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A copper (I or II)/diethylphosphite catalytic system for base-free additive dimerization of alkynes

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ABSTRACT

Copper (I) or copper (II) salts and oxides promote regioselective head-to-head additive dimerization of aromatic and aliphatic terminal alkynes in the presence a catalytic amount of diethylphosphite. The reaction proceeds under ambient conditions without any added base with the formation of 1,4-disubstituted 1,3-enynes with the E isomer as major product in good to excellent yields. A plausible mechanism for additive dimerization of terminal alkynes is proposed.

1. Introduction

In our earlier study of the copper-catalyzed addition of S–H[1] and P(O)–H[2] bonds to alkynes we have serendipitously observed that the Cu(II) catalyzed reaction of phenylacetylene with $(RO)_2P(O)H$ (R = Et, Ph), gives in high yield (up to 90%) the corresponding conjugated enyne, resulting from the additive dimerization of alkyne, instead of the expected H–P(O) addition product (Scheme 1).

Since conjugated enynes are very important building blocks for the synthesis of biologically active molecules[3] and materials for molecular electronics,[4] we decided to study this reaction in more detail. It is known that stereodefined enynes (E or Z) can be obtained by cross-coupling reactions of alkenyl halides with terminal alkynes under Cu(I)[5] or Pd[6] catalysis, by the reaction of vinylsilanes with bromoalkynes,[7] or using a Heck reaction.[8]

However, the simplest and most atom-economical route to conjugated enynes is certainly the metal-catalyzed additive dimerization of alkynes. This reaction was studied for various (early or late) transition metal catalysts and lanthanides.[9a,b] Surprisingly, the general copper catalyzed version of this transformation is still unknown, with a notable exception of acetylene itself; its dimerization on CuCl-based Nieuwland catalyst is used in the industrial production of vinylacetylene and is mentioned in many textbooks,[10] while acetylene dimerization with copper acetylenide is known as the Strauss reaction.[11] The most common problem in the additive dimerization of unsymmetrical alkynes is the formation of head-to-head (E and Z) and head-to-tail isomer mixtures (Scheme 2).

Dimerization can be also accompanied by the formation of Glaser-type[12] 1,3-diynes ($R-\equiv-\equiv-R$), and, under early transition metal catalysis, of triene byproducts ($R-=\cdot=\cdot=-R$). In addition to all these difficulties, related to regio- and stereoselectivity, there is a problem of finding a catalyst equally effective for aromatic and aliphatic acetylenes. In his pioneering work B. Trost developed the palladium catalyzed conditions, which allowed to obtain head-to-tail isomers selectively.[13] However, it was soon shown that changing the palladium catalyst, the type of alkyne, using a different base and other additives, allows to obtain either head-to-head[14,15] or head-to-tail isomers.[15a,b] For example, head-to-head isomer is formed in the reaction of terminal alkyne with activated internal alkyne in water under joint $CuBr-PdCl_2(PPh_3)_2$ catalysis.[16] In this paper we extended our reaction[2] on variety terminal alkynes using Cu (I) and Cu (II) salts and oxides in the presence of catalytic amount of $(EtO)_2P(O)H$.

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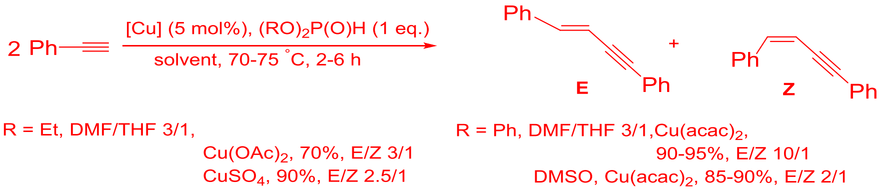
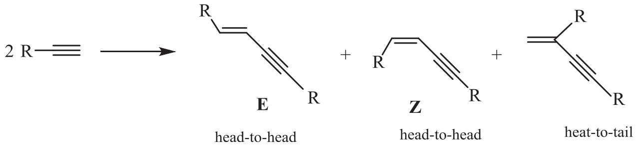


Scheme 1. Dimerization of phenylacetylene.



Scheme 2. Enynes formed by catalytic dimerization of terminal alkynes.

2. Results and discussion

Initial optimization of reaction conditions was performed using phenylacetylene dimerization as a model reaction.

Under aerobic conditions this reaction[17] in DMF-THF (3:1) gave 1,4-diphenylbutadiyne as the only product formed. Depending on the Cu(II) salt catalyst and additive (Table 1) its yield varied from low (entries 2, 4, 5, 8) to moderate (entries 1, 6, 7, 9) or even nearly quantitative (entry 3).

To avoid this unwanted dimerization all subsequent reactions were carried out under a dry argon atmosphere.

We tested different Cu(II) salts as well as Cu_2O and CuO oxides in the presence of different additives, which can serve as ligands or reducing agents (Table 2). In the presence of such additives as amine base (entries 1, 2), acid (entry 3), reducing agents (Zn – entry 4, sodium ascorbate – entry 5) no enyne product is formed.

The addition of phosphine or triethyl phosphite as ligand was also ineffective, since only minor amounts of the enyne product (<10%) were observed. Slightly better results were obtained with inorganic phosphoric and hypophosphorous acids (entries 14 and 15), which are weak ligands but good reducing agents. However, only the use of diorganophosphites – $(PhO)_2P(O)H$ (entry 16) and $(EtO)_2P(O)H$ (entries 17–20) effectively promoted the additive dimerization with high yield of enyne product.

