some cases, for example, when using 2-octanone, a significant amount (up to 30%) of terminal acetylene dimerization products were formed.

Interestingly, despite the use of two equivalents of pyrrolidine and cyclohexanone, 1,7-octadiyne selectively gave aminomethylation product of only one terminal bond (Scheme 2).



Scheme 2. The aminomethylation of 1,7-octadiyne.

It is obvious that the organometallic compound (TIBAL) promotes the ionization of copper iodide forming active ionic complex. In this regard, the choice of dichloromethane as a solvent is quite reasonable. Dichloromethane facilitates the ionization of the resulting complex without greatly reducing the activity of copper ions.

3. Conclusions

CuI-TIBAL catalytic system (20 mol. %) is efficient to carry out three-component couplings of ketones, alkynes, and amines (KA^2 reaction) in dichloromethane or dichloroethane in quantitative yield even at room temperature.

4. Experimental Part

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer in $CDCl_3$, chemical shifts were reported relative to TMS. Mass spectra were obtained on a Shimadzu GCMS QP2010 Plus GC-MS instrument (capillary column SPB-5 of 30 m × 0.25 mm, carrier gas–helium, from 40 to 300 °C at a rate 8 deg/min, temperature of vaporizer 280 °C, ion source temperature 200 °C, ionization energy 70 eV). Chromatographic analysis was carried out on a chromatograph Shimadzu GC-9A, GC-2014 [column of 2 m × 3 mm, stationary phase silicone SE-30 (5%) on Chromaton N-AW-HMDS, from 50 to 270 °C, heating rate 8 deg/min, carrier gas-helium (47 mL/min)].

Synthesis of 1-(1-(Phenylethynyl)cyclohexyl)piperidine

To a 25-mL argon-swept flask in an ice bath, equipped with a magnetic stirrer and rubber septa, was added 0.2 mmol of CuI suspended in CH_2Cl_2 (4 mL). To the solution was added dropwise 1 mmol of phenylacetylene (102 mg), 1 mmol of cyclohexanone (98 mg), 1 mmol of piperidine (85 mg), 0.5 mmol of TIBAL and stirred at room temperature for 8 h. Then, the reaction mixture was diluted with hexane (5 mL) and H_2O (3 mL) was added dropwise while cooling the reactor flask in an ice bath. The precipitate was filtered on a filter paper. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $CaCl_2$. Evaporation of solvent and purification of the residue by column chromatography (hexane/ethyl acetate, 5:1) gave 1-(1-(phenylethynyl)cyclohexyl)piperidine as a colorless oil. The spectral parameters of the obtained compound are in good agreement with the published data [5].

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