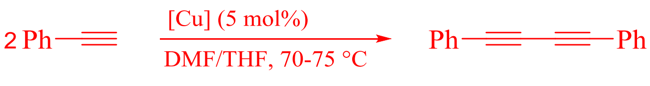
In the following runs diethylphosphite was used as a cheaper and easily available reagent (Table 3). It was found that irrespective of the Cu-source (5 mol%) except copper bromide, prolinate and trifluoroacetylacetonate (entries 1–3) the reaction in the presence of $(EtO)_2P(O)H$ (10–20 mol%) in DMF/THF (entries 4, 8–10, 12, 13–17) gave the head-to-head 1,3-enyne in high yield and of the mostly of E-configuration: E/Z = 2.5/1–3/1.

The yield decreases in DMSO or neat THF (entries 6, 7, 11). In case of copper oxides CuO and Cu_2O the addition of one equivalent of phosphite increases their solubility, and so improves yield of the product as compared with 20 mol% $(EtO)_2P(O)H$ (entries 14, 16 and 15, 17). It is also worth noting that the salts and oxides of Cu(I) and Cu(II) in the presence of $(EtO)_2P(O)H$ showed roughly the same efficiency.

On finding the optimum reaction conditions we have carried out the additive dimerization of different aromatic and aliphatic alkynes (Table 4). Electron donating substituents in the alkyne make the reaction more difficult, and electron withdrawing substituents facilitate it (entries 1–3).

The aliphatic alkynes are therefore less reactive than aromatic (entries 4–8), while the propiolic acid is the most reactive substrate (entry 9). There is a clear correlation between the alkyne reactivity and the E/Z-product ratio: the less reactive alkylacetylenes produce a higher content of E isomer, while with propargylic alcohol and

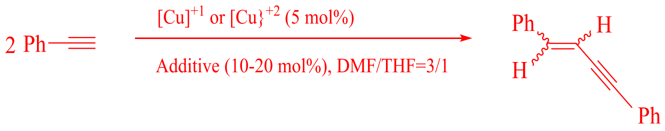
Table 1
Reaction of phenylacetylene catalyzed by ligand–free copper salts under air.



Entry	[Cu]-salts	Time [h]	Yield [%][a,b]
1	$Cu(acac)_2$	5	65
2	$Cu(acac)_2/Zn$ [10 mol%]	2	40
3	$Cu(acac)_2/Ph_3P$ [10 mol%]	3	90
4	$Cu(acac)_2/Et_3N$ [2 mol]	6	<10
5	$[F_3C(O)CH_2C(O)CH_3]_2Cu$	4	<10
6	$[F_3C(O)CH_2C(O)CH_3]_2Cu/Ph_2P(O)OH$ [10 mol%]	2	70
7	$[F_3C(O)CH_2C(O)CH_3]_2Cu/CH_3COOH$ [10 mol%]	2	50
8	Copper prolinate/CH_3COOH [10 mol%]	6	30
9	$Cu(OAc)_2$	4	75
10	$CuSO_4$	4	50

[a] Reaction conditions: phenylacetylene (1 mmol), [Cu}-salts (5 mol%), DMF/THF = 3/1 mL.
[b] Isolated yield.

Table 2
Screening of the efficiency of Cu-precursors and additives for the dimerization of phenylacetylene.



Entry	[Cu]-catalyst	Additive	Time [h]	Yield [%][a,b]
1	$Cu(acac)_2$	Et_3N (2 equiv.)	8	n.d.
2	$Cu(OAc)_2$	Et_2NH (1 equiv.)	8	n.d.
3	$Cu(OAc)_2$	CH_3COOH/H_2O	15	n.d.
4	$Cu(acac)_2$	Zn	2	<5
5	$CuSO_4$	Sodium ascorbate	8	n.d.
6	$Cu(acac)_2$	Ph_3P	17	n.d.
7	$CuSO_4$	Ph_3P	8–20	<10[c]
8	$Cu(OAc)_2$	Ph_3P	8	<10[c]
9	$Cu(OTf)_2$	Ph_3P	8	<10[c]
10	CuO	Ph_3P	20	n.d.[c]
11	Cu_2O	Ph_3P	30	n.d.
12	$Cu(OTf)_2$	$(EtO)_3P$	8	n.d.
13	$Cu(OTf)_2$	Bu_3P	8	n.d.
14	$CuSO_4$	H_3PO_3	8	30
15	$CuSO_4$	H_3PO_2	8	15
16	$Cu(acac)_2$	$(PhO)_2P(O)H$	6	90
17	$CuSO_4$	$(EtO)_2P(O)H$	2	90
18	$Cu(OTf)_2$	$(EtO)_2P(O)H$	4	88
19	$Cu(OAc)_2$	$(EtO)_2P(O)H$	4	90
20	CuO	$(EtO)_2P(O)H$	7	86

[a] Phenylacetylene (1 mmol), copper catalyst (5 mol%), additive (10–20 mol%), DMF/THF = 3/1 mL, 70–75 °C, under argon.
[b] Inspect of the reaction on the TLC (Silufol, eluent-toluene/hexane = 1/3).
[c] ^{31}P NMR spectrum always showed signal of $[Cu](Ph_3P)_2$ complexes ($\delta_p = 23–25$ m.d.